Improvements in acute coronary syndrome diagnosis: Focus on pre-hospital management

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Improvements in acute coronary syndrome diagnosis:
focus on pre-hospital management

Verbetering in de diagnose van acuut coronair syndroom:
focus op het pre-hospitale traject
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof.dr. H.R.B.M. Kummeling, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op dinsdag 27 november 2018 des middags te 4.15 uur

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Contents

Chapter 1

General introduction

Acute coronary syndrome (ACS) is a life threatening disease in which the oxygen requirements of the myocardium is not met due to a sudden reduction of blood flow, typically resulting in chest pain. ACS consists of ST-elevated myocardial infarction (STEMI), non-STEMI (NSTEMI) and unstable angina pectoris (UAP), differing in presentation as well as optimal treatment strategies.[1] The mortality of ACS is high with an early mortality, defined as within 30 days, of 6.1% in STEMI patients and 3.7% in NSTEMI patients and late mortality, defined as longer than 30 days, of 1.9% in STEMI patients and 2.6% in NSTEMI patients.[2] The associated complications of ACS are debilitating, with an incidence in major adverse cardiac events (MACE) of 6.9% in STEMI patient and 4.5% in NSTEMI patients within 30 days and 8.0% in STEMI patients and 9.1% in NSTEMI patients after 30 days.[1, 2] The development of coronary revascularisation with fibrinolytic therapy and later percutaneous coronary intervention (PCI) greatly improved outcomes for STEMI and NSTEMI patients.[3-6] Figure 1 shows the PCI technique in which a stent is placed in the (nearly) occluded artery. Catheter introduction is achieved through the femoral or radial artery. A stent around a balloon is inserted in the culprit artery and expanded by balloon inflation after which the expanded stent is left in the artery. This procedure is performed in a designated catherization laboratory (cath lab) under X-ray tubes to visualize the coronary arteries.

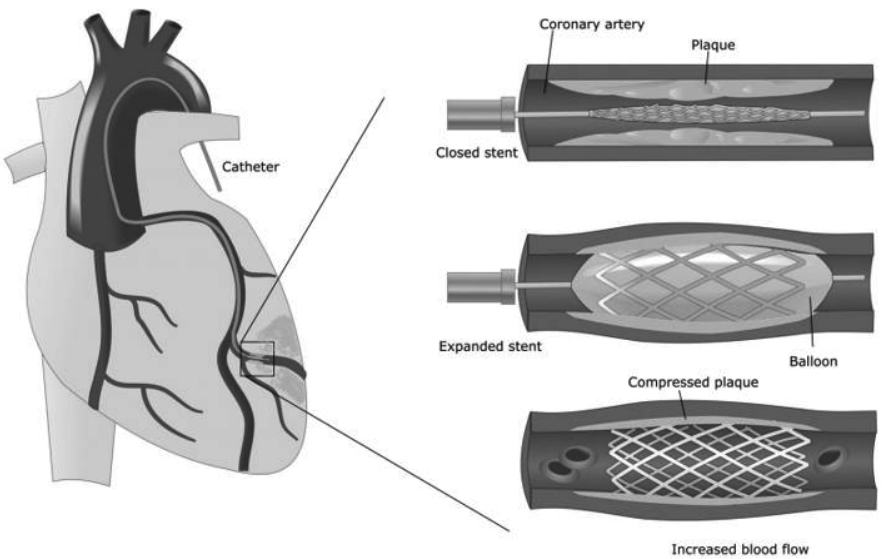

Figure 1. Percutaneous coronary Intervention

PART I: PRE-HOSPITAL DELAYS

STEMI

STEMI patients have an occluded, or nearly occluded, culprit coronary artery. This results in on-going transmural ischemia and reveals itself as ST-elevation on an ECG giving it the name

"ST-elevated myocardial infarction". A direct relationship between duration of coronary artery occlusion and the extent of myocardial necrosis has been demonstrated in animal models. Myocardial cell death begins within 20 minutes of coronary artery occlusion and is complete within six hours. This period may be extended through intermittent episode of reperfusion and other (clinical) factors.[7] Due to the time dependent aspect in myocardial infarction it is known as "time is muscle", indicating that STEMI patients should undergo reperfusion as soon as possible.

Reperfusion treatment with either fibrinolytic therapy or PCI are both time dependent, however PCIs rely more on logistic and economic constraints than fibrinolytic therapy. Early studies implied that the benefits associated with PCI as reperfusion compared to fibrinolytic therapy were lost with longer delays.[8, 9] This was later contradicted when newer studies demonstrated that PCI was superior regardless of delays.[5, 10, 11] The guidelines have a preference to PCI as reperfusion strategy above fibrinolytic therapy, if treatment delays can be upheld.[1, 12] Patients treated with PCI have a 37% reduction in 30-day mortality compared to fibrinolytic therapy with a mortality decrease from 7.9% to 5.3%.[5]

Delays

Early reperfusion in STEMI patients, either through fibrinolytic therapy or PCI, results in a decrease of mortality, better recovery of left ventricular ejection faction, less heart failure and less re-occlusions.[13-15] Worse outcomes are seen in patients with a delay of more than one hour, also known as the "golden hour".[14, 15] After numerous studies with comparable results the European Society of Cardiology (ESC) as well as the American College of Cardiology Foundation and the American Heart Association (ACCF/AHA) recommended the decrease of delays in the network of ACS patients in their guidelines.[1, 12]

In the Netherlands a patient with chest pain can contact either the general practitioner (GP) or emergency medical transport (EMT) or the patient can present at a hospital as a self-referral, as depicted in Figure 2. As a result of these options, the ACS network consist of GPs, EMTs and specialists. This first contact between a patient and a medical professional, either by phone or physical, is referred to as "the first medical contact (FMC)". In the ACS network various delays can be differentiated such as the patient delay, the doctor delay, the transport delay and the door-to-balloon (DTB) delay. The exact definition of these delays varies in studies.[13-23] In this dissertation the delays are defined as:

- Patient delay: the time of symptom onset to the first call or presentation to a medical professional, the FMC
- Doctor delay: the time between FMC to hospital referral
- Transport delay: the transportation time to a PCI-capable hospital
- DTB delay: the time of patients arrival at a hospital (PCI-capable or non-capable) until the time of wire passage during PCI

- System delay: the time from FMC to treatment. Further defined as *any* contact, call or visit, with a medical professional about symptoms to PCI

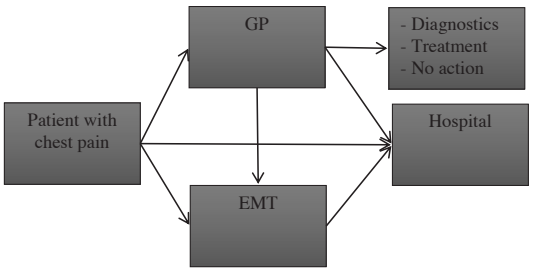

Figure 2. Flow chart of patient with chest pain
GP: general practitioner, EMT: emergency medical transport

The ESC and ACCF/AHA have specific recommendations about the delays in which STEMI patients should receive reperfusion (Figure 3).[1, 12]

- The total system delay should be 90 minutes or less in 90% of the patients
- The diagnosis of a STEMI should take less than 10 minutes
- DTB should be less than 60 minutes

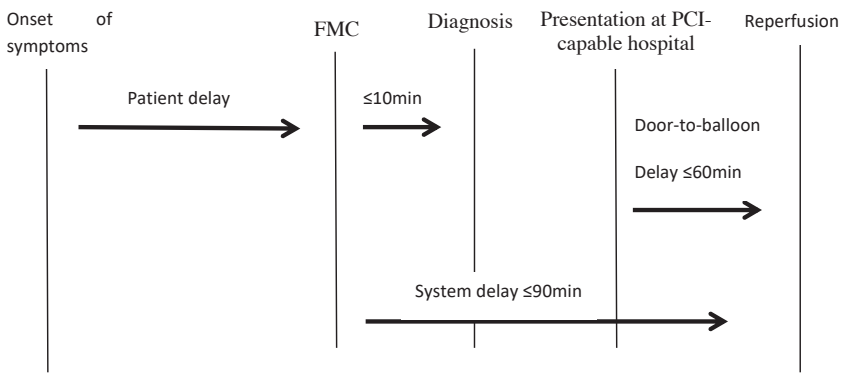

Figure 3. Guideline recommended delays.
FMC: first medical contact, any contact with a (para)medic about cardiac symptoms, PCI: percutaneous coronary intervention, min: minutes

To decrease delays in STEMI patients and achieve guideline recommendations the initial studies focussed mainly on in-hospital delays. As PCI treatment was initiated, PCI centres were rare, resulting in long transportation delays.[16] The long DTB delays were partly caused by the delay between the first hospital the patients presented (the "door") and the treatment at the PCI-capable hospital ("the balloon"). The long DTB delays were, however, also seen in patients presenting directly to a PCI-capable hospital.[17] Various strategies were implemented to improve the DTB delays. These strategies included education and feedback for all medical professionals

involved in the ACS network, improved communication between PCI and non-PCI capable hospitals, an active role for EMT, direct cath lab activation and even nation-wide programs. Despite improvements of the DTB delay through these strategies, the delays were still long.[17-20] Delays varying from 94 to 189 minutes decreased to delays just below 90 minutes (81-88 minutes) with only limited studies showing improvements to under 30 minutes.[19]

EMT

The attention within the pre-hospital network of ACS mostly focussed on EMT or transport delay.[21] Following recommendations in the guidelines, many ambulances installed a 12-lead ECG to diagnose a STEMI as soon as possible. This resulted in decreases in FMC-to-balloon delay, DTB, as well as door-to-needle delays up to 78 minutes.[22, 23] The in-hospital delays decreased as a result of bypassing the emergency department (ED) and immediate activation of the cath lab. As expected this decrease in delays also resulted in a decrease of mortality.[23]

Besides the reduction in delays, patients transported by EMT also benefit from continuous monitoring during transportation to the hospital. EMT personnel are equipped and trained to manage a cardiac arrest, as 5.6% of patients suspected of ACS have a cardiac arrest in the ambulance.[24]

Off-site PCI

In the Netherlands the guideline preference of PCI as the primary revascularisation treatment of STEMI patients and the increasing age of the public resulted in an increase of PCIs. Subsequently a progressive number of patients waiting for PCI's was seen. To meet this demand, off-site PCI centres, PCI centres without on-site surgical backup, were initiated.[25] The need for emergent cardiac surgery to treat complications related to PCI had dramatically decreased from 10% in the first PCI procedures to 0.15% in 2002,[26, 27] warranting the safety of off-site PCI centres. The initiation of off-site PCI centres resulted in a decrease time on the waiting list and ensured the availability of timely primary PCI in all regions.[25]

Aim part I

Despite the vast improvements in the delays within the ACS network, delays in STEMI patients are still substantial and the guideline recommended delays are not yet met.[28] The *first aim* of this dissertation is to review interventions that aim to shorten the pre-hospital delays of STEMI patients. These interventions include the start of an off-site PCI centre and the start of an ACS focus group involving Cardiologists, GPs and EMT.

PART II ACCURACY OF REFERRALS

In the efforts to reduce delays in ACS patients and not miss ACS, many patients with chest pain are referred directly to the ED with the ambulance. While this certainly decreased delays in ACS, ACS is but one of a variety of disorders associated with chest pain.[29] Referring all these patients thus results in a high number of unnecessary referrals.

Non-cardiac chest pain

The prevalence of non-traumatic chest pain in the primary care varies from 0.7% to 2.7%. The prevalence of ACS or ischemic heart disease within this group of patients varies from 1.5% to 8%,[30-32] while the largest amount of patients have non-cardiac chest pain (NCCP). Life-threatening diagnoses to consider are aortic dissection, pulmonary embolism, pneumothorax and perforated ulcus, though these are rare. Non-life threatening diagnoses include cardiac diseases such as pericardial and benign rhythm disorders or heart failure, chest wall syndrome or musculoskeletal symptoms, respiratory disorders such as pneumonia, COPD or asthma, psychological disorders such as anxiety and gastro-intestinal disorders such as oesophagitis, cholecystitis, or pancreatitis.[29, 32]

NCCP is more frequently seen in young patients, women, immigrants and patients with a lower educational level.[33] NCCP patients often seek care due to recurrent and persistent chest pain. They also have high levels of anxiety due to symptom severity and the possibility of a serious disease with the continued believe that the chest pain is related to heart problems.[33, 34] This anxiety is higher than in control patients[35] and also reportedly higher than in patients diagnosed with ACS.[34] The emotional distress and persistent symptoms has an impairment on daily activities and results in high work absenteeism.[34.36]

General practitioners

In the Netherlands the GPs have a “gatekeepers” role in which they select patients for referral to secondary care. This is beneficial due to the above mentioned low prevalence of ACS within chest pain patients. The risk of missing or delaying ACS patients is however not to be ignored. GPs deal with situations in which there is a real, but low likelihood of a serious disease.[37] Accepting too many risks leads to missed cases, late diagnosis and sometimes avoidable death. It also undermines the credibility of GPs in the eyes of the patients. Chest pain makes the doctor ánd patient concerned about the possibility of ACS.[31]

If GPs fail to shoulder any diagnostic risks the health care system will overload. The EMT and EDs are already overcrowding with NCCP patients, using up valuable resources.[38] Every tenth patient shows signs of over investigation.[38] In addition to the stress on the ED through, this exposes patients to risks and psychological stress. This stress reaches beyond the individual patient, also affecting their families and work.

Triage

Triaging patients with chest pain for referral to the ED, is not straightforward. It is not possible to diagnose ACS solely on signs and symptoms of patients.[39] The 'typical' symptoms of ACS such as a tight, squeezing, heavy or pressure-like chest pain with radiation to the jaw, neck, throat, left arm or left shoulder do not discriminate between the presence of ACS or NCCP.[40] Furthermore the available tests for GPs do not improve the triage. An ECG can help diagnose a STEMI, however NSTEMI and UAP are not distinguished by ECG abnormalities.[41] Because of this, it has been suggested that GPs should not make an ECG in the work-up of chest pain, as a suspicion of ACS should always lead to referral of the patient.[42] Troponin testing in the GPs office has not been recommended for logistical as well as safety reasons.[43] If a patient is suspected of having ACS, they should not be sent to get bloodwork done and then wait, unmonitored, for the results. As of late, there are point-of-care testers on the market, boasting easy and fast troponin results. This would all but eliminate the logistical and safety arguments against troponin testing in the GPs office.[44]

To aid doctors many clinical decisions rules have been developed and tested.[45-47] Combining the symptoms, ECG, and troponin resulted in the HEART score.[48] This is a validated score aimed to help make accurate diagnostic and therapeutic decisions in chest pain patients presenting at the ED. It would be interesting to see the implementation of the HEART score in the GPs office with the help of a point-of-care troponin tester to aid the GPs in the triage of chest pain patients.

Aim part II

Referring all patients with chest pain to the ED is neither beneficial to the health care system nor the patients. The *second aim* of this dissertation is to improve the accuracy of referrals from the pre-hospital network and in particular the GPs. We analyzed the scope of NCCP referrals and investigated the use of the HEART score in the GP cooperation (GPC) to decrease NCCP referrals while maintaining low delay times and a low risk of misdiagnosis.

OUTLINE OF THIS THESIS

Introduction

To shorten pre-hospital delays and achieve an improvement in accuracy of referrals, the scope of the problem needs to be analysed. In *chapter two* we reviewed all available data on chest pain patients and in particular ACS patients with regards to the pre-hospital network. We discussed the pathophysiology, delays in STEMI and NSTEMI patients, chest pain incidence, patient delay, GP or doctor delay, (nurse) triage and delays in EMT.

Part one: Pre-hospital delays

In order to achieve the first aim of this dissertation, namely the evaluation of interventions aimed at decreasing the pre-hospital delays in STEMI patients, we evaluated the delays and outcomes of STEMI patients after the start of an off-site PCI centre. In *chapter three* we first analysed the procedural and six months clinical outcomes of the first year of PCI in an off-site hospital. In *chapter four* we analysed the same off-site PCI centre, now looking at the outcome of the primary PCIs for STEMI and unstable NSTEMI patients. Finally in *chapter five* we investigated the effect of the start of an off-site PCI centre and the start of an ACS focus group involving Cardiologists, GPs and EMTs on the pre-hospital delays of STEMI patients.

Part two: Accuracy of referrals

Decreasing delays in ACS patients frequently comes with an excessive referrals of NCCP patients. In *chapter six* we outline the diagnostic challenge for GPs in regards to chest pain patients. GPs do not want to miss or even delay the treatment of ACS patients, however the excess in referrals of NCCP patients brings in many risk associated with the additional diagnostics. *Chapter seven* analyses the amount of diagnostics within NCCP patients.

To help GPs in the pre-hospital network in the triage of chest pain patients, we implemented the Heart score within the GPC. The HEART score combines history, ECG, age, risk factors and troponin testing in to a score to differentiate between a low, intermediate and high risk of a MACE in patients with chest pain.[48] *Chapter eight* is a pilot study that analyses the safety and feasibility of the use of the HEART score at the GPC to triage chest pain patients more accurately.

REFERENCES

1. Steg PG, James SK, Atar D, Badano LP, Blomstrom-Lundqvist C, Borger MA, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. European heart journal. 2012;33(20):2569-619.
2. Park HW, Yoon CH, Kang SH, Choi DJ, Kim HS, Cho MC, et al. Early- and late-term clinical outcome and their predictors in patients with ST-segment elevation myocardial infarction and non-ST-segment elevation myocardial infarction. International journal of cardiology. 2013;169(4):254-61.
3. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Lancet. 1994;343(8893):311-22.
4. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet. 2003;361(9351):13-20.
5. Boersma E, Primary Coronary Angioplasty vs. Thrombolysis G. Does time matter? A pooled analysis of randomized clinical trials comparing primary percutaneous coronary intervention and in-hospital fibrinolysis in acute myocardial infarction patients. European heart journal. 2006;27(7):779-88.
6. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. FRagmin and Fast Revascularisation during InStability in Coronary artery disease Investigators. Lancet. 1999;354(9180):708-15.
7. Nallamothu BK, Bradley EH, Krumholz HM. Time to treatment in primary percutaneous coronary intervention. The New England journal of medicine. 2007;357(16):1631-8.
8. Nallamothu BK, Antman EM, Bates ER. Primary percutaneous coronary intervention versus fibrinolytic therapy in acute myocardial infarction: does the choice of fibrinolytic agent impact on the importance of time-to-treatment? The American journal of cardiology. 2004;94(6):772-4.
9. Pinto DS, Kirtane AJ, Nallamothu BK, Murphy SA, Cohen DJ, Laham RJ, et al. Hospital delays in reperfusion for ST-elevation myocardial infarction: implications when selecting a reperfusion strategy. Circulation. 2006;114(19):2019-25.
10. De Luca G, Biondi-Zoccai G, Marino P. Transferring patients with ST-segment elevation myocardial infarction for mechanical reperfusion: a meta-regression analysis of randomized trials. Annals of emergency medicine. 2008;52(6):665-76.
11. Pinto DS, Frederick PD, Chakrabarti AK, Kirtane AJ, Ullman E, Dejam A, et al. Benefit of transferring ST-segment-elevation myocardial infarction patients for percutaneous coronary intervention compared with administration of onsite fibrinolytic declines as delays increase. Circulation. 2011;124(23):2512-21.
12. O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Jr., Chung MK, de Lemos JA, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;127(4):e362-425.
13. Terkelsen CJ, Sorensen JT, Maeng M, Jensen LO, Tilsted HH, Trautner S, et al. System delay and mortality among patients with STEMI treated with primary percutaneous coronary intervention. Jama. 2010;304(7):763-71.

14. Goel K, Pinto DS, Gibson CM. Association of time to reperfusion with left ventricular function and heart failure in patients with acute myocardial infarction treated with primary percutaneous coronary intervention: a systematic review. American heart journal. 2013;165(4):451-67.

15. Koul S, Andell P, Martinsson A, Gustav Smith J, van der Pals J, Schersten F, et al. Delay from first medical contact to primary PCI and all-cause mortality: a nationwide study of patients with ST-elevation myocardial infarction. Journal of the American Heart Association. 2014;3(2):e000486.

16. Henry TD, Sharkey SW, Burke MN, Chavez IJ, Graham KJ, Henry CR, et al. A regional system to provide timely access to percutaneous coronary intervention for ST-elevation myocardial infarction. Circulation. 2007;116(7):721-8.

17. Mehta RH, Bufalino VJ, Pan W, Hernandez AF, Cannon CP, Fonarow GC, et al. Achieving rapid reperfusion with primary percutaneous coronary intervention remains a challenge: insights from American Heart Association's Get With the Guidelines program. American heart journal. 2008;155(6):1059-67.

18. Blankenship JC, Scott TD, Skelding KA, Haldis TA, Tompkins-Weber K, Sledgen MY, et al. Door-to-balloon times under 90 min can be routinely achieved for patients transferred for ST-segment elevation myocardial infarction percutaneous coronary intervention in a rural setting. Journal of the American College of Cardiology. 2011;57(3):272-9.

19. Muller UM, Eitel I, Eckrich K, Erbs S, Linke A, Mobius-Winkler S, et al. Impact of minimising door-to-balloon times in ST-elevation myocardial infarction to less than 30 min on outcome: an analysis over an 8-year period in a tertiary care centre. Clinical research in cardiology : official journal of the German Cardiac Society. 2011;100(4):297-309.

20. Jollis JG, Roettig ML, Aluko AO, Anstrom KJ, Applegate RJ, Babb JD, et al. Implementation of a statewide system for coronary reperfusion for ST-segment elevation myocardial infarction. Jama. 2007;298(20):2371-80.

21. Hannan EL, Zhong Y, Jacobs AK, Holmes DR, Walford G, Venditti FJ, et al. Effect of onset-to-door time and door-to-balloon time on mortality in patients undergoing percutaneous coronary interventions for st-segment elevation myocardial infarction. The American journal of cardiology. 2010;106(2):143-7.

22. Zegre Hemsey JK, Drew BJ. Prehospital electrocardiography: a review of the literature. Journal of emergency nursing: JEN : official publication of the Emergency Department Nurses Association. 2012;38(1):9-14.

23. Nam J, Caners K, Bowen JM, Welsford M, O'Reilly D. Systematic review and meta-analysis of the benefits of out-of-hospital 12-lead ECG and advance notification in ST-segment elevation myocardial infarction patients. Annals of emergency medicine. 2014;64(2):176-86, 86 e1-9.

24. Becker L, Larsen MP, Eisenberg MS. Incidence of cardiac arrest during self-transport for chest pain. Annals of emergency medicine. 1996;28(6):612-6.

25. Peels JO, Hautvast RW, de Swart JB, Huybregts MA, Umans VA, Arnold AE, et al. Percutaneous coronary intervention without on site surgical back-up; two-years registry of a large Dutch community hospital. International journal of cardiology. 2009;132(1):59-65.

26. Gruntzig AR, Senning A, Siegenthaler WE. Nonoperative dilatation of coronary-artery stenosis: percutaneous transluminal coronary angioplasty. The New England journal of medicine. 1979;301(2):61-8.

