Periprocedural prophylactic antithrombotics in arterial procedures: The road to consensus…

Periprocedurele profylactische antitrombotica in arteriële procedures: De weg naar consensus…

(met een samenvatting in het Nederlands)

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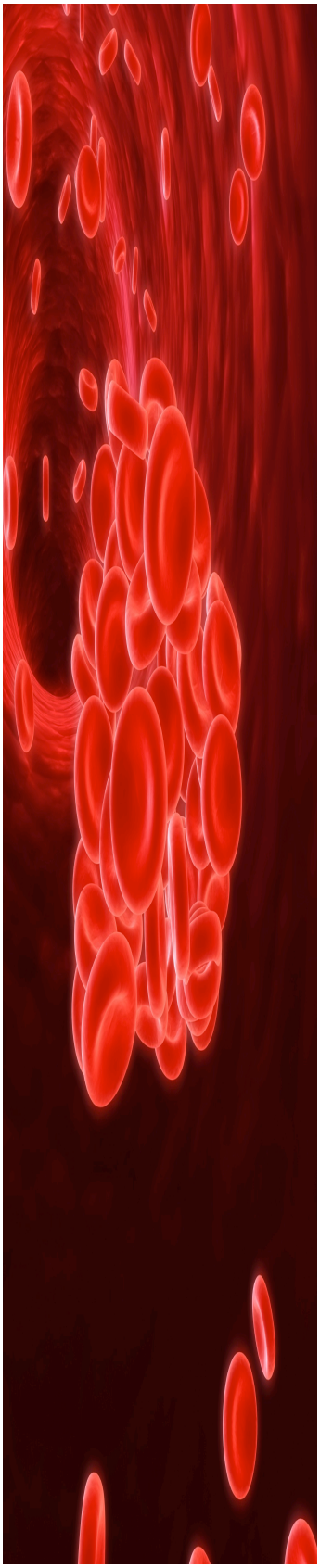
Aan mijn vader Hans (†):

“Jongen, je kent het en je kunt het”

Contents



Chapter 1

General introduction

General introduction

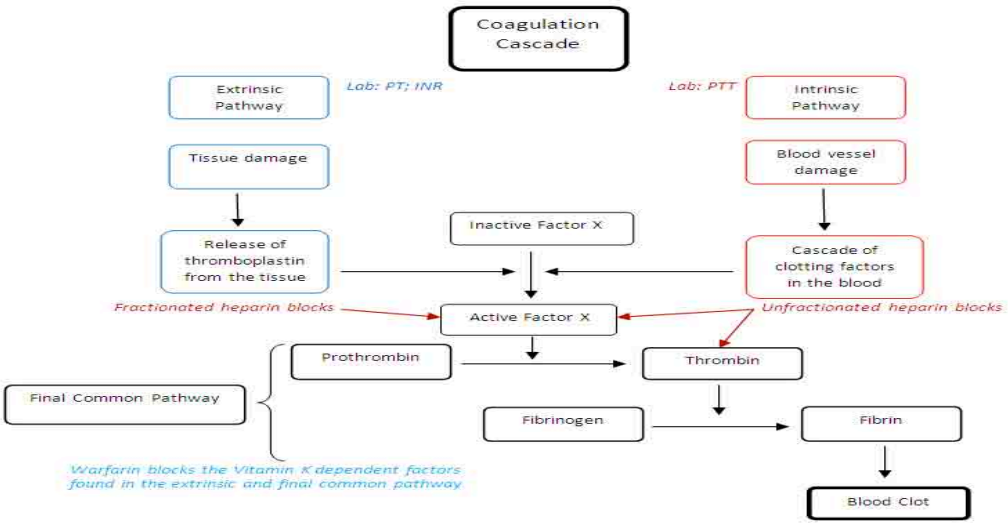
In 1940 Murray[1] published his paper on the role of "heparin in surgical treatment of blood vessels". The introduction of heparin as a periprocedural prophylactic antithrombotic (PPAT) in vascular surgery, caused an increase in the development of surgical interventions in the arterial circulation by enhancing the technical possibilities and increasing the results of those interventions.[2] Heparin was soon implemented in daily practice by vascular surgeons around the world. Heparin reduces the clotting of blood while clamping arteries and thereby reduces thrombotic complications while performing arterial reconstructions.[2] This permitted the pioneers of vascular surgery to expand the possibilities of operations on the arterial and venous blood vessels.[3] After those early days of vascular surgery it became even possible to extend the scope of surgery to the heart. The invention and introduction of the heart-lung machine in cardiac surgery in 1953,[4] was merely possible by the grace of a strong and efficacious anti-thrombotic: heparin. After Charles Dotter published on the first percutaneous transluminal angioplasty (PTA) in 1964,[5] this form of endovascular interventions in the arterial circulation rapidly developed, and became standard of care in the treatment of arterial disease.[6,7] Heparin started being administered during all of these (percutaneous) endovascular interventions without many (randomized) trials, mainly because it appeared to be successful during open procedures and percutaneous coronary interventions. Soon wires and catheters became coated with heparin to further reduce the thrombogenicity of endovascular arterial interventions.[8,9]

The advantage of using heparin in vascular surgery and interventional radiology, is self-evident as it prevents blood from clotting. However it became soon apparent that this use of heparin also has a major clinical disadvantage: the prolonged clotting of blood causes an increase in bleeding complications. The prolonged coagulation by heparin increases peri- and post-procedural bleeding. This can lead to (life-threatening) acute blood loss and the need for blood transfusions.

The negative side effects of blood transfusion are nowadays widely recognized.[10] Blood transfusion may cause a serious allergic reaction and can cause, despite extensive matching, the formation of antibodies. Also transfusions can lead to the transmission of viral, bacterial and parasitological infectious diseases. Finally, blood transfusion suppresses the immune

system and can influence the coagulation cascade. More periprocedural blood loss increases procedure time, possibly leading to more (infectious) complications. Additionally, the incidence and severity of post-procedural hematoma at site of operation or puncture may cause other complications, such as pain and infection. Hematoma thereby increases the incidence of wound infection, a serious complication, which leads to more re-interventions and even a higher mortality for patients undergoing open or endovascular arterial interventions.[11,12] The use of heparin can also lead to the development of heparin induced thrombocytopenia (HIT) syndrome.[13] This is an unpredictable response of the immune system on the administration of heparin. It can occur even after only a single bolus dose of heparin. HIT can lead to clinically relevant arterial and venous thrombo-embolic complications, which can lead to amputation and in its most severe form even to death. The incidence of HIT varies in literature from 0.5 to 5%.[13]

Another major disadvantage of the use of heparin as a periprocedural prophylactic antithrombotic is the fact that heparin has no linear dose-response curve and no linear elimination curve in vascular patients.[14-16] Heparin is a glycosaminoglycan and influences the coagulation cascade mainly through an interaction with antithrombin III (AT-III). Heparin also interacts with heparin cofactor II and directly with factor Xa. Heparin forms a biochemical complex with AT-III and this combination of enzyme and inhibitor inactivates coagulation enzymes including thrombin (IIa), but also factor IXa, Xa, XIa and XIIa. Heparin influences coagulation mostly by interaction with thrombin (IIa), the most sensitive to inhibition by heparin/AT-III.[17-19]



Heparin is heterogeneous in its size and weight of molecules, its effect on coagulation and its pharmacokinetic effects. These facts explain why heparin has a non-linear effect on coagulation: on average approximately 33% of heparin molecules exert AT-III mediated anticoagulant activity; heparin molecules with a chain-length of less than 18 saccharides have no influence on AT-III/antithrombin and the higher molecular weight molecules of heparin are subject to a faster biological clearance from the blood. These molecules however, exhibit low activity on AT-III and are therefore of less clinical influence on coagulation. Furthermore heparin binds non-specifically to proteins and cells in the blood of the patient. This causes a further limiting of the clinical effect of heparin administration. This non-specific binding causes low bioavailability at low doses of heparin, also a short plasma half-life time and creates a large variability in anticoagulant effect among patients with vascular disease.[17-19] Since 1972, it is also known from literature, that differences in the potency of heparin exists between heparin brands.[20,21] This increases the non-predictable response in the vascular patient undergoing arterial interventions.
Heparin is not absorbed through the gastro-intestinal mucosa and is preferentially administered intravenously. Subcutaneous injection is also possible, but it takes longer for heparin to reach therapeutic levels and the doses of heparin should be 10% higher to equal the bioavailability reached by the intravenous route.[17-19]

To measure the clinical effect of the applied dose of heparin, the activated partial thromboplastin time (APTT) was the first test used. This test measures the inhibitory effect of heparin on thrombin, IXa and Xa.[18] The actual heparin concentration correlates only moderate with the APTT. However, the higher levels of anticoagulation required during cardiopulmonary bypass surgery (CPB) in cardiac surgery and during percutaneous coronary interventions (PCI) necessitated the development of a test that correlated better than the APTT with actual coagulation status during those interventions. The activated clotting time (ACT) proved to meet those demands, also in non-cardiac vascular surgery.[22-24] Measuring an ACT at a point of care station at the operating room or interventional suite is nowadays standard of care in case of CPB, PCI, major cardio-vascular endovascular interventions on the aorta. In non-cardiac vascular surgery and interventional radiology, this point of care measurement of ACT or heparin concentration seems not to be widely accepted and applied.

The mentioned differences in potency of different brands of heparin, also underline the importance of measuring the actual effect of heparin.

Considering all the above about heparin, the mechanisms of interaction and the proven variability of bio-activity in the vascular patient, the introduction of measuring the actual effect of heparin should be reconsidered in vascular surgery and interventional radiology. Recently new devices are marketed, such as the Hemostasis Management® System (Medtronic®) and the Rotem®, which uses rotational thrombo-elastometry to evaluate current coagulation status. Results have to be awaited from large trials to evaluate the applicability and accuracy of these new tests.

To reduce the higher bleeding tendency caused by heparin administration, protamine sulphate has been used to reverse the effect of heparin. Protamine is a heterogeneous mixture of highly cationic polypeptides, originally purified from salmon sperm, but nowadays produced through recombinant biotechnology. Protamine has been subject of much controversy. It can cause adverse and potentially life-threatening complications such as a severe allergic reaction, systemic arterial hypotension, decreased cardiac output, decreased oxygen consumption, bradycardia and even death.[25] When used during carotid surgery, contradictive reports have been published on the question whether protamine increases the incidence of stroke.[26-30] Additionally, when protamine is not bound to heparin in blood, it expresses anticoagulant properties, thereby creating a contradictive effect in the vascular patient when the dose of protamine is not exactly matched with the circulating heparin at that precise moment. Considering the fact that only a vast minority of vascular surgeons and interventional radiologists measure the actual, clinical effect of heparin in the patient and the fact that heparin has no linear dose-response curve and elimination curve, standardized reversal of heparin with protamine seems, at least, not evidence based. Measuring the effect of heparin should be fundamental when administering heparin as PPAT in vascular surgery or interventional radiology, let alone before using protamine to reverse heparin. The current use of such a measurement by vascular surgeons and interventional radiologists will be evaluated in this thesis.

To increase insight in the current use of periprocedural prophylactic anticoagulation and to develop evidence based guidelines on this topic for vascular surgery and interventional radiology, a study group was instituted in the Netherlands: CAPPA: Consensus on Arterial PeriProcedural Anticoagulation. This group consists of Dutch vascular surgeons and interventional radiologists and is supported by the Dutch Boards of Vascular Surgery and Interventional Radiology. Aim of the CAPPA group and this thesis, is to thoroughly inventory current practice on periprocedural anticoagulation and antithrombotics in the Netherlands amongst vascular surgeons and interventional radiologists. After a reliable depiction of current daily practice, results of those inventories will be compared with contemporary literature by means of systematic reviews and compared with existing (inter)national guidelines. After evaluating current daily practice and the systematic reviews, multiple randomized controlled trials will be designed on the use of periprocedural anticoagulation in open and endovascular arterial procedures.

Ultimate goal of the CAPPA study group and this thesis, is to create a road to consensus on a topic that is subject to much discussion and involves every day practice around the world during arterial interventions in the vascular patient: periprocedural prophylactic antithrombotics (PPAT).

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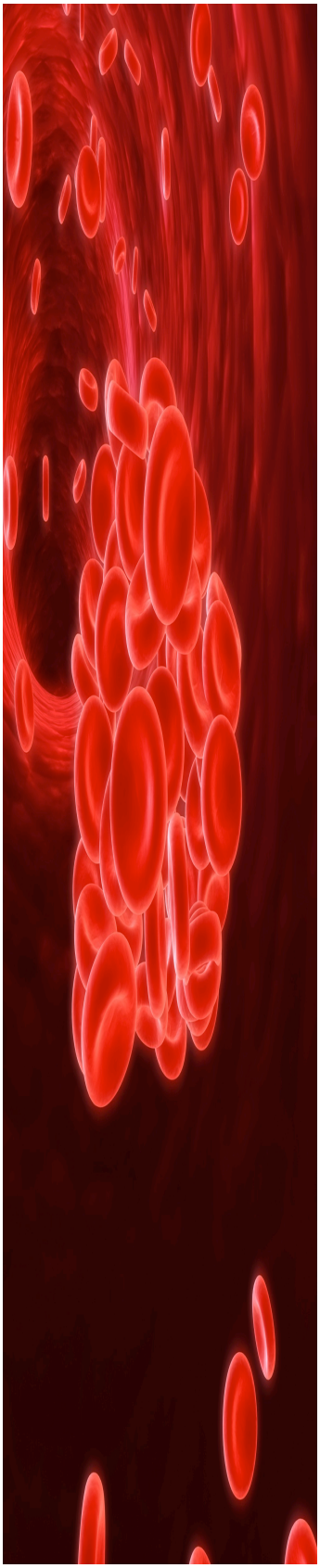

Chapter 2

The history of heparin

Part 1:

The discovery:

An intriguing story, tainted by intrigue

Cornelis M.A. Bruijninckx

Arno M. Wiersema

Submitted

Summary

This narrative is about deciding who should be cherished as the discoverer of heparin. The young and totally inexperienced junior researcher who, supervised by an elder and very experienced researcher, stumbles upon an unexpected finding, subsequently attributing this finding to an acidification of the solutions used? Or the elder researcher, who in a period of over 10 years sifted out the agent responsible for the unexpected finding? For short, Jay McLean or William Henry Howell? After weighing all the evidence, abridged provided in this article, the reader can only support our conclusion in this matter, we fervidly hope.

Introduction

Jay McLean (born 1890-1957) claimed his discovery of heparin[1] as the consequence of his "determination to become a physiology-based surgeon rather than an anatomy-based surgeon". He was born into a physicians' family, as he proudly had liked to remind his audience to be, at the New York Academy of Medicine in New York City on the 25th of February 1958 during a symposium on the 'Historical and Physiological Aspects of Anticoagulants'. His father was a physician, his cousin was a Professor of Anatomy at the University of California (whom he met only once), and his uncle, his father's elder brother, was a Professor of Surgery and Dean at the Medical School of the University of California. The latter was honoured after his death as "California's First Master Surgeon".[1] Sad to say, McLean would not be able to deliver his address at the mentioned New York Academy in February 1958, since he died suddenly of myocardial ischemia on November 14, 1957, at the age of 67 years. The unfinished notes for this lecture were published posthumously in 1959.[1] The following description of the life of Jay McLean, up to 'his discovery', has been largely derived from these notes.

The early years and the road to Johns Hopkins of Jay McLean

His life had a rather sad start. When Jay was 4 years old, his father died. His mother remarried when he was 9 years old. The earthquake and fire of San Francisco in 1905 ruined his stepfather's business and the family home. In the following years he took on all kinds of odd jobs to finish Lowell High School in San Francisco, and to enter the premedical school of the University of California at Berkeley in 1909. During his freshman and sophomore years, his stepfather would pay only for board and room and had declared to continue to do so for 4 more years of medical school at Berkeley, leaving the rest to be earned by Jay himself. However, Jay "deliberately choose the fiercest student competition" by aspiring to enter Johns Hopkins' Medical School in Baltimore. This required 3 instead of 2 years of college. His stepfather then annulled his financial contributions, which forced Jay to work for 15 months in a Mojave goldmine at Randsberg, to earn him enough money "to re-enter college for the third year of preparation for Johns Hopkins". During that year, he again had to take on odd jobs to earn for his living, ranging from blood and urine analyses in the College Infirmary, to scrubbing the decks of ferryboats. After he had finished his third year of college at Berkeley,

he entered in the fall of 1913 the medical school of the University of California, graduating in May 1914 with a BS degree. During that first year in Medical School he had studied physiology from William Henry Howell's "Textbook of Physiology for Medical Students and Physicians", which had revived his interest in pursuing a career as researcher in John Hopkins.

He applied for admission there, although he had "no money for the transcontinental journey, let alone for the expenses for an academic year at Johns Hopkins". However, admission to Johns Hopkins Medical School was denied to him, for which he blames the Dean at the University of California. This Dean had written to the Dean at Johns Hopkins that Jay McLean "was not the kind of man Hopkins sought". Whether this is the truth, cannot be proven, and McLean does not speculate in his autobiographic sketch about possible motives his Dean might have had for his destructive act. "Being broke again", he "returned to remunerative labour, this time drilling oil wells". Again, after 15 months, he had saved enough funds for one year at medical school and boldly took a train to Baltimore to present himself in person to the Registrar and the Dean of Johns Hopkins Medical School in August 1915. He told them he had received the letter of denial of the Registrar but still wanted to join Johns Hopkins Medical School. To reach this goal, he told them, he had planned for the next year to combine working for a living and study organic chemistry, which had been added to the requirements for admission to Johns Hopkins Medical School. After that year he hoped to qualify for admission. The day after, he was summoned to see the Dean who informed him he could be admitted to the second year of medical school because of an "unexpected vacancy". Jay promptly paid the fees for a year as medical student, planning however not to take medical school courses but instead called on prof. dr. William Henry Howell "and told him of my desire to prepare for an academic career in surgery and that I wished to devote one whole year to physiological research now".

At Johns Hopkins with William Howell

William Howell then gave Jay McLean "the problem of determining the value of the thromboplastic substance of the body".[1] Howell had postulated before, that there was a balance between a circulating clotting inhibitor, termed by him 'antithrombin', and a procoagulant, termed by him 'thromboplastin'. He believed that coagulation started at the site

of vascular damage with the release of thromboplastin by damaged tissue cells, platelets and leukocytes which then neutralized the antithrombin in shed blood, thereby permitting at that site activation of prothrombin by calcium.[2-5] Howell thought this thromboplastin to be cephalin, a lipoid or phosphatide (to day it would be called a phospholipid) he assumed to be present in every tissue of the body. He had succeeded in obtaining cephalin as a crude extract of animal brains and thymuses. However, he was unsure whether the thromboplastic action was indeed due to cephalin or possibly to some impurity in the extracts. Also he was curious if far-related phosphatides would exhibit a similar property.[6] Howell therefore assigned McLean to prepare this cephalin as pure as possible from crude ether-alcohol brain extracts and, moreover, to test other phosphatides for their thromboplastic activity. McLean eagerly applied himself to this task. On top of that he also entered both the organic chemistry course at Johns Hopkins and an advanced course in German "to better read the German chemistry literature on lipoids (phosphatides)".[1]

MacLean described his workplace 42 years later "a sink and attached table-drain board with a shelf over the sink in a large student physiology laboratory (not used as such then), across the hall from dr. Howell's office and private laboratory". Furthermore he mentioned 5 other persons working in the department who "lunched together, with dr. Howell, but I was not invited to join them. I was not a colleague". To this sad lamentation he immediately adds that his exclusion might partly have been caused "because my drying tissues produced an all-pervading insufferable odour". How different is this picture from the one he sketched in his letter to William Howell from October 2, 1916 wherein he expressed the gratification he had experienced from working in Howell's laboratory, and reminisced his "little old desk".[7] Working "nights, Saturdays and Sundays … without receiving any stipend" (sic!), he did not succeed in purifying cephalin from brain extracts and therefore could never make sure the thromboplastic activity of these extracts was due to cephalin.[1] Then, in December 1915, he reasoned that if the thromboplastic activity of the brain extracts were due to "some other substance, adherent to or absorbed by cephalin, this might not be so in organs which did not contain such a large amount of cephalin as the brain does".[1] This substance could be the source of the thromboplastic activity. In reading German chemical literature on phosphatides, he had found articles describing phosphatides extracted from bovine hearts (called cuorin)[8]

and horse's and dolphin's livers (called heparphosphatid)[9] by a process similar to that was used in Howell's laboratory to obtain cephalin from animal brains. Therefore, he reasoned, "these products might be heart and liver cephalin".[1] To this he adds: Howell "had not known about cuorin or heparphosphatide".[1] Now it seems McLean is glorifying his role somewhat. Howell himself had recognized that the thromboplastic action of the brain extract "might be due to some adherent impurity rather than the phosphatide [cephalin; *CB, AW*] itself", and had McLean instructed to sort this out and furthermore to test "other related phosphatides".[6]

William Howell and research on blood coagulation

William Henry Howell (1860-1945) at that moment in time, was the world's most prominent expert in coagulation.[10] Having obtained his PhD in 1884 on the thesis titled 'The origin of fibrin formed in the coagulation of the blood', he would stay dedicated to unravelling the process of blood coagulation the rest of his life. At the end of the 19th century, especially by the work of Alexander Schmidt (1831-1894; universally recognized as "the father of blood coagulation"), it had been shown that in the clotting of blood a water-soluble protein, called fibrinogen, was converted to the insoluble fibrin. This conversion was mediated through the action of an enzyme called thrombin. This thrombin itself was hypothesized to be formed from a, at that time hypothetical, precursor called prothrombin. The formation of thrombin from prothrombin was catalysed through the action of 'zymoplastic or thromboplastic substances' in the presence of calcium ions. Damaged tissues, platelets or leukocytes could furnish these 'zymo-or thromboplastic substances'. This led to the then known 3 *circulating* coagulation factors: fibrinogen, prothrombin (hypothetical), and calcium. More or less pure fibrinogen and thrombin could be obtained at that time from blood,[2,3,11] and, as Howell aptly had it formulated, "the secret of coagulation" at that time was "concealed in the process which lead to the actual production of thrombin".[3] The exact role of the 'zymo-or thromboplastic substances' was not known. Morawitz,[12] and Fuld,[13] had simultaneously, but independent from each other, in 1904 proposed the theory that in shed mammalian blood, quickly disintegrating platelets furnished a zymoplastic substance that *enzymatically* facilitated, in the presence of calcium ions, the conversion of (the hypothetical) prothrombin in thrombin.[4,14] Considering its enzymatically character, Morawitz[12] called this substance 'thrombokinase', and Fuld[13] called it 'cytozym'.

Howell however, found it then difficult to believe that circulating blood could keep its fluidity while calcium and prothrombin were circulating together. Therefore, he proposed a circulating 'antithrombin' that prevents the activation of prothrombin to thrombin by calcium, probably by binding to prothrombin and thrombin. Thromboplastin, as Howell called the 'zymo-and thromboplastic substances', is derived from blood platelets or from external tissues. It neutralizes this restraining effect of antithrombin, thereby initiating coagulation of the blood.[3] The presence of an antithrombin in mammalian plasma, and in excess in dog's peptonized blood, was at that time generally assumed and beyond reasonable doubt proven by Howell's experiments in 1910-1911,[2-3] but Howell was the first to appreciate its role in inhibiting the clotting of circulating blood. In 1915, two of his research fellows were to show that this antithrombin was probably produced in the liver.[14]

Considering the importance of this, all researchers of coagulation attached to the initiation of coagulation by these thromboplastins. Howell understandably centred from then on his research on these thromboplastins. Already one year later he could more or less prove it was not "lecithin as it usually is defined, but rather the related unsaturated phosphatid, kephalin, or else, although this suggestion seems highly improbable, some unknown substance which adheres to the kephalin fraction of the phosphatid material".[4] He firmly believed this thromboplastin to be present in every tissue. Two more years later he described a method to extract prothrombin from blood plasma and demonstrated that its conversion in thrombin in the presence of calcium ions did not need the thromboplastins. Hereby he definitively proved Morawitz's[12] and Fuld's[13] theory for coagulation wrong.[5] Since in 1916, the exact nature and mechanism of action of cephalin (as it was spelled from then on) was still unknown and Howell was not completely sure whether an impurity might play a role, McLean's assignment at that time fitted well in the order of Howell's research.

Heparin discovered or phosphatides with anticoagulating properties?

In his article of 1916, Jay McLean[6] described duly how he prepared cephalin from pig brains by different methods taken from literature and from Howell himself. Soon he started to prepare cephalin from other organs but also other 'phosphatides' like 'cuorin' from bovine hearts following the method of Erlandsen[8] and 'heparphosphatid' from horse's liver following the method of Baskoff.[9] These last 'phosphatides' were not only chemically different from

cephalin (i.e. insoluble in alcohol at 60^0C), but also demonstrated strong anticoagulating powers. McLean reports this in the body of the article, adding that the anticoagulating action of heparphosphatid "is being studied and will be reported on later". In his conclusions, the anticoagulating effects of these phosphatides were not mentioned. Later McLean would write to Charles H. Best, that dr. Howell had opposed to its revelation altogether, - feeling that it should be studied more thoroughly and only thereafter a paper should be written -, but finally had agreed to its revelation "in the body of the paper".[15] This befits the rather methodical pattern of Howell's scientific publications.

McLean describes 41 years later,[1] in preparation for the historical symposium on anticoagulants to be held in New York in 1958, very vividly how he "one morning in 1916 went to the door of dr. Howell's office and said: Dr. Howell, I have discovered antithrombin. He [Howell; *CB, AW*] smiled and said: antithrombin is a protein, and you are working with phosphatides. Are you sure that salt is not contaminating your substance? " [Concentrated neutral salt solutions may inhibit coagulation markedly; *CB, AW*].
Howell was, at that time, according to McLean, "most sceptical". McLean then had an orderly bleed a cat, stirred all of a proven batch of heparphosphatides into a small beaker full of its blood, and placed that beaker on dr. Howell's table and asked him to tell when it clotted. It never did clot. Howell still did not believe McLean had discovered a natural anticoagulant, but decided at this point to participate himself actively in the research on the possible anticoagulating effects of this heparphosphatide. After McLean had prepared new batches of this heparphosphatid, most probably monitored by Howell himself, and again could demonstrate in vitro its anticoagulant activity, Howell had been convinced that McLean's unexpected finding was not caused by technical failure. Considering Howell's preoccupation with antithrombins, and his (and other researchers') presumption, that the liver might be the organ producing these antithrombins,[14] it is conceivable that his first thought was that they were on the track of the origin of antithrombin. This explains the vigour with which both in vitro and in vivo experiments, and the search for heparphosphatide in other organs, were launched in the ensuing months. The written account by Jay McLean ends with the note "…we planned the first in vivo experiment with a dog and administered the heparin intravenously".[1]

For the academic year 1916-1917 McLean had accepted a fellowship from the University of Pennsylvania, for which Howell had recommended him.[7] In Philadelphia he studied pharmacology and continued his research on cephalin under the supervision of Richard Pearce in the John Herr Musser Department of Research Medicine. After that year, the University of Pennsylvania awarded him a degree in Master of Arts7 or Master of Science16. The Johns Hopkins Medical School credited him with his second year of medical school. In August 1917 his second article on cephalin was published.[17] This described how cephalin solutions lost their thromboplastic activity while aging (a phenomenon Howell already had described),[4] due to saturation of its unsaturated fatty acids. Furthermore he described, that 2 solutions, one 6 months old and another one -that he had got "through the kindness of Dr. Howell"- 2 years old, were shown to *retard* coagulation, the older more so than the younger one. He attributed the anticoagulating power of these aged cephalin solutions to their acidity, in time acquired. Isn't it striking that McLean referred to his first article without ever mentioning 'his discovery' of the marked power of heparphosphatid to inhibit coagulation of the blood, and that he, on top of that, owes the anticoagulating power of the (very) aged cephalin solutions to their *acidity*, not to 'a lurking impurity that in essence was 'the antithrombin' he already had discovered one year before'? Clearly at that time he had no notion of 'his discovery' from 1916, and indeed, how could he have had? At that time, clinical attention was focused rather on haemophilic than on thrombotic clotting disorders. Howell's curiosity too had been only roused because he thought they had found the substance that preserved circulating blood's fluidity.[18]

McLean's first publication,[6] reported the already known inactivation of cephalin solutions when it aged, not an anticoagulating effect. In that study anticoagulating activity had been demonstrated in *freshly* prepared cuorin and heparphosphatid solutions. In contradiction with these 2 publications, McLean claimed in his posthumous published article[1] to have detected anticoagulating activity in *aged* batches of cuorin and heparphosphatide because of decay of accompanying cephalin, concluding that: "If I had not saved them, *I would probably not have found heparin*" [italicized by authors]. Here his memory of past events should be characterized at least as clouded. Firstly, in 1916 he had not found *heparin* since that name was to be coined 2 years later by Howell and Holt.[19] Secondly, he had found, unexpectedly, anticoagulating activity in *freshly* prepared cuorin and heparphoshatid solutions, not in *aged*

solutions of these phospholipids. Thirdly, he was to work with *aged cephalin* (not cuorin or heparphosphatid) solutions one year later, and in finding anticoagulant activity in these solutions, he did not attribute this activity to the presence of 'heparin' or any other anticoagulant, but to the acidification of the solutions in time!

After that and many years later, McLean only published 2 obscure articles concerning case histories: one on heparin in the treatment of sub-acute bacterial endocarditis in 1941[20] (no success, but the authors saw possibilities with some adjustments in treatment protocols) and one on heparin in treating a case of gangrene following a fractured leg in 1946.[21] He also wrote a chemical study on heparin–barium-salt in collaboration with Melville Lawrence Wolfrom, a well-known chemist at Ohio State University, who would make substantial contributions to unravelling heparin's chemical composition and structure.[22]

Heparin finally discovered, by Howell

In contrast with McLean, Howell appears to have centred his research wholly on these phosphatides as soon as McLean had demonstrated that he had made no mistakes in preparing the cuorin and heparphosphatid. In an elaborate article in 'The Harvey Lectures' from 1916-1917,[18] on page 312, Howell credits McLean with finding 2 phosphatides: cuorin and heparphosphatid, that had a marked inhibitory effect upon coagulation. He describes series of experiments he and several junior researchers had already done or were still involved in. These experiments proved that these phosphatides inhibited the generation of thrombin when added in vitro or in vivo, and had no inhibiting effect upon the reaction between fibrinogen and thrombin. Therefore he had "provisionally" named them "antiprothrombins".[18] They could be found in heart-muscle, liver, lymph glands, and uterus.[18,23] Howell had the chemistry of his cuorin and heparphosphatid tested at the Rockefeller Institute in New York by Phoebus T. Levene, and wrongly concluded from these measurements that the nitrogen N:phosphor P ratio for cuorin equalled 2 to 1 "in accordance with Erlandsen's analysis for cuorin" and 1 to 2.4 for heparphosphatid "which would indicate a relation of this substance to the jecorin".[18] Wrong for 2 reasons: wrong computation and wrong citation of literature. By dividing the recorded weights of the elements with their atomic mass, the computed N:P ratio is 1:2 for cuorin (so, a monoamino-diphosphatid) and this really is in accordance with Erlandsen's

analysis,[8] and 2.2:1 for heparphosphatid (thus a diamino-monophosphatid) which ratio concurs with that of Baskoff's Jecorin.[9] This mistake on Howell's side must have been 'a slip of the pen' since otherwise Howell appears very scrupulous in his writings. According to Erlandsen,[8] cuorin was the only monoamino-diphosphatid he knew. About the diamino-phosphatides he remarked that they appeared to be present in every tissue and are probably indispensible parts of every cell. Lecithin and cephalin, also to be found in nearly every tissue, belonged to the monoamino-monophosphatides.[8]

Howell speculated in "The Harvey lectures" on the presence of this antiprothrombin in blood in small amounts whereby it might safeguard blood's fluidity rather than antithrombin. He described in vivo studies of intravenous injections of antiprothrombin in dogs and a new test to measure its anticoagulating effect he called the 'prothrombin time'. He defined this as the time of clotting of an, in oxalate solution drawn, sample of blood plasma after optimal recalcification. Dog's blood after intravenous injection of antiprothrombin demonstrated "a picture comparable to that found in the blood of hereditary haemophilies, namely a great delay in the prothrombin time with indications of a distinct increase in antithrombin". Howell therefore, at that time, speculated hereditary haemophilia to be due to an abnormal high amount of antiprothrombin in the blood.

Probably in the summer of 1917 Howell started a project to purify the antiprothrombin heparphosphatid, together with a medical student named Luther Emmett Holt. Howell and Holt had varied the method of preparation of heparin from dog livers in many different ways, looking for a rapid and economical process for its isolation from tissues. It proved very difficult, indeed impossible to get rid of adherent cephalin. Finally, they adopted a still expensive and time-consuming method with many repetitions of precipitations, centrifugations, and dissolvings, resulting in a (to modern standards) very crude and impure, but active anticoagulating extract, completely soluble in saline. Opalescence of a solution denoted admixture with cephalin. Such solutions were best kept for some weeks or even months where upon their anticoagulating power was greatly improved.[19] This "antiprothrombin" was renamed 'heparin' by Howell to indicate it was extracted from the liver, and possibly also to make way to denote a hypothetical substance in blood serum "pro-antithrombin". Based on in vitro experiments, this 'pro-antithrombin', was thought to be converted to antithrombin under the influence of heparin. Furthermore, heparin was found to

inhibit the conversion of prothrombin into thrombin, also in vitro. It had, in vitro, no inhibiting effect on the action of thrombin on fibrinogen. Howell assumed from several experiments that heparin "reacts in some way with the prothrombin to prevent its activation by calcium". One milligram of this heparin prevented clotting of one ml of cat blood for 24 hours, which became known as one Howell unit per milligram.[16]
In this landmark article from Howell and Holt,[19] Jay McLean has been credited for "first calling attention to this substance". According to McLean in a letter to prof. Charles Best, Howell had offered McLean "to place my name on his 1918 paper in consideration of the intravascular injection work we had done. I declined and told him I had participated to such a small extent in this later work that I did not feel entitled to the privilege offered".[24] This article[19] was to be the last wherein Howell would cite McLean's paper of 1916, or would acknowledge him for drawing attention to the anticoagulating properties of heparphosphatid and cuorin. Probably, Howell would later on not again cite McLean's work since he got convinced that by constantly changing his methods for extraction, the inhibitor he was tracking was unrelated to McLean's "heparphosphatid" (see below).

In 1922 Howell delivered a lecture in Toronto, Canada, at the 35th Meeting of the American Physiological Society. In that lecture, he presented a simpler aqueous extraction method for the preparation of heparin from dogs' livers, resulting in a water-soluble end product that was far more effective than the initial product, and that could be purchased from a pharmaceutical firm in Baltimore called Hynson, Wescott and Dunning.[25] This product had a potency of 5 Howell units/mg.[16] However, soon thereafter Mason from the Henry Ford Hospital reported toxic side effects caused by this preparation when used as an anticoagulant for blood transfusions,[26] which however did not lead to adaptations of the procurement by the firm cited above.[27] After this publication Howell wrote an indignant letter to Frank Hartman, chief of Pathology at the Henry Ford Hospital, under whose supervision Mason had done his work, for not citing his, but McLean's protocol for the isolation of heparin. Howell insisted that the form of the inhibitor he had discovered was not related to McLean's 'heparphosphatid'.[7,16] In 1925 Howell was able to produce a better purified heparin, and now noted it did not contain phosphorus at all.[28] Apparently the large phosphorus contents of the crude heparin extracts from before were due to impurities. Furthermore he had noted the presence of carbohydrate

grouping. He found this heparin reacted with a thermo-labile plasma protein to form antithrombin and furthermore somehow interfered with the activation of prothrombin into thrombin. Its potency had now risen to 40 Howell units/mg.[16] Evidence was given to show that heparin is present in the plasma of normal blood and in greatly increased amounts in peptonized plasma. Howell again hypothesized in this article heparin to be the inhibitory factor preserving the fluidity of circulating blood that may be overcome by the phosphatide material furnished by damaged platelets or tissue cells. Also he announced to test whether blood of haemophiliacs contained abnormal great amounts of heparin. Already one year later he concluded from testing in his laboratory this was not the case,[29] and soon after that, he concluded from further experiments, that slow disintegration of platelets accounts for the delayed clotting in haemophilic blood.[30] When in 1930 Fuchs and Falkenhausen from Breslau, Germany, revived the theory that haemophilia is caused by an excess of circulating antiprothrombin, Howell felt compelled to examine this issue again. He used Fuchs' own test to recover 'antiprothrombin (heparin)' from small amounts of blood plasma (the, in 1917 by Howell, provisionally designated name of 'antiprothrombin' for the heparphosphatide and which he later had called 'heparin', was still widely used at that time). Howell hereby demonstrated that haemophilic blood even "contains less rather than more antiprothrombin, as compared with normal blood".[31] Concerning the chemical composure of heparin, Howell had found out in 1928 that it had to be a water-soluble carbohydrate containing sulphur (glucuronic acid), completely distinct to the former substances.[32] This was to be his last article on the nature of heparin. By then his heparin extracts demonstrated a potency of 50 to 100 Howell units/mg.[6] Further development of heparin into a reliable and financially affordable product without toxic effects had to await the genius of another man, Charles Herbert Best (see part II).

Jay McLean, the physician – Jack-of-all-trades, master of none.

After McLean had submitted his second article in May 1917, he volunteered for the American Ambulance Corps and found himself in France on the 2nd of June 1917, taking care of wounded French soldiers in Juilly,[7,16] as if he was already a physician. The U.S.A. was to declare war on Germany and Austria that year on December 7. By then McLean already had returned to Baltimore starting his third year of medical school in October 1917. Supported by

a Joseph LeConte Fellowship from the University of California, McLean returned to work in Howell's laboratory, this time on the adsorption of cephalin to gauze to control bleeding during surgical operations. In contemporary letters he gave 2 reasons for this surprising choice: one was that he taxed the task of isolating anticoagulating phosphatides beyond his ability, and the other was that he believed the procoagulant cephalin to be more applicable to the war effort.[7] Considering his short experience as an 'army doctor' to wounded French soldiers, the second argument might have been decisive for him. For his research, the Hynson, Westcott and Dunning company had him supplied with gauzes coated with cephalin. McLean had planned to publish his results in the summer of 1918. This however, was thwarted by the submission of a manuscript to the American Journal of Physiology on April 24, 1918, from Berkeley, California concerning a study similar to McLean's. Howell had, as an editor of this journal, reviewed and rejected the manuscript.[7] In spite of that, this manuscript was published in the July 1918 issue of the journal.[7] Certainly a disappointment to McLean.

In letters to his mother in 1918, McLean reveals his intention to interrupt medical school after completion of his 3rd year to work yet on the isolating of heparphosphatid.[7] He also stated that Robert Pearce had offered him a position in his laboratory over the 1918 summer break. However, with approval of Pearce and Howell, he subsequently had arranged to work with Walter Bloor, biochemist at Harvard's physiological chemistry department. This plan, however, was thwarted by Bloor leaving Harvard that summer to become professor of biochemistry at the University of California, Berkeley.[7] It is not clear why McLean did not join yet Pearce's laboratory at that time. Maybe because at that same time, he received a second Joseph LeConte Memorial Fellowship enabling him to continue research in Howell's laboratory. However, he was not offered to work on the isolating of heparphosphatid, probably because Howell then was already working on this with Luther Emmett Holt Jr. Instead, McLean was assigned to determine whether hereditary haemophilia was caused by an excess of natural heparin or by a shortage of circulating cephalin. No clear conclusion was reached and no scientific publication was to appear, all but a chapter on haemophilia in Oxford Medicine. He succeeded still to include in this chapter his results with cephalin-coated gauze.[7]

After graduation in 1919, McLean became William Stewart Halsted's research assistant for one year, and then started his residency in surgery with Halsted. Howell had recommended

him for this position, for which he otherwise had not stood a chance having graduated forty-second in his class.[7] McLean interrupted his residency in 1922 when he received a National Research Council Fellowship that allowed him to study surgery in Europe. The first year he studied under Erwin Payr in Leipzig, to whom Halsted had recommended McLean in a letter as "an unusually gifted young man". After that, he spent a year in a Paris hospital, under whom is not revealed.[7,16]

According to a letter from McLean to prof. Charles Best in November 1940, McLean, then still in Paris, was offered a fulltime position as "assistant attending surgeon" on the staff of Allen Whipple, professor of surgery at Columbia University and Surgeon in Chief at the Presbyterian Hospital in New York City, later to become famous for his pancreatic resections.[16] Apparently, Whipple did not think high of McLean's research or operative capacities, since, as McLean put it, "I could not interest Dr. Whipple in heparin. He was resolved that I spent my research time in helping perfect the follow-up system and outpatient clinic of the hospital". [Typical tasks for a member of a surgical staff for whom a position has been created, without much perspective; *CB, AW*]. Not surprisingly he left Columbia within a year. According to McLean because "they abandoned the full-time staff system", which was not true.[7] He then "entered private practice in New York City".[16] According to Marcum,[7] McLean then worked at several academic institutions. McLean, in his letter to Best, restarts his autobiographic sketch in 1928, by describing his involvement in experimental research in the New York Hospital on dogs concerning possible prevention of post-pneumonia consolidation in the lungs by heparinization. However, this undertaking was hindered by his mother's death in San Francisco, for which he had to leave New York immediately.[7,16] No success, again.

McLean, in his letter to Best, takes up the thread in 1931.[16] In that year he studied the use of heparin in preventing abdominal adhesions after perforation of the appendix in dogs, at the Surgical Research Department at the Presbyterian Hospital under direction of Dr. Arthur Purdy Stout. The latter being a surgeon, who would become famous as a surgical pathologist.[7, 16] However, the heparin obtained from Hynson, Westcott and Dunning (H,W& D) from Baltimore was too toxic for the dogs "and their yelps caused Dr. Stout fears that the

Humane Society would investigate, so he found a diplomatic excuse to halt my work".[16] No success, again.

In 1932-33 McLean was "desperately ill" and had been treated in 3 hospitals, among them the Johns Hopkins Hospital, for a total period of one year. "Since then my practice has been devoted to cancer … at the Memorial Hospital for Cancer in New York".[16] It appears McLean had left the practice of surgery sometime in the mid-1920s. Thereafter he worked as a (research) assistant in various pathology laboratories in New York City and became involved in radiation treatment for cancer [possibly as a consequence of himself having suffered from cancer?; *CB, AW*] Apparently McLean was from about 1933 employed as "Fellow at the Memorial Hospital" and as such involved in organizing 4 weeks-courses in cancer for 4th years students of the Medical College of Cornell University.[33] In July 1939 he left New York for Columbus, Ohio, where he had "a consulting appointment at the University of Ohio and still do some work in connection with the Memorial Hospital for Cancer in New York City, which requires my presence there about every 2 months".[16] It appears that he had joined the medical practice of a local physician, Dr. Edward Reinert, locally known as a 'radium pioneer', who seems to have treated women with uterine cervical cancer.[7,34,35] McLean also practiced radiology and oncology at the city's Grand Hospital. In a letter to Roy D. McClure, the first Surgeon-in-Chief of the Henry Ford Hospital in Detroit, trained as a surgeon under Halsted, McLean wrote in 1943 that his current clinical research represented "magnificent possibilities with heparin".[7] Possibly he referred to his appointment as Associate Professor in the Department of Surgical Research at Ohio State University in 1943.[7] An unsalaried position, coming with the following duties: teaching assistants, interns, assistant residents and residents in the principles of blood coagulation and its application to surgical disease, and developing his researches concerning heparin and its application in the field of surgery. No tangible results from this affiliation were to come. He kept trying to secure a full-time salaried position, but failed herein. When he resigned officially from Ohio State University on October first 1947, the university hired no one to replace him.[7] He approached McLure about a position at the Henry Ford Hospital, to no avail. Eventually he found a position with the Health Department in Washington, D.C., as director of the Bureau of Cancer Control.[7] Again, a sad end to a largely unsuccessful period.

In Columbus, frustrated in his goal to secure a salaried academic position, McLean's quest for recognition and renown had been reawakened. He then launched a carefully orchestrated campaign to appropriate the credit for the discovery of heparin. To this end, he wrote several detailed letters to Charles Best, shortly before Best was to deliver his Harvey Lecture in New York (28th of November 1940).[7,16,36] McLean took care to be in the audience when Best delivered his lecture, undoubtedly taking delight in Best's acknowledgment of his presence in the audience: "I am honoured this evening by the presence of Dr. Jay McLean, who in 1916 in Professor Howell's laboratory obtained evidence of the presence of the anticoagulant, heparin, in animal tissues".[18] McLean also wrote such letters on how he had discovered heparin, to the surgeons of the Henry Ford Hospital in Detroit, which had close connections with the Johns Hopkins Hospital in Baltimore.[7] Furthermore, he lectured in the Henry Ford Hospital about his role in the discovery of heparin, and delivered in 1940 the annual lecture of AlphaOmegaAlpha, Ohio State's Chapter of the National Honorary Medical Society in Columbus. This lecture was open to the public and a film by Best and co-workers was shown there on the formation of white thrombi and its inhibition by heparin.[7] In 1945 McLean was interviewed by the famous Milton Cross on national radio. Here he addressed his largest audience ever on his role in the discovery of heparin, and its possible therapeutic role in acute coronary artery thrombosis.[7,16] It was the first (and likely the only) time in his life that he was introduced to his audience as 'the discoverer of heparin'.[16]

Already in 1929 McLean had started to collect articles on heparin, in preparation for the monograph on heparin, which he had planned to publish 25 years after his presumed discovery in 1916. His collection of reprints had by 1941, grown to 'monumental proportions, containing over 1300 numbered, abstracted, and cardboard-mounted reprints of articles, as well as his notebooks from 1916'.[16] He then envisioned writing a monumental monograph on heparin as a cooperative effort of William Howell, Charles Best, Gordon Murray (or Alfred Blalock since Murray had declined cooperation), Melville Wolfrom, and McLean himself.[16] McLean than would take care of presenting the history of heparin. In preparation for this work, he in October 1943 requested by letter, Roy McLure a letter, which Howell had written in 1931 to McLure to dissuade him from use of heparin as a routine procedure after all operations, to prevent postoperative thrombosis since it might cause troublesome

haemorrhage. McLean in his letter judged this advice a shame, since as a consequence "heparin was developed by foreigners", i.e. scientists and surgeons from Toronto and Stockholm. McLure dryly replied: "In spite of Dr. Howell's advice, I did try heparin, made supposedly as you have made it. This was used on 2 patients who developed severe reactions. So, of course, I never repeated it, especially in view of Dr. Howell's opposition". Few, if any, of the approached authors to be, accepted his request for writing a chapter.[7] The monograph on heparin as envisioned by McLean was never completed.

Driven by a precarious financial situation, McLean tried to sell his collection of reprints, offering it to a number of people and institutions without avail.[7] Eventually, Charles Best in 1948 accepted McLean's offer to take charge of his collection.[7,15]

Within 2 years McLean moved in 1949 from Washington to Savannah in Georgia, where he became Director of Radiation Therapy and Consultant in Malignant Disease at the Savannah Tumor Clinic and remained so until his death, 8 years later.[16] McLean's final attempt to establish himself as the discoverer of heparin was to be the conference in February 1958 under the title "The discovery and early development of anticoagulants: a historical symposium". His untimely death prevented this, and his notes for the lecture appeared unfinished. McLean's collection of reprints and his notes from 1916 appeared to have been lost after the death of Charles Best in 1978.[16]

Overlooking McLean's life as a physician, as a surgeon-to-be, one notices a sad life, full of wasted or lost opportunities.

Discussion

The first 3 extracts from dog's livers with anticoagulating properties from Howell's laboratory, were achieved by variations of an ether extraction technique and thus fat-soluble.[10] The 1922 product was achieved by aqueous extraction technique, resulting in a 5 times more potent but still very impure product. Most probably the first 3 products were a mixture of inositol phosphatides, sphingomyelin and phosphatidylserine, which all may have anticoagulant as well as procoagulant properties.[10,37] It now is also known that oxidation of phospholipids, especially phosphatidylserine, potentiates the ability of protein S to enhance APC-mediated factor Va inactivation.[38] So, the anticoagulant activity of aged 'cephalin' solutions may be explained by this phenomenon. Therefore, it is safe to say that heparin as we

know it now, was not discovered at all in 1916, nor in 1918, but only in 1928 when Howell reported a much more active agent that he identified as a water-soluble complex carbohydrate containing sulphur (and no phosphor).[32]

In retrospect, it was a serious mistake to label the mixture of phospholipids with anticoagulant properties in 1918 as 'heparin'. Howell, in 1928, had been on the hunt for this 'antiprothrombin' for 10 years before he had it literally 'discovered' from all sorts of impurities, and recognized as the first human being that it was a complex sulphur containing carbohydrate.[28] The gate to this discovery had been opened by Howell himself, in 1922, when he decided to leave the beaten path of ether extraction of the liver in favour of (the radically opposite) aqueous extraction.[25] Only then, the sugar heparin for the greater part is, could be dissolved and thus extracted from the liver tissue. The stroke of genius, or the mere luck, of this drastic change in method of extraction was Howell's, not McLean's. In fact, this argumentation should suffice for debunking Jay McLean's campaign for appropriating total credit for the discovery of heparin as an act of arrogating.

For those entertaining romantic feelings of a fight over scientific recognition between a young brilliantly ambitious medical student and a haughty over-the-top professor in physiology, and therefore favouring the first, a few more arguments will be furnished to refute McLean's coaxing on this part.

Firstly, Howell, dying at 84 years of age in 1945 from a myocardial infarction, had never has the notion that McLean was contesting him as the discoverer of heparin, since McLean stepped up his campaign only after Howell had died. The only time Howell somewhat indignantly claimed he had discovered 'heparin' was in his February 1924 letter to Frank Hartman, Chief of Pathology at the Henry Ford Hospital in Detroit.[7,16] In this letter Howell made clear that the heparin Mason and Hartman had purchased from H,W&D was "not liver phosphatid prepared according to the findings of McLean. McLean was my pupil and was, and is, my friend. The work of his you quote was done under my direction and according to my methods. The small portion of it bearing upon liver phosphatides had nothing to do with the subsequent preparation of heparin. This latter substance I discovered and isolated by a method worked out by myself and published an account in the paper by Holt and myself".[16] By this statement, Howell increased the ambiguity he was to create by naming every new anticoagulating product he created by extraction from dog's livers "heparin". In fact, Hartman

and Mason were not using the heparin Howell and Holt had created, but the heparin Howell himself had created with aqueous extraction in 1922, the recipe of which he had supplied to H,W&D.[25] So, in retrospect, it already concerned the 'real' heparin, be it with a lot of toxic impurities, and was his claim in this sense justified.

Secondly, McLean's behaviour at the time of his alleged discovery was not in the least consistent with that of the staunched discoverer he started to sketch during his campaign for recognition. One would expect in that case that he would have thrown himself upon testing the agent, researching its physiological and possible therapeutic role. None of that happened, or more accurate still, the opposite happened. He seized a chance to research the *coagulant* properties of cephalin more in depth! And at that, when founding that aged batches of cephalin solutions not only had lost their procoagulant activity but demonstrated a distinct *anticoagulating* property, he concluded this should be attributed to in time acidification of these solutions! So, it is clear he had at that time no notion about a possible anticoagulant hiding itself in these solutions. Furthermore, it is most probable these fat-soluble solutions only contained phospholipids whose anticoagulant activity increases with oxidation.[38]
It was Howell, who in 1916 immediately realized that his pupil might have stumbled upon a new factor in the system that safeguards blood's fluidity while circulating in blood vessels, and therefore devised series of experiments and methods to purify the agent from the crude liver extracts. Howell gracefully recognized several times in lectures as well as in papers that it was his pupil McLean who had drawn his attention to the anticoagulating powers of parts of liver extracts. Rightfully, he denied McLean as the discoverer of heparin in his letter to Hartman since at that time it already concerned a crude form of the 'real' heparin as we know it now, and after that Howell would never again acknowledge McLean for drawing his attention in this matter.
It is utterly nonsense if the one who drew in some way a scientist's attention, rightfully might claim the results of this scientist's diligent creative research as his discoveries. If this would be the rule, Pavlov, Morawitz, and Doyon would have been better candidates.[10] Especially Morawitz, who in 1905 described that extractions of tissues by organic solvents yielded procoagulants, whereas aqueous of the residue after extraction with organic solvents showed anticoagulant activity, seems to have been very close to its discovery.[10]

Thirdly, at the time McLean was launching his campaign for recognition, he was not a young student anymore. In 1940, at the obvious start of his campaign, he was 50 year of age, entertaining bitter remembrances of his times as a working student; of being betrayed by his own Dean; of being excluded from lunch with Howell and his fellow researchers; of his time with Whipple; and, of failing to secure a position as attending surgeon. In that bitter mood, haunted by the 5 sentences he had written in 1916 on anticoagulating phosphatides,[16] reading literature in which Howell was referred to as the discoverer of heparin, McLean got convinced it was *he* who was entitled to that crown, and launched his campaign, twisting the truth of events, flattering contemporary scientists and physicians to get them on his side, and debunking Howell.

It may seem remarkable that McLean seems to have convinced Charles Best from his precedence in the discovery of heparin, Best denoting McLean in his speech before the New York Academy of Medicine on the 25th of February 1958 without any reserve as "the discoverer of heparin" of whom he "had many friendly letters".[15] This, however, is not so remarkably as its seems, since Best had been scheming all his life to appropriate priority as the discoverer of insulin, in this process blackening 'his' professor J.J.R. Macleod, who got the 1923 Nobel prize for this work, and unjustly downplaying the far more important than his own contribution of Banting (who shared the Nobel award with Macleod) and Collip (with whom Mcleod shared his prize money, Banting sharing his prize money with Best).[39] Still worse, even *Johns Hopkins Medicine*, representing the entire medical enterprise of Hospital and School of Medicine, on its website recognizes 1915 as the year "Medical student Jay McLean discovers the anticoagulant heparin, vital for preventing dangerous blood clots".[40] Considering the evidence proving this qualification untrue, and the monumental role Howell has played in the development of the Johns Hopkins Medical School, this website's recognition must be judged as heavily unjust.

To put things in perspective, some aspects of Howell's professional life besides his (heparin) research should be discussed.
Howell had studied and worked in the Department of Biology of Johns Hopkins University from 1876 until 1889, when he was appointed Professor in Physiology and Histology at the

University of Michigan in Ann Arbor.[41] In 1892 he had accepted an appointment as Associate Professor under the famous physiologist Henry Pickering Bowditch at Harvard, with whom (and others) he had founded the American Physiological Society in 1887.[41,42] In 1893 Daniel Coit Gilman, the first President of the Johns Hopkins University, requested Howell to return and to accept the appointment as full Professor of Physiology at the Medical School of Johns Hopkins University that was to be founded that year. Howell accepted eagerly, for, as he put it, " I had …. a deep affection for the University that had done so much for me, everything, in fact, so far as my career was concerned".[42] He held this position to 1916. From 1899 to 1911, he also was the Dean of the Medical School.

In 1916 William Henry Welch, - one of the so-called 'big four' founding professors at the Johns Hopkins Hospital that opened its door in 1889, and the first Dean of its Medical School -, together with Howell founded Johns Hopkins School of Hygiene and Public Health. Welch was appointed Director and Howell Assistant Director. It proved a very fruitful cooperation. In 1925 Welch resigned as Director, strongly advocating Howell as his successor who accepted this position gracefully and continued as a Director of the School until his retirement in 1931 at the age of 70. Thereafter he would continue his scientific research until the day before his death on the 6th of February, 1945.

Howell had demonstrated on every level of his professional and social life human warmth, sincerity, modesty, tact, and sensitivity, together with a life-long commitment to rationality and humanitarian principles.[41,42] He was known as a superb teacher, his lectures characterized by an entire lack of dogmatism or ostentation. His 'Textbook of Physiology for Medical Students and Physicians', firstly published in 1905, was in its 14th edition at the time of Howell's death, every edition revised by him, with more than 140,000 copies sold. On top of all that, Howell has contributed much to the promotion of public health and personal hygiene.[41,42] Already in 1921 he warned of the dangers of the automobile "…slaying its thousands annually; at such a rate in fact that if not checked it bids fair to become one of the major causes of mortality".[42]

A last word from Howell on the spirit on investigation seems warranted. The statement dates from 1926: "In medical research at present there is a keen, almost cruel, competition to secure results that will attract attention. It has its good side no doubt in stimulating productivity but it does tend to distort values and set up standards that give to scientific research something of

the low motives of commercial warfare".[42] This differed completely from the 'spirit of research' he had experienced while working with Henry Newell Martin, the first Professor in Physiology of the Johns Hopkins University. There "The sole animating motive was that we had the privilege of adding something new to the state of physiological knowledge".[41]
From this limited résumé it may be concluded that Howell has attributed immensely to the development of the Johns Hopkins Medical School and University into the high standing institutes they are at present. Furthermore, from it follows clearly that William Henry Howell was not in the least a haughty professor, on the contrary.

In conclusion, it is high time the scientific community, and in its wake society as a whole, forgets about Jay McLean, and recognizes William Henry Howell as the sole discoverer of heparin.