27. Seshadri N, Whitlow PL, Acharya N, Houghtaling P, Blackstone EH, Ellis SG. Emergency coronary artery bypass surgery in the contemporary percutaneous coronary intervention era. Circulation. 2002;106(18):2346-50.

28. Widimsky P, Wijns W, Fajadet J, de Belder M, Knot J, Aaberge L, et al. Reperfusion therapy for ST elevation acute myocardial infarction in Europe: description of the current situation in 30 countries. European heart journal. 2010;31(8):943-57.

29. Knockaert DC, Buntinx F, Stoens N, Bruyninckx R, Delooz H. Chest pain in the emergency department: the broad spectrum of causes. European journal of emergency medicine : official journal of the European Society for Emergency Medicine. 2002;9(1):25-30.

30. Bosner S, Becker A, Haasenritter J, Abu Hani M, Keller H, Sonnichsen AC, et al. Chest pain in primary care: epidemiology and pre-work-up probabilities. The European journal of general practice. 2009;15(3):141-6.

31. Nilsson S, Scheike M, Engblom D, Karlsson LG, Molstad S, Akerlind I, et al. Chest pain and ischaemic heart disease in primary care. The British journal of general practice : the journal of the Royal College of General Practitioners. 2003;53(490):378-82.

32. Verdon F, Herzig L, Burnand B, Bischoff T, Pecoud A, Junod M, et al. Chest pain in daily practice: occurrence, causes and management. Swiss medical weekly. 2008;138(23-24):340-7.

33. Mourad G, Alwin J, Stromberg A, Jaarsma T. Societal costs of non-cardiac chest pain compared with ischemic heart disease--a longitudinal study. BMC health services research. 2013;13:403.

34. Eslick GD, Coulshed DS, Talley NJ. Review article: the burden of illness of non-cardiac chest pain. Alimentary pharmacology & therapeutics. 2002;16(7):1217-23.

35. Webster R, Norman P, Goodacre S, Thompson A. The prevalence and correlates of psychological outcomes in patients with acute non-cardiac chest pain: a systematic review. Emergency medicine journal : EMJ. 2012;29(4):267-73.

36. Eslick GD, Talley NJ. Non-cardiac chest pain: predictors of health care seeking, the types of health care professional consulted, work absenteeism and interruption of daily activities. Alimentary pharmacology & therapeutics. 2004;20(8):909-15.

37. Buntinx F, Mant D, Van den Bruel A, Donner-Banzhof N, Dinant GJ. Dealing with low-incidence serious diseases in general practice. The British journal of general practice : the journal of the Royal College of General Practitioners. 2011;61(582):43-6.

38. Glombiewski JA, Rief W, Bosner S, Keller H, Martin A, Donner-Banzhoff N. The course of nonspecific chest pain in primary care: symptom persistence and health care usage. Archives of internal medicine. 2010;170(3):251-5.

39. Bruyninckx R, Aertgeerts B, Bruyninckx P, Buntinx F. Signs and symptoms in diagnosing acute myocardial infarction and acute coronary syndrome: a diagnostic meta-analysis. The British journal of general practice : the journal of the Royal College of General Practitioners. 2008;58(547):105-11.

40. Swap CJ, Nagurney JT. Value and limitations of chest pain history in the evaluation of patients with suspected acute coronary syndromes. Jama. 2005;294(20):2623-9.

41. Rutten FH, Kessels, A.G.H, Willems, F.F, Hoes, A.W. Is elektrocardiografie in de huisartsenpraktijk nuttig? Huisarts & Wetenschap. 2001;44:179-83.

42. Chan L, Willemsen, R, Konings, K. Elektrocardiografie in de huisartsenpraktijk. Huisarts & Wetenschap. 2014(4):57.

43. Marshall GA, Wijeratne NG, Thomas D. Should general practitioners order troponin tests? The Medical journal of Australia. 2014;201(3):155-7.

44. Amundson BE, Apple FS. Cardiac troponin assays: a review of quantitative point-of-care devices and their efficacy in the diagnosis of myocardial infarction. Clin Chem Lab Med. 2015;53(5):665-76.

45. Bruins Slot MH, Rutten FH, van der Heijden GJ, Geersing GJ, Glatz JF, Hoes AW. Diagnosing acute coronary syndrome in primary care: comparison of the physicians' risk estimation and a clinical decision rule. Family practice. 2011;28(3):323-8.

46. Gencer B, Vaucher P, Herzig L, Verdon F, Ruffieux C, Bosner S, et al. Ruling out coronary heart disease in primary care patients with chest pain: a clinical prediction score. BMC medicine. 2010;8:9.

47. Bosner S, Haasenritter J, Becker A, Karatolios K, Vaucher P, Gencer B, et al. Ruling out coronary artery disease in primary care: development and validation of a simple prediction rule. CMAJ. 2010;182(12):1295-300.

48. Backus BE, Six AJ, Kelder JC, Bosschaert MA, Mast EG, Mosterd A, et al. A prospective validation of the HEART score for chest pain patients at the emergency department. International journal of cardiology. 2013;168(3):2153-8.

Chapter 2

Delays in the treatment of patients with acute coronary syndrome: Focus on pre- hospital delays and non-ST-elevated myocardial infarction

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ABSTRACT

Delays in patients suspected of acute coronary syndrome (ACS) should be kept as short as possible to reduce complications and mortality. In this review we discuss the substantial pre-hospital delays of ST-elevated myocardial infarction (STEMI) patients as well as non-STEMI patients.

The pre-hospital delays include patient, doctor and emergency medical transport (EMT) delay. Patient delay is among the longest in the pre-hospital chain of ACS patients. Interventions as mass media campaigns or individual education programs have not yet shown much improvement. Patients with chest pain most often contact the general practitioner (GP) instead of the recommended EMT, increasing delays as well. To decrease the delays by referring all patients promptly and without restriction to the emergency department (ED) is not feasible. Up to 80% of the patients with chest pain do not have a cardiac diagnosis and thus referral of all these patients would result in overcrowding of the ED. Triage is therefore crucial. Triage of patients with chest pain is therefore imperative and there is a great need of (validated) triage tools.

INTRODUCTION

Despite vast improvements in the management of acute coronary syndrome (ACS), there still is a great mortality risk.[1] Delays should be kept as short as possible, to reduce complications and mortality. A great deal of research has been conducted to achieve shorter delays in ACS patients. Focus on delays has resulted in improved door-to-balloon (DTB) delays, however a substantial number of ACS patients is not yet treated within a preferred time delay.[2] Pre-hospital delays are the longest in the ACS chain and thus the greatest time benefits can be achieved within this section.[3] The pre-hospital delays include patient, doctor and emergency medical transport (EMT) delay.[4]

There are several ways a patient with symptoms suspected of ACS can reach out for help and be referred to the hospital. In most countries patients with chest pain will, as depicted in Figure 1, contact the primary care physician or general practitioner (GP),[5] the EMT, or go directly to the hospital. The GP can decide to refer the patient to the hospital, implement further diagnostics or treatment, or reassure the patient without referral.

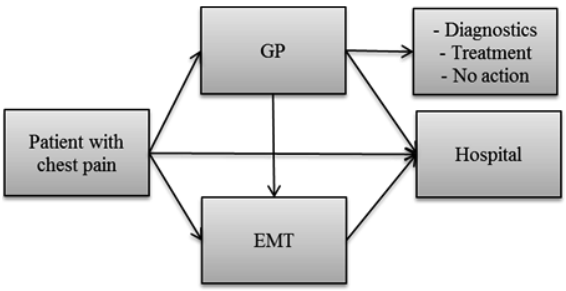

Figure 1. Flow chart patient with chest pain. GP: general practitioner, EMT: Emergency Medical Transport

To diminish delays in patients with ACS, the European Society of Cardiology (ESC) as well as the American College of Cardiology Foundation and the American Heart Association (ACCF/AHA) guidelines advise to bypass GPs altogether.[4,6] GPs have been advised to refer all patients with new or recently changed chest complaints to the hospital without further delay, in order to avoid missing any myocardial infarctions.[7] In a society that is less tolerant of missing a diagnosis with an increasing number of lawsuits for not (timely) diagnosing a serious illness,[8] GPs are rather safe than sorry. [7] This low threshold for referral has a downside: up to 80% of the patients are unnecessarily referred to the hospital,[9] which induces crowding of the emergency department (ED) as well as additional stress on the patients.[10] The key to ensuring timely treatment without overloading medical services with non-cardiac patients is triage.

This review will outline the pre-hospital delays and triage of patients with chest pain. We will discuss pathophysiology, delays in ST-elevated myocardial infarction (STEMI) and non-STEMI (NSTEMI) patients, chest pain incidence, patient delay, GP or doctor delay, (nurse) triage, and delays in EMT.

REVIEW

Pathophysiology

Over the last decade the rate of NSTEMI has increased and has surpassed the STEMI incidence (60 vs 40%).[11] STEMI and NSTEMI patients moreover differ in mortality: STEMI patients have higher short-term mortality rates,[12] while NSTEMI patients have higher long-term mortality.[12,13]

Until recently, STEMI patients were thought to have an occluded culprit artery, on-going transmural ischemia and ST-elevations on the electrocardiogram (ECG), while NSTEMI patients have a patent culprit artery, without on-going ischemia and no ST-elevation on ECG.[6,14] This resulted in a different approach to and advice about delays. More recent studies indicate that the pathophysiology between STEMI and NSTEMI patients is not as different as previously assumed.[11] Besides similar symptoms and essentially the same physical examination, ECGs do not always differentiate between occluded and open vessels. The left circumflex artery, for example, is notorious for minimal ST-deviations on ECG, even when occluded. Moreover occluded arteries or transmural ischemia are not exclusive to patients with a STEMI. Transmural ischemia is seen in 63% of STEMI patients and 27% of NSTEMI patients. Coronary artery occlusion ranges from 27 to 51% in patients presenting with NSTEMI.[11] These insights have caused an adjustment in advice about delays.

Delays in STEMI patients

Delays in the reperfusion of STEMI patients increase the mortality.[15-17] Earlier reperfusion results in superior clinical outcomes, better recovery of left ventricular ejection fraction, less heart failure and less re-occlusions.[15,17]

In light of these studies, the ESC, as well as the ACCF/AHA, has set up guidelines to decrease the mortality of STEMI patients.[4,6] The ESC recommends that, as depicted in Figure 2, the delay between first medical contact (FMC) and diagnosis should be less than 10 minutes, the system delay (the time between FMC and reperfusion) must be less than 90 minutes and DTB delay must be less than 60 minutes.[4]

The recommended maximum delays in the guidelines for STEMI patients are rarely met. A system delay of 90 minutes or less is achieved in between 10 to 82%.[18-20] The average system delay of European countries varies between 60 and 177 minutes, with an overall mean of 110 minutes.[21]

Delays in NSTEMI patients

Numerous studies have analysed the timing of angioplasty in NSTEMI patients. There are three major meta-analyses, which together include ten randomised-controlled trials and four observational studies.[22-24] Most studies define early intervention as immediate or within 24 hours and define later intervention as more than 24 hours. Overall, there is no significant difference in the risk of mortality or myocardial infarction between early and late angioplasty.[22-24] Combining

the data of the studies, as done in the meta-analysis, also gave no significant differences. There is, however, a significant difference in recurrent ischemia, with less recurrence in the early angioplasty group. However, the studies reviewed in the meta-analyses all vary extensively, with high heterogeneity within.[22-24] Of the three studies that have shown a significant difference in mortality, two studies had much longer delays than the others, with a delay in angioplasty up to seven days, and are therefore not comparable to the other studies.

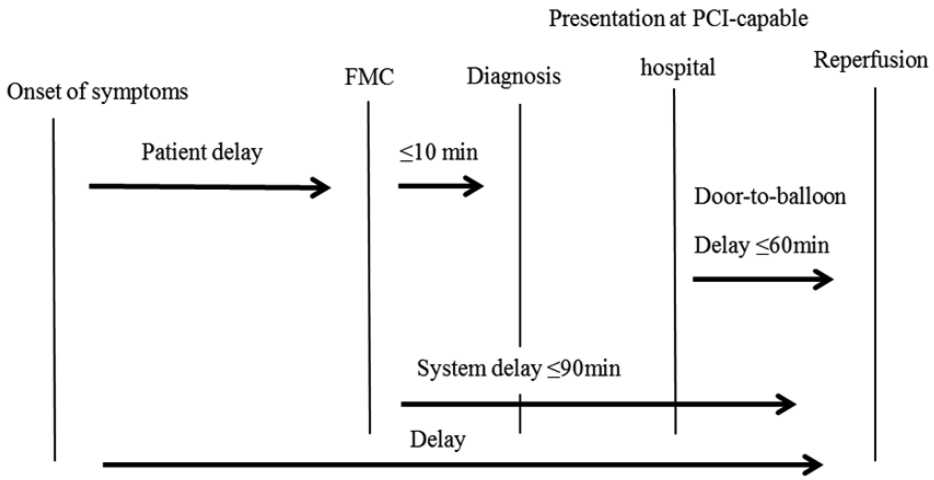

Figure 2. Recommended delays. FMC: First Medical Contact, PCI: percutaneous coronary intervention.

The ESC guidelines now advise very high-risk patients to undergo angioplasty within 2 hours, high risk patients within 24 hours and intermediate risk patients within 72 hours. In other patients non-invasive diagnostics can be considered.[25]

It is also crucial to start pharmacological therapy as soon as possible in patients with NSTEMI as well as STEMI. Therefore patients with suspected ACS should be referred promptly to the hospital for diagnostics and treatment.

Chest pain prevalence

Referring all patients with chest pain without restriction to reduce delays in ACS, however, is not feasible as chest pain in the community is a common symptom with an incidence of 23 to 28%.[26] Around 50 up to 80% of the patients at the ED with suspected ACS are diagnosed with a non-cardiac diagnosis.[9,10,27] In the primary care setting this is even more common with non-cardiac chest pain (NCCP) incidence of about 80%.[28] Self-referrals to the hospital are more frequently diagnosed with a non-cardiac condition than patients referred by the EMT or GP.[9] Even in patients admitted to the hospital with suspected ACS, up to 30% have a different discharge diagnosis.[29]

NCCP can be of musculoskeletal, gastro-intestinal, psychological, or respiratory origin, [9,26,30,31] though the prevalence of these conditions is not well known.[26] Potentially life-threatening disorders as pulmonary embolism or thoracic aortic dissection have a low incidence in patients suspected of ACS.[9]

Mortality in patients with NCCP is significantly lower than in patient with chest pain of cardiac origin: the one-year mortality of patients with ACS is 18%,[32] compared to 3.2% in patients with NCCP.[30,32] The mortality in NCCP patients is only slightly higher than in the general population, though they do have an increased risk of cardiovascular disease.[31] Males and older patients with NCCP are more at risk to develop ischemic heart disease than other populations.[31]

Despite the low mortality rate of NCCP patients, they are exposed to risk and stress by needless referral or admittance to the hospital. Furthermore, it has a psychological impact on them as well as their families. [10,29,33] These patients make unnecessary use of resources, with high health care utilization[27,30,33] and frequent readmissions,[32] additionally resulting in high health care and societal costs.[26,33,34]

Patient delay

The longest delay in the ACS-chain is the patient delay, with a median varying between two to five hours.[35-38] Only around 25% of the patients wait less than an hour and up to 60% exceed a delay of six hours.[39] There does seem to be a cultural difference in delay times, as it has been found that patients from North-America and Australia wait considerably less to contact help than patients from Europe or South-America.[3]

The two most important predictors of patient delay are the patients subjective feeling of the severity of the chest pain and the role of the spouse.[40] Delay times are longer in females, patients with lower education or income, and old age. Cognitive reasons for patients not to seek help are that they do not expect the symptoms to be cardiac or life threatening. Patients are also ashamed to ask for help and afraid of the consequences.[41] Ignorance of symptoms is another reason for patient to delay: while 80 to 90% of the patients know that chest pain is associated with myocardial infarction,[42] only 11 to 26% of the patients actually recognize a myocardial infarction.[39,43,44] Patients do know smoking is a risk factor for ACS, but do not know the other risk factors,[43,44] nor do patients with risk factors have more awareness about myocardial infarction.[42,43] Patients do not know that they have to call the EMT, as only 26 to 34% contact the EMT themselves.[44] As EMT use reduces delays and patients are monitored for cardiac arrest at an earlier stage, this is an important aspect in the pre-hospital delay.[21,44]

Several measures have been initiated to reduce patient delay, through mass media campaigns[35-38,44-50] and educational programs targeted to specific patient groups.[51-53] The media campaigns have shown conflicting results, with some showing improvement in patient delay,[35,36] while others showed no improvement.[37,38,45] They did show that patients were more knowledgeable about ACS[47,48] or contacted the EMT more often.[37] Only two mass media campaign studies showed an improvement in the time delays in STEMI as well as NSTEMI patients[49,50].

Of the studies targeting a specific patient group, two showed a decrease in patient delay.[51,52] One individual education program resulted in an increase in knowledge; however there was no decrease in delay.[53]

The downside to these campaigns was that significantly more patients were admitted to the ED with suspected ACS, with equal increase of patients with the diagnosis of NCCP.[46] Finally the effectiveness of the campaigns wears off fast, with both the benefits and disadvantages disappearing within a couple of months of the campaign.[46]

General practitioner

Primary care based health systems are widely implemented in Europe and thus the GP has an important role in the system delay of patients with chest pain. The primary care facilities in Europe are organized in GP practices during the day and GP cooperatives, rota groups or deputizing services for out-of-hours care.[5] Triage of primary care patients are predominantly performed by trained nurses, either via telephone or physical triage.[54]

In patients with ACS 37 to 75% consult a GP.[55,56] Studies have shown an extra delay from 20 up to 160 minutes when STEMI patients contact a GP first instead of the EMT.[55,57] The GP delay can be divided into the time for the GP to arrive at the patient, 11 minutes on average, and decision time, up to 82 minutes.[58] This delay is furthermore influenced by the working hours of the GPs with the longest delays between eight and twelve o'clock in the morning and the shortest in the evening between eight and midnight.[55] The longer delay when contacting the GP could be a consequence of less typical symptoms in patients, depicted in longer patient delays as well if they call the GP. [56,59]

To diminish these delays, GPs are increasingly referring patients with chest pain to the hospital immediately.[8] This is contrary to the guidelines of The Dutch College of GPs (Nederlands Huisartsen Genootschap) as they do advise the GPs to send an ambulance immediately to patients with suspected ACS, but also to see the patient themselves.[60] GPs are therefore in great need of diagnostic tools to help distinguish patients with chest pain for referral,[7] as it is not possible to diagnose a patient with ACS solely on patient history and physical examination.[61] ECGs do not rule out ACS and are therefore not advised to trust on solely. Testing troponin, a biomarker used to assess myocardial injury, is not encouraged in GP offices for logistic as well as safety reasons.[62] Furthermore GPs classify chest pain patients more accurately than the currently available clinical decision rules.[63] The most validated clinical decision rules, the HEART score and TIMI score, include troponin testing, which, as stated above, is not advised in the GP practice.[61,64]

To circumvent GPs all together as the ESC guidelines suggest[4] is not feasible, as the burden on hospitals would be considerable. About 80% of the patients consulting the GP with chest pain have a non-cardiac diagnosis and bypassing GPs would result in exposure of patients to unnecessary risks and the use of valuable resources.[65] Triage of patients with chest pain is for these reasons imperative.

Triage

The great challenge for GP and EMT triage is to distinguish between patients with ACS, who require prompt referral to a (PCI-capable) hospital, and patients with NCCP.

There are many different triage systems used around the world. The most commonly used systems are the:

- Australasian Triage System (Australia/New Zealand)[66-68]
- Canadian Triage and Acuity System (mostly Canada)[68,69]
- Emergency Severity Index (mostly United States of America)[68,70,71]
- Manchester Triage System (mostly United Kingdom)[68,72]
- Netherlands Triage System (the Netherlands)[54,73]

These are all 5-level based triage systems, dividing patients into 5 urgency levels. Triage systems based on 3-levels have been proven to be insufficient.[54] Other countries use local triage systems or one adapted and/or translated from the above.[68]

Studies have been conducted to validate the triage systems. None of the triage systems are ideal, with their own agreement percentages, sensitivity and specificity. Studies of these triage systems also show different results, sometimes with wide ranges of results.[66,68,69] These studies are based on various scenarios, with no head-to-head studies and only one study focussed on patients with chest pain.[74] This study researched, retrospectively, the risk stratification of chest pain with the Manchester Triage System (MTS). They found that a great majority of patients diagnosed with an ACS were given high priorities by the MTS. Moreover a correlation was found between MTS priority category in chest pain patients and the final diagnosis of ACS.[74] We have not identified any studies on the other triage systems focussing on patients with chest pain or ACS.

Nurse triage

Trained nurses are a cost and quality efficient way to triage patients and thus they have been widely implemented around the world. Nurse triage performed by telephone has shown to have a sensitivity of 64 to 75% with a specificity of 95 to 97%[54,75] and is considered safe. Nurses, however, have been found to underestimate the urgency level.[75] They furthermore have a low compliance with computer based triage systems[73] and have been shown not to ask enough or not the right questions in some studies.[76,77]

Emergency Medical Transport

If ACS is suspected, patients should be referred to the hospital with EMT, to decrease the delays and to be able to monitor the patients at an earlier stage.

In recent years the pre-hospital delays in STEMI patients have decreased mostly as a result of improvements within the EMT. Following the recommendation of the ESC and ACCF/AHA many ambulances are now equipped with a 12-lead ECG.[4,6] Pre-hospital ECGs have been shown

to improve FMC-to balloon as well as the door-to-needle and DTB delays, and to have a modest mortality benefit.[2,78,79]

Patients with suspected ACS should be continuously monitored during transport and the EMT personnel trained and equipped to manage cardiac arrest. A study has shown that 5.6% of patients with coronary symptoms have a cardiac arrest in the ambulance.[80] Thus besides the shorter delay, these patients also have an added benefit of faster protection through monitoring.[52,56]

Regrettably patients usually consult their GP first or go to the ED as self-referrals. Only 26 to 34% of the patients call the EMT and bystanders are responsible for another 29% of the calls to the EMT.[4,44,81] Around 60% of all patients with ACS are transported by EMT.[80,81]

CONCLUSION

Rapid recognition and transportation of patients with ACS is crucial for their treatment. This has been extensively proven for STEMI, however NSTEMI patients also benefit from reduced delays.[22-24] Furthermore, the pathophysiology of STEMI and NSTEMI patients do not differ as significantly as previously thought and the incidence as well as the long-term mortality of NSTEMI patients is higher.[11-13] This had consequences on the advice about the delays of NSTEMI patients.[25]

In an era in which the DTB-delays have been significantly reduced, pre-hospital delays are still substantial and should be a continuous point of focus.

Patient delay is the longest in the pre-hospital chain and a difficult aspect to modify, as previous campaigns have shown.[35-38,44-50] New research and interventions should be focussed towards diminishing these delays. Studies have shown that individual education programs have been more successful than mass media campaigns.[51,52] In addition, with the rise of social media, there are also new ways to reach patients.