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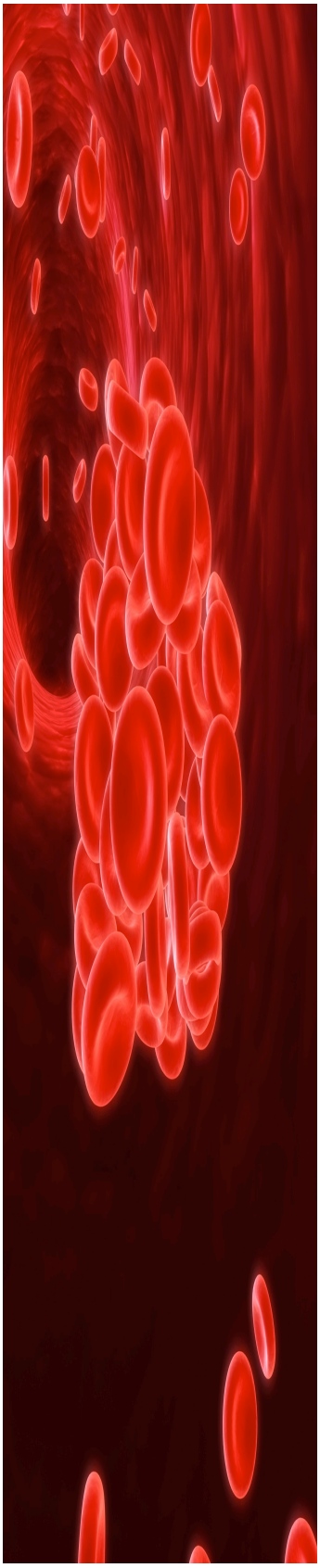

Chapter 2

The history of heparin

Part 2:

The early development

and the road to clinical use

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Summary

After the discovery of heparin it were the pioneers of vascular surgery who introduced heparin in clinical practice. For the use of heparin during arterial and venous vascular surgery this was Gordon Murray from Toronto. From the current narrative it hopefully will be concluded that he may be called “one of the founding fathers of modern vascular surgery”. In Europe, it was Erik Jorpes in Stockholm who contributed to the further development of heparin. The use of heparin as prophylaxis to prevent venous thrombosis is discussed briefly, as it is a landmark in the development of heparin. Finally the vital role heparin has played in the introduction of artificial circulation in medicine is summarized.

Introduction

After Howell in 1923 had changed from ether to water to extract the anticoagulating agent he had discovered from dog's livers, he had licensed the Baltimore pharmaceutical firm Hynson, Westcott & Dunning (H,W&D) to produce this crude heparin.[1] This product had a potency of 5 Howell units/mg.[2] One Howell unit had been defined as the amount of product to prevent clotting of 1 ml of cat blood for 24 hours. Howell kept trying to purify his heparin extracts and by 1925 he produced an extract with a potency of 40 Howell units/mg. At that time he discovered heparin to be no phospholipid but a nitrogen containing carbohydrate.[3] In his own words "Owing to the small amount of material (....) a thorough chemical examination has not been possible". In 1928 he found that heparin contained glucuronic acid.[4] Although again a better product, it still was impure and could only be produced in small quantities by a laborious process. The agent therefore still appeared expensive and troubled with toxic side effects precluding its clinical use.[2,5,6] Howell, although no trained chemist, loved to do the organic chemistry work himself and he indeed came far in determining the complex composition of heparin. But he had to acknowledge, when his years were running out, that expert organic chemists were needed to purify heparin and to disclose its chemical composition.[7] These most needed chemists proved to be Arthur Charles and David Scott, both at Connaught Laboratories of the University of Toronto under direction of Charles Best, and Erik Jorpes from the Karolinska Institute in Sweden.[7]

The Toronto Connection – Physiologists, Chemists and a Surgeon

The pioneers

On September 18 resp. October 9, 1923, the Canadian Intellectual Property Office resp. the United States Patent Office had granted 3 of the 4 discoverers of insulin patents on its production (Frederick Grant Banting, Charles Herbert Best and James Bertram Collip). They, in turn, had assigned their patent rights for one dollar each to the Board of Governors of the University of Toronto (UT). UT used the funds from licensing agreements with pharmaceutical companies to establish the Banting Research Foundation for funding medical research. This Foundation is still active nowadays. Banting was appointed Professor of Medical Research on account of the Provencal government, and was awarded a life annuity of $7,500 by the federal government.[8] In 1930 the Banting Institute would open, located opposite

to the Toronto General Hospital and headed by Banting until his untimely death in 1941.[9] During 1922 Best was appointed head of the Insulin Division of Connaught Laboratories and commissioned to realize the commercial production of insulin.[10] Charles Herbert Best (1899-1978) was a research assistant to prof. Macleod and had been assigned to assist Banting with measurements of sugar and nitrogen contents in blood and urine of the experimental animals. On December 10, 1923, The Noble Prize in Physiology or Medicine 1923 was awarded to Frederick Grant Banting and John James Richard Macleod for the discovery and development of insulin as the first effective treatment of diabetes mellitus. This bestowment of honour would be followed by a lifetime of shameful intrigues on Best's side to appropriate credit as the real discoverer of insulin, partly allied with Banting in discrediting Macleod.[8,10,11] Banting, in his (unjustified) anger over having had to share his Noble award with Macleod, shared the prize money with Best, after which Macleod shared his prize money with the biochemist James Bertram Collip.[10]

Best had entered his first year of medical school as director of the Insulin Division of Connaught Laboratories. Nevertheless, being surrounded by very competent young chemists like Peter J. Moloney, David M. Findlay and David A. Scott,[12,13] he gradually succeeded in producing insulin on a rather great scale for clinical use. After graduating from medical school at the top of his class in 1925, Best had left Toronto for London, England, to work under Henry Hallett Dale at the National Institute for Medical Research, on blood pressure lowering extracts from livers, thereby earning his Doctor of Science from the London University in 1927. Shortly thereafter he had returned to Toronto where he became head of the Department of Physiological Hygiene and associate director of the Connaught Laboratories. In 1928, Macleod accepted the Chair in Physiology in Aberdeen in his homeland, glad to leave a climate poisoned by the continuing rancour of his fellow Nobel laureate whose institute was under his jurisdiction. In 1929 Best succeeded Macleod as professor and head of the Department of Physiology.

The physiologist and his chemists

After Best had returned to Toronto he continued his research on histamine in the Connaught Laboratories. During perfusion experiments, they had used the heparin produced according to Howell's 1923 protocol by a pharmaceutical firm in Baltimore.[1,14] Apparently, they found this

heparin to be ineffective and decided to prepare it themselves in the Connaught Laboratories.[2] They started with Howell's most recently described technique, using dog livers. Next, first experiments were carried out on *beef* liver by McHenry and Deborah Glaister, applying the method of extraction and purification of Howell. Of course, beef liver was more readily available than dog liver. They succeeded in preparing "small quantities of an anticoagulant".[15] Then, Best had Arthur Frank Charles, one of Best his first graduates in Physiology who also had been working on the isolation of heparin from beef liver, transferred to Connaught Laboratories to join David Alymer Scott in further work on this crude heparin. Scott had assisted Best on the production of insulin since 1922 and had been awarded a PhD for his work on insulin by UT in 1925.[16] Scott at that time had to be persuaded to give up his on-going work on insulin.[2] Probably, at this start, Best was convinced they would succeed in a rather short time to produce an effective non-toxic anticoagulant in great quantities. Funds, resources, and equipment at the Connaught Laboratories were greatly superior to those Howell had had at his disposal.[2] Surprisingly, however, advancement would prove to be rather slow and discouraging. In June 1930, Best wrote in a letter to Dale: "The procedures for the preparation of heparin are so drastic that one sometimes wonders if the material has any physiological significance".[2]

Charles and Scott had made some radical changes in Howell's protocol for extraction and purification, whereat more protein-like materials could be removed.[15] A good 3 years later they published their results in 3 articles in the *Journal of Biological Chemistry*.[15,17,18] From 100 pounds of ox liver they were able to produce on average 17 gram of heparin when the livers were extracted immediately, and 56 gram when the livers after mincing were left to autolysis for 24 hours.[15] Its potency was about 10 Howell units (HU)/mg. So, twice more effective compared to '1923 Howell heparin' that demonstrated an activity of 5 HU/mg, but 1/4-th the activity Howell already had reached in 1925 and only 1/10-th of Howell's '1928 heparin'![2,17,18] However, soon thereafter they claimed to have produced a heparin with an activity of 200 Howell units/mg,[18,19] not much later followed by mixed amorphous-crystalline heparin products with an activity of 400 to 500 Howell units/mg.[18] The breakthrough appeared to be their finding that 'at a pH of about 5 much foreign material could be separated from the active principle by means of organic solvents or inorganic substances with little loss of activity'.[18] Furthermore they found heparin to be most abundant in dog's liver, and for ox

tissues most abundant in the lungs.[17] Thereafter procurement of heparin shifted from ox liver to ox lung,[20] that was much cheaper since it was not, like liver, on the menu. In the following years phosphoric impurities were further eliminated by adding benzidine into the process of refinement, and in 1936 an almost pure crystalline barium salt of heparin was produced with an activity level of 500 Howell units/mg.[20] Since this product appeared free from toxic side-effects in experimental animals after subsequent complete removal of the barium, the time was ripe for extensive experimental research with heparin in animals and, possibly, even in human beings.

The surgeon

Donald Walter Gordon Murray (1894-1976) had enrolled in medicine at UT in September 1914, shortly after the start of the Great War in Europe in which Canada immediately became involved, being a member of the British Empire. The Faculty of Medicine and its university hospital, the Toronto General Hospital (TGH), had been reorganized drastically during former years and in the process had grown into one of the best Medical Schools in North America. TGH had been rebuilt adjacent to the UT, opening its doors in 1913. The curriculum contained next to its traditional base of anatomy, physiology, and pathology, rapidly expanding subjects like physics, chemistry, and biology.[21] In March 1915 Murray enlisted for active duty in the army and got assigned to the 26th Field Battery as a gunner, refusing an assignment to the Moore British Hospital. In January 1916 he and his Battery embarked for France, where he would serve as an artillery gunner for 17 months. In the fall of 1917, Murray returned to medical school to start his second year of the 5 year medical program, graduating in 1921 at the age of 27. Thereafter he served 18 months in an apprenticeship with Dr. Lorne Robertson, a beloved rural country doctor he had been assisting previous summers. He then decided on a career in general surgery for which he had to develop a self-imposed program of study and apprenticeships under distinguished surgeons and physicians. He started as junior assistant pathologist in 1923 in the Mayo Clinic, Rochester, which had been turned into a leading surgical centre by the brothers and surgeons Willy and Charles Mayo. After only a few months he left the U.S.A. for London, England, where he studied and trained in anatomy and surgery in several hospitals for 3 years, after which he passed the demanding fellowship examinations of the Royal College of Surgeons. By that time he had developed into a skilful

and confident surgeon. Also he had found his way into British 'high society' thanks to an older first cousin of him who had studied in Oxford, who had been married to an English woman and was working for the BBC, and was well connected in London society.[21] Nevertheless, Murray was determined to get back to Toronto in the fall of 1926. Still in London, he had secured a position as a surgical resident in the TGH with professor Clarence Leslie Starr starting at the summer of 1927. Starr (1868-1928), formerly Surgeon-in-Chief of the Hospital for Sick Children in Toronto and a skilled surgeon, had been appointed Professor of Surgery at UT and TGH in 1921. Starr demanded that this would be a full-time task since too him directing the teaching programs in Surgery in the Faculty of Medicine took precedence over every other interest. Back in Toronto, Murray renewed his courtship with Helen Tough, a talented pianist and graduate from the Toronto Conservatory of Music, and he also arranged a 6 month period as house surgeon at the New York Hospital, one of the largest and oldest private hospitals in the United States and distinguished for the achievements of its surgical staff.[21] There Murray worked under professor Eugene H. Pool, a gifted surgeon and teacher who spent a considerable amount of his spare time in surgical research, experimenting on animals to research and improve methods of surgical treatment. Murray was delighted and inspired by the American enthusiasm for experimental surgery and the constant search for innovative treatments. In July 1927 Murray returned to Toronto for good, ending a for that time unusual long 7 year period of postgraduate training that had brought him from rural practice to the elite and innovative surgical research centres of Britain and the USA.[21] Personally, he had evolved from a country boy into a true cosmopolitan, having seen the horrors of war, and having lived and worked in 3 different cultures.

By 1927 TGH had developed into an elite university hospital, and the surgical department had modern operating theatres and equipment, also for animal experiments. From the very start of their cooperation, Murray liked Starr, in whom he had found his mentor. Vice versa, Starr quickly came to depend upon Murray who assisted him at all his operations, and who replaced him in his absence to lecture medical students and to attend his private patients. From the other staff surgeons and attending surgeons, together about 40 professionals, Murray kept his distance. He considered them "men of limited training, acquired usually in local hospitals only, and as a result their interest in research and progress was limited".[21] One year later he was appointed junior surgeon on Ward "C" under Norman Shenstone and next to another

junior surgeon, Robert Janes, who had been appointed 6 years earlier. In addition Murray was cross-appointed to the UT as a clinical instructor at the Department of Surgery. In this function he delivered numerous lectures and conducted bedside teachings during hospital rounds with flocks of medical students. Also his affiliation with the UT gave him access to research laboratories, and to a small office in the Medical Arts Building on campus where he could see private patients each afternoon. In August 1928 Murray married Helen Tough, his "fair-haired blue-eyed beauty".[21] On Christmas Day of that year Murray was hit hard by the sudden death of his mentor Scott. He then contemplated to leave Toronto, being offered a position in the New York Hospital. However, he stayed. It was the first of several occasions Murray would get to leave Toronto, and later on regretted for not taking on. His long-time associate William Edward Gallie who was a very talented surgeon, teacher and investigator then succeeded Starr. He immediately launched a well-designed 3 years surgical training course. He encouraged his staff in expanding the scope of clinical surgery by investigating and developing new procedures and approaches to unsolved problems. To this end he immediately had secured lab space on the 5-th floor of the new Banting Institute that was under construction directly across from the TGH.[21] So, Murray found himself in a scientifically orientated, stimulating environment, aiming at solving clinical problems one way or the other.

The surgeon's choice

In February 1932 Murray rushed a student to the operating theatre. This student was near dying from excessive blood loss from his arm that had been injured during an explosion in the engineering laboratory. After tying off the big squirting artery to save this young man's life, he had to watch in agony how the arm became gangrenous. He there and then decided to investigate the possibility of surgical repair of damaged blood vessels, which up to that moment, was impossible due to clotting problems. Probably, sometime that year Gallie had Murray introduced to Best who then still was struggling to produce a non-toxic, effective anticoagulant. At that time Murray already had clinical experience in vascular surgery without the use of heparin, having had operated upon 17 patients with acute ischemia of one or both legs caused by peripheral arterial embolism of which 3 were located in the aorta. He concluded: "Analysis of our cases supports the opinion that there are few operations in

surgery so eminently satisfactory (...) as embolectomy for arterial embolus".[22] To be successful, the operation had to be undertaken before 6 hours had elapsed after first symptoms had appeared.[22] Performed later, embolectomy nearly always was followed by re-occlusion. Also he lost 6 patients because of recurrent embolism to the brain or the lungs. From this experience, he had concluded: "What was required to make this operation a success … would be the addition of some substance which would prevent further thrombosis and clotting of blood".[16] It appears Murray had started already in 1932 "a long series of experiments upon animals" with heparin.[23] He had used the 5 HU/mg material and noticed "marked toxic effects when administered intravenously to dogs. Some of these animals died from the toxic effects". Thereafter he used the 10 HU/mg material that also demonstrated marked toxic effects. However, with the 200 HU/mg material he had not noticed toxic effects. With the purified crystalline barium salt he got at his disposal in 1936, he had done in 1939 hundreds of experiments on various animals, injecting "large quantities without injurious effects of any kind".[24] With his animal experiments he had shown that with postoperative 'regional heparinization' (local administration of heparin without generalized effect) patency of arterio-arterial anastomoses increased significantly.[23] The same applied to arteries after 'embolectomies' that were undertaken after the experimental 'embolus' had been in situ for more than 24 hours;[23] and to the splenic vein after splenectomy and concomitant damaging of this vein.[23] Apparently Murray had administered in 1934 the 200 HU/mg material to "several patients … half of them [showing] toxic effects in the form of headache, nausea, vomiting, faintness, pallor, chills, rapid pulse and a fairly marked fall in blood pressure".[23] Further use had then been abandoned until the barium salt of heparin had been developed. The administration to patients then had been resumed, and favourable results were seen in patients with acute peripheral arterial embolism who were treated with this heparin alone, and as an adjunct in 5 patients after 'late' embolectomies.[23] Up to May 1938, 315 patients scheduled for major orthopaedic and general surgical operations had received this heparin *prophylactically* - to prevent postoperative pulmonary embolism -, from 4 tot 24 hours after the operation during several days until they were fully mobilized. In none there had been evidence of pulmonary embolism or deep venous thrombosis, while 'normally' in the TGH 2.2-7.5% of patients undergoing gastrectomy, colectomy, abdominoperineal rectal resection, fixation of fractured neck of femur, or prostatectomy died of pulmonary embolism. Finally, good clinical results

(without controls) were seen from heparin treatment of 7 patients with (recurring) pulmonary embolism, and 28 patients with 'spontaneous thrombophlebitis'.[23] Interestingly, Murray stated that by applying meticulously Carrell his "unprecedented technique for anastomosis of blood-vessels" on carotid arteries in animals, "a fair number of anastomoses may be carried out with success and the vessels remain patent. However, by applying less care and doing the anastomoses with *ordinary operating-room technique* [not elucidated; *CB, AW*], most of these vessels become occluded by a thrombus at the suture line and this extends into the distal segment". With postoperative regional heparinization during at least 72 hours all of the 'sloppy' anastomoses remained patent up to one year after the experiment.[24] The same held true for organ transplantations, and for the patency of external jugular vein used as carotid interposition graft on the condition that regional heparinization had to be continued for 7 days.[24]

Since this barium salt of heparin appeared remarkably uniform in potency, the 'Toronto heparin team' decided to adopt this material as the new standard for estimating the potency of other heparin products, defining one milligram of this product to contain 100 units of anticoagulant activity, which makes this unit 5 times larger than the formerly used Howell units.[25] At the same time it had become clear that protamine injections were able to neutralize the anticoagulant effect of heparin in vivo and in vitro.[25] Of course, this also enhanced the safety of clinical use of heparin. Nevertheless, it appears that still in 1940 "some lots of heparin appearing on the market have shown some of the toxic effects which were observed in the earlier preparations".[26]

In 1940 Murray had published his magnum opus on the experimental and clinical use of heparin.[26] In this article, again, he stated that in animal experiments postoperative heparin treatment saved all less careful constructed arterio-arterial anastomoses as well as venous interposition grafts from otherwise dead certain thrombosis.[26] The same applied for experimental 'late embolectomies', i.e. after 48 hours, of plugs of blood clot and foreign bodies introduced in dog arteries.[26] He had started these experiments in 1938, and firstly lost many dogs to haemorrhage or pneumonia. By the fall he succeeded in keeping them alive, but did not succeed in preventing thrombosis with heparin. Murray toiled and moiled on, improving his vascular surgical techniques, and refining heparin dosage and methods for reliable extended intravenous administration of heparin in these animals.[26] Early in 1939 he

finally succeeded to prove heparin's beneficial effect on the patency of earlier mentioned reconstructive arterial procedures.[21] However, already in 1938 he successfully had treated several patients with acute limb-threatening disorders. One concerned a patient with a crushed elbow whose hand got dark blue, cold and insensitive within a few hours accompanied by great swelling of the antecubital fossa. At exploration the brachial artery showed lacerations and had been injured over 3.2 cm. This segment was resected and the ends were reconnected by an end-to-end anastomosis, followed by continuous intravenous administration of heparin for 5 more days. The reconstructed artery was still working one and a half year later, the arm functioning well and the patient back at his work as a garage mechanic.[26] He shortly described several more successfully treated patients, amongst others a patient in who during a thyroidectomy "an excellent surgeon" had divided the common carotid artery "just below its bifurcation". In this patient, after trimming of the damaged portions of the artery "there was considerable difficulty in bringing the ends into apposition", but he succeeded in it "by flexion, lateral bending and rotation of the neck", supporting the patient's head and neck postoperatively in a plaster cast. However, given his success with venous interposition grafts, he was not to shrink from applying them in clinical practice. In a more elaborate described acute case of a rapid enlarging popliteal artery aneurysm accompanied by paralysis, he had resected the aneurysm and replaced it by interposition of a "considerably smaller" and also somewhat too short segment of external jugular vein. After this operation the patient was given intravenous heparin, keeping clotting time at a level of about 15 minutes for 2 weeks. Circulation in the foot remained normal for 2.5 weeks. Then he suddenly noticed a recurrence of pain in the popliteal space. At reoperation there was a large false aneurysm, feeded by a rupture of a 1.8 cm saccular 'aneurysm' of the external jugular vein. Then, "flaps were cut in such a fashion that the lumen of the vessel was maintained and the aneurysm repaired". Afterwards the patient again "was heparinized". The circulation of the foot remained normal and 14 months after the operation, "at the time of writing" the manuscript of this article, "the patient is able to do light work".[26] He then described 6 patients with mesenteric arterial thrombosis in whom gangrenous bowel, from 45 cm up to 2 meter, had been resected and who, according to their attending surgeon, all were doomed. After their operation they had been treated with intravenous heparin for 10-14 days, and 4 out of 6 were alive and well more than one year thereafter.[26] Furthermore, in 12 patients treated for peripheral arterial embolism

by embolectomy with afterwards intravenous administration of heparin for 3 to 14 days, all 12 vessels remained patent. Next, he discussed in general terms the treatment with heparin of 81 patients with "thrombophlebitis" – both deep vein thrombosis as well as spontaneous phlebitis of varicose vein –, expressing his and his surgical associates amazement with the speed of recovery of these patients.[26] Encouraged by these results, they had treated 31 patients with "massive pulmonary embolism" with heparin, several with multiple attacks. Although death seemed imminent for some, all patients survived except 2. One died of generalized peritonitis following partial gastrectomy. Autopsy of these patients, also treated for postoperative symptomatic pulmonary embolism with heparin, had shown the lung infarcts resolving. The other patient had recovered well from his pulmonary embolism to die 4 months later of bowel obstruction, bleeding duodenal ulcer and renewed pulmonary embolism that was not treated with heparin because of the bleeding ulcer.[26] Patients with embolism, be it pulmonary or arterial, who were so unfortunate to end up in the wards of Internal Medicine, headed by professor Duncan Graham, were not treated with heparin. Graham considered heparin dangerous after he had done a small trial with heparin himself, on patients with sub-acute endocarditis - at that time a uniformly fatal disease -, and no one had survived.[21] Lastly in this 1940 article, Murray revealed that up to late 1939, 440 patients who had undergone major surgery in TGH, had been treated prophylactically with heparin postoperatively and none of them had developed a venous thrombo-embolic complication.[26]

Gordon Murray had lectured on his animal experiments and clinical experience with heparin at the American Surgical Association on May 3, 1938, in Atlantic City (NJ);[23] before the Royal College of Surgeons on June 12, 1939, in London (UK);[16,24] and before the American College of Surgeons in 1940.[2] His work had been accepted as "marvellous", as "a tremendous advance", and "opening up an entire new field in surgery".[2,23] Ronald J. Baird[2] therefore concludes that Gordon Murray should have the major claim "if vascular surgery ever seeks its father".[2] Alexis Carrel has been generally designated as 'the father of vascular surgery'. He was awarded the 1912 Nobel Prize in Physiology or Medicine "in recognition of his work on vascular suture and the transplantation of blood vessels and organs". Carrel was a true genius with a highly innovative and imaginative mind, and gifted with an unusual manual dexterity.[27] In his life-time he has worked out all the principles of cardiovascular surgery including

anastomotic techniques; use of autologous, homologous, heterologous and alloplastic grafts and patches; preservation of tissues and organs; organ transplantation (heart, lung and kidney); replantation of organs and extremities; aorto-coronary bypass; heart–lung machine.[25] All his work concerned experimental work on animals. He never had operated upon human beings. Murray has been the first surgeon to bring Carrel's work into clinical practice on a regular scale, and had emerged at that time as (one of) the most experienced vascular surgeon.[21] Murray had studied Carrel's techniques and had them mastered, also by exercise on animals. It is highly probable he who was famous for his craftsmanship had to convert to what he designated 'ordinary operation-room technique' without further specifications, to create the possibility for adjunctive heparin treatment to make a difference. However, it is implausible that he would underperform while operating on patients. So, differences in patencies between clinical patients, one group treated prophylactically with heparin and the other group with a placebo, could have revealed whether heparin really made the difference. However, at that time there was no doubt that positive results obtained in animal studies implied positive results in patients. Furthermore, like to-day surgeons, Murray attached great value to his personal experiences. Seeing his 'late' embolectomies staying open with heparin where they immediately had re-occluded previously, he was convinced heparin had made the difference. But 70 years later, the efficacy of prophylactic intraoperative and immediately postoperative administration of heparin during arterial interventions still has not been demonstrated in a randomized clinical trial. This is contrary to the prophylactic use of heparin in surgical patients to prevent *venous* thromboembolism, as will be outlined briefly further on in this paper.

The Stockholm Connection – Followers or Competitors?

The Stockholm connection in development of the production of heparin was centred around prof. Johan Erik Jorpes (1894-1973). Jorpes grew up in a fishing village on the island of Kökar in the Åland archipelago under poor circumstances, his family belonging to the Swedish-speaking minority of Finland. Thanks to a newly graduated female schoolteacher he was able to continue his education at the Classical Swedish Lyceum in Turku, mainland Finland. After graduation in 1914 he started medical studies in Turku and continued them at the University of Helsinki, passing the Bachelor of Medicine examination in January 1918,

with the highest possible mark in medical chemistry.[28] After Finland had declared its independence from Russia in December 1917, civil war broke out. Jorpes joined the Red forces and worked in a field hospital as the only 'doctor'. In April 1918 the 'Whites' with the help of German volunteers defeated the 'Reds' who had been supported by Russian soldiers. 'Reds' and Russian soldiers fled into Russia, Jorpes going with them in his medical capacity. The fugitives were quartered northeast of Moscow under deplorable circumstances. Jorpes nearly died from typhoid fever, and after being recovered he travelled to Moscow where he was one of the founders of the Finnish Communist Party. He secretly returned to Finland in September 1919 where friends urged him to flee to Sweden since they feared he might be tried for treason. So he came to Stockholm as a political refugee in October 1919.[28] Here he applied for admission to the Karolinska Institute, the Medical School of Stockholm, to continue his medical studies. After a vicar, who also came from the Åland islands, had convinced Hjalmar Brantin, then leader of the Social Democrats and Minister of Finance, that Jorpes was a knowledgeable medical student who had cured and not killed people in the recent war, he had been admitted to Karolinska Institute in 1920. To earn his living and costs for study, he contacted Einar Hammarsten who was Associate Professor in the Department of Biochemistry at Karolinska Institute, and just had started his studies of nucleic acids. Hammarsten employed him as assistant. Jorpes' first scientific publication in 1922, with Hammarsten, was on nucleic acids of beef pancreas, and by the time he completed his medical education at the Karolinska Institute in 1925, he had published 4 more on nucleic acids. He never worked as a physician. In 1924 he had been appointed assistant in the Department of Chemistry, and in 1928 he succeeded Hammarsten.[28] In that year Jorpes received a Rockefeller Foundation fellowship, spending most of this time in New York at the Rockefeller Institute for Medical Research, again working on nucleic acids which resulted in 2 publications with the director of the Institute, Phoebus Levene. During the summer of 1929 Jorpes spent some time at the (still well-known) Marine Biological Laboratory in Woods Hole (Cape Cod, Mass). Probably at that time he became interested in the research on and manufacture of insulin, since on his return from the USA in 1929 he immediately tried to persuade several pharmaceutical companies to get into the production of insulin. Gösta Bjurling, who ran Vitrum, a rather small pharmaceutical company, showed interest. Jorpes returned to North-America, Canada this time, accompanied by Gösta Bjurling to visit

Connaught Laboratories in Toronto. They were well received there and learned much about the process of insulin production. Back in Stockholm again, Jorpes devised a method of insulin production in close cooperation with Gösta Bjurling, and got it started by Vitrum in 1930. Jorpes and co-workers would refine the preparation considerably in the next 30 years. Jorpes was to receive very high royalty incomes from this production. Most of it went straight to his research activities, including salaries of young researchers.[28]

According to Jorpes, his attention to heparin had been drawn in this stirring year 1929, by Clarence Crafoord (1899-1984), a pioneering thoracic surgeon, who asked him "to get out the heparin of Howell to be tried as a prophylactic against pulmonary embolism".[29] Apparently Crafoord at that time was familiar with Howell's heparin. He had conducted over 20 pulmonary embolectomies (Trendelenburg operations) in patients who were on the brink of death. After this life-saving operation the large majority showed considerable cerebral damage. It is therefore understandable he was looking for ways to prevent the occurrence of pulmonary embolism, which at that time was a most dreaded complication leading to death of 3% of patients after otherwise uncomplicated operations.[30] Jorpes had answered his question: "non possumus". As late as 6 years later, Jorpes in his turn would approach Crafoord with the request to try out his own heparin preparations. "Crafoord immediately started a series of experiments heparinizing patients postoperatively".[29] Jorpes in his papers never mentioned he had visited Best and his co-workers at the Connaught Laboratories to learn about their heparin production process, or that he had been informed on the side during this visit about their first attempts at producing and purifying Howell's heparin.

Jorpes would formally thank Best for his hospitality in a letter he wrote to Best as late as May 1935, expressing specifically he had "greatly benefited" from his experience in the manufacture of *insulin*; not a word about heparin.[16] It is assumed that Jorpes after his return to Stockholm more or less 'immediately' began his work on heparin.[7] In our opinion this is unlikely, for several reasons. Firstly, Jorpes had to put in a lot of work to realize a production line for insulin from scratch, next to his busy job as Associate Professor at Karolinska Institute that he took very seriously.[28] Secondly, he appeared to have had very bad feelings about heparin. Answering Crafoord with a clear no, he had pointed out to Crafoord that a negative phase occurred after the anticoagulant effect had worn off, and that the preparation had toxic effects that were impossible to avoid in preparing heparin on a large scale.[28] Thirdly,

in Jorpes' first article on heparin, published in 1935, he has stated that *after* having read the widely diverging opinions of Howell, Charles and Scott, and Schmitz and Fischer, on the chemical nature of heparin, his curiousness had been aroused. So, it appears that at the outset it was more the chemist in him than the physiologist that was sucked into this adventure. He then resumes his introduction as follows: "The author therefore prepared heparin from ox and horse liver, following the principles outlined by Charles and Scott".[31] Howell's article had been published already in 1928, but the articles of Charles and Scott, and of Schmitz and Fischer, had been published in 1933, that of Charles and Scott on the October first. So, Jorpes most probably had begun the process of extracting of heparin at the earliest at the end of 1933. He had modified Charles and Scott's technique "in some details" amongst other things by applying tryptic digestion, thereby reaching an anticoagulating potency of 500 Howell units/mg.[31]

This high potency was for him not something to boast about. He only revealed it as an argument to prove he was researching the right compound.[31]

In accordance with Howell, and contrary to Charles and Scott, he concluded it evident that a hexuronic acid was present in considerable amounts.[31] Next he concluded that heparin contained hexosamine in equimolecular quantities to the hexuronic acid.[31] His most striking finding was its high content of sulphate. His tentative conclusion was that heparin preparations consisted of a mixture of chondroitinpolysulphuric acids, and the higher the sulphate content of such an acid the higher the anticoagulant activity, so the active component of heparin was to be chondroitintrisulphuric acid.[31] He himself would prove one year later this tentative conclusion wrong, identifying the hexosamine as a glucosamine, thereupon labelling heparin as a polysaccharide polysulphuric acid or mucoitin polysulphuric acid.[32] He had completed this study with the medical student who already had done some analyses for the 1935 article, Sune Bergström (1916-2004), who would be awarded the 1982 Nobel Prize in Physiology or Medicine for his research on prostaglandins.[32] In that same year 1936, Jorpes read the claim of Charles and Scott that they had succeeded in isolating a crystalline barium salt of heparin.[20] He immediately realized this claim could not be correct, for several reasons, amongst other things its reported rather low sulphate content.[33] He appears in particular incensed because "Charles & Scott (1936) did not feel convinced [by Jorpes' 1935 article; *CB, AW*] that heparin contained hexuronic acid and hexosamine".[33] His anger might still be

felt, reading: “The situation is somewhat perplexing when biochemists of to-day are unable to trace a substance [meaning glycuronic acid*; CB, AW*] which constitutes 25-30% of the preparation and which was discovered by a *physiologist* [*italics introduced by CB, AW*] 10 years ago”, referring to Howell’s 1928 publication.[33] Challenged, Jorpes and Bergström declared to have “repeated their earlier experiments on a larger scale and subjected the different fraction of heparin to a very careful S analysis and a thorough biological standardization. No corrections of our earlier views have been found necessary”.[33] They conclude that ”the alleged crystallinze barium salt of heparin isolated by Charles & Scott in 1936 (…) cannot be considered as the anticoagulant substance itself. Its homogeneous nature must be doublted”.[33] Charles was not amused by the way Jorpes had phrased his critic, taking offense particularly at the word ‘*alleged*’, and was looking for support with Best, and with Robinson, professor of Organic Chemistry in Oxford, “who would not hesitate to tell us if he thought we were wrong”.[16]

Jorpes would continue research on the chemical composition of heparin and its presence in different tissues with several students up to late in the 1950s.[28] Definite prove that Howell had be right about the uronic acid would be delivered only 30 years later.[32] Also, Jorpes published a monograph on heparin in 1939 that was very well received,[34] as was its second and much-enlarged edition in which the clinical (as well as the socio-economic!) aspects of deep venous thrombosis and pulmonary embolism, and its therapy with heparin were discussed extensively.[35] In 1940 he organized in Stockholm a symposium on Heparin and Thrombosis.[28] Clearly as far as it concerned heparin, in a few years he was transformed from a sceptic into a zealous advocate of its use to prevent and to combat venous thromboembolic disease and complications.

Now back to the spring of 1935. Jorpes had produced a highly active heparin preparation of about 70 Toronto units per milligram, and had revealed some very important secrets of its chemical nature. Although a non-practicing medical doctor, he of course realized its therapeutically potentials, and he remembered the demand of the young ambitious thoracic surgeon from the Sabbatsberg Hospital. One of Jorpes’ co-workers, Olof Wilander, apparently had a medical connection in the St. Görans Sjukhus in Stockholm in the person of Per Hedenius, since they had published together one preliminary article in 1936, and Hedenius on

his own a more elaborate one in 1937 on the heparinization of blood donors for blood transfusions, concluding that this method "fulfils all the requirements of an ideal blood transfusion method".[36] Clarence Crafoord had this method for blood transfusion introduced in Sabbatsberg Hospital,[36] and noticing in the spring of 1935 that heparin injections in human beings appeared safe, Crafoord started "a systematic series of experiments on patients in August 1935" to evaluate heparin prophylaxis for postoperative venous thrombosis.[37] Apparently not all preparations of heparin were adequate, given the phrase: "If the heparin used was sufficiently pure, it was found possible to perform the necessary heparinization of patients".[37] Mean potency of the preparations was about 70 Toronto units/mg (equalling 350 Howell units/mg), but variations up to 15% were common.[37] They found it "less advisable to start the heparinization prior to or during the operation because of complicating haemorrhage". Like Murray, they had observed this complication could be avoided by giving the first injection 3-4 hours after the operation. Contrary to Murray, they found "the use of intravenous drip to be fraught with such drawbacks that it was discontinued".[37] Heparin was given in single injections postoperatively, 4 to 6 times daily 50 to 100 mg daily, to "persons over 35 years of age suffering from diseases with a fairly high percentage of thromboembolic complications", and continued for 7 days. Coagulation times varied between 9 and 23 minutes.[37] Preliminary results had been published in 1937, and a second report in 1939. The latter included 126 patients treated prophylactically with heparin, no one showing a definite thromboembolic complication, compared to 8% in a historical control series of 809 patients, and also compared to 16% in a contemporary series of 129 patients who were not heparinized because their thromboembolic risk had been taxed to be low.[37] The difference in incidence of "distinct thrombosis" between the historic and the contemporary control series is striking, and more so because it is twice in the contemporary series that was supposed to contain only patients with low risk for venous thromboembolic complications. The authors did not comment on this difference. It is very probably caused by heightened awareness of the doctors and nurses for this complication in the contemporary series, demonstrating the limited value of historic series for comparison. In the following 18 months the contemporary series had been expanded into 325 patients treated and 302 untreated. In the treated group no one developed a certain thromboembolic complication, in the control group 33 (11%) did. Nine patients in the control group died from pulmonary embolism, and 18 patients demonstrated

pain in the side and bloody sputum.[37] Given the present-day discussion whether anticoagulation might be discontinued when there still is a venous clot present, it is interestingly Crafoord and Jorpes pose that "in case of existing thrombi" treatment with heparin "should be continued for as long a time as possible".[37] Experiments with the first 12 patients had been described by Crafoord in a preliminary report, published in 1937.[38] In the first 6 patients the first lot of heparin preparations were used, and injections were given at the time of the operation. This caused significant bleeding in the area of the operation. Also the preparations appeared impure, causing the patients to shake with fever. Jorpes has told that the rattling of their beds could be heard from the hospital vestibules! The subsequent 6 patients were given a better-purified heparin, and injections were started at the earliest 3 hours after the operation had been finished. From then on, all went well.[38]

Early adopters of the use of heparin

All the above considered, the Stockholm group around J. Erik Jorpes were followers as well as pioneers. Jorpes only started his research late in 1933, inquisitive about the true chemical nature of heparin. Being able to apply Charles and Scott's break through he made up arrears, and soon was to be in the front concerning the elucidation of heparin's complex chemical nature as well as promoting its use to prevent and to treat venous thrombo-embolism. From the Toronto connection in particular Murray proved to have been the driving force behind advocating the clinical use of heparin, not only to treat and prevent venous thromboembolism, but also to enable vascular surgical interventions. Best his article on 'Heparin and Thrombosis' in the British Medical Journal[25] had been accompanied by an editorial that appeared favorably disposed towards clinical use of heparin.[39] A pledge was made for reliable standardization of the preparations of heparin. It discussed clinical use of heparin in blood transfusions, in preventing postoperative deep-venous thrombosis and pulmonary embolism, and in the prevention of clotting of arterial and venous reconstructions. The terms 'general and regional heparinization', introduced by Murray,[23] were elucidated. Both subcutaneous as well as intravenous administration were mentioned as possible routes to deliver the drug. Finally, its low price (one shilling for 10 mg) was applauded.[39]

One of the early adopters of clinical use of heparin has been Gunnar Bauer, chief-surgeon at the General Hospital in Mariestad, Sweden.[38] He was worried about the costs and the demands

on the nursing staff in case of *general* use of heparin to prevent postoperative venous thromboembolism.[40] He therefore thought it had to be restricted to patients who had contracted this complication. However, treatment of "fully manifest thrombosis" appeared not to be a great success.[37,40] But, so he reasoned, early treatment of "those who are just getting it", could be beneficial. In the preceding years Bauer had mastered much experience with phlebographic examinations of the lower extremity, and by that also in diagnosing venous thrombosis on rather subtle but nevertheless for the connoisseur clear early signs and symptoms.[40] He thereby had found that "almost without exception the thrombotic process has its origin in the deep venous trunks of the lower part of the leg".[40] More precisely, he had hypothesized that the process started, for some unknown reason, with a clot protruding from a muscle vein into the lumen of one of the axial lower leg deep veins. Furthermore he had been convinced that extension of the thrombus into the femoral vein might result in pulmonary embolism. So, if he could detect cases of deep venous thrombosis confined to the lower leg veins, he reasoned, he could arrest in time extension into more proximal veins by administering heparin. Firstly, he described 32 patients in whom he had diagnosed such a confined deep venous thrombosis phlebographically, and whom he had treated "in the generally accepted ways", so without heparin. In short, devastating results. After the summer of 1940 Bauer and his staff started to treat phlebographically proven cases with confined deep venous thrombosis of the lower leg with heparin, and all had been doing well after only 3 to 5 days of intravenous heparin treatment. Since this practice arrested effectively the harmful evolution of deep venous thrombosis, he called this therapy 'abortive treatment with heparin'.[40] In 1946 Bauer published a paper comparing the rate of postoperative venous thromboembolism in "the largest series of conservatively treated [i.e. without heparin*; CB, AW*] cases of thrombosis that have been published of no fewer than 2,196,841 surgical cases", with his own historic series of 264 treated conservatively, and his series of 209 patients treated with heparin.[41] Frequency of postoperative thrombosis in these groups was 1.61%, 1.03%, resp. 1.27%; mortality among cases of thrombosis was 16.0%, 17.8%, resp. 1.44%; total mortality from thromboembolism 0.26%, 0.18% resp. 0.018%. So, total mortality from pulmonary embolism in Bauer's hospital had dropped to one tenth of what it was before.[41] Bauer stressed in his articles the importance of early ambulation of patients with venous thrombosis. Confinement to bed for about 40 days was the accepted rule, in Mariestad these

patients were free to move around with the leg in an Unna's paste stocking after an average period of 4.7 days, and "forceful active leg movements were insisted on from the first day".[41] Furthermore he draw attention to the possible "incapacitating after-effects" of venous thrombosis like post-thrombotic leg ulcers: "The social importance of the post-thrombotic leg ulcers and the amount of pain and risk of infection with accompanies the post-thrombotic state can hardly be overrated".[41] From his own and other contemporary studies Bauer concluded that with conservative therapy all patients with deep venous leg thrombosis ultimately would suffer from permanent swelling of the leg, and that more than 90% acquire indurative lesions and about 80% leg ulcers.[41] Finally Bauer stressed the absence of bleeding complications with heparin treatment, judging "there are hardly any contraindications to the use of heparin as a treatment for thrombosis".[41] The cited percentages for total mortality from pulmonary embolism in postoperative surgical cases without heparin prophylaxis in Bauer's paper are strikingly low: 0.26% for the series collected from the literature en 0.18% in his historic series, compared to the percentages cited by Murray (2.2%-7.5% depending upon type of operation)[23] and Crafoord (3%).[37] Possibly in the series cited by Bauer the majority concerned minor surgery? If not, it seems that many cases of fatal pulmonary embolism have gone unnoticed.

Another early adopter has been Geza De Takats (1892-1985), vascular surgeon at St. Luke's Hospital and the University of Illinois in Chicago. He started using intravenous heparin infusion at St. Luke's in 1938 for treatment of acute arterial and venous thromboembolism as well as for prophylaxis of venous thromboembolism.[42] He had introduced in 1943 the 'heparin tolerance test', which he had simplified in 1950 by limiting measurements of capillary clotting time in 2 blood samples: one drawn immediately before and one drawn 10 minutes after intravenous injection of 10 mg of heparin. Thereby he had found a decreased response, and thus a hypercoagulable state, amongst other things in old people, in patients after operations, in patients with malignancies, and in patients with acute thrombosis.[42] Immediately after reading Crafoord and Jorpe's article from 1941,[37] he had changed to intermittent intravenous injections since the continuous intravenous drip method prevented ambulation and required frequent estimation of coagulation times.[42] Later on he started using intramuscular injections of depot preparations of heparin once daily after an intravenous

priming dose of 30-50 mg., both therapeutically as well as prophylactically. For prophylactic purpose the dose was 25-50% of the therapeutic dose since "it takes much less heparin to prevent clotting than to treat it".[42] Dosage was, if needed, adjusted according to measurements of capillary clotting tomes twice a day, aiming for 4-8 minutes for prophylactic purposes and 8-12 minutes for therapeutic purpose. Average duration of prophylactic administration of heparin amounted to 14 days. Much longer periods could be necessary, since in his opinion: "Heparin therapy must be kept until the patient is entirely ambulatory and no signs of increased clotting activity such as an increased heparin resistance is present", and "Effective heparin therapy has only failed me in patients in whom the drug was discontinued too early".[42] De Takats drew attention to the fact that postoperative thromboembolic complications had been more than halved in the decade after 1940 due to "early ambulation, early movement in bed and better postoperative care regarding fluid, electrolyte and nitrogen balance". Nevertheless, he concluded: "All these factors limit but by no means abolish the usefulness of anticoagulant prophylaxis". To this statement he added "(…) for which I favour intramuscular heparin therapy".[42] In a subsequent paper, published in the same year, he revealed that the so-called intramuscular injections had been examined by biopsy and were found to be "deep subcutaneous".[43] In this paper several depot preparations of heparin for subcutaneous administration were presented, and attention was drawn to the rather unpredictable anticoagulating effect of heparin, necessitating dosing according to body weight and readiness to correct overdosing with intravenous administration of protamine sulfate.[43]

In 1942, Leo Loewe, cardiologist at the Jewish Hospital of Brooklyn, had developed in close cooperation with the pharmaceutical firm Roche-Organon a slow-release depot preparation, the "Heparin-Pitkin menstruum", available in ampules with 200 or 300 mg heparin per ampule. The effect of one single injection lasted for 48 hours or more. So, much less heparin appeared necessary by using this method to obtain satisfactory results. Dosage was adjusted to bodyweight: about 4.5 mg per kilogram.[44] The injections appeared to cause fever, and local pain, swelling and tenderness. These disadvantages however, in the opinion of the authors, were far outweighed by the benefits of the subcutaneous route which were freedom of intravenous lines, increased mobility, and controlled slow release of the drug.[44] The at that

time, widespread use of ligations of thrombosed veins above the thrombus, up to the inferior caval vein if necessary, consequently was banned from the authors' hospital.[44]
Interestingly, both De Takats and Loewe regarded the in 1941 introduced anticoagulant treatment with dicumarol too tainted by unpredictable treatment failures and high risk for severe haemorrhagic complications,[42,44] and too slow in its action[42] for use in prophylaxis and treatment of venous thromboembolism.

First controlled trials

During World War II (1939-1945) the spread of new techniques was hampered, but after the war a happy explosion of exchange of knowledge and introduction of new valuable techniques was seen. The number of publications on heparin rose steeply from about 10 in one year before 1945 to over 3000 per year in the 1960s.[38] In 1960 the first prospective randomized placebo-controlled trial with heparin has been published.[45] It concerned a trial conducted in the Departments of Medicine and Cardiology of the United Bristol Hospitals, United Kingdom. The goal was to establish the effects of treatment of pulmonary embolism with heparin, followed up by oral vitamin-K antagonist treatment. The authors felt themselves compelled to conduct this study since as they had put is: "The risk of haemorrhage has made many physicians and surgeons unwilling to use anticoagulants routinely in the treatment of pulmonary embolism *on existing evidence* [italicized by *CB, AW*]".[45] Endpoints of the study were the course of the first embolism (death or alive), and iterating attacks.[45] In this study, contrary to Bauer's view, treatment with heparin was withheld in case of "a recent operation", and in case of "a history suggestive of recent peptic ulceration".[45] Bauer was "not afraid of heparinizing even patients bleeding from gastric ulcers; nevertheless, some caution should probably exercised in cases of that kind".[41] Of course, this firm stance of him rooted in his large personal experience with the devastating consequences of *not* treating deep venous thrombosis.
The trial had started in March 1957. Those patients randomized to anticoagulant treatment got 6 doses of 10,000 units of heparin every 6 hours without laboratory control, and started immediately with an orally administered vitamin-K antagonist (acenocoumarol). After 35 patients had been included in April 1958, it appeared that of 19 patients in the control group, 5 had died of pulmonary embolism and 5 others had had non-fatal recurrences of pulmonary

embolism. Of the 16 patients treated with anticoagulants only one patient had died, not from pulmonary embolism but from suppurative pneumonia combined with haemorrhage from a duodenal ulcer.[45] Therefore it was felt the trial could not be continued in its original form. In order to be able to confirm (or refute) the attained low mortality in the treated series, the trial was continued with the same inclusion and exclusion criteria, but from then on everyone presenting with a pulmonary embolism had to be treated. By July 1959 the trial had been stopped. At that time the same 19 untreated patients from the first series and 54 treated patients had been included. All cause mortality amounted to 5 out of 19 in the untreated group (all due to pulmonary embolism), and to 2 out of 54 in the treated group (P=0.011). Total cases of pulmonary embolism amounted to 10 out of 19 in the untreated group, and 2 out of 54 in the treated group. The corresponding P-value amounted to 14.10^{-7}.[45] Given, as we know now, the short treatment period, it is remarkable that among the 54 treated patients there were just 2 (non-fatal) cases of recurrence.[45] After this study, *placebo*-controlled studies on the treatment of pulmonary embolism with anticoagulants have been considered unethical.

Interestingly, the use of *intravenous* heparin to *prevent* venous thromboembolism has never been studied in a placebo-controlled randomized clinical trial (RCT). The first placebo-controlled (but not randomized) clinical trial on prophylactic use of heparin pertained *subcutaneously* injected and low dosed heparin (LDH). It concerned the study of Vijay V. Kakkar, vascular surgeon at King's College (London, UK), conducted in the Department of Surgery of King's College Hospital in close cooperation with Stanford Wessler and E. Thye Yin, both from the Department of Medicine of the Jewish Hospital and the Washington University School of Medicine in St. Louis (Missouri, USA).[46] The study population was a consecutive series of 53 patients over the age of 50 admitted for elective repair of inguinal hernia under general anaesthesia. The first 27 acted as controls, and the next 26 were given "slow-release heparin" (Calciparine®) subcutaneously. All patients were screened for venous thrombosis in the legs by the radioactive iodide fibrinogen uptake test (FUT). This test appeared positive in 7 (26%) of the patients in the control group and in only one (4%) of the heparin group, with a P-value of 0.026. Thrombin-clotting times during the postoperative days did not differ between both groups.[46] So, from this study it followed that LDH could prevent development of thrombi in calf veins in patients operated upon under general

anaesthesia to correct an inguinal hernia (i.e. 'minor surgery'). The endpoint in this study clearly was a substitute for 'clinically relevant deep venous thrombosis'. In the discussion section of their paper, Kakkar revealed that the idea of prophylaxis for postoperative venous thromboembolism with LDH stemmed from a coincidental observation of Yin, one of the American co-authors, that a small amount of heparin could increase considerably the biological activity of antithrombin in inhibiting factor Xa without any effect on whole-blood clotting time.[46]

In 1972 Kakkar et al. published a placebo-controlled double-blind trial on the efficacy of subcutaneously administered "low dose" heparin (LDH) in preventing deep venous thrombosis after "major surgery".[47] Thrombi were diagnosed by the FUT. The control group as well as the LDH group contained each 39 patients. FUT was positive in 17 patients in the control group (42%), and in only three in the LDH group (8%; P-value < 0.001).[47] None of the patients in this study developed clinical evidence of pulmonary embolism. Furthermore, they reported on 183 consecutive patients undergoing major surgery, who were considered to have a high risk to develop postoperative deep venous thrombosis, all being treated conform the LDH regimen. In 3 of all 172 patients (1.7%) on LDH, bleeding during surgery posed a problem. In this randomized trial LDH reduced incidence of a positive FUT after elective major surgery from 42% to 8%, meaning a number-to-treat of 3 to prevent one positive FUT. Two months earlier Kakkar and co-workers had published a paper on 50 patients with femoral neck fractures whose legs had been studied with the FUT every day and with venography performed after admission. In these patients FUT was positive in 54% of the fractured limbs and in 34% in the un-fractured limbs, being positive in both limbs in 28% of the patients. Interestingly, FUT appeared positive in no less than 75% in case of a pertrochanteric fracture compared to 34% in subcapital fractures.[48] Remarkably, no patient developed clinical symptoms or signs of pulmonary embolism. The authors explained the failure of LDH prophylaxis by assuming that as a consequence of the fracture, coagulation already has been activated, and then LDH would be a case of "too little heparin, too late".[47] For this reason, LDH in order to be effective always should be started before surgery, before activation of the coagulation through surgical trauma to tissues. Thanks to the venographic examinations in the last study, the authors could prove that also in case of femoral neck fractures venous

thrombosis is initiated in the calf veins, since they never had observed a thrombus *confined* to veins above the knee.[48]

It is worth mentioning they had done heparin assays in volunteers after subcutaneous injections of 5000, 7500 and 10000 IU of heparin, and in 10 consecutive patients after injection of 5000 IU. With increasing dose serum level of heparin started to rise earlier, rose higher, and was maintained prolonged on a higher level. At the time of the peak concentration partial thromboplastin-time was slightly increased. However, there were striking variations among individuals in these parameters.[47]

Within 4 months of publication of the former paper, Nicolaides et al. from St. Mary's Hospital Medical School, published a study that had been undertaken "to assess the efficacy of small doses of subcutaneous heparin not only in reducing the incidence of early thrombi, but also the incidence of the extensive thrombi endangering life".[49] They reasoned that if this could be established, then LDH also will prevent postoperative pulmonary embolism. The study population had to undergo 'major surgery', and, as in the other studies, should be over the age of 40. Both groups received the usual hospital routine of wearing elastic stockings and having supervised leg exercises before and after operation. According to this same routine sitting in a chair with dependent legs was prohibited, and patients were made to walk as early as possible. The study was not blinded. The test group received 5000 IU heparin subcutaneously 2 hours before the operation and then twelve-hourly for 7 days. If by that time the patient still was not ambulant, the period was stretched to 10 days, which proved necessary in 5 patients. All patients were examined daily for local tenderness in calves and thighs, and for pitting oedema at the ankle. There were 251 patients admitted to the trial, and 7 subsequently excluded for good reasons. The remaining 244 patients were randomized equally divided over both groups. The results were spectacular. In the control group FUT had been positive in 29 patients (24%), and in the test group only one (0.8%). The P-value belonging to the found difference between groups amounted to 3.10^{-7} After heparin had been discontinued according to protocol after 7 days, FUT became positive in one patient one day later and in another patient 2 days later. In the control group in not one FUT became positive at this late stage. These 2 cases of late positive FUTs should be added to the one mentioned before. Thus, FUT positive in the test group in 3 of 122 cases (2,5%). Still a spectacular

result. In the control group the thrombus extended subsequently in more proximal veins in 9 patients (7.4%), and in none of the test group (P=0.0017). In all 9 patients proximal extension of thrombus subsequently had been confirmed by venography, and all were immediately thereafter treated with intravenous heparin and oral anticoagulant. None of these or any other patients in the trial developed clinical evidence of pulmonary embolism. There were no major bleeding complications, and only 5 wound hematomas, none requiring evacuation: 3 in control group and 2 in test group. In 2 patients hematomas at the injection site occurred, both caused by too superficial deposition of the content.

The results of both trials[47,49] differ markedly. To grasp these differences the results have been clustered in table I. In particular it is remarkable than in Kakkar's consecutive series of 133 patients, all treated with LDH prophylaxis, FUT was positive in no less than 10% of the patients, while this amounts in Nicolaides' series only to 2.5%. Furthermore, but in conformity with this observation, in Nicolaides' series of LDH treated patients, no one developed proximal extension of venous thrombosis, while in Kakkar's series this phenomenon had been seen in 2% of the cases. The most striking difference between Kakkar's consecutive patients series and Nicolaides' randomized patients series, seems to be the inclusion of 15 patients in Kakkar's series who had been scheduled for elective total hip replacement. In these patients FUT became positive in 4 patients (27%), and one of them died from pulmonary embolism. In Nicolaides' series orthopaedic surgery maximally amounts to 5 patients in the control group and 7 patients in the test group, being the numbers of patients grouped under "Miscellaneous" operations.[49]

Table I: Comparison of results of the studies of Kakkar et al.[49] and of Nicolaides et al.[51] CT=controlled trial. RCT=randomized controlled trial. Numbers after "CT" and "RCT" refer to numbers of patients in control group:test group. FUT=radioactive iodide fibrinogen uptake test. PVT=proximal venous thrombosis, meaning formation of thrombus in veins proximally to calf veins (i.e. popliteal and femoral veins, and beyond).

	Kakkar et al. 1972[47] CT series 39:39	Kakkar et al. 1972[47] Series of 133 patients	Nicolaides et al. 1972[49] RCT 122:122
Controls FUT +	17 (42%)	No controls	29 (24%)
LDH FUT +	3 (8%)	13 (10%)	3 (2.5%)
Controls PVT +	0	No controls	9 (7.4%)
LDH PVT +	0	3 (2%)	0

Surprisingly, it took some more years before a study was started addressing possible improvement of the efficacy of LDH to prevent venous thromboembolic complications in patients who had to be operated upon for total hip replacement. Obviously, the key to improvement had been thought to be higher or more frequent dosing of the heparin, without affecting the principles of the administration of heparin in low doses. Kakkar and co-workers presented their results to the Surgical Research Society of Great Britain and Ireland at the meeting held on January 9, 1976, at the Royal College of Surgeons of England in London. Their work was published on May 29, 1976, in The Lancet.[50] Study population consisted of 52 patients scheduled for total-hip replacement (THR) who were randomly allocated, by drawing envelopes, to receive heparin (Calciparine®) or a combination of heparin and dihydroergotamine (DHE). In conclusion, proximal deep venous leg thrombosis, feared for its potency to generate fatal pulmonary emboli, had been reduced by this regimen of LDH with increased frequency of administration of the doses, from 53% to 8%. An absolute risk reduction of 45%, implying that to prevent one case of proximal vein thrombosis 2 to 3 patients should be treated conform this regimen. Still, the regimen failed in about 8% of cases, meaning that vigilance to detect possibly life-threatening thromboembolic complications as early as possible in these patients should be maintained.