GPs are an important part of the pre-hospital chain, as many patients with chest pain phone their GP.[55,56] Up to 80% of these patients do not have a cardiac diagnosis and thus the burden on the hospital would be considerable without GP triage and treatment within the primary care. However as every minute counts in patients with a myocardial infarction and as society is not as forgiving, more and more patients are referred to the hospital immediately.[8] As ECGs are not sensitive and troponin testing not recommended due to logistics,[62] the GPs need tools to help them distinguish patients with and without ACS. This would aid the GPs not to excessively burden the ED but also not to miss ACS or delay the treatment of these patients. The triage systems available are validated for the overall population group;[68] it may be interesting to see how they score on chest pain. Moreover a risk stratification tool is being developed to stratify patients with chest pain, but without ST-elevations on ECG. It aims to safely identify high-risk NSTEMI patients who should be referred to a PCI-capable hospital, patients at intermediate risk

who can be referred to the nearest (non-PCI) hospital and patients at low risk for ACS who can be treated within the primary care.[82]

Nurse triage is widely implemented as it is (cost) efficient. It has been proven that trained nurses provide a better sensitivity and specificity and thus it is crucial to educate triage nurses more intensively to improve the safety and effectiveness of triage in chest pain patients.[75,83]

The dilemma in the pre-hospital chain of ACS patients is challenging. To improve the delays in ACS patients by referring them promptly and without restriction stands in contrast to not needlessly burdening the ED with an excess of NCCP patients. Triage of patients with chest pain is therefore imperative and there is a great need of validated triage tools.

REFERENCES

1. Leening MJ, Siregar S, Vaartjes I, et al. Heart disease in the Netherlands: a quantitative update. Neth Heart J. 2014;22(1):3-10. Epub 2013/12/18.
2. Nam J, Caners K, Bowen JM, et al. Systematic review and meta-analysis of the benefits of out-of-hospital 12-lead ECG and advance notification in ST-segment elevation myocardial infarction patients. Ann Emerg Med. 2014;64(2):176-86, 86 e1-9. Epub 2013/12/26.
3. Goldberg RJ, Spencer FA, Fox KA, et al. Prehospital Delay in Patients With Acute Coronary Syndromes (from the Global Registry of Acute Coronary Events [GRACE]). Am J Cardiol. 2009;103(5):598-603. Epub 2009/02/24.
4. Steg PG, James SK, Atar D, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J. 2012;33(20):2569-619. Epub 2012/08/28.
5. Huibers L, Giesen P, Wensing M, et al. Out-of-hours care in western countries: assessment of different organizational models. BMC Health Serv Res. 2009;9:105. Epub 2009/06/25.
6. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;127(4):e362-425. Epub 2012/12/19.
7. Willemsen R. Pijn op de borst. Huisarts & Wetenschap. 2015(7):58.
8. Giard RW. [Jurisprudence judging mistakes made during telephone triage]. Ned Tijdschr Geneeskd. 2009;153(8):364-7. Epub 2009/03/20. Juridische beoordeling van fouten bij telefonische triage.
9. Knockaert DC, Buntinx F, Stoens N, et al. Chest pain in the emergency department: the broad spectrum of causes. Eur J Emerg Med. 2002;9(1):25-30.
10. Webster R, Norman P, Goodacre S, et al. The prevalence and correlates of psychological outcomes in patients with acute non-cardiac chest pain: a systematic review. Emerg Med J. 2012;29(4):267-73.
11. IJkema BB, Bonnier JJ, Schoors D, et al. Role of the ECG in initial acute coronary syndrome triage: primary PCI regardless presence of ST elevation or of non-ST elevation. Neth Heart J. 2014;22(11):484-90. Epub 2014/09/10.
12. Park HW, Yoon CH, Kang SH, et al. Early- and late-term clinical outcome and their predictors in patients with ST-segment elevation myocardial infarction and non-ST-segment elevation myocardial infarction. Int J Cardiol. 2013;169(4):254-61. Epub 2013/09/28.
13. Terkelsen CJ, Lassen JF, Norgaard BL, et al. Mortality rates in patients with ST-elevation vs. non-ST-elevation acute myocardial infarction: observations from an unselected cohort. Eur Heart J. 2005;26(1):18-26. Epub 2004/12/24.
14. Fuster V, Badimon L, Badimon JJ, et al. The pathogenesis of coronary artery disease and the acute coronary syndromes (1). N Engl J Med. 1992;326(4):242-50. Epub 1992/01/23.
15. Goel K, Pinto DS, Gibson CM. Association of time to reperfusion with left ventricular function and heart failure in patients with acute myocardial infarction treated with primary percutaneous coronary intervention: a systematic review. Am Heart J. 2013;165(4):451-67. Epub 2013/03/30.

16. Terkelsen CJ, Sorensen JT, Maeng M, et al. System delay and mortality among patients with STEMI treated with primary percutaneous coronary intervention. JAMA. 2010;304(7):763-71. Epub 2010/08/19.

17. Koul S, Andell P, Martinsson A, et al. Delay from first medical contact to primary PCI and all-cause mortality: a nationwide study of patients with ST-elevation myocardial infarction. J Am Heart Assoc. 2014;3(2):e000486. Epub 2014/03/07.

18. Ali M, Englert D, Sharma N, et al. An unexpected silver lining to Katrina: elimination of inter-campus transfer delay in STEMI care. J La State Med Soc. 2012;164(4):216-8. Epub 2012/09/08.

19. Sandouk A, Ducasse JL, Grolleau S, et al. Compliance with guidelines in patients with ST-segment elevation myocardial infarction after implementation of specific guidelines for emergency care: results of RESCA+31 registry. Arch Cardiovasc Dis. 2012;105(5):262-70. Epub 2012/06/20.

20. Vermeulen RP, Jaarsma T, Hanenburg FG, et al. Prehospital diagnosis in STEMI patients treated by primary PCI: the key to rapid reperfusion. Neth Heart J. 2008;16(1):5-9. Epub 2008/03/05.

21. Widimsky P, Wijns W, Fajadet J, et al. Reperfusion therapy for ST elevation acute myocardial infarction in Europe: description of the current situation in 30 countries. Eur Heart J. 2010;31(8):943-57. Epub 2009/11/26.

22. Katritsis DG, Siontis GC, Kastrati A, et al. Optimal timing of coronary angiography and potential intervention in non-ST-elevation acute coronary syndromes. Eur Heart J. 2011;32(1):32-40. Epub 2010/08/17.

23. Milasinovic D, Milosevic A, Marinkovic J, et al. Timing of invasive strategy in NSTE-ACS patients and effect on clinical outcomes: A systematic review and meta-analysis of randomized controlled trials. Atherosclerosis. 2015;241(1):48-54. Epub 2015/05/13.

24. Navarese EP, Gurbel PA, Andreotti F, et al. Optimal timing of coronary invasive strategy in non-ST-segment elevation acute coronary syndromes: a systematic review and meta-analysis. Ann Intern Med. 2013;158(4):261-70. Epub 2013/02/20.

25. Roffi M, Patrono C, Collet JP, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J. 2015. Epub 2015/09/01.

26. Eslick GD, Coulshed DS, Talley NJ. Review article: the burden of illness of non-cardiac chest pain. Aliment Pharmacol Ther. 2002;16(7):1217-23.

27. Glombiewski JA, Rief W, Bosner S, et al. The course of nonspecific chest pain in primary care: symptom persistence and health care usage. Arch Intern Med. 2010;170(3):251-5.

28. Bosner S, Becker A, Haasenritter J, et al. Chest pain in primary care: epidemiology and pre-work-up probabilities. Eur J Gen Pract. 2009;15(3):141-6. Epub 2009/11/04.

29. Handrinos A, Braitberg G, Mosley IT. Acute coronary syndrome diagnosis at hospital discharge: how often do we get it right in the emergency department? Emerg Med Australas. 2014;26(2):153-7.

30. Leise MD, Locke GR, 3rd, Dierkhising RA, et al. Patients dismissed from the hospital with a diagnosis of noncardiac chest pain: cardiac outcomes and health care utilization. Mayo Clin Proc. 2010;85(4):323-30.

31. Ruigomez A, Masso-Gonzalez EL, Johansson S, et al. Chest pain without established ischaemic heart disease in primary care patients: associated comorbidities and mortality. Br J Gen Pract. 2009;59(560):e78-86.

32. Ruddox V, Mathisen M, Otterstad JE. Prevalence and prognosis of non-specific chest pain among patients hospitalized for suspected acute coronary syndrome - a systematic literature search. BMC Med. 2012;10:58.

33. Eslick GD, Talley NJ. Non-cardiac chest pain: predictors of health care seeking, the types of health care professional consulted, work absenteeism and interruption of daily activities. Aliment Pharmacol Ther. 2004;20(8):909-15.

34. Mourad G, Alwin J, Stromberg A, et al. Societal costs of non-cardiac chest pain compared with ischemic heart disease--a longitudinal study. BMC Health Serv Res. 2013;13:403.

35. Gaspoz JM, Unger PF, Urban P, et al. Impact of a public campaign on pre-hospital delay in patients reporting chest pain. Heart. 1996;76(2):150-5.

36. Herlitz J, Hartford M, Blohm M, et al. Effect of a media campaign on delay times and ambulance use in suspected acute myocardial infarction. Am J Cardiol. 1989;64(1):90-3.

37. Luepker RV, Raczynski JM, Osganian S, et al. Effect of a community intervention on patient delay and emergency medical service use in acute coronary heart disease: The Rapid Early Action for Coronary Treatment (REACT) Trial. JAMA. 2000;284(1):60-7.

38. Moses HW, Engelking N, Taylor GJ, et al. Effect of a two-year public education campaign on reducing response time of patients with symptoms of acute myocardial infarction. Am J Cardiol. 1991;68(2):249-51.

39. Leslie WS, Urie A, Hooper J, et al. Delay in calling for help during myocardial infarction: reasons for the delay and subsequent pattern of accessing care. Heart. 2000;84(2):137-41. Epub 2000/07/25.

40. Johansson I, Stromberg A, Swahn E. Factors related to delay times in patients with suspected acute myocardial infarction. Heart Lung. 2004;33(5):291-300.

41. Khraim FM, Carey MG. Predictors of pre-hospital delay among patients with acute myocardial infarction. Patient Educ Couns. 2009;75(2):155-61. Epub 2008/11/28.

42. Mata J, Frank R, Gigerenzer G. Symptom recognition of heart attack and stroke in nine European countries: a representative survey. Health Expect. 2014;17(3):376-87. Epub 2012/03/07.

43. Greenlund KJ, Keenan NL, Giles WH, et al. Public recognition of major signs and symptoms of heart attack: seventeen states and the US Virgin Islands, 2001. Am Heart J. 2004;147(6):1010-6. Epub 2004/06/17.

44. Tummala SR, Farshid A. Patients' understanding of their heart attack and the impact of exposure to a media campaign on pre-hospital time. Heart Lung Circ. 2015;24(1):4-10. Epub 2014/09/23.

45. Bett JH, Tonkin AM, Thompson PL, et al. Failure of current public educational campaigns to impact on the initial response of patients with possible heart attack. Intern Med J. 2005;35(5):279-82.

46. Eppler E, Eisenberg MS, Schaeffer S, et al. 911 and emergency department use for chest pain: results of a media campaign. Ann Emerg Med. 1994;24(2):202-8. Epub 1994/08/01.

47. Goff DC, Jr., Mitchell P, Finnegan J, et al. Knowledge of heart attack symptoms in 20 US communities. Results from the Rapid Early Action for Coronary Treatment Community Trial. Prev Med. 2004;38(1):85-93.

48. Ho MT, Eisenberg MS, Litwin PE, et al. Delay between onset of chest pain and seeking medical care: the effect of public education. Ann Emerg Med. 1989;18(7):727-31.

49. Bray JE, Stub D, Ngu P, et al. Mass Media Campaigns' Influence on Prehospital Behavior for Acute Coronary Syndromes: An Evaluation of the Australian Heart Foundation's Warning Signs Campaign. J Am Heart Assoc. 2015;4(7). Epub 2015/07/08.

50. Naegeli B, Radovanovic D, Rickli H, et al. Impact of a nationwide public campaign on delays and outcome in Swiss patients with acute coronary syndrome. Eur J Cardiovasc Prev Rehabil. 2011;18(2):297-304. Epub 2011/04/01.

51. Rowley JM, Hill JD, Hampton JR, et al. Early reporting of myocardial infarction: impact of an experiment in patient education. Br Med J (Clin Res Ed). 1982;284(6331):1741-6.

52. Mooney M, McKee G, Fealy G, et al. A randomized controlled trial to reduce prehospital delay time in patients with acute coronary syndrome (ACS). J Emerg Med. 2014;46(4):495-506. Epub 2014/01/15.

53. McKinley S, Dracup K, Moser DK, et al. The effect of a short one-on-one nursing intervention on knowledge, attitudes and beliefs related to response to acute coronary syndrome in people with coronary heart disease: a randomized controlled trial. Int J Nurs Stud. 2009;46(8):1037-46. Epub 2009/02/27.

54. van Ierland Y, van Veen M, Huibers L, et al. Validity of telephone and physical triage in emergency care: the Netherlands Triage System. Fam Pract. 2011;28(3):334-41. Epub 2010/11/26.

55. Birkhead JS. Time delays in provision of thrombolytic treatment in six district hospitals. Joint Audit Committee of the British Cardiac Society and a Cardiology Committee of Royal College of Physicians of London. BMJ. 1992;305(6851):445-8. Epub 1992/08/22.

56. Hitchcock T, Rossouw F, McCoubrie D, et al. Observational study of prehospital delays in patients with chest pain. Emerg Med J. 2003;20(3):270-3. Epub 2003/05/16.

57. Heriot AG, Brecker SJ, Coltart DJ. Delay in presentation after myocardial infarction. J R Soc Med. 1993;86(11):642-4. Epub 1993/11/01.

58. Bleeker JK, Simoons ML, Erdman RA, et al. Patient and doctor delay in acute myocardial infarction: a study in Rotterdam, The Netherlands. Br J Gen Pract. 1995;45(393):181-4. Epub 1995/04/01.

59. Bouma J, Broer J, Bleeker J, et al. Longer pre-hospital delay in acute myocardial infarction in women because of longer doctor decision time. J Epidemiol Community Health. 1999;53(8):459-64. Epub 1999/11/24.

60. Backx JC, Bruins Slot, M.H.E, van Casteren-van Gils, B.C.A.M, Derks, C.J.T, Rambharose, V.R, Rutten, F.H. NHG-Standaard Acuut coronair syndroom (eerste herziening)2012 10-02-2016.

61. Fanaroff AC, Rymer JA, Goldstein SA, et al. Does This Patient With Chest Pain Have Acute Coronary Syndrome?: The Rational Clinical Examination Systematic Review. JAMA. 2015;314(18):1955-65. Epub 2015/11/10.

62. Marshall GA, Wijeratne NG, Thomas D. Should general practitioners order troponin tests? Med J Aust. 2014;201(3):155-7. Epub 2014/08/19.

63. Bruins Slot MH, Rutten FH, van der Heijden GJ, et al. Diagnosing acute coronary syndrome in primary care: comparison of the physicians' risk estimation and a clinical decision rule. Fam Pract. 2011;28(3):323-8. Epub 2011/01/18.

64. Backus BE, Six AJ, Kelder JC, et al. Chest pain in the emergency room: a multicenter validation of the HEART Score. Crit Pathw Cardiol. 2010;9(3):164-9. Epub 2010/08/31.

65. Sramek M, Post W, Koster RW. Telephone triage of cardiac emergency calls by dispatchers: a prospective study of 1386 emergency calls. Br Heart J. 1994;71(5):440-5. Epub 1994/05/01.

66. Ebrahimi M, Heydari A, Mazlom R, et al. The reliability of the Australasian Triage Scale: a meta-analysis. World J Emerg Med. 2015;6(2):94-9. Epub 2015/06/10.

67. Hodge A, Hugman A, Varndell W, et al. A review of the quality assurance processes for the Australasian Triage Scale (ATS) and implications for future practice. Australas Emerg Nurs J. 2013;16(1):21-9. Epub 2013/04/30.

68. Christ M, Grossmann F, Winter D, et al. Modern triage in the emergency department. Dtsch Arztebl Int. 2010;107(50):892-8. Epub 2011/01/20.

69. Mirhaghi A, Heydari A, Mazlom R, Ebrahimi M. The reliability of the Canadian triage and acuity scale: Meta-analysis. North Am J Med Sci. 2015;7:299-305.

70. Mirhaghi A, Heydari A, Mazlom R, et al. Reliability of the Emergency Severity Index: Meta-analysis. Sultan Qaboos Univ Med J. 2015;15(1):e71-7. Epub 2015/02/17.

71. Storm-Versloot MN, Ubbink DT, Kappelhof J, et al. Comparison of an informally structured triage system, the emergency severity index, and the manchester triage system to distinguish patient priority in the emergency department. Acad Emerg Med. 2011;18(8):822-9. Epub 2011/08/17.

72. Storm-Versloot MN, Vermeulen H, van Lammeren N, et al. Influence of the Manchester triage system on waiting time, treatment time, length of stay and patient satisfaction; a before and after study. Emerg Med J. 2014;31(1):13-8. Epub 2013/01/11.

73. van Veen M, Huibers, L., Giesen, P., Moll, H. A triage system for the emergency department and the general practitioner cooperative: a reliability and validity. 2009.

74. Leite L, Baptista R, Leitao J, et al. Chest pain in the emergency department: risk stratification with Manchester triage system and HEART score. BMC Cardiovasc Disord. 2015;15:48. Epub 2015/06/13.

75. Giesen P, Ferwerda R, Tijssen R, et al. Safety of telephone triage in general practitioner cooperatives: do triage nurses correctly estimate urgency? Qual Saf Health Care. 2007;16(3):181-4. Epub 2007/06/05.

76. Huibers L, Giesen P, Smits M, et al. Nurse telephone triage in Dutch out-of-hours primary care: the relation between history taking and urgency estimation. Eur J Emerg Med. 2012;19(5):309-15. Epub 2011/10/20.

77. Derkx HP, Rethans JJ, Muijtjens AM, et al. Quality of clinical aspects of call handling at Dutch out of hours centres: cross sectional national study. BMJ. 2008;337:a1264. Epub 2008/09/16.

78. Zegre Hemsey JK, Drew BJ. Prehospital electrocardiography: a review of the literature. J Emerg Nurs. 2012;38(1):9-14. Epub 2011/12/06.

79. van 't Hof AW, Rasoul S, van de Wetering H, et al. Feasibility and benefit of prehospital diagnosis, triage, and therapy by paramedics only in patients who are candidates for primary angioplasty for acute myocardial infarction. Am Heart J. 2006;151(6):1255 e1-5. Epub 2006/06/20.

80. Becker L, Larsen MP, Eisenberg MS. Incidence of cardiac arrest during self-transport for chest pain. Ann Emerg Med. 1996;28(6):612-6. Epub 1996/12/01.

81. Cabrita B, Bouyer-Dalloz F, L'Huillier I, et al. Beneficial effects of direct call to emergency medical services in acute myocardial infarction. Eur J Emerg Med. 2004;11(1):12-8. Epub 2004/05/29.

82. Ishak M, Ali D, Fokkert MJ, et al. Fast assessment and management of chest pain without ST-elevation in the pre-hospital gateway: rationale and design. Eur Heart J Acute Cardiovasc Care. 2015;4(2):129-36. Epub 2014/09/10.

83. Lattimer V, George S, Thompson F, et al. Safety and effectiveness of nurse telephone consultation in out of hours primary care: randomised controlled trial. The South Wiltshire Out of Hours Project (SWOOP) Group. BMJ. 1998;317(7165):1054-9. Epub 1998/10/17.

Part I

Pre-hospital delays

Chapter 3

The first year of the Venlo percutaneous coronary intervention program: procedural and 6-month clinical outcomes

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ABSTRACT

Objectives

Analysis of the first results of off-site percutaneous coronary interventions (PCI) and fractional flow reserve (FFR) measurements at VieCuri Medical Centre for Northern Limburg in Venlo.

Background

Off-site PCI is accepted in the European and American Cardiac Guidelines as the need for PCI increases and it has been proven to be a safe treatment option for acute coronary syndrome.

Methods

Retrospective cohort study reporting characteristics, PCI and FFR specifications, complications and 6-month follow-up for all consecutive patients from the beginning of off-site PCI in Venlo until July 2012. If possible the data were compared with those of Medical Centre Alkmaar, the first off-site PCI centre in the Netherlands.

Results

Of the 333 patients 19 (5.7%) had a procedural complication. At 6 months a major adverse cardiovascular event (MACE) occurred in 43 (13.1%) patients. There were no deaths or emergency surgery related to the PCI or FFR procedures. There was no significant difference in occurrence of a MACE or adverse cerebral event between the Alkmaar and Venlo population in the 30 day follow-up.

Conclusion

This study demonstrates off-site PCI at VieCuri Venlo to have a high success rate. Furthermore there was a low complication rate, low MACE and no procedure related mortality.

INTRODUCTION

The number of percutaneous coronary interventions (PCIs) has increased worldwide,[1] as PCIs are widely accepted as a safe treatment option for stable angina and acute coronary syndrome (ACS).[2, 3] This increase is caused in part by demographic reasons (aging population) and lifestyle choices increasing cardiovascular risk.[4] The need for urgent cardiac surgery due to complications of PCIs has decreased since the introduction of coronary stents, better techniques, and improved antiplatelet drugs.[2, 3, 5-7]

To meet the increase in need for PCIs, it was proposed to start PCIs at hospitals that do not have on-site facilities for cardiac surgery back-up, so-called off-site PCIs. Initially the American cardiac societies advised against off-site (non-primary) PCIs, [8, 9] but this was adjusted after numerous studies showed it to be safe.[10-18] In the Dutch and British Guidelines off-site PCIs have been accepted for some time now.[19, 20] However, off-site centres do require high operator and institutional volumes, as well as a proven, tested plan for rapid transport to a nearby hospital with cardiac surgical capability.[18-20] A good collaboration with cardiac surgeons, with regular heart team meetings between cardiac surgeons and cardiologists is another key factor for success of off-site PCI.[12] Despite this, there are also contradicting results showing off-site PCIs to have a higher mortality.[21]

The delay in the treatment of ST segment elevation myocardial infarction (STEMI) patients should be 90 minutes or less.[22, 23] This should be achieved in the Netherlands in 90% of the STEMI patients.[24] In the Venlo area this goal is only achieved in about 60%.[25]

Off-site PCI started in the Netherlands in 2003. The Medical Centre Alkmaar (MCA) was designated by the Dutch Government as a trial off-site PCI centre.[12] After the success of this PCI centre, 14 other Dutch hospitals started performing off-site PCIs. VieCuri Medical Centre for Northern Limburg in Venlo started off-site PCIs in 2011, firstly driven to shorten the delay in treatment of STEMI patients .[26]

In this article we report the first results of off-site PCI and Fractional Flow Reserve (FFR) measurement at our institution.

METHODS

This is a retrospective cohort study from the start of PCIs at VieCuri Venlo in September 2011 until July 2012.

All patients scheduled for a PCI and/or FFR procedure at VieCuri Venlo were included. Patients undergoing FFR measurements were also included, as the complications of these patients can be similar.[4, 27, 28] No patients were excluded after scheduling. The data of our study were, if possible, compared with data from MCA.[12]

PCI and FFR procedures

Patients were scheduled for a PCI and/or FFR procedure in Venlo if they had ischemic coronary artery disease. Ischemic coronary artery disease was defined as angina with proven myocardial ischemia or ACS. All indications were deliberated with and agreed on by the Heart Team, led by an interventional cardiologist and a cardio-thoracic surgeon, from Maastricht University Medical Centre (MUMC), by using an advanced webviewer (Evocs®, Fysicon, the Netherlands). Emergency (surgical) back-up was also arranged via MUMC.

Patients did not undergo the procedure in Venlo if they were eligible for PCI but classified as 'high risk'. These patients were sent to a tertiary hospital and were (mostly) patients with unprotected left main artery vessel disease or 3-vessel coronary disease. In our first year most patients in need of primary PCI were sent to Catharina Hospital Eindhoven (CZE). No patients were sent for rescue PCI, as thrombolysis is no longer a treatment option for ACS in the Netherlands.

The choice for drug-eluting or bare-metal stent, intravascular ultrasound and intra-aortic balloon pump was left to the discretion of the interventional cardiologist. Rotablation was not available in our hospital.

During the procedure, patients were given intravenous heparin. All patients were treated with double antiplatelet therapy.

Data and Outcome measures

Baseline characteristics, PCI and FFR characteristics and complications were retrospectively found in medical records. Lesion types are given according to the guidelines.[29]

The primary endpoint of this study was major adverse cardiovascular events (MACE) at 6 months, a combined endpoint of mortality, myocardial infarction (MI) and/or revascularization. The secondary endpoint was major adverse cardiovascular and cerebral events (MACCE) at 6 months, including (non-)cardiac mortality, (non-) target vessel MI, target, non-target or FFR vessel re-PCI, emergency or semi-elective coronary artery bypass graft (CABG), and ischemic or haemorrhagic cerebrovascular accident, major or minor bleeding described by the thrombolysis in myocardial infarction bleeding criteria (TIMI)[30] and the need for blood transfusion. Follow-up was found in medical records or acquired through the general practitioner.

Only elective PCIs were compared between Venlo and Alkmaar as the study from Alkmaar included patients who underwent PCI (and not FFR measurements), and our study primarily consisted of elective PCIs. As Alkmaar only started elective PCIs their second year, our first year results are compared to their second year results. The endpoints are compared at 30-day follow-up.

Data analysis

Data were collected and analysed by an independent researcher in SPSS version 19. Frequencies, means and medians were calculated and the χ^2 or the Fishers' exact test was used to

compare the results of the 2 hospitals. A p-value of <0.05 was considered to be statistically significant.

RESULTS

A total of 333 patients underwent a PCI and/or FFR procedure in the study period at VieCuri. In these patients 330 lesions were treated with PCI and 143 lesions were evaluated with FFR. No patients were excluded.

Characteristics

Baseline characteristics including risk factors and co-morbidities are summed up in Table 1. All characteristics were normally distributed among the PCI and FFR groups. A $P2Y_{12}$-inhibitor has been prescribed in 94.0% of the patients. In the group of patients who underwent a PCI, a $P2Y_{12}$-inhibitor was prescribed in 100% of the patients before the procedure.

Table 1. Baseline Characteristics and Prescribed Medication

Characteristics	
Mean age, yrs (sd)	65.1 (11.4)
Male gender, n (%)	243 (73.0%)
Diabetes, n (%)	72 (21.6%)
Hypertension, n (%)	161 (48.5%)
Hypercholesterolemia, n (%)	163 (49.1%)
Smoker, n (%)	122 (40.7%)
Family history of CAD, n (%)	146 (43.8%)
Peripheral vessel disease, n (%)	31 (9.3%)
Previous MI, n (%)	93 (27.9%)
Previous PCI, n (%)	107 (32.1%)
Previous CABG, n (%)	27 (8.1%)
Previous Stroke/TIA, n (%)	41 (12.3%)
Renal disease, n (%)	21 (6.3%)
Metastatic cancer, n (%)	4 (1.2%)
LVEF <0.40, n (%)	20 (6.7%)
LVEF, mean(sd)	58.75 (11.0)
Medication	
Aspirin, n (%)	313 (94.0%)
Vitamin K antagonist, n (%)	33 (9.9%)
$P2Y_{12}$-inhibitor, n (%)	313 (94.0%)
ACE-inhibitor, n (%)	110 (33.0%)
Angiotensin-II-inhibitor, n (%)	82 (24.6%)

Table 1. Baseline Characteristics and Prescribed Medication (continued)

Characteristics	
Beta blocker, n (%)	288 (86.5%)
Statin, n (%)	310 (93.1%)
Nitrate, n (%)	201 (60.4%)
Calcium antagonist, n (%)	105 (31.5%)
Alfa-1-inhibitor, n (%)	10 (3.0%)
Diuretics, n (%)	84 (25.2%)

CAD: coronary artery disease, TIA: transient ischemic attack, LVEF: left ventricular ejection fraction, ACE: angiotensin-converting-enzyme

Table 2. Technical PCI and FFR specifications and angiographic details

Specifications	
Total sites	473
Primary PCI, n (%)	23 (6.9%)
Stents/PCI	1.35
Stents/target lesion	1.05
Average stent length, mm	16.7
Final stent diameter, mm	3.19
DES stent, (%)	300 (86.7%)
Unsuccessful, n (%)	17 (5.1%)
Vessel	
LM, n (%)	10 (2.1%)
LAD, n (%)	227 (48.0%)
RCX, n (%)	98 (20.7%)
RCA, n (%)	141 (29.8%)
Graft, n (%)	7 (1.5%)
Vessel disease	
1-Vessel, n (%)	263 (79.0%)
2-Vessels, n (%)	61 (18.3%)
3-Vessels, n (%)	9 (2.7%)
Lesions	
1, n (%)	229 (68.8%)
2, n (%)	72 (21.6%)
3, n (%)	28 (8.4%)
4, n (%)	4 (1.2%)
Diameter lesion	
Not significant, n (%)	13 (2.8%)
<50%, n (%)	26 (5.5%)
50%, n (%)	44 (9.3%)
50-70%, n (%)	92 (19.5%)

Table 2. Technical PCI and FFR specifications and angiographic details (continued)

Specifications	
70-90%, n (%)	121 (25.6%)
90-99%, n (%)	157 (33.2%)
100%, n (%)	20 (4.2%)

PCI: percutaneous coronary intervention, DES: drug eluting stent, LM: left main coronary artery, LAD: left anterior descending coronary artery, RCX: ramus circumflex coronary artery, RCA: right coronary artery

Angiographic characteristics

Of the 257 PCIs, 23 were primary PCIs. The procedures were successful in 94.9% of the patients. Multi-vessel PCI was performed in 26 patients. The patients with 4 lesions all had at least one FFR measurement.

The procedure was unsuccessful in 20 cases. This was mostly due to failure to cross the lesion with a wire or the need for rotablation. Causes for the inability to pass a wire across the lesions were small vessels, extensive calcifications or ≥90˚ bends in the vessels. Lesion types were as followed: type A 25.2%, type B1 20.1%, type B2 31.1% and type C 23.7%. Further angiographic characteristics are mentioned in Table 2.

Procedural complications

In total, 19 (5.7%) patients had a procedural complication.

In 3 patients PCI was complicated by no-reflow. The first patient had a PCI of a venous graft and suffered from an inferior MI due to no-reflow. No embolic protection device was used, as it was judged not necessary in this patient. In the other 2 patients, no-reflow in native vessels during PCI was accepted and treated conservatively. One of these patients suffered from a non-STEMI, the other had a minimal isolated rise in troponin.

No patients died due to a complication of the procedure or required cardiac surgery as a result of the procedure. One patient did, however, require surgery at the arterial access site due to excessive bleeding. The median fluoroscopy time was 7.13 minutes This was longer during PCIs then during FFR procedures (7.27 vs. 4.26 minutes) and the longest in patients who required both FFR measurement and PCI (10.41 min).

There were 32 (9.6%) patients with minimal bleeding. This was not defined as a complication. In Table 3 an account of the complications in the study population is given.

Table 3. Procedural complications of PCI and/or FFR

Complications	
Total, n (%)	19 (5.7%)
Unsuccessful with complication, n (%)	5 (1.5%)
Acute vessel closure, n (%)	2 (0.6%)
Coronary dissection, n (%)	9 (2.7%)
Femoral/radial dissection, n (%)	1 (0.3%)

Table 3. Procedural complications of PCI and/or FFR (continued)

Complications	
Stent thrombosis, n (%)	1 (0.3%)
No-reflow, n (%)	3 (0.9%)
MI, n (%)	2 (0.6%)
Coronary Perforation, n (%)	0 (0.0%)
Cardiac Tamponade, n (%)	0 (0.0%)
Hemodynamic instability, n (%)	1 (0.3%)
CVA, n (%)	0 (0.0%)
Major bleeding, n (%)	1 (0.3%)
Minor bleeding, n (%)	4 (1.2%)
Transfusion, n (%)	1 (0.3%)
Need of Cardiac Surgery, n (%)	0 (0.0%)
Death, n (%)	0 (0.0%)
Fluoroscopy time, median min(sd)	7.13 (9.5)

MI: myocardial infarction, CVA: cerebrovascular accident, Bleeding as described by the TIMI bleeding criteria

Table 4. Six month follow-up

Endpoint	
MACE, n (%)	43 (13.1%)
Death total, n (%)	7 (2.1%)
Cardiac Death, n (%)	4 (1.2%)
Non-Cardiac Death, n (%)	3 (0.9%)
MI total, n (%)	5 (1.5%)
Target Vessel MI, n (%)	3 (0.9%)
Non-Target Vessel MI, n (%)	2 (0.6%)
Re-PCI total, n (%)	32 (9.8%)
Target Vessel PCI, n (%)	13 (4.0%)
Non-Target Vessel PCI, n (%)	14 (4.3%)
PCI of FFR lesion, n (%)	7 (2.1%)
CABG total, n (%)	11 (3.4%)
Emergency CABG, n (%)	3 (0.9%)
Semi-elective CABG, n (%)	8 (2.4%)
CVA Total, n (%)	9 (2.7%)
Ischemic CVA, n (%)	7 (2.1%)
Haemorrhagic CVA, n (%)	2 (0.6%)
Major Bleeding, n (%)	1 (0.3%)
Minor Bleeding, n (%)	2 (0.6%)
Transfusion, n (%)	2 (0.6%)

MACE: major adverse cardiac events, MI: myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft, Bleeding as described by the TIMI bleeding criteria

Follow-up at 6 months

At the 6 month follow-up a MACE occurred in 43 (13.1%) patients. In the follow-up period of 6 months 7 patients died. None of the deaths were related to the PCI or FFR procedures.

Among the 7 deaths, there were 3 non-cardiac deaths. One patient died of severe chronic obstructive pulmonary disease. The second patient died of cerebral haemorrhage (using double antiplatelet therapy) and the third patient died of hypoxic respiratory failure due to pneumonia. The other 4 patients had cardiac related deaths. In 2 patients, admitted with severe hemodynamic instability due to acute MI, primary PCIs were performed in our hospital as transportation to CZE was judged impossible. Both patients did not have a PCI before this event. One of these patients suffered from a massive subacute anterior wall MI. Despite thrombosuction and stent placing during PCI, flow was not restored. The patient acquired pneumonia and died 2 days later. The other patient suffered from an inferior MI with expansion to the right ventricle. Coronary flow was restored during PCI. However, the patient had pulseless electrical activity at the intensive care unit during hypothermia treatment despite pacing and medication. The third cardiac related death was a patient who died due to a posterior wall rupture during weaning from the heart-lung machine after mitral valve surgery for endocarditis. The former PCI was a work-up before surgery. The last patient, with an extensive history including pulmonary disease and recent operated rectal carcinoma, died after resuscitation for sudden bradycardia followed by asystole. This happened 4 months after bare-metal stent implantation for diffuse stenosis of the right coronary artery. The family did not consent to autopsy.

All bleedings during follow-up were of gastro-intestinal origin (Table 4).

Characteristics and Follow-up compared to MCA

When comparing the populations from Venlo and Alkmaar most characteristics and specifications did not differ significantly. However, the Alkmaar population had significantly more patients with 2 lesions and significantly less patients with 1 lesion (Table 5).

The 30-day MACCE free survival is not significantly different between the Venlo and Alkmaar populations. The other endpoints did not occur enough to compare statistically (Table 6).

Table 5. Comparison Venlo and Alkmaar

Characteristics	***Venlo***	***Alkmaar***	***P***
Total PCI, n	257	781	
Elective PCI, n	237	483	
PCI target lesions	330	1020	
Men, n (%)	188 (73.2%)	545 (70%)	NS
Mean age, yrs (sd)	65.0 (11.6)	64.5	
Stents/PCI	1.35	1.2	
Stents/target lesion	1.05	0.91	
Average stent length, mm	16.7	15.99	

Table 5. Comparison Venlo and Alkmaar (continued)

Characteristics	*Venlo*	*Alkmaar*	*P*
Vessel			
LM, n (%)	0 (0%)	16 (1.6)	0.02
LAD, n (%)	146 (44.2%)	417 (40.9%)	NS
RCX, n (%)	72 (21.8%)	234 (22.9%)	NS
RCA, n (%)	105 (31.8%)	327 (32.1%)	NS
Graft, n (%)	7 (2.3%)	26 (2.5%)	NS
Lesions			
1, n (%)	200 (77.8%)	542 (69.4%)	<0.01
2, n (%)	41 (15.8%)	203 (26%)	<0.01
3, n (%)	16 (6.2%)	36 (4.6%)	NS
Final balloon size	3.19	3.55	
LVEF <0.40	13 (6.2%)	72 (14.9%)	<0.01

PCI: percutaneous coronary intervention, LM: left main coronary artery, LAD: left anterior descending coronary artery, RXC: ramus circumflex coronary artery, RCA: right coronary artery, LVEF: left ventricular ejection fraction

Table 6. 30 day follow-up Venlo and Alkmaar

Endpoint	*Venlo (n=257)*	*Alkmaar (n=781)*	*P*
Death, n (%)	0 (0.0%)	0 (0.00%)	
Re-PCI, Target Vessel, n (%)	5 (2.1%)	4 (2.34%)	
Re-PCI, non-Target Vessel, n (%)	2 (0.8%)	1 (0.58%)	
Emergency CABG, n (%)	0 (0.0%)	0 (0.00%)	
Semi-elective CABG, n (%)	2 (0.8%)	4 (2.34%)	
AMI, n (%)	2 (0.8%)	1 (0.58%)	
CVA, n (%)	1 (0.4%)	1 (0.58%)	
Major Bleedings, n (%)	0 (0.0%)	5 (2.92%)	
Cath lab MACE, n (%)	1 (0.4%)	4 (2.34%)	
MACCE, n (%)	10 (3.0%)	20 (11.70%)	NS

PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft, AMI: acute myocardial infarction, CVA: cerebrovascular accident, MAC(C)E: major adverse cardiovascular (and cerebral) events, Cath lab: catheterisation laboratory

DISCUSSION

This study reports the first results of off-site PCI and/or FFR procedures in Venlo. The results show low occurrence of complications and MACE resulting in a successful early outcome of off-site PCIs.

In the study population 19 (5.7%) patients suffered from a procedural complication. In the 6 month follow-up a MACE occurred in 43 (13.1%) patients, mostly re-PCI. Only 7 patients died. None of the deaths were directly related to the PCI or FFR procedure. The success rate was high with 94.9%.

Patients who underwent FFR without subsequent PCI, were either proven to have significant 3-vessel disease by FFR evaluation and considered eligible for CABG, or were proven to have no significant vessel disease at all.

For the first stage of off-site PCIs at VieCuri it was decided to perform only elective PCIs. Despite this, 23 primary PCIs were performed in the study period, mostly because the condition of the patients was judged to be too critical for transportation to a tertiary hospital. Two of these patients died within 2 days due to the extent and complications of the acute MI. Around-the-clock intervention of primary PCIs will be introduced in a second stage after which the delay in STEMI patients in our region is expected to be significantly cut down as transportation to a tertiary centre is no longer needed. The goal of 90% of the patients within 90 minutes should be achieved when primary PCIs are introduced in the Venlo area. [25]

As all patients scheduled for a PCI with stent placing require a $P2Y_{12}$-inhibitor,[18] analysis of prescribed medication in our study population was performed. In total 94.0% of the patients received a $P2Y_{12}$-inhibitor. All of the 20 patients not receiving a $P2Y_{12}$-inhibitor had only a FFR measurement. There were 2 reasons these patients did not receive a $P2Y_{12}$-inhibitor. They were either scheduled for a diagnostic coronary catheterisation during which the interventional cardiologist decided to evaluate a moderate stenosis with FFR, or they were scheduled for CABG and further evaluation of a moderate stenosis was needed.

When comparing the elective PCIs of this study to the elective PCIs of the first off-site PCI centre, Alkmaar, most baseline characteristics and PCI specifications are not significantly different. However a significant difference is the amount of lesions per patient. This can partly be explained by the fact that we compared our first year data to their second year data. At the start of the off-site PCIs in Venlo it was decided to perform high risk procedures at a tertiary hospital. Excluding high risk patients from treatment at an off-site PCI centre is recommended by the Society for Cardiac Angiography and Interventions.[9] However, more high risk procedures could be performed in Venlo as numerous studies have shown acceptable outcomes in high risk patients.[12-14, 31]

The 30 day follow-up in both study groups do not differ significantly, thus showing the early outcome of off-site PCI at Venlo to be as successful as Alkmaar.

Limitations

As this is a retrospective study, not all data could be obtained. Also not all our data could be compared to the study population from Alkmaar as the studies looked into other baseline characteristics and specifications of the PCI procedures.

CONCLUSION

This study reports the outcome of the first stage of off-site PCIs and FFR measurements at VieCuri Medical Centre for Northern Limburg in Venlo. It demonstrates that, though in a limited patient group, off-site PCI at VieCuri Venlo to have a high success rate. Furthermore it shows a low complication rate, low MACE and no procedure related mortality.

REFERENCES

1. Maier W, Windecker S, Boersma E, Meier B. Evolution of percutaneous transluminal coronary angioplasty in Europe from 1992-1996. European heart journal. 2001;22 (18):1733-40.
2. Yang EH, Gumina RJ, Lennon RJ, Holmes DR, Jr., Rihal CS, Singh M. Emergency coronary artery bypass surgery for percutaneous coronary interventions: changes in the incidence, clinical characteristics, and indications from 1979 to 2003. Journal of the American College of Cardiology. 2005;46 (11):2004-9.
3. Seshadri N, Whitlow PL, Acharya N, Houghtaling P, Blackstone EH, Ellis SG. Emergency coronary artery bypass surgery in the contemporary percutaneous coronary intervention era. Circulation. 2002;106 (18):2346-50.
4. Miller LH, Toklu B, Rauch J, Lorin JD, Lobach I, Sedlis SP. Very long-term clinical follow-up after fractional flow reserve-guided coronary revascularization. The Journal of invasive cardiology. 2012;24 (7):309-15.
5. Karvouni E, Katritsis DG, Ioannidis JP. Intravenous glycoprotein IIb/IIIa receptor antagonists reduce mortality after percutaneous coronary interventions. Journal of the American College of Cardiology. 2003;41 (1):26-32.
6. McGrath PD, Malenka DJ, Wennberg DE, Shubrooks SJ, Jr., Bradley WA, Robb JF, et al. Changing outcomes in percutaneous coronary interventions: a study of 34.752 procedures in northern New England, 1990 to 1997. Northern New England Cardiovascular Disease Study Group. Journal of the American College of Cardiology. 1999;34 (3):674-80.
7. Tamburino C, Russo G, Nicosia A, Galassi AR, Foti R, Scriffignano V, et al. Prophylactic abciximab in elective coronary stenting: results of a randomized trial. The Journal of invasive cardiology. 2002;14 (2):72-9.
8. Smith SC, Dove, J.T, Jacobs, A.K, et al. American College of Cardiology/American Heart Association Task Force on Practice Guideline and the Society for Cardiac Angiography and Interventions (Committee to Revise the 1993 Guidelines for Percutaneous Transluminal Coronary Angioplasty); ACC/AHA Guidelines for Percutaneous Coronary Intervention (Revision of the 1993 PTCA Guidelines) - executive summary. Circulation. 2001;103 (24):3019-41.
9. Dehmer GJ, Blankenship, J, Wharton T.P. Jr, et al. The current status and future direction of percutaneous coronary intervention without on-site surgical backup: an expert consensus document from the Society for Cardiovascular Angiography and Interventions. Catheterization and Cardiovascular Interventions. 2007;69 (471-8).
10. Aversano T, Aversano, L.T, Passamani, E, et al. Thrombolytic therapy vs primary percutaneous coronary intervention for myocardial infarction in patients presenting to hospitals without on-site cardiac surgery: a randomized controlled trial. Journal of the American Medical Association. 2002;287:1943-51.
11. Melberg T, Nilsen, D.W.T, Larsen, A.I, et al. Nonemergent coronary angioplasty without on-site surgical backup: a randomized study evaluating outcomes in low-risk patients. American heart journal. 2006;152:888-95.
12. Peels JOJ, Hautvast, R.W.M, de Swart, et al. Percutaneous coronary intervention without on site surgical back-up; two-years registry of a large Dutch community hospital. International Journal of Cardiology. 2007;132:59-65.

13. Ting HH, Raveendran G, Lennon RJ, Long KH, Singh M, Wood DL, et al. A total of 1.007 percutaneous coronary interventions without onsite cardiac surgery: acute and long-term outcomes. Journal of the American College of Cardiology. 2006;47 (8):1713-21.

14. Zavala-Alarcon E, Cecena F, Ashar R, Patel R, Van Poppel S, Carlson R. Safety of elective--including "high risk"--percutaneous coronary interventions without on-site cardiac surgery. American heart journal. 2004;148 (4):676-83.

15. Singh PP, Singh, M, Bedi, U.S, et al. Outcomes of nonemergent percutaneous coronary intervention with an without on-site surgical backup: a meta-analysis. American Journal of Therapeutics. 2011;18:22-8.

16. Wharton TP. Nonemergent Percutaneous Coronary Intervention With Off-Site Surgery Backup; An Emerging New Path tot Access. Critical Pathways in the Cardiology. 2005;4 (2):98-106.

17. Paraschos A, Callwood D, Wightman MB, Tcheng JE, Phillips HR, Stiles GL, et al. Outcomes following elective percutaneous coronary intervention without on-site surgical backup in a community hospital. The American journal of cardiology. 2005;95 (9):1091-3.