General prophylaxis with intravenous heparin had not taken on since it demanded conscientious and frequent control of clotting times and dose adjustments, thereby exhausting allocated personnel and budgets.[40] Therefore Kakkar and Wessler had been looking for a method that should satisfy 4 criteria in addition to efficacy: it should be well tolerated by the patient, it should be free of side effects, it should require no monitoring other than that the patient receives the drug appropriately, and, finally, it should produce no excessive bleeding when the patient is subjected to major tissue trauma.[46,51] LDH prophylaxis seemed to fulfil these requirements rather well, and, measured by the reduction of positive FUTs, LDH had proven effective except in patients with femoral neck fractures. Unfortunately, it had not banned thromboembolic complications completely since positive tests still showed up in about 8-13% of the treated patients, and even possibly life-threatening proximal venous leg thrombosis keep arising in 2% to 8% of the cases, depending upon the disease or disorder and the method of its treatment, notwithstanding prophylactic treatment tailored to the occasion.

To its advocates, it seemed logical that LDH also would reduce the frequency of "life-threatening postoperative venous thromboembolism". However, this view was not at all shared by the majority of surgeons.[52]

Therefore Kakkar and co-workers organized a multinational multicentre. The results of this trial have been published on July 12, 1975, in The Lancet.[53] The study was supposed to answer 2 questions. One: Does LDH prophylaxis prevent fatal pulmonary embolism in postoperative patients? Two: Does a standard regimen of LDH prophylaxis increase the risk of operative and postoperative bleeding? Patients older than 40 years, scheduled for an elective 'major' operation were eligible. An operation was 'major' when performed under general anaesthesia, lasted more than half an hour, and required postoperative hospitalization for at least 7 days. On the assumptions that 0.5% of patients subjected to major surgery dies postoperative from massive pulmonary embolism, and that LDH would reduce this to a third, it had been calculated that the study population had to amount to at least 10000 patients.[53] Twenty-eight centres from 10 different countries were to participate. The control group did not receive specific prophylaxis. The test group received 5000 IU of Calciparine® subcutaneously 2 hours before the operation and eight-hourly thereafter for 7 days, and more days if the patient at 7 days still was not ambulant. Primary endpoints were fatal pulmonary embolism (PE) proven by autopsy, and bleeding complications. Also clinically suspect PE had to be recorded as well as clinically detected and venographically confirmed deep-vein thrombosis (DVT). The trial had not been designed to be double-blinded for 2 reasons: firstly, it was felt unlikely that bias could play a significant role when death is used as the primary endpoint, and secondly it was considered unethical to give up to 30 placebo injections to thousands of patients in the control group.[52] After the trial had been under way for some time and 2000 patients had been included an interval analysis had been done by which it was found that the incidence of fatal PE in the control group was twice as high as had been assumed. Therefore the intake to the trial was closed when approximately 4500 patients had been admitted.[52,53] It appeared that 4471 patients were admitted, of whom 350 had to be excluded because of protocol violations. The control group contained 2076 patients, and the test group 2045. The key results, namely the findings at autopsies of postoperatively deceased patients as to which condition primarily caused their death, have been summarized in table II.[53]

	Controls n=2076	Testgroup n=2045	Absolute risk reduction
All cause mortality	100 (4.8%)	80 (3.9%)	- 0.9% (P < 0.001)
Number of autopsies	72 (72%)	53 (66%)	
PE	16 (0.78%)	2 (0.10%	- 0.68% (P < 0.005)
PE incid. or contribut.	6 (0.29%)	3 (0.15%)	- 0.14%
MI	13 (0.63%)	7 (0.34%)	- 0.29% (P > 0.50)
Hemorrhage	5 (0.24%)	4 (0.20%)	- 0.04%
Miscellaneous	38 (1.83%)	40 (1.95%)	+ 0.12%
Unaccounted cause of death	38 (1.83)	27 (1.32%)	

Table II: Primary causes of mortality as judged by pathologists after autopsy. Percentages are related to total number of patients per group. 'PE incid. or contribut.' means there was another condition responsible for death but there were also pulmonary emboli found that were thought to be there without contributing to the death of the patient (incidental PE) or possibly contributing to death (contributory). The group of "miscellaneous" death causes concerned non-thromboembolic events like pneumonia, peritonitis, pulmonary oedema, carcinomatosis, sepsis, hepatic failure, renal failure, and "others".

This trial appeared to have furnished proof, for the first time in history, that prophylaxis with LDH in patients undergoing major surgery reduces the incidence of fatal PE. Already before the study was published, Kakkar had been invited to present the results of the trial at Reston (Virginia, USA) on April 24, before 24 leading American and Canadian scientists involved in thrombosis research. Apparently, some "members of the scientific community" had him reproached unethical behaviour "to deny prophylactic therapy to the controls" in view of the proven effective reduction of FUT thrombi. Of course, Kakkar strongly disagreed, pointing to the sparse use by most surgeons of anticoagulant prophylaxis at that time. He concerned 3 criticisms pertinent. Firstly, was the autopsy rate high enough to avoid imbalance between autopsied and non-autopsied cases? Secondly, to what extent could errors in pathologic interpretation have influenced the results? And thirdly, to what extent could bias have influenced the results? Firstly, he considered the autopsy rate of 70% high enough. Secondly, having competent pathologist doing the autopsies and in view of the striking differences in causes of death, he considered the influence of errors in pathologic interpretation "relatively small". Thirdly, bias, in his opinion, "was hardly likely to be of great influence when death

was used as the primary endpoint". It was therefore concluded at this meeting that unless this trial was considered as a conspiracy on the part of all the participants and pathologists, one was forced to the conclusion that the differences in the primary endpoint between the 2 groups were real, and that the study should be used "to influence the practice habits of the profession for preventing fatal pulmonary embolism occurring following abdominal surgery".[52] In order to increase acquaintance with this landmark study, as Kakkar himself called it, they had organized an *International Heparin Symposium* held at King's College Hospital Medical School the 18th-19th of July, 1975. Over 300 scientists and clinicians attended this symposium from continental Europe and North America. The year before Kakkar had received a large grant from the Medical Research Council for 5 years "to establish a multidisciplinary team of researchers to continue with further expansion of research in venous thromboembolic disease". This grant would be renewed in 1979 and 1984, providing uninterrupted support for 15 years. In 1977 Kakkar was appointed to the Chair of Surgical Science from the University of London. He was to make many more contributions to heparin prophylaxis and the introduction of the low molecular weight heparins. However, he also had to conclude, somewhat bitterly, in the following years that in spite of the evidence "a significant proportion of surgeons in the UK and the USA, as well as some in Europe, remained critical of the data generated by the International Multicentre Trial", and "In spite of what appeared at times very hard and unjustified criticism of the results of our trial on both sides of the Atlantic, I continued my efforts to popularize fixed dose heparin prophylaxis by presenting our results of the Multicentre Trial at several international meetings ….". It appears that surgeons in continental Europe - Kakkar mentioning particularly France, Germany and Switzerland -, were more eager to adopt this regime than those in the USA and the UK.[52]

Heparin enabling artificial circulation

In the 1910s Leonard G. Rowntree, assisting John J. Abel, professor in Pharmacology and director of the Pharmacological Laboratory of the Johns Hopkins University, had tried to remove diffusible substances from the circulating blood of living animals by dialysis.[53] The first aim was to enable the study of the "numerous constituents of the blood derived from various organs and of vital significance to the economy [*economy* in the sense of 'milieus

interieure'; *CB, AW*]", since these substances became inaccessible by adhering firmly to precipitating proteins after blood had drawn from an experimental animal. By removing them from flowing blood "as fast as they poured into it", without at the same time removing blood proteins or blood cells, they would be able "to accumulate them in sufficient amounts for study". Furthermore, they envisioned a method to provide a substitute for organs that eliminate toxic products from the blood. For this they had "devised a method by which the blood of a living animal may be submitted to dialysis outside the body, and again returned to the natural circulation without exposure to air, infection by micro-organisms, or any alteration which would necessarily be prejudicial to life". They coined the term "vivi-diffusion" for this process, and the apparatus had been designated before as an artificial kidney.[53] The dialyzing membrane consisted of tubes made from nitrocellulose (celloidin or collodion) through which the blood would flow. The tubes were immersed in a bath filled with serum or any other desired fluid.[53] They presented detailed drawings of their artificial kidney, which remarkably look alike the concept of the modern machines. Blood coagulation was prevented by adding a hirudin solution via an ingeniously constructed fine "glass jet" attached to the glass made arterial cannulae. The hirudin they made themselves by extracting the heads and the immediate adjoining segment of leeches.[53] About 75-90% of the hirudin calculated to be necessary to render the whole blood of the animal incoagulable for 12 hours was introduced into the apparatus that had been primed with a saline solution, before arterial blood was admitted to the celloidin tubes. Clotting times were checked in blood drawn from a hind limb of the animal.[53]

Rowntree, in 1915, had accepted an offer to become Chairman of Medicine at the University of Minnesota. However, World War I intervened soon and he entered the US Army. After the war, he accepted William J. Mayo's offer, and in 1920 became Professor of Medicine at the Mayo Foundation and in 1922 Chief of the Department of Medicine, next to professor Henry Plummer who retained the title Chief of Medicine of the Mayo Clinic. Apparently Rowntree got a free hand to recruit promising medical specialists to make the clinic as important in Medicine as it already was in Surgery.[58] Rowntree with his group of recruited physicians had a remarkable effect on medical research at the Mayo Clinic: "Almost overnight, everyone in the Clinic seemed to become interested in clinical investigation and the output of publication

shortly became enormous".[54] Together with Takuji Shionoya, a Japanese physician and fellow of the Rockefeller Foundation, he had started experiments to study thrombus formation in vivo.[55] He got interested in thrombus formation after learning from the necropsy records of the Mayo Clinic that pulmonary embolism had been responsible for 7.3% of the postoperative deaths during the last 10 years.[55] Remembering his former experiments with the artificial kidney, which were troubled by clot formations in the celloidin tubes despite generous hirudin administration, he assumed extracorporeal circulation to provide a good model to study the evolution of thrombi, particularly that of white thrombi. Of course, the apparatus need for this goal could be much simpler than the artificial kidney Abel had built. One celloidin tube connected to an artery and a vein of an experimental animal, immersed in some physiologic solution, would suffice. Normally, this extracorporeal flow will cease within 4 to 10 minutes due to blood coagulation. This may be delayed or prevented by paraffining the tubes or by previous injection of anticoagulants like heparin and hirudin. However, despite the presence of these anticoagulants, white thrombi still are formed and eventually thrombosis will supervene. The model, according to Rowntree, lent itself readily for the study of the influence of mechanical, physical and chemical factors affecting the process of thrombosis.[55]

For all experiments rabbits had been used, being "more economical in the use of anticoagulants" which by that time were rather expensive.[55] The animals were injected with about heparin produced by Hynson, Westcott and Dunning (H,W&D) from Baltimore in a dose of 20 mg per kilogram bodyweight (about 100 Howell units/kg bodyweight). Then the extracorporeal loop was attached to the carotid artery and the jugular vein, and the clamps released. Despite heparinization (or hirudinization) numerous white thrombi, increasing in volume in time, were seen developing in the glass cannulae and the celloidin tube (especially at wrinkles of the celloidin membrane), firstly most marked at the venous side, propagating against the current.[56] Apparently, wherever whirlpools, eddies and stagnation occur, platelets come in contact with foreign surfaces, agglutinate and form white thrombi.[56] Charles Best and co-workers[57] repeated these experiments some 10 years later with real heparin, the H,W&D 'heparin' most probably being a mixture of phospholipids with anticoagulating properties. They used a shunt composed of 2 glass cannulas connected by a cellophane (made from cellulose) tube, and anticoagulated their experimental animals with heparin that they

themselves had extracted and purified in a dose of 450 units/kg bodyweight of the animal. In dogs, heparin prevented formation of white thrombi completely in 16 of 18 experiments. In 2 of these experiments small accumulations of platelets had been observed. In cats in all 10 experiments heparin completely prevented the formation of white thrombi. In Rhesus monkeys heparin prevented formation of white thrombi completely in 3 of 8 experiments. In the other 5 the loop stayed open but either very small accumulations of platelets or definite small thrombi were noticed.[57] Subsequently, they constructed an extracorporeal loop of pyrex glass with centrally placed a dilatation, the 'glass cell', enabling real time microscopically study of the formation of white thrombi. As with the cellophane tubes, white thrombi developed in all cases in which no heparin was used, resulting in total occlusion in all except one. With heparin the extracorporeal pathway remained open in all 5 experiments, and no thrombi could be observed in 2 of these. In rabbits heparin appeared less effective in preventing the formation of "clumps of platelets" than in the other animals, however occlusion of the extracorporeal pathways never occurred if heparin had been used.[57] In conclusion, Best and co-workers had proven that heparin reliably did prevent occlusion of extracorporeal circulatory pathways. This finding would renew former interest in designing machines with extracorporeal circulation to substitute (temporarily) internal organs like kidney, heart and lungs.[58,59] It is safe to say that without heparin, being a naturally present anticoagulant, these machines never would have made their appearance into clinical practice.

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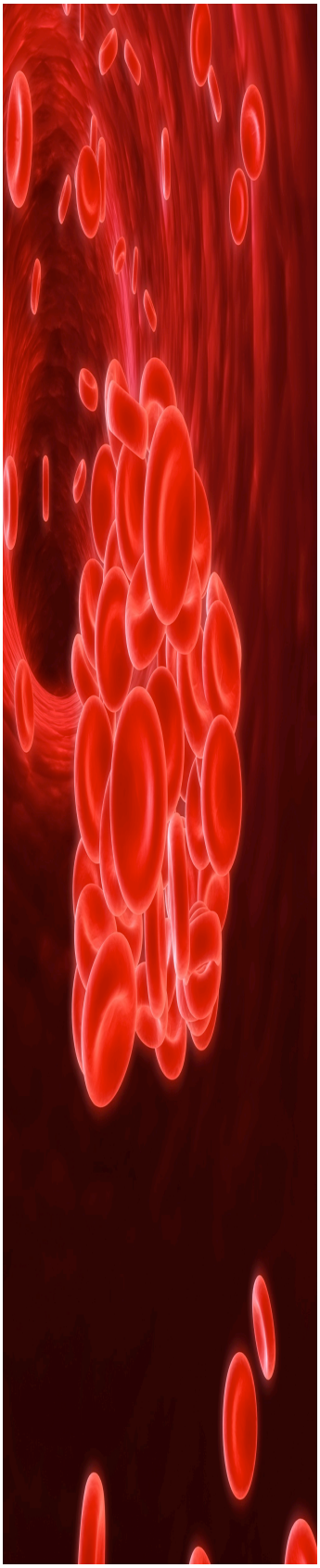

Chapter 3

Perioperative prophylactic antithrombotic strategies in vascular surgery: current practice in the Netherlands

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Abstract

Aim

To evaluate the current practice of the use of perioperative antithrombotic drugs to prevent arterial thrombo-embolic complications during arterial vascular surgery by Dutch vascular surgeons. Aim was also to compare the results with the literature and to evaluate the effect of guidelines.

Methods

A comprehensive questionnaire was sent to all Dutch vascular surgeons performing arterial reconstructive surgery.

Results

The response rate was 84%. ASA was continued perioperatively by most surgeons (91%). Clopidogrel was discontinued by the majority of respondents (65%). During operation 97% of surgeons administered unfractionated heparin before arterial clamping. A minority (11%) measures peroperatively anticoagulant activity in patients' blood. After infrainguinal venous bypass most surgeons (81%) preferred monotherapy with vitamin K antagonists (VKA), in agreement with the Dutch guideline in this respect. Before the introduction of the guideline in 2005, a survey was performed in 2004. Results of our 2011 survey showed more respondents (6% to 11%) prescribed ASA or VKA according to these guidelines.

Conclusion

This survey showed a recognizable pattern of variation for perioperative arterial thrombosis prophylaxis amongst Dutch vascular surgeons, in agreement with reports from other countries over the past 20 years. Although a higher percentage of surgeons complied in 2011 with existing guidelines than in 2004, guidelines were not completely met. Possibly because current guidelines are not fully supported by evidence and do not cover all aspects of perioperative arterial thrombosis prophylaxis. Clearly there is need for (more) convincing data based on RCT's concerning the various aspects of perioperative arterial thrombosis prophylaxis.

Introduction

The use of prophylactic antithrombotic drugs to prevent arterial thrombosis in the perioperative period of reconstructive arterial surgery still is a matter of dispute. Although guidelines exist,[1,2] surveys throughout Europe[3-5] and the US[6] have shown a wide variety in the use of perioperative antithrombotics exists for the past 20 years.

It is commonly felt that the use of perioperative antithrombotics, heparin being the first,[7] is essential for successful performance of reconstructive arterial surgery, with an acceptable incidence of thrombotic events and bleeding complications. After the clinical introduction of heparin in vascular surgery by Murray,[8] many other antithrombotic drugs have been used for the prevention of anticipated arterial thrombosis such as antiplatelet agents,[9-15] vitamin-K antagonists,[16-18] Dextran,[18-22] iloprost,[23-25] low-molecular-weight-heparins[26-29] and recently a new generation of antithrombotic drugs, the direct thrombin inhibitors.[30-32] The aim of our study was to describe and discuss the results of a survey concerning the current practice of perioperative arterial thrombosis prophylaxis by Dutch vascular surgeons during open arterial reconstructions and to compare these results with those from a questionnaire conducted in 2004.

Materials and Methods

In cooperation with the Dutch Society of Vascular Surgery and the Dutch Society of Interventional Radiology a study group was formed: CAPPA, Consensus on Arterial Peri-Procedural Anticoagulation. This group devised a comprehensive questionnaire (appendix 1), which was sent to all Dutch vascular surgeons in 2011, which routinely perform arterial reconstructive surgery. This questionnaire covered many aspects of perioperative care (pre-, per- and postoperative), with an emphasis on perioperative arterial thrombosis prophylaxis. The questionnaire contained 35 questions and covered all aspects of possible prophylactic and therapeutic regimes of pre-, intra- and immediate post-operative use of antithrombotic agents from the time of surgery to hospital discharge. Distinction was made for the different anatomic levels of surgical reconstruction: carotid, thoracic (including supra-renal aneurysms), aorto-iliac and infrainguinal. A separate item was included for endovascular interventions to assess any differences in antithrombotic regimes between open and endovascular procedures. Questions did not pertain to patients who were on long-term antithrombotic medication for

pre-existing conditions like venous thrombo-embolic disease, atrial fibrillation, (drug eluting) cardiac stents, prosthetic heart valves or recent other vascular interventions. Departments or sections of vascular surgery were offered the possibility to reply with one form on behalf of all their vascular surgeons. In 2004 a survey on postoperative care was done among Dutch vascular surgeons before the introduction of the guideline 'diagnosis and treatment of patients with peripheral vascular disease'.[2] The results of the postoperative care of this survey were compared with results of the current survey. Statistical analysis was performed using IBM®SPSS® software version 19. For calculating statistical significance relative risk was calculated with 95% confidence intervals.

Results

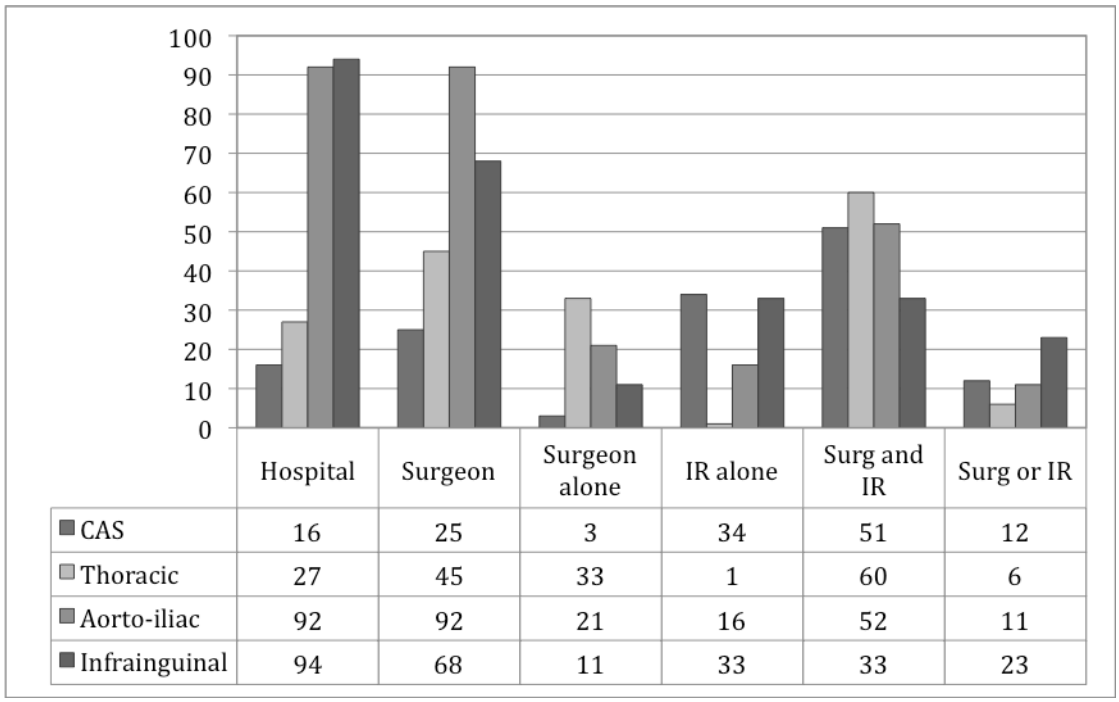
Response

245 vascular surgeons, being active members of the Dutch Society of Vascular Surgery, performing arterial vascular surgery in 50 training hospitals and 27 non-training hospitals were invited. In total 62 departments of vascular surgery responded (81%, 88% from all training hospitals and 67% from all non-training hospitals). In all, 205 out of 245 individual surgeons returned the questionnaire (84%): 91% of the vascular surgeons from training hospitals responded and 58% of those from non-training hospitals responded. After evaluation, 203 questionnaires were included in the results. Two forms were rejected as they only contained 4 answered questions. Survey is attached in appendix I.

Vascular surgery procedures

Open carotid surgery was performed by 192 respondents (95%) and in 58 of 62 hospitals (94%). Open surgical treatment of the thoracic aorta, including supra-renal aneurysm repair, was carried out in 39% of responding departments of vascular surgery and by 50% of responding vascular surgeons. Aorto-iliac open vascular surgery was performed by all respondents (N=203), of which 92% also performed endovascular procedures (57 of 62 hospitals). Infrainguinal reconstructive arterial surgery was also available in all responding departments and performed by all 203 surgeons. In figure I the number of hospitals involved

in the different endovascular procedures and the professionals performing these procedures are depicted.



	Hospital	Surgeon	Surgeon alone	IR alone	Surg and IR	Surg or IR
CAS	16	25	3	34	51	12
Thoracic	27	45	33	1	60	6
Aorto-iliac	92	92	21	16	52	11
Infrainguinal	94	68	11	33	33	23

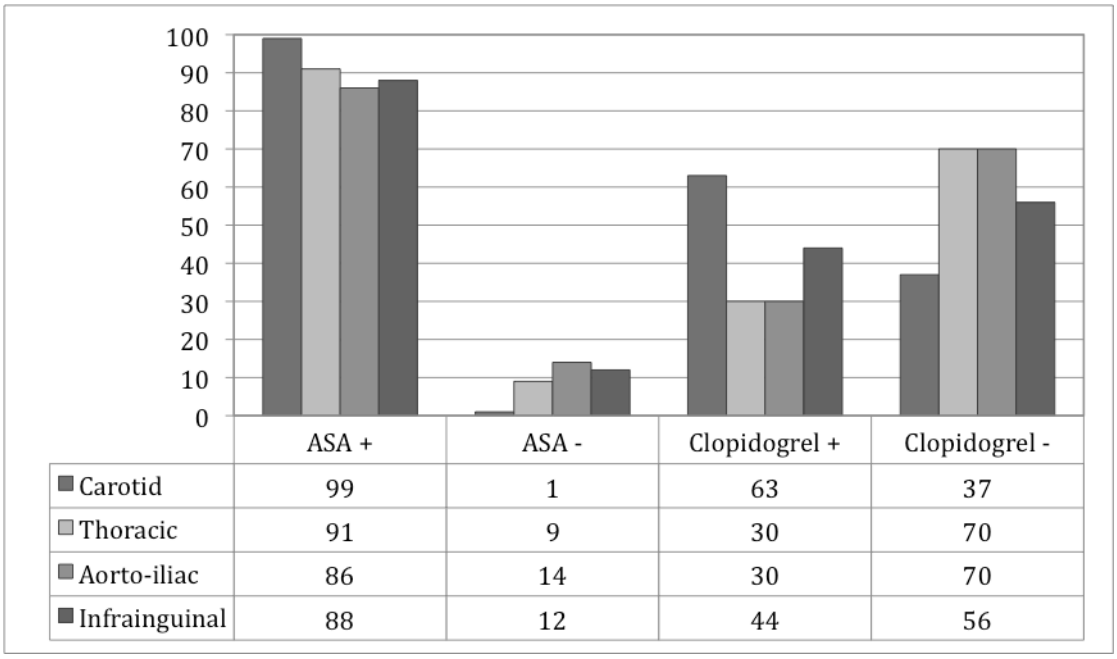
Figure I.

Endovascular procedures performed for carotid (CAS), thoracic, aorto-iliac and infrainguinal vascular disease and by whom the procedure was performed (IR = interventional radiologist), presented as the percentages of responding hospitals and responding vascular surgeons.

Preoperative antithrombotic treatment

Preoperative cessation or continuation of acetylsalicylic-acid (ASA) and clopidogrel for different types of surgery are depicted in figure II. Current ASA medication would be continued by 86% of respondents. Of those who discontinued this medication, 49% would stop it 7 days before operation and 15% 10 days before. The majority of respondents would discontinue clopidogrel before the operation, 31% 7 days before the operation and 69% any time between 1 to 10 days before the operation. No specific details were provided on the use of dipyridamol in case of carotid surgery. Commonly in the Netherlands this drug is started in combination with ASA by the neurologist before operation and both are continued after carotid surgery. In case of carotid surgery 63% of respondents would continue current

clopidogrel medication. In patients not on current clopidogrel and destined for carotid surgery medication, 13% of respondents would start them on clopidogrel the evening before operation (mostly 75 mg.). Respondents discontinued vitamin K antagonists (VKA, nearly always acenocoumarol) before open operation in 79%, 86%, 92% and 81% in case of carotid, thoracic, aorto-iliac and infrainguinal surgery respectively. A wide range of maximally allowed international normalised ratio (INR) existed in patients allowed to continue VKA's.



	ASA +	ASA -	Clopidogrel +	Clopidogrel -
Carotid	99	1	63	37
Thoracic	91	9	30	70
Aorto-iliac	86	14	30	70
Infrainguinal	88	12	44	56

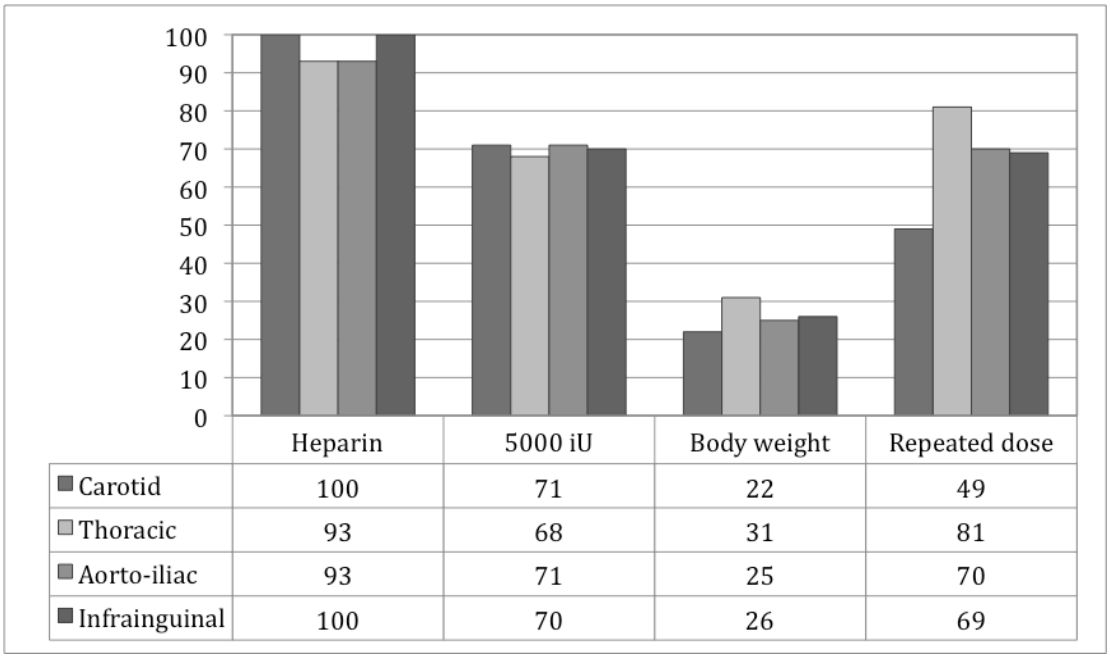
Figure II.

The preoperative continuation or cessation of ASA and clopidogrel for different anatomic levels of surgical reconstruction, presented as the percentages of responding vascular surgeons. + = continuation, - = cessation of ASA or clopidogrel.

Peroperative anticoagulation

During carotid, thoracic, aortic-iliac and infrainguinal surgery respectively 100%, 93%, 93% and 100% of respondents administered unfractionated heparin (UFH) intravenously before cross clamping. See figure III for details on UFH usage, dosages and percentages of vascular surgeons using body weight dependent doses. Dosage varied largely. Most surgeons used a single dose of 5000 IU i.v. before cross-clamping regardless of patient body weight. Body weight depended used doses varied from 50 IU per kilogram up to 100 IU per kilogram.

Percentages of surgeons who used a repeated dose of UFH and details are depicted in figure III. The criteria for a repeated dose of UFH were the operation time, the amount of blood loss or the measurement of an anticoagulation value. Of those vascular surgeons who used a repeated dose of UFH, the duration of the operation was used as a criterion by 44% of the surgeons in carotid surgery, by 76% in thoracic cases, by 66% in aorto-iliac surgery and by 61% in infrainguinal reconstructions. Approximately 20% of those surgeons used a cut-off point of operation time of more than 3 hours for the administration of a second dose of UFH, an operation time of more than 2 hours was applied as a cut-off point by 10% of respondents using a repeated dose of UFH. Only a small percentage of surgeons (4%) used the estimated amount of blood loss as a criterion for a repeated dosage of UFH during aorto-iliac and infrainguinal surgery. In those cases a blood loss of 2 litres or more was used as cut-off value. 9%, 16%, 8% and 11% of surgeons applying a second dose of UFH, for carotid, thoracic, aorto-iliac and infrainguinal surgery respectively performed perioperative measurement of the level of anticoagulation. For carotid surgery, both the ACT (activated clotting time) and the APTT (activated partial thromboplastin time) were equally used as a dosage criterion by respondents who repeated the dosage of UFH. These criteria were also equally used for dosage determination during thoracic and aorto-iliac vascular surgery.
In the case of infrainguinal vascular surgery, the ACT was used more often than the APTT (68% ACT and 32% APTT).



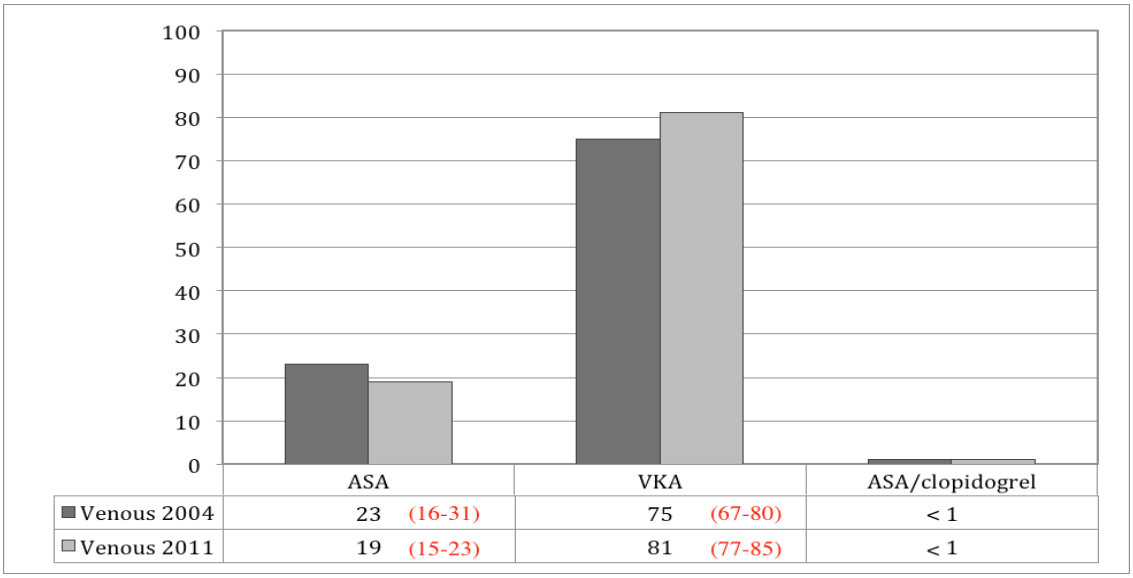
	Heparin	5000 iU	Body weight	Repeated dose
Carotid	100	71	22	49
Thoracic	93	68	31	81
Aorto-iliac	93	71	25	70
Infrainguinal	100	70	26	69

Figure III.

Details of unfractionated heparin (UFH) use before cross clamping for different anatomic levels of surgical reconstruction, presented as the percentages of responding vascular surgeons. 5000 IU is standard dose of UFH intravenously. Body weight is usage of body weight depend dose for UFH. Repeated dose depicts the percentage of responding vascular surgeons who use a repeated dose of UFH during different types of surgery.

Postoperative anticoagulation for infrainguinal bypass, also compared to 2004

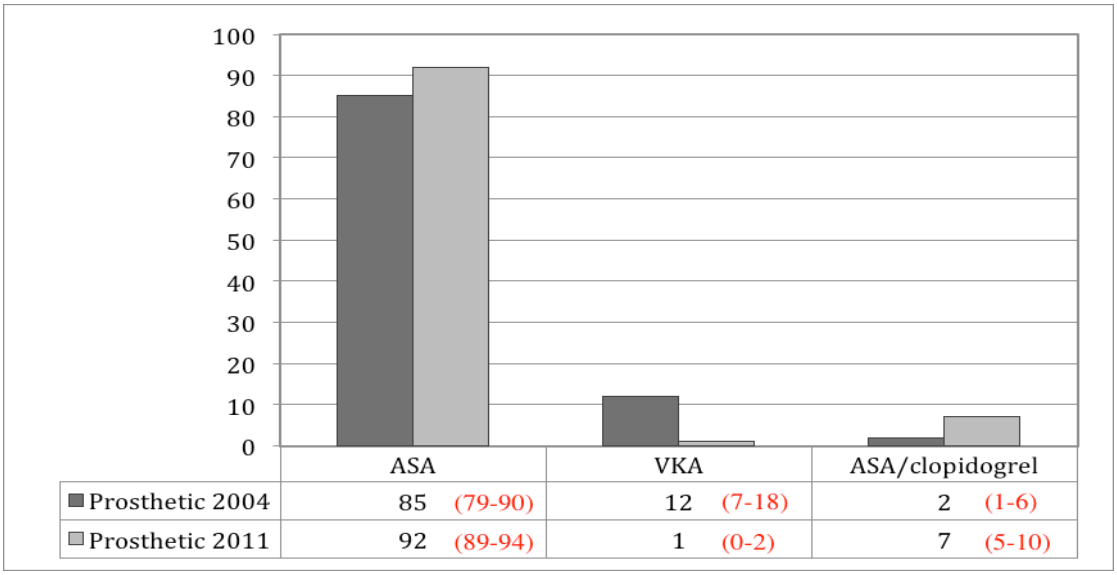
The results for the use of ASA, clopidogrel and VKA after infrainguinal venous and prosthetic bypass are depicted in figure IV a-b. Current results of 2011 are compared to the results of a similar questionnaire on this specific topic in 2004.[33] The response rate of the 2004 survey amongst vascular surgeons was 60% compared to 84% in 2011. In 2004 more respondents prescribed ASA after venous bypass than in 2011 (23% (95% CI 16-31) versus 19% (95% CI 15-23). In 2004 less (6%) vascular surgeons used VKA's after venous bypass: 75% (95% CI 67-80) in 2004 and 81% (95% CI 77-85) in 2011. After prosthetic conduit for infrainguinal bypass, 85% (95% CI 79-90) of surgeons prescribed ASA in 2004 and 92% (95% CI 89-94) in 2011, a 7% statistically significant difference. For VKA use after prosthetic bypass these percentages were 12% (95% CI 7-18) in 2004 and 1% (95% CI 0-2) in 2011 (significant difference of 11%), while the combination of ASA and clopidogrel was used in 2004 by 2% (95% CI 1-6) and in 2011 by 7% (95% CI 5-10) of respondents.



	ASA	VKA	ASA/clopidogrel
Venous 2004	23 (16-31)	75 (67-80)	< 1
Venous 2011	19 (15-23)	81 (77-85)	< 1

Figure IV a.

Direct postoperative anticoagulation for infrainguinal venous bypass presented as the percentages (with 95% confidence intervals) of responding vascular surgeons in 2004 and 2011. ASA = acetylsalicylic acid, VKA = vitamin K antagonist and ASA/clopidogrel = combination of both drugs.



	ASA	VKA	ASA/clopidogrel
Prosthetic 2004	85 (79-90)	12 (7-18)	2 (1-6)
Prosthetic 2011	92 (89-94)	1 (0-2)	7 (5-10)

Figure IV b.

Direct postoperative anticoagulation for infrainguinal prosthetic bypass presented as the percentages (with 95% confidence intervals) of responding vascular surgeons in 2004 and 2011. ASA = acetylsalicylic acid, VKA = vitamin K antagonist and ASA/clopidogrel = combination of both drugs.

Postoperative anticoagulation for carotid, thoracic and aorto-iliac operations

An inventory was made of the preferred "standard" for the immediate postoperative use of UFH or LMWH for a certain period of time in overlap with the start of ASA, acenocoumarol or clopidogrel, separately or in any combination. Immediate postoperative prescription of ASA only, was the preferred practice for 48%, 74% and 80% of respondents, respectively for carotid, thoracic and aorto-iliac vascular surgery. Only a small percentage of respondents (11%) used UFH for a predefined postoperative period of time, while a dose of twice daily 0.3 ml. sc. LMWH was added to ASA, acenocoumarol and/or clopidogrel by 9%, 13%, 11% and 23% of respondents for carotid, thoracic, aorto-iliac and infrainguinal vascular procedures, respectively. If UFH or LMWH was administered and at the same time ASA or clopidogrel or both was started, most surgeons strived for APTT values of 60-90 seconds for a period of 3 days postoperatively. When VKA was instituted for long-term anticoagulation, UFH or LMWH was continued until INR reached a value of 2.5-3.5, for a single day; for infrainguinal reconstructions 17% of surgeons required such INR values for a period of 2 successive days. During the administration of UFH or LMWH and acenocoumarol, the strived value for the APTT was also 60-90 seconds.

When the respondents were asked specifically if they used another regimen of anticoagulation after endovascular procedures, 95 of 203 (47%) of surgeons indicated that they applied the same regimen as for open surgery. All respondents who performed carotid artery stenting (CAS) stated that they added clopidogrel to ASA, before and after the procedure. When PTA without stenting was used for aorto-iliac or infrainguinal lesions, 19% of respondents added clopidogrel to ASA. This percentage increased to 45% after PTA with stenting.

Discussion

The response rate for this questionnaire was high. ASA was preoperatively withdrawn before aorto-iliac and infrainguinal operations by a minority of surgeons. This result seems consistent with recent publications, indicating that no consensus is present for the perioperative continuation of ASA[34] amongst vascular surgeons. 24% of Canadian vascular surgeons discontinues ASA in their patients before vascular surgery procedures.[35] Clopidogrel was preoperatively stopped before carotid surgery by one third of surgeons and a majority in case of thoracic and aorto-iliac vascular surgery. For infrainguinal operations almost half of

vascular surgeons stopped clopidogrel preoperatively. A recent study, however, suggests that clopidogrel may be continued safely for carotid, aorto-iliac and infrainguinal vascular surgery.[36] No significant bleeding complications occurred in patients undergoing arterial surgery in whom clopidogrel was continued either alone or as dual antiplatelet therapy.
A vast minority (13%) of respondents started clopidogrel before carotid surgery in spite of proof of its efficacy in reducing cerebral emboli during and immediately after carotid reconstruction.[37,38] A single dose of clopidogrel 75 mg. the night before surgery reduced postoperative thrombo-embolic potential significantly.
Nearly all the Dutch vascular surgeons used UFH before arterial cross clamping. A fixed dose of 5000 IU was most commonly applied. If, why and when a second dose of UFH was administered during arterial surgery varied widely. Despite studies showing that the activated clotting time (ACT) is the preferable method of assessing the anticoagulation status perioperatively,[39-41] only a vast minority of Dutch vascular surgeons used the ACT as a metric. When specifically asked for direct postoperative use of ASA, clopidogrel or VKA after venous or prosthetic infrainguinal bypass, not all respondents did comply with contemporary literature or guidelines.[2,10,13,42] According to the current Dutch guideline, published after the results of the BOA-trial,[13,16] VKA should be prescribed for at least 2 years after infrainguinal venous bypass and ASA after prosthetic bypass.[2] Recent studies suggest the use of ASA in combination with clopidogrel after prosthetic infragenual bypass.[42] Results of the current survey were compared with a previous survey, conducted 4 years after the BOA-publication, but before the publication of the Dutch guidelines in 2004.[2] The results of the 2011 survey showed an increase in the use of VKA after venous bypass of 6% and a 4% decrease in the use of ASA. In 2011 statistically significant more respondents (7%) prescribed ASA after prosthetic bypass infrainguinally. Also the combination of ASA and clopidogrel was used more often (5%, statistically significant) and the use of VKA after prosthetic bypass decreased with a statistically significant 11% compared to 2004. These results show that after publication of Dutch guidelines more, but not all, Dutch vascular surgeons apply this guideline.

Conclusion

Current practice of Dutch vascular surgeons concerning perioperative arterial thrombosis prophylaxis showed a rather wide variation, in agreement with previous reports from Europe

and the USA.[3-6] Applied regimes were not always in conformity with current guidelines. Apparently these guidelines leave room for a worldwide variety and moreover, they do not cover all aspects of perioperative arterial thrombosis prophylaxis. These shortcomings in current guidelines are a consequence of lack of scientific evidence. Clearly less detailed en less scientific authoritive guidelines necessitate practising surgeons to act individually and this understandably results in more or less variety in the execution of this prophylaxis. In our opinion randomized controlled trials (RCT's) are strongly needed to develop evidence-based medicine guidelines in this area. These RCT's should in particular concern the efficacy of the continuation or withdrawal of ASA and/or clopidogrel before vascular surgery and the efficacy of intraoperative heparinisation and other drugs for intraoperative arterial thrombosis prophylaxis.

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Appendix I. Survey.

CAPPA vaatchirurgie

1.

Naam:

2.

Kliniek:

3.

Aantal vaatchirurgen:

4.

Opleidingskliniek:

- Ja
- Nee

5.

Ingevuld namens hele vakgroep vaatchirurgie

6.

Indien bij u CHIVO's werkzaam zijn, hoeveel:

7.

Indien bij u vaat-differentianten werkzaam zijn, hoeveel:

8.

Welke ingrepen worden door u of in uw kliniek verricht?

	Open	Endovasculair door vaatchirurg met radioloog	Endovasculair door vaatchirurg alleen	Endovasculair door radioloog alleen	Endovasculair door of vaatchirurg of radioloog
Alle chir	☐	☐	☐	☐	☐
Carotis	☐	☐	☐	☐	☐
Thoracaal (incl supra-renale aneurysmata)	☐	☐	☐	☐	☐
Centraal (aorta-iliacaal)	☐	☐	☐	☐	☐
Perifeer	☐	☐	☐	☐	☐

9.

Indien patient ascal gebruikt, stopt u dat dan pre-operatief?
Indien nee, ga na antwoord naar vraag 10.

	Alle chir	Carotis	Thoracaal	Centraal	Perifeer
nee	☐	☐	☐	☐	☐
ja, in opdracht chirurg	☐	☐	☐	☐	☐
ja, in opdracht anaesthesist voor loco-regionale:	☐	☐	☐	☐	☐
Ja, in opdracht anaesthesist voor algehele narcose	☐	☐	☐	☐	☐
Nee, in opdracht anaesthesist bij algehele narcose	☐	☐	☐	☐	☐

10.

Indien pre-operatief gestopt, hoeveel dagen voor de ingreep stopt u Ascal dan?

	Alle chir	Carotis	Thoracaal	Centraal	perifeer
5 dagen pre-operatief	☐	☐	☐	☐	☐
7 dagen pre-operatief	☐	☐	☐	☐	☐
10 dagen pre-operatief	☐	☐	☐	☐	☐
Anders te weten:					

11.

Indien patient Plavix (Clopridogel) gebruikt, stopt u dat pre-operatief?

	Alle chir	Carotis	Thoracaal	Centraal	Perifeer
Nee	☐	☐	☐	☐	☐
ja, in opdracht chirurg	☐	☐	☐	☐	☐
ja, in opdracht anaesthesist	☐	☐	☐	☐	☐
Start juist voor ingreep					

12.

Indien u Plavix (Clopridogel) pre-operatief stopt of juist start, hoelang voor de ingreep doet u dat dan?

	Alle chir	Carotis	Thoracaal	Centraal	Perifeer
3 dagen pre-operatief	☐	☐	☐	☐	☐
5 dagen pre-operatief	☐	☐	☐	☐	☐
7 dagen pre-operatief	☐	☐	☐	☐	☐
Anders:					
Oplaaddosis bij juist starten pre-operatief:	☐	☐	☐	☐	☐
Schema oplaaddosis					

13.

Indien patient pre-operatief Sintrommitis (acenocoumarol) gebruikt, stopt u dat dan pre-operatief?

	Alle chir	Carotis	Thoracaal	Centraal	Perifeer
Nee	☐	☐	☐	☐	☐
Ja, in opdracht chirurg	☐	☐	☐	☐	☐
Ja, in opdracht anaesthesist	☐	☐	☐	☐	☐
Anders:					
Maximale INR voor operatie:					

14.

Dient u patient nog thrombose profylaxe toe?
indien nee, ga na antwoord naar vraag 15.

	Alle chir	Carotis	Thoracaal	Centraal	Perifeer
Ja	☐	☐	☐	☐	☐
Nee	☐	☐	☐	☐	☐
Nee, indien ascal of plavix doorgebruikt	☐	☐	☐	☐	☐
Nee, indien Sintrommitis doorgebruikt	☐	☐	☐	☐	☐

15.

Zo ja:

Welk product, dosering en toedieningswijze?

(Vb. Fraxiparine 0,3 ml, s.c.)

16.

Dient u standaard anti-biotica profylaxe toe en zo ja, welke dan en in welke dosering?

	Alle chir	Carotis	Thoracaal	Centraal	Perifeer
Nee	☐	☐	☐	☐	☐
Ja	☐	☐	☐	☐	☐
Soort					
Dosering					

17.

Dient u patienten heparine of ander antithrombotica toe voor het afklemmen?

	Alle chir	Carotis	Thoracaal	Centraal	Perifeer
Ja heparine	☐	☐	☐	☐	☐
Nee heparine	☐	☐	☐	☐	☐
Ander anti-thrombotica en dosering:					
Nee, helemaal geen anti-thrombotica	☐	☐	☐	☐	☐

18.

Indien u heparine toedient, welke dosis geeft u dan?

	Alle chir	Carotis	Thoracaal	Centraal	Perifeer
3.000 iU	☐	☐	☐	☐	☐
5.000 iU	☐	☐	☐	☐	☐
Afhankelijk van lich. gewicht					
Anders:					

19.

Indien u heparine toedient of ander anti-thrombotica, meet u dan een waarde van antistolling tijdens of aan eind operatie? En coupeert u eventueel de heparine? Gaarne korte toelichting indien antwoord ja.

20.

Herhaalt u soms het gift heparine tijdens een operatie? Zo ja, op welke indicatie of doet u een meting en besluit dan om heparine te herhalen?

	Alle chir	Carotis	Thoracaal	Centraal	Perifeer
Nee	☐	☐	☐	☐	☐
Ja, afhankelijk tijdsduur operatie	☐	☐	☐	☐	☐
Bij duur operatie:					
Ja, afhankelijk bloedverlies	☐	☐	☐	☐	☐
Bij bloedverlies van:					
Ja, afhankelijk van gemeten waarde	☐	☐	☐	☐	☐
Soort bepaling is dan					

21.

Wat is uw standaard directe post-operatieve antistollings beleid na open procedure? (dus net na operatie tot en met dag 3 of langer).

	Alle chir	Carotis	Thoracaal	Centraal	Perifeer
Direct Ascal	☐	☐	☐	☐	☐
Direct Plavix	☐	☐	☐	☐	☐
Direct start Sintrom	☐	☐	☐	☐	☐
Direct ascal of sintrom afh van type graft	☐	☐	☐	☐	☐
Heparine i.v. en ascal of sintrom	☐	☐	☐	☐	☐
Dubbele dosis fraxiparine en ascal of sintrom	☐	☐	☐	☐	☐
Anders:					

22.

Indien uw beleid voor infra-inguinale bypass afhankelijk is van het soort graft, wat geeft u dan in principe voor antistolling direct post-operatief?
Indien u geen heparine of andere anti-thrombotica toedient standaard, ga dan na antwoord op deze vraag naar vraag 29.

	Ascal	Plavix	Ascal en Plavix	Sintrom
Veneuze graft supra-genuaal	☐	☐	☐	☐
Veneuze graft infra-genuaal	☐	☐	☐	☐
Kunststof graft supra-genuaal	☐	☐	☐	☐
Kunststof graft infra-genuaal	☐	☐	☐	☐

23.

Is uw directe anti-stollingsbeleid anders na endovasculaire ingreep? Zo ja gaarne invullen.

	Van toepassing:
Nee	○
Ja, voor carotis	○
Ja, voor pta zonder stent infra-inguinaal	○
Ja, voor pta met stent infra-inguinaal:	○
Ja, voor	

24.

Indien ja, gaarne korte omschrijving:

25.

Indien u direct post-operatief heparine i.v.of LMWH of ander anti-thrombotica toedient, en ascal/plavix start, hoelang geeft u dan de heparine (of andere middel)?

	Alle chir	Carotis	Thoracaal	Centraal	Perifeer
24 uur	☐	☐	☐	☐	☐
3 x 24 uur	☐	☐	☐	☐	☐
Anders:					

26.

Indien heparine of LMWH of ander anti-thrombotica, welke dosering geeft u dan?

	Alle chir	Carotis	Thoracaal	Cenraal	Perifeer
20.000 iU per 24 uur, pomp, geen APTT-controle	☐	☐	☐	☐	☐
4 x 5.000 iU per 24 uur, geen APTT-controle	☐	☐	☐	☐	☐
wel APTT-controle, streefwaarde: 60-90	☐	☐	☐	☐	☐
wel APTT en streef 2 x verlengen uitgangsAPTT	☐	☐	☐	☐	☐
Anders:					

27.

Indien u direct post-operatief heparine of LMWH of een ander anti-thrombotica toedient en na 1 dag sintrom start, hoelang geeft u dan de heparine (of ander middel)?

	Alle chir	Carotis	Thoracaal	Centraal	Perifeer
Tot INR tussen 2,5 en 3,5	☐	☐	☐	☐	☐
24 uur	☐	☐	☐	☐	☐
3 x 24 uur	☐	☐	☐	☐	☐
Anders:					

28.

Indien u direct post-operatief heparine of LMWH of ander anti-thrombotica toedient en na 1 dag sintrom start, in welke dosering geeft u dat dan?

	Alle chir	Carotis	Thoracaal	Centraal	Perifeer
20.000 iU per 24 uur, pomp, geen APTT-controle	☐	☐	☐	☐	☐
4 x 5.000 iU per 24 uur, geen APTT-controle	☐	☐	☐	☐	☐
Met APTT-controle en streefwaarde 60-90	☐	☐	☐	☐	☐
Met APTT-controle en streefwaarde 2 x verlenging	☐	☐	☐	☐	☐
Anders:					

29.

indien u post-operatief antistolt met heparine en/of Sintrom of ander anti-thrombotica (geen ascal of plavix) , geeft uw anaesthesist dan de patient epiduraal of spinaal anesthesie?

	Alle chir	Centraal	Thoracaal	Perifeer
Ja, zowel spinaal of epiduraal	☐	☐	☐	☐
Alleen spinaal	☐	☐	☐	☐
Geen van beide	☐	☐	☐	☐

30.

Indien u post-operatief patient behandeld met ascal of plavix, geeft uw anaesthesist dan epiduraal of spinaal anaesthesie?

	Alle chir	Centraal	Thoracaal	Perifeer
Ja, zowel spinaal als epiduraal	☐	☐	☐	☐
Alleen spinaal	☐	☐	☐	☐
Geen van beide	☐	☐	☐	☐

31.

Indien patient epiduraal heeft post-operatief, wanneer wordt deze dan verwijderd?

	Alle chir	Centraal	Thoracaal	Perifeer
Na 1 dag	☐	☐	☐	☐
Na 2 dagen	☐	☐	☐	☐
Na 3 dagen	☐	☐	☐	☐
Anders:				

32.

Wordt voor het verwijderen van de epiduraal de antistolling gestaakt?

○ Ja
○ Nee

33.

Indien ja, gaarne kort weergeven hoelang antistolling gestaakt en welke INR wordt dan eventueel gehanteerd?

34.

Indien u een protocol hanteert voor de peri-operatieve antistolling bij vaatoperaties (gemaakt met of zonder anaesthesie), wilt u dan hieronder een korte samenvatting invullen of liever nog: een kopie hiervan op (laten) sturen, dan wel via mail bijvoegen? Dank.

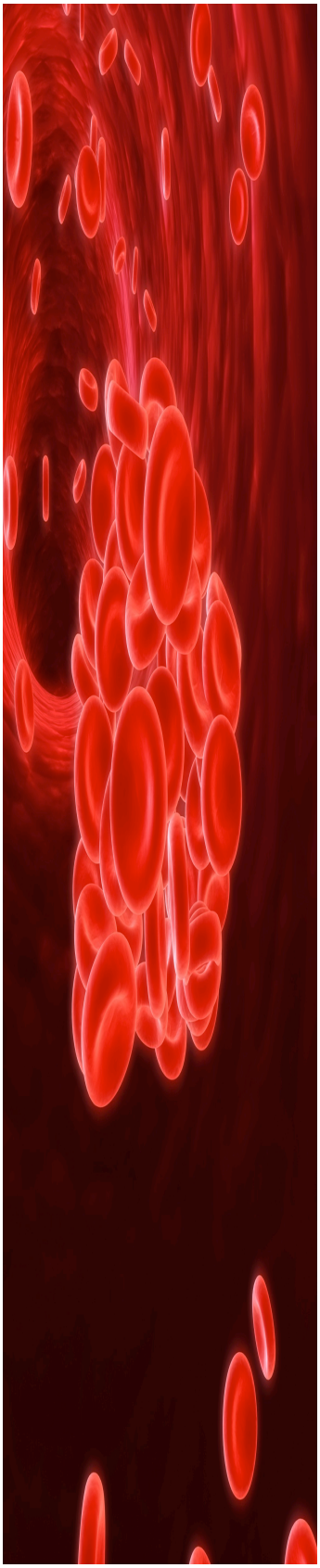
35.

Is uw beleid bij een endoprothese van de aorta abdominalis anders dan bij open procedure? Indien ja, gaarne korte toelichting.

36.

Dank voor uw tijd, indien u nog vragen en/of opmerkingen heeft, graag:

VERSTUUR !!! Dank voor uw medewerking.



Chapter 4

Periprocedural prophylactic antithrombotic strategies in interventional radiology: current practice in the Netherlands and a comparison with the United Kingdom

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Abstract

Purpose

The use of prophylactic antithrombotic drugs to prevent arterial thrombosis in the periprocedural period during (percutaneous) peripheral arterial interventions (PAI) is still a matter of dispute, and clear evidence-based guidelines are lacking. To create those guidelines a study group was formed in the Netherlands in cooperation with the Dutch Society of Vascular Surgery and the Society of Interventional Radiology: CAPPA, Consensus on Arterial Peri-Procedural Anticoagulation.

Materials and Methods

The CAPPA study group devised and distributed a comprehensive questionnaire amongst Dutch interventional radiologists (IR).

Results

142 IR responded (68%). Almost no IR stopped acetyl-salicylic-acid (ASA) before interventions. 40% stopped clopidogrel before PAI, but not before CAS. A flushing solution on the side-port of the sheath was used routinely by 30% in PAI and during CAS by 50%. A minority used a heparinised flushing solution (28%). Unfractionated heparin (UFH) was used by 95% as bolus. 5000 IU was the most used dosage. Timing of administration varied widely. A majority of IR (75%) would repeat a gift of heparin after 1 hour.

Conclusion

A substantial variety exists amongst IR in the Netherlands on the use of prophylactic periprocedural antithrombotic drugs to prevent arterial thrombosis during PAI. When compared to varying results on the use of heparin from the UK, the variety in the Netherlands showed a different pattern. The proven variety in these countries, but also between these countries emphasises the need for authoritative studies in order to develop evidence-based practical guidelines.

Introduction

Unfractionated heparin (UFH) is widely used during percutaneous arterial interventions (PAI) as prophylactic periprocedural antithrombotic agent to prevent arterial thrombo-embolic complications (ATEC).[1-5] PAI include thoracic, aorto-iliac and infrainguinal interventions and endovascular aneurysm repair (EVAR), but exclude cardiac/coronary interventions. Heparin is used to coat catheters and wires, in flushing solutions for sheaths and intravenously (iv) or intra-arterially as a bolus. The main harmful side effect of heparin is a higher bleeding tendency, possibly causing local and systemic haemorrhagic complications.[6,7] Also heparin can result in the possibly life-threatening heparin-induced thrombocytopenic (HIT) syndrome.[8] In percutaneous coronary intervention (PCI) it is well recognized that bleeding complications, especially those requiring transfusion, are independent, strong predictors of worse outcome of procedures.[9,10] It has been well established that protocols on the use of UFH in PAI vary widely between countries, hospitals and doctors.[11-13] This variation in UFH administration and/or dosage includes amongst others, the usage of a standard or bodyweight dependent dose, the timing of UFH administration, the mode of administration (drip or flushing solution) and if and how UFH induced anticoagulation is monitored during PAI. This variation exists despite current international guidelines, such as TASC II (Inter-Society Consensus for the Management of Peripheral Arterial Disease)[14] and CIRSE (Cardiovascular and Interventional Radiological Society of Europe) guidelines.[15] These guidelines recommend administration of UFH and the measurement of an activated clotting time (ACT) during arterial endovascular interventions despite the possible lack of trial data or other sound scientific evidence on its efficacy. In table 1 a summary of these guidelines and comments are provided.

The use of new antithrombotic agents, the direct thrombin inhibitors, has been the subject of several trials. Results showed a beneficiary effect when compared with UFH during coronary interventions and cardiovascular surgery. Main beneficiary effects were a more predictable dose-response pattern, shorter plasma half-life and less bleeding complications.[16-18] During PAI the direct thrombin inhibitors showed a good safety profile but no major beneficiary effects compared to UFH.[19-21]Also specifically during endovascular aneurysm repair (EVAR), no beneficiary effect could be demonstrated for bivalirudin.[22] An important disadvantage of the direct thrombin inhibitors is their substantial higher costs compared to UFH. Further

results from trials have to be awaited before the role of direct thrombin antagonists during PAI will be clear.

For the purpose of a systematic investigation of the necessity and effectiveness of periprocedural arterial thrombosis prophylaxis, a study group was formed in the Netherlands. This group was instituted in close collaboration between the Dutch Society of Vascular Surgery and the Dutch Society of Interventional Radiology (NGIR). The study group was named CAPPA, Consensus on Arterial Peri-Procedural Anticoagulation. The first task the study group took on was to establish the current practice of periprocedural care, emphasising on anticoagulation and antithrombotics. Therefore a comprehensive questionnaire for vascular surgeons and interventional radiologists (IR) was devised.

In 2005 new guidelines from the Dutch Society of Vascular Surgery were published on 'Diagnosis and treatment of arterial disease of the lower extremity'.[23] Before this publication a survey was held among Dutch vascular surgeons and IR.[24] The results for preferred prescription of anticoagulation after PTA with or without stent from that survey are compared to results from the current questionnaire. Also historic results from a recent survey from the United Kingdom (UK) on the use of UFH[13] are, where possible, compared to results from the Netherlands in the current article. The data from the UK[13] were deducted from results of a survey in the UK to assess the current use of heparinized saline and bolus doses of heparin in non-neurological interventional radiology.

Main objective of our current study was to explore if the described variation for other countries also exists in the Netherlands for peri-procedural anticoagulation during PAI.

Materials and Methods

A comprehensive questionnaire (appendix 1) was devised and sent to all Dutch IR who were members of the NGIR and who routinely perform PAI. The questionnaire encompassed 35 questions and focused on all aspects of possible prophylactic and therapeutic regimens of pre- and perprocedural use of antithrombotic agents and immediate post-procedural use of these drugs from the time of intervention to hospital discharge. Distinctions were made among the different anatomical areas of arterial pathology: carotid, thoracic (including supra-renal aneurysms), aorto-iliac and infrainguinal. Questions did not pertain to patients who were on long term antithrombotic drugs for pre-existing conditions like venous thrombo-embolic

disease, atrial fibrillation, (drug eluting) coronary stents, prosthetic heart valves or recent other vascular interventions. Other aspects of periprocedural care were also incorporated in the survey.

Departments or sections of IR were offered the possibility to reply with one form on behalf of all their radiologists. After a 6-weeks period non-respondents were contacted, and a new request for a response was made. After a new period of 8 weeks, the final analysis of the completed questionnaires was performed.

For a comparison of a number of results between the current survey and recently published data from the UK[13] additional data were asked for and kindly supplied by email by the authors and the current manuscript was discussed with both authors from the UK study (A.C. Durran and C. Watts).

Results

Response

It was estimated that 210 IR, being active members of the NGIR, were performing PAI. A total of 44 departments of IR responded and 142 out of 210 individual IR returned the questionnaire (68%). A majority of respondents (66%) performed between 200 and 400 PAI's per year. Less than 100 procedures per year were performed by 7% of respondents, while 16% performed more than 800 procedures per year.

Anatomical areas of arterial pathology

Carotid artery stenting (CAS) was performed by 51 respondents (36%). This procedure was performed by IR alone by 82% of respondents and by 14% of respondents together with the vascular surgeon. 133 IR performed EVAR (94%), predominantly (85%) together with a vascular surgeon. All respondents (100%) performed aorto-iliac PTA and infrainguinal PAI.

Preprocedural anticoagulation

Preprocedural cessation or continuation of acetyl-salicylic-acid (ASA) and clopidogrel for different types of procedures are shown in figure 1. For aorto-iliac and infrainguinal interventions 4% respectively 6% of Dutch IR stopped ASA preprocedurally. When

clopidogrel was discontinued most IR (40%) ordered this 7 days before PAI, 31 % did so 5 days and 29% 10 days before PAI. Almost all respondents (94%) discontinued vitamin-K antagonists (VKA).

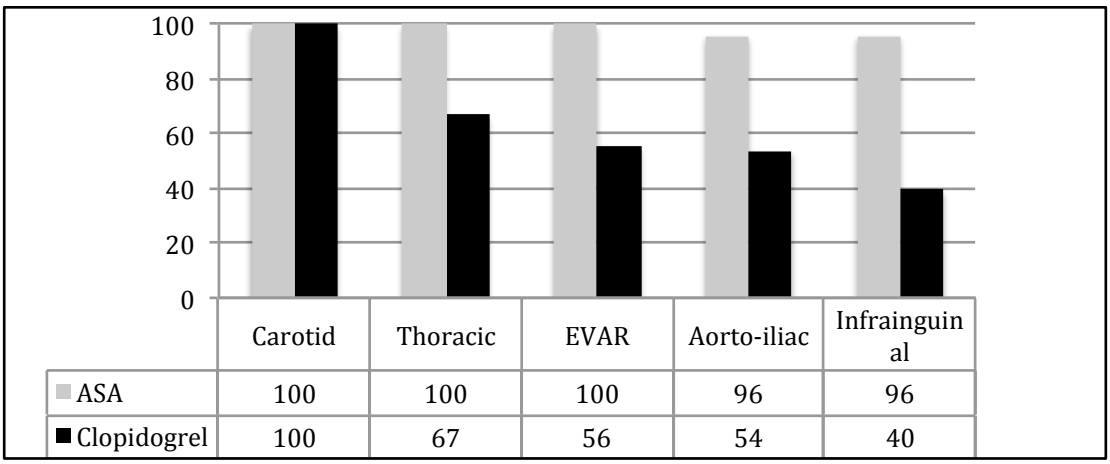


Figure 1.

The percentages of respondents who allowed continuation of acetyl-salicylic-acid (ASA) or clopidogrel before PAI.

Perprocedural care

When asked if intravenous (i.v.) access was established before start of PAI, 96% of IR stated that they did so during CAS, during thoracic interventions 73% and during aorto-iliac and infrainguinal interventions 76% and 78% respectively.

Flushing solution.

The use of a flushing solution on the side-port of an inserted sheath varied considerably. Only 52% of respondents used this during CAS. For thoracic, aorto-iliac and infrainguinal procedures 29% of IR used a flushing solution on the side-port. If a flushing solution was used only a minority of respondents used a heparinised solution. UFH was used in saline (23% of respondents) and in glucose/saline (5%). The concentrations of UFH used varied widely, most commonly used was 5000 IU/500 cc (63%). See figure 2 for details.

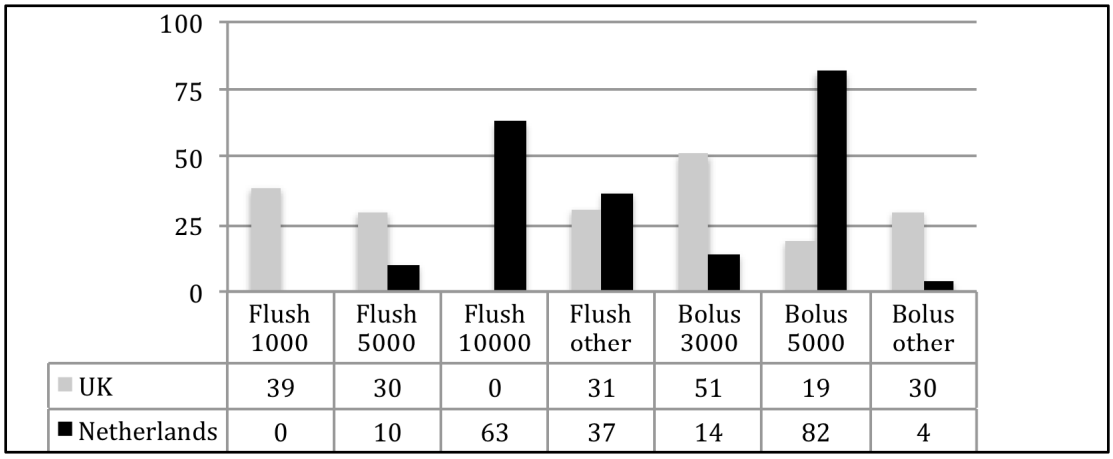


Figure 2.

Comparison of results for the Netherlands and the UK on details for heparin used in flushing solutions or as bolus. Expressed as percentages of respondents using heparin for both countries.

(Flush 1000 = 1000 IU/l (/l=per liter), 5000 = 5000 IU/l and 10000 = 10000 IU/l, Bolus 3000 = 3000 IU and 5000 = 5000 IU).

Perprocedural anticoagulation

During PAI almost all respondents indicated that they used UFH as arterial thrombosis prophylaxis. A dose of 5000 IU i.v. was used predominantly (82%). A body weight dependent dose was used by 14% of IR, details are depicted in figure 2. A vast majority (85%) of those IR who used UFH did not perform a measurement of a clotting parameter. Only 1% indicated they performed periprocedural measurement of ACT (activated clotting time) while the other 14% did not specify if they monitored clotting parameters.

A repeated bolus of UFH was administered by 75% of IR, whereby 74% of those stated that they used the elapsed time of the procedure as a criterion (more than 1 hour) whereas 3% indicated they used a repeated bolus because of the value of the measured ACT. No minimal value of ACT was provided by respondents for which they administered a second dose of UFH.

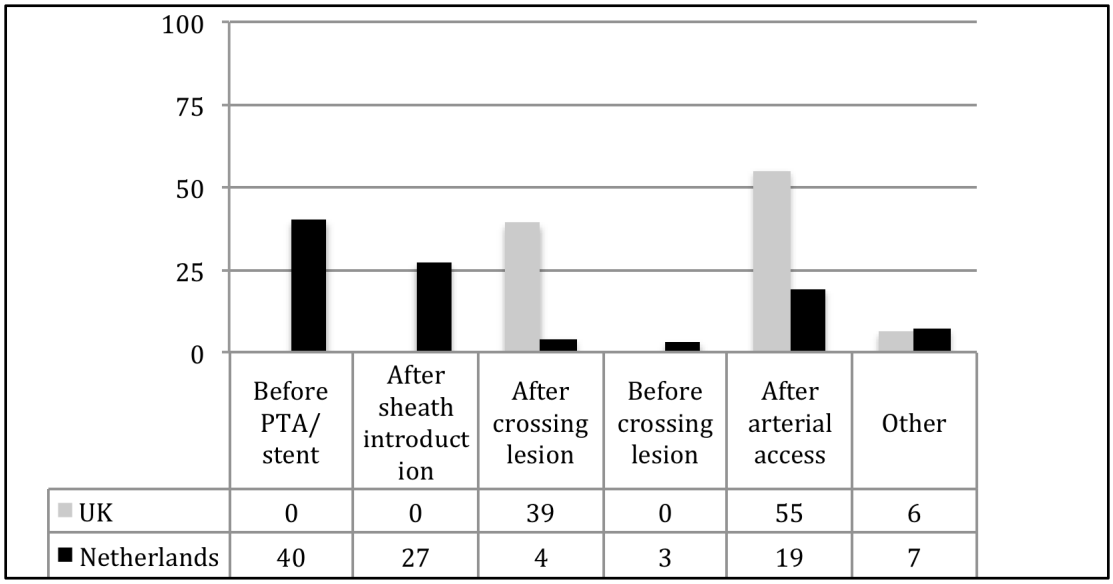
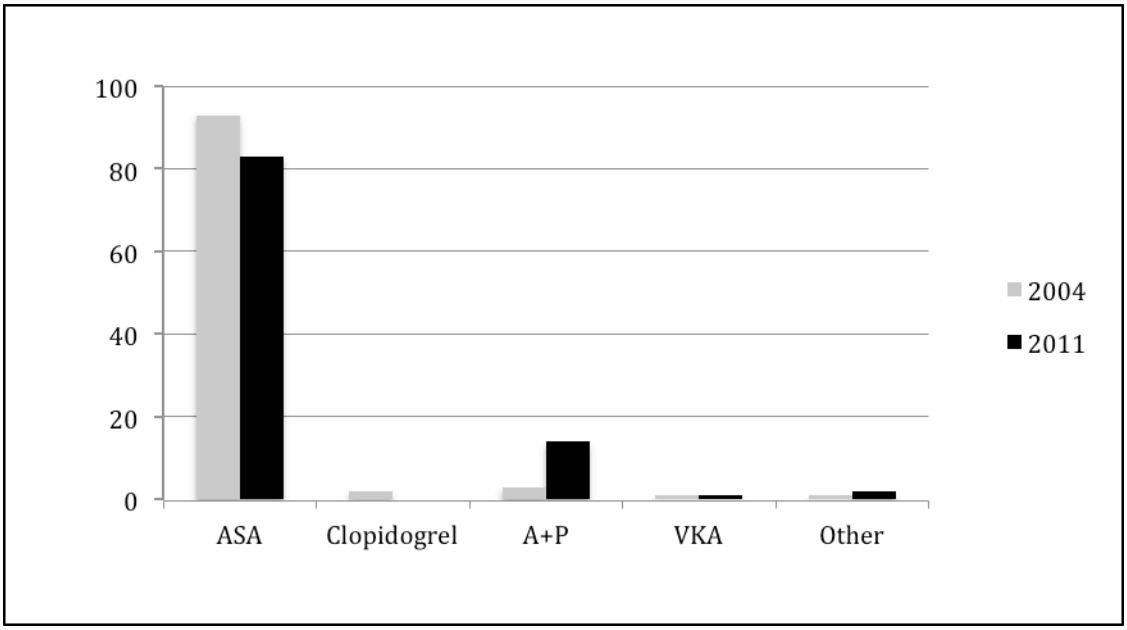


Figure 3.

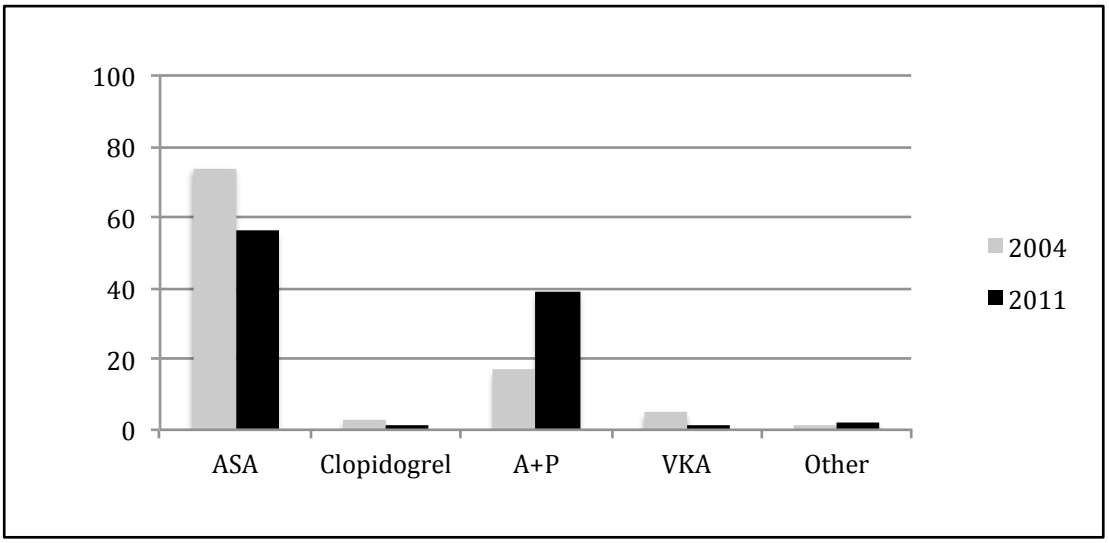
Comparison of results for the Netherlands and the UK on the timing of the bolus of heparin, expressed as percentages of responding IR.

Postprocedural anticoagulation

Details on anticoagulation after PTA with and without stenting are depicted in figure 4. No consensus existed on the duration of the combination of ASA and clopidogrel. Duration of adding clopidogrel to ASA varied from 6 weeks to 12 months, after which all respondents continued ASA as mono-therapy. The same variation as observed for PTA without stenting considering the duration of adding clopidogrel to ASA was present for PTA with stenting.



2004	92 (81-98)	2 (0-11)	4 (1-14)	2 (0-11)	0 (0-8)
2011	83 (76-87)	0 (0-3)	14 (9-21)	1 (0-4)	2 (1-7)



2004	74 (60-85)	4 (0-14)	17 (8-30)	4 (0-14)	1 (0-11)
2011	56 (48-64)	1 (0-4)	38 (30-47)	1 (0-4)	4 (2-9)

Figure 4.

Post-procedural prescription of anticoagulants in the Netherlands after PTA without stenting (upper figure) and after PTA with stenting (lower figure) compared between 2004 and 2011. Percentages depicted with 95% confidence intervals.

Discussion

The results of the current survey amongst Dutch IR show that the known variation existing in other countries[1,11-13] for the use of prophylactic periprocedural anticoagulation during PAI also exists in the Netherlands. The preprocedural cessation or continuation of ASA and/or clopidogrel, the routinely use of intravenous access and the use of flushing solutions on a side port of a sheath are apparently still under debate. No convincing trial data are available on these topics. Compared to a survey from 2004 in the Netherlands,[24] the most striking difference in post-procedural anticoagulation was the increased use of clopidogrel, in combination with ASA, after stenting procedures (figure 3). Existing guidelines are only partially met by Dutch and UK interventionists. As depicted in table 1, the TASC II guidelines advocate the periprocedural measurement of an ACT. No literature references are provided and TASC II state that evidence is extrapolated from results for the coronary circulation. Our results show that only 1% of Dutch IR actually performs an ACT and in the UK this is only 4%. CIRSE guidelines state that for occlusive arterial disease 5000 IU of heparin are administered following arterial access. No literature is provided with this statement. For EVAR the open surgical experience with heparinization during AAA repair is extrapolated to the EVAR procedure. The CIRSE guidelines provide literature references for open AAA repair. A recently published systematic review however showed that there is no convincing evidence for the beneficiary role op heparin in open and endovascular AAA repair.[25]

Despite the fact that in the UK more coherence amongst IR seems to exist since the publication by Gaines et al. in 1996,[12] a substantial variation still exists in the use of UFH in flushing solutions and as a perprocedural bolus.[13] Remarkably the variation as depicted in the Netherlands and the UK was not identical. Dosages and concentrations of heparin used for flushing solution and bolus varied not only within both countries, but also between them (figure 4 and 5). Authors from the UK study[13] concluded: “although there remains no absolute consensus (in the UK) regarding heparin administration, there seems to be some coherence amongst practising interventionists”. The same could be stated about Dutch interventionists for the dosage of bolus and flushing solution with heparin. As depicted in figure 2, this coherence in the UK and the Netherlands varies.

Possible explanations for these wide variations are numerous and most are speculative. It appears that IR's continue to use the "protocols" acquired during their training. The above-described lack of evidence in existing guidelines may undermine the authority of these guidelines in the PAI setting and may reduce compliance by IR around the world. The lack of evidence also weakens the recommendations by key opinion leaders.

In the current era of evidence-based-medicine the medical and surgical community should strive to achieve level 1 evidence-based guidelines, in particular in case of the prophylactic use of potentially hazardous medications. Administration of UFH during PAI, especially in higher doses, may result in an unpredictably high level of anticoagulation, resulting in bleeding complications and need for transfusion.[6] To reduce the number of bleeding complications from the access site the use of arterial closure devices has been advocated. Despite favourable reports concerning safety and costs-effectiveness,[26,27] this use of closure devices has not gained widespread use in the Netherlands and in other countries[28] amongst IR. Apparently Dutch IR still believe that the complication rate and costs are high and they use a closure device only selectively.

The majority of the professionals involved, deem it self-evident that a too low a concentration of UFH may cause arterial thrombo-embolic complications (ATEC). However there are no data that unshakably support this notion. It appears that the vast majority of professionals involved seems to underestimate the chance and the seriousness of bleeding complications (and of the rare but catastrophic heparin induced thrombocytopenia syndrome), since only very few monitor the level of anticoagulation after administration of UFH by means of ACT. The variation in prophylactic periprocedural antithrombotics also could also have an influence on the results of published trials of PAI and PTA with or without stenting. The rate of ATEC could be influenced by the used dosages of UFH that might be different between hospitals and IR individually from participating centres. Patencies and ATEC could also be influenced by whether or not heparinised flushing solutions are used and in which concentrations. Much research has been done in interventional cardiology concerning pre-, per- and post-procedural coagulation. Reasons why the results and protocols from cardiology or cardiac surgery[30,31] should be extrapolated with caution and should be tested in trials for perprocedural use in interventional radiology in PAI, are numerous and subject to discussion. Catheters, wires and other devices used during coronary interventions are different from those used in PAI, the

target vessels differ in size and probably histopathologic responses to balloon- and stent-dilatation and local drug deliverance by balloon or stent. Also the hemodynamics in the coronary system might be different from that in the aorto-iliac and infrainguinal arterial vessels. The myocardium is a different muscle system than that in the leg. Furthermore the risk-benefit ratio in the heart is completely different than that from the leg, the reserve and regeneration capacities from the muscles in the leg are far more extensive that that from the myocardium. Because of this a higher percentage of bleeding complications can be accepted in coronary intervention at the benefit of less myocardial infarctions and possible deaths. In carotid artery interventions by IR and/or vascular surgeons, some aspects of periprocedural use of protocols and pharmaceuticals in coronary interventions have been tested and applied. The preprocedural use of the combination of ASA and clopidogrel and the perprocedural use of bivalrudin (a direct thrombin inhibitor (DTI))[32-34] instead of heparin are examples of that extrapolation from coronary interventions and were performed in trial settings. To further determine the role of DTIs in PAI after successful reports from coronary interventions, study results in PAI will have to be awaited with large number of patients.

We propose that multiple randomized controlled trials (RCT) should be started on prophylactic periprocedural anticoagulation during PAI. These studies should focus on the cessation or continuation of clopidogrel preprocedurally and evaluate the effect of UFH and direct thrombin inhibitors. Since a concentration of 1000 IU/l of UFH in saline is expected to have no systemic effect on anticoagulation, we would suggest (for the time being) to permit its use as flushing solution in these studies in order to attract enough participants in these studies, as potential participants might otherwise be reluctant to participate. Despite these limitations we strongly advocate that RCT's on the subject of arterial prophylactic periprocedural anticoagulation will be developed and that these RCT's will preferably be performed in cooperation between interventional radiologists and vascular surgeons internationally. Goal of these RCT's must be the development of authoritative and therefore widely accepted and applied evidence-based guidelines.

In conclusion our survey on the use of prophylactic periprocedural anticoagulation in interventional radiology in the Netherlands shows that a very significant variation still exists between hospitals and between different countries, emphasizing the need for comprehensive evidence-based guidelines.

Table 1. Guidelines TASC-II and CIRSE.

Guideline:	**Summary and comments:**
TASC II-guidelines	F3.1 Endovascular treatment of infrainguinal arterial occlusive disease. Page 182-183: "Standard therapy is heparinization during the intervention to increase activated clotting time to 200-250 seconds. Much of the Supporting evidence for periprocedural antiplatelet and adjuvant therapy is extrapolated from that related to the coronary circulation." No literature references provided. No separate recommendation stated about periprocedural antithrombotics.
CIRSE-guidelines	Standard Operating Procedures. Aorto-occlusive disease: "This (arterial access, AW) is followed by the administration of 5000 U of heparin." No literature references provided. EVAR: "Although there are no trial data regarding routine use of intraoperative heparin during EVAR, the open surgical experience with heparinization has been widely applied to endograft procedures." Protocol: either 5000 IU or bodyweight dependent dose. Recommendation: "… anticoagulation monitoring may improve anticoagulation during vascular surgery." Literature references: only on surgical procedures

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Appendix 1. Survey.

CAPPA Intervention-Radiology

Start

www.enquetecompagnie.nl

CAPPA Intervention-Radiology

1.

Name:

2.

Hospital:

3.

Training-hospital:

○Yes

○No

4.

Number of interventional radiologists:

5.

Respons on behalf of department?

6.

Number of IR in training?

7.

How many procedures are performed at your department?

0-100	○
100-150	○

150-200	○
200-400	○
400-800	○
800+	○

8.

Which procedures are performed by you or your department?

	Endovascular by IR together with vascular surgeon	Endovascular by IR alone	Endovascular by vascular surgeon alone	Endovascular by either IR or vascular surgeon
All	☐	☐	☐	☐
Carotid	☐	☐	☐	☐
Thoracic	☐	☐	☐	☐
EVAR	☐	☐	☐	☐
Aortic PTA	☐	☐	☐	☐
Infra-inguinal	☐	☐	☐	☐
Comments:				

9.

If patients uses ASA, will you stop this before procedure?

	All	Carotid	Thoracic	EVAR	Aorto-Iliac PTA	Infra-inguinal
No	☐	☐	☐	☐	☐	☐
No, start before procedure	☐	☐	☐	☐	☐	☐
Yes, ordered by vascular surgeon	☐	☐	☐	☐	☐	☐
Yes, ordered by IR	☐	☐	☐	☐	☐	☐
Comments:						

10.

If you stop or start ASA before procedure, how many days before procedure?

	All.	Carotid	Thoracic	EVAR	Aorto-iliac PTA	Infra-inguinal
5 days	☐	☐	☐	☐	☐	☐
7 days	☐	☐	☐	☐	☐	☐
10 days	☐	☐	☐	☐	☐	☐
Different - comments:						

11.

If patients uses plavix (clopidogrel), will you stop this before procedure?

	All	Carotid	Thoracic	EVAR	Aorto-iliac PTA	Infra-inguinal
No	☐	☐	☐	☐	☐	☐
No, start before procedure	☐	☐	☐	☐	☐	☐
Yes, ordered by vascular surgeon	☐	☐	☐	☐	☐	☐

Yes, ordered by IR	☐	☐	☐	☐	☐	☐
Comments:						

12.

If you stop or start plavix (clopidogrel) before procedure, how many days before procedure?

	Alle interv.	Carotid	Thoracic	EVAR	Aorto-iliac PTA	Infra-inguinal
5 days	☐	☐	☐	☐	☐	☐
7 days	☐	☐	☐	☐	☐	☐
10 days	☐	☐	☐	☐	☐	☐
Different:						
Starting dose:	☐	☐	☐	☐	☐	☐
Details oplaaddosis						
Comments:						

13.

If patients uses a vitamin-K antagonist (VKA), will you stop this before procedure?

	All	Carotid	Thoracic	EVAR	Aorto-iliac PTA	Infra-inguinal
No	☐	☐	☐	☐	☐	☐
Yes, ordered by vasc surgeon	☐	☐	☐	☐	☐	☐
Yes, ordered by IR	☐	☐	☐	☐	☐	☐
Different - comments:						

14.

If you stop VKA before procedure, how many days before procedure?

	All	Carotid	Thoracic	EVAR	Aorto-iliac PTA	Infra-inguinal
3 days	☐	☐	☐	☐	☐	☐
5 days	☐	☐	☐	☐	☐	☐
7 days	☐	☐	☐	☐	☐	☐
Different:						
Maximal INR before procedure:						
Comments:						

15.

Do you prescribe venous thrombosis-profylaxis before procedure?

	All	Carotid	Thoracic	EVAR	Aorto-iliac PTA	Infra-inguinal
Yes	☐	☐	☐	☐	☐	☐
No, start before procedure	☐	☐	☐	☐	☐	☐
No if patient uses ASA or clopidogrel	☐	☐	☐	☐	☐	☐
No if patient uses VKA	☐	☐	☐	☐	☐	☐
Comments:						

16.

If so, what sort?

17.

Do you use standard intra-venous access?

	All	Carotid	Thoracic	EVAR	Aorto-iliac PTA	Infra-inguinal
Yes	☐	☐	☐	☐	☐	☐
No, start before procedure	☐	☐	☐	☐	☐	☐
Depending on sort of procedure						
Comments:						

18.

Do you administer antibiotics as prophylaxis?

	All	Carotid	Thoracic	EVAR	Aorto-iliac PTA	Infra-inguinal
No	☐	☐	☐	☐	☐	☐
Yes	☐	☐	☐	☐	☐	☐
Only when stent is used	☐	☐	☐	☐	☐	☐
Name of antibiotic						
Dosering						
Comments:						

19.

Do you use flushing solution on side port sheath?

	All.	Carotid	Thoracic	EVAR	Aorto-iliac PTA	Infra-inguinal
No	☐	☐	☐	☐	☐	☐
Yes with saline	☐	☐	☐	☐	☐	☐
Yes, saline/glucosis	☐	☐	☐	☐	☐	☐
Yes, heparin and saline	☐	☐	☐	☐	☐	☐
Yes, saline/glucosis and heparin	☐	☐	☐	☐	☐	☐
Comments:						

20.

If yes, what concentration of heparin do you use?

21.

Do you apply a heparin bolus routinely or another anti-thrombotic?

	All	Carotid	Thoracic	EVAR	Aorto-iliac PTA	
No	☐	☐	☐	☐	☐	☐
Yes, heparin	☐	☐	☐	☐	☐	☐
Yes, other antithrombotic:						
Dose of other antithrombotic:						
Not intravenously, but:						
Comments:						

22.

If yes, what dose do you use as a bolus?

	All	Carotid	Thoracic	EVAR	Aorto-iliac PTA	infra-inguinal
3.000 IU	☐	☐	☐	☐	☐	☐
5.000 IU	☐	☐	☐	☐	☐	☐
Body weight dependend:	☐	☐	☐	☐	☐	☐
Dose:						
Different:						
Comments:						

23.

When during the procudure do you administer the bolus?

24.

If you apply a bolus of heparin or another antithrombotic, do you ever use a repeated dose?

	Answer:
No	☐
Yes depending on duration of procedure	☐
If so, after how long?	
Yes, depending on a measured value	☐
If so, which value?	
Comments:	

25.

Do you measure a value of anticoagulation? please provide details.

26.

What do you prescribe for anticoagulation routinely post-procedure after PTA without stenting?

	All	Carotid	Thoracic	Aorto-iliac PTA	Infra-inguinal
ASA	☐	☐	☐	☐	☐
Clopidogrel	☐	☐	☐	☐	☐
ASA and clopidogrel	☐	☐	☐	☐	☐
VKA	☐	☐	☐	☐	☐
Double dose of LMWH and ASA and/or clopidogrel or VKA:	☐	☐	☐	☐	☐
Heparin iv and ASA and/or clopidogrel or VKA:	☐	☐	☐	☐	☐
Different - comments:	☐	☐	☐	☐	☐

27.

For how long do you prescribe anticoagulant use after PTA without stenting?

	All	Carotid	Thoracic	Aorto-iliac PTA	Infra-inguinal
6 weeks	☐	☐	☐	☐	☐
3 months	☐	☐	☐	☐	☐
6 months	☐	☐	☐	☐	☐
1 year	☐	☐	☐	☐	☐
life long	☐	☐	☐	☐	☐
If ASA and clopidogrel, when will you stop clopidogrel?	☐	☐	☐	☐	☐
Different - comments:	☐	☐	☐	☐	☐

28.

What do you prescribe for anticoagulation routinely post-procedure after PTA with stenting?

	All	Carotl	Thoracic	Aorto-iliac PTA	Infra-inguinal
ASA	☐	☐	☐	☐	☐
Clopidogrel	☐	☐	☐	☐	☐
ASA and clopidogrel	☐	☐	☐	☐	☐
VKA	☐	☐	☐	☐	☐
Double dose of LMWH and ASA and/or clopidogrel or vka:	☐	☐	☐	☐	☐
Heparin iv and ASA and/or clopidogrel or vka:	☐	☐	☐	☐	☐
Different - comments:	☐	☐	☐	☐	☐

29.

For how long do you prescribe anticoagulant use after PTA with stenting?

	All	Carotid	Thoracic	Aorto-iliac PTA	Infra-inguinal
6 weeks	☐	☐	☐	☐	☐
3 months	☐	☐	☐	☐	☐
6 months	☐	☐	☐	☐	☐
1 year	☐	☐	☐	☐	☐

Life long	☐	☐	☐	☐	☐
If ASA and clopidogrel, for how long do you prescribe clopidogrel?					
Different - comments:					

30.

If you use heparin iv directly after procedure, for how long? I

	All	Carotid	Thoracic	EVAR	Aort-iliac PTA	Infra-inguinal
24 hours	☐	☐	☐	☐	☐	☐
3 x 24 hours	☐	☐	☐	☐	☐	☐
Diferent - comments:						

31.

If you use heparin after procedure and start ASA/clopidogrel, what dosage of heparin do you use?

	All	Carotid	Thoracic	EVAR	Aorto-iliac PTA	Infra-inguinal
20.000 IU per 24 hours, pump, no APTT	☐	☐	☐	☐	☐	☐
4 x 5.000 IU per 24 hours, no aptt	☐	☐	☐	☐	☐	☐
APTT 60-90	☐	☐	☐	☐	☐	☐
aptt and desired value 2 x original value.	☐	☐	☐	☐	☐	☐
Different - comments:						

32.

If you use heparin after procedure and start VKA, for how long do you prescribe the heparin?

	All	Carotid	Thoracic	EVAR	Aorto-iliac PTA	Infra-inguinal
24 hours	☐	☐	☐	☐	☐	☐
3 x 24 hours	☐	☐	☐	☐	☐	☐
Till INR 2,5 - 3,5	☐	☐	☐	☐	☐	☐
Different - comments:						

33.

If you use heparin after procedure and start VKAI, what dosage of heparin do you use?

	All	Carotid	Thoracic	EVAR	Aorto-iliac PTA	Infra-inguinal
20.000 IU per 24 hours, pump, no APTT controle	☐	☐	☐	☐	☐	☐
4 x 5.000 IU per 24 hours, no APTT	☐	☐	☐	☐	☐	☐
APTT and desired value 60-90	☐	☐	☐	☐	☐	☐
APTT en desired value 2 x original aptt	☐	☐	☐	☐	☐	☐
Different - comments:						

34.

Do you apply a different protocol for interventions?

- ◯ Yes
- ◯ Yes when stenting
- ◯ No if patient uses ASA or clopidogrel

35.

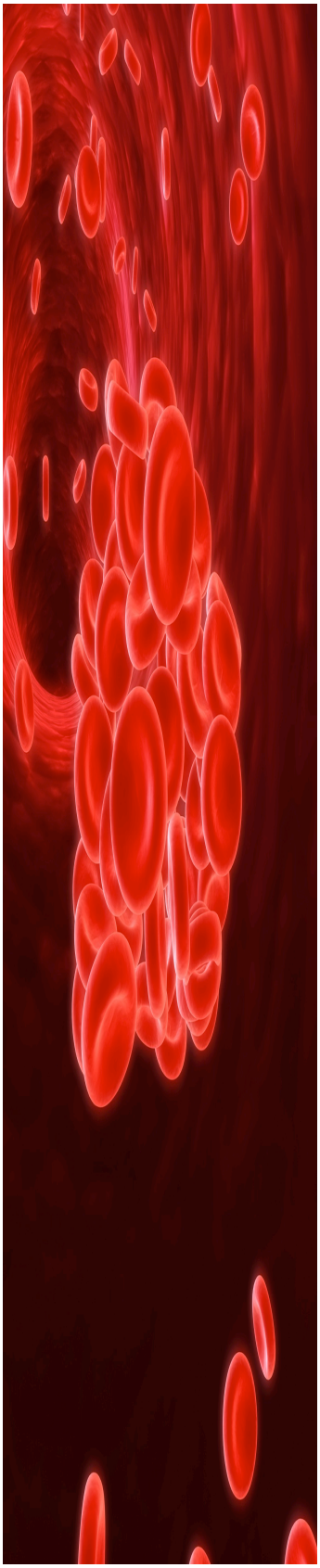
If yes, please details:

36.

If you use aprotocol with or without your vascular surgeon could you send us a copy or depict it here?

37.

Please comment:



Chapter 5

Prophylactic perioperative antithrombotics in open and endovascular abdominal aortic aneurysm (AAA) surgery: a systematic review

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Abstract

Objective

Heparin is used worldwide by vascular surgeons as prophylaxis for arterial thrombo-embolic complications during open and endovascular arterial surgery. Possible harmful effect of heparin use is more perioperative blood loss, resulting in a higher morbidity and mortality. To evaluate the evidence for the use of heparin during aorto-iliac arterial surgery a review was performed.

Methods

A systematic review was performed of literature from MEDLINE, EMBASE and Cochrane databases, last search performed on March 8, 2012.

Results

For open surgery for abdominal aortic aneurysm (AAA), only 5 studies were eligible for review and for endovascular aneurysm repair (EVAR) only 1 study. Overall methodological quality of the included studies was poor. One randomized trial could be retrieved. Possible harmful effects of heparin were found of increasing operation time, more blood loss and more transfusion requirements when heparin was used for open AAA surgery in one study. No data were found comparing heparin to no intervention for EVAR. One study compared heparin to a direct thrombin inhibitor during EVAR, showing no differences in clinical outcomes.

Conclusion

Despite limitations this review showed no compelling evidence on the beneficiary effect of the prophylactic perioperative use of heparin during open surgery for (r)AAA. Authors will promote a randomized controlled multi-center trial on this topic for elective open surgical repair of AAA.

Introduction

Ever since Murray in 1940[1] produced experimental and (sparsely) clinical evidence that heparin could prevent thrombosis during and after arterial reconstructions and embolectomies, local or systemic perioperative heparinisation has been adapted worldwide by vascular surgeons as a standard procedure to reduce perioperative arterial thrombo-embolic complications (ATEC).

However, the possible disadvantages of using heparin during arterial reconstructive surgery were also soon recognised. One of those disadvantages could be increased peri- and post-operative bleeding, possibly resulting in more perioperative blood loss, and necessitating more blood transfusions. The negative side effects of blood transfusions are well recognised.[2,3] Increased blood loss is also related to a prolonged operation time, both independently enhancing infectious complications resulting in increased morbidity and mortality. Especially infected vascular grafts are life and limb threatening.

Another factor complicating the prophylactic perioperative use of heparin during arterial surgery is the unpredictable pharmacokinetic response of individual patients. Heparin has no linear dose-response and elimination curve after the administration of a standard dose.[4] This phenomenon is enhanced by the deregulated coagulation cascade[5,6] in vascular surgical patients. For this reason monitoring the level of anticoagulation produced by heparin is recommended.[4,7] The preferred method is to measure the activated clotting time (ACT), which correlates with the antithrombotic effect of heparin better than the activated partial thromboplastin time (APTT).[8] Nevertheless, measuring heparin activity perioperatively has not gained widespread use.[9]

Since the introduction of heparin 70 years ago only one comparative controlled randomized trial has been performed on the perioperative prophylactic use of heparin in open AAA surgery.[10] Despite this lack of evidence, some guidelines strongly advocate for the use of heparin during open or endovascular AAA surgery. In the 2008 American College of Chest Physicians (ACCP)-guidelines, Sobel et al.[11] stated that level 1A evidence exists for the intraoperative use of heparin for patients undergoing vascular reconstructive surgery. The Society for Vascular Surgery (SVS) guidelines for the care of patients with an abdominal aortic aneurysm[12] state that heparinisation is utilised by almost all vascular surgeons, although no references were supplied. With respect to the use of heparin during endovascular

procedures the Society of Interventional Radiology (SIR) stated in their recent Standards of Practice[13] on EVAR: "Although there are no trial data regarding routine use of intraoperative heparin during EVAR, the open surgical experience with heparinisation has been widely applied to endograft procedures".

Surveys of the use of heparin in daily practice of vascular surgeons and interventional radiologists have been performed throughout Europe,[14,15] the United Kingdom (UK),[16-18] the United States (US).[9,19] They showed a variety in all aspects of the prophylactic use of heparin (and protamine for heparin reversal) perioperatively in reconstructive arterial surgery, both for open and endovascular procedures.

In the course of developing a new evidence based protocol for perioperative anticoagulation during AAA surgery in the Netherlands and before possibly starting a RCT comparing heparin with a direct thrombin inhibitor, literature was searched for evidence on this topic and extensive surveys were performed amongst all Dutch interventional radiologists and vascular surgeons.

To objectively assess the results of these surveys and to assess the beneficial and possibly harmful effects of heparin in open as well in endovascular aorto-iliac arterial surgery, a systematic review and, when possible, a meta-analysis was performed. The present study investigated: 1) Has the perioperative use of heparin or any other antithrombotic drug been proven to have a beneficial effect during open or endovascular abdominal aorto-iliac surgery? 2) Have other pharmaceuticals been compared with heparin (in randomized clinical trials) for open or endovascular abdominal aorto-iliac arterial surgery?

Methods

A systematic review was performed in accordance with the PRISMA 2009 (Preferred Reporting Items for Systematic reviews and Meta-Analyses)[20] and MOOSE (Meta-analysis Of Observational Studies in Epidemiology Group)[21] guidelines.

Search strategy

On February 2, 2011, 2 independent investigators (AW and CB) searched MedLine (from January 1966 to February 2011) and EMBASE (from January 1988 to February 2011) databases and the Cochrane Database of Systematic Reviews (from 1990 to February 2011).

The following combinations of medical subject headings (MESH) were used: iliac aneurysm, Leriche syndrome, abdominal aortic aneurysm, abdominal aorta, iliac artery, surgery, anticoagulants or antithrombotics. No filters or other restrictions were applied. By cross-referencing the bibliographies cited in the included articles, additional studies were identified and assessed for suitability. From all of the studies identified in the search, 2 independent investigators (AW and CB) selected potentially eligible studies according to the information provided by titles and abstracts. Review of materials & methods-sections led to further exclusion of studies. Final inclusion was performed after full-text review. Any disagreement between the investigators was reconciled by a repeated review of the studies in question and consensus was reached. The flowchart for open AAA surgery is presented in figure 1. On October 11, 2011, the same search was performed again, to capture any recent publications. The above method was followed in detail to search for articles concerning EVAR and periprocedural use of anticoagulants and/or antithrombotics. To minimize the risk of missing any articles on this subject, a separate MESH-search was performed using the extension "surgery or endovascular surgery" in the above depicted search strategy. No new hits were found.

Inclusion criteria

This review included (randomized) clinical trials (RCT) and prospective and retrospective case series on open or endovascular abdominal aorto-iliac arterial reconstructive surgery (EVAR, endarterectomy, grafting procedures, or combinations) for both occlusive and aneurismal disease. Studies had to compare patient groups with and without periprocedural arterial thrombosis prophylaxis or to compare heparin prophylaxis with another antithrombotic. Antithrombotic agents had to be administered during operation. Reported outcomes should include postoperative mortality, morbidity from myocardial infarction (MI) or arterial thrombotic complications (ATEC). Data on blood loss and blood transfusion requirements during and immediately after the operation should be evaluated. Only studies reported in English language were included.

Exclusion criteria

Reports with an unsuitable study design (e.g. dose finding studies or lacking a group of patients without antithrombotic prophylaxis) or with surrogate endpoints (e.g. clotting time after heparin administration) were excluded.

Methodological assessment

Two authors (AW and VJ) separately assessed the methodological quality of the included articles. A checklist was used that included the following items:

-) study population clearly defined?

-) sufficient exclusion of selection bias?

-) method of intervention clearly described?

-) outcomes clearly described?

-) independent or blinded observers for data collection?

-) complete follow up for hospital stay up to discharge?

-) detailed information about exclusion criteria and excluded patients?

-) information about confounders available?

To further assess the quality of the selected studies, a system was developed to score the study characteristics. Items selected from studies were: consecutive series of patients reported, prospective or retrospective series, detailed information about surgical procedure, details about heparin and protamine usage, details on blood loss, detailed information on blood transfusions requirements, incidence of MI and ATEC. Differences in assessments between AW and VJ were solved by discussion. A shortcoming in the methodological quality of the study was not an exclusion criterion.

Data extraction

Data were extracted from eligible studies by 2 independent authors (AW and VJ). AW extracted data from included studies using a data extraction sheet, and VJ checked extracted data. Disagreement was followed by repeated review and consensus was reached. Data were labelled as "no details" if they were not reported explicitly in text or tables. Two authors of included studies were contacted by AW to provide further details that were not revealed in the original publication.[22,23]

Standardization of outcome measures

Mortality should preferably be defined as mortality within 30 days of the operation. Morbidity from MI and ATEC should be reported in the same time window as outcome measures. Mortality was death by any cause. Morbidity from MI should preferably be documented by an increase in cardiac enzymes in peripheral blood samples and/or ECG changes or post-mortem findings. ATEC was defined as: any thrombosis or embolism in the arterial vascular system during or after surgery that did or did not require (surgical) intervention, including mesenteric ischemia and trash foot.

Statistical analysis

Statistical analysis was performed using IBM SPSS,[24] version 19. Relative risk with 95% confidence interval was calculated for dichotomous variables. Continuous data were expressed as means and standard deviations. For continuous outcomes, if mean values were not available, medians were used. All analyses were based on intention-to-treat principle.

Results for open AAA surgery

Literature search

A total of 571 studies were identified, of which 502 publications were excluded after evaluation of the title. The remaining 69 were studied by evaluation of abstracts. Two duplicate studies were excluded. No perioperative intervention was performed in 2 studies and no groups with and without heparin or other antithrombotic were present in 15 studies. In 21 publications no open abdominal vascular surgery was examined. No proper endpoints were evaluated in 23 studies. The remaining 6 articles were studied by full-text analysis. It was then found that no groups with or without intervention were present in 3 studies. After adding 2 articles from the reference list of the 3 remaining articles, 5 studies met all criteria for inclusion. See figure 1 for flowchart. Two studies were performed in the United Kingdom, the other studies were performed in Canada, Australia and the United States, respectively.

Characteristics of included studies

The selected reports were published between 1988 and 2008, representing a total study population of 1491 patients. Data were collected prospectively in 3 studies[22,25,26] and

retrospectively in one study.[27] One study concerned a RCT.[10] In all studies intravenous administration of heparin before cross clamping was used and results were compared to a blank control group.

In one study[27] both patients with occlusive aortic-iliac disease (AIOD) as with aneurismal disease were included. Since only a minority of the patients suffered from AIOD (38 AIOD vs. 161 AAA), these were left out of the evaluation in the article and consequently from this review. The 4 other studies[10,22,25,26] concerned only patients with AAA, of which one studied[25] patients with ruptured AAA (rAAA), 2 studies[10,26] included elective repair of AAA and one study[22] combined asymptomatic and symptomatic patients with non-ruptured AAA.

In all studies blood loss and transfusion requirements were assessed to evaluate whether increased bleeding occurred when heparin was used. Overall mortality for the heparin and the no-heparin groups was evaluated in 3 studies and incidence of MI (fatal and non-fatal) for both groups was described in detail in the same 3 studies.[10,25,26] The incidence of ATEC could be retrieved from 4 studies.[10,25-27] Mortality details were reported as data within 30 days of the operation in 3 studies,[10,22,25] details for MI and ATEC within 30 days in 2 studies,[10,25] one study[26] provided the in-hospital data and from one study[27] no details could be retrieved about the time-relation between surgery and postoperative mortality and morbidity. Main patient and study characteristics are shown in table 1a and 1b.

Methodological quality

The results of the quality assessment and the checklist for methodological quality are shown in table 2. Overall methodological quality of the included studies was poor with only one randomized controlled trial.[10] Selection bias was suspected in all other studies[22,25-27] and in 3 studies a selective loss to follow-up could not be excluded.[22,26,27] None of the studies presented details about exclusion criteria and excluded patients. A clear description of confounders could not be retrieved from any of the studies. Only one study[26] offered adequate details about operative technique and antithrombotic dosage. There was substantial clinical heterogeneity between studies, concerning both studied populations and methods of intervention.

Heparin and protamine

Neither the type nor manufacturer of heparin was specified in any of the studies. The protocol for the administration of heparin varied widely between the studies. In 2 studies[25,27] administration of heparin was up to surgeon's preference, with 3 surgeons using heparin as a standard procedure and 2 surgeons not using heparin. In the randomised study,[10] the options were local surgeon's normal intra-operative heparin regimen or no heparin at all. Using heparin selectively for multiple pre-defined reasons was protocol in one study[26] and in another study the use of heparin was according to local hospital protocol,[22] which resulted in 85% of patients receiving heparin.

In all studies heparin was administered intravenously (i.v.), with a standard dosage of 5000 IU in 3 studies,[10,25,26] irrespective of patient weight. In one study[22] no details were given about dosage and in one study[27] 5000, 7500 and >7500 IU were used (in 35, 85 and 5 patients respectively), related to length of operation.

Heparin was administered before cross-clamping of the aorta in 4 studies,[10,22,25,27] with one study[27] specifying administration of heparin 3 minutes before cross clamping. In one study[26] wherein next to preoperative also *per*operative indicators were used for selective administration of heparin it was administered after cross clamping in 10 patients. Repeated doses of heparin were given in one study "if clotting became a problem during prolonged procedures".[27] No further details could be retrieved about this repeated dose.

In 4 studies protamine was used to reverse the anticoagulation effect of heparin.[10,22,26,27] In one study wherein heparin was administered in a standard dose of 5000 IU, protamine 50 mg was used uniformly for reversal of heparin.[26] If post-reversal bleeding took "longer than expected" the ACT was measured and more protamine (usually 10 mg) was given. In 2 other studies the dose of protamine had to be sufficient to reverse one-half of the given heparin.[10,27] In one of these studies this resulted in a standardised dose of 25 mg in only 13/145 patients (9%)[10] and in the other study protamine was given "in most instances in a dose usually sufficient to reverse one-half of the administered heparin".[27] In some patients who had short clamping times (no number retrieved), the entire heparin dose was reversed. From the remaining 2 studies[22,25] no details could be retrieved whether protamine was used or not. In personal communication between AW with the first author of one of these publications,[22] it was established that during that study "most often (at individual surgeon's preference), protamine

was given after completion of the arterial reconstruction at a dose of 50-100 mg, depending on the original dose of heparin. The usage of protamine was not APTT related".

Operative details

The abdominal aorta was cross clamped above the renal arteries in 45 patients (6.8%) in one study[22] and in 38 patients (37%) in another study.[26] When suprarenal clamping was indicated, heparin use was mandatory.[26] No differences in outcomes between heparin or no-heparin groups and level of cross clamping could be retrieved from these studies. In the other 3 studies[10,25,27] the site of cross clamping was not specified.

In the study by Johnston et al.[22] the average cross clamping time of the abdominal aorta was 55 ± 31 minutes (min). No differences in outcomes could be identified between the heparinised and non-heparinised groups related to clamp times. Clamp times over 70 minutes were associated with a higher incidence of postoperative MI, but there was no difference in mortality. Furthermore there was no significant difference in the incidence of cardiac events and mortality between suprarenal and infrarenal clamping. The other studies did not address the details of aortic cross clamping time. Thompson et al.[10] did not depict cross clamping times, but the operation time in heparinised patients was slightly longer than non-heparinised cases (120 vs. 105 min). This trend just escaped statistical significance (P=0.06). In the study of Samson et al.[26] clamping time over one hour was a separate indication for administering heparin (2 patients). They too found operation time in heparinised patients to be longer than in non-heparinised patients for the group treated with tube grafts (median 150 min vs. 132 min, P<0.004).

Blood loss

Two subsets of patients showed a statistically significant difference for blood loss in favour of no-heparin usage. One subset constituted those treated with a tube graft in the study by Samson et al.[26] However in this group operation time was substantially less than in the group with heparinised patients with tube grafts. In an attempt to nullify the variability of blood loss with the duration of the operation, Burnett et al.[27] grouped their patients into 3 operation time periods (<2.5 h, 2.5-3.5 h and > 3.5 h) and analysed the relationship between blood loss and heparin dose for these groups. Dose categories were 0, 5000 IU, 7500 IU and > 7500 IU of

heparin. Only within the shortest operation time group (< 2.5 hrs) a meaningful comparison could be made. In this group, mean blood loss increased significantly with each increment of heparin (P<0.05). Increased operation time, however, was statistically significantly associated with increased blood loss for each heparin dose category (P<0.05). In this study, heparin increased blood loss by a significant amount (P<0.05) in both the tube and bifurcated graft group; heparin increased operation time only in the tube graft group.

The other 3 studies did not find a statistically significant difference in median blood loss between heparinised and non-heparinised patients.[10,22,25] However, Chinien et al.[25] encountered clinically significant blood loss (defined as blood loss over 5000 ml) in only 1 heparinised patient compared to no less than 12 non-heparinised patients. This counter-intuitive finding betrays a grave selection bias in their population of patients with ruptured AAA, massively bleeding patients apparently being spared of ill-advised heparin administration. For details on blood loss, see table 3a.

Transfusion requirements

In accordance with their finding concerning intraoperative blood loss in heparinised and non-heparinised patients receiving tube grafts, Samson et al.[26] found that the non-heparinised patients were significantly less likely to require cell-save transfusions and postoperative blood transfusions (P<0.004) when a tube graft was implanted. These differences were not noted for patients treated with bifurcated grafts. However, the study included 189 tube grafts and only 50 bifurcated grafts.

Three studies[10,22,25] stated that no difference was found in the transfusion requirements of heparinised and non-heparinised patients without providing detailed information. One study did not mention transfusion requirements at all.[27] Details on transfusion requirements are depicted in table 3a.