18. Levine G, Bates, E.R, Blankenship, J.C, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Journal of the American College of Cardiology. 2011;58:44-112.

19. Nederlandse Vereniging voor Cardiologie: Dutch guidelines for interventional cardiology; Institutional and operator competance and requirements for training. 2004.

20. Dawkins KD, Gershlick, T, de Belder, M. et al. Joint Working Group on Percutaneous Coronary Intervention of the British Cardiovascular Intervention Society and the British Cardiac Society; Percutaneous coronary intervention: recommendations for good practice and training. Heart. 2005;91:1-27.

21. Wennberg DE, Lucas FL, Siewers AE, Kellett MA, Malenka DJ. Outcomes of percutaneous coronary interventions performed at centers without and with onsite coronary artery bypass graft surgery. JAMA : the journal of the American Medical Association. 2004;292 (16):1961-8.

22. Task Force on the management of STseamiotESoC, Steg PG, James SK, Atar D, Badano LP, Blomstrom-Lundqvist C, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. European heart journal. 2012;33 (20):2569-619.

23. O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Jr., Chung MK, de Lemos JA, et al. 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2012.

24. Piek JJ, Aengevaeren, W.R, Appelman, Y, et al. Praktijkgids Optimale Zorg bij Acute Coronair Syndroom: VMSzorg; 2010.

25. Mol KA, Meeder, J.G, Duygun, A. et al. Treating ST-elevation myocardial infarction within 90 minutes in the Netherlands: goal not yet achieved. 2013.

26. www.nvvc.nl. [homepage from the internet]. Witte lijsten PCI. Nederlandse Vereninging voor Cardiologie; 2013 [cited 2013 25-02-2013]. Available from: https://www.nvvc.nl/witte-lijsten.

27. Puymirat E, Peace A, Mangiacapra F, Conte M, Ntarladimas Y, Bartunek J, et al. Long-term clinical outcome after fractional flow reserve-guided percutaneous coronary revascularization in patients with small-vessel disease. Circulation Cardiovascular interventions. 2012;5 (1):62-8.

28. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van' t Veer M, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. The New England journal of medicine. 2009;360 (3):213-24.

29. Ryan TJ, Faxon DP, Gunnar RM, Kennedy JW, King SB, 3rd, Loop FD, et al. Guidelines for percutaneous transluminal coronary angioplasty. A report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Subcommittee on Percutaneous Transluminal Coronary Angioplasty). Circulation. 1988;78 (2):486-502.

30. Chesebro JH, Knatterud G, Roberts R, Borer J, Cohen LS, Dalen J, et al. Thrombolysis in Myocardial Infarction (TIMI) Trial, Phase I: A comparison between intravenous tissue plasminogen activator and intravenous streptokinase. Clinical findings through hospital discharge. Circulation. 1987;76 (1):142-54.

31. Frutkin AD, Mehta SK, Patel T, Menon P, Safley DM, House J, et al. Outcomes of 1.090 consecutive, elective, nonselected percutaneous coronary interventions at a community hospital without onsite cardiac surgery. The American journal of cardiology. 2008;101 (1):53-7.

Chapter 4

Off-site primary percutaneous coronary intervention in a starting centre is safe: Comparing clinical outcomes with a hospital with surgical backup

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ABSTRACT

Objectives

To evaluate the procedural and clinical outcomes of a new primary percutaneous coronary intervention (PPCI) centre without surgical back-up (off-site PCI) and to investigate whether these results are comparable with a high volume on-site PCI centre in the Netherlands.

Background

Controversy remains about the safety and efficacy of PPCI in off-site PCI centres.

Methods

We retrospectively analysed clinical and procedural data as well as 6 month follow-up of 226 patients diagnosed with ST-elevated myocardial infarction (STEMI) who underwent PPCI at VieCuri Medical Centre Venlo and 115 STEMI patients that underwent PPCI at Catharina Hospital Eindhoven.

Results

PPCI patients in VieCuri Medical Centre had similar procedural and clinical outcomes as PPCI in Catharina Hospital. Overall there were no significant differences. The occurrence of procedural complications was low in both groups (8.4% VieCuri versus 12.3 % Catharina Hospital). In the VieCuri group there was one procedural related death. No patients in either group needed emergency surgery. At 30 days 17 (7.9%) patients in the VieCuri group and 9 (8.1%) in the Catharina Hospital group had a major adverse cardiac event.

Conclusion

Performing PPCI in an off-site PCI centre is safe and effective. The study results show that the procedural and clinical outcomes of off-site PPCI centre are comparable with an on-site high volume PPCI centre.

INTRODUCTION

Primary percutaneous coronary intervention (PPCI) at hospitals without surgical back-up (off-site PCI) has been frequently investigated and debated. PPCI is an effective treatment in acute coronary syndrome (ACS) and superior to thrombolytic therapy [1-3]. The knowledge that a decrease in time to reperfusion leads to decreased infarct size and incidence of major adverse cardiac events (MACE), contributed to the rise of off-site PCI centres [2, 4-6].

Introduction of PCI at off-site hospitals has been a gradual process in the Netherlands and implementation is strictly regulated [7]. Numerous studies have reported no difference in safety and effectiveness of PCI between off-site PCI centres and medical centres with surgical back-up (on-site) [3, 8-12], including two large Dutch studies [13, 14]. The need for bail-out surgery after on-site PCI has dropped dramatically the past decades, from 6.6% in the initial years to 0.3%-0.6% currently [15, 16]. The mortality rates for patients requiring emergency surgery are the same in off-site and on-site PPCI centres [17, 18]. The European Society of Cardiology (ESC) recommends (Ib) PPCI to be performed by experienced operators in a 24 hour/7 day service [6]. No distinction is made between on-site and off-site centres while, according to the American College of Cardiology (ACC)/ American Heart Association (AHA) guidelines, PPCI at off-site centres is a class IIa indication [19]. Both the ESC and ACC recommend that operators performing PCI for ACS should have an annual volume of at least 75 procedures at institutions performing at least 400 PCI's per year [19, 20].

The aim of this study is to investigate whether the results at the VieCuri Medical Centre Venlo are comparable with a high-volume on-site PCI centre, in this case Catharina Hospital Eindhoven. We assume the procedural and clinical outcomes are similar for off-site PPCI compared with on-site PPCI.

METHODS

This study is a two-centre, retrospective cohort study. In the period from 1 September 2012 to 1 September 2013, 122 patients in the VieCuri Medical Centre/Laurentius Hospital Roermond area received PPCI in Catharina Hospital. From September 2013, patients from Laurentius Hospital and VieCuri were treated at VieCuri Medical Centre.

All STEMI patients who were signed up for PPCI were included. Patients with an out-of-hospital cardiac arrest were excluded. VieCuri is an intermediate-volume hospital which started PPCI in September 2013. Laurentius Hospital is an intermediate-volume hospital without PCI facilities. Before September 2013 patients from VieCuri and Laurentius Hospital who needed PPCI were transported to Catharina Hospital.

PCI procedure

PPCI is limited to the culprit vessel with the exception of patients presenting with cardiogenic shock or persistent ischaemia after PCI of the presumed culprit lesion.[20] The choice for drug-eluting stent (DES) versus bare metal stent and the use of an intra-aortic balloon pump or glycoprotein IIb/IIIa inhibitors, was left to the discretion of the interventional cardiologist.

Data collection and outcome measures

Patient characteristics, PCI characteristics, complications and follow-up data were retrospectively found in the medical records. Missing data from PPCI patients were ac- quired by calling general practitioners. Foreign patients, transferred to different countries for rehabilitation, were considered as lost to follow-up.

The primary outcomes of this study were complications during the procedure and the incidence of a major adverse cardiac event (MACE) at 30 days and 6 months. Only procedural complications were registered and no complications as a result of the myocardial infarction itself. The combined endpoint MACE consists of death, myocardial infarction and revascularisation (target-lesion, target-vessel or non-target-vessel). Secondary outcomes are the incidence of major adverse cardiovascular and cerebral events (MACCE) and consist of death of any cause, myocardial infarction, revascularisation (target-lesion, target-vessel or non-target- vessel), emergency or semi-elective coronary artery bypass graft (CABG), occurrence of cerebral vascular accidents, probable or definite stent thrombosis, TIMI major and minor bleeding[21] and the need for transfusion. Emergency CABG was defined as CABG performed within 24 hours after PCI for a procedural complication. Secondary outcomes were analysed with a maximum follow- up period of 6 months.

Primary outcome registration was accomplished by definitions from the Academic Research Consortium (ARC).[22] All deaths are considered cardiac unless an unequivocal noncardiac cause could be established. Re-PCI was defined following ARC definitions with target lesion revascularisation, target vessel revascularisation and non-target vessel revascularisation. Target lesion revascularisation be- fore 30 days is considered to be a safety endpoint, because this time is too short for fibrointimal hyperplasia.[22, 23] Stent thrombosis was classified as definite, probable and possible and timing of the stent thrombosis as acute, subacute or late.[22]

Data analysis

Data were collected and analysed by an independent investigator in SPSS version 22. Descriptive statistics were used to calculate frequencies and means. The independent sample T-test and the Mann-Whitney test were used to compare means. Chi-square or Fisher's exact test were used to compare the VieCuri data with those of Catharina Hospital.

RESULTS

A total of 122 and 237 PPCIs in patients diagnosed with STEMI were conducted in Catharina Hospital and VieCuri, respectively. This consists of 115 and 226 patients. There were 74 patients from Laurentius Hospital who underwent PPCI in VieCuri Medical Centre. In the Catharina Hospital group, 21 patients (18.3 %) were first admitted to VieCuri before transportation to Catharina Hospital for PPCI.

Table 1. Baseline Characteristics

Characteristics	*VieCuri (n = 226)*	*(n = 115)*	***p***
Mean age, years (SD)	62.83 (12.34)	62.29 (13.40)	0.708
Male gender, *n* (%)	165 (73.0 %)	81 (70.4 %)	0.616
Mean BMI (SD)	27.03 (4.10)	26.92 (3.93)	0.946
Diabetes, *n* (%)	30 (13.6 %)	9 (8.0 %)	0.131
Hypertension, *n* (%)	91 (41.2 %)	44 (38.9 %)	0.693
Hypercholesterolaemia, *n* (%)	66 (29.9 %)	41 (36.3 %)	0.234
Smoker, *n* (%)	106 (48.0 %)	46 (40.4 %)	0.122
– Unknown, *n* (%)	24 (10.9 %)	10 (8.8 %)	–
Family history of CAD, *n* (%)	97 (43.9 %)	53 (46.5 %)	0.900
– Unknown, *n* (%)	44 (19.9 %)	22 (19.3 %)	–
Peripheral vessel disease, *n* (%)	22 (10.0 %)	14 (12.4 %)	0.497
Previous MI, *n* (%)	30 (13.6 %)	19 (16.5 %)	0.468
Previous PCI, *n* (%)	26 (11.8 %)	16 (13.9 %)	0.572
Previous CABG, *n* (%)	7 (3.2 %)	4 (3.5 %)	1.000
Previous stroke/TIA, *n* (%)	17 (7.7 %)	7 (6.2 %)	0.616
Renal disease, *n* (%)	16 (7.2 %)	6 (5.3 %)	0.507
Metastatic cancer, *n* (%)	5 (2.3 %)	4 (3.5 %)	0.494
LVEF <0.40, *n* (%)	17 (8.3 %)	7 (7.1 %)	0.720
Mean CK max u/g (SD)	1363 (1709)	1385 (1450)	0.882
Killip class 1	148 (81.8 %)	112 (92.6 %)	<0.01
Killip class II	15 (8.3 %)	3 (2.5 %)	0.037
Killip class III	7 (3.9 %)	2 (1.7 %)	0.323
Killip class IV	11 (6.1 %)	4 (3.3 %)	0.418
TIMI risk score (SD)	3.06 (2.55)	2.23 (1.95)	0.047
Medication[a]			
Aspirin, *n* (%)	208 (96.7 %)	104 (91.2 %)	0.031
Clopidogrel, (%)	54 (25.1 %)	29 (25.4 %)	0.949
Prasugrel, *n* (%)	85 (39.5 %)	37 (32.5 %)	0.206
Ticagrelor, *n* (%)	73 (34.0 %)	47 (41.2 %)	0.192
Vitamin K antagonist, *n* (%)	11 (5.1 %)	10 (8.8 %)	0.197

Table 1. Baseline Characteristics (continued)

Characteristics	*VieCuri (n = 226)*	*(n = 115)*	***p***
ACE inhibitor, *n* (%)	162 (76.1 %)	93 (81.6 %)	0.251
Angiotensin-II inhibitor, *n* (%)	46 (21.6 %)	16 (14.0 %)	0.096
Beta blocker, *n* (%)	199 (92.6 %)	112 (98.2 %)	0.031
Statin, *n* (%)	213 (99.1 %)	114 (99.1 %)	0.546
Nitrate, *n* (%)	99 (46.0 %)	57 (50.0 %)	0.494
Calcium channel blockers, *n* (%)	17 (7.9 %)	8 (7.0 %)	0.772
Diuretics, *n* (%)	25 (11.6 %)	20 (17.5 %)	0.137
Aldosterone antagonist, *n* (%)	14 (6.5 %)	17 (14.9 %)	0.013
Proton pump inhibitor, *n* (%)	277 (82.3 %)	105 (92.1 %)	0.016

BMI: body mass index, CAD: coronary artery disease, MI: myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft, TIA: transient ischaemic attack, LVEF: left ventricular ejection fraction, CK: creatine kinase, ACE: angiotensin-converting-enzyme, DES: drug-eluting stent

[a] Prescribed medication at discharge

Characteristics

Baseline characteristics and prescribed medication are shown in Table 1. The patient groups were clinically well balanced for all risk factors; however, there were significantly more patients with Killip class II in the VieCuri group and the TIMI risk score was significantly higher compared with the Catharina Hospital group. There was a significant difference in the prescription of aspirin, beta blockers, aldosterone antagonist and proton pump inhibitors between VieCuri and Catharina Hospital. Several patients did not have dual antiplatelet therapy because either no stent had been placed or CABG was necessitated.

PCI specifications

Figures 1, 2, 3 and 4 show the PCI specifications. Most patients had one-vessel disease (54.4 %) and the right coronary artery was the most common culprit vessel (44.0 %), which is shown in Figures 1 and 2, respectively. Data from Catharina Hospital show the same distribution. There was a significant difference in the number of patients with one lesion (Figure 3), which was higher in the Catharina Hospital group. In most patients, the diameter of the stenosis was 100 % (Figure 4).

Table 2 shows the PCI specifications of both VieCuri and Catharina Hospital. In 215 of the 237 PPCIs a stent was placed in one of the coronary arteries. In 80.7 % this was a DES. There were 22 procedures in which no stent was inserted. In 6 cases stent placement was not successful. In 4 cases the operator decided, after spontaneous reperfusion, not to place a stent due to multivessel disease or stenosis of the left main coronary artery needing CABG. In both groups only a few radial procedures were performed, because this was up-coming at that period. The time from first medical contact to start of PCI (system delay) was significantly longer in the Catharina Hospital group.

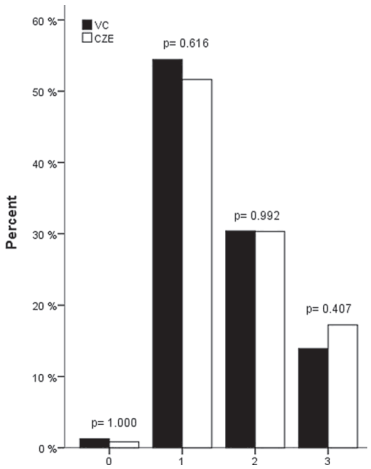

Figure 1. Number of vessel disease
VC: VieCuri Medical Centre Venlo, CZE: Catharina Hospital Eindhoven

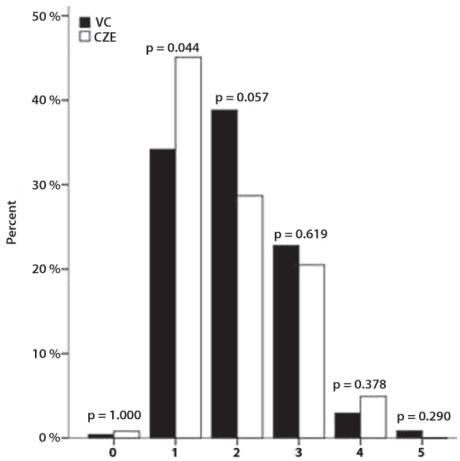

Figure 2. Culprit vessel
VC: VieCuri Medical Centre Venlo, CZE: Catharina Hospital Eindhoven, LM: left main, LAD: left anterior descending, RCX: right circumflex, RCA: right coronary artery

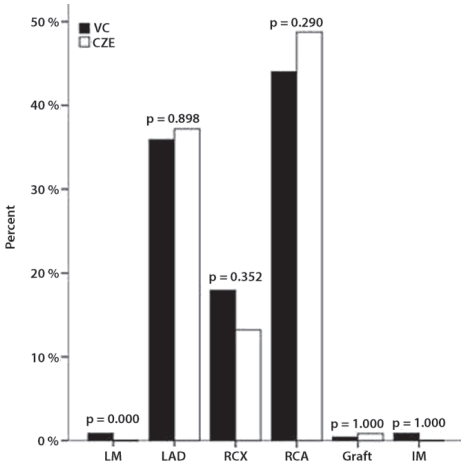

Figure 3. Number of lesions
VC: VieCuri Medical Centre Venlo, CZE: Catharina Hospital Eindhoven

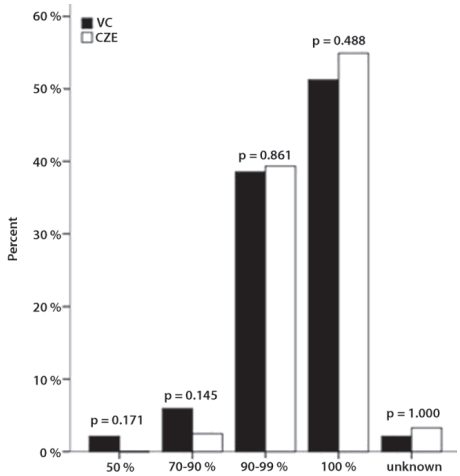

Figure 4. Diameter stenosis as percentage
VC: VieCuri Medical Centre Venlo, CZE: Catharina Hospital Eindhoven

Procedural complications are also shown in Table 2. Cardiac arrest was the most common complication (2.1 %) followed by stent thrombosis (1.7 %). In 4 procedures (1.7 %) coronary dissection occurred. One patient (0.4 %) had coronary perforation with tamponade. One patient had tamponade most likely due to a temporary pacemaker lead. Before transport to Maastricht University Medical Centre for emergency cardiac surgery, this patient died as a result of rupture of the right ventricle. This was considered a procedure-related death. Procedural complications of patients receiving PPCI at Catharina Hospital are also shown in Table 2. There is no significant difference in procedural outcomes between these two groups.

Table 2. Procedural Specifications

Procedural specifications[a]	*VieCuri (n=237)*	*Catharina (n=122)*	***p***
Procedures without stent placing	22 (9.3 %)	8 (6.9 %)	0.377
– Unsuccessful, *n* (%)	6 (2.5 %)	4 (3.3 %)	0.242
– Multivessel disease necessitating CABG, *n* (%)	4 (1.7 %)	1 (0.8 %)	0.711
– Only balloon dilatation	12 (5.1 %)	3 (2.5 %)	0.231
Radial procedure, *n* (%)	8 (3.4 %)	5 (4.1 %)	0.769
DES, *n* (%)	268 (80.7 %)	135 (90.0 %)	–
Stents/PCI	1.53	1.28	–
Mean total stent length, mm (SD)	19.67 (6.12)	16.05 (6.01)	0.445
Time FMC to start PCI, min (SD)	76 (32)	101 (91)	<0.01
Total complications, *n*	28	22	–
Procedures with complications, *n* (%)	20 (8.4 %)	15 (12.3 %)	0.065
Unsuccessful with complication, *n* (%)	1 (0.4 %)	1 (0.8 %)	1.000
Acute vessel closure, *n* (%)	0 (0.0 %)	1 (0.8 %)	0.340
Coronary dissection, *n* (%)	4 (1.7 %)	3 (2.5 %)	0.693
Femoral/radial dissection, *n* (%)	0 (0.0 %)	0 (0.0 %)	–
Stent thrombosis, *n* (%)	4 (1.7 %)	3 (2.5 %)	0.693
No-reflow, *n* (%)	0 (0.0 %)	1 (0.8 %)	0.340
MI, *n* (%)	2 (0.8 %)	0 (0.0 %)	0.550
Cardiac arrest, *n* (%)	5 (2.1 %)	3 (2.5 %)	1.000
– Ventricular fibrillation, *n* (%)	4 (1.7 %)	2 (1.6 %)	–
Coronary perforation, *n* (%)	1 (0.4 %)	1 (0.8 %)	1.000
Cardiac tamponade, *n* (%)	2 (0.8 %)	0 (0.0 %)	0.550
Haemodynamic instability, *n* (%)	3 (1.3 %)	2 (1.6 %)	1.000
CVA, *n* (%)	0 (0.0 %)	0 (0.0 %)	–
TIMI major bleeding, *n* (%)	0 (0.0 %)	0 (0.0 %)	–
TIMI minor bleeding, *n* (%)	1 (0.4 %)	2 (1.6 %)	0.267
Pseudoaneurysm[b], *n* (%)	3 (1.3 %)	2 (1.6 %)	1.000
Transfusion, *n* (%)	1 (0.4 %)	3 (2.5 %)	0.116
Need for cardiac surgery, *n* (%)	0 (0.0 %)	0 (0.0 %)	–
Procedure related death, *n* (%)	1 (0.4 %)	0 (0.0 %)	1.000

FMC: first medical contact, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft, DES: drug-eluting stent, MI: myocardial infarction, CVA: cerebrovascular accident, TIMI: thrombolysis in myocardial infarction (bleeding as described by the TIMI bleeding criteria)

[a] Including all procedures

[b] The number of patients with a pseudoaneurysm consists of patients treated with either surgery or if transfusion was necessitated

Table 3. Cumulative follow-up

End point	*VieCuri*	*Catharina*	***p***
0–30 days follow-up			
Total[a],n	218	111	–
Lost to follow-up	10	4	–
MACE total, *n* (%)	17 (7.9 %)	9 (8.1 %)	0.797
Death	7 (3.2 %)	2 (1.8 %)	0.723
– Cardiac, *n* (%)	5 (2.3 %)	2 (1.8 %)	1.000
– Non-cardiac, *n* (%)	2 (0.9 %)	0 (0.0 %)	0.546
MI, *n* (%)	3 (1.4 %)	4 (3.6 %)	0.232
Re-PCI total, *n* (%)	7 (3.2 %)	3 (2.7 %)	1.000
– Target lesion, *n* (%)	5 (2.4 %)	2 (1.8 %)	1.000
– Target vessel, *n* (%)	1 (0.5 %)	0 (0.0 %)	1.000
– Non-target vessel, *n* (%)	1 (0.5 %)	1 (0.9 %)	1.000
0–6 months follow-up			
Total[a], *n*	214	111	–
MACE total, *n* (%)	32 (15.0 %)	13 (11.7 %)	0.311
Death	13 (6.1 %)	3 (2.7 %)	0.191
– Cardiac, *n* (%)	5 (2.4 %)	2 (1.8 %)	1.000
– Non-cardiac, *n* (%)	8 (3.7 %)	1 (0.9 %)	0.282
MI, *n* (%)	9 (4.2 %)	5 (4.5 %)	1.000
Re-PCI total, *n* (%)	10 (4.7 %)	5 (4.5 %)	1.000
– Target lesion, *n* (%)	5 (2.3 %)	2 (1.8 %)	1.000
– Target vessel, *n* (%)	2 (0.9 %)	0 (0.0 %)	0.549
– Non-target vessel, *n* (%)	3 (1.4 %)	3 (2.7 %)	0.415
CABG emergency, *n* (%)	0 (0.0 %)	0 (0.0 %)	–
CABG semi-elective, *n* (%)	5 (2.3 %)	1 (0.9 %)	0.657
CVA, *n* (%)	2 (0.9 %)	2 (1.8 %)	0.607
Ischaemic CVA, *n* (%)	2 (0.9 %)	2 (1.8 %)	0.607
Major bleeding, *n* (%)	0 (0.0 %)	0 (0.0 %)	–
Minor bleeding, *n* (%)	8 (3.7 %)	2 (1.8 %)	0.513
Transfusion, *n* (%)	2 (0.9 %)	3 (2.7 %)	0.341

MACE: major adverse cardiac events, MI: myocardial infarction, PCI: percutaneous coronary interventions, CABG: coronary artery bypass graft, CVA: cerebrovascular accident

[a] Patients with multiple procedures are counted as one

Follow-up

The follow-up period was 6 months. Ten patients were lost to follow-up. These were all foreigners who were transferred to a hospital in their home country for further rehabilitation. The follow-up data are shown in Table 3. During the first 30 days, 7 patients (3.2 %) died, of whom 5 (2.3 %) suffered a cardiac death. Two patients died a few minutes after the operator made the decision that continuing the procedure was no longer helpful. One patient died as a result of stent thrombosis after an elective multivessel PCI four days earlier in another hospital. This patient was unsuitable for CABG before the initial PCI. One patient died as a result of persisting cardiogenic shock after re-PCI for stent thrombosis. There was one procedure-related death as discussed earlier. There were 7 re-PCIs, 5 (2.4 %) were in the target vessel as a result of stent thrombosis.