Overall mortality

All cause mortality is shown in table 3b. The study by Chinien et al.[25] (concerning only patients with rAAA) showed a statistically significant difference in favour of heparin in case of rAAA (n=10 vs. n=29: 16% vs. 43%, RR 0.37, 95% CI 0.16-0.85). This finding however is heavily biased by the fact that hemodynamically unstable patients were cross-clamped as

quickly as possible, even before heparin could be given. Samson et al.[26] found mortality to be higher in heparinised patients (n=4 vs. n=1: 3.9% vs. 0.7, RR 5.67, 95% CI 0.62-51.49) while Thompson et al.[10] found it to be lower (n=6 vs. n=11: 4.1% vs. 7.9%, RR0.52, 95% CI 0.19-1.45). These differences for mortality between heparin or no-heparin groups in both studies were not statistically significant. The other 2 studies either did not report mortality at all[27] or did not report mortality separately for heparinised and non-heparinised patients.[22]
As far as this last study concerns it was learned in personal communication that intraoperative heparin use did not influence mortality.[22]

Myocardial infarction

The overall incidence of MI is depicted in table 3b. Chinien et al.[25] found in their study on ruptured AAA post-operative cardiac ischemia to be present in 9 (15%) patients in the heparin group compared to 5 (10%) in the no-heparin group. A fatal MI was diagnosed in 1 (of 63, 1.6%) and 2 (of 68, 2.9%) patients in the heparin and no-heparin groups, respectively. In total fatal and non-fatal MI in 10 (16%) of heparinised patients compared to 7 (10%) in non-heparinised patients (RR 1.54, 95% CI 0.55-4.33). This is remarkable since it is very probable that hemodynamically unstable patients ended up in the no-heparin group by selection bias. In the study by Samson et al.,[26] no non-fatal MI was observed in either group. In the heparin group 3 patients (2.9%) died of a fatal MI, while no non-fatal MIs occurred in the no-heparin group. Thompson et al.[10] reported that 1 (out of 145) patient in the heparin group and 4 (out of 139) patients in the no-heparin group developed a non-fatal MI. Fatal MI was diagnosed in 2 (out of 145) patients in the heparin group and in 8 (out of 139) patients in the no-heparin group (RR 0.24, 95% CI 0.05-1.15). Addition of fatal and non-fatal MI in both groups resulted in a statistically significant difference (n=3 vs. n=12: RR 0.24, 95% CI 0.07-0.87) in favour of the heparinised group. Concerning this major outcome of more cardiac events in the no-heparin group, Thompson et al.[10] stated themselves: “As this surprising result [of less MI in the heparin group, AW] was serendipitous and outside the original study design, no stratification for cardiac risk factors was available for analysis, but in view of the large numbers in the two categories it is felt that the groups should be comparable”. No details on MIs for heparin or no-heparin groups could be retrieved from the studies by Burnett et al.[27] and Johnston et al.[22] In personal communication between Johnston and AW, it was stated by

Johnston that they did not observe a difference in the number of MI between heparinised and non-heparinised groups.

Arterial Thrombo-Embolic complications (ATEC)

Overall incidences of ATEC for all studies are shown in table 3b. In the study on rAAA by Chinien et al.[25] embolectomy after completion of surgery was necessary in 5 patients (8%) from the heparin group and in 8 (12%) patients from the no-heparin group. When patients who died intra-operatively were excluded, these figures were 8% for the heparin group versus 14% for the no-heparin group Other ATECs in both groups were listed as: stroke (4), limb-ischemia (5), bowel ischemia (8) and paraplegia (2), all showing no statistically significant difference between heparin and no-heparin group (All ATECs: n=14 vs. n=18: RR 0.84, 95% CI 0.38-1.87). In the study of Samson et al.[26] one non-heparinised patient receiving a tube graft died 2 months after operation because of colonic ischemia and respiratory failure, and another non-heparinised patient developed colonic ischemia without necessitating surgical treatment. In the heparin group they found one athero-embolic event that resolved spontaneously without tissue loss. Distal embolectomy was performed in 4 patients, 2 from the heparin group and 2 from the no-heparin group (one embolus was plaque material). All together 3 (2.9%) ATECs in the heparin-group vs. 4 (2.7%) in the no-heparin group (RR 1.06, 95% CI 0.23-4.84). In the study by Thompson et al.[10] 3 patients from the heparin group versus 8 patients from the no-heparin group underwent embolectomy to remove a distal thrombus (2.1% vs 5.8%: RR 0.36, 95% CI 0.09-1.39). Furthermore athero-emboli, responding well to conservative treatment, occurred in 4 and 3 patients in the heparin and no-heparin group respectively. Total: n=7 vs. n=11, 4.8% vs 7.9%: RR 0.61, 95% CI 0.23-1.62. Out of the 161 patients in the study by Burnett et al.,[27] 6 (3.7%) patients, all from the heparin group, suffered distal ischemic episodes: 4 cases of micro-embolic trash syndrome involving the feet, for which no operation or amputation was necessary and 2 cases of major vessel occlusion treated with embolectomy. Johnston et al.[22] stated in personal communication with AW, that they found no statistically significant differences between heparinised and non-heparinised groups for graft thrombosis, atheromatous embolization, distal thrombosis or amputations; further details were not provided.

Meta-analysis

A pooled meta-analysis of the above-described results was considered not justified because of the quality of included studies, heterogeneity in and between studies and detected bias towards the use of heparin.

Results for endovascular AAA surgery

Literature search

There were no publications found concerning EVAR wherein one group of patients did receive perioperative arterial thrombosis prophylaxis and another group did not. One study was found wherein 2 prophylactic antithrombotic agents were compared.[23] This study compared UFH with bivalirudin (a direct thrombin inhibitor) during EVAR.

Characteristics of study

Details are depicted in table 1 and 3. The selected study was conducted in the USA, published in 2009 and included EVAR performed between March 1994 and November 2006 (N=740 consecutive patients). It was a retrospective data analysis out of a prospectively maintained database. In this study the perprocedural use of UFH (n=642) was compared to the use of bivalirudin (n= 98) in elective AAA patients. Procedural outcomes were scored according to the reporting standards for endovascular aortic aneurysm repair.[28] Major complications, minor and major bleeding complications and the need for transfusions were retrieved. Details on death and MI were not reported.

Methodological quality

Details and score for study quality are depicted in table 2. No randomization was performed for heparin or bivalirudin. The choice of anticoagulant was left to the discretion of the interventionists and no specific guidelines were supplied for this choice hereby creating selection bias. No detailed description of confounders was retrieved from article.

Heparin and bivalirudin

Heparin was administered i.v. as a bolus of 100 IU/kg before placement of arterial sheath and bivalirudin i.v. as a bolus of 0.75 mg/kg followed by continuous infusion of 1.75 mg/kg/hr for

the duration of the procedure. No (details on) measurements of anticoagulation values were depicted for either heparin, or bivalirudin.

Operative details

Types of anaesthesia and arterial access differed for both groups: 39.8% (n=39) of patients from the bivalirudin group was operated under general anaesthesia compared to 20.1% (n=129) from the heparin group: RR 1.98, 95% CI 1.25-3.10. For the use of regional anaesthesia these numbers were: 48 patients from the bivalirudin group (49%) and 462 from the heparin group (72%): RR 0.68, 95% CI 0.44-1.05. Arterial access in the combination of cut down/percutanous was used in 12 (12.2%) of patients in the bivalirudin group and in 238 (37.1%) from the heparin group: RR 0.33, 95% CI 0.18-0.62. These differences were also included into the above mentioned multivariable regression model for the evaluation of results.

Blood loss and blood transfusion

Details are depicted in table 3a. No statistically significant difference could be calculated for any types of blood loss and any blood transfusion categories.

Overall mortality and myocardial infarction

No specific details could be retrieved on in-hospital or 30-days mortality. These patients are included in the major complications grade 3. For the total percentage of these complications, no statistically significant difference could be calculated between the heparin and bivalirudin groups: n=25 vs. n=2, 4% vs. 2%: RR 0.5, 95% CI 0.12-2.14.

No specific details on (fatal and non-fatal) MI could be retrieved from article. These patients are included in major complications grade 1, 2 and 3. For grade 2 and 3 no statistical significant difference could be calculated, but for grade 1 the difference was statistical significant in favour of the bivalirudin group: 12.2% versus 25.1% (n=12 vs. n= 161, RR 0.49, 95% CI 0.26-0.92). The definition of grade 1 cardiac complications however is: little or no hemodynamic consequences.

Arterial Thrombo-embolic complications (ATEC)

Only 1 of 21 (1.5%) major complications could be attributed to ATEC in the bivalirudin group (n=98) compared to 12 of 247 (1.9%) in the heparin group (n=642): RR 0.79, 95% CI 0.10-6.17.

Discussion

Since the clinical introduction of heparin more than 70 years ago for the "prevention of thrombosis when operation for repair of blood vessels is undertaken",[1] this concept has never been really challenged. Inventories concerning perioperative arterial thrombosis prophylaxis in open reconstructive arterial surgery showed a wide variety of regimens amongst vascular surgeons throughout the world for the past 20 years.[9,14-17] This variety also exists for arterial endovascular procedures.[18,19] To assess the efficacy of this prophylaxis in open or endovascular aorto-iliac arterial surgery the CAPPA study group from the Netherlands performed a systematic review of the literature on this subject.

For open aorto-iliac surgery only 5 studies[10,22,25-27] could be included in this review. The overall methodological quality of the included studies was poor. Only one randomized trial[10] could be retrieved. Clinical heterogeneity between studies was detected, concerning both studied populations and methods of intervention. All studies used heparin as a prophylactic antithrombotic drug. Only 2 studies reported detailed information about the usage and dosage of protamine for the reversal of heparin.[10,26]

Two studies[26,27] reported significantly more blood loss and a longer operation time in heparinised patients treated with tube grafts and one of these studies[27] found that blood loss increased when heparin dosage increased. Statistically significantly more blood transfusions were needed in heparinised patients compared to non-heparinised patents in one study.[26] One study[25] (on rAAA) reported a lower operative mortality in heparinised patients (n=10 vs n=7, 16% vs. 43%: RR 0.37, 95% CI 0.16-0.85). This finding appears heavily biased because particularly unstable patients ended up in the non-heparinised group because their aortas were hurriedly cross-clamped before heparin could be administered. In addition, senior registrars began operations in these patients prior to the arrival of a consultant surgeon. These facts

readily could explain the signalled difference in mortality between heparinised and non-heparinised patients in this study. The other 4 studies[10,22,26,27] did not report statistically significant differences between heparinised and non-heparinised patients for non-fatal MI, fatal MI or operative mortality. However, in the RCT,[10] the combination of fatal and non-fatal MIs proved to be significantly more frequent in non-heparinised patients (n=3 vs. n=12, 8.6% vs. 2.0%: RR 0.24, 95% CI 0.07-0.87). This outcome was, however, outside original study design and the distribution of cardiac risk factors over both groups was unknown. Therefore, this difference could result from over-presentation of patients prone to cardiac ischemia in the non-heparinised group. Furthermore, this study excluded patients taking ASA thereby excluding the cardio-protective effect of ASA perioperatively. In all included studies no statistically significant differences were found for the incidence of ATEC between heparin and no-heparin groups.

A meta-analysis could not be justified, because of the quality of the included studies, the detected heterogeneity in and between studies and the bias found to be present in studies.

No studies comparing heparin with no-heparin were found in literature for EVAR nor studies comparing another antithrombotic than heparin to a no-antithrombotic group of patients. The only study that could be included was a retrospective, non-randomized analysis of a small group (N=98) receiving bivalirudin and a larger group (N=642) receiving perprocedural heparin.[23] No significant reduction in bleeding complications or blood transfusions was observed. Also mortality and incidence of MI and ATEC were not statistically significant different. Thus, a reduction of bleeding complications when using a direct thrombin inhibitor (bivalirudin) instead of heparin, as documented for coronary and peripheral endovascular procedures,[29,30] could not be established for EVAR.

The present systematic review has several limitations. A small number (5) of studies was eligible for open AAA surgery and only 1 for EVAR. Moreover the studies for open AAA surgery were published over a time period of 20 years. In those 20 years the perioperative care of the vascular surgical patient has improved considerably, resulting in better outcomes for AAA patients undergoing surgery. For example, the introduction of statins and the increased use of beta-blockers nowadays in the perioperative period may influence the

incidence of MI. Methodological quality of the studies was poor, numbers of patients studied relatively small and there was significant clinical heterogeneity between studies.

Despite these limitations this systematic review showed no sound evidence on the beneficial effect of the prophylactic perioperative use of heparin during open surgery for (r)AAA. This review showed that possible harmful effects of increased operation time, more blood loss and greater transfusion requirements when heparin was used in open surgery could be present. Clearly 70 years after its introduction into clinical practice, there is no compelling evidence for the efficacy of the perioperative use of heparin in open AAA surgery. For EVAR no trial data could be found comparing heparin to no-heparin. Despite promising results of direct thrombin inhibitors in cardiovascular surgery and endovascular coronary- and peripheral interventions, no studies could be found on these drugs during open AAA surgery. During EVAR a direct thrombin inhibitor (bivalirudin) showed no clear benefit compared to heparin in one retrospective study. The CAPPA study group will promote a randomized controlled multi-center trial of the open elective surgical repair of AAA and the use of heparin versus no-heparin and possibly versus a direct thrombin inhibitor before aortic cross clamping. Hypothesis of such an RCT could be a reduction of 30% of blood loss, a 50% reduction of blood transfusion and a 50% reduction in bleeding related wound complications. A power calculation based on these premises showed that we would need 197 patients with open AAA repair in each group for heparin or no-heparin ($\alpha = 0.05$ and $\beta = 0.10$). For EVAR a 50% reduction of blood transfusion would require 85 patients per group for heparin or no-heparin.

In conclusion this systematic review showed that there is no concluding evidence on the beneficiary role of heparin in open and endovascular AAA surgery.

Figure 1.

Flowchart of literature search.

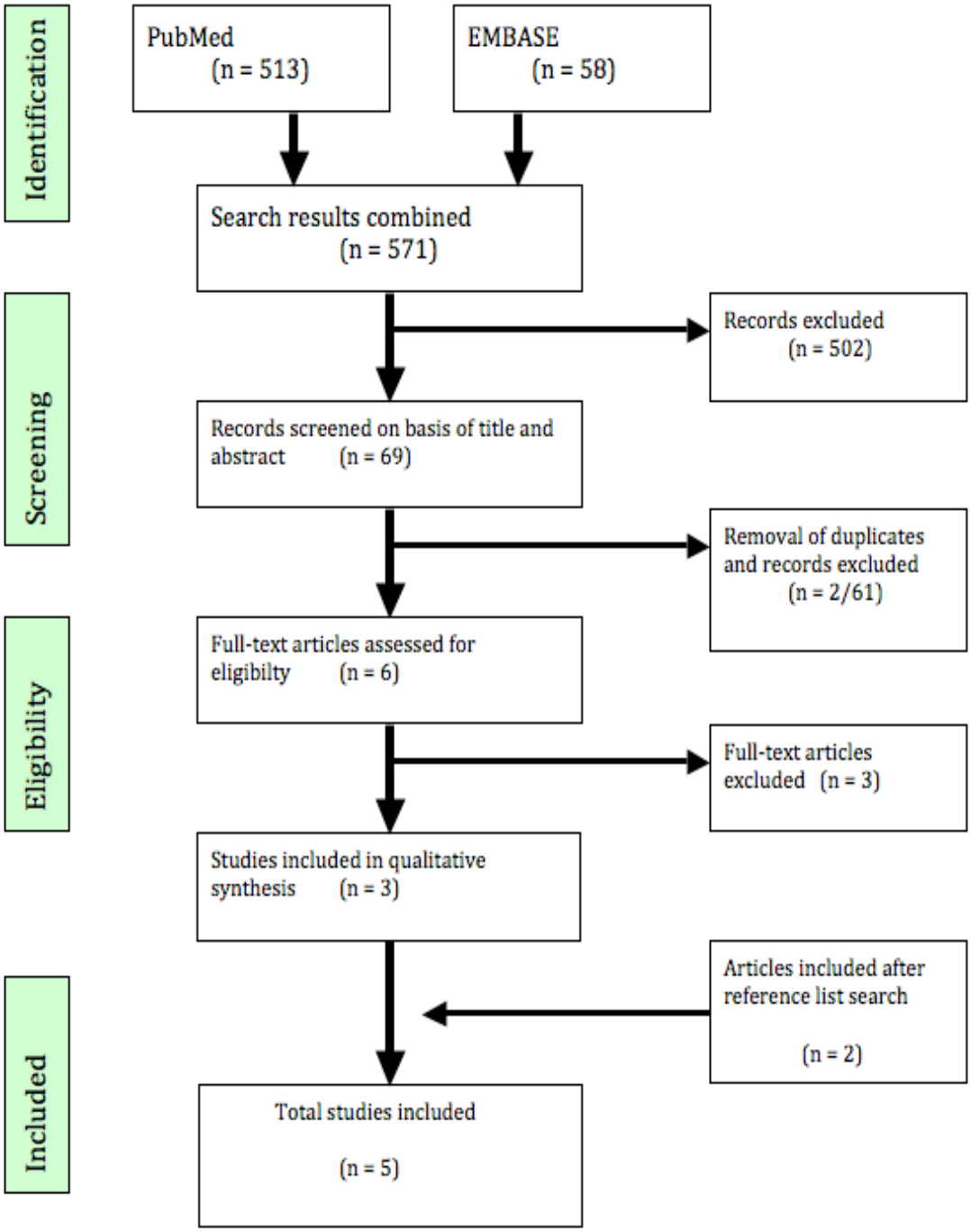

Table 1a.

Main patients and study characteristics for open and endovascular AAA surgery.

Authors, Year	Study design	# of patients	Male / Female	Age in years
Chinien et al. 2008 rAAA	Prospective data collection Jan. 1999-jan. 2004 Use of heparin up to surgeon's preference.	131	hep +: 78 % / 22 % hep -: 79 % / 21 % 79 % / 21 %	hep +: 75 (median, 54-86) hep -: 75 (median, 53-87)
Samson et al. 2002	Prospective data evaluation Study period not stated Selective use of heparin.	249	86 % / 14 %	73 (median, 46-93)
Thompson et al. 1996	Randomised prospective multi-center trial Study period not stated. Randomized, sealed envelop. Surgeon's normal intraoperative heparin or no-heparin.	284	hep +: 82 % / 18 % hep -: 88 % / 12 %	no details retrieved
Burnett et al. 1988	Retrospective data analysis Jan 1984-June 1986 2 surgeons using heparin, 1 no heparin	161	92 % / 8 %	66 (median, 56-88)
Johnston et al. 1988	Prospective data collection multi-center March 1986-Dec. 1986 Heparin use local hospital protocol.	666	80 % / 20 %	69.2 (mean, +/- 7.7)
Total open AAA		1 491		
Stamler et al. 2009 EVAR	Prospective data collection March 1994 -November 2006 Use of heparin or bivalirudin up to interventionalist' preference.	740	heparin: 88 % / 12 % bivalirudin: 91 % / 9 % 90 % / 10 %	heparin: 75.7 (mean ± 7.7) bivalirudin: 76.1 (mean ± 7.5)
Total EVAR		740		

Table 1b.

Main patients and study characteristics for open and endovascular AAA surgery.

Authors, Year	Type of disease	Heparin +/-	Protamine use in heparin group
Chinien et al. 2008 rAAA	rAAA	63 / 68 Standard dose 5 000 IU	No details
Samson et al. 2002	AAA	103 / 146 Standard dose 5 000 IU	+ : 100 %
Thompson et al. 1996	AAA	145 / 139 Standard dose 5 000 IU	13/145 (9%)
Burnett et al. 1988	AAA	125 / 36 No details on dosage 5 000 - > 7 500 IU	+ : no details "most instances"
Johnston et al. 1988	AAA	566 / 100 Dose not stated	+ : no details "most often"
Total open AAA		1 002 / 489	
Stamler et al. 2009 EVAR	EVAR for AAA elective	642 / 98 (heparin/bivalirudin)	None

Table 2.

The results of the quality assessment and the checklist for methodological quality for both open and endovascular AAA

Author	Year	Study Population	No selection bias	Method of intervention	Description of outcomes	Independent observers	No selective loss to FU	Description of confounders	Details on exclusion criteria and excluded patients
Chinien	2008	+	-	+/-	+	-	-	+/-	-
Samson	2002	+	-	+	+	-	-	+/-	-
Thompson	1996	+	+	-	+	-	+	+/-	+/-
Burnett	1988	+/-	-	+/-	+/-	-	+	+/-	-
Johnston	1988	+	-	-	-	-	-	-	-
Stamler	2009	+	-	+	+/-	-	+	+/-	-

Author	Year	Consecutive series of pt.	Prospective series of pt.	Surgery details	Heparin details	Blood loss details	Transfusion details	Myocardial infarction	ATE events details	Total Score (maximum = 16)
Chinien	2008	0	2	0	0	2	1	2	2	9
Samson	2002	0	1	2	1	2	2	2	2	12
Thompson	1996	0	2	1	0	2	2	2	2	11
Burnett	1988	2	1	0	1	2	0	0	1	7
Johnston	1988	2	2	1	0	1	1	0	0	7
Stamler	2009	2	0	2	2	2	2	0	1	11

0 = no details retrieved from study 1 = incomplete details retrieved 2 = complete details retrieved

Table 3a.

Results for open and endovascular AAA surgery.

Authors, Year	Blood loss median value heparin + / -	Blood transfusion details heparin + / -				
Chinien et al. 2008 rAAA	2 000 / 2 500 ml. P = NS	P = NS, no further details				
Samson et al. 2002	Tubegraft: 1 350 / 700 ml. P < 0.004 P < 0.004	cell saver: 600 / 250 ml P < 0.004	post-operation: 11.9 % / 3.8 %			
	Bifurcated graft: 1 200 / 775 ml. P = NS	500 / 500 ml P = NS	11.4 % / 6.3 % P = NS			
Thompson et al. 1996	1 400 / 1 500 ml. P = NS	3-6 / 4-6 units P = NS				
Burnett et al. 1988	2 270 / 280 ml. (mean value) P < 0.05	no details				
Johnston et al. 1988	P = NS "no difference"	P = NS "no difference"				
	Blood loss: retroperitoneal bleeding/hematoma heparin/ bivalirudin	**Blood loss:** minor bleeding heparin/bivalirudin	**Blood loss:** major bleeding heparin/bivalirudin	**Blood transfusion:** PRBC heparin/bivalirudin	**Blood transfusion:** any heparin/bivalirudin	**Blood transfusion:** > 2 heparin/bivalirudin
Stamler et al. 2009 EVAR	0.3% / 1% n=2 / n=1	14% / 12% n=90/ n=12	14 % / 10 % n=91 / n=10	12 % / 16 % n=79 / n=16	8 % / 6 % n=50 / n=6	11 % / 13 % n=68 / n=13
	RR 3.28 (95% CI 0.29-36.52)	RR 0.87 (95% CI 0.46-1.66)	RR 0.72 (95% CI 0.36-1.44)	RR 1.33 (95% CI 0.74-2.39)	RR 0.79 (95% CI 0.33-1.89)	RR 1.25 (95% CI 0.66-2.36)

Table 3b.

Results for open and endovascular AAA surgery.

Authors, Year	Overall mortality heparin + / -	Myocardial infarction (≈) heparin + / -	Arterial thrombo-embolic complications heparin + / -
Chinien et al. 2008 rAAA	16 % / 43 % (*) n=10 / n=29 RR 0.37 (95% CI 0.16-0.85)	16 % / 10 % (*) n=10 / n=7 RR 1.54 (95% CI 0.55-4.33)	22 % / 27 % (*) n=14 / n=18 RR 0.84 (95% CI 0.38-1.87)
Samson et al. 2002	3.9 % / 0.7 % (‡) n=4 / n=1 RR 5.67 (95% CI 0.62-51.49)	2.9 % / 0 % (‡) n=3 / n=0 2.9 (95% CI 0.76-8.90) 0 (95% CI 0-3.2)	2.9 % / 3.4 % (‡) n=3 / n=4 RR 1.06 (95% CI 0.23-4.84)
Thompson et al. 1996	4.1 % / 7.9 % (*) n=6 /n=11 RR 0.52 (95% CI 0.19-1.45)	2.0 % / 8.6 % (*) n=3 / n=12 RR 0.24 (95% CI 0.07-0.87)	4.8 % / 7.9 % (*) n=7 / n=11 RR 0.61 (95% CI 0.23-1.62)
Burnett et al. 1988	No details retrieved	No details retrieved	4.8 % / 0 % n=6 / n=0 4.8 (95% CI 1.97-10.60) 0 (95% CI 0-12.01)
Johnston et al. 1988	"No difference" Total for heparin + and -: 4.8 % (*)	"No difference"	"No difference"
(≈) = fatal and non-fatal	(*) = 30 days post-operative	(‡) = in hospital	
	Overall mortality heparin/bivalirudin	**Myocardial infarction** heparin/bivalirudin	**Arterial thrombo-embolic complications** heparin/bivalirudin
Stamler et al. 2009 EVAR	No statistically significant difference No details retrieved (*)	No statistically significant difference No details retrieved (*)	1.9 % / 1 % (*) n=12 / n=1 RR 0.79 (95% CI 0.10-6.17)

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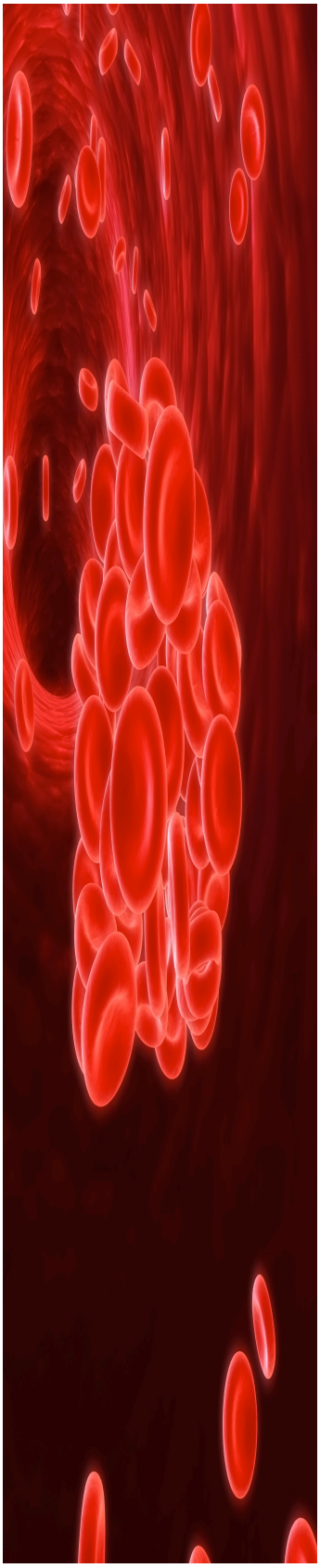

Chapter 6

Prophylactic intraoperative antithrombotics in open infrainguinal bypass surgery (IABS): a systematic review

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Abstract

Background

Unfractionated heparin (UFH) is used intra-operatively as antithrombotic by most vascular surgeons worldwide during infra-inguinal bypass surgery (IABS) to reduce the risk of peroperative and early graft thrombosis. To reduce the harmful side effects of UFH (bleeding complications, HIT) and to reduce peroperative and early graft failure, other pharmaceuticals have been suggested for IABS.

Methods.

A systematic review was performed using MEDLINE, EMBASE and Cochrane databases.

Results.

Only 9 studies on IABS and intra-operative antithrombotic use were eligible for review. Between studies heterogeneity was high and investigated study populations were often of small size. No study was retrieved comparing UFH to no-UFH. Dextran, human antithrombin and iloprost showed no beneficial effect compared to UFH alone for patency, mortality and morbidity. Low molecular weight heparin (LMWH) has potential benefits compared to UFH, but a statistically significant effect could not be demonstrated from the current review.

Conclusion

The use of UFH during IABS to prevent intra-operative graft thrombosis has not been proven in randomized clinical trials. Dextran, human antithrombin and iloprost showed to be of no added beneficial effect for the patient compared to UFH alone. Data on the use of LMWH instead of UFH are promising, but no statistically significant benefit could be reproduced from literature. Results from a recent Cochrane review were favourable for LMWH, but it appeared that included data were not complete in that review. Randomized controlled trials are required for intra-operative use of antithrombotics and to improve peroperative and early patency after IABS.

Introduction

Infrainguinal arterial bypass surgery (IABS) for patients with peripheral arterial occlusive disease (PAOD) carries a high risk of peroperative and early postoperative arterial thrombosis (5-35%). This risk of this graft failure is determined by several factors: a more distal acceptor artery for anastomosis; poor in- or outflow; the use of prosthetic grafts (in the absence of suitable vein grafts) and disturbance of haemostasis caused by surgery and enhanced thrombogenicity in the vascular patient during IABS. To reduce this risk of peroperative and early arterial thrombosis, unfractionated heparin (UFH) has been used as an antithrombotic during IABS since its clinical introduction approximately 70 years ago. Goal of intra-operative antithrombotics is to reduce peroperative graft failure and to ensure an open infrainguinal bypass graft during and immediately after surgery. An acute occlusion (<72 hours after surgery) of an infrainguinal graft can be caused by technical problems, on which prophylactic intraoperative antithrombotics have little or no influence. However, an acute per- or postoperative occlusion can also be caused by small thrombus formation during surgery. This can occur proximally and distally of arterial clamps and in the graft itself. Those small thrombi can grow and cause thrombosis of the bypass graft. This process can be decreased or prevented when prophylactic intraoperative antithrombotics are administered. So to create the foundation for an open infrainguinal bypass graft with long-term patency, prophylactic intraoperative antithrombotics are essential, followed by postoperative antithrombotic therapy.

A study group was instituted in the Netherlands (CAPPA: Consensus on Arterial PeriProcedural Anticoagulation). This group was formed with active participation of the Boards of Dutch Vascular Surgery and Interventional Radiology. Ultimate goal of the CAPPA group is to develop new, evidence-based guidelines regarding the peri-procedural prophylactic use of antithrombotics (AT) during arterial procedures (open and endovascular). An extensive survey amongst vascular surgeons in the Netherlands has been performed.[1] Results showed that all Dutch vascular surgeons use UFH during IABS, comparable with results from other countries.[2-4] A recent systematic review on the use of UFH in open repair of abdominal aortic aneurysm (AAA) by the CAPPA group, however did not produce compelling evidence for the beneficial effect of UFH.[5] Furthermore there is no consensus

regarding dosage, routing or timing of UFH as arterial thrombotic prophylaxis.[6] On top of that, especially the last decades, disadvantages of UFH became apparent: UFH does not inhibit thrombin bound to fibrin, it has an unpredictable non-linear dose-response curve in patients and UFH causes rather frequently formation of heparin-associated antiplatelet antibodies leading to enhanced coagulability of the blood and in more severe form to life and limb threatening heparin-induced-thrombocytopenia (HIT) syndrome.[7] The clinically obvious major harmful side effect of UFH is the higher bleeding tendency, causing more bleeding complications such as more blood loss, higher transfusion needs and serious local wound complications possibly resulting in infected grafts. Because of these harmful side effects of heparin, other pharmaceuticals to prevent early bypass thrombosis have been tested like dextran,[8-10] iloprost,[11-13] human antithrombin,[14] and low-molecular-weight-heparin (LMWH).[15-17] Recently, newly developed direct-thrombin-inhibitors have been tested for their safety in IABS.[18,19] Most current guidelines on the treatment of peripheral arterial disease do not include an advise on intraoperative prophylactic antithrombotics,[20-22] possibly because current guidelines only include level 1 evidence. In the 2008 ACCP guidelines by Sobel et al.,[23] it was stated that "UFH should be administered before application of cross-clamps in a dose of 100-150 IU/kg iv and supplemented every 45-50 minutes with 50 IU/kg". The only reference from literature in this guideline is the study by Norgren et al.[17] This study is discussed in detail in the current systematic review.

We performed a systematic review to assess the possibly beneficial and harmful effects of intra-operative use of UFH or other pharmaceuticals in open IABS in patients with chronic PAOD.

Methods

This systematic review was performed in accordance with the PRISMA[24] and MOOSE[25] guidelines.

Search strategy

On July 18, 2012, 2 independent investigators (AW and CB) searched MedLine (from January 1966 to July 2012) and on July 22, 2012 EMBASE (from January 1988 to July 2012)

databases and the Cochrane Database of Systematic Reviews (from 1990 to July 2012). The following combinations of medical subject headings (MESH) were used: anticoagulants/therapeutic use, vascular patency, vascular surgical procedures, lower extremity. No filters or other restrictions were applied. By cross-referencing the bibliography cited in the included articles, additional studies were sought and assessed for suitability for review. From all studies identified by our search 2 independent investigators (AW and CB) firstly selected possible eligible studies according to the information provided by titles and abstracts. Then review of materials & methods-sections of this selection, led to further exclusion of studies. Final inclusion was performed after full-text review. In case of disagreement between investigators, this was reconciled by repeat review of the studies in question and consensus was reached. On May 17, 2013, the same search was performed again, to capture any recent publications. No new hits were found.

Inclusion criteria

This review included RCTs and also prospective and retrospective case series on open IABS for chronic PAOD. Studies on acute occlusions (contrary to elective IABS for chronic PAOD) were excluded because this has to be considered a different pathophysiologic entity in which antithrombotics are considered necessary because of acute hypercoagulability. Studies on IABS had to compare patient groups with and without periprocedural arterial thrombosis prophylaxis or to compare 2 antithrombotics. Antithrombotic agents had to be administered during operation. No restrictions for inclusion were used concerning post-operative anticoagulation protocols. Reported primary outcomes should include detailed information on primary patency and per- and postoperative mortality and morbidity. The latter should include details on myocardial infarction (MI) and (major) amputations. Data on blood loss and blood transfusion requirements during and immediately after the operation should be evaluated. General complications and complications related to the investigated antithrombotics (such as bleeding complications) should be retrievable from article. Data should be reported at least up to 30 days postoperatively. Only studies reported in English language were included.

Exclusion criteria

Reports with an unsuitable study design (e.g. dose finding studies or prophylaxis started before or after operation) or with surrogate endpoints (e.g. only limb salvage or amputation-free survival) were excluded.

Methodological assessment

Two authors (AW and VJ) separately assessed the methodological quality of the included articles. A checklist was used concerning fulfilment of the following requirements:

-) study population clearly defined
-) sufficient exclusion of selection bias
-) method of intervention clearly described
-) outcomes clearly described
-) independent or blinded observers for data collection
-) complete follow up for hospital stay up to discharge
-) information about confounders available

For further quality assessment of selected studies, a score system of study characteristics was developed. Items selected from studies were: consecutive series of patients reported, prospective or retrospective series, detailed information about surgical procedure, details about antithrombotic usage, details on blood loss, detailed information on blood transfusions requirements, details on patency, incidence of myocardial infarction and other arterial thrombo-embolic complications. Differences in assessments between AW and VJ were followed by discussion until consensus was reached. Shortcomings in methodological quality of the studies were not an exclusion criterion.

Data extraction

Data were extracted from eligible studies by 2 independent authors (AW and VJ). AW extracted data from included studies using a data extraction sheet, and VJ checked extracted data. Disagreement was followed by repeated review and consensus was reached. Data were labelled as “no details” if they were not reported explicitly in text or tables. In case of a lack of clarity of data in studies, original data were asked for and provided by authors.[16,17]

Standardization of outcome measures

Mortality should be defined as death by any cause within 30 days of the operation. Morbidity from MI should be reported in the same time window as outcome measures. Blood loss should be reported in millilitres perioperatively. Detailed information on determining early patency (at least at 30 days) should be provided in article. Numbers of amputations should preferably be provided. Possible conflicts of interest (COI) from included studies were looked for.

Statistical analysis

Statistical analysis was performed using RevMan 5.1.7, provided by the Cochrane Collaboration. The odds ratio (OR) and relative risk ratio (RR) with 95% confidence interval (depicted between brackets) were calculated for dichotomous variables. RR's were calculated using Clinical Epidemiology Calculator (sumsearch.org). Continuous data were expressed as means and standard deviations. For continuous outcomes, if mean values were not available, medians were used. To determine a pooled estimated effect, a random-effects model as described by DerSimonian and Laird[26] was used. Heterogeneity was explored using forest plots and the χ^2 test with significance set at $P < .100$; I^2 was used to quantify heterogeneity.[27]

Results

Literature search

For the flowchart see Figure 1 and reasons for exclusion Table 1.

Characteristics of included studies

Included studies were published between 1984 and 2004 and concerned in total 2028 patients. Two studies were double-blind, placebo controlled, one of which was single-centre[12] and one multi-centre,[11] 4 were open, controlled and multi-centric[8,10,15,17] and 3 single-centric.[9,14,16] Primary AT studied was dextran 40 or 70 in 3 studies,[8-10] iloprost in 2 studies,[11,12] human antithrombin in one study[14] and LMWH in 3 studies.[15-17] All studies but one[17] concerned open IABS in patients with PAOD, mostly of the severe form (Fontaine III or IV). In the study by Norgren et al.[17] details of IABS could be retrieved from the described results from more sorts of arterial reconstructions. In 7 studies perioperative mortality was expressed.[8-10,11,12,14,15]

However, causes of death were not specified, except for reporting fatal MI in 3 studies.[8,11,14] Non-fatal MIs were reported in 4 studies.[8,10,12,15] Detailed data on blood loss, blood transfusion and bleeding complications could only be retrieved from 3 studies.[8,10,15] In 2 studies[16,17] no details on experimental drug related complications were denoted. Rates of major amputation were only revealed in 2 studies.[11,12] See Table 2, 3, 4, 5 and 6 for patient and study characteristics. Median primary patency after 30 days was 89% (range 17-100%).

Methodological quality

Details of the checklist for methodological quality and the results of the quality assessment are depicted in Table 7. The quality assessment form for randomized clinical trials is shown in Table 8. Although all studies were described as randomized trials, important information concerning the method of inclusion and randomization of patients was often lacking and selection bias could therefore not be excluded in all but one study.[15] All studies except one[16] revealed adequate information on the method of determining patency.

Unfractionated heparin (UFH)

No studies could be retrieved from the literature search in which UFH was compared to a group not receiving UFH (no-UFH) in open IABS.

Dextran

In 3 studies[8-10] intravenous infusion of dextran solutions was evaluated as experimental antithrombotic drug (Table 2 and protocol of administration in Table 6). In 2 studies[8,9] oral anticoagulant therapy and platelet-inhibitors were withdrawn 2-7 days before the operation and re-administered from the seventh postoperative day. Total number of included patients in these 3 studies amounted to 686 patients (715 legs). The use of dextran appeared to induce fluid overload and congestive heart failure in all 3 studies, reaching statistical significance in one study[10] (12.8% vs 0.7%; RR 17.47 (2.31-132.29)). Primary patency rates were not different for dextran or no-dextran in case of autologous venous femoro-popliteal bypass with moderate run-off.[8] From none of the studies data on major amputations after bypass graft occlusions could be retrieved.

A meta-analysis was only allowed to pool results for patency at 30 days and mortality from 2 studies,[8,9] because the other study[10] consisted of a different study group (dextran and LMWH instead of only control). Results from meta-analysis showed no significant difference in patency and mortality (OR 0.88 (0.49-1.56) for patency and 1.54 (0.48-4.93) for mortality; see Figure 2).
No statement about possible COI was provided in 2 studies,[8,9] while the other study[10] stated as acknowledgement that a grant was received from Rhone-Poulenc Rorer (now Aventis, manufacturer of used enoxaparin) to Swedvasc.

Antithrombin III

Antithrombin was compared to UFH in one study,[14] which included only 13 patients. In the antithrombin-group thrombosis in the graft occurred in 5 out of 6 patients during surgery compared to no thrombosis in the UFH group. All grafts in the antithrombin-group were rescued by thrombectomy and after 1 month all grafts in the heparin group were patent and 5 out of 6 in the antithrombin-group. No details on the clinical outcome of the patient with the occluded graft could be retrieved. The high rate of intraoperative thrombosis necessitated termination of the study after including 13 patients instead of the planned 20.
No possible COI was retrieved from the included study.[14]

Iloprost

In 2 studies iloprost was evaluated as experimental antithrombotic drug[11,12] (Table 2-6). Iloprost was compared to placebo in both studies. In the study of Smith et al.[11] no information was provided on possible concomitant intraoperative use of UFH and short or long-term use of other antithrombotic drugs. The other study[12] stated "heparin, oral anticoagulants and dextrans were used both during and after treatment with the study substance according to each center's policy". No data whether this had any influence on results were provided.
Total number of studied patients was 600, all patients with critical ischemia from chronic PAOD and scheduled for femoro-distal bypass. In the Iloprost Bypass International Study Group (IBISG) study,[12] the iloprost group contained more patients with ulcers and necrosis, more (partial or complete) prosthetic grafts, slightly more females and slightly smaller graft diameters. No information on blood loss or bleeding complications was provided in these

studies. A typical iloprost related complication is hypotension. This was noted in one study[11] in all patients during the operation immediately after intragraft administration. In the other study[12] operative hypotension (not specified) was seen in 14.6% in the iloprost group vs. 4.0% in the placebo group (RR 3.65 (1.78-7.48)). In this study 'any adverse experience' was noted by 57.7% in the iloprost group vs. 37.2% in the placebo group (RR 1.45 (1.02-2.06)). However, these were not serious enough to result in more patients discontinuing infusions in the iloprost group than in the placebo group.

In the study with a much smaller number of included patients,[11] primary patency at one month was better in the iloprost group (98% vs. 83%; $P < .05$) but was equal at 12 months (67% vs. 65%). In the other study,[12] in contrast, primary patencies at 3 days, 3 months and 12 months of autologous venous grafts were comparable in both groups. In this study, however, prosthetic grafts in the iloprost group demonstrated a statistically significant better primary patency at 3 days (94.5% vs. 74.3%; $P < .01$), which statistical significance, again, had disappeared after 3 months (66% vs. 57%). The statistically significant differences in patencies in this study[12] should be interpreted with caution. Authors stated in their power-calculation that it would take 221 included patients per treatment group (iloprost or no-iloprost) to evaluate a 13% difference in patency in vein grafts. Only 209 (iloprost) and 215 (no-iloprost) vein grafts could be included for analysis. No power calculation was provided in the article to establish statistical significant differences in the prosthetic graft groups which only contained 57 respectively 35 patients.

No meta-analysis could be performed because of different time intervals for patency and mortality in both studies.[11,12]

A possible COI was retrieved from the study by Smith et al.[11]: iloprost was supplied by Schering Healthcare Ltd. No details on possible COI were retrieved from the other study.[12]

Low molecular weight heparin (LMWH)

LMWH was compared to UFH in 3 studies,[15-17] including 700 patients: 363 in the LMWH group and 337 in the UFH group (Table 2-6). In one study[15] and in the study by Norgren et al.[17] both autologous vein or prosthetic grafts were used, while in the third study[16] only autologous saphenous vein grafts were used. Patients taking oral anticoagulants or antiplatelet agents prior to admission, were excluded in one study.[15]

Overall mortality and MI did not differ between groups in 2 studies.[15,16] Blood loss was also not significantly different in these 2 studies. No specific complications related to the use of LMWH were recorded in all 3 studies. In the study of Samama et al.[15] the primary patency at day 10 was 92% in the LMWH group and 78% in the UFH group (P = .009). This difference remained statistically significant at day 30 (89% vs. 76%, P = .025). In the study of Norgren et al.[17] primary patency rates at day one and 30 were excellent in both groups, but not reaching statistical significant difference. From none of the studies data could be retrieved on amputation rates.

A meta-analysis was performed to pool results for patency and mortality at 30 days. From the study by Samama et al.[15] and Norgren et al.[17] data were eligible from articles. From the other study[16] no adequate details were provided in the article, but after retrieving the original data from the authors by e-mail, the 30-day patency and mortality could be pooled for all studies on LMWH. Results showed no significant differences for patency (OR .66 (.36-1.22, I^2=33%)) or mortality (OR .63 (.32-1.24, I^2=0%)) (Figure 3).

No details on a possible COI were retrieved from all included LMWH studies.[15-17]

Discussion

Since the introduction of the clinical use of heparin around 1940, it has been used until today by almost all vascular surgeons around the world during IABS to prevent perioperative graft thrombosis. Intuitively this feels like good clinical practice since patients with PAOD demonstrate a hypercoagulable state, which is enhanced by operative trauma and reduced by administration of UFH (or LMWH).[14,16] On the other hand this use of UFH is associated with harmful side effects like increased bleeding but also increased coagulability in patients with heparin-associated antiplatelet antibodies.[27] Main focus of research has been on postoperative antithrombotic therapy, thus *after* IABS, and long term patency. The current review focuses on *perioperative* antithrombotic management, which is used to increase patency during and immediately after IABS.

Although some authors suggested that "there are no data to support the view that heparin could be beneficial in arterial reconstructive surgery",[6] UFH remains the gold standard. We performed the current systematic review to evaluate the available evidence for the use of

heparin intra-operatively during open IABS and to find if any alternatives for UFH have been properly investigated and with what results.

No study could be retrieved in our review in which *UFH* was compared to a group without UFH.

Dextran,[8-10] antithrombin,[14] iloprost[11,12] and LMWH[15-17] were studied as (partial) alternatives for UFH. Partial, since in several studies[8-10] these drugs were adjunctive to peroperative administration of UFH, the studies with iloprost[11,12] not mentioning whether UFH was or was not administered during the operation. So the only real alternatives for UFH studied were human antithrombin[14] and 2 brands of LMWH (enoxaparin and dalteparin).[15-17] Because of the fact that the most recent and largest RCT was on the role of LMWH,[17] the discussion is mostly focused on UFH and comparison with LMWH. Despite the use of antithrombotics in all patients, incidence of early graft thrombosis was high in the investigated studies. Median primary patency after 30 days was 89%.

Dextran 40 or 70 is a high molecular weight polysaccharide with a mean weight of 40000 or 70000 Dalton. It increases flow and decreases coagulability by decreasing platelet adhesiveness, reducing factor VIII activity and increasing clot lysability. In addition it decreases viscosity, reduces thrombogenicity and acts as a volume expander and thereby significantly increasing peripheral flow. Not surprisingly, it increases the risk of clinical fluid overload especially in patients with cardiac disease, as many vascular surgery patients are. The included studies[8-10] showed no beneficiary effect of dextran on graft patencies at one month or 90 days. Although no serious anaphylactic reactions were detected in the included dextran patients, from literature fatal incidents following dextran infusion have been reported.[29] Bleeding and mortality were not influenced by dextran.

Antithrombin III is the most important protease inhibitor in plasma. It inactivates thrombin, resulting in the formation of thrombin-antithrombin complex and thereby reducing the formation of fibrin from fibrinogen. When antithrombin is administered instead of heparin it could, on theoretical grounds, be used therapeutically with a favourable antithrombotic effect. The only included study[14] planned to include 20 patients undergoing IABS, but was terminated after 13 patients since in the antithrombin group perioperative thrombosis of the graft occurred in 5 of 6 patients compared to no thrombosis in the UFH group.

Iloprost, a carbacyclin derivate, is a prostacyclin-mimetic causing vasodilatation and demonstrating anti-neutrophil and antiplatelet properties. It reduces peripheral vascular resistance during IABS and thereby increases blood flow through the bypass per- and postoperatively. Hypothesis is that this effect could result in a better patency in "difficult" femoro-distal grafts. No significant difference in mortality for iloprost or no-iloprost was detected in the 2 included studies,[11,12] as for incidence of MI and CVA. Iloprost related, temporary hypotension was recorded in a majority of patients, however without any serious persistent negative effects for patients. No (long-term) beneficiary effect on patencies could be found for the use of iloprost during IABS.

Compared to UFH, *LMWH* does not enhance platelet aggregation, is less sensitive to neutralisation by activated platelets and demonstrates a higher antithrombotic activity, higher bioavailability and longer half-life time than UFH. Also HIT caused by LMWH is less frequent. Only one study[15] provided information on adverse events. In this study the incidence of mortality, MI and bleeding complications did not differ between groups. Blood loss differed not clinically relevant. Only this study[15] found a significantly higher primary patency (at day 10 and 30) in the LMWH group. The relatively high incidence of major bleeding of 12% in both treatment groups (in the only study which reported side-effects),[15] is probably due to the extended postoperative administration of study medication in high doses[30] and may be the price to be paid for the reported enhanced early patency.[15] The finding that extended perioperative administration of enoxaparin demonstrated enhanced early patency over UFH, supports the notion that perioperative arterial thrombosis prophylaxis using LMWH in IABS might be worth the effort, although its efficacy or that of UFH, has never been established by a randomized, double-blind, placebo-controlled study. Also the established hypercoagulability in patients with PAOD, enhanced during and immediately after surgery,[14,16] supports the plausibility of this prophylaxis. A major disadvantage of the use of LMWH is the fact that no reversal can be performed using an antagonist, as opposed to UFH, which can be antagonised using protamine. However, faced with serious side-effects of UFH (and to a lesser extent of LMWH), like increased bleeding, and, paradoxically, increased thrombogenicity[28] and HIT syndrome,[7] prophylactic application of these drugs should not be undertaken lightly.

Recently the newly developed *direct-thrombin-inhibitors* (DTI's) have been tested for their safety in IABS[18] after they were proven to be beneficiary in cardiac surgery by reducing

bleeding complications, showing a shorter plasma half-life time and a more predictable dose-response pattern than UFH.[19] Further trial results have to be awaited to determine the role of DTI in IABS.

This systematic review has several limitations. Only 9 studies could be included, investigating 4 different types of antithrombotic agents. Despite the fact that all studies were presented as randomized controlled trials, methodological quality of the included studies varied and selection bias could not be sufficiently excluded in all but one study.[15] Investigated study populations were often of small size or did not include enough patients as was calculated beforehand in a power calculation.[12] Furthermore, some studies did not report all outcomes of interest. Hence, comparison of outcomes between the studies was difficult and meta-analysis could only be performed between 2 pairs of studies. Results for meta-analysis should be interpreted with caution, numbers are low, but the calculated heterogeneity was considered acceptable. Also patient and procedure characteristics differed between studies and the post-operative regimens were not consistent. The degree of influence of these limitations remains uncertain, adding to the surprisingly paucity of overall data on intra-operative antithrombotics during IABS. Despite these shortcomings meta-analysis was performed since calculated heterogeneity was low in studies concerning Dextran. Although calculated heterogeneity was higher between studies concerning LMWH, meta-analysis was performed since a contemporary Cochrane review[31] provided a different meta-analysis on the same studies with different data. Recently an update was published of that review by the Cochrane Collaboration® on "Antithrombotic agents for preventing thrombosis after infrainguinal arterial bypass surgery".[31] The main focus of this review is directed towards the post-operative and long-term use of antithrombotics. A small section is included on intra-operative interventions such as the current gold standard UFH. The current review includes more studies, provides a more detailed and more in-depth analysis of intra-operative use of antithrombotics. Main difference in the results between the Cochrane[31] and current review is the evaluation of the studies by Norgren et al.[17] and Swedenborg et al.[16] on LMWH versus UFH. As stated above, we performed a limited meta-analysis for this group, which was also described in the Cochrane review.[31] After retrieving information on raw data from the authors,[16,17] it appeared that the Cochrane review did not include all patients with infrainguinal

procedures from the study by Norgren et al.[17] and did not include 30 day patency and mortality rates from Swedenborg et al.[16] Because of that the Cochrane results showed an OR in favour of LMWH.[30] In the current review all appropriate procedures were included and with this correct data a meta-analysis does not show a statistically significant difference for patency between LMWH and UFH (figure 3).

Conclusions

More than 70 years after its introduction for preventing arterial thrombosis during arterial operations, the benefit of intra-operative administration of UFH in IABS still has not been proven by a RCT. Dextran, iloprost or human antithrombin have been proven to have no beneficial effect for the patient compared to UFH alone. LMWH instead of UFH could produce better results for the patient in IABS, but conclusive data are presently lacking. A recent Cochrane review[31] appeared to overestimate the beneficiary effect of LMWH. Therefore we strongly advocate that for the perioperative prevention of graft thrombosis during IABS randomized, double-blinded, placebo-controlled studies using UFH, LMWH and DTI should be started.

Figure 1.

Flowchart of literature search.

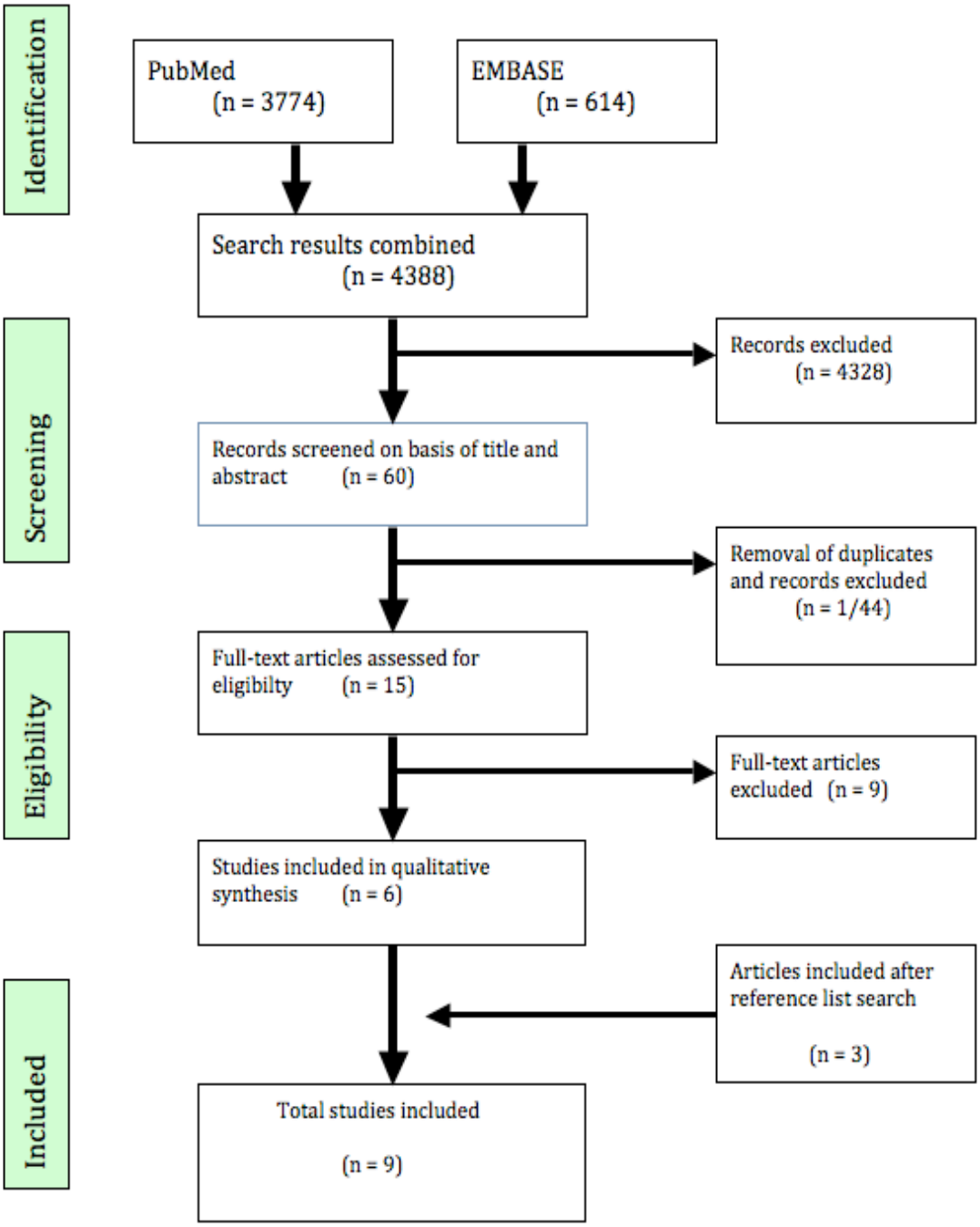


Table 1.

Exclusion and inclusion of studies.

Reasons for exclusion of studies after evaluation of title:	
Venous disease	411
Other diseases	476
Pharmacology	85
Animal studies	63
Studies on 1 or 2 grafts	15
Aortic disease	32
Haemostasis or coagulation	75
Long-term/postoperative	30
Heparin induced thrombocytopenia	93
Trauma	43
Anaesthesiology	17
Non-operative studies	29
Access/closure	177
Case reports	299
(Operative) techniques	91
Endovascular	184
Review, guidelines or expert opinion	1197
Cardiac	1011
Total	**4328**

Reasons for exclusion of studies after reading abstracts:	
Non-operative studies	1
Review, guideline or expert opinion	11
Other diseases	1
Endovascular	2
No antithrombotics compared	3
Plastic surgery	1
Studies on 1 graft	1
Animal studies	1
Access	1
Study on acute ischemia	1
Soft outcomes	7
Cardiac	2
Long-term/postoperative	8
Operative techniques	2
Total	**44**

Reasons for exclusion of studies after reading full-text articles:	
Only 1 study group or 1 graft studied	4
Review	3
Plastic surgery	2
Total	**9**

Table 2. Study and patient characteristics.

Author, year (Study period)	Indication for surgery	Type of bypass surgery	Postoperative anticoagulation
Rutherford 1984 (jan.83-may 84)	Patients expected to undergo infra-inguinal bypass considered to be at high risk for early postoperative thrombosis. No further details.	I Fem-pop with autologous vein (AV) with poor runoff II Fem-pop using other grafts than AV (PTFE, Dacron, umbilical vein, composite) III Single or sequential bypass to infra-popliteal arteries IV Bypass to pop or infra-pop arteries and adjunctive procedures (endarterectomy, thrombectomy, angioplasty, PTA)	After 7-th postoperative day according to each center's routine No further details
Katz 1998 (july 92-june 96)	Claudication (26%) Non-healing ulcer (26%) Ischemic rest pain (25%) Gangrene (23%)	Popliteal artery (53%; 38% above and 62% below knee) Infrapopliteal arteries (47%) Autogenous vein: 91 % GSV, 8% arm vein and 1% LSV	Restarted 1 week after surgery, chronic oral anticoagulants or antiplatelet agents, as used before surgery. No further details.
Logason 2001 ("a 2 year period")	Patients scheduled to undergo bypass from groin to a distal site. Acute ischemia (2%), claudication (16%), rest pain (30%) and ulcer or gangrene (52%)	Fem-pop above knee (33%), fem-pop below knee (38%) and fem-crural (29%). Vein graft (52%) and synthetic or composite (48%). No further details.	Antiplatelet drugs allowed and left to the discretion of responsible surgeon. No further details.
Nydahl 1992 (no information)	Patients admitted for infrainguinal reconstruction and not treated with ASA or oral anticoagulants. Rest pain (77%), claudication (15%) and non-healing ulcer (8%).	Above-knee anastomosis in 92% and below-knee in 8% of patients. No further details.	No details.
Smith 1993 (no information)	Patients who underwent vascular reconstruction for critical ischemia.	To anterior (55%), posterior (27%) or peroneal artery (18%). Upper 1/3 (18%), middle 1/3 (18%) and lower 1/3 (64%). Autologous in-situ vein grafts.	No details.
IBSG[a] 1996 (1990-1992)	Bypass for critical ischemia: trophic lesions or persistent rest pain.	Distal anastomosis to pop. art. (1.7%), tibioperoneal trunk (8.5%), ATA (34.6%), PTA (27.9%), peroneal art. (26.9%) or dorsal pedal art. (0.4%). In-situ vein (56.5%), reversed vein (17.4%), PTFE (12%) Other prosthetic grafts (0.2%) or composite (13.7%).	After study period op 3 day post-operative: according to the policy of each individual centre.
Samama 1995 (nov. 90-nov. 92)	Patients scheduled to undergo femoro-distal bypass. No further details.	Above-knee popliteal (9.6%), below-knee popliteal artery (35.2%), prox. Infra-popliteal (49.8%),and distal infra-popliteal (5.5%). Autologous vein (67.8%), PTFE (23.6%) and other (8.5%).	After end of study period (10 days), long-term prophylaxis was left to discretion of the investigator, regardless of further use of antithrombotic drugs.
Swedenborg 1996 (no information)	Patients to undergo infra-inguinal bypass: claudication (17%), rest pain (33%) and ulcer or gangrene (50%).	Femoro-distal (72%), infragenual (17%) and supragenual (11%). All autologous vein grafts.	Not applicable.
Norgren 2004 (nov. 00-dec. 02)	Patients undergoing vascular surgery. No further details for subset of infra-inguinal reconstructions. Critical limb ischemia (55%) and claudication (24%).	No detailed information retrievable.	Postoperative antithrombotic treatment given at discretion of the individual hospital, mostly ASA, but Dextran or LMWH was allowed during the first days after surgery.

[a] = Iloprost Bypass International Study Group (IBSG)

Table 3. Study and patient characteristics.

Author, year (Study period)	Study design	Randomization	Experimental antithrombotic	Number of patients Eligible	Randomized	Excluded	Studied
Rutherford 1984 (jan.83-may 84)	Prospective, randomized open, controlled multi-center	Series sequentially numbered envelopes, color coded, each category separately numbered and randomized	**Dextran 40** / control (all patients heparin bolus perioperatively, 100 IU/kg)	?	211 100/111	55 27/28	156 73/83
Katz 1998 (july 92-june 96)	Prospective, randomized open, controlled single-center	Drawing of opaque sealed envelopes, no further details	**Dextran 40** / control (all patients heparin bolus perioperatively, 5000 IU)	?	292	19	273 126/147
Logason 2001 ("a 2 year period")	Prospective, randomized open, controlled, multi-center	Separate randomization by each center, seq. numbered envelopes, group in envelop generated by computer random lists	**Dextran 70** / LMWH (all patients heparin bolus perioperatively, 5000 IU)	?	314	28	286 149/137
Nydahl 1992 (no information)	Prospective, randomized open, controlled single-center	No details	**Antithrombine III** / UFH	20	13 6/7	0	13 6/7
Smith 1993 (no information)	Prospective, randomized double-blind, single-center placebo controlled	No details	**Iloprost** / placebo (no information on peripoperative concomitant UFH-bolus use)	?	?	?	83 45/38
IBSG[a] 1996 (1990-1992)	Prospective, randomized double-blind, multi-center placebo controlled	Stratified by center, no further details	**Iloprost** / placebo (UFH and other antithrombotics perioperatively allowed, no details)	?	528	11	517 267/250
Samama 1995 (nov. 90-nov. 92)	Prospective, randomized open, controlled multi-center	Randomly allocated: blocks of 4, separate for each center	**LMWH** / UFH	?	201 100/101	2	199 99/100
Swedenborg 1996 (no information)	Prospective, randomized open, controlled single-center	No details	**LMWH** / UFH	?	18 9/9	0	18 9/9
Norgren 2004 (nov. 00-dec. 02)	Prospective, randomized open, controlled multi-center, open-label	Sealed envelop principle, in blocks of 20 per hospital	**LMWH** / UFH	?	483 255/228	0	483 255/228

[a] = Iloprost Bypass International Study Group (IBISG)

Table 4. Study and patient characteristics.

Author, year (study period)	Primary & secondary patencies	Methods of determining patency	Primary and secondary patencies AT studied				Control	
Rutherford 1984 (jan.83-may 84)	Primary patency @ day 1, week 1 and month 1	Angiography and patency only accepted without if >0.15 raise in ABI[a]. Patency maintained by thrombectomy not allowed	day 1 week 1 month 1	100 % 93 % 85 %			90 % 80 % 79 %	P < .05 P < .05 NS
Katz 1998 (july 92-june 96)	Primary patency @ day 30	Duplex scan at day 30 or at suspicion of early occlusion	day 30	94 %			93 %	NS
Logason 2001 ("a 2 year period")	Primary patency @ day 1, 7, 30 and day 90	Palpable graft and ankle pulse, ABI>0.15 and clinical judgement. All cases of uncertainty: duplex scan or angiography	day 1 day 30 month 3	99 % 95 % 88 %			96 % 89 % 83 %	NS NS NS
Nydahl 1992 (no information)	Primary and secondary patency	Palpable pulse and ABI > 0.20	perioperatively secondary	17 % 83 %			100 % 86 %	P < .05 NS
Smith 1993 (no information)	Primary and assisted prim. patency (app) @ month 1 and 12	Duplex	month 1 month 12	98 % (app 98%) 67 % (app 88%)			83 % (app 86%) P < .05 65 % (app 79%) NS	
IBISG[b] 1996 (1990-1992)	Primary and secondary patency* @ day 1, 2, 14 and month 3 and 12	Duplex optional, no further details	vein grafts day 3 month 3 month 12 prosthetic day 3 month 3 month 12	95 % 68 % 55 % 95 % 66 % 44 %			95 % 65 % 54 % 74 % 57 % 47 %	NS NS NS P = .01 NS NS
Samama 1995 (nov. 90-nov. 92)	Primary patency @ day 12 and 30	Angiography at day 10±2 or sooner if suspicion of thrombosis If no angio: clinical assessment	day 10 day 30	93 % 89 %			78 % 76 %	P = .009 P = .025
Swedenborg 1996 (no information)	Primary and secondary patency	No details	?	78 %			78 %	NS
Norgren 2004 (nov. 00-dec. 02)	Primary patency @ day 1 and 30	Pulse palpation and clinical judgement. Periop. flow measurement 357 pts. If doubts: duplex. Trial did not specifically ask for that method.	fem-pop fem-distal	day 1 day 30 day 1 day 30	96 % 90 % 93 % 83 %		97 % 86 % 91 % 87 %	NS NS NS NS

[a] = Ankle-brachial index.
[b] = Iloprost Bypass International Study Group (IBISG)

Table 5. Study and patient characteristics.

Author, year (study period)	Death, MI and other complications	AT studied	Control		Major amputation rate	AT studied	Control
Rutherford 1984 (jan.83-may 84)	Death @ day 30	3 %	2 %	NS	No information		
	Fluid overload	5 %	3 %	NS			
	Bleeding complications	10 %	10 %	NS			
	Stop exp. medication	9 %	0 %				
Katz 1998 (july 92-june 96)	Death @ day 30	3.2 %	2.1 %	NS	No information		
	Stop exp. medication	3.2 %	0 %				
Logason 2001 ("a 2 year period")	Death @ day 30	3.4 %	2.9 %	NS	No information		
	Heart failure	12.8 %	0.7 %	RR 17.47 (2.31-132.29)			
	Bleeding	6.1 %	2.3 %	NS			
Nydahl 1992 (no information)	Operative graft thrombosis	83.3 %	0 %		No information		
Smith 1993 (no information)	Death @ day 30	2.2 %	5.3 %	NS	At 30 days	1 (2.2%)	5 (13.2%)	NS
	Death @ 12 months	11 %	10 %	NS			
	Hypotension < 15 min. (no clin. relevance)	100 %	0 %				
IBISG[a] 1996 (1990-1992)	Death @ day 14	3.4 %	2.4 %	NS	Vein at month 12	18.2%	19.5%	NS
	Non-fatal MI @ day 14	3.7 %	4.4 %	NS			
	CVA @ day 14	1.1 %	0.8 %	NS	Prosthetic at month 12	26.3%	28.6%	NS
	Operative hypotension	14.6 %	4.0 %	RR 3.65 (1.78-7.48)			
	Any adverse event	57.7 %	37.2 %	RR 1.45 (1.02-2.06)			
Samama 1995 (nov. 90-nov. 92)	Death @ day 30	5 %	9 %	NS	No information		
	Major bleeding	12 %	12 %	NS			
Swedenborg 1996 (no information)	No information				No information		
Norgren 2004 (nov. 00-dec. 02)	No details				No information		

[a] = Iloprost Bypass International Study Group (IBISG)

Table 6. Protocols of administration of studied antithrombotics and control groups.

Author, year (study period)	**Protocols of administration of antithrombotics**	
	Experimental	**Control**
Rutherford 1984 (jan.83-may 84)	**Dextran 40:** 500 ml @ 100 ml/hr after anesthesia induction, then 500 ml @ 75ml/hr and 500 ml on each of next 3 post-op days at 75 ml/hr.	**No-dextran** and in both groups: UFH 100 IU/kg iv before arterial clamping.
Katz 1998 (july 92-june 96)	**Dextran 40:** 500 ml in 5 hrs after anesthesia induction, then constant infusion of 500 ml during each 24-hour period for 72 hours.	**No-dextran** and in both groups: 5000 IU UFH iv before arterial clamping.
Logason 2001 ("a 2 year period")	**Dextran 70:** 500 ml after anesthesia induction, 500 ml post-op after first 500 ml, then 500 ml on the morning of post-o. days 1, 2 and 3. Also 5000 IU iv UFH before arterial clamping.	**LMWH** (enoxaparin): 40 mg sc on day before surgery and same dose for 7 days post-op and 20 mg before arterial clamping.
Nydahl 1992 (no information)	**Antithrombine III:** 1500 IU directly in opened femoral artery for a 5 min period after arterial clamping.	**UFH:** 5000 IU single dose before arterial clamping.
Smith 1993 (no information)	**Iloprost:** 3000 ng in flacon of 15 ml saline into graft before wound closure.	**Placebo:** same protocol.
IBISG[a] 1996 (1990-1992)	**Iloprost:** 3000 ng in flacon of 15 ml saline into graft before wound closure. After that: infusion of 500 ml after induction of anesthesia at 20 ml/hr for 1 hr. Then 1 hr after operation: 6-hr infusion up to 20 ml/hr. Then 2 following days: 6-hour infusion up to 40 ml/hr.	**Placebo:** same protocol.
Samama 1995 (nov. 90-nov. 92)	**LMWH:** Enoxiparin, 75 anti-Xa U/kg iv before arterial clamping, flushing of graft with LMWH in saline. Subsequently 75 anti-Xa IU/kg sc starting 8 hrs after first dose and then every 12 hrs for 10 days.	**UFH:** same protocol, 50 IU/kg iv before arterial clamping and 150 IU/kg postop.
Swedenborg 1996 (no information)	**LMWH:** Dalteparin, single dose 70 anti-Xa IU/kg iv before arterial clamping	**UFH:** same protocol, 70 IU/kg iv
Norgren 2004 (nov. 00-dec. 02)	**LMWH:** Enoxiparin, single dose of 40 mg iv before arterial clamping; flushing graft and vessels with LMWH in saline.	**UFH:** same protocol, 5000 IU iv

[a] = Iloprost Bypass International Study Group (IBISG)

Table 7. Details and results of methodological and quality assessment.

Author, year (study period)	Study population	No selection bias	Method of intervention	Description of outcomes	Independent observers	No selective loss to FU	Description of confounders
Rutherford 1984 (jan.83-may 84)	±	±	+	±	-	+	±
Katz 1998 (july 92-june 96)	±	±	+	±	-	+	±
Logason 2001 ("a 2 year period")	+	±	+	+	+	+	-
Nydahl 1992 (no information)	+	±	+	-	-	+	-
Smith 1993 (no information)	±	±	+	±	-	+	-
IBISG* 1996 (1990-1992)	+	±	+	+	+	-	+
Sanama 1995 (nov. 90-nov. 92)	±	+	+	+	-	±	+
Swedenborg 1996 (no information)	+	±	+	±	-	+	-
Norgren 2004 (nov. 00-dec. 02)	±	±	+	+	+	±	±

- = no
± = partially
+ = yes
* = Iloprost Bypass International Study Group

Table 7. Details and results of methodological and quality assessment.

Author, year (study period)	Consecutive series of pts	Prospectivire series	Details of surgery	Details of antithrombotic	Details of blood loss	Details of transfusion	Details of MI	Details of patency	AT related complications	Total score
Rutherford 1984 (jan.83-may 84)	2	2	1	1	0	0	2	2	2	12
Katz 1998 (july 92-june 96)	2	2	2	2	0	0	0	2	0	10
Logason 2001 ("a 2 year period")	2	2	2	2	2	2	1	2	2	17
Nydahl 1992 (no information)	0	0	1	2	0	0	1	1	2	7
Smith 1993 (no information)	2	2	2	2	0	0	0	2	1	11
IBISG 1996 (1990-1992)	2	2	2	2	0	0	1	2	1	12
Samama 1995 (nov. 90-nov. 92)	2	2	2	2	2	2	1	2	2	17
Swedenborg 1996 (no information)	2	2	1	2	0	0	0	1	0	8
Norgren 2004 (nov. 00-dec. 02)	2	2	1	2	2	0	0	2	1	12
									Maximum total score =	**18**

0 = no details retrieved from study
1 = incomplete details retrieved
2 = complete details retrieved
* = Iloprost Bypass International Study Group

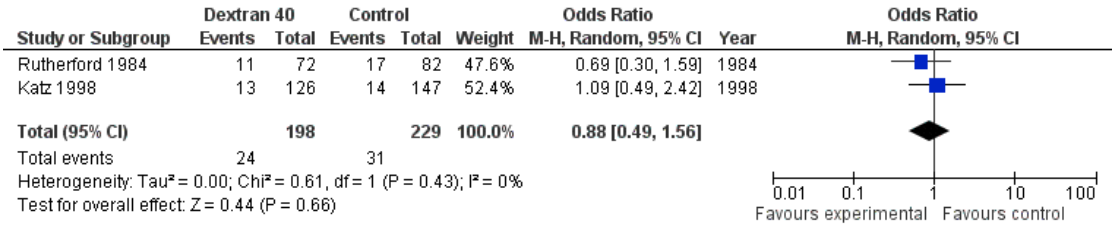
Table 8. Quality assessment form for randomized clinical trials .

Author, year (study period)	Patients randomized?	Inclusion unknown?	Patients blinded?	Physician blinded?	Researchers blinded?	Groups comparable?	Follow-up long enough?	Intention-to treat?	Equal treatment?
Rutherford 1984 (jan.83-may 84)	+	+	-	-	-	-	+	±	+
Katz 1998 (july 92-june 96)	+	+	-	-	-	+	+	-	+
Logason 2001 ("a 2 year period")	+	+	-	-	+	+	+	+	+
Nydahl 1992 (no information)	+	-	-	-	-	a	+	-	+
Smith 1993 (no information)	±	±	-	-	-	+	+	±	+
IBISG* 1996 (1990-1992)	+	+	+	+	+	+	+	+	+
Samama 1995 (nov. 90-nov. 92)	±	±	-	-	-	+	+	+	+
Swedenborg 1996 (no information)	±	±	-	-	-	±	+	±	+
Norgren 2004 (nov. 00-dec. 02)	+	+	-	-	-	±	+	+	+

- = no
± = partially
+ = yes
* = Iloprost Bypass International Study Group

Figure 2.

Forest plots of patency and mortality at 30 days for dextran studies.



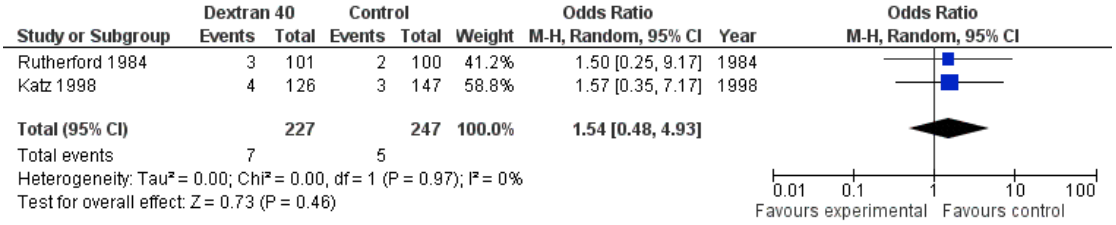
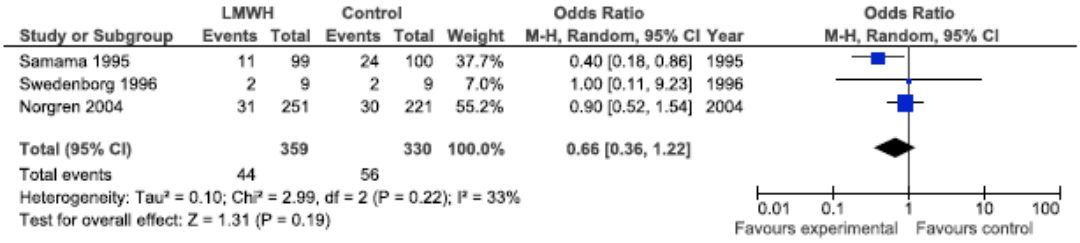
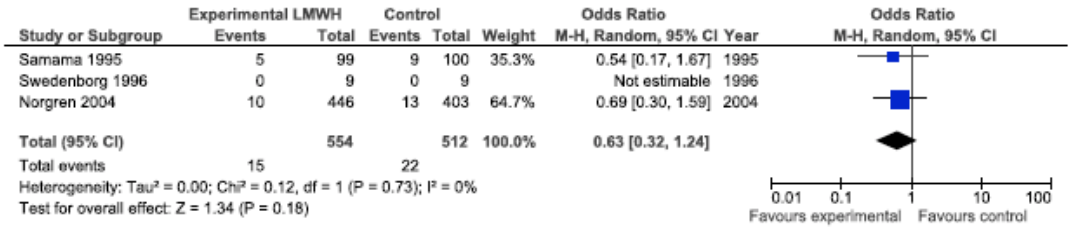


Figure 3.

Forest plots of patency and mortality at 30 days for LMWH studies.





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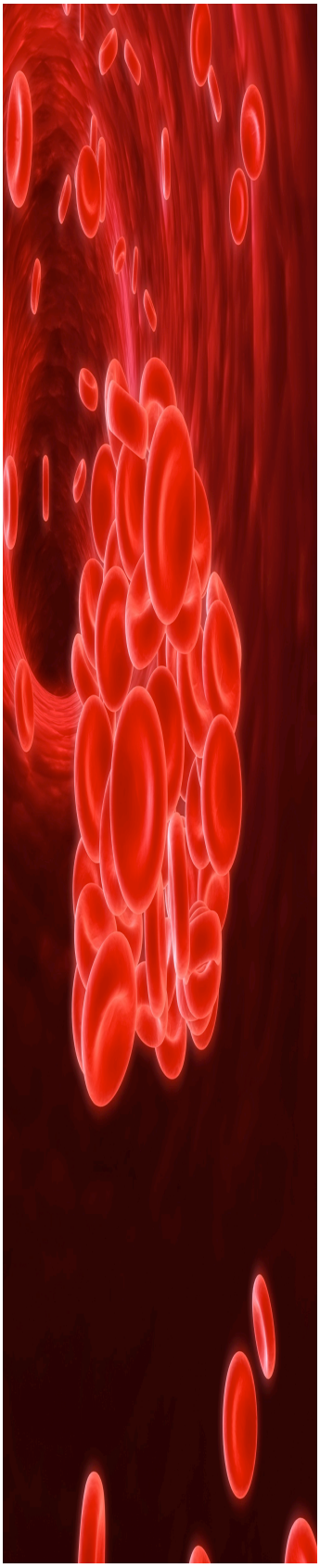

Chapter 7

The use of heparin during endovascular peripheral arterial interventions: a synopsis

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Abstract

There are significant differences between hospitals in many aspects of the use of heparin as periprocedural prophylactic antithrombotic during peripheral arterial interventions (PAI). This variation is present not only within countries, but also between them. Alarmingly, no level-1 evidence exists on the use of heparin, precluding the preparation of a comprehensive systematic review. The current article provides a synopsis of the scant literature on heparin use in interventional radiology.

The variation in heparin use could influence the reproducibility of patencies and complication rates described for PAI in literature. Randomized controlled trials should be performed to gather data and create international evidence based guidelines. An activated-clotting-time measurement should be mandatory during PAI to assess actual anticoagulation status.

Introduction

Recent extensive surveys amongst interventional radiologists (IR) have shown that (unfractionated) heparin is used by almost all European IR during peripheral arterial interventions (PAI).[1,2] PAI being defined as all non-cardiac and non-cerebral arterial interventions. Heparin is used as a periprocedural prophylactic antithrombotic (PPAT) agent to prevent distal and proximal arterial thrombo-embolic complications (ATEC). Additionally, heparin reduces the formation of thrombus on catheters and prevents the formation of blood clots within catheters. Heparin is also used during PAI as a flushing solution on the sideport of a sheath, mostly diluted with saline and to coat catheters and wires. This current widespread use of heparin is in accordance with earlier reports from Europe and the United States.[3-5]

The harmful side effects of heparin are also well recognized: a higher bleeding tendency, resulting in local and systemic bleeding complications. It is self evident, that all bleeding complications enhanced or caused by heparin, have a negative influence on results of PAI. The use of heparin may also result in heparin-induced-thrombocytopenia (HIT), a rare but possibly limb or indeed life-threatening complication.[6]

From literature it is known that heparin has no linear dose-response curve and elimination curve in the vascular patient.[7,8] This underscores the necessity of measuring the actual, clinical effect of heparin either by checking the activated clotting time (ACT) or performing a heparin concentration or dose-response test.[9,10]

The incidence of the complications caused by the use of heparin in PAI could be underestimated. A majority of interventional radiology departments do not apply a strict complication registry and no centralized complication registration is mandatory for IR in The Netherlands. In most Dutch and UK hospitals the vascular patients for PAI are admitted on a vascular surgery ward by a vascular surgeon, who also performs the follow-up of the patients after those interventions. Consequently, any late complications are probably registered by the vascular surgeon and not by the IR. Additionally, it has been stipulated that a general under-registration of complications by medical specialists exists.[11]

Current guidelines in IR, such as TASC II[12] and CIRSE,[13] advise the use of heparin as periprocedural prophylactic antithrombotic. But despite these guidelines and the worldwide use of heparin for the past 30-plus years, there still is no consensus on many aspects of its use

in PAI. Mentioned surveys in the UK and The Netherlands,[1,2,4,5] showed a significant variation in all aspects of heparin use during PAI. Alarmingly, the described variation in The Netherlands and the UK were not only present in both countries, but the variation was also different between those countries. This emphasises the need for new, practical level I evidence based guidelines. For the purpose of creating such guidelines, a study group was formed in the Netherlands, CAPPA: Consensus on Arterial Peri-Procedural Anticoagulation.[2,14-16] Collaboration was established between authors from the UK survey and the Dutch Survey and results of those combined data were incorporated in a recent publication.[2]

To objectively assess the results of both surveys from The Netherlands and the UK, we intended to perform a systematic review on the intra-procedural use of heparin or other antithrombotic drugs. It appeared that no systematic review according to PRISMA guidelines could be justified, due to the lack of randomized data. Only one RCT was found in literature.[17] Therefore we decided to perform an in-depth analysis of all available literature on heparin (or other PPAT) in IR.

Heparin in flushing solution and as bolus

Heparin is a glycosaminoglycan and influences the coagulation cascade predominantly through an interaction with antithrombin III (AT-III). This combination of enzyme and inhibitor inactivates coagulation enzymes, mainly thrombin (IIa) and Xa. Heparin is heterogeneous in its size and weight of molecules, its effect on coagulation and its pharmacokinetic effects. These facts explain why heparin has a non-linear effect on coagulation.[18]

Heparin is used during arterial angiography, both as a bolus and in the flushing solution. It presumably reduces thrombotic complications by reduction of thrombus formation on wires, sheaths and catheters and by reducing the effects of the hyper-coagulable state present in vascular patients.[19]

During the early days of angiography,[20] periprocedural anticoagulation received considerable attention. Because of its rapidly adopted standardized use, most publications on heparin in IR date from the 1970's and 80's.[21] When heparin is used as a bolus instead of only in the flushing solution, significant fewer thrombotic complications occurred, while no increase in

haemorrhagic complications was found.[21,22] It was also shown that heparin used as a bolus, resulted in immediate effective anticoagulation, while heparin in the flushing solution resulted in maximal anticoagulation effect at the end of the procedure. Another study[23] indicated that bolus injection of heparin provided a better anticoagulation effect than continuous infusion. Since the 1990's,[3] all these publications resulted in widely accepted and advocated use of heparin as PPAT in PAI.

Recommendations included the administration of 2000-3000 IU intra-arterially or intravenously as bolus and 2000 IU/L heparin in saline as flushing solution.

More recently, only a limited number of studies have been published on heparin as PPAT or on the comparison of heparin with new anticoagulants. In 2002 a study was performed[24] on coronary and peripheral interventions in which heparin was replaced as antithrombotic by a low-molecular-weight-heparin (LMWH, enoxaparin) that was combined with a glycoprotein IIb/IIIa receptor antagonist (eptifibatide). No robust conclusions could be made on whether this combination provided better results than heparin alone, among others because only a small number of peripheral arterial interventions (n=21) were included. In 2009 Sheikh et al. reported[25] that no ACC/AHA guidelines existed on the use of heparin as PPAT and that most anticoagulation strategies in PAI were directly extrapolated from studies performed during coronary interventions.

Studies during coronary interventions indicated that bivalirudin has the same efficacy as heparin as PPAT, but with less ischemic and bleeding complications.[26] However, no clinically relevant differences were found in a non-randomized, non-blinded study, comparing heparin with bivalirudin during PAI. Additionally, heparin is considerably less expensive than bivalirudin (US $ 6 versus $ 547 per procedure).[25] The same conclusions could be drawn from a study comparing heparin and bivalirudin during EVAR.[27] All studies[25,28] on bivalirudin concluded that RCTs are needed to further evaluate the possible advantages of direct thrombin inhibitors over heparin during PAI. Thus far however, no results of such RCTs have been published.

Another alternative for heparin are the low molecular weight heparins (LMWH). Compared to heparin, LMWH is less sensitive to neutralisation by activated platelets and demonstrates a higher antithrombotic activity, higher bioavailability and longer half-life than heparin. Also HIT caused by LMWH is less frequent.[28] The use of LMWH versus heparin has been well

established for coronary interventions. LMWH proved to reduce major bleeding complications, while not increasing ischemic study endpoints.[29,30] Duschek et al.[17] performed a RCT using LMWH or heparin during PAI. This is the only RCT on the use of 2 different periprocedural prophylactic antithrombotics during PAI that could be retrieved from literature. In this study the primary composed endpoints were better for enoxaparin than for heparin. Endpoints were defined as the peri-interventional rate of thrombo-embolic occlusion (efficacy) of endovascular reconstructed areas, the rate of bleeding complications and of any necessary re-intervention for any PTA related bleeding (10.5% heparin vs. 2.5% enoxaparin, $P < 0.05$). The concomitant use of acetyl-salicylic-acid increased the incidence of bleeding complications in the heparin group, but not in the enoxaparin group. In 2012 a retrospective evaluation of using heparin or no-heparin during peripheral interventions was published (n = 330).[31] Although applied doses varied, a dose of 5000 IU was used predominantly. All procedures were performed with a flushing solution with a heparin concentration of 1000 IU per 500 mL. This study showed an increased risk for bleeding complications at the access site (OR = 5.7; 95% CI=1.3-25) without a reduction of arterial thrombo-embolic complications in the heparin group. The authors stressed the absence of level 1 data to support the use of heparin as PPAT during peripheral arterial interventions and concluded that RCTs should be started.

Heparin and contrast medium

Although taken for granted nowadays by most IR, the type of contrast medium (CM) and its influence on clotting and arterial thrombo-embolic complications have been the subject of considerable discussion.

Already in 1896, almost within a year of the introduction of X-ray by Röntgen, CM was used[32] in a cadaver model. CM that are clinically usable, all use iodine as its X-ray attenuation component. As iodine is toxic, it is always bound to a macromolecule to be administrable in the vascular system. The first CM were all ionic, until stable non-ionic monomers were developed in the late 1960's. It took until 1985 when non-ionic contrast medium was introduced for use in angiography.[33] Both ionic and non-ionic contrast mediums exhibit pro- or anti-thrombotic properties.[34-37] Clot formation can be inhibited by ionic CM (e.g. ioxaglate), but only if it is present in blood in a more than 8% concentration. Despite dilution when the

CM mixes with blood, it is highly probable that a concentration of 8% of ionic CM is reached. For non-ionic contrast this threshold for anti-thrombotic effect is a 30% concentration. So therefore it is likely that ionic CM reduces clot formation more than non-ionic.[4,38-40] However ionic CM generally cause more patient discomfort and have a greater tendency to cause adverse events, when compared to non-ionic CM.[41] A reduction in the thrombogenicity during angiography by thrombus formation in and on the angiography catheter could be achieved by the additional administration of heparin. The anticoagulant effects of ionic contrast and heparin are cumulative and thereby increase the active anticoagulation period from 4 hours with systemic heparin alone to 6 hours with the combination of heparin and ionic contrast medium.[42,43]

Heparin and guide wires, sheaths and catheters

Guide wires, sheaths and catheters can play an important role in angiography related arterial thrombo-embolic complications. Clots may form on the outside surface of these devices and thrombus can also be encased inside the lumen and then be pushed into the circulation when wires or other devices are inserted through that lumen. In addition, the injection of contrast medium through the lumen can cause dispersing of thrombus material. Another pathway of thrombotic complications caused by wires, sheaths and catheters is when they are removed from the puncture site. Formed clots, which are adherent to the devices, can be stripped of and thrombus is thereby released in the arterial circulation distal to the puncture site. Since the introduction of angiography, focus has been directed to reducing this thrombogenicity of wires, sheaths and catheters. It was shown that clot formation could be detected on all catheters when these were positioned inside a blood vessel.[44-46] In the 1970's heparin coated catheters were introduced in clinical practice.[47-49] At first the heparin was washed rapidly from the catheters when in contact with blood, but from the 1980's, the heparin was stabilized and not washed off within the hour when in contact with blood. This "striking reduction of thrombogenicity achieved with heparinization"[50] was later confirmed by several other studies and enhanced by a hydrophilic coating. The combination of heparin and hydrophilic coating proved to be highly non-thrombogenic.[51]

Measuring the clinical effect of heparin

As mentioned earlier, heparin as PPAT during peripheral arterial interventions was introduced mainly by extrapolation from coronary interventions. The use of a bolus of heparin and its dosage was adopted and implemented as 'standard of care' in IR. Surprisingly though, the standardized use of performing a reliable measurement of the actual effect of heparin on coagulation status was not directly extrapolated and implemented in daily use from coronary to peripheral interventions. Every now and then focus is directed towards the topic of measuring the actual effect of heparin during PAI. As was convincingly proven during coronary interventions, the activated-clotting-time (ACT) correlates better with the effect of heparin than the previously used activated partial thromboplastin time (APTT).[52-57] At the start of the 21-st century, it was advocated that during and after PAI, monitoring of anticoagulation is a "crucial responsibility".[58] It was stipulated that data should be gathered as soon as possible, on how to monitor anticoagulation and what actions to take at different values of ACT during PAI.[58] Jackson et al.[4] stated in their 1995 inventory of angiographic practice in the UK: "… radiologists should be prepared to follow cardiologists and invest in ACT meters if heparinization is to be more than folklore in the important area of angioplasty".
It took until 2010 before a large cohort patients (n=4743) was described[54] in which a correlation was sought between heparin dosage, measured ACT and the optimal degree of anticoagulation related to clinical parameters during PAI. Main conclusions from this large registry were, that a higher total heparin dose (> 60 IU/kg) and a peak procedural ACT of > 250 seconds, were strong predictors of significantly increased post-procedural bleeding events. The technical and procedural success was high and did not differ between the described groups with higher or lower heparin dose or peak ACT. Deduced from these results, it was strongly suggested that during PAI, a body-weight-dependent dose of up to 60 IU/kg should be administered, while the ACT should have a target peak value of < 250 seconds.

Protamine

To reduce the higher bleeding tendency caused by heparin administration, protamine sulphate has been used to reverse the effect of heparin. Protamine is a heterogeneous mixture of highly cationic polypeptides, originally purified from salmon sperm, but nowadays produced through recombinant biotechnology. Protamine has been subject of much controversy. It can cause

adverse and potentially life-threatening complications such as a severe allergic reaction, systemic arterial hypotension, decreased cardiac output, decreased oxygen consumption, bradycardia and even death.[58] Additionally, when protamine is not bound to heparin in blood, it expresses anticoagulant properties, thereby creating a contradictive effect in the vascular patient when the dose of protamine is not exactly matched with the circulating heparin at that precise moment. In the Netherlands the use of protamine by interventional radiologists is incidental (<1%).[2] No current data are available on the use of protamine in other countries. Considering the fact that only a small minority of interventional radiologists measure the actual, clinical effect of heparin in the patient and the fact that heparin has no linear dose-response curve and elimination curve, standardized reversal of heparin with protamine seems, at the very least, not evidence based.

Discussion

Systemic heparin administration is used by many interventionists around the world as PPAT during PAI. Heparin is also used as a coating on all disposables to reduce the thrombogenicity of those materials. Additionally, heparin is used in the flushing solution with saline and heparin has a cumulative anticoagulant effect when used in combination with ionic contrast medium. No level-1 evidence exists on the use of heparin as a bolus as PPAT during peripheral arterial interventions. Despite the fact that the vast majority of the IR community uses systemic heparin administration during PAI, it has never been conclusively proven that its benefits outweigh the potential complications. In the view of the authors this should be subject of randomized trial.

A wide variation exists between institutions and between countries on all aspects of the use of heparin during these interventions. Patencies, re-interventions and complications described in studies for PAI could be influenced by the large variety of protocols on heparin use, as more thrombo-embolic complications or bleeding complications might occur, especially when no measurement of actual coagulation status is performed. Although the use of heparin as PPAT in PAI was extrapolated from coronary interventions, the use of a measurement of actual anticoagulation effect has not been widely incorporated as standard of care by interventional radiologists. Heparin has a non-linear response curve and elimination pattern in the vascular patient. It has been shown that such a measurement is essential to tailor the anticoagulant

therapy in the individual patient. Measurement of the ACT with a point-of-care device during PAI should, in our view, become standard of care.

In conclusion, in the current era of evidence-based medicine, the use of heparin as periprocedural prophylactic antithrombotic during peripheral arterial interventions is still subject to wide variation. This use of heparin needs to be evaluated by means of RCTs. International guidelines should be based on results from those RCTs. A measurement of actual anticoagulation status during PAI, should become standard of care. The CAPPA group from The Netherlands aims to institute such trials, in collaboration with UK interventional radiologists.

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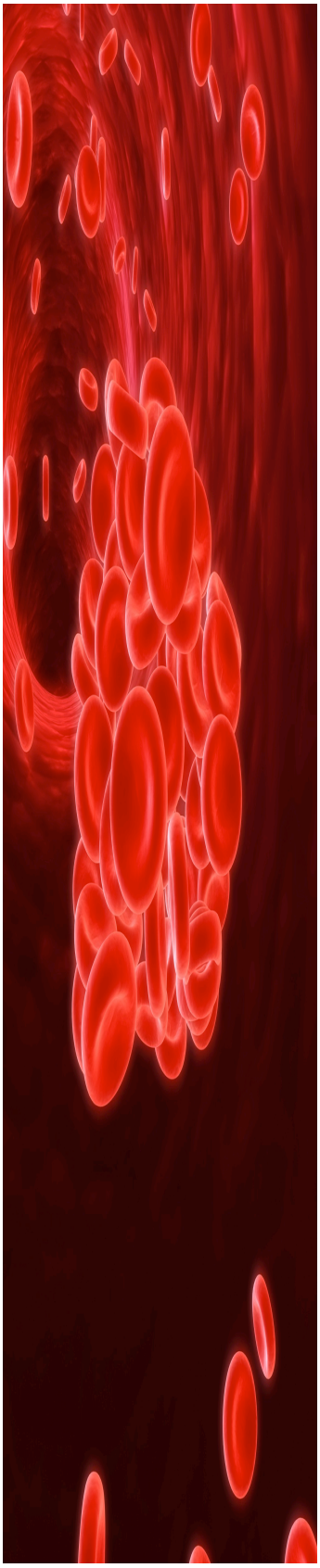

Chapter 8

The DREAM of using heparin during open abdominal aortic aneurysm repair

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Submitted after revisions.

Abstract

Objective

The use of heparin as periprocedural prophylactic antithrombotic (PPAT) during open abdominal aortic aneurysm (AAA) repair, has been evaluated in an extensive survey and systematic review. The survey from the Netherlands, showed a wide variety in aspects of use of heparin. The review showed no beneficial effect, but a trend towards more bleeding related complications in the heparin group compared to no-heparin. To increase insight in this role of heparin during open AAA repair, data of a randomized trial on open and endovascular repair (DREAM) were evaluated for results in the open repair group related to heparin or no heparin bolus administration.

Method

Data from the open AAA repair group from the DREAM-trial were related to the administration of a heparin bolus or no heparin.

Results

In the open repair group 137 patients (80.6%) received a heparin bolus and 33 (19.4%) did not. A dose of 5000 IU was used predominantly (74%). No significant differences were present for bleeding related or arterial thrombo-embolic complications (ATEC). Mortality was higher in the no-heparin group (15.2% vs. 2.2%). In depth analysis showed that none of the death in the no-heparin group could be related to refraining from heparin administration.

Conclusions

The DREAM trial was not designed to evaluate the role of heparin as PPAT during open AAA repair and only 170 patients could be evaluated. Despite these limitations, not administering heparin did not result in statistically significant more ATEC, including myocardial infarction. A systematic review showed a trend towards harmful effects of this use of heparin. This evaluation of DREAM data underlines the importance of an upcoming randomized controlled trial, in which patients will be randomized to heparin or no heparin during open AAA repair. Bleeding complications and ATEC will be evaluated to determine the beneficial or harmful effect of heparin as PPAT.

Introduction

The majority of vascular surgeons use unfractionated heparin (UFH) as a periprocedural prophylactic antithrombotic (PPAT) to prevent arterial thrombosis during cross clamping of the aorta while performing open abdominal aortic aneurysm (AAA) repair.[1-3] Nevertheless, about 10-15% of vascular surgeons refrain from the standardized use of heparin as a prophylactic antithrombotic.[1-3] A recent systematic review on the use of heparin during open (and endovascular) repair of (r)AAA,[4] showed that no compelling evidence presently exists on the beneficiary effect of heparin administered for this indication. Despite the surprisingly small number of studies that could be included for that review, the incidence of arterial thrombo-embolic complications (ATEC) was not higher without the use of heparin compared to the group with the use of heparin during open AAA repair. Additionally, the assumed cardio-protective effect of a single bolus of heparin could not be confirmed in that review.[4] Despite this lack of evidence supporting the use of heparin during open AAA repair, contemporary guidelines[5,6] still advocate the use of a bolus heparin before cross-clamping of the aorta during AAA repair. Considering the above it appears that, after its introduction in clinical practice in the 1940's,[7] the prophylactic use of a bolus of heparin during open AAA repair is still under debate, despite its current widespread use by vascular surgeons worldwide.

In order to increase the insights on the outcomes of patients receiving heparin or no heparin during open AAA repair, a sub-analysis was performed on the data of a trial on open and endovascular AAA repair: the Dutch Randomized Endovascular Aneurysm Management[8] (DREAM) trial. Aim of this analysis was to evaluate the possible role of heparin as arterial thrombosis prophylaxis during open AAA surgery.

Materials and methods

The DREAM trial was instituted to compare open and endovascular AAA repair with the endpoints being operative (30 day) mortality and 2 composite endpoints of operative mortality and severe complications and operative mortality and moderate or severe complications.[8] For the current analysis, the original data from the DREAM trial were evaluated for the group of patients that underwent open AAA repair. Predefined outcomes of data were compared for the heparin and no-heparin groups: baseline characteristics, bleeding related outcomes, defined as

estimated blood loss (millilitres (mL)), autologous blood returned (mL), homologous blood transfused (units), replaced blood total (mL), replaced fresh frozen plasma (FFP) (units), replaced blood platelets (units) and replaced blood SAGM/PC (units). Furthermore, other parameters that could have been heparin-administration related were evaluated, namely: duration of surgery (minutes (min)), total duration of procedure (min), hospital admission stay (days), moderate-severe complications including death (yes or no), incidence and severity of ATEC and incidence of myocardial infraction (MI). Complications were classified and graded according to the reporting standards of the Ad Hoc Committee for Standardized Reporting Practices in Vascular Surgery of the Society for Vascular Surgery/International Society for Cardio-Vascular Surgery.[9,10] In-hospital mortality and complications were defined as those that occurred within 30 days after surgery or more than 30 days after surgery, but during the same admission.

Heparin administration in the DREAM protocol[8] was not standardized and left at the discretion of the operating surgeon. Details on heparin administration (yes or no and the amount of bolus in international units) were scored in the initial case record forms (CRF) and retrieved from original database from DREAM.

Statistical analysis

Relative risk with 95% confidence interval was calculated for dichotomous variables. Data for continuous variables were expressed as mean ± standard deviation (SD) for normal distribution and as median with a range for skewed distribution. Differences between categorical variables were analysed with Chi-Square or Fisher's Exact Test (two-sided). Differences between continuous variables were analysed with the Student's two-tailed test (normal distribution) or Mann-Whitney *U* test (skewed distribution). A P-value of $< .05$ was considered statistically significant. Statistical analysis was performed using IBM SPSS®, version 20.

Results

In the DREAM-trial[8] 178 patients were randomized to undergo open repair of their AAA. Of those 178 patients 3 declined treatment, one died from a rupture before elective scheduled

surgery. In 4 patients an endovascular procedure was converted to open surgery. This resulted in 170 patients to be included in analysis for the open repair group.
In 137 (80.6%) of the included 170 patients an intravenous (iv) bolus of heparin was administered before aortic cross clamping and 33 (19.4%) patients received no heparin. Baseline characteristics of both groups are depicted in table 1. Patients in the no-heparin group were of older age (72.4 vs. 68.9 years, P = 0.009) and more were non-smokers (36.4 % vs. 57.7 %, P = 0.033). More patients from the no-heparin group suffered from known carotid-artery disease (27.3% vs. 10.9%, P = 0.024) and less patients were labelled as ASA class I (3.0% vs. 30.7%, P = 0.001). Dosages of applied heparin bolus varied, but predominantly 5000 international units (IU) (74%) were used (table 2). The amounts of blood loss, replaced blood or other blood products administered, were not statistically significant different between the heparin or no-heparin groups. Also the duration of surgery and hospital admission time did not differ between both groups. The complication-rate for minor and major complications excluding death was also comparable between heparin or no-heparin groups (table 3). No statistical significant difference was found for the incidence of arterial thrombo-embolic complications (ATEC) for the use of heparin or no-heparin (table 4).
The 30-day mortality, or in-hospital mortality during the same admission, was 2.2% (3 of 137 patients) in the heparin group and 15.2% (5 of 33 patients) in the no-heparin group (RR 6.92, 95% CI 1.56-30.65). An in-depth analysis of the causes of death showed that none of the death was considered to be related to no-heparin admission, see table 5 for the details on mortality.

Discussion

The current analysis of data from the open AAA repair group from the DREAM trial[8] showed that, regardless the fact that no heparin was administered, not more significant arterial thrombo-embolic complications (ATEC) were present, compared to the group in which heparin was administered. The incidence of complications listed as minor and major, including myocardial infarction but excluding death, was similar in the heparin and no-heparin groups. Moreover, Also bleeding-related complications or blood products related outcomes were not different. Mortality, however, defined as death within 30 days of operation or later than 30 days after surgery but during the same admission, showed a higher mortality

rate in the group that did not receive heparin during surgery. Although the number of included patients for analysis of death is small, we analysed the causes of mortality separately. None of those deaths from the no-heparin group could be regarded as related to ATEC or otherwise be related to the refraining of heparin administration. Interestingly, 3 of 5 patients died of bleeding-related complications, while no heparin was administered. Two of 5 patients died of sepsis that was confirmed at autopsy, of which one patient had an infected hematoma. Another patient died of massive blood loss, probably at anastomosis and one patient developed a multiple organ dysfunction syndrome after an intra-operative shock, presumably caused an allergic reaction on fresh frozen plasma. In only one patient, who eventually died of an aspiration-pneumonia, a "silent" myocardial infarction could not completely be ruled out. This patient died of massive aspiration. A multivariate analysis on confounders for mortality was considered, but declined. To perform a statistically reliable multivariate analysis, minimally 100 events and a ratio of at least 10 events per 1 investigated extra variable should be present. These demands were, by far, not met, therefore the multivariate analysis was not performed.

Since the introduction of heparin in vascular surgery some 70 years ago,[7] it has been used by most vascular surgeons around the world during open AAA repair. Supposedly heparin decreases the incidence of ATEC and has a cardio-protective effect for the patient. The use of heparin during non-cardiac vascular surgery has mostly been extrapolated directly from cardiac surgery without large trials establishing the exact role of heparin in major non-cardiac vascular surgery. From inventories amongst vascular surgeons in Europe, the UK and the USA in the past 20 years, it is known that 10-15% of surgeons refrain from the standard use of heparin during open AAA repair.[1-4] One of the main reasons for this is the possible harmful side effect of heparin: a higher bleeding tendency, resulting in longer operation duration, more perioperative blood loss, a higher blood transfusion need and thereby resulting in a higher morbidity and possibly higher mortality.[11,12] Additionally, the use of heparin may result in the onset of heparin-induced-thrombocytopenia (HIT), a rare, but possibly life threatening auto-immune reaction after heparin administration.[13]
A recently performed systematic review on the use of heparin as prophylaxis during open AAA repair[4] could include only 5 studies, a surprisingly low number of studies considering

the fact that 85% of all vascular surgeons around the world use this drug in their everyday practice. The methodological quality of included studies was poor and only one randomized trial could be included. Results from this review indicated that a trend was present towards longer operation time, more blood loss and higher blood transfusion requirements when heparin was used while not more arterial thrombo-embolic complications occurred if no heparin was administered. The only randomized trial, published by Thompson et al.,[14] showed that the incidence of the combination of fatal and non-fatal myocardial infarction (MI) was significantly higher in non-heparinised patients (8.6% vs. 2.0%: RR 0.24, 95% CI 0.07-0.87). However, this result was outside the original study design and the distribution of cardiac risk factors over the heparin and no-heparin group was unknown. Therefore, the difference could be caused by over-presentation of patients prone to cardiac ischemia in the no-heparin group. Besides this, the concerning study excluded patients taking platelet inhibitors, thereby excluding the perioperatively cardio-protective effect of these drugs. Currently all patients who undergo AAA repair use a platelet inhibitor and a statin, which are continued, or even started, perioperatively and they have proven to reduce the occurrence of MI during non-cardiac vascular surgery.[5,15]

During the process of developing a RCT on the use of heparin during open AAA repair by the CAPPA study group[3,4,16] and to further increase our knowledge of the effect of heparin during that type of vascular surgery, the current sub-analysis from the DREAM data was performed. It appeared from this trial data that in the open repair group almost 20% of patients (170 patients, 137 with heparin, 33 no heparin) were operated on without the adjunctive administration of heparin as prophylactic. Results showed no clear benefit from the administration of heparin during open AAA repair.

Of course these result should be considered with caution. The DREAM trial[8] was not designed to analyse the efficacy of heparin usage during open AAA repair. The reasons why no heparin was administered are numerous and may cause bias, both surgeon and patient related and “random” bias. The operating surgeon could have forgotten to administer heparin during surgery, or the surgeon could be convinced that heparin is harmful during open AAA repair and therefore always refrains from its use during this type of vascular surgery. Heparin could intentionally be not administered due to bleeding or coagulation disorders in the medical history of an individual patient. Also the low number of included patients (170, of

which 33 received no heparin), may have influenced the reliability of the study and of any robust conclusions based on this sub-analysis from DREAM data.

In conclusion, despite the internationally widespread us of heparin as a prophylactic to prevent ATEC during open AAA repair, this sub-analysis from the DREAM trial could not show any beneficial effect of the use of heparin in the open operation group. Although these results should be interpreted with caution, it stresses the need for robust randomized data to show for once and for all the beneficial or harmful effect of heparin for the patient during open AAA repair. The CAPPA group from the Netherlands will start this trial called **NANDA?** (**N**o **A**nticoagulation **N**eeded **D**uring open **A**AA repair**?**) at the end of 2014.

Table 1.

Baseline characteristics for no-heparin and heparin groups.

Characteristic	No-heparin (N = 33)	Heparin (N = 137)	Significance
Age (years)	72.4 (±6.1)	68.9 (±6.9)	***0.009***
Male sex (no. (%))	32 (97.0%)	121 (88.3%)	0.200
Mild, Moderate or severe SVS/ICVS risk factor (%)*			
Diabetes mellitus	3 (9.1%)	13 (9.5%)	1.000
Tobacco use	12 (36.4%)	79 (57.7%)	***0.033***
Hypertension	14 (42.4%)	77 (56.2%)	0.176
Carotid-artery disease	9 (27.3%)	15 (10.9%)	***0.024***
Cardiac disease	15 (45.5%)	63 (46.0%)	1.000
Renal disease	3 (9.3%)	11 (8.0%)	0.737
Pulmonary disease	7 (21.2%)	24 (17.5%)	0.620
Sum of SVS/ICVS risk-factor scores			
	4.12 (2.5%)	4.40 (2.4)	0.552
FEV-1 (liters/sec)	2.73 (0.68%)	2.58 (0.69)	0.291
Body-mass index	26.0 (3.7%)	26.7 (4.0)	0.383
ASA class (no. %)			
I (rel. healthy status)	1 (3.0%)	42 (30.7%)	***0.001***
II (mild systemic disease)	23 (69.7%)	80 (58.4%)	
III (severe systemic disease)	9 (27.3%)	15 (10.9%)	
Previous abdominal surgery (no. %)			
	14 (42.4%)	42 (30.7%)	0.219
Maximal diameter of AAA (mm)			
Mean	60.4 mm (±7.8)	59.9 mm (±8.7)	0.794
Median	60.0 mm	58.0 mm	0.491
Anticoagulation or antiplatelet before surgery			
	18 (54.5%)	75 (54.7%)	1.000

Table 2.

Dosages of bolus of heparin, intravenously in international units (IU).

2000 IU	1	=	<1	%
2500 IU	10	=	8	%
3000 IU	9	=	6	%
4000 IU	2	=	1	%
5000 IU	**101**	**=**	**74**	**%**
7000 IU	7	=	5	%
7500 IU	3	=	2	%
8500 IU	1	=	< 1	%
unknown	3	=	2	%
Total	137	=	100 %	

Table 3. Results for no-heparin and heparin groups.

	No-heparin	Heparin	Significance
Duration of surgery (min)			
Mean	239.69	220.70	P = NS
Median	227	215	
I-Q range	165-315	150-290	
Estimated blood loss (ml)			
Mean	1738.13	1655.19	P = NS
Median	1625	1500	
I-Q range	735-2515	215-3095	
Replaced blood total (ml)			
Mean	480	656.92	P = NS
Median	350	200	
Replaced blood autologous (ml)			
Mean	409.76	518.55	P = NS
Median	412	452.50	
Replaced blood cryo (units)			
Mean	0.18	0	P = NS
Median	0	0	
Replaced blood FFP (units)			
Mean	0.18	0.37	P = NS
Median	0	0	
Replaced blood platelets (units)			
Mean	0	0.003	P = NS
Median	0	0	
Complications moderate-severe incl. death (yes-no)			
Mean	0.33	0.28	P = NS
Median	0	0	
Hospital stay (days)			
Mean	15	12.88	P = NS
Median	11	10	
I-Q range	7-23	7-19	

Table 4.

Arterial thrombo-embolic complications for no-heparin and heparin groups.

	No-heparin (N = 33)	**Heparin (N = 137)**	**Significance**
Perioperative haemorrhagic complications			
	4 (12.1%)	11 (8.0%)	RR 1.51 (95% CI 0.45-5.08)
Perioperative haemorrhagic complications requiring intervention			
	2 (6.1%)	9 (6.6%)	RR 0.92 (95% CI 0.19-4.47)
Arterial thrombo-embolic complications			
Thrombo-embolectomy (procedural)			
	2 (6.1%)	2 (1.5%)	RR 4.15 (95% CI 0.56-30.62)
Postprocedural thrombo-embolectomy or bypass			
	1 (3.0%)	1 (0.7%)	RR 4.15 (95% CI 0.25-68.14)
Ischemic bowel	1 (3.0%)	2 (1.5%)	RR 2.08 (95% CI 0.18-23.66)
Renal insufficiency (thrombo-embolic)			
	0 (0%)	1 (0.7%)	NS
Ischemic stroke	0 (0%)	0 (0%)	NS
Total	**5 (15.2%)***	**7 (5.1%)***	**RR 2.97 (95% CI 0.88-10.04)**

* = In both groups 2 thrombo-embolic complications occurred in one patient.

Table 5. Details of mortality for the no-heparin and heparin groups.

No-heparin group.

Number:	*Cause of death:*	*No-heparin related:*
I	Massive aspiration	Not related
II	Sepsis, infected graft (autopsy) Encephalopathy as co-morbidity after intervention	Not related
III	Massive blood loss, probably anastomosis	Not related
IV	Sepsis, autopsy: infected hematoma	Not related
V	MODS, intra-operative anaphylactic shock due to FFP[¶]?	Not related

Heparin group.

Number:	*Cause of death:*	*Heparin related:*
I	MODS[*]/ARDS[#], adipose	Not related
II	Dementia, refusal to eat/drink	Not related
III	Ischemic bowel, MODS[*]	Not related

[*]MODS = Multiple Organ Dysfunction Syndrome
[#]ARDS = Acute Respiratory Distress Syndrome
[¶]FFP = Fresh Frozen Plasma

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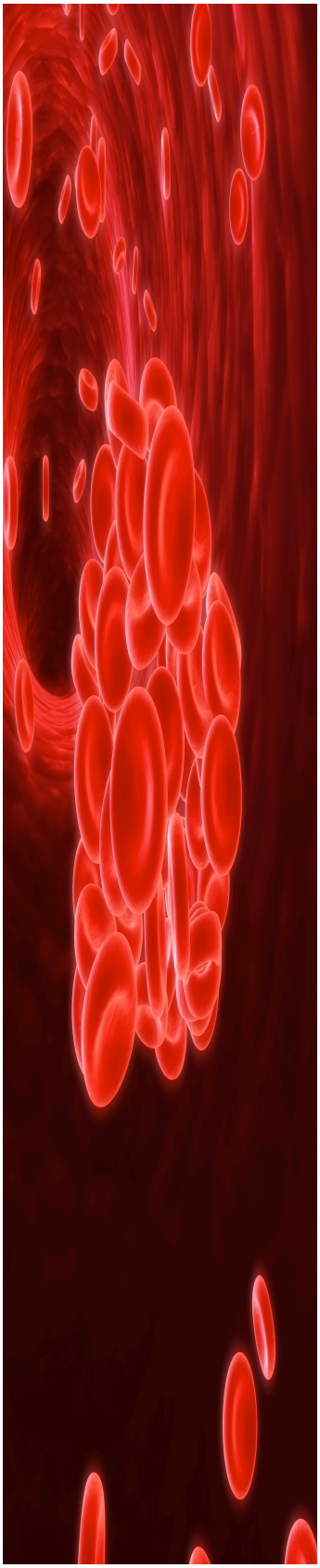

Chapter 9

No Anticoagulation Needed During open abdominal aortic Aneurysm repair? The NANDA? trial: background, design and methods

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Abstract

Objectives

The **N**o **A**nticoagulation **N**eeded **D**uring open abdominal aortic **A**neurysm repair**?** (NANDA?) trial aims to assess the role of heparin as periprocedural prophylactic antithrombotic during open juxta-en infra-renal abdominal aortic aneurysm (AAA) repair. The beneficiary or harmful effect of heparin during that type of infrarenal AAA surgery, will be determined in terms of blood loss and need for blood transfusions, the incidence of arterial thrombo-embolic complications and mortality.