During the total follow-up period of 6 months, 13 patients (6.1 %) died. All cardiac deaths occurred in the first 30 days after the PPCI procedure. During the follow-up period of 6 months there was no significant difference in primary and secondary outcomes in patients receiving PPCI in VieCuri compared with Catharina Hospital.

DISCUSSION

This study presents procedural complications and clinical outcomes of a new off-site PPCI centre in the Netherlands. As shown in previous studies our study confirms PPCI in STEMI patients at an off-site PCI centre to be safe and effective in the Netherlands. [3, 8, 14] The percentage of emergency surgery in our study was 0.0 % which corresponds with the 0–1 % found in the literature. Patient characteristics and procedural specifications were similar in VieCuri and Catharina Hospital, although in the VieCuri group there were significantly more patients with Killip class II and the TIMI risk score was significantly higher.

In the Catharina Hospital group the system delay was significantly longer than in the VieCuri group. This is mainly due to a longer travel time. Furthermore, there were 21 patients who were first admitted to VieCuri before undergoing PPCI in Catharina Hospital, which will affect the time registration in a negative way. The occurrence of procedural complications was low in both groups. There was no significant difference in procedural complications between the two groups.

The study period in VieCuri was shorter (9 months) than in Catharina Hospital (12 months). Nevertheless, the number of patients in the VieCuri group was higher. There are a few explanations for this difference. First, part of this difference can be explained by adding the number of patients (n = 74) sent from non-PCI centres for PPCI in VieCuri. The Catharina Hospital group included only patients from VieCuri, and no patients from surrounding hospitals were included. Despite this, the difference in the number of patients remains high. Although the majority of

STEMI patients were sent to Catharina Hospital, it is possible that some patients were sent to Maastricht University Medical Centre when Catharina Hospital was already occupied.

There is a significant difference in aspirin prescription, which can be corrected by the number of patients receiving a vitamin K antagonist due to atrial fibrillation. When no beta blocker was prescribed, a clear motivation was found in medical records.

The percentage of 30-day MACE was low in both the VieCuri and Catharina Hospital group at 7.9 and 8.1 %, respectively. Despite a longer reperfusion time in the Catharina Hospital group, there was no significant difference be- tween the occurrence of MACE. This might be due to a reduced door-to-balloon time with a longer travel distance.[24] Moreover, VieCuri is a new PPCI centre. All cardiac deaths (2.3 %) occurred within 30 days for the VieCuri group. In the literature the percentage of in-hospital deaths of patients receiving PPCI in hospitals without surgical back-up varies from 4 to 9.8 %.[10, 25] In both trials the number of in-hospital deaths was significantly higher for the off-site PCI group. Occurrence of 30-day mortality in the study by Tomassini et al. was 7.1 %.[11] For the VieCuri group 30-day all-cause mortality was 3.2 % com- pared with 1.8 % in the Catharina Hospital group, which is not significant. In comparison with previously mentioned studies this percentage of total deaths is low. The occurrence of secondary outcomes is also very low in both study groups.

Limitations

Our retrospective study has some limitations. First, this study group is relatively small and providing a larger dataset would be preferred as this would stimulate the power of the study and gives a higher possibility to catch rare events. In this study the door-to-balloon time was not investigated, due to a difference in definition between VieCuri and Catharina Hospital. New studies should investigate whether, in geographically isolated areas, performing PPCI in experienced off-site PCI centres is superior to on-site PPCI due to a shorter reperfusion time and therefore decreased infarct size. In this study only STEMI patients were included. A study by IJkema et al.[26] shows that not all ECGs of patients with a transmural myocardial infarction have ST elevation. New studies should investigate the time to reperfusion and occurrence of MACE in this category too.

CONCLUSION

This study reports the procedural and clinical outcomes in STEMI patients who underwent off-site PPCI at VieCuri Medical Centre. Results were compared with the results of STEMI patients who underwent on-site PPCI at Catharina Hospital. In both study groups the occurrence of procedural complications and MACE were low and no significant differences were found. The study results therefore con- firm that the procedural and clinical outcomes of a new off- site intermediate-volume PPCI centre are comparable with those of an on-site high-volume PPCI centre.

REFERENCES

1. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarc- tion: a quantitative review of 23 randomised trials. Lancet. 2003;361:13–20.
2. Boersma E. Does time matter? A pooled analysis of randomized clinical trials comparing primary percutaneous coronary interven- tion and in-hospital fibrinolysis in acute myocardial infarction pa- tients. Eur Heart J. 2006;27:779–88.
3. Shahian DM, Meyer GS, Yeh RW, et al. Percutaneous coronary in- terventions without on-site cardiac surgical backup. N Engl J Med. 2012;366:1814–23.
4. Pinto DS, Kirtane AJ, Nallamothu BK, et al. Hospital de- lays in reperfusion for ST-elevation myocardial infarction: im- plications when selecting a reperfusion strategy. Circulation. 2006;114:2019–25.
5. Wharton TP Jr., Grines LL, Turco MA, et al. Primary angioplasty in acute myocardial infarction at hospitals with no surgery on-site (the PAMI-No SOS study) versus transfer to surgical centers for primary angioplasty. J Am Coll Cardiol. 2004;43:1943–50.
6. Steg PG, James SK, Atar D, et al. ESC Guidelines for the manage- ment of acute myocardial infarction in patients presenting with ST- segment elevation. Eur Heart J. 2012;33:2569–619.
7. Nederlandse Vereniging voor Cardiologie. Dutch guidelines for in- terventional cardiology; Institutional and operator competance and requirements for training. 2004.
8. Tebbe U, Hochadel M, Bramlage P, et al. In-hospital outcomes after elective and non-elective percutaneous coronary interventions in hospitals with and without on-site cardiac surgery backup. Clin Res Cardiol. 2009;98:701–7.
9. Hannan EL, Zhong Y, Racz M, et al. Outcomes for patients with ST-elevation myocardial infarction in hospitals with and without onsite coronary artery bypass graft surgery: the New York State experience. Circ Cardiovasc Interv. 2009;2:519–27.
10. Ting HH, Raveendran G, Lennon RJ, et al. A total of 1.007 percuta- neous coronary interventions without onsite cardiac surgery: acute and long-term outcomes. J Am Coll Cardiol. 2006;47:1713–21.
11. Tomassini F, Gagnor A, Montali N, et al. Primary percutaneous coronary intervention without on-site cardiac surgery backup in un- selected patients with ST-segment-elevation myocardial infarction: the Rivoli ST-segment elevation myocardial infarction (RISTEMI) registry. Cardiovasc Revasc Med. 2013;14:9–13.
12. Singh M, Holmes DR Jr., Dehmer GJ, et al. Percutaneous coronary intervention at centers with and without on-site surgery: a meta- analysis. JAMA. 2011;306:2487–94.
13. Mol KA, Rahel BM, Eerens F, et al. The first year of the Venlo per- cutaneous coronary intervention program: procedural and 6-month clinical outcomes. Neth Heart J. 2013;21:449–55.
14. Peels JO, Hautvast RW, de Swart JB, et al. Percutaneous coronary intervention without on site surgical back-up; two-years registry of a large Dutch community hospital. Int J Cardiol. 2009;132:59–65.
15. Yang EH, Gumina RJ, Lennon RJ, et al. Emergency coronary artery bypass surgery for percutaneous coronary interventions: changes in the incidence, clinical characteristics, and indications from 1979 to 2003. J Am Coll Cardiol. 2005;46:2004–9.
16. Seshadri N, Whitlow PL, Acharya N, et al. Emergency coronary artery bypass surgery in the contemporary percutaneous coronary intervention era. Circulation. 2002;106:2346–50.

17. Kutcher MA, Klein LW, Ou FS, et al. Percutaneous coronary inter- ventions in facilities without cardiac surgery on site: a report from the National Cardiovascular Data Registry (NCDR). J Am Coll Car- diol. 2009;54:16–24.

18. Lemkes JS, Peels JO, Huybregts R, et al. Emergency cardiac surgery after a failed percutaneous coronary intervention in an interventional centre without on-site cardiac surgery. Neth Heart J. 2007;15:173–7.

19. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/ SCAI guideline for percutaneous coronary intervention. A report of the American college of cardiology foundation/American heart association task force on practice guidelines and the society for cardiovascular angiography and interventions. J Am Coll Cardiol. 2011;58:e44–e122.

20. Windecker S, Kolh P, Alfonso F, et al. ESC/EACTS guidelines on myocardial revascularization. Rev Esp Cardiol (Engl Ed). 2014;2015(68):144.

21. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the bleeding academic research consortium. Circulation. 2011;123:2736–47.

22. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circula- tion. 2007;115:2344–51.

23. Kimura T, Nosaka H, Yokoi H, et al. Serial angiographic follow-up after Palmaz-Schatz stent implanta- tion: comparison with conven- tional balloon angioplasty. J Am Coll Cardiol. 1993;21:1557–63.

24. IJkema BBLM, Bonnier JJRM, et al. Role of the ECG in ini- tial acute coronary syndrome triage: pri- mary PCI regardless presence of ST elevation or of non-ST elvation. Neth Heart J. 2014;22:484–90.

25. Pride YB, Canto JG, Frederick PD, et al. Outcomes among patients with ST-segment-elevation myo- cardial infarction presenting to in- terventional hospitals with and without on-site cardiac surgery. Circ Cardiovasc Qual Outcomes. 2009;2:574–82.

26. Postma S, Dambrink JHE, de Boer MJ, et al. The influence of res- idential distance on time to treat- ment in ST-elevation myovardial infarcion patients. Neth Heart J. 2014;22:513–9.

Chapter 5

Achieving the recommendations of international guidelines in ST-elevation myocardial infarction patients after start of an off-site percutaneous coronary intervention centre and a network focus group:

More attention must be paid to pre-hospital delay

Accepted by: Interventional Cardiology

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ABSTRACT

Objective

Delays in the treatment of patients with ST-segment elevation myocardial infarction (STEMI) are still substantial and achieving the guideline recommendations is challenging. Specifically pre-hospital delays, including general practitioner (GP) and emergency medical transport (EMT) receive little scientific attention. Our objective is to achieve the international guideline recommendations for pre-hospital delay in STEMI patients.

Methods

This is a prospective, observational, cohort study evaluating the delays of STEMI patients. To diminish delays within the studied region an off-site percutaneous coronary intervention (PCI) centre and an acute coronary syndrome focus group comprising the Cardiology Departments, EMT service and GPs were set up. Delays before and after the start of the off-site PCI centre and focus group were analysed.

Results

The median system delay (from any first medical contact to start of PCI) significantly decreased from 80 to 65 minutes. Median electrocardiogram-to-PCI delay decreased from 64 to 48 minutes. The percentage of patients with a system delay <90 minutes improved from 73% to 85% and the percentage with an electrocardiogram-to-PCI delay <90 minutes improved from 92 to 96%. GPs play an important role within the STEMI network with 45% of the patients contacting the GP first, resulting in a slight increase in delays compared to EMT as first medical contact.

Conclusion

The guideline recommendations are achieved within the studied region after start of an off-site PCI centre and a focus group including Cardiologists, GPs and EMT service, demonstrating that focussed attention can effectively result in a decrease in pre-hospital delays.

INTRODUCTION

Delays in the treatment of patients with ST-segment elevation myocardial infarction (STEMI) should be kept as short as possible to limit the extend of necrosis and to decrease the risk of heart failure and mortality.[1, 2] Percutaneous coronary intervention (PCI) is the preferred reperfusion therapy in STEMI patients, if performed within guideline recommended timeframes. The guidelines advise that at least 90% of STEMI patients should have a system delay of 90 minutes or less. Other recommended delays are depicted in Figure 1.[3]

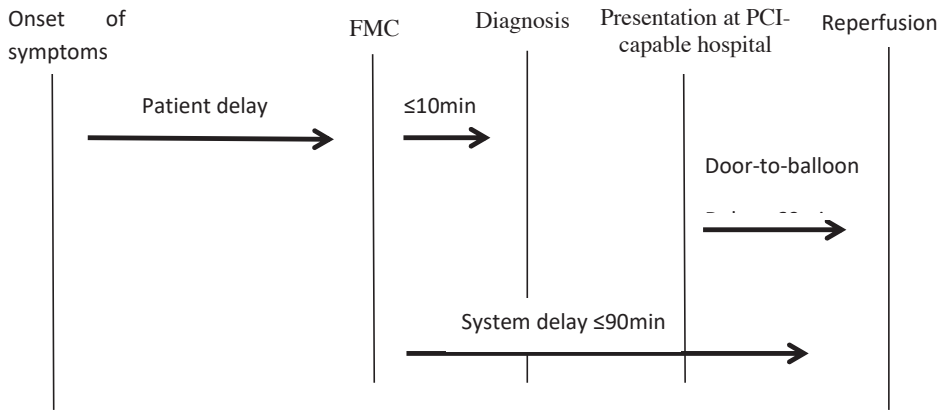

Figure 1. Guideline recommended delays
FMC: first medical contact; any contact with a (para)medic about cardiac symptoms, PCI: percutaneous coronary intervention, min: minutes

Despite decreased door-to-balloon as well as diminished emergency medical transport (EMT) delays,[4] the recommendations in the guidelines are rarely met.[5, 6] Most studies define the FMC as first ECG,[1, 7-9] neglecting the time from first call to the arrival of a (para)medic or general practitioner (GP) and the triage of the EMT service. Contacting a GP first can increase the delay in reperfusion up to 95 minutes[10] and as studies report that 37% to 75% of STEMI patients contact a GP;[11, 12] this is an important point of focus. It is recommended that the entire network involved in triage, transport and treatment of STEMI patients should work closely together.[7, 13]

To meet the increased demand of PCIs and to decrease the pre-hospital delays a focus group comprising of the Cardiology departments, EMT service and GPs was set up and an off-site PCI centre was started.[14] Off-site PCI centres, with no surgical back-up in the own hospital, have been proven to be safe,[15, 16] if they have high operator and intuitional volumes.[17]

This study evaluates the effect of starting an off-site PCI centre and a focus group on the delays of STEMI patients.

METHODS

Study design

This study is a prospective, observational, cohort study. To achieve the recommended delays in STEMI patients from North and Middle Limburg, the Netherlands, the Cardiology departments, EMT service (Ambulance Zorg Limburg Noord), and GPs (Cooperation Cohesie), set up the Acute Coronary Syndrome-Limburg North (ACS-LN) focus group. This focus group designed a protocol for the assessment and treatment of ACS patients. They devised a questionnaire requesting time points in the STEMI network, filled in by EMT personnel, to evaluate the delays and protocol use. To limit the influence of human error, time stamps were used as much as possible. Data from patients who were referred directly to the emergency department (ED), without any use of EMT, were retrospectively retrieved from the medical files. The system delay was defined as FMC to the start of the PCI procedure. The FMC was any contact with a (para) medic about cardiac symptoms, including GPs, EMT and the ED.

The mortality of the study population was compared to the Thrombolysis in Myocardial Infarction (TIMI) risk score study.[18]

Setting and population

All consecutive patients with a STEMI from North Limburg referred to a PCI-capable centre for primary PCI were included from June first 2011 until November first 2015. Until September 2013 the STEMI patients were referred to Catharina Hospital Eindhoven, the Netherlands, at that time the closest primary (on-site) PCI-capable hospital. In September 2013 VieCuri Medical Centre Venlo, the Netherlands, started as an off-site PCI centre, bypassing the 60 km transport of STEMI patients. This off-site PCI centre performs more than 1200 PCIs per year. The patient group who underwent their PCI at Catharina Hospital Eindhoven (the on-site group) and the patient group who underwent their PCI at VieCuri Medical Centre Venlo (the off-site group) all came from the same region (North Limburg), therefore the results given are not a representation of the system delay of Catharina Hospital Eindhoven.

Patients with an out-of-hospital resuscitation were excluded. STEMI patients treated with shocks for ventricular tachycardia or fibrillation from the EMT and/or hospital with rapid conscience recovery, were included.

Statistical analyses

All data were collected by an independent investigator and analysed with SPSS version 22. The categorical data are presented as number of patients and percentages. Continuous data are presented as means and standard deviations (SD) in case of normally distributed data and as medians and interquartile ranges (IQR) in case of skewed data. Patients with (some) missing data were included for analysis of non-missing values. Missing data were not replaced and are given per variable in the tables.

The Student t-test was used for normally distributed continuous variables and the Mann-Whitney U-test was used for skewed distributed continuous variables. Categorical variables were analysed using a chi-square test. To check for possible confounding we analysed whether baseline variables that differed between the two groups (on-site and off-site group) correlated with the delays using the Pearson's correlation coefficient.

A p-value of less than 0.05 was considered significant.

RESULTS

Baseline

A total of 227 patients were included from June first 2011 until September first 2013 who were referred to Catharina Hospital Eindhoven for primary PCI (the on-site group) and 339 patients were included from September first 2013 until November first 2015 who were referred to VieCuri Venlo (the off-site group). Baseline characterisations are presented in Table 1. Gender, presentation during office hours, mortality and TIMI score were not significantly different between the groups. The patients referred to the off-site centre were significantly older (63 years and 62 years respectively), though there was no correlation found between age and the delays.

The FMC of the patients did not differ significantly between the two groups (Figures 2 and 3).

Table 1. Baseline characteristics

	On-site	*Off-site*	*P-value*
Study population, n	227	339	-
Male gender, n (%)	164 (72.2%)	239 (70.5%)	0653
Age, years (SD)	62.†(13.8)	63.3†(12.7)	0.36
Presentation during office hours, n (%)	76 (35.5%)	133 (39.5%)	0.160
Mortality 30 day, n (%)	6 (2.6%)	7 (2.1%)	0.578
TIMI score, (IQR)	2.2*(5.7)	2.2*(5.7)	0.310

TIMI: Thrombolysis in Myocardial Infarction risk score, SD: standard deviation
*median,
†mean

Guidelines adherence

The system delay, i.e. FMC to start PCI, significantly decreased from 80 minutes to 65 minutes. The delay between ECG diagnosis to the start of the PCI procedure, was also significantly lower in the off-site group (Table 2).

Patients contacted the GP more often in the off-site group than in the on-site group, namely 49 vs 39%, although this difference was not significant. The delays associated with the GP did not differ either. The EMT delay, i.e. the time from calling the EMT until ambulance arrival, did

increase from 8 to 9 minutes (Table 2). When comparing FMC as GP vs FMC as EMT over the whole group (on- and off-site groups combined) the system delay was 68 min vs 75 min (p=0.12)

The off-hour presentation was not different between the groups and is therefore presented for both groups together. The overall delay in the off-hours did not significantly differ from the delay during daytime. Moreover the GP delay also did not differ between off-hours and daytime (Table 3).

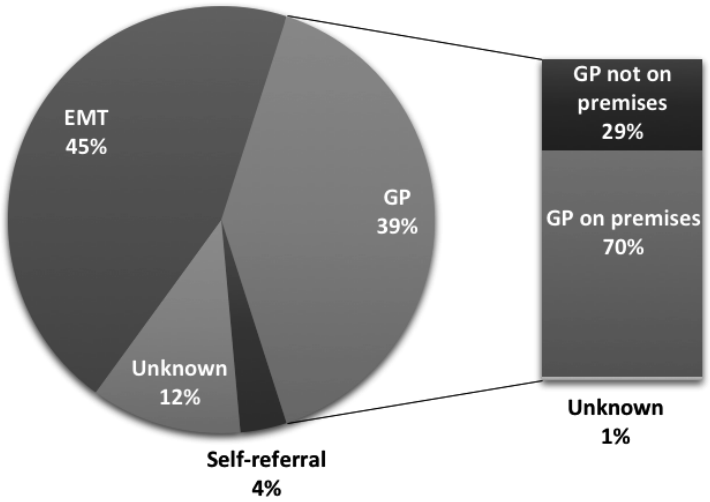

Figure 2. First medical contact of patients to (para)medic in the on-site group, n = 227
EMT: emergency medical transport, GP: general practitioner

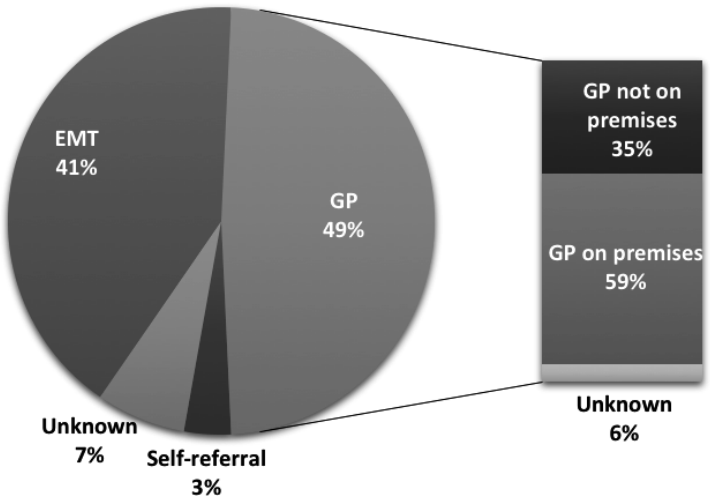

Figure 3. First medical contact of patient to (para)medic in the off-site group, n=339
EMT: emergency medical transport, GP: general practitioner

Table 2. Delays

	On-site	n (missing)	Off-site	n (missing)	P-value
System delay: FMC until PCI start, min (IQR)	80*(20)	131 (96)	65*(25)	265 (74)	<0.001
Percentage FMC until PCI start <90 min	73.3%	131 (96)	85.3%	265 (74)	0.004
ECG until PCI start, min (IQR)	64*(19)	147 (37)	48*(19)	302 (37)	<0.001
Percentage ECG until PCI start <90 min	89.1%	147 (37)	93.0%	302 (37)	0.155
ECG until Cath lab, min (IQR)	55*(18)	195 (32)	39*(22)	298 (41)	<0.001
GP					
Call-to-GP until GP- call-to-EMT, min (IQR)	5*(18)	63(19)	5*(19)	84 (53)	0.447
Call-to-GP until GP-call-to-EMT with GP on premises, min (IQR)	10*(24)	40 (17)	9*(23)	50 (35)	0.523
Call-to-GP until ECG diagnosis, min (IQR)	20*(20)	65 (17)	25*(20)	85 (52)	0.206
EMT					
Call-to-EMT until ambulance arrival, min (SD)	8†(3)	147 (31)	9†(4)	264 (6)	<0.001
Call-to-EMT until ECG diagnosis, (IQR)	13*(6)	153 (25)	15*(8)	243 (27)	<0.001
Departure-to- and arrival-at-Cath lab, (IQR)	35*(10)	140 (38)	22*(15)	252 (18)	<0.001
Patient delay					
Patient delay: symptom onset to FMC, min (IQR)	47*(98)	161 (66)	58*(190)	237 (102)	0.096
Patient delay when FMC is GP, min (IQR)	67*(141)	66 (25)	74*(207)	96 (69)	0.337
Patient delay when FMC is not GP, min (IQR)	32*(76)	95 (15)	42*(163)	141 (10)	0.098

Values are minutes or n,
FMC: first medical contact; any contact with a (para)medic about cardiac symptoms, PCI: percutaneous coronary intervention, ECG: electrocardiogram, Cath lab: catheterization laboratory, IQR: interquartile range, GP: general practitioner, EMT: emergency medical transport
*median
†mean

Table 3. Off-hour presentation delay

	Off-hour	n (missing)	On-hour	n (missing)	P-value
System delay, min (IQR)	70*(24)	250 (104)	72*(35)	146(63)	0.915
System delay with FMC is GP, min (IQR)	75*(35)	84(48)	77*(38)	79(44)	0.968

Values are minutes or n
FMC: first medical contact; any contact with a (para)medic about cardiac symptoms, GP: general practitioner, IQR: interquartile range
*median

Patient delay

The median patient delay was longer in the off-site group, although this difference was not significant (Table 2). The mean delay of the groups combined is almost 3 hours (170 minutes) with 6% of the patients waiting more than 12 hours before contacting a (para)medic.

Patients contacting the GP waited significantly longer to contact a (para)medic, than patients contacting the EMT directly.

DISCUSSION

The most important finding in our study is that the guideline recommended system delays in STEMI patients were achieved. With the close collaboration of the entire ACS network involved in triage, transport and treatment of STEMI patients and the start of an off-site PCI centre the delay in STEMI patients has decreased. The system delay in our region from any FMC to initiation of PCI, is 68 minutes, a much lower delay than reported in other studies.[2, 5, 19] Most studies moreover report ECG to initiation of PCI as system delay, varying from 60 to 210 minutes. [7, 20] In our study we achieved a median ECG to initiation of PCI delay of only 48 minutes .

The percentage of patients with a system delay of 90 minutes or less also improved significantly from 73% to 85%, and thus the target of 90% is almost reached. When using the more frequently applied definition of system delay, from ECG to initiation of PCI, more than 90% of the patients are treated within 90 minutes, thereby reaching target. This is much higher than the 22 to 82% reported in other studies.[5-8]

The mortality and TIMI scores of the two groups were identical and, as published before, the occurrence of procedural complications and MACE were low with no significant differences.[21]

General practitioner

The findings in our study show that patients contacted the GP frequently with 39% in the on-site group and 49% in the off-site group, a non-significant difference. This is comparable to previous studies with 37 to 75% of the STEMI patients consulting the GP.[10-12] Within the study period the number of GP visits decreased over time: the GPs visited 74% of the patients who contacted the GP in the on-site group (from June first 2011 to September first 2013) and only 59% of the patients in the off-site group (from September first 2013 to November first 2015). This (non-significant) decrease might be due to the recent recommendation of the cardiac guidelines that STEMI patients should bypass the GP when experiencing chest pain.[3]

The system delay was slightly, though significantly, longer when the GP was consulted first rather than the EMT (68 vs 75 min). These delays are lower than the delays in other studies,[11, 12] which might be a consequence of the recommendation within the cardiac guidelines to diminish GP participation within the network.[3, 22] To advise all patients with chest pain to contact the EMT, and thus bypassing the GPs entirely in the STEMI network is not feasible, as not all patients with chest pain have a STEMI or even ACS. Up to 80% of the patients within the primary care setting with chest pain do not have ACS and therefore without GP triage the EMT and hospitals would be overcrowded.[23]

As this study shows that the guidelines can be achieved with GP involvement, we recommend regular meetings with all participants in the ACS network including Cardiology departments, EMTs and GPs to improve the delays in STEMI patients, but not dismiss GPs from the ACS network.

Emergency transport delay

The EMT delay was low with 8 and 9 minutes response time, well within the recommended target of 15 minutes.[24] Although the one minute increase was statistically significant, it is unlikely to be clinically relevant. Possible explanations of this difference could be the changes in shift hours and ambulance locations during the study.

Off-hour presentation

Off-hour presentation of STEMI patients is reported to be associated with longer delays and higher mortality.[25] In our study, off-hour presentation did not result in significant longer delays. Off-hour presentation to a GP also did not significantly delay PCI. Studies suggest that the delaying factor of off-hour presentation can be improved with a multidisciplinary and protocol driven network with a high-volume PCI-centre[26, 27], as is the case in our region.

Patient delay

The above mentioned delays are all organization related delays, however a crucial part of the pre-hospital delay includes patient delay. In this study we have found median patient delays of 47 and 58 minutes, a non-significant increase and lower than reported in previously published studies.[28, 29] However a small group of patients waited more than 12 hours making the mean delay almost three hours, a substantial delay which needs to be diminished.

Patients contacting the GP, waited longer to call for help, than patients contacting the EMT. Patients contacting the GP might have less typical symptoms, not recognize a heart attack and thus not contact the EMT immediately. This could increase the GP delay as well, as it is more difficult to diagnose these patients.

Reducing the patient delays has proven to be complex, with most studies not leading to a reduction of the delays.[29, 30] The patient delays depicted in this study are much lower than the earlier studies and comparable to other, more recent studies.[19] There may be improvements within patient delay that have already taken place, such as increased awareness. However, as any delay increases the risks and some patients wait more than twelve hours, these delays are too long, and should still be a point of focus.

Strengths and Limitations

The strength of our study is that we included the FMC to any (para)medic, as most other studies do not report the pre-hospital delays before ECG. Missing data, mainly due to handwritten forms, are a limitation. Patients with a STEMI but not referred to the hospital are not part of this study. Patients with out-of-hospital resuscitation were excluded, however these patients also benefit of decreased delays and more research should be conducted within this group.

CONCLUSION

This study shows that the delays of STEMI patients can be improved by focussing on pre-hospital delays and thus achieving the recommended delays in the guidelines. The guideline recommendations are met within the studied region after the start of an off-site PCI centre and with a multidisciplinary and protocol-driven network, including the Cardiology departments, GPs and EMT service.

REFERENCES

1. Koul S, Andell P, Martinsson A, Gustav Smith J, van der Pals J, Schersten F, et al. Delay from first medical contact to primary PCI and all-cause mortality: a nationwide study of patients with ST-elevation myocardial infarction. Journal of the American Heart Association. 2014;3(2):e000486.
2. Terkelsen CJ, Sorensen JT, Maeng M, Jensen LO, Tilsted HH, Trautner S, et al. System delay and mortality among patients with STEMI treated with primary percutaneous coronary intervention. Jama. 2010;304(7):763-71.
3. Steg PG, James SK, Atar D, Badano LP, Blomstrom-Lundqvist C, Borger MA, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. European heart journal. 2012;33(20):2569-619.
4. Nam J, Caners K, Bowen JM, Welsford M, O'Reilly D. Systematic review and meta-analysis of the benefits of out-of-hospital 12-lead ECG and advance notification in ST-segment elevation myocardial infarction patients. Annals of emergency medicine. 2014;64(2):176-86, 86 e1-9.
5. Helve S, Viikila J, Laine M, Lilleberg J, Tierala I, Nieminen T. Trends in treatment delays for patients with acute ST-elevation myocardial infarction treated with primary percutaneous coronary intervention. BMC cardiovascular disorders. 2014;14:115.
6. Sandouk A, Ducasse JL, Grolleau S, Azema O, Elbaz M, Farah B, et al. Compliance with guidelines in patients with ST-segment elevation myocardial infarction after implementation of specific guidelines for emergency care: results of RESCA+31 registry. Archives of cardiovascular diseases. 2012;105(5):262-70.
7. Tra J, van der Wulp I, de Bruijne MC, Wagner C. Exploring the treatment delay in the care of patients with ST-elevation myocardial infarction undergoing acute percutaneous coronary intervention: a cross-sectional study. BMC health services research. 2015;15:340.
8. Vermeulen RP, Jaarsma T, Hanenburg FG, Nannenberg JW, Jessurun GA, Zijlstra F. Prehospital diagnosis in STEMI patients treated by primary PCI: the key to rapid reperfusion. Netherlands heart journal : monthly journal of the Netherlands Society of Cardiology and the Netherlands Heart Foundation. 2008;16(1):5-9.
9. de Boer MJ, Zijlstra F. STEMI time delays: a clinical perspective : Editorial comment on the article by Verweij et al. Netherlands heart journal : monthly journal of the Netherlands Society of Cardiology and the Netherlands Heart Foundation. 2015;23(9):415-9.
10. Bleeker JK, Simoons ML, Erdman RA, Leenders CM, Kruyssen HA, Lamers LM, et al. Patient and doctor delay in acute myocardial infarction: a study in Rotterdam, The Netherlands. The British journal of general practice : the journal of the Royal College of General Practitioners. 1995;45(393):181-4.
11. Birkhead JS. Time delays in provision of thrombolytic treatment in six district hospitals. Joint Audit Committee of the British Cardiac Society and a Cardiology Committee of Royal College of Physicians of London. BMJ. 1992;305(6851):445-8.
12. Hitchcock T, Rossouw F, McCoubrie D, Meek S. Observational study of prehospital delays in patients with chest pain. Emergency medicine journal : EMJ. 2003;20(3):270-3.
13. NVVC Connect [Available from: http://www.nvvcconnect.nl/.
14. Mol KA, Rahel BM, Eerens F, Aydin S, Troquay RP, Meeder JG. The first year of the Venlo percutaneous coronary intervention program: procedural and 6-month clinical outcomes. Netherlands

heart journal : monthly journal of the Netherlands Society of Cardiology and the Netherlands Heart Foundation. 2013;21(10):449-55.

15. Peels JO, Hautvast RW, de Swart JB, Huybregts MA, Umans VA, Arnold AE, et al. Percutaneous coronary intervention without on site surgical back-up; two-years registry of a large Dutch community hospital. International journal of cardiology. 2009;132(1):59-65.
16. Ting HH, Raveendran G, Lennon RJ, Long KH, Singh M, Wood DL, et al. A total of 1.07 percutaneous coronary interventions without onsite cardiac surgery: acute and long-term outcomes. Journal of the American College of Cardiology. 2006;47(8):1713-21.
17. Dutch guidelines for interventional cardiology. 2016 [Available from: https://www.nvvc.nl/media/richtlijn/188/2016_Praktijkdocument_interventiecardiologie.pdf.
18. Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, Papuchis G, et al. The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. Jama. 2000;284(7):835-42.
19. Thilo C, Bluthgen A, von Scheidt W. Efficacy and limitations of a STEMI network: 3 years of experience within the myocardial infarction network of the region of Augsburg - HERA. Clinical research in cardiology : official journal of the German Cardiac Society. 2013;102(12):905-14.
20. Widimsky P, Wijns W, Fajadet J, de Belder M, Knot J, Aaberge L, et al. Reperfusion therapy for ST elevation acute myocardial infarction in Europe: description of the current situation in 30 countries. European heart journal. 2010;31(8):943-57.
21. Koolen K, Mol KA, Rahel BM, Eerens F, Aydin S, Troquay RP, et al. Off-site primary percutaneous coronary intervention in a starting centre is safe: comparing clinical outcomes with a hospital with surgical backup Netherlands heart journal : monthly journal of the Netherlands Society of Cardiology and the Netherlands Heart Foundation. 2016.
22. Backx JC, Bruins Slot, M.H.E, van Casteren-van Gils, B.C.A.M, Derks, C.J.T, Rambharose, V.R, Rutten, F.H. NHG-Standaard Acuut coronair syndroom (eerste herziening)2012 10-02-2016.
23. Mol KA, Rahel BM, Meeder JG, van Casteren BC, Doevendans PA, Cramer MJ. Delays in the treatment of patients with acute coronary syndrome: Focus on pre-hospital delays and non-ST-elevated myocardial infarction. International journal of cardiology. 2016;221:1061-6.
24. Rijksinstituut voor Volksgezondheid en Milieu [Available from: www.volksgezondheidenzorg.info.
25. Sorita A, Ahmed A, Starr SR, Thompson KM, Reed DA, Dabrh AM, et al. Off-hour presentation and outcomes in patients with acute ischemic stroke: a systematic review and meta-analysis. European journal of internal medicine. 2014;25(4):394-400.
26. Casella G, Ottani F, Ortolani P, Guastaroba P, Santarelli A, Balducelli M, et al. Off-hour primary percutaneous coronary angioplasty does not affect outcome of patients with ST-Segment elevation acute myocardial infarction treated within a regional network for reperfusion: The REAL (Registro Regionale Angioplastiche dell'Emilia-Romagna) registry. JACC Cardiovascular interventions. 2011;4(3):270-8.
27. Sorita A, Lennon RJ, Haydour Q, Ahmed A, Bell MR, Rihal CS, et al. Off-hour admission and outcomes for patients with acute myocardial infarction undergoing percutaneous coronary interventions. American heart journal. 2015;169(1):62-8.
28. Naegeli B, Radovanovic D, Rickli H, Erne P, Seifert B, Duvoisin N, et al. Impact of a nationwide public campaign on delays and outcome in Swiss patients with acute coronary syndrome. European

journal of cardiovascular prevention and rehabilitation : official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology. 2011;18(2):297-304.

29. Tummala SR, Farshid A. Patients' understanding of their heart attack and the impact of exposure to a media campaign on pre-hospital time. Heart, lung & circulation. 2015;24(1):4-10.

30. Neubeck L, Maiorana A. Time to get help? Acute myocardial infarction and delay in calling an ambulance. Heart, lung & circulation. 2015;24(1):1-3.

Part II

Accuracy of referrals

Chapter 6

Acute chest pain, a diagnostic challenge for general practitioners: Timely versus excessive referral

submitted

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ABSTRACT

Background

Acute chest pain is a diagnostic dilemma for general practitioners (GPs). Patients with acute coronary syndrome (ACS) should be referred promptly, without excess referrals of non-cardiac chest pain (NCCP) patients. The aim of this study is to investigate the triage systems of referred patients to the hospital with suspected ACS.

Method

This study is a prospective, observational, prevalence-based cohort conduced from the 1st of September 2015 to the 28th of February 2016 with a year follow-up. We assessed the factors that play a role in the concordance with the eventual diagnosis and reviewed the differences between the referrals of patients contacting on- and off-hour GPs. The primary endpoint was the accuracy of referral by on- and off-hour GPs. Mortality and the major adverse cardiac events (MACE) at one-year were compared between patients referred by on- or off-hour GPs as well as between ACS and NCCP patients. For comparison between groups the Student t-test, Mann-Whitney U-test, chi-square test, logistic regression analyses and multivariate logistic regression model were used where applicable.

Results

Patients referred with suspected ACS after evaluation by on-hour GPs were more likely to be diagnosed with ACS than patients referred by off-hour GPs (27.1% vs 20.1%, p=.007). The doctor delay was however significantly longer when patients contacted on-hour GPs (median of 5 min vs 34 min, p<.001). Mortality was low in patients with NCCP versus ACS (one year mortality rate of 2.1% vs 6.8% respectively, p<.001), however MACE in the follow-up period were still high (5.2%).

Conclusion

GPs are frequently contacted by patients with chest pain. With the low mortality of NCCP patients it would be beneficial to exclude these patient from direct referral. Symptoms, history nor risk factors could not sufficiently exclude patients to dismiss ACS. GPs are thus in need of tools for the triage of chest pain patients.

INTRODUCTION

Acute chest pain is a diagnostic challenge for general practitioners (GPs). Missing or even delaying a diagnosis of acute coronary syndrome (ACS) could have serious consequences.[1,2] ACS is however not frequently encountered by the individual physician in the primary care setting, with non-cardiac chest pain (NCCP) diagnosed in 80% of the patients presenting with chest complaints.[3] NCCP patients have a mortality rate comparable to the general population and much lower than patients with cardiac chest pain.[4]

To diminish delays in patients with ACS, international cardiac guidelines advise to bypass GPs altogether.[5, 6] GPs are advised to refer all patients with new or recently changed chest complaints to the hospital without further delay, in order to avoid missing any myocardial infarctions (MI).[5, 6] With society decreasingly less tolerant for missing a diagnosis, resulting in a multitude of lawsuits for not (timely) diagnosing a serious illness, GPs are rather safe than sorry.[7, 8]

The dilemma of chest pain complaint lies in that patients unnecessarily referred to the hospital with NCCP are exposed to avoidable risk and stress. These referrals have a psychological impact on patients and their families. This results in high health care utilization[9-11] and frequent readmissions,[4] with high health care[9, 12] and societal costs.[12, 13] To circumvent GPs all together as cardiac guidelines indicate,[6] would increase the burden on patients, their families and the hospitals.[14]

The aim of this study is to investigate the triage systems of referred patients to the hospital with suspected ACS. We assessed the factors that play a role in the concordance with the eventual diagnosis and reviewed the differences between the referrals of patients contacting the on-hour or off-hour GPs.

METHODS

Study design

This study is a prospective, observational, prevalence-based cohort study conducted from the 1st of September 2015 to 28th of February 2016 with a year follow-up until 28th of February 2017.

Study sample and setting

All patients age 18 years and older with suspected ACS referred to the (cardiac) emergency department (ED) of VieCuri Medical Centre Venlo, the Netherlands, a medium sized teaching and off-site percutaneous coronary intervention (PCI) centre, were included. Patients are referred to the ED through emergency medical transport (EMT), GP, specialist, or as self-referrals. This article focuses on the referrals by GPs.

During daytime patients contact their own GP (on-hour GP). During off-hours (evenings, nights, weekends and holidays) patients can contact a GP cooperative (off-hour GP). The GPs from this region almost solely refer patients to the only hospital in the region, VieCuri Medical Centre Venlo. The off-hour GPs have a access to the medical files of the patient from the on-hour GPs and thus can see the history of the patient.

Data collection

Data was collected through medical files and a questionnaire given to patients with additional queries not retrievable from medical files. Collected data included demographics, history, symptoms, medication, discharge diagnosis and delays.

A one-year follow-up has been included with mortality and major adverse cardiac events (MACE). MACE included any ST-elevated MI (STEMI), non-STEMI (NSTEMI), unstable angina pectoris (UAP), angina pectoris (AP), PCI and coronary artery bypass grafting (CABG) after discharge. An ACS diagnosis and/or treatment at initial admittance was not considered a MACE.

MI was defined as a detection of a rise and/or fall of cardiac biomarker values with symptoms of ischemia, (presumed) new significant ST-segment-T wave changes or left bundle branch block, development of pathological Q waves, new loss of viable myocardium or regional wall motion abnormality, or identification of an intracoronary thrombus. STEMI was defined as MI with ST-segment elevation in at least two contiguous leads and NSTEMI was defined as MI without ST-segment elevation. UAP was defined as myocardial ischemia at rest or minimal exertion in the absence of cardiac biomarkers. AP was defined as stable coronary artery disease. NCCP was defined as chest pain not attributed to underlying ischemic heart disease and could have any other or an unknown diagnosis.

Data analysis

Data were analysed using SPSS version 22. Baseline characteristics, mortality and MACE are given per patient. Triage, referral and transport details, delays and diagnosis are given per presentation, as these can differ per presentation. Categorical data are presented as number and percentages of patients or presentations when applicable. Continuous data are presented as means and standard deviation (SD) in case of normally distributed data and as medians and interquartile ranges (IQR) when data is skewed. Patients with missing values are included, with exception of their missing values and percentages are calculated with respect to the available data, thus excluding missing values. For comparison between groups the Student t-test was used for normally distributed continuous variables and the Mann-Whitney U-test was used for skewed distributed continuous variables. Categorical variables were analysed using a chi-square test. To investigate if symptoms were related to on- or off-hour GPs, or to diagnosis, we used logistic regression analyses. Those factors significant in univariate models were entered into a multivariate logistic regression model. The resulting odds ratios (OR) are presented with their 95% confidence intervals (CI). A p-value of less than 0.05 was considered statistically significant.

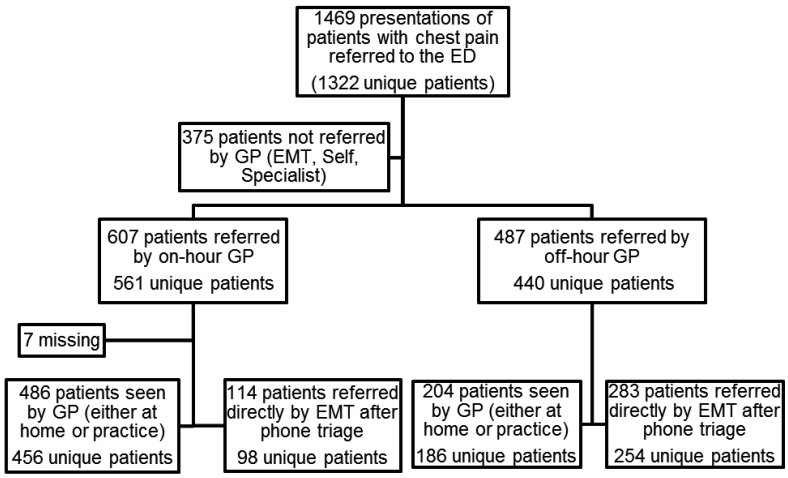

Figure 1. Patient route to the emergency department

ED: emergency department, GP: general practitioner, GPC: GP cooperation, EMT: emergency medical transport, self: self-referral.