Design

Randomized controlled, double-blinded and multi-center trial. Male and female patients who will be scheduled to undergo open repair of a primary juxta- or infrarenal abdominal aortic aneurysm, will be randomized to receive either heparin or no-heparin (saline) before supra- or infrarenal cross clamping of the abdominal aorta. Primary endpoints will be blood loss and blood transfusion, estimated to be 30% less in the no-heparin group. All arterial thrombo-embolic complications, including lethal and non-lethal myocardial infarction are suppose to be equal in heparin and no-heparin groups. A power calculation showed that for a 30% reduction in blood loss, 197 patients per group are necessary.

Introduction

Heparin is used by most vascular surgeons worldwide during open or endovascular abdominal aortic aneurysm (AAA) repair.[1-3] It is administered before aortic cross clamping to prophylactically reduce arterial thrombo-embolic complications (ATEC). These ATECs can be located in the arteries proximal and distal from clamped artery, resulting in ischemic kidneys or lower extremities but can also be systemic, resulting in bowel ischemia, cerebro-vascular ischemic events and myocardial infarction (lethal or non-lethal). Since its introduction in clinical practice by Murray in 1940,[4] heparin has been adopted by (cardio)vascular surgeons and interventional radiologists as periprocedural prophylactic antithrombotic (PPAT).[3,5] Heparin permitted vascular surgical interventions to a increase, but the disadvantages of using heparin were also soon recognized: more peri- and postoperative bleeding. This can result in life threatening blood loss during surgery and the need for (more) blood transfusions. Blood transfusion can cause a serious allergic reaction and can cause, despite extensive matching, the formation of antibodies. Blood transfusions also may lead to the transmission of viral, bacterial and parasitological infectious disease. Finally, blood transfusion suppresses the immune system and can influence the coagulation cascade.[6]
Increased blood loss during surgery can lead to a prolonged operation duration, which can also enhance infectious complications. Deep wound infections or graft infections are serious complications, increasing morbidity and even mortality from AAA repair and increasing the incidence of re-operations. Heparin used as PPAT can also cause an auto-immune reaction, heparin induced thrombocytopenia (HIT) syndrome. This is an unpredictable response of the immune system on the administration of heparin. It can occur even after only a single intra-venous (iv) bolus dosage. HIT can lead to clinically relevant arterial and venous thrombo-embolic complications, which can lead to amputation and in its most severe form even to death. The reported incidence of HIT varies from 0.5% to 5%.[7]
Because of these described harmful side effects of the administration of heparin as PPAT during open AAA repair, some surgeons refrain from the use of heparin during surgery of the dilated abdominal aorta.[8]
To increase insight in the daily use of PPAT and to develop new, evidence based guidelines on this topic, a study group was formed in the Netherlands, CAPPA: Consensus on Arterial PeriProcedural Anticoagulation. The group consists of vascular surgeons and interventional

radiologists and is supported by Dutch Boards of Vascular Surgery and Interventional Radiology (IR). An extensive survey was held amongst vascular surgeons by the CAPPA group on the use of PPAT in daily practice in the Netherlands.[3] From this survey it appeared that almost all (93%) surgeons administer heparin as PPAT during open AAA surgery. However, applied doses, whether or not a repeated dose was applied and the use of protamine for heparin reversal, varied widely. Also only a vast minority of vascular surgeons performed a measurement of actual anticoagulation effect of administered heparin (11%). These results are in compliance with results from other countries.[1,2]

To further evaluate the role of heparin as PPAT during open AAA surgery a systematic review was performed.[8] This review showed that for open AAA repair only 5 studies were eligible for evaluation, including only 1 randomized controlled trial (RCT). Two studies[9,10] reported significantly more blood loss and a longer operation time in heparinized patients treated with tube grafts and one of these studies[10] found that blood loss increased when heparin dosage increased. Statistically significantly more blood transfusions were needed in heparinised patients compared to non-heparinised patents in one study.[9]

All studies on elective AAA repair[9-12] did not report statistically significant differences between heparinized and non-heparinized patients for non-fatal myocardial infraction (MI), fatal MI or operative mortality. However, in the RCT,[11] the combination of fatal and non-fatal MIs proved to be significantly more frequent in non-heparinised patients (n=3 vs n=12, 8.6% vs. 2.0%: RR 0.24, 95% CI 0.07-0.87) . This outcome was, however, outside original study design and the distribution of cardiac risk factors over both groups was unknown. Therefore, this difference could result from over-presentation of patients prone to cardiac ischemia in the non-heparinised group. Furthermore, this study excluded patients taking ASA thereby excluding the cardio-protective effect of ASA perioperatively. In all included studies no statistically significant differences were found for the incidence of ATEC between heparin and no-heparin groups.

In conclusion, the systematic review showed, despite its limitations, no compelling evidence for the beneficiary effect of heparin as PPAT during AAA repair. On the contrary, a trend was observed towards harmful effects of heparin, such as increased operation time, increased blood loss and more blood transfusions needed.

In the Netherlands a large randomized trial was performed, the DREAM trial (the Dutch Randomized Endovascular Aneurysm Management trial).[13] This trial compared open repair of infrarenal AAA with endovascular repair. From the open repair group a subset analysis was performed to evaluate any differences in results for the group with heparin compared to the no-heparin group. In 20% of patients from the open repair group no heparin was used. No differences for patient related outcomes were found between the heparin and no heparin group. So from this analysis it appears that not administering heparin has no harmful effect on patient outcomes during open infrarenal AAA repair. Both peri-operative strategies of using heparin or no-heparin are currently applied in the Netherlands.

Because of the lack of evidence in current literature and the doubts on beneficiary effects of heparin during open AAA repair, a thorough evaluation of the beneficiary or harmful effect of heparin as PPAT during open AAA repair will be performed: the NANDA? trial (No Anticoagulation Needed During open abdominal aortic Aneurysm repair?). This study will be a randomized controlled, double blind and multi-center trial, in which patients are randomized to heparin or no-heparin before aortic cross clamping.

Materials and methods

Design

Randomized controlled, double blind and multi-center trial. Results will be analysed on intention-to-treat basis. The study is approved by Dutch local medical ethics committee. Trial is registered at clinicaltrials.gov, nr…… Study protocol was consulted with the Dutch association of cardio-vascular patients and their comments were implemented in study protocols.

Inclusion and exclusion criteria and recruitment

Patients are male or female of at least 18 years of age and should be able to give performed consent. Patients should be scheduled to undergo open repair of a primary juxta- or infra-renal abdominal aortic aneurysm. No patient with a re-operation for an anastomotic aneurysm or after other previous surgery on the abdominal aorta is permitted to be included. Also patients

with soft tissue diseases resulting in abdominal aneurysms are to be excluded. No anticoagulation disorder or previous HIT may be present in medical history of patient. All patient should be on statin treatment and platelet aggregation inhibitors (such as ASA or clopidogrel) or vitamin K antagonists (such as acenocoumarol).
Recruitment will be done at outpatient clinic by attending vascular surgeon. All required patient information will be supplied and after 5 days minimum, another vascular surgeon or research nurse will get informed consent.

Operation details

Juxta- or infra-renal aortic aneurysm has to be operated on through the abdominal approach, trans- or retro-peritoneal. Cross clamping of the aorta can be supra- or infra-renal, not above the inferior mesenteric artery (IMA). During surgery locally administering a heparin/saline solution is permitted in the renal, iliac or femoral arteries and the IMA. Concentration of the heparin/saline solution should be registered in case record form (CRF, appendix 1) and also the amounts injected and in which vessel. Other details of surgery are depicted in the CRF, appendix 1.

Data management

In the Netherlands a registry for all AAA operations is mandatory for all vascular surgeons, Dutch Surgical Aneurysm Audit (DSAA, dsaa.clinicalaudit.nl). These data will be used for the CRF. In this CRF more details of surgery, blood tests and complications are implemented. The CRF is designed in accordance with the reporting standards of the Ad Hoc Committee for Standardized Reporting Practices in Vascular Surgery of the Society for Vascular Surgery/International Society for Cardio-Vascular Surgery.[14,15] Data management will be done using IBM SPSS®, version 20.

Randomization

A randomization list for each participating hospital is made by the pharmacy of University Medical Center Utrecht (UMCU), according to protocol from UMCU (I-O2-18/002/Jan2009). In each participating hospital 2 independent persons from the operation room department will be certified to obtain either heparin or saline in a syringe from the standard medication

supply. The heparin or saline will be presented to the anesthesiologist or certified anaesthesiology-assistant in a blank syringe. Medication will than be administered to patient. All members of OR team are thereby blinded for study medication. A randomization list is available in all participating hospitals, in case of the need to know whether the patient received heparin or not, this can immediately be known by assessing the randomization list. The decision to break the randomization code is entirely up to the participating/operating surgeon and/or the other members of the medical team treating the patient. The decision to break the randomization will always be communicated with the principal investigator (PI) and project leader.

Main study parameters/endpoints

Primary endpoints:

Blood loss and administration of blood and blood products from start of surgery to 30 days postoperatively or during same admission. A reduction of 30% in blood loss when no-heparin is used compared to the heparin group is used for the power-calculation. Blood loss registration and methods of measurement are specified in CRF (appendix 1). Endpoints of study will be death by any cause, wish from the patient to discontinue participation in the study and end of follow-up: 30 days after surgery or end of admission in which surgery was performed.

Secondary endpoints:

All (coagulation related) complications scored according to reporting standards of the Ad Hoc Committee for Standardized Reporting Practices in Vascular Surgery of the Society for Vascular Surgery/International Society for Cardio-Vascular Surgery.[14,15] All parameters according to Dutch National Aneurysm Audit (see attached CRF, appendix 1). Complications and in-hospital mortality are defined as those that occurred within 30 days after surgery or more than 30 days after surgery but during the same admission.

Sample size

The required sample size was estimated at 394 patients. This was estimated on the premise that a 30% reduction in blood loss will be present in the no-heparin group. To be able to

detect this reduction in blood loss with a statistical power of 90% ($\beta = 0.1$) and $\alpha = 5\%$, 197 patients per group are required. When 20% of patients refuse participation in the study, 490 eligible patients are necessary. After an evaluation of the open infrarenal AAA repairs of probably participating hospitals, it appeared that per year 200 open repairs are performed. Based on our sample size calculation, inclusion should be terminated within 3 years.

Statistical analysis

Description of nominal and ordinal data will be described using frequency tables, mode and median. Interval/ratio variables will be described using the mean, the standard deviation and 95%-confidence intervals.

Relations between nominal or ordinal variables will be analysed using the chi square test. Differences for ordinal variables with respect to subgroups will be analysed using the Mann-Whitney U test or the Kruskall-Wallis test. Differences with respect to subgroups of interval/ratio variables will be analysed using Student's-T test or analysis-of-variance (ANOVA) if data are normally distributed. Or, in case of a non-normal distribution, using the Mann-Whitney U or the Kruskall-Wallis test Normality of interval/ratio variables will be tested using the Kolmogorov-Smirnof test.

Comparison of data mutually (depending on the level of measurement) will be done using the Chi-squared test, the Wilcoxon signed-rank test, the Friedman test and Pearson or Spearman's correlation coefficients.

Multivariate regression analysis will be performed to estimate causal relationships between variables and to correct for possible confounders.

All statistical analysis will be performed using Statistical Package for the Social Sciences (SPSS©, version 20) by IBM.

Interim analysis

After one year and 2 years from start of study (inclusion date of first patient), an interim-analysis will be executed and also when 200 patients (100 in each group) are included. The study will be stopped when mortality in the one of the groups is > 50% than expected from literature. The same applies for the incidence of moderate-severe thrombo-embolic complications and for myocardial infarction (lethal and non-lethal). All other serious adverse

events (SAEs) will be evaluated and study will be stopped if the difference between heparin and no-heparin groups is > 100%. Also an interim analysis will be performed earlier than inclusion of 200 patients when decided by PI/coordinating investigator (CI) or on request of individual collaborators in case of a suspected higher frequency of SAEs than known from literature.

Monitoring and Quality Assurance

According to UMCU guidelines and NFU (Dutch Federation of University Hospitals) guidelines, the current study is labelled "medium-risk". All demands for a "medium-risk" study are met (table 1).

Monitoring will be performed by an independent monitoring committee, legally qualified, with permission of UMCU (TFS Trial Form Support International AB®). A written report will be delivered by monitor to coordinating investigator after each monitoring visit. This report will be stored at the division of vascular surgery by coordinating investigator, next to the CFRs and will always be available for auditing. Local investigators will receive a written summary of each monitoring visit to the participating centre.

The monitoring visit report will contain:

- a summary of which data monitor has evaluated
- a general description of quality
- a list of important findings, discrepancies and shortcomings
- a list with needed recommendations to improve protocol acquittal.
- general conclusions

Also the written results of the initiation monitoring visit and close-out visit for each participating centre will be provided to coordinating investigator and participating centre.

Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to open infra-renal AAA surgery or heparin administration or saline administration. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded. All adverse events are

registered in all participating centres and by all participating vascular surgeons, as standard of care, in the Dutch Surgical Aneurysm Audit. All participating vascular surgeons in this study will grant access to their audit data and these are incorporated in the CRF. So all AEs are registered. All AEs are also scored in the CRF. Possible groups of AEs are:
Myocardial infarction, TIA/CVA, venous thrombosis, pulmonal embolus, coagulation disorders, renal insufficiency, bowel ischemia, graft infection, local complication of graft or native artery, kinking graft, anastomotic bleeding, graft thrombosis, graft enteric complication, unexpected tissue-loss or amputation, athero-embolic complications, spinal cord ischemia, non-infectious fluid collection, wound infection, lymphatic complication, urethra complication and sexual dysfunction.

Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that at any dose:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardize the subject or may require an intervention to prevent one of the outcomes listed above.

The handling of SAEs is depicted in a protocol by the UMCU. All study details are performed according to all applicable instructions and protocols from the UMCU. All SAEs are to be reported by local investigators to coordinating investigator/sponsor. The coordinating investigator/sponsor is responsible for reporting the SAE according to protocol safety reporting from UMCU and accredited METC that approved the study protocol.
SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse event. This is for a preliminary report with another 8 days for completion of the report.

Final analysis

One month after the last patient is included, or after the admission of that patient in case this patient is longer admitted in hospital than 30 days, analysis will be performed.

Conclusion

The NANDA? trial will hopefully answer the question if no-heparin is beneficial for the patient compared to heparin as periprocedural prophylactic antithrombotic during open juxta- or infra-renal AAA surgery by decreasing blood loss related complications with the same incidence of arterial thrombo-embolic complications including myocardial infarction.

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Appendix 1. Case Record Form.

Case Record Form NANDA-I.

Coördinating investigators form.

Studie nummer	
Kliniek	
Patiënt-nummer kliniek	
Geslacht	**M** **F**
Geboortedatum	
Voorletters	
Tussenvoegsel	
Eigennaam	
Naam partner	
Postcode	

Datum eerste polibezoek	
Diameter AAA eerste poli	

Cardiale VG	**Ja**	**Nee**	**Onbekend**
Acuut infarct/ischemische hartziekten	**Ja**	**Nee**	**Onbekend**
Hartfalen/dec cordis	**Ja**	**Nee**	**Onbekend**
Borderline cardiomyopathie	**Ja**	**Nee**	**Onbekend**
Cardiomegalie	**Ja**	**Nee**	**Onbekend**
Hypertensie (al dan niet adequaat behandeld)	**Ja**	**Nee**	**Onbekend**
Hypercholesterolaemie	**Ja**	**Nee**	**Onbekend**
COPD/Longfibrose	**Ja**	**Nee**	**Onbekend**
CVA	**Ja**	**Nee**	**Onbekend**
Maligniteit	**Ja**	**Nee**	**Onbekend**

Curatief > 5 jr	**Curatief < 5 jr**	**Palliatief/meta's op afstand**	**Anders**	
Diabetes mellitus	**Ja**	**Ja, met eindorgaanfalen**		
	Nee	**Onbekend**		
Nierfunctiestoornis	**Ja**	**Ja, dialyse**	**Onbekend**	
	Nee	**Niertransplantatie**		
Klinisch PAOD	**Ja**	**Nee**	**Onbekend**	
Eerdere buikoperaties	**Ja**	**Nee**	**Onbekend**	

Details:

Voorgeschiedenis.

Vasculair Open **Ja** **Nee** **Onbekend**

Details operatie 1: **Jaar:**

Aard:

Details operatie 2: **Jaar:**

Aard:

Details operatie 3: **Jaar:**

Aard:

Coronair **Jaar:**

Aard:

Endovasculair: **Ja** **Nee**

Details endo 1: **Jaar:**

Aard:

Details endo 2: **Jaar:**

Aard:

Details endo 3: **Jaar:**

Aard:

Coronair: **Jaar:**

Aard:

Datum wachtlijst

Lengte

Gewicht

Roken **Actueel** **< 1 jr stop** **> 1 jr stop** **Nooit**

Drugs **Actueel** **Stop** **Nooit** **Onbekend**

Medicatie preoperatief

Antihypertensiva **Ja** **Nee** **Onbekend**

Ascal **Ja** **Nee** **Onbekend**

Gestopt voor operatie **Ja** **Nee** **Onbekend**

Statine **Ja** **Nee** **Onbekend**

Beta-blokker **Ja** **Nee** **Onbekend**

Digoxine **Ja** **Nee** **Onbekend**

Vit K. antagonisten **Ja** **Nee** **Onbekend**

Immunosuppressiva **Ja** **Nee** **Onbekend**

Clopidogrel **Ja** **Nee**

Dosering **75 mg 1 x1** **Anders**

Gestopt voor operatie **Ja** **Nee** **Onbekend**

Andere antistollingsmiddelen **Ja** **Nee** **Onbekend**

Soort/dosering

Ascal dosering:

Statine soort/dosering:

Cardiale status pre-operatief

Geen

Medicatie: hypertensie, ang pect,diuretica,digoxine

Perifeer oedeem, vit K antagonist, border cardiomegalie

Verhoogde CVD, cardiomegalie

Onbekend

Pulmonale status pre-operatief

Geen dyspneu

Dyspneu inspanning
Invaliderende dyspneu

Dyspneu rust, consolidatie, fibrose op X thorax

Bloeddruk bovendruk

Bloeddruk onderdruk

Hartfrequentie

ASA **I** **II** **III** **IV**

Enkel-arm index in rust

R

L

ONBEKEND

CT-A pre-operatief **Ja** **Nee**

Angio DSA pre-operatief	**Ja**	**Nee**
MRA	**Ja**	**Nee**

Grootste diameter AAA pre-op.
(mm)

Laboratorium onderzoek pre-operatief	
Datum	
Hb	
Leucocyten	
Natrium	
Kalium	
Kreatinine	
EGFR	
Trombocyten	

Laatste ECG	**Niet afwijkend**
	Atriumfibrilleren met freq. 60-90

	Ischemie			
	Elke andere afwijking			
	Geen ECG			
MDO	**Ja**	**Nee**	**Onbekend**	
datum				
OPERATIE				
Datum operatie				
Urgentie	**Urgent**	**< 24 uur**	**Electief**	
Aantal procedures	**I**	**II**		**>II**
Supra-renaal geklemd	**Ja**	**Boven 1**	**Boven 2**	**Nee**
Peritoneale contaminatie **Geen**	**Minimaal vocht**	**Abces**	**Darminhoud**	
Peroperatieve complicatie	**Ja**	**Nee**		
	Reanimatie/Myocardinfarct			
	Niet geplande afsluiting AII			
	Geplande afsluiting AII			
	Darmletsel, overhecht			
	Ureterletsel, overhecht			
	Anders:			
Details operatie.				

Proximale klem:

Klem infra-renaal **Ja** **Nee**

Klem supra-renaal **Ja** **Nee**

Boven nierarterie L en R **Boven L nierarterie** **Boven R nierarterie**

Distale klem:

R **AIC** **AIE en AII** **AFC** **AFS en APF**

Anders:

L **AIC** **AIE en AII** **AFC** **AFS en APF**

Anders:

Heparine **Ja** **Nee**

Dosis 5000 IU iv **Ja** **Nee**

Tijd voor klemmen in **minuten:**

Herhaalgift **Ja** **Nee** **Dosis:**

Reden

Opspuiten heparine/zoutoplossing: **Ja** **Nee**

Concentratie: **10.000 IU/L** **5.000 IU/l** **Anders:**

Anders =

R nierarterie **L nierarterie**

R AIC **L AIC** **R femoraal** **L femoraal**

Klemtijd Boven nierarterie

Onder nierarterie

Totale klemtijd

Totaal geschat peroperatief bloedverlies incl.cell-saver (in cc)

Geschat bloedverlies niet in cellsaver opgevangen

Dus in cellsaver

Bloedverlies in gazen

Eventuele spill (niet in zuig of cellsaver of gazen

Aantal pc via cellsaver retour

Bloed retour in cc uit cellsaver

Bloedtransfusie (in pc) na operatie en dag waarop

Trombos (eenheden)

Fresh frozen plasma

Postoperatief:

Aard en dag postoperatief

Behandeling complicatie **Ja** **Nee**

Embolectomie **Ja** **Nee**

	Standaard	Geen backflow
Resultaat		

Overige behandeling peri-operatieve en postoperatieve complicaties en dag waarop:

Tijdstip start inleiding	
Tijdstip start incisie	
Tijdstip start sluiten huid	

1-ste operateur **Arts-assistent**

Vaatdifferentiant

CHIVO/Fellow

Vaatchirurg < 5 jr

Vaatchirurg 5-10 jaar

Vaatchirurg > 10 jaar

Postoperatief.

Na operatie **Hb** **Trombo's**

Indien bepaald:

Dag 1

Dag 2

Dag 3

Dag 4

Dag 5

Dag 6

Dag 7

Aantal dagen op IC/MC/PACU

Geen **Onbekend**

Complicatie < 30 dagen

Ja **Nee** **Onbekend**

Chirurgische complicatie

Ja **Nee** **Onbekend**

Soort

Nabloeding

Darmischemie

Occlusie nierarterie

Arteriële occlusie elders, incl. trashfoot

Dwarslaesie

Prothese infectie

Abdominaal abces, sepsis

Darmletsel

Miltletsel

Fasciedehiscentie

Ileus

Diepe wondinfectie

Re-interventie voor deze complicatie

Ja **Nee**

	Endovasculair		
	Radiologisch		
	Re-laparotomie		
Stoma	**Ja**	**Nee**	
Major amputatie	**Ja**	**Nee**	
Cardiale complicatie	**Ja**	**Nee**	
Pulmonale complicatie	**Ja**	**Nee**	
Nierinsufficiëntie	**Ja**	**Nee**	
		Tijdelijk/CVVH	
		Blijvend dialyse	
Infectieuze complicatie	**Ja**	**Nee**	
Multi-orgaanfalen	**Ja**	**Nee**	
Neurologische complicatie	**Ja**	**Nee**	
LHCR gradatie	**Volledig herstel zonder interventie**		
		Volledig herstel na re-interventie	
		Langdurig, > 3 mnd, of blijvende schade	
		Overleden tgv complicaties	
Ontslagdatum			
Ongeplande heropname < 30 dgn	**Ja**	**Nee**	**Onbekend**

Overleden tijdens opname **Ja** **Nee**

Overleden < 30 dagen **Ja** **Nee**

Datum

COMPLICATIES SCORE

0 = geen
1 = mild
2 = matig
3 = ernstig

Systemisch en/of op afstand

Cardiaal

Ectopisch/arrhytmieen **1 = geen/weinig hemodynamische consequenties**

Congestief hartfalen **2 = sympt/therapie noodzakelijk**

Myocard infarct **3 = hartstilstand/fataal**

TIA/CVA

1 = TIA/tijdelijke schade

2 = permanente schade

3 = fataal

Diep veneuze trombose

Verdacht **1 = opname niet verlengd**

Bevestigd **2 = therapie en verlengde opname**

3 = operatie

Longembolie

Verdacht	**1 = mild, antitrombotica**
Bevestigd	**2 = ernstig, resuscitatie**
	3 = zwaar, embolectomie of fataal

Stollingscomplicatie

Spontane bloeding	**1 = opgelost zonder behandeling**
Trombocytopenie	**2 = farmaca noodzakelijk**
"Wit stolsel syndroom"	**3 = operatie of fataal**
Trombose door ATIII of prot C/S def.	
HIT (heparin induced thrombocytopenia)	

Nierinsufficiëntie

Contrast geïnduceerd	**1 = voorbijgaand, geen dialyse**
Trombo-embolisch	**2 = voorbijgaand, wel dialyse**
Ischemisch (ATN)	**3 = permanent (dialyse, NTx)**
Obstructief	

Darmischemie

Sigmoïd	**1 = conservatief**
Colon	**2 = operatief trombectomie**
Dundarm	**3 = operatief resectie**
Combinatie	**4 = fataal**

Lokaal/vasculair

Graft infectie

Vroeg of laat > 30 dgn	**1 = succesvol lokale therapie**

Kweek positief/negatief **2 = graft verwijderen/bypass**

Non-invasief **3 = amputatie/fataal**

Invasief (graft of anastomose)

Compl graft/native vat

Intima hyperplasie **1 = geen therapie**

Proximale anastomose **2 = lokale therapie**

Distale anastomose **3 = redo-operatie**

Pseudoaneurysmata

Mechanisch

Infectieus

Graft complicatie niet bij anastomose

Dilatatie/aneurysma **1 = geen therapie**

Stenose (focaal/diffuus) **2 = lokale therapie**

3 = redo-operati

Elongatie/kinking

Intrinsiek, structureel defect **1 = geen therapie**

Atherosclerotisch **2 = lokale therapie**

Technisch **3 = redo-operatie**

Anastomose bloeding

Externe bloeding **1 = observatie**

Interne bloeding (hematoom) **2 = aspiratie, drainage**

3 = operatie met revisie anastomose

Graft trombose

Vroeg/laat (30 dgn) **1 = geen therapie of geen operati**

Oorzaak bekend **2 = revisie of redo-operatie**

Oorzaak onbekend **3 = weefselverlies of amputatie**

Graft-enteric reactie

Fistel op anastomose vs niet op anastomose

Primaire infectie vs secundaire infectie

1 = therapie zonder weefselverlies

2 = permanent weefselverlies

3 = fataal

Onverwacht weefselverlies/amputatie

1 = wond zonder amputatie

2 = kleine amputatie (teen/voorvoet)

3 = grote amputatie

Atheroembolie **1 = zonder weefselverlies**

2 = weinig weefsel/kleine amputatie

3 = groot weefsel/amputat

Ruggemergischemie **1 = voorbijgaand**

2 = klein blijvend verlies

3 = groot blijvend verlies

Lokaal/niet-vasculair

Niet-infectieuze vochtcollectie

Hematoom	**1 = conservatief, geresorbeerd**
Seroom	**2 = aspiratie**
Lymfocele	**3 = chirurgische drainage**

Wondinfectie

Oppervlakkig	**1 = antibiotica alleen**
Diep	**2 = drainage**
Gecontamineerde graft	**3 = graft verwijderen/bypass**

Lymfe

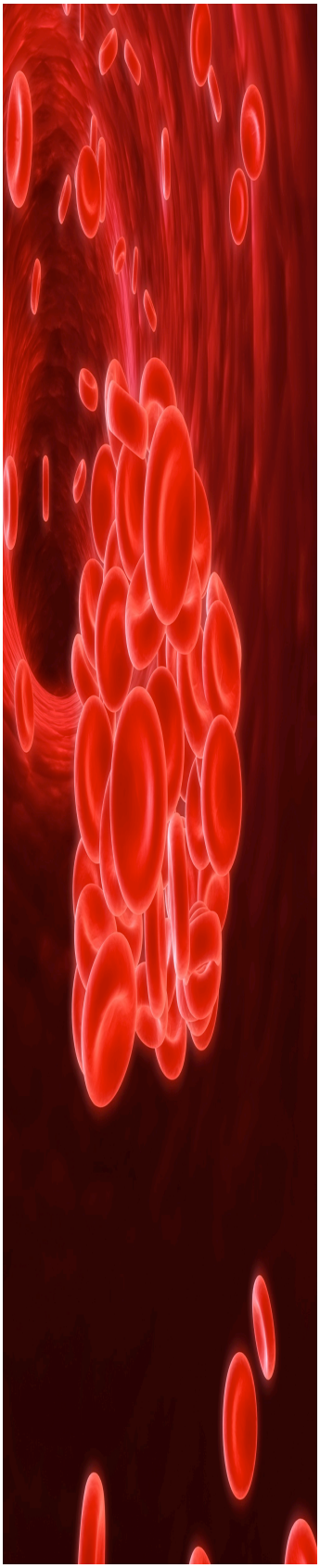
Lymfoedeem	**1 = geen therapie**
Lymfocele	**2 = aspiratie, drainage**
Lymfe fistel	**3 = exploratie chirurgisch**

Urethra

Complete obstructie	**1 = spontaan genezen**
Partiële obstructie	**2 = drainage, diversie**
Urinoom	**3 = chir correctie/nefrostomie**
Urine fistel	

Seksuele dysfunctie

Retrograde ejaculatie	**1 = mild-geen effect op seksualiteit**
Fertiliteit	**2 = verminderde seksualiteit**
Erectie	**3 = geen seksuele activiteit**



Chapter 10

Letters to the editor:

I: The use of heparin in patients with ruptured abdominal aortic aneurysms

Arno M. Wiersema

Michel M.P.J. Reijnen

Cornelis M.A. Bruijninckx

The CAPPA study group (Consensus on Arterial Periprocedural Anticoagulation)

Vascular 2013; 21:119.

To the editor of Vascular.

Regarding: “The use of heparin in patients with ruptured abdominal aortic aneurysms”.
By: A.P. Graham, E. Fitzgerald O’Connor, R.J. Hinchliffe, I.M. Loftus, M.M. Thompson and S.A. Black.
Vascular 2012, Vol. 20 No. 2, 61-4.

Dear Sir

We would like to compliment the authors on their article on the use of heparin in patients with ruptured abdominal aortic aneurysms (rAAA). The use of heparin during arterial procedures is established, but still under debate, especially in patients with a rAAA. The Dutch CAPPA study group has also focused on the routine use of heparin during (r)AAA repair. We have documented that in the Netherlands the perioperative use of heparin during AAA repair is common practice[1] and comparable to the UK and USA. Furthermore we performed a systematic review of this topic that has been accepted for publication in the EJVS.[2] In that review we found evidence of bias in the studies that Graham et al. have used in their article and we would like to discuss our thoughts with the authors.

The study performed by Thompson et al.[3] concerning elective open AAA repair found a reduction in mortality and morbidity when heparin was used. However this conclusion could only be reached when fatal and non-fatal myocardial infarctions (MI) were added together. Concerning this finding Thompson et al. stated themselves: “As this surprising result [of less MI in the heparin group; *AW*] was serendipitous and outside the original study design, no stratification for cardiac risk factors was available for analysis”. Therefore, this difference could result from over-presentation of patients prone to cardiac ischemia in the non-heparinised group. Furthermore, this study excluded patients taking acetyl salicylic acid (ASA), thereby excluding the cardio-protective effect of ASA perioperatively. We doubt that strong conclusions can be drawn on the beneficial effect of heparin during open AAA surgery based on this study.

The study by Chinien et al.[4] on rAAA is also likely to be biased. This study reported a lower operative mortality in heparinised patients (n=10 vs. n=7, 16% vs. 43%: RR 0.37, 95% CI 0.16-0.85). The use of heparin was entirely up to the surgeon's preference at the time of surgery. Since clinically significant blood loss (defined as blood loss of more than 5 litres) was encountered in only one of 63 heparinized patients and in no less than 12 of 68 non-heparinized patients, we suspect that hemodynamically instable patients will have ended mostly in the non-heparinized group. Furthermore, in particular those patients were operated on by senior registrars prior to arrival of a consultant surgeon. These facts readily could explain the signalled difference in mortality between heparinised and non-heparinised patients in this study.

Because of this bias in the available literature we think that further studies are appropriate. The CAPPA group is in the process of initiating a randomized controlled trial to hopefully finally establish once and for all the beneficial or harmful effect of heparin during open AAA surgery.

We would very much like to further discuss our plans with the highly regarded authors (Graham et al.), who apparently share our interest in one of the foundations of vascular surgery.

Highest regards

On behalf of the CAPPA study group:

Arno M. Wiersema, M.D.

Michel M.P.J. Reijnen, M.D., PhD

Cornelis M.A. Bruijninckx, M.D., PhD

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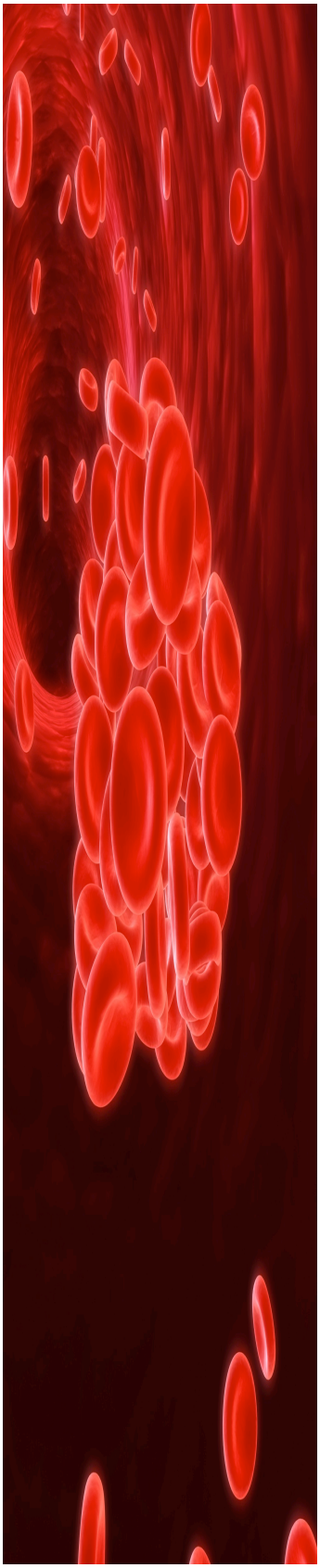


Chapter 10

Letters to the editor:

II: Antithrombotic agents for preventing thrombosis after infrainguinal arterial bypass surgery: a Cochrane review

Arno M. Wiersema

Vincent Jongkind

Cornelis M.A. Bruijninckx

The CAPPA study group (Consensus on Arterial Periprocedural Anticoagulation)

Cochrane Database of Systematic Reviews, 2011; CD000536; CAPPA feedback, 10 April 2014, page 93-5.

To the editor of the Cochrane Database of Systematic reviews
Regarding: “Antithrombotic agents for preventing thrombosis after infrainguinal arterial bypass surgery”.
By: Geraghty AJ and Welch K.
Cochrane Database Syst Rev 2011 Jun 15;(6):CD000536

Dear Sir,

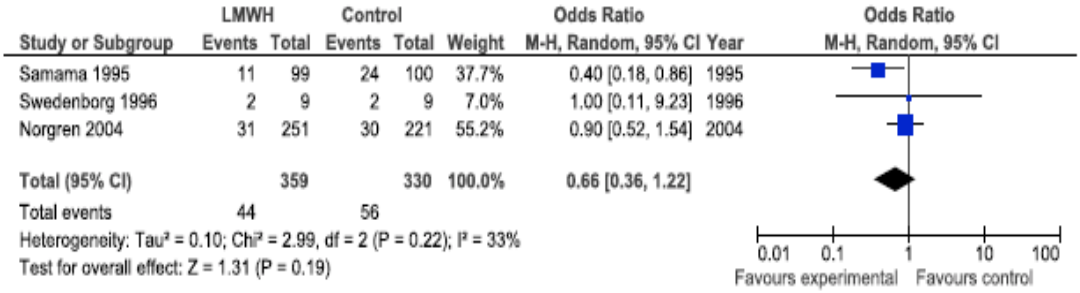
First of all we like to compliment authors with their extensive work[1] on the topic of antithrombotics and infrainguinal arterial bypass surgery. Periprocedural prophylactic antithrombotics (PPAT) involves every day practice around the world during arterial interventions in the vascular patient, but is subject to much discussion and evidence based consensus is lacking.
To increase insight in periprocedural prophylactic anticoagulation and to develop evidence based guidelines on this topic for vascular surgery and interventional radiology, a study group was instituted in the Netherlands: CAPPA: Consensus on Arterial PeriProcedural Anticoagulation. This group consists of Dutch vascular surgeons and interventional radiologists and is supported by the Dutch Boards of Vascular Surgery and Interventional Radiology. In our effort to elucidate PPAT we have found 2 misinterpretations of study data in your review. Correction of this data alters the interpretation and outcome of part of the meta-analysis in your review.

After 2 extensive surveys on daily practice of antithrombotics amongst vascular surgeons[2] and interventional radiologists,[3] we performed a systematic review[4] on the subject of “prophylactic periprocedural antithrombotics in open and endovascular abdominal aortic (AAA) repair”. Another systematic review was performed on the subject of “prophylactic intraoperative antithrombotics in open infrainguinal bypass surgery (IABS)”. This review has recently been published in the Journal of Cardiovascular Surgery (Torino).[5]
While performing this systematic review, we thoroughly studied the manuscripts of the Cochrane review on antithrombotics administered during surgical procedure, especially the

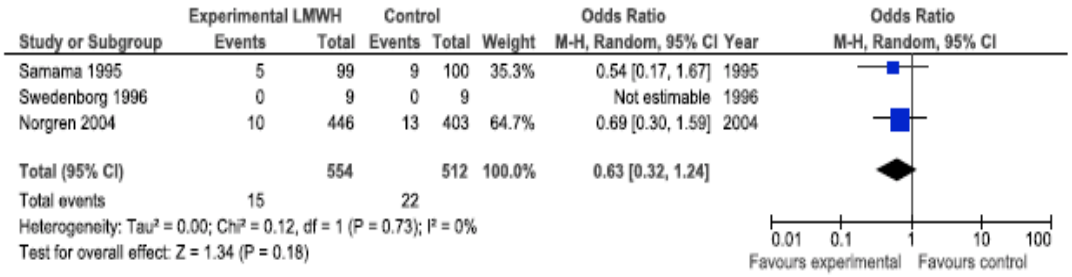
sub-heading “Unfractionated heparin (UFH) versus low molecular weight heparin (LMWH)”, on page 6, 10 and 12. For accurate interpretation of the data we have contacted authors of included studies. The work by Norgren et al.[6] is one of the key studies of the review and the exact definition of distal reconstructions depicted in his study was not completely clear for us. Dr Norgren clarified to us by mail:

“Distal reconstructions imply a distal anastomosis below the BK popliteal artery (mainly crural arteries or ADP). Proximal reconstructions mean aorto-iliac, aorto-femoral and iliaco-femoral”. This means that the numbers depicted in the meta-analysis in the Cochrane review should be corrected for the patency and mortality at day 30: included patients for infrainguinal reconstructions should be: 174 +77 for the LMWH group and 221 for the UFH group. This alteration of data affects the outcome of the meta-analysis, since now no significant difference between the 2 groups can be found.

Patency at day 30.



Mortality at day 30.



On the study of Swedenborg et al,[7] it was stated on page 10 of the Cochrane review, that "No time points were included and so the data could not be included in the meta-analysis". After additionally contacting prof. Swedenborg by mail, it was established that the follow up in his study[7] was 30 days. Therefore we included the data from that study in our meta-analysis. Stated by the authors of the Cochrane in the discussion on page 12 is that "Pooled intention-to-treat data at day 30 did show a marginally positive effect for LMWH over UFH but a much larger cohort of patients receiving venous and artificial bypasses would have to be evaluated for reliable comparison in the future". From our forest plot it can be deducted that not even this marginal effect is present.

We realize that our remarks are of only very minor importance and we agree with the conclusion of authors that more RCTs should be executed on this topic before any reliable conclusion can be drawn on the topic of LMWH versus UFH as periprocedural prophylactic antithrombotic. We would be obliged if our, small, additions to the Cochrane Review will be published in your Journal.

Highest regards,
On behalf of the CAPPA study group,

Arno M. Wiersema, M.D.
Department of Surgery, Division of Vascular Surgery, University Medical Center Utrecht, University of Utrecht

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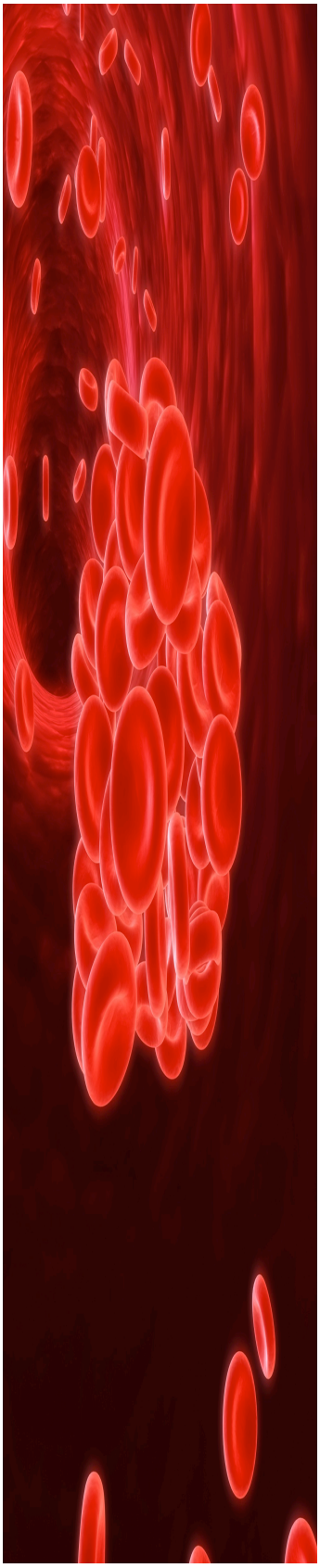


Chapter 11

Summary,

general discussion and

the road ahead…

Summary

Introduction

This thesis aims to investigate the use of antithrombotics/anticoagulants by vascular surgeons and interventional radiologists, with a focus on heparin. The use of these drugs, before, during and after therapeutic procedures in the arterial system in the vascular patient, is evaluated. Hereby focus is directed to the periprocedural prophylactic use of antithrombotics. Unfractionated heparin (UFH) is used predominantly during these (endovascular) procedures to prevent arterial thrombo-embolic complications (ATEC). Although this use of heparin as periprocedural prophylactic antithrombotic (PPAT) is widely spread amongst vascular surgeons and interventional radiologists around the world, not much robust data seemed to be present on this use of heparin. The benefit of heparin is that it reduces the clotting of blood, and thereby reduces local and systemic thrombo-embolic complications. Harmful effects of this use of heparin are the increased bleeding tendency, causing local and systemic complications. Additionally, the administration of heparin, even a single bolus, can lead to heparin induced thrombocytopenia (HIT). This is an adverse reaction, mediated by the immune system of the patient. It can lead to serious thrombo-embolic complications and even to death. To thoroughly evaluate all aspects of periprocedural anticoagulation during arterial interventions, a study group was formed. Ultimate goal of this study group is to create practical, level 1, evidence based guidelines on periprocedural anticoagulation. The study group was named CAPPA: Consensus on Arterial PeriProcedural Anticoagulation and was established in close cooperation with the Dutch Board of Vascular Surgery and Interventional Radiology.

In **Chapter 2** the intriguing story of the discovery of heparin and its introduction in clinical practice, are described in detail. This chapter provides an extensive insight in the history of a major breakthrough in (cardio)vascular surgery and later in interventional radiology. It allows the reader an impression of the personal victories, deceptions and frustrations of some of the pioneers of medical research. The story of the discovery and the subsequent clinical implementation of heparin, should remind us of the great achievements of our predecessors. From this chapter**,** it can be concluded that Howell, and not McLean should be credited for the

discovery of heparin and that Gordon Murray from Canada, was mainly responsible for the introduction of heparin in clinical vascular surgery.

The results of an extensive survey amongst Dutch vascular surgeons on the daily use of periprocedural anticoagulation, is depicted in **Chapter 3**. The high response rate of 84 %, permits, for the first time, a reliable inventory of current practice by vascular surgeons on this topic. Amongst others, results showed that in 2011, still 10% of respondents, discontinued the use of acetyl-salicylic acid (ASA) perioperatively for open arterial procedures, accept for carotid surgery (0%). On average, 35% of vascular surgeons, did not permitted the continuation perioperatively of clopidogrel in case of thoracic and abdominal aortic surgery and infrainguinal bypass surgery. Unfractionated heparin (UFH) was used as PPAT by almost all (97%) vascular surgeons before arterial cross clamping. In case of abdominal aortic aneurysm (AAA), 83% of surgeons used heparin. However, the used dosages of heparin varied, with a bolus of 5000 IU used predominantly (70%). A body weight dependent dose was used by 25%. The applied dose, when a body weight dependent dose was administered, varied from 50 to 100 IU/kg.
A repeated dose of heparin as PPAT was applied by 50-80% of surgeons, depending on the specific type of surgery. Large variation was discovered on why and when this repeated dose was used. Mainly the amount of blood loss and the duration of surgery were used as criterions to administer a second dose of heparin. A measurement of the actual effect of heparin bolus and thereby creating insight in actual (anti)coagulation status, was performed by only 10% of Dutch vascular surgeons. To perform such a measurement, the activated thrombo-plastin time (APTT) or activated clotting time (ACT) were used with an equal distribution. For carotid surgery, the ACT was used predominantly. Postoperative anticoagulation after infrainguinal bypass surgery was compared with results from a survey performed in 2004. In 2005 new guidelines on (the treatment of) peripheral arterial disease by the NVvV were issued after the publication of the Dutch Bypass Oral anticoagulants or Aspirin (BOA) trial. This comparison of 2004 with 2011, showed an increase of the use of vitamin-K antagonists after venous bypass (+6%) and a decrease in the prescription of ASA after venous bypass (-4%). In 2011, statistically significant more vascular surgeons prescribed ASA after infrainguinal prosthetic bypass. Overall results showed that more, but by far not all, Dutch vascular surgeons comply

with the current national guidelines regarding the postoperative use of antithrombotics. The described use and variety on all aspects of heparin as PPAT amongst all Dutch vascular surgeons, are in accordance with previous reports from other countries and seems to be consistent over the past decades.
The described variety in many aspects of the use of anticoagulants and antithrombotics can partially be explained by shortcomings in current (inter)national guidelines. These guidelines lack detailed information on the use of periprocedural prophylactic antithrombotics and are not based on any robust data as foundation for these guidelines. This permits the individual vascular surgeon to act individually, which creates the described variety in aspects of use of antithrombotics.
Despite this variety, the need to monitor the clinical effect of the administered heparin by means of ACT, seems not to be standard of care by Dutch vascular surgeons. As heparin has an unpredictable dose response curve in the individual patient and the elimination curve is not linear, more convincing data on the need of performing such a measurement during surgical vascular procedures are to be obtained. Additionally, the lack of data in current guidelines necessitates the start of multiple RCTs, amongst others on the continuation or cessation of ASA and/or clopidogrel and the use of heparin during open arterial surgical procedures. The introduction of performing an ACT measurement should be advocated as standard of care.

To evaluate the use of anticoagulant drugs amongst Dutch interventional radiologists (IR), a second survey was conducted. The results from that survey are described in **Chapter 4**. The response of this survey was good (68%). ASA was continued by all IR before arterial endovascular interventions, but clopidogrel was stopped by 40% of IR, except before carotid artery stenting. Those IR, who perform the latter procedure, continued ASA and pre-loaded those patients with clopidogrel. Upload doses varied from 75 to 300 mg. Standardized use of a flushing solution on the sideport of a sheath, was applied by 30% of respondents. Only 28% of those IR, who use a flushing solution, add heparin to the saline of the flushing solution (hepsal). Concentrations of hepsal varied, with 63% of respondents using a heparin concentration of 5000 IU/500cc. Almost all IR (95%) use heparin as a periprocedural prophylactic antithrombotic. Predominantly used bolus dosage is 5000 IU (82%), while 14% of respondents used a body weight dependent dose.

Only 1% of Dutch IR indicated that they monitor the actual coagulation status after heparin administration, all by measuring the ACT. A repeated bolus of heparin was administered by 75% of IR, mostly based on a procedure time of more than 1 hour. A certain value of the ACT was applied by 3% of respondents to determine if a repeated bolus of heparin was deemed necessary. No details of a cut-off value of that ACT were provided by respondents. Compared to results from a limited survey in 2004, IR prescribed more ASA in combination with clopidogrel (+24%) after PTA with stenting. The duration of this dual-therapy varied from 6 weeks to 12 months, after which all respondents continued with mandatory mono-therapy of ASA. Results for IR from the UK showed that in the UK also substantial variation exists regarding the use of heparin as PPAT. In chapter 4 it is described that remarkably, this variation in the UK is different from that in The Netherlands. Dosages, concentrations of hepsal, bolus and timing of the bolus of heparin varied not only within those countries, but also between them. The preprocedural cessation or continuation of ASA and/or clopidogrel, the routinely use of intravenous access and the use of flushing solutions on a side port of a sheath are apparently still under debate. No convincing trial data are available on these topics. Existing guidelines (such as TASC, CIRSE) are only partially met by Dutch and UK interventional radiologists. Possible explanations for these wide variations are numerous and most are speculative. It appears that IR's continue to use the "protocols" acquired during their training. The described lack of evidence in existing guidelines may undermine the authority of these guidelines in the PAI setting and may reduce compliance by IR around the world. This lack of evidence also weakens the recommendations by key opinion leaders.

The majority of the professionals involved, deem it self-evident that a too low a concentration of heparin may cause arterial thrombo-embolic complications (ATEC). However there are no data that unshakably support this notion. It appears that the vast majority of professionals involved, seems to underestimate the chance and the seriousness of bleeding complications (and of the rare but catastrophic heparin induced thrombocytopenia syndrome), since only few monitor the level of anticoagulation after administration of heparin by means of ACT. The variation in prophylactic periprocedural antithrombotics also could also have an influence on the results of published trials of PAI and PTA with or without stenting and the incidence of ATEC. Patencies and ATEC could also be influenced by whether or not heparinised flushing solutions are used, and in which concentrations.

Despite the limitations of our survey, we strongly advocate that RCT's on the subject of arterial periprocedural prophylactic anticoagulation in IR will be developed and that these RCT's will preferably be performed in cooperation between interventional radiologists and vascular surgeons internationally. Special attention must be focused on the measurement of the actual effect on (anti)coagulation of heparin or other PPAT by use of the ACT. Routinely measuring such an ACT to tailor anticoagulation effect in the individual patient should be a foundation of modern endovascular interventions.

In order to thoroughly evaluate the results of the described surveys, systematic reviews of available literature according to contemporary guidelines on systematic reviews were performed. The first of those reviews was performed on "Periprocedural prophylactic antithrombotics in open and endovascular abdominal aortic aneurysm (AAA) surgery", and results are depicted in **Chapter 5**. Literature was searched for studies comparing a group with an antithrombotic administered during operation and a group without the administration of a PPAT. Only 5 studies met all inclusion criteria for open AAA repair, all using heparin as PPAT. These studies were performed between 1988 and 2008. For endovascular aneurysm repair only one study could be found (comparing heparin to bivalirudin). Overall quality of studies on open repair was poor, and only one RCT could be retrieved from literature dating from 1996. In conclusion, during open AAA repair a trend was present towards harmful, and not beneficial effects, of heparin. Those trends included longer operation duration, more blood loss and more blood transfusions needed in the heparin groups. Refraining from the use of heparin did not lead to a higher incidence of arterial thrombo-embolic complications, including myocardial infarction. In the RCT the combination of fatal and non-fatal myocardial infarctions proved to be significantly more frequent in non-heparinized patients (n=3 vs. n=12, 8.6% vs. 2.0%: RR 0.24, 95% CI 0.07-0.87). This outcome was, however, outside original study design and the distribution of cardiac risk factors over both groups was unknown. Therefore, this difference could result from over-presentation of patients prone to cardiac ischemia in the non-heparinized group. Furthermore, this study did not include patients taking ASA, thereby excluding the cardio-protective effect of ASA perioperatively. For EVAR no trial data could be found comparing heparin to no-heparin. Despite promising results of direct thrombin inhibitors in cardiovascular surgery and endovascular coronary- and

peripheral interventions, no studies could be found on these drugs during open AAA surgery. During EVAR a direct thrombin inhibitor, bivalirudin showed no clear benefit compared to heparin in one retrospective study. The costs for the use of bivalirudin were significantly higher than for heparin. The present systematic review has several limitations. A small number (5) of studies were eligible for open AAA surgery and only one for EVAR. Moreover the studies for open AAA surgery were published over a time period of 20 years. In those 20 years the perioperative care of the vascular surgical patient has improved considerably, resulting in better outcomes for AAA patients undergoing surgery. For example, the introduction of statins and the increased use of beta-blockers nowadays in the perioperative period may influence the incidence of myocardial infarction. Methodological quality of the studies was poor, numbers of patients studied relatively small and there was significant clinical heterogeneity between studies. Despite these limitations this systematic review showed no sound evidence on the beneficial effect of the prophylactic perioperative use of heparin during open surgery for (r)AAA.
Clearly the beneficial or harmful role of heparin during open and endovascular AAA repair needs to be established definitely by means of a RCT. In that RCT patients will need to be randomized to heparin or no heparin. Presumptions of that RCT will be that a reduction in bleeding related complications, including blood loss and blood transfusions, will be present when no heparin is administered as PPAT. The refraining from heparin should not result in an increase in arterial thrombo-embolic complications, including non-fatal and fatal myocardial infarction.

The systematic review on the "use of intra-operative antithrombotics in infrainguinal arterial bypass surgery (IABS)" is displayed in **Chapter 6**. During IABS heparin is used worldwide by most vascular surgeons, with the presumption that heparin reduces intra-operative and early postoperative graft failure. For the use of antithrombotics during bypass surgery, 9 studies could be included, dating from 1984 to 2004. The heterogeneity between studies and in studies was high and study populations of studies were often of small size. No study could be retrieved in which an antithrombotic was compared to no-antithrombotic. No publication was found in which a heparin group was compared to a no-heparin group. Other PPATs evaluated were dextran, human antithrombin, iloprost and low molecular weight heparin

(LMWH). All antithrombotics, but LMWH, showed no beneficial effect on patency, morbidity and mortality.
More than 70 years after its introduction for preventing arterial thrombosis during arterial operations, the benefit of intra-operative administration of heparin in IABS still has not been proven by a RCT. Dextran, iloprost or human antithrombin have been proven to have no beneficial effect for the patient compared to heparin alone. LMWH instead of heparin could produce better results for the patient in IABS, but conclusive data are presently lacking. A recent Cochrane review appeared to overestimate the beneficiary effect of LMWH. Therefore we strongly advocate that for the perioperative prevention of graft-thrombosis during IABS, randomized, double-blinded, placebo-controlled studies using UFH, LMWH and direct thrombin inhibitors should be started.

The next planned systematic review was on the use of heparin, or other PPAT, during (percutaneous) endovascular interventions by interventional radiologists and vascular surgeons. After a literature search and trying to execute a review according to PRISMA guidelines, it appeared that no systematic review could be justified due to the lack of data for PPAT use in peripheral arterial interventions (PAI), which are defined as all endovascular non-cardiac and non-cerebral arterial interventions. Because of this lack of data, we decided to create a synopsis of all available literature on heparin in endovascular interventions, **Chapter 7**. After a short description of the pharmacokinetics and mechanisms of action, the relation of heparin with contrast medium, guide wires, sheaths and catheters is described and available literature discussed. Despite the fact that not much recent, robust evidence is available and no RCTs were performed on the topic of heparin and contrast medium, the anticoagulation effect could be enhanced when ionic contrast is used in combination with heparin. The combination of heparin and a hydrophilic coating proved to be highly non-thrombogenic on angiographic equipment. Subsequently, literature is summarized on the use of heparin or other drugs, as PPAT. Such other drugs are the LMWHs and a direct thrombin inhibitor (DTI; bivalirudin). On the use of LMWH, no unequivocal conclusions could be made on whether this provided better results than UFH, amongst others because of the fact that only a small number of arterial interventions were included in those studies. On the use of DTIs, the authors of studies concluded that RCTs are needed to further evaluate the possible

advantages of direct thrombin inhibitors over heparin during peripheral arterial interventions. Until today, no results of such trials are published. In 2012, a retrospective evaluation of using heparin or no-heparin during peripheral interventions was published. Results were described for 220 arterial procedures with the use of a bolus of heparin and 110 procedures in which no bolus of heparin was administered. All procedures were performed with a flushing solution with a heparin concentration of 1000 IU per 500 mL. This comparison of heparin and no-heparin bolus, showed an increased risk for bleeding complications in the heparin group at the access site (OR = 5.7; 95% CI=1.3-25), without a reduction of arterial thrombo-embolic complications in the heparin group. All authors of the studies published on PPAT during endovascular interventions stressed the absence of level 1 data to support the use of heparin, or other PPAT, during peripheral arterial interventions and concluded that RCTs should be started.

A summary of contemporary literature on measuring the actual effect of antithrombotics during endovascular interventions is also depicted in chapter 7. Consensus exists that monitoring the actual coagulation status during those procedures is mostly absent in daily practice.