RESULTS

A total of 1469 patients were referred to the ED with suspected ACS through EMT, GP, specialists or self-referrals. Some patients were referred more than once, resulting in 1322 unique patients. Of the 1469 presentations, 1094 patients were referred after contact with a GP or a (triage) nurse working for the GP. The on-hour GPs were contacted by 561 patients with 607 contacts in total and the off-hour GPs were contacted by 440 patients with 487 contacts in total (Figure 1).

Characteristics

Patients contacting on-hour GPs were older (mean of 64.5 vs 60.8 years p<.001), more likely to have diabetes (19.3% vs 14.3%, p=.038), and more likely to have hypercholesterolemia (44.0% vs 37.7%, p=.046). All other demographics were not significantly different (Table 1).

Table 1. Characteristics compared between on- and off-hour GP subsets and between ACS and NCCP patients

	On-hour GP (n=561)	*Off-hour G (n=440)*	*P-value*	*ACS (n=247)*	*NCCP (n=614)*	*P-value*
Caucasian, No.(%)	543 (96.8)	415 (94.3)	0.055	581 (94.6)	239 (96.8)	0.180
Age, mean (SD), yrs	64.5 (14.2)	60.8 (16.0)	<0.001	66.3 (12.7)	60.9(15.5)	<0.001
Male gender, No.(%)	304 (54.2)	219 (49.8)	0.200	168 (68.0)	268 (43.6)	<0.001
BMI >25, No.(%)	238 (42.7)	177 (40.6)	0.880	114 (46.2)	240 (39.1)	0.056

Smoker, No.(%)	184 (33.5)	150 (35.0)	0.071	98 (40.8)	194 (32.4)	0.020
Diabetes mellitus, No.(%)	108 (19.3)	63 (14.3)	0.038	46 (18.6)	93 (15.2)	0.210
Hypercholester-olemia, No.(%)	245 (44.0)	166 (37.7)	0.046	119 (48.4)	228 (37.3)	0.003
Hypertension, No.(%)	257 (45.8)	190 (43.2)	0.410	115 (46.6)	267 (43.5)	0.410
Positive family history, No.(%)	207 (39.7)	153 (37.7)	0.530	108 (45.2)	203 (36.1)	0.017
History of CVD, No.(%)	176 (31.4)	131 (29.8)	0.590	76 (30.8)	170 (27.7)	0.370

GP: general practitioner, ACS: acute coronary care, NCCP: non-cardiac chest pain, BMI: body mass index, Smoker: current or quit within 10 years, EMT: emergency medical transport, CVD: cardiovascular disease.

Table 2. Triage, referral, transport and diagnosis compared between on- and off-hour patient presentation to the GP

	On-hour GP (n=607)	*Off-hour GP (n=487)*	*P-value*
Triage[a]			
Examination by GP, No.(%)	486 (81.0)	204 (41.9)	<0.001
Consultation at home, No.(%)	79 (13.2)	29 (6.0)	<0.001
Consultation at practice, No.(%)	403 (67.2)	175 (35.9)	<0.001
EMT referral after phone triage, No.(%)	113 (18.8)	283(58.1)	<0.001
Referral to policlinic, No.(%)	4 (0.7)	0 (0.0)	
Transportation[b]			
Self/bystander, No.(%)	189 (31.1)	155 (31.9)	0.950
EMT, No.(%)	412 (67.9)	331 (68.0)	0.950
EMT call by[c]			
GP, No.(%)	403 (97.8)	324 (97.9)	0.950
Patient/bystander, No.(%)	6 (1.5)	6 (1.2)	0.700
Specialist or caretaker, No.(%)	3 (0.7)	1 (0.2)	0.430
Referral delay of all patients[d]			
Patient delay, median(IQR), min	180 (615)	108 (237)	0.001
Doctor delay, median(IQR), min	34 (55)	5 (6)	<0.001
FMC-hospital no EMT, median(IQR), min	125 (189)	59 (39)	<0.001
Transport delay, median(IQR), min	41 (15)	46 (17)	<0.001
Referral delay of ACS patients[e]			
Patient delay, median(IQR), min	180 (570)	76 (235)	0.012
Doctor delay, median(IQR), min	36 (95)	4 (7)	<0.001
FMC-hospital no EMT, median(IQR), min	183 (243)	51 (85)	<0.001
Transport delay, median(IQR), min	41 (17)	45 (16)	0.280
Diagnosis			
ACS, No.(%)	165 (27.2)	98 (20.1)	0.007
STEMI, No.(%)	22 (3.6)	33 (6.8)	0.018
NSTEMI, No.(%)	92 (15.1)	56 (11.5)	0.079
UAP, No.(%)	51 (8.4)	9 (1.8)	<0.001
Non-ischemic CCP, No.(%)	107 (17.6)	56 (11.5)	0.005

Table 2. Triage, referral, transport and diagnosis compared between on- and off-hour patient presentation to the GP (continued)

	On-hour GP (n=607)	*Off-hour GP (n=487)*	*P-value*
NCCP-K, No.(%)	41 (6.8)	37 (7.6)	0.590
NCCP-U, No.(%)	294 (48.4)	296 (60.8)	<0.001

GP: general practitioner, EMT: emergency medical transport, FMC: first medical contact, Patient delay: time of onset of pain to FMC, Doctor delay: time of FMC to call to EMT or hospital, Transport delay: EMT to hospital delay, ACS: acute coronary syndrome, STEMI: ST-elevated myocardial infarction, NSTEMI: non-STEMI, UAP: unstable angina pectoris, CCP: cardiac chest pain, NCCP-K: non-CCP-known, NCCP-U: NCCP-unspecified.

[a] 7 (1.2%) patients missing data in on-hour GP subset

[b] 1 (0.2%) patient missing data in off-our GP subset, 86 (17.7%) patients already in hospital in off-hour GP subset, 4 (0.7%) patients already in hospital in on-hour GP subset

[c] Patients referred by on-hour GP with EMT n=412 and by off-hour GP with EMT n=331

[d] All patients: on-hour GP n= 195 – 607 and missing data 25.7 – 55.2% and off-hour GP n= 155 – 487 and missing data 2.6 – 22.7%

[e] ACS patients: on-hour GP n= 56 – 165 and missing data 34.9 – 48.5% and off-hour GP n= 26 – 98 and missing data 3.9 – 18.1%

Triage, referral and transportation

Referral data is depicted in Table 2. The majority of the patients were examined by a GP, all others were referred directly after phone triage. More than 80% of on-hour presentations were examined by a GP, significantly more than off-hour presentations (81.0% vs 41.9%, p<.001), and these patients were more often examined at home (13.2% vs 6.0%, p<.001). A substantial amount of patients examined by off-hour GPs were not referred by EMT, as the off-hour GP cooperation is located within the hospital.

Diagnosis

The diagnoses made at the ED or after hospitalization are depicted in Table 2. Patients referred by on-hour GPs were more likely to be diagnosed with ACS than patients referred by off-hour GPs (27.2% vs 20.1%, p=.007) and they had significantly more non-ischemic CCP (17.6% vs 11.5%, p=.005). There was no difference in accuracy of ACS diagnosis if the patients were examined by the GP or referred directly after phone triage (24.2% vs 23.7%, p=.85).

Patients evaluated by on-hour GPs were significantly less likely to have a STEMI (3.6% vs 6.8%, p.018) and significantly more likely to have UAP (8.4% vs 1.8%, p<.001). We did not find a statistically significant difference in NSTEMI diagnoses (15.1% vs 11.5%, p=.079).

The final diagnosis, ACS or NCCP, did not have any effect on triage, referrals or transportation.

Symptoms

We compared the symptoms of patients referred by on-hour GPs to patients referred by off-hour GPs. No differences were found in location of chest pain, nor in radiating complaints. Patients presenting at the off-hour GP did have more associated symptoms, with more nausea (29.2% vs 35.3%, p=.033) and vomiting (5.0% vs 8.8%, p=.015). Patients presenting at the

on-hour GP had more symptoms induced by exercise (34.3% vs 18.2%, p<.001) and dyspnoea complaints (29.9% vs 22.8%, p=.009). With multivariate analysis only the amount of patients presenting with symptoms induced by exercise remained significantly different (OR 2.254, 95% CI 1.682-3.019).

When comparing symptoms between ACS and NCCP patients, more significant differences were found: reproducible pain by palpation (12.7% vs 39.7%, p<.001), radiating pain to the arms (54.4% vs 43.8%, p= .004), diaphoresis (40.6% vs 28.3%, p<.001), dizziness (23.3% vs 30.4%, p=.031), palpitations (9.5% vs 16.6%, p=.006) and symptoms induced by exercise (41.6% vs 21.8%, p<.001). With multivariate analysis the differences in the amount of patients presenting with reproducible pain by palpation (OR .248, 95% CI .116-.530), diaphoresis (OR 2.735, 95% CI 1.474-5.074), dizziness (OR .396, 95% CI .200-.785) and symptoms induced by exercise (OR 3.040, 95% CI 1.665-5.552) remained significant.

ACS patients versus NCCP patients

We analysed the characteristics of ACS versus NCCP patients (Table 1). Risk factors such as high age (mean of 66.3 vs 60.9 years, p<.001), male gender (68.0% vs 43.6%, p<.001), hypercholesterolemia (48.4% vs 37.3%, p=.003), positive family history (45.2% vs 36.1%, p=.017) and current smoker (40.8% vs 32.4%, p=.020) were all more frequently seen within ACS patients, though they were still high in NCCP patients. Characteristics of ACS versus NCCP between the on and off-hour GP subsets did not differ from the analyses over the whole group.

Delays

Patients contacting on-hour GPs had a longer patient delay (time from onset of pain to first medical contact (FMC)) compared to patients contacting off-hour GPs (median of 180min vs 108min, p=.001) (Table 2). The doctor delay (time from FMC to call to EMT or hospital) was significantly longer when patients contacted on-hour GPs (median of 34min vs 5min, p<.001). These delays were also significantly longer when only analysing the ACS patients (Table 2). Separate analysis of STEMI patients was not reliable due to the small number of patients (22 patients referred by on-hour GPs and 31 referred by off-hour GPs). Nevertheless, the doctor delay was again longer for patients contacting the on-hour GP diagnosed with a STEMI: 13 versus 2 min. Of the STEMI patients 38.1% were referred immediately by on-hour GPs with EMT compared to 69.7% by off-hour GPs.

Mortality and MACE

ACS patients have a significantly higher mortality and MACE rate than NCCP patients (one year mortality rate of 6.8% vs 2.1%, p<.001 and one year MACE 10.9% vs 5.2%, p=.001) (Table 3).

Mortality and MACE did not significantly differ between patients referred by on- or off-hour GPs. We also evaluated the mortality and MACE of ACS versus NCCP patients within the on- and off-hour GP subsets, however the numbers were too low for a meaningful analysis.

Table 3. Mortality and MACE

	On-hour GP (n=561)	*Off-hour GP (n=440)*	*P-value*	*ACS (n=247)*	*NCCP (n=614)*	*P-value*
Mortality						
In hospital, No.(%)	6 (1.1)	3 (0.7)	0.52	6 (2.4)	3 (1.1)	0.011
30 day, No.(%)	5 (0.9)	3 (0.7)	0.71	5 (2.0)	3 (0.5)	0.035
1 year, No.(%)	22 (3.9)	17 (3.9)	0.960	16 (6.8)	13 (2.1)	<0.001
MACE						
30 day, No.(%)	9 (1.6)	4 (0.9)	0.27	9 (3.6)	4 (0.7)	0.001
1 year, No.(%)	48 (8.6)	29 (6.6)	0.24	27 (10.9)	32 (5.2)	0.002

GP: general practitioner, ACS: acute coronary syndrome, NCCP: non-cardiac chest pain, , MACE: major adverse cardiac event

DISCUSSION

Role of the GP

GPs in the studied region are still frequently contacted by patients with chest pain. The diagnostic dilemma that these patients encompass, namely timely referral of ACS patients without an excess of NCCP patients, is proven with 76% of the patients referred to the ED by the GP with a suspicion of ACS not diagnosed with ACS at the hospital.

Many patients were seen by on-hour GPs, with almost 80%, in contrast to 41.9% patients examined by the off-hour GPs. This difference is mostly explained by the Netherlands Triage System (NTS) used by the off-hour GP cooperation and not by on-hour GP practices.[15] The NTS is a 5-level triage system based on the Manchester Triage System and validated for pre-hospital triage by phone or physical triage. With a sensitivity of 75% and a specificity of 97%,[16] the NTS refers patients with chest pain more rapidly to the EMT than triage by GPs without the NTS.

Diagnosis

Patients referred by off-hour GPs (examined or not) were significantly less often diagnosed with ACS and significantly more often with NCCP compared to patients referred by on-hour GPs. We have analysed a number of factors that could contribute to this difference in accuracy. The patients referred by on-hour GPs were older, and more likely to have hypercholesterolemia or diabetes mellitus, known risk factors for ACS. We found differences in symptoms between ACS and NCCP patients, none however that can differentiate adequately between the two subsets. After multivariate analyses we did find that symptoms induced by exercise were seen significantly more in the on-hour GP subset after multivariate analysis, confirmed by the higher amount of UAP within the this subset.

More than half (60%) of STEMI patients presented at off-hour GPs as a result of more than 70% of the week covered by off-hour GPs. The reason the frequency of STEMI is higher in the off-hour GP subset compared to the on-hour subset is explained by the higher UAP frequency

within the on-hour GP subset, presumably as these patients are not unstable and thus wait for their own GP (on-hour) to contact for help.

There was no difference in accuracy of ACS diagnosis if the patients were examined by the GP or referred directly after phone triage. Perhaps as patients referred by phone triage were patients with more typical complaints then patients referred for physical triage by the GPs after phone triage.

Delays

The downside to the more accurate referral of chest pain patients by on-hour GPs were longer delays. A possible explanation for longer patient and doctor delays is that higher frequency of UAP in the on-hour GP subset in contrast to higher frequency of STEMIs in the off-hour subset. Delays in STEMI have specific guideline recommendations[6] explaining at least part of the shorter delays in the off-hour GP subset. Moreover as the patient delay is long, this could influence the GP to wait longer until referral to the ED, choosing to run diagnostics first.

The off-hour GP cooperation in our region is located within the hospital, which explains some of the shorter delays. However this does not have an influence on patient delay, nor doctor delay (as doctor delay is the FMC to call to EMT or hospital, not including transportation). The shorter doctor delay in the off-hour GP subset is partly explained by the NTS, referring patients more rapidly to the ED with EMT, without examination by a GP first.

Prognosis

There were no significant differences in mortality or MACE between patients referred by on- or off-hour GPs. Thus the longer delays in patients referred by the on-hour GPs do not influence the mortality or MACE.

ACS patients did have a higher mortality and MACE in the one year follow-up than the NCCP patients. Despite the low mortality in NCCP patients, the frequency of MACE was still considerable with 4.9% of patients with NCCP at first presentation with a MACE within one year. The majority of these MACE were seemingly not related to the initial referral to the ED with chest pain, as the frequency of MACE was only 0.5% within 6 weeks.

Comparison to literature

Off-hour GPs were significantly less accurate in ACS diagnosis resulting in a higher number of ED referrals. This has been found in other studies with the most NCCP referrals between eleven o'clock at night and seven in the morning.[17, 18] In our region off-hour GPs are younger with less experience compared to the on-hour GPs, which could also influence the accuracy of diagnosis. We however did not find, in contrast to other studies, that off-hour GPs disproportionately influence the prognosis of the patient nor did we find other factors such as consultation at home to be associated with more referrals.[18, 19]

Our study confirms the lower mortality in NCCP patients compared to ACS patients with a mortality rate comparable to the general population.[4, 11, 20] The one-year mortality of ACS patients in our study is much lower with 6.8% compared to 18% mentioned in previous studies.[4, 21, 22] We believe this to be a consequence of a better treatment for ACS patients, as the previous studies are mostly from before the PCI and troponin eras.[4, 21, 22] Despite the lower mortality of NCCP patients, they do have an increased risk of a cardiac event or MACE. This study reviews a specific subset of patients, namely patients referred by GPs with a suspicion of ACS. These patients have a higher amount of risk factors for ACS than the general population, explaining the higher amount of cardiac events.[11, 23] GPs should exclude NCCP patients from referral to the ED to avoid exposing them to unnecessary risks,[10] however they should not exclude further treatment of their cardiac risk factors. With the high amount of MACE in both the ACS and NCCP groups, GPs should aggressively treat these cardiac risk factors and consider the referral of patients to the Cardiology as out-patients.

Further research

With the low mortality in NCCP patients it would be beneficial to exclude these patients from referral to lower complications, costs,[12, 13] and stress for patients, their families and the ED.[24]

Symptoms, history nor risk factors can differentiate ACS from NCCP adequately either by phone triage or examination by the GPs. The GPs are thus in need of tools for triage of chest pain patients.[25] The on-hour GPs are significantly more accurate in the referral of ACS patients. In part because the on-hour GP is familiar with the patients: the GP knows the medical history, family history, social background, illness behaviour and way of communicating. However the accuracy in diagnosis could also be a consequence of the availability to run more diagnostic tests during on-hours such as an ECG and/or troponin testing with off-hour GPs advised against troponin testing, due to logistics.[26]

To assist the GPs in the diagnostic dilemma of chest pain, we need a fast way to exclude low risk patients. The HEART score has been validated to exclude low risk patients at the ED as well as within the EMT.[27, 28] The HEART score uses history, ECG, age, risk factors and troponin testing within two hours to differentiate between patients with a low, intermediate or high risk of a cardiac event.[27] Recently available point-of-care (POC) testers boast a minimal wait for accurate troponin testing, an asset for off-hour GPs.[29] As patients with a low risk of ACS do no benefit from admission[30] and the POC troponin testers do not exclude patients,[31] it would be interesting to see if the HEART score combined with the POC troponin testers could support the (off-hour) GPs in excluding low risk patients from referral to the ED.

Study strengths and limitations

All patients referred to the ED with suspected ASC were included, making it an unselected, clinical study population with a good representation of daily practice. This, however, also made it a highly heterogeneous population and resulted in missing variables.

CONCLUSION

GPs are frequently contacted by patients with chest pain. The dilemma between timely referral of ACS patients without an excess of NCCP patients is tremendous. With the low mortality of NCCP patients it would be beneficial to exclude these patient from referral to the ED. Symptoms, history nor risk factors exclude patients sufficiently to dismiss ACS. GPs are thus in need of tools for the triage of chest pain patients.

REFERENCES

1. Mehta RH, Eagle KA. Missed diagnoses of acute coronary syndromes in the emergency room--continuing challenges. N Engl J Med. 2000;342(16):1207-10.
2. Pope JH, Aufderheide TP, Ruthazer R, Woolard RH, Feldman JA, Beshansky JR, et al. Missed diagnoses of acute cardiac ischemia in the emergency department. The New England journal of medicine. 2000;342(16):1163-70.
3. Bosner S, Becker A, Haasenritter J, Abu Hani M, Keller H, Sonnichsen AC, et al. Chest pain in primary care: epidemiology and pre-work-up probabilities. The European journal of general practice. 2009;15(3):141-6.
4. Ruddox V, Mathisen M, Otterstad JE. Prevalence and prognosis of non-specific chest pain among patients hospitalized for suspected acute coronary syndrome - a systematic literature search. BMC medicine. 2012;10:58.
5. O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Jr., Chung MK, de Lemos JA, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;127(4):e362-425.
6. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). European heart journal. 2017.
7. Giard RW. [Jurisprudence judging mistakes made during telephone triage]. Nederlands tijdschrift voor geneeskunde. 2009;153(8):364-7.
8. Willemsen R. Pijn op de borst. Huisarts & Wetenschap. 2015(7):58.
9. Eslick GD, Talley NJ. Non-cardiac chest pain: predictors of health care seeking, the types of health care professional consulted, work absenteeism and interruption of daily activities. Alimentary pharmacology & therapeutics. 2004;20(8):909-15.
10. Glombiewski JA, Rief W, Bosner S, Keller H, Martin A, Donner-Banzhoff N. The course of nonspecific chest pain in primary care: symptom persistence and health care usage. Archives of internal medicine. 2010;170(3):251-5.
11. Leise MD, Locke GR, 3rd, Dierkhising RA, Zinsmeister AR, Reeder GS, Talley NJ. Patients dismissed from the hospital with a diagnosis of noncardiac chest pain: cardiac outcomes and health care utilization. Mayo Clinic proceedings. 2010;85(4):323-30.
12. Eslick GD, Coulshed DS, Talley NJ. Review article: the burden of illness of non-cardiac chest pain. Alimentary pharmacology & therapeutics. 2002;16(7):1217-23.
13. Mourad G, Alwin J, Stromberg A, Jaarsma T. Societal costs of non-cardiac chest pain compared with ischemic heart disease--a longitudinal study. BMC health services research. 2013;13:403.
14. Mol KA, Rahel BM, Meeder JG, van Casteren BC, Doevendans PA, Cramer MJ. Delays in the treatment of patients with acute coronary syndrome: Focus on pre-hospital delays and non-ST-elevated myocardial infarction. International journal of cardiology. 2016;221:1061-6.
15. van Ierland Y, van Veen M, Huibers L, Giesen P, Moll HA. Validity of telephone and physical triage in emergency care: the Netherlands Triage System. Family practice. 2011;28(3):334-41.

16. van Veen M, Huibers, L., Giesen, P., Moll, H. A triage system for the emergency department and the general practitioner cooperative: a reliability and validity. 2009.

17. Birkhead JS. Time delays in provision of thrombolytic treatment in six district hospitals. Joint Audit Committee of the British Cardiac Society and a Cardiology Committee of Royal College of Physicians of London. BMJ. 1992;305(6851):445-8.

18. Rossdale M, Kemple T, Payne S, Calnan M, Greenwood R. An observational study of variation in GPs' out-of-hours emergency referrals. The British journal of general practice : the journal of the Royal College of General Practitioners. 2007;57(535):152-4.

19. Ingram JC, Calnan MW, Greenwood RJ, Kemple T, Payne S, Rossdale M. Risk taking in general practice: GP out-of-hours referrals to hospital. The British journal of general practice : the journal of the Royal College of General Practitioners. 2009;59(558):e16-24.

20. Weinstock MB, Weingart S, Orth F, VanFossen D, Kaide C, Anderson J, et al. Risk for Clinically Relevant Adverse Cardiac Events in Patients With Chest Pain at Hospital Admission. JAMA internal medicine. 2015;175(7):1207-12.

21. Aune E, Endresen K, Fox KA, Steen-Hansen JE, Roislien J, Hjelmesaeth J, et