During the process of designing a RCT on heparin during open AAA repair, it was deemed desirable to gain more insight in the possibly available data on heparin used as PPAT during open abdominal aneurysm surgery. In **Chapter 8**, the results of an analysis of data of a trial on open or endovascular AAA repair are provided. From this trial: Dutch Randomized Endovascular Aneurysm Management (DREAM), the data from the open repair group were analysed for the heparin and no-heparin group. In the open repair group from DREAM, 170 patients could be included, of which 137 (80.6%) received heparin as PPAT, and 33 (19.4%) did not.

Dosages of applied heparin bolus varied, but predominantly 5000 IU iv. (74%) were used. The amounts of blood loss, replaced blood or other blood products administered, were not statistically significant different between the heparin or no-heparin groups. Also the duration of surgery and hospital admission time did not differ between both groups. The complication-rate for minor and major complications excluding death was also comparable between heparin or no-heparin groups. No statistical significant difference was found for the incidence of arterial thrombo-embolic complications (ATEC) for the use of heparin or no-heparin. The 30-

day mortality, or in-hospital mortality during the same admission, differed: 2.2% (3 of 137 patients) in the heparin group and 15.2% (5 of 33 patients) in the no-heparin group (RR 6.92, 95% CI 1.56-30.65). After a thorough evaluation of all the deaths in both groups, it appeared that none of the death could be directly related to the refraining from the use of heparin in the no-heparin group.
In conclusion, despite the internationally widespread us of heparin as a prophylactic to prevent ATEC during open AAA repair, this sub-analysis from the DREAM trial could not show any beneficial effect of the use of heparin in the open operation group. Although these results should be interpreted with caution because of the limitations of our analysis, it stresses the need for robust randomized data to show for once and for all the beneficial or harmful effect of heparin for the patient during open AAA repair. The CAPPA group from the Netherlands designed such a trial called **NANDA?** (**N**o **A**nticoagulation **N**eeded **D**uring open **A**AA repair**?**).

The design for this first RCT on behalf of the CAPPA study group is described in **Chapter 9**. The NANDA? trial aims to assess the role of heparin as periprocedural prophylactic antithrombotic during open juxta- and infra-renal abdominal aortic aneurysm (AAA) repair. To evaluate the beneficiary or harmful effects of heparin as PPAT during that type of vascular surgery, bleeding related outcomes will be evaluated, as the incidence of arterial thrombo-embolic complications. All other possibly heparin related outcomes will be evaluated, including non-lethal and lethal myocardial infarction. This trial will be randomized, controlled, double-blinded and multi-centric. Patients will be scheduled to undergo elective repair of a primary abdominal aortic aneurysms. Aortic cross clamping can be done either infra- or supra-renally. A power calculation for a reduction of blood loss with 30%, showed that 197 patients per group have to be included. All arterial thrombo-embolic complications, including non-fatal and fatal myocardial infarction are supposed to be equal in heparin and no-heparin groups. The NANDA? Trial is aimed to start in November 2014.

In **Chapter 10,** two letters to the editors (LTE) are depicted. The first provides a reaction on a "systematic review", published in Vascular. In this review on "The use of heparin in patients with ruptured abdominal aortic aneurysms", the authors from the UK stated that only one

paper on this topic could be included. This paper was also analysed in our review on PPAT during AAA repair, described in Chapter 5. Authors in Vascular stated that they would support the more routine use of heparin in ruptured aneurysms in line with the policy in elective aneurysm repair. In our LTE we described the imperfections of the included study by authors of the review and we, once again, stressed the absence of solid data on the use of heparin as PPAT in open (ruptured) abdominal aortic aneurysm repair and the need for well-designed RCTs.
In the second LTE, we described the flaws in the review on "Antithrombotic agents for preventing thrombosis after infrainguinal arterial bypass surgery" by the Cochrane group, as described in chapter 6. Stated by the authors of the Cochrane review, is that "Pooled intention-to-treat data at day 30 did show a marginally positive effect for LMWH over UFH but a much larger cohort of patients receiving venous and artificial bypasses would have to be evaluated for reliable comparison in the future". The forest plot we created on the basis of extra information gathered from authors of included studies, showed that not even this marginal effect is present.

General discussion

In this thesis the daily use of anticoagulation and antithrombotics during arterial interventions by vascular surgeons and interventional radiologists in The Netherlands is evaluated. A noticeable variety exists for many aspects of the use of these drugs. This described variety in The Netherlands is consistent with the fact, that in other countries also a variety exists. Remarkable, the variety in The Netherlands was different from that in the UK for the use of antithrombotics in interventional radiology. Variation is present in the preprocedural cessation or continuation of ASA and clopidogrel, either as mono- or as dual-therapy. This variation was present amongst vascular surgeons and interventional radiologists. Concerning endovascular interventions, a variety was also found for the routinely use of intravenous access, the use of flushing solutions on a side port of a sheath and the use and addition and concentration of heparin in the flushing solution.
Unfractionated heparin is used by almost all vascular surgeons and interventional radiologists as periprocedural prophylactic antithrombotic, although dosages and the repeated administration of a bolus of heparin varied. Heparin has self-evident beneficial effects during

arterial vascular procedures: it reduces thrombogenicity and thereby reduces thrombo-embolic complications in the vascular patient, local and systemic. The harmful side effects of heparin also can be deducted from its ability to reduce the clotting of blood: prolonged bleeding. This causes more blood loss, higher need for blood transfusions and other bleeding related complications during arterial interventions. Additionally, heparin can lead to heparin-induced-thrombocytopenia, a rare but serious adverse reaction on, even a single dose, of heparin. This reaction can cause morbidity and even mortality during and after arterial reconstructive procedures.

Despite the worldwide use of heparin, an alarmingly lack of robust data is present, when performing systematic reviews of literature. This lack of data is also present in current (inter)national guidelines. As shown in this thesis, these guidelines are not applied by most surgeons and radiologists. Also noteworthy, is the fact that monitoring the actual, clinical effect of the administered heparin in the vascular patient is not standard-of-care by vascular surgeons and interventional radiologists. This is remarkable, because the use of heparin as PPAT in open and endovascular non-cardiac procedures has largely been extrapolated from cardiac surgery and percutaneous coronary interventions. In those cardiac and coronary interventions, it is mandatory and standard-of-care to measure an activated clotting time (ACT). This thesis underlines the importance of measuring such an ACT in vascular surgery and interventional radiology, when using heparin, or another drug, as PPAT. Such a measurement is absolutely mandatory to tailor the (anti)coagulation status of the patient during arterial interventions.

The road to consensus…

In the current era of evidence-based medicine and mandatory protocols based on (inter)national guidelines, the proven variety in the use of PPAT during arterial procedures needs to be fiercely reduced. It should be our duty as vascular surgeons and interventional radiologists to start multiple RCTs and thereby create data to fill the currently existing gap of evidence on periprocedural prophylactic antithrombotics. Preferably international cooperation between vascular specialists should be established for those RCTs, in order to include as many patients as possible to increase significance of gathered data. These data are necessary

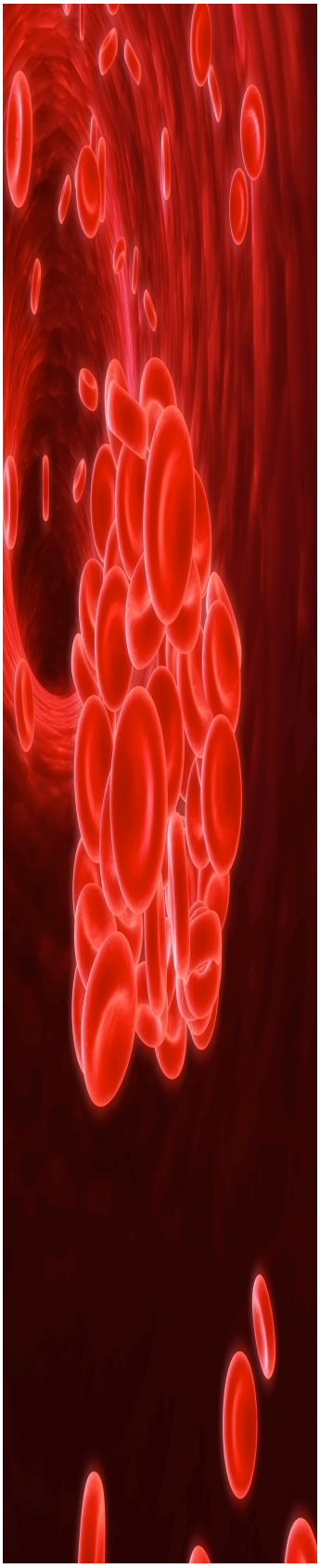
to answer important questions on various aspects of the beneficial or harmful effects of PPAT.

Starting point of further research should be the topic of periprocedural cessation or continuation of ASA and/or clopidogrel during open and endovascular procedures. Presumption of a RCT on this topic should be that the continuation of both these platelet inhibitors will result in less thrombo-embolic complications in the vascular patient. The continuation of ASA and/or clopidogrel, as mono- or dual-therapy, should not result in an increase of bleeding related complications.

Further RCTs need to be designed for vascular surgeons and interventional radiologists on the use of heparin or other antithrombotics as PPAT. Firstly, it needs to be established definitely if heparin is beneficial or harmful during arterial procedures.

As described in this thesis, separate attention should be focused on the monitoring of the actual, clinical effect of the administered periprocedural antithrombotic. Performing an activated clotting time-measurement should be standard-of-care by vascular surgeons and interventional radiologists. Considering the fact that for the last decades the majority of these vascular specialists have refrained from using such a measurement, the task of convincing them to redesign their daily practice, seems heavy. This refraining from such a measurement is still daily practice, despite the fact that multiple studies clarified the need for performing an ACT measurement.

This thesis demonstrated that the use of periprocedural prophylactic antithrombotics by vascular surgeons and interventional radiologists needs consensus. This consensus must be based on solid data, which should preferably be gathered by international cooperation. These data should result in new, practical; evidence based (inter)national guidelines. This consensus is warranted to ensure the vascular patient of tailored treatment with proven beneficial effects of periprocedural prophylactic antithrombotics during arterial interventions.



Chapter 12

Samenvatting,

discussie

en de (nabije) toekomst…

Samenvatting

Introductie

Dit proefschrift behandelt het gebruik van antitrombotica/anticoagulantia, met de nadruk op heparine, door vaatchirurgen en interventieradiologen. Het gebruik van deze farmaca net voor, tijdens en na therapeutische interventies in het arteriële systeem bij de vaatpatient wordt geëvalueerd. Focus ligt hierbij op het periprocedurele profylactische gebruik van antitrombotica. Heparine wordt het meest gebruikt als antitrombotica tijdens arteriële (endovasculaire) ingrepen ter voorkoming van arteriële trombo-embolische complicaties (ATEC). Hoewel dit gebruik van heparine als periprocedureel profylactisch antitromboticum (PPAT) wereldwijd verspreid is, lijkt het alsof weinig robuust bewijs voor dit gebruik in de literatuur aanwezig is. Het voordeel van het gebruik van heparine is dat het de vorming van bloedstolsels verminderd en daardoor het optreden van lokale en systemische trombo-embolische complicaties verminderd. Schadelijke effecten van heparine komen ook voort uit deze verminderde stolling. Hierdoor ontstaat een grotere bloedingsneiging, welke lokale en systemische complicaties kunnen veroorzaken. Tevens kan de toediening van heparine, zelfs een eenmalige bolus, leiden tot de ontwikkeling van het 'heparine-geïnduceerde-trombocytopenie' syndroom. Dit is een reactie op heparine, aangestuurd door het immuunsysteem van de patiënt en kan leiden tot ernstige trombo-embolische complicaties en zelfs tot de dood.

Om alle aspecten van het gebruik van periprocedurele profylactische antistollingsmiddelen tijdens arteriële interventies grondig te evalueren, is een studiegroep in Nederland opgericht. Het uiteindelijke doel van deze studiegroep is het creëren van praktische, level 1, evidence based richtlijnen betreffende periprocedurele antistolling. De studiegroep werd opgericht met actieve medewerking van de besturen van de Nederlandse Vereniging voor Vaatchirurgie en het Nederlands Genootschap voor Interventieradiologie en heet CAPPA: **C**onsensus over **A**rteriële **P**eri**P**rocedurele **A**ntistolling.

Hoofdstuk 2 vertelt het intrigerende verhaal over de ontdekking van heparine en de introductie ervan in de klinische praktijk. Dit hoofdstuk verschaft de lezer een uitgebreid

inzicht in de geschiedenis van een majeure doorbraak in (cardio)vasculaire chirurgie en later in de interventieradiologie. Het geeft de lezer een goede indruk van de persoonlijke overwinningen, teleurstellingen en frustraties van een aantal pioniers van medisch onderzoek. Het verhaal over de ontdekking en de introductie van heparine in de kliniek, moet ons herinneren aan de grote daden van onze voorgangers. Uit dit hoofdstuk zal de lezer hopelijk kunnen concluderen, dat Howell en niet McLean de eer verdient van de ontdekking van heparine. Ook blijkt dat Gordon Murray uit Canada verantwoordelijk is voor de toepassing van heparine in de vaatchirurgie.

De resultaten van een uitgebreide enquête onder Nederlandse vaatchirurgen over het dagelijks gebruik van periprocedurele antistolling, worden beschreven in **Hoofdstuk 3**. Door het hoge respons percentage van 84% bestaat nu voor het eerst een betrouwbaar inzicht in de dagelijkse praktijk van de vaatchirurgen over dit onderwerp. Resultaten laten onder andere zien dat 10% van de vaatchirurgen, nog steeds, ascal stopt voor arteriële ingrepen, behalve voor carotis chirurgie (0%). Gemiddeld stopt 35% clopidogrel (Plavix®) preoperatief voor thoracale en abdominale aorta-chirurgie en perifere bypass chirurgie. Heparine wordt door bijna alle vaatchirurgen (97%) gebruikt als PPAT voor het afklemmen van arteriën. De gebruikte dosis van heparine varieerde, het meest werd een bolus van 5000 IU iv gebruikt (70%). Een lichaamsgewicht afhankelijke bolus werd toegediend door 25% van de respondenten waarbij 50-100 IU/kg de meest gebruikte dosering was. Een peroperatief herhaalgift van heparine werd gegeven door 50-80% van de vaatchirurgen, afhankelijk van het type reconstructie. Grote variatie is aanwezig betreffende het waarom en wanneer dit herhaalgift wordt toegepast. Meest voorkomende reden is de hoeveelheid bloedverlies (> 2 L.) of de duur van de ingreep (> 90 min.). Het verrichten van een meting van het effect van de toegediende heparine en daarmee inzicht verkrijgen in de actuele stollingsstatus, wordt slechts verricht door 10% van de Nederlandse vaatchirurgen. Het gebruik daarvoor van een geactiveerde trombo-plastine tijd (APTT) of geactiveerde stollingstijd (ACT) was evenredig verdeeld. Het direct postoperatieve antistollingsbeleid kon vergeleken worden met de resultaten van een enquête uit 2004. In 2005 verschenen hierover nieuwe richtlijnen. Het blijkt dat in 2011 meer, maar lang niet alle, Nederlandse vaatchirurgen zich conformeren aan de vigerende richtlijnen. Het gebruik van heparine als PPAT en de variatie daarin onder Nederlandse vaatchirurgen, is

in overeenstemming met eerdere resultaten uit andere landen en lijkt consistent te variëren gedurende de afgelopen decennia. De aanwezige variatie kan (deels) verklaard worden uit tekortkomingen in huidige (inter)nationale richtlijnen. In deze richtlijnen ontbreekt gedetailleerde informatie over het gebruik van PPAT en deze richtlijnen zijn niet gebaseerd op robuust wetenschappelijk bewijs. Hierdoor kan de individuele vaatchirurg zijn 'eigen' beleid maken, resulterend in de in hoofdstuk 3 beschreven variatie.
De noodzaak van het meten van het effect van de toegediende heparine is nog niet doorgedrongen tot de dagelijkse praktijk van de Nederlandse vaatchirurgen. Gezien het feit dat heparine een niet-lineaire dosis-response curve heeft en een niet-lineaire eliminatie curve in de vaatpatient, moet meer overtuigend bewijs blijkbaar geleverd worden over dit meten. Ook het verdere gebrek aan data over periprocedurele profylactische antistolling onderstreept de noodzaak tot het starten van randomized controlled trials (RCT). Het wel of niet continueren van ascal en/of plavix en het wel/niet gebruik van heparine als PPAT moeten onderwerp zijn van dergelijk RCTs. De introductie van het standaard meten van het effect van heparine door middel van een ACT moet nagestreefd worden.

Om het gebruik van antitrombotica/anticoagulantia onder Nederlandse interventieradiologen (IR) te evalueren werd ook een uitgebreide enquête verricht. De resultaten hiervan worden weergegeven in **Hoofdstuk 4**. Het response percentage was hoog (68%). Ascal werd door alle IR gecontinueerd voor endovasculaire arteriële interventies, maar clopidogrel werd gestopt door 40%, behalve voor carotis ingrepen. Het standaard gebruik van een flushing vloeistof op een sideport van een ingebrachte sheath werd maar door 30% van de IR toegepast. Van die 30% gebruikt maar weer 28% heparine in die flushing vloeistof. De concentraties van die heparine vloeistof varieert fors, waarbij 63% een concentratie heparine gebruikt van 5000 IU per 500 cc NaCl. Bijna alle IR gebruiken een heparine bolus als PPAT, met als meest gebruikte dosering 5000 IU (82%). Slechts 1% van de Nederlandse IR geven aan dat zij de actuele stollingsstatus monitoren na toediening van heparine en dan gebruiken zij de ACT. Een herhaalgift heparine wordt toegediend door 75% van de IR, meestal gebaseerd op een procedure tijd van meer dan 1 uur. Vergeleken met een beperkte enquête uit 2004, bleek dat in 2011 meer radiologen ascal in combinatie met clopidogrel voorschrijven na PTA met stentplaatsing (+24%). De resultaten voor de Nederlandse IR konden vergeleken worden met

de resultaten van een recente enquête onder Engelse IR. Ook in de United Kingdom (UK) bleek een grote variatie betreffende het gebruik van PPAT. Opvallend en alarmerend is dat de gevonden variatie in de UK en in Nederland niet overeenkomt. Blijkbaar zijn het wel/niet stoppen preprocedureel van ascal en/of clopidogrel, het routinematig gebruik van een sheath en het gebruik van een flushing vloeistof met/zonder heparine, nog onderhevig aan discussie. Geen overtuigend bewijs voor deze keuzes is voorhanden in de huidige literatuur.
Bestaande richtlijnen (TASC, CIRSE) worden maar deels gevolgd door Engelse en Nederlandse IR. De redenen hiervoor zijn talrijk en meest speculatief. Het lijkt dat de meeste IR de tijdens de opleiding aangeleerde protocollen blijven gebruiken. Het gebrek aan harde data en bewijs in de vigerende richtlijnen geeft ruimte aan individuele protocollen. De meeste IR zijn overtuigd dat een te lage concentratie heparine meer kans geeft op arteriële trombo-embolische complicaties, anders zouden zij geen heparine gebruiken. Het blijkt wel dat de meest IR de kans op bloedingscomplicaties door overdosering van heparine onderschatten, evenals de kans op ATEC bij onderdosering. Dit blijkt uit het feit dat bijna geen IR het actuele effect van de toegediende heparine bolus meet. De gevonden variatie in het gebruik van PPAT zou tevens invloed kunnen hebben op resultaten bereikt bij arteriële endovasculaire ingrepen. Patencies en direct technisch succes van PTA met of zonder stent kunnen beïnvloed zijn door onder- of overdosering van heparine. Dit onderstreept dat het gebruik van een routinematige meting van de actuele stollingsstatus d.m.v. een ACT noodzakelijk zou kunnen zijn om 'op maat gesneden' antitrombotica te gebruiken door IR.
Om de beschreven resultaten van de enquêtes objectief te kunnen beoordelen werd de literatuur beoordeeld door middel van 'state-of-the-art' systematic reviews. In de eerste review, **Hoofdstuk 5**, wordt de bestaande literatuur geëvalueerd over het periprocedureel profylactisch gebruik van antitrombotica tijdens open en endovasculaire chirurgie van het abdominale aorta aneurysma (AAA). De literatuur werd doorzocht voor studies waarin het gebruik van een antitromboticum werd vergeleken met een groep die dit geneesmiddel niet kreeg tijdens de operatie. Slechts 5 studies konden geïncludeerd worden voor open chirurgisch herstel van het AAA en maar 1 studie voor endovasculair herstel. De studies werden verricht tussen 1988 en 2008. De overall kwaliteit van de geïncludeerde studies was matig en maar 1 RCT kon in de literatuur gevonden worden, uit 1996. Uit de resultaten van de review kan geconcludeerd worden dat een trend aanwezig is naar schadelijke in plaats van

gunstige effecten van heparine voor de patiënt tijdens open AAA herstel. Deze trends behelzen langere operatieduur, meer bloedverlies en meer noodzakelijk bloedtransfusies in de heparine groep. Geen heparine geven resulteerde niet in meer arteriële trombo-embolische complicaties, inclusief myocardinfarcten. In de geïncludeerde RCT bleek de combinatie van fatale en niet-fatale myocardinfarcten significant hoger in de niet-heparine groep (n=3 vs n=12, 8.6% vs. 2.0%: RR 0.24, 95% CI 0.07-0.87). Deze uitkomst is echter buiten het originele studie ontwerp en bovendien was de verdeling van cardiale risicofactoren over beide groepen onbekend. Hierdoor zou het gevonden verschil verklaard kunnen worden door meer cardiaal gecompromitteerde patiënten in de niet-heparine groep. Verder werden in deze studie de patiënten die ascal slikten voor operatie, geexcludeerd. Hierdoor werd het cardio-protectieve effect van het perioperatief gebruik van ascal teniet gedaan.

Voor het endovasculaire aneurysma herstel (EVAR), kon geen studie gevonden worden welke een perioperatieve heparine groep vergeleek met een niet-heparine groep. Ondanks veelbelovende resultaten van de directe trombine inhibitors (DTI) in cardiovasculaire chirurgie en endovasculaire coronaire- en perifere interventies, konden geen studies met DTIs gevonden worden in open AAA chirurgie. Uit een retrospectieve studie bij EVAR bleek dat een DTI, bivalirudine, geen voordeel opleverde voor de patiënt vergeleken met heparine. De kosten voor bivalirudine waren significant hoger dan voor heparine.

De verrichte systematic review heeft een aantal beperkingen. Slechts 5 studies konden worden geïncludeerd voor open AAA chirurgie en slechts één voor EVAR. De studies voor open AAA herstel werden gepubliceerd over een periode van 20 jaar. In die tijd is de perioperatieve zorg voor de vaatpatient fors verbeterd, resulterend in betere uitkomsten na open AAA herstel. Dit wordt mede veroorzaakt door het perioperatieve gebruik van ascal, statines en beta-blokkers, welke de incidentie van het perioperatieve myocardinfarct zouden kunnen verlagen. De methodologische kwaliteit van de onderzochte studies in deze review was matig, het aantal geïncludeerde patiënten relatief laag en significante heterogeniteit was aanwezig in en tussen de studies. Ondanks deze beperkingen leverde de systematic review geen betrouwbaar bewijs voor het gunstige effect van het periprocedureel profylactisch gebruik van heparine tijdens (r)AAA chirurgie.

Het gunstige of schadelijke effect van heparine tijdens open en endovasculair AAA herstel dient nader onderzocht te worden middels een RCT. In een dergelijke RCT dienen patiënten

gerandomiseerd te worden voor wel of geen heparine. Uitgangspunten van die RCT dienen te zijn dat geen heparine toedienen zal leiden tot een vermindering van bloeding gerelateerde complicaties, zoals bloedverlies en benodigde bloedtransfusies. Het niet gebruiken van heparine als PPAT zal dan niet mogen resulteren in een hoger aantal arteriële trombo-embolische complicaties, inclusief fataal en niet-fataal myocardinfarct.

De systematic review over "het gebruik van intra-operatieve antitrombotica tijdens infra-inguinale arteriële bypass chirurgie" is weergegeven in **Hoofdstuk 6**. Tijdens perifere bypass chirurgie wordt heparine als PPAT wereldwijd gebruikt door bijna alle vaatchirurgen. Achterliggende gedachte hiervan is dat dit gebruik vermindering geeft van intra-operatieve en vroeg-postoperatieve graft occlusies. Voor het gebruik van antitrombotica tijdens perifere bypass chirurgie werden 9 studies aangetroffen in de literatuur, waarbij de studies dateren uit 1984 tot 2004. De heterogeniteit in en tussen studies was hoog en de onderzochte studiepopulaties waren vaak van kleine omvang. Een studie waarin een groep *met* antitrombotica werd vergeleken met een groep welke *geen* antitrombotica kreeg toegediend peroperatief, kon niet worden gevonden in de literatuur. Ook werd geen studie gevonden waarin een heparine groep werd vergeleken met een niet-heparine groep. Andere antitrombotica die wel onderzocht zijn tijdens perifere bypass chirurgie zijn dextran, humaan antitrombine, iloprost en de laag moleculaire gewicht heparines (LMWH).
Meer dan 70 jaar na de introductie van heparine ter preventie van arteriële trombose tijdens arteriële interventies, is de gunstige werking van heparine bij perifere bypass chirurgie nog steeds niet aangetoond. Voor dextran, humaan antitrombine of iloprost is duidelijk bewezen dat deze farmaca geen gunstig effect hebben als PPAT vergeleken met heparine alleen tijdens perifere bypass chirurgie. LMWH in plaats van heparine zou mogelijk betere resultaten kunnen geven tijdens deze operaties, maar conclusieve data zijn nog niet voorhanden. Een recente Cochrane review overschatte de resultaten van LMWH, zoals aangetoond in de review in dit proefschrift. Ten einde de rol van LMWH goed te bepalen als PPAT tijdens perifere bypass chirurgie dient een RCT gestart te worden, met LMWH, heparine en een direct trombine inhibitor als PPAT.
Om de rol van heparine of andere antitrombotica als PPAT tijdens (percutane) endovasculaire arteriële procedures te bepalen, werd getracht een systematic review van de bestaande

literatuur te verrichten. Echter het bleek dat te weinig data aanwezig is in de literatuur om een goede review te kunnen verrichten volgens de PRISMA/MOOSE richtlijnen voor reviews. Daarom werd een synopsis gemaakt van alle aanwezige data over PPAT tijdens endovasculaire arteriële interventies, **Hoofdstuk 7**. Hierin wordt de relatie tussen heparine en contrastmiddel beschreven, evenals de relatie tussen heparine en voerdraden, sheaths en angiografie-katheters. Ondanks het feit dat weinig recent en overtuigend bewijs aanwezig is en geen RCTs bekend zijn, lijkt het antitrombotisch effect van heparine versterkt te zijn wanneer ionisch contrast gebruikt wordt in combinatie met heparine. Het toevoegen van een duurzame coating van heparine aan hydrofiele angiografie materialen heeft geresulteerd in hoog non-trombogene eigenschappen van dit angiografie equipment. Vervolgens wordt een samenvatting gegeven van de beschikbare, spaarzame literatuur over het gebruik van heparine of andere farmaca als PPAT, zoals de LMWHs en een directe trombine remmer, bivalirudine. Wat betreft het gebruik van LMWH als PPAT bij endovasculaire arteriële interventies bestaan geen eenduidige conclusies of de LMWHs betere resultaten geven dan heparine, mede omdat het aantal geïncludeerde interventies in die studies laag was. Over het gebruik van DTIs kon alleen de conclusie getrokken worden dat meer RCTs nodig zijn om de werking van bivalirudine te kunnen vergelijken met heparine. Tot nu toe zijn geen resultaten van dergelijke studies verschenen in de literatuur.

In 2012 werd een retrospectieve studie gepubliceerd waarin heparine werd vergeleken met een groep die geen heparine kreeg toegediend tijdens perifere arteriële interventies. Bij 220 patiënten werd een bolus heparine gegeven en bij 110 patiënten niet. Alle procedures werden uitgevoerd met het gebruik van een flushing vloeistof met een heparine concentratie van 1000 IU per 500 cc NaCl. Deze vergelijking tussen wel en geen heparine resulteerde in een verhoogde kans op bloedingscomplicaties in de heparine groep bij de aanprik plaats (OR = 5.7; 95% CI = 1.3-25). Het gebruik van heparine resulteerde niet in minder arteriële trombo-embolische complicaties.

Alle auteurs van gepubliceerde studies over het gebruik van PPAT tijdens perifere endovasculaire interventies in het arteriële systeem concluderen dat geen level 1 bewijs bestaat voor alle aspecten van het gebruik van PPAT. Allen concluderen dan ook dat RCTs dringend gewenst zijn. Ook wordt in hoofdstuk 7 een overzicht gegeven van de literatuur over de noodzaak tot het verrichten van een meting van de actuele stollingsstatus bij het gebruik

van PPAT door middel van een ACT. Consensus bestaat dat deze meting, onterecht, zeer weinig wordt toegepast in de huidige praktijk van endovasculaire interventies.

Tijdens het opstellen van een protocol voor een RCT betreffende wel of geen heparine gebruik tijdens open AAA herstel, werd het belangrijk geacht om nog meer inzicht te krijgen in de resultaten van de dagelijkse praktijk. In **Hoofdstuk 8** worden de resultaten beschreven van een analyse van de data van een trial met open en endovasculair herstel van het AAA. Uit deze trial, de Dutch Randomized Endovascular Aneurysm Management (DREAM) trial, werden de data uit de open herstel groep geanalyseerd van de wel-heparine en geen-heparine groep. In deze open operatie groep uit DREAM konden 170 patiënten geïncludeerd worden, waarvan 137 (80.6%) wel heparine als PPAT toegediend kregen en 33 patienten (19.4%) geen heparine. De gebruikte doseringen van de heparine bolus verschilden, maar 5000 IU werd het meest toegediend: 74%. De hoeveelheden bloedverlies, benodigde transfusies en de toegediende overige bloedproducten waren niet significant verschillend tussen de wel of geen heparine groepen. Ook de duur van de operatie en de opnameduur in het ziekenhuis verschilden niet tussen beide groepen. De incidentie van "minor en major, uitgezonderd mortaliteit" complicaties was vergelijkbaar tussen de wel- en geen-heparine groepen. Tevens werd geen statistisch significant verschil gevonden tussen beide groepen in de incidentie van alle arteriële trombo-embolische complicaties. De 30 dagen mortaliteit of mortaliteit tijdens dezelfde ziekenhuisopname verschilde wel: 2.2% (3 van de 137 ptn.) in de heparine groep en 15.2% (5 van de 33 ptn.) in de geen-heparine groep (RR 6.92; 95% CI 1.56-30.65). Na een uitvoerige evaluatie van alle overleden patiënten, bleek dat geen van de doden direct gelieerd kon worden aan het *niet* gebruiken van heparine.
Concluderend blijkt uit deze sub-analyse van de data van de DREAM trial geen gunstig effect voor de patiënt van het gebruik van heparine tijdens open herstel van het AAA. Deze sub analyse en resultaten moeten wel met de nodige voorzichtigheid geïnterpreteerd worden. De DREAM trial was niet opgezet om het wel of niet gebruik van heparine te evalueren en de aantallen geïncludeerde patiënten voor deze sub-analyse zijn laag. Desondanks onderstrepen de weergegeven resultaten de noodzaak van een RCT om eindelijk de waarde van de heparine bolus als PPAT tijdens open AAA herstel te bepalen. De CAPPA groep heeft een dergelijke RCT ontworpen: **NANDA?** trial (**N**o **A**nticoagulation **N**eeded **D**uring open **A**AA repair**?)**

De opzet van de NANDA? trial wordt beschreven in **Hoofdstuk 9**. Deze trial zal de toegevoegde waarde van het geven van heparine als PPAT evalueren tijdens open herstel van een juxta- of infra-renaal AAA. Alle bloeding gerelateerde uitkomsten zullen geëvalueerd worden, evenals de incidentie en ernst van arteriële trombo-embolische complicaties, inclusief fataal en niet-fataal myocardinfarct. Alle andere, mogelijk heparine gelieerde, parameters zullen worden gescoord. De trial zal gerandomiseerd, multicenter en dubbelblind uitgevoerd worden. Alle patiënten die electief een primair herstel ondergaan van een AAA via een abdominale benadering kunnen worden geïncludeerd. Het klemmen van de aorta mag zowel supra- als infra-renaal. Een powercalculatie toonde aan dat voor een reductie van 30% van het bloedverlies bij geen heparine gebruik, 197 patiënten per groep nodig zijn. Uitgangspunt is verder dat het voorkomen van arteriële trombo-embolische complicaties inclusief myocardinfarct gelijk zal zijn in de wel- en geen-heparine groepen. De NANDA? trial zal naar verwachting starten in november 2014.

Hoofdstuk 10 bestaat uit 2 “Letters-To-the-Editor” (LTE). De eerste geeft een reactie op een “systematic review” gepubliceerd in Vascular. In die review, over het gebruik van heparine in patiënten met een geruptureerd AAA (r(AAA)), beweren de auteurs uit Engeland dat maar 1 studie over dit onderwerp bestaat in de literatuur. Deze studie is ook geëvalueerd in onze systematic review, zoals beschreven in hoofdstuk 5. De auteurs in Vascular verklaren dat zij het meer routine matig gebruik van heparine bij de open behandeling van het rAAA ondersteunen, in analogie met het gebruik van heparine bij electief herstel van het AAA. In onze LTE beschrijven wij de tekortkomingen in de beschreven studie door Engelse auteurs. Tevens onderstrepen wij nogmaals het absolute gebrek aan solide data over het gebruik van heparine als PPAT bij het open herstel van het (r)AAA, evenals het belang van op te starten RCTs over dit onderwerp.
In de tweede LTE worden de tekortkomingen beschreven van een Cochrane review getiteld: 'Antithrombotic agents for preventing thrombosis after infrainguinal arterial bypass surgery', zoals eerder deels weergegeven in hoofdstuk 6. De auteurs van de Cochrane review concluderen dat “de gepoolde intention-to-treat data op dag 30 na operatie, een marginaal positief effect laten zien voor LMWH boven heparine, maar dat een veel groter cohort patiënten die een veneuze of kunststof bypass operatie ondergaan geëvalueerd moet worden

om een betrouwbare vergelijking te kunnen maken in de toekomst". De forest plot die door ons werd gemaakt op basis van extra informatie, verkregen door ons na opvragen bij auteurs van de geïncludeerde studies, laat zelfs het marginale positieve effect van de Cochrane review niet zien. Concluderend is in de huidige literatuur geen bewijs te vinden dat de resultaten van LMWH beter zijn dan met heparine als PPAT tijdens infrainguinale arteriële bypass chirurgie.

Discussie

In dit proefschrift wordt het dagelijks gebruik van anticoagulantia en antitrombotica tijdens arteriële interventies door vaatchirurgen en interventieradiologen geëvalueerd. Een aanmerkelijke variatie bestaat aangaande vele aspecten van het gebruik van deze farmaca. Deze beschreven variatie in Nederland is consistent met het feit dat in andere landen ook een variatie bestaat. Opmerkelijk hierbij is dat de gevonden variatie in Nederland anders is dan de variatie die aanwezig is in het Verenigd Koninkrijk voor het gebruik van antitrombotica door interventieradiologen. Variatie is onder andere aanwezig in het preprocedureel wel of niet stoppen van ascal en clopidogrel, als mono- of duale-therapie. De gevonden variatie was aanwezig bij vaatchirurgen en interventieradiologen. Bij de endovasculaire interventies werd tevens variatie aangetroffen aangaande het routinematig gebruik van intraveneuze toegang, het gebruik van flushing vloeistof op een zijpoort van een sheath en het gebruik en toevoeging en de concentratie van heparine in de flushing vloeistof.

Heparine wordt door bijna alle vaatchirurgen en interventieradiologen gebruikt als periprocedureel profylactisch antitromboticum, waarbij de gebruikte doseringen en het wel of niet toepassen van een herhaalgift tijdens de procedure, varieerden. Heparine lijkt evidente voordelen te hebben tijdens arteriële procedures: het vermindert de trombogeniciteit van bloed en daardoor vermindert heparine theoretisch de kans op trombo-embolische complicaties in de vaatpatient, zowel lokaal als systemisch. De schadelijke (bij)werking van heparine komt ook voort uit de verminderde trombogeniciteit: verhoogde kans op bloedingscomplicaties, zoals meer bloedverlies. Dit kan resulteren in meer benodigde bloedtransfusies. Daarbij kan heparine leiden tot de ontwikkeling van het heparin-induced-thrombocytopenia syndroom, een zeldzame, maar ernstige reactie die zelfs op kan treden na een eenmalige bolus toediening van heparine. Dit syndroom geeft morbiditeit en zelfs mortaliteit tijdens en na arteriële reconstructieve procedures.

Ondanks het wereldwijd gebruik van heparine als PPAT, bestaat een verontrustend gebrek aan bewijs wanneer gezocht wordt in de literatuur. Dit gebrek aan data ter ondersteuning van het gebruik van heparine is ook aanwezig in huidige (inter)nationale richtlijnen. Zoals aangetoond in dit proefschrift, worden deze richtlijnen door de meeste chirurgen en radiologen niet consequent toegepast. Tevens blijkt dat het monitoren van de actuele, klinische stollingsstatus tijdens toediening van heparine als PPAT, niet gouden standaard is bij vaatchirurgen en interventieradiologen. Dit is opmerkelijk, temeer daar het feit dat het effect van het gebruik van heparine als PPAT tijdens open en endovasculaire cardiale procedures altijd wordt gemeten door middel van een geactiveerde stollingstijd (ACT). Dit proefschrift onderstreept het belang van het meten van de ACT tijdens heparine gebruik als PPAT bij vaatchirurgische ingrepen en endovasculaire interventies. Een dergelijke meting lijkt absoluut noodzakelijk om de vaatpatient te voorzien van “op maat gesneden” (anti)stolling tijdens arteriële procedures.

De weg naar consensus…

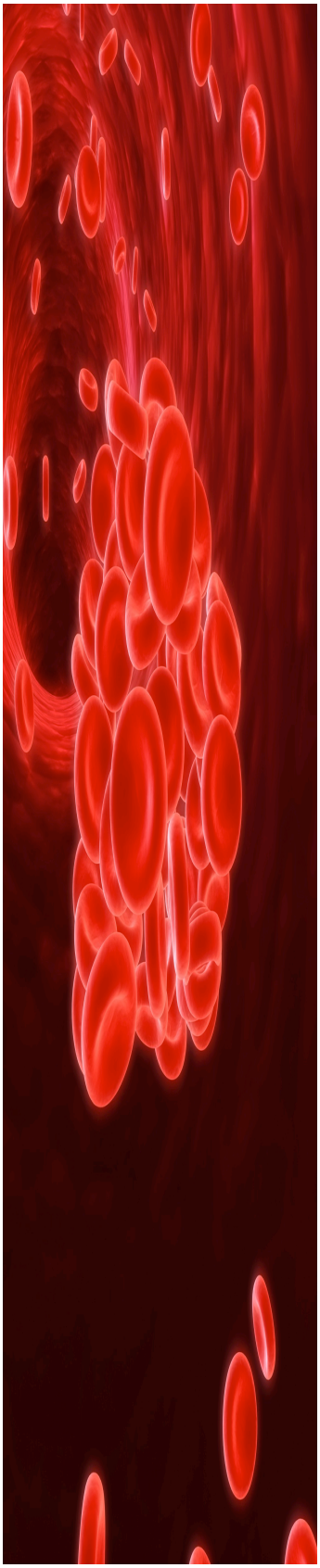
In de huidige tijd van evidence based medicine en verplichte protocollen, gebaseerd op (inter)nationale richtlijnen, moet de gevonden variatie in het gebruik van heparine als PPAT verminderd worden. Het moet onze taak zijn, als vaatchirurgen en interventieradiologen, om meerdere RCTs te starten ten einde data te genereren om het huidige gebrek aan bewijs rond het gebruik van periprocedurele profylactische antitrombotica te verminderen. Bij voorkeur dienen deze RCTs uitgevoerd te worden door samenwerking tussen vasculaire specialisten om op die manier zoveel mogelijk patiënten te kunnen includeren in studies en daarmee de bewijskracht van dergelijke studies te verhogen.

Startonderwerp van RCTs dient het preprocedureel starten of stoppen van ascal en clopidogrel te zijn, zowel voor open als endovasculaire procedures. Uitgangspunt van een dergelijke studie dient te zijn dat het doorgebruiken van beide trombocytenaggregatieremmers zal resulteren in minder trombo-embolische complicaties, zonder toename van het aantal bloedingscomplicaties.

Volgende RCTs dienen gericht te zijn op het gebruik van heparine als PPAT tijdens open en endovasculaire arteriële ingrepenp, waarbij allereerst definitief bepaald moet worden of heparine überhaupt gunstige effecten heeft voor de vaatpatient bij gebruik als PPAT.

Zoals weergegeven in dit proefschrift dienen vaatchirurgen en interventieradiologen overtuigd te worden van het feit dat het meten van een ACT ten einde het actuele, klinische effect van de toediening van heparine te bepalen, noodzakelijk is en als “standaard” geïmplementeerd dient te worden. Gezien het feit dat de afgelopen decennia de ruime meerderheid van deze vasculaire specialisten deze meting niet heeft toegevoegd aan de dagelijkse routine in de klinische praktijk, zal dit nog grote inspanning vergen. Gedegen klinische onderzoek zal, nogmaals, de noodzaak moeten aantonen van het doen van een ACT bepaling, gezien de grote variatie van het effect van heparine in de individuele vaatpatient.

Dit proefschrift toont aan, dat dringend behoefte bestaat aan consensus over het gebruik van periprocedurele profylactische antitrombotica. Deze consensus dient bereikt te worden door het creëren van solide data, bij voorkeur te verkrijgen door (inter)nationale samenwerking tussen vasculaire specialisten. Deze data zullen moeten resulteren in nieuwe, praktisch toepasbare, evidence based richtlijnen. Deze consensus is vereist teneinde de vaatpatient “op maat gesneden” behandeling te kunnen garanderen met positieve effecten van periprocedurele profylactische antitrombotica tijdens arteriële interventies.



DANKWOORD

Dankwoord

Tsja… wie had dat nou ooit gedacht, een proefschrift van Wiersema en dan ook nog iets met consensus in de titel?

Nu dan het meest gelezen "hoofdstuk" van alle proefschriften, ongetwijfeld ook van het mijne. Vele jaren heb ik de dankwoorden van anderen mogen lezen, echter het is mij nu pas duidelijk geworden hoe oprecht die kunnen zijn.

Professor F.L. Moll, beste Frans, hoe kan ik nog iets toevoegen aan de dankwoorden in de vele proefschriften van al jouw promovendi? Ik kan alle loftuitingen aan jou volledig onderschrijven. Dank dat jij je over mij "ontfermd" hebt. Mijn suggestie, om iets wat heel triviaal lijkt diepgaand uit te gaan zoeken, werd door jou met respect en enthousiasme ontvangen en als één van de weinigen zag jij mijn, nog steeds groeiende, serieuzere kant. Dank voor al je adviezen, bemiddelingen en "bewegwijzeringen" in mijn wetenschappelijke en vaatchirurgische carrière. Ook waardeer ik het zeer dat jij mij altijd serieus benaderd hebt, ook in mijn Boven-IJ tijd. Ik zal hopelijk mogen blijven genieten van de halve uurtjes op jouw kamer, waarin ons onderzoek, maar ook alle lokale, nationale en internationale (vaatchirurgische) zaken besproken en vaak ook direct geregeld werden. Ook mij is het een genoegen en een grote eer om bij jou te mogen promoveren.

Dr. C.M.A. Bruijninckx, beste Boy, meester-gezel, meester-tovenaarsleerling, maar voor mij ook een soort vader-zoon en later vriend-vriend relatie. Gemakkelijk kan ik meerdere pagina's wijden aan de jaren die wij delen. Dank voor het feit dat ik dankzij jou de opleiding überhaupt kon beginnen… Nooit ben je gestopt met mij te steunen c.q. verdedigen, ook al wist ik vaak helemaal niet dat dat nodig was. Jij hebt vanaf dag 1 gezien dat het goed zou komen. Heel veel heb ik van jou mogen leren, chirurgisch, wetenschappelijk en ook levensbeschouwelijk. Ik leer nog elke dag van jouw niets en niemand ontziende drang naar perfectie, volledigheid en maximaal resultaat, alles in het belang van de patiënt. Dit proefschrift, en jouw grote rol hierin, zie ik als een soort bekroning van onze "opleidingsrelatie". Jouw technische vaardigheden heb ik altijd geprobeerd te evenaren, of dat

gelukt is laat ik gaarne aan jou. Dank ook voor jouw/jullie steun bij onze major life events. Nanda, de girlz en ik hopen op nog vele mooie jaren met jou en **Margriet**. De laatste wil ik ook nog apart danken voor alle steun, maar ook voor het broodnodige relativeren, heerlijk.

Dr. J.A. Vos, Fox, wie had gedacht dat het door mij regelen van een golfbaan in Athene tijdens CIRSE 2007 zou leiden tot jouw co-promotorschap van mijn promotie? Wetenschap, de geneugten des levens incl. AJAX bezoeken, mijn verdere introductie in de interventieradiologie, het proberen te regelen van het convenant NVvV-NGIR ….. en dat allemaal met een opmerkelijk gevoel van vertrouwen. Fox, top, dank voor het hele package en ik kijk uit naar nog vele mooie en stimulerende momenten met jou.

Michel Reijnen, Mich, ook wanneer ik heel diep nadenk kan ik mij niet *het* moment herinneren waarop onze (wetenschappelijk) samenwerking en vriendschap zijn begonnen. Het voelt voor mij alsof dat altijd al aanwezig was. Mooi om te zien hoe jij jouw energie kanaliseert: opleider, innovator, wetenschapper, levensgenieter, vader, en ook nog echtgenoot, chapeau. Ik blijf jou als lichtend voorbeeld zien, ondanks dat je na mij begonnen bent in Nijmegen… Dank voor je altijd stimulerende rol en zonder jouw steun, hulp en vertrouwen was ik dit traject niet eens begonnen. Ik ben benieuwd naar wat wij nog meer mee gaan maken en ik hoop op nauwe(re) samenwerking.

Clark Zeebregts, **professor,** ook met jou begon de kennismaking in Nijmegen. Goed hoe hoog je bent geklommen op de medische ladder, complimenten. Dank voor jouw rol als stimulator en co-auteur, iets meer op de achtergrond maar altijd aanwezig en snel reagerend met goed commentaar. Dank voor jouw positieve invloeden bij mijn eerste stappen op de genoemde ladder.

Verse **professor van Delden, Otto**. Fox stuurde mij naar jou met ons idee voor onderzoek naar heparine. Direct reageerde jij enthousiast, mede als voorzitter NGIR. Veel heb jij voor mij en voor ons onderzoek geregeld, vooral in de IR wereld. Onze relatie van wederzijds respect en sympathie dateert al van mijn Boven-IJ tijd. Deze relatie heeft ook gezorgd voor een “vruchtbare bodem” voor het bereiken van een convenant tussen vaatchirurgen en

interventieradiologen. Misschien is dat wel net zo een grote prestatie als dit proefschrift… Dank en de "roast" op jouw was feest was uniek.

Anco Vahl, dank voor je medewerking aan dit proefschrift en je positieve energie jegens mij en dit onderzoek.

Beste AIOS vaatchirurgie ooit (tot nu toe dan en op mij na natuurlijk), **Vincent Jongkind**, dank voor jouw introductie in de wonderlijke wereld van de systematic reviews en jouw nuchtere kijk op zaken. Ik hoop in de (nabije) toekomst weer met je te mogen samenwerken, in ieder geval de komende jaren als medebestuurslid van de NVvV.

De **chirurgen** in het Westfriesgasthuis (**WFG**). Nou vooruit dan maar, nog 1 x op schrift: "ik ben blij dat ik bij jullie mocht gaan werken": gedegen opleiding, goede sfeer en top patiëntenzorg. Nu maar hopen op en werken voor behoud van deze speciale sfeer met de fusies op komst. **Haan**, dank voor alle foto's en de rest…. soulmate.
Jur Kievit, mijn directe klinische partner. Ik koester het feit dat wij, ondanks onze verschillen, zo een goede band hebben en de vaatchirurgie samen tot een afdeling maken om trots op te zijn. Dank voor het regelen dat ik jou collega mocht worden en voor de veilige en vertrouwde samenwerking. Oh ja: gelukkig baalde jij dat ik eerst de gedachte had om op 4 juli te gaan promoveren, dat was achteraf inderdaad nooit wat geworden, dank, ook daarvoor.

De ladies van het secretariaat in Utrecht, **Cobie van Veen en Susan Hora Siccama**. Dank voor jullie onmisbare hulp. Susan, aangezien dinsdag mijn academische dag is, heb ik jou het meest gezien en gesproken. Mijn chocolaatjes en jouw positivisme en alles voor mij regelen, gouden combi.

Dr. Rob Kaatee, onze "huisfotograaf". Eervol dat jij in de corona mag en wil plaats nemen. Dank voor mijn introductie in de wereld van de interventieradiologie, zowel sociaal als praktisch. Heel veel van je geleerd en jouw steun bij het opzetten van o.a. het EVAR programma in het Boven-IJ was onontbeerlijk. Ik mis je wel op de werkvloer, maar gelukkig

is onze vriendschap alleen maar geroeid, ook met **Ingunn**. Gaan wij nu eindelijk naar jullie paleisje op IJsland?

Rutger Klicks, fijn om te weten dat iemand mij altijd gesteund heeft en zal steunen. Wat een geweldige tijd heb ik met jou gehad in het Boven-IJ. Thx, ook voor je begrip en support toen ik toch "verder" wilde.

Na jaren geweldige samenwerking via het Boven-IJ met de **vaatchirurgen en IR in het AMC**, waarvoor dank, heb ik nu het genoegen om gelieerd te zijn aan de **vaatchirurgie van het VUMC**. Inmiddels ervaar ik die samenwerking als zeer goed en hoop die in de nabije toekomst uit te mogen bouwen, ook qua wetenschap. Professor **Willem Wisselink**, ook dank voor je deelname aan mijn manuscriptcommissie. Professor **Jan Blankensteijn**, dank voor al jouw hulp en hoop op meer wetenschap samen. Ook op de VU mag ik dan hopelijk weer wetenschappelijk gaan samenwerken met **Kak Khee Yeung**, uniek persoon, dank voor je stimulerende energie en visies.

Altijd lastig om de juiste woorden te kiezen voor iemand die een meester is in het schrijven van teksten: **Kees Post**. Ook de emation van dit boekje is van jouw hand, dank. Sinds jouw Alderliefste tijd zijn wij naar elkaar gegroeid en hebben wij vele pieken en dalen gekend en gedeeld. Fijn hoe jij en jouw gezin geluk uitstralen. Ik hoop dat je nog vele mooie teksten wilt maken voor onze komende hoogtepunten.

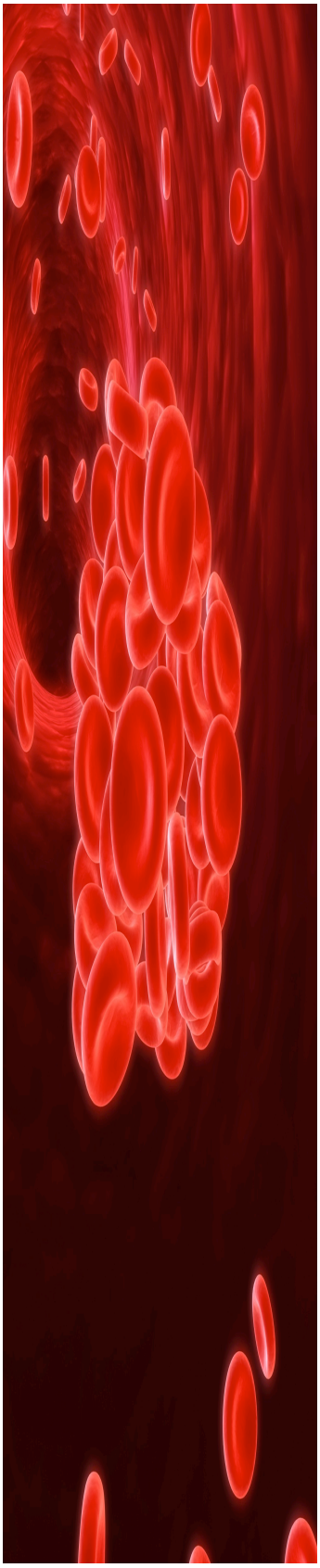
Vrijdag 10 december 1999 mocht ik paranimf zijn bij de promotie van Michiel H.J. Verhofstad, inmiddels **professor Verhofstad**. Tijdens onze kennismaking in Nijmegen "mijn" coassistent met een scala aan bijzondere eigenschappen. Mooi om te zien dat jij mijn harde leerschool van toen hebt geperfectioneerd en mij ver voorbijgestreefd bent. Ware vriendschap heb ik in jou gevonden met steun in alle mooie en nare major life events. Top dat jij mij nu vandaag bij gaat staan en *ik* vind het niet erg wanneer jij jouw wijze raad zal etaleren tijdens de verdediging zelf. Chielowitz, dank voor het simpele en tegelijkertijd zeer ingewikkelde feit dat jij mijn vriend wilt zijn.

En dan mijn “oudste” vriend, **Gerard Jan Alderliefste**. Samen gestudeerd en de vriendschap is al die jaren alleen maar gegeroeid. Top muzikant, beroemd, super vader, verslavingsarts, hulde voor al die prestaties. Dank dat ik bij veel momenten aanwezig mocht zijn. Wat heb ik daardoor veel gezien en meegemaakt, een verrijking van mijn leven, bijvoorbeeld Vondelpark met Ramses en in juni “Cormidable”. Kippenvel en tranen, maar wel van geluk. Ook soms van verdriet, maar altijd ben je dan aanwezig voor steun. Ook voor jou: dank voor het simpele en tegelijkertijd zeer ingewikkelde feit dat jij mijn vriend wilt zijn.

Lieve **vader en moeder**, wat erg dat ik te laat ben met dit boekje… Ik weet zeker dat jullie trots meekijken vandaag. Dank voor een echt onbezorgde jeugd en alle liefde, ook daarna. Vandaag missen wij jullie nog meer dan anders, maar wij doen dan nog 1 rondje voor en van jullie.
Hennie, een betere schoonmoeder kan ik mij niet wensen, dank.

Onze girlz: **Zomer en Puck**. Alle clichés zijn waar! Het leven is nog veel mooier sinds jullie met ons mee reizen. Wat een genot om jullie op te zien groeien en aan de zijlijn te proberen het zo goed mogelijk te doen als vader. Ook het cliché dat het voltooien van een proefschrift ten koste gaat van de tijd voor en met jullie is helaas waar gebleken.
Zomer: Perge et instituisti, libera et innocens. Puck: Aut viam iveniam aut faciam.
Beide geboortespreuken kloppen helemaal, dank voor jullie “zijn” en ga zo door!!!

Eindelijk mag ik dan iets schrijven over **Nanda**, mijn “reisgenote”. Wat heeft zij een hekel aan dit soort emotionele en officiële zaken. Ik zal het kort proberen te houden. Dank voor het verschijnen in mijn leven en daarmee ervoor zorgen dat ik compleet (gelukkig) ben. Jij houdt mij in evenwicht. Ook accepteer je al mijn “grillen”, hoewel deze van dat onderzoek wel lang duurt, meer tijd kostte dan gedacht en misschien wel blijft. Ik kijk uit naar alle mooie jaren die hopelijk volgen en dank dat jij altijd zorgt dat alles goedkomt voor mij en onze dochters.



Curriculum Vitae

Curriculum vitae

Arno Mac Wiersema, geboren 17 juli 1964 te Amsterdam, studeerde geneeskunde aan de Vrije Universiteit te Amsterdam. Na zijn militaire dienstplicht werd hij opgeleid tot chirurg in het Radboud ziekenhuis te Nijmegen (prof. R.J.A. Goris) en het Leyenburg ziekenhuis te Den Haag (dr. C.M.A. Bruijninckx). Tijdens zijn opleiding heeft hij zich verdiept in de vaatchirurgie, gevolgd door een fellowship vaatchirurgie en laparoscopie in het Weezenlanden ziekenhuis te Zwolle (dr. E.G.J.M. Pierik). Daarna was hij gedurende 10 jaar werkzaam in het Boven-IJ ziekenhuis te Amsterdam, als algemeen chirurg met aandachtsgebied vaatchirurgie. Sinds december 2011 is hij werkzaam in de opleidings-vakgroep chirurgie van het Westfriesgasthuis te Hoorn. Het onderzoek, wat heeft geresulteerd in dit proefschrift, werd verricht aldaar en in het UMC Utrecht onder leiding van prof. dr. F. L. Moll. Buiten zijn klinisch werk en dit onderzoek is hij, onder andere, bestuurslid van de Nederlandse Vereniging voor Vaatchirugie, lid van de Beroeps Belangen Commissie van de Nederlandse Vereniging voor Heelkunde en lid van de richtlijn commissie Anti-trombotisch beleid van het KIMS (Kennis Instituut van Medisch Specialisten).
Arno Wiersema is getrouwd met Nanda en zij hebben 2 dochters, Zomer en Puck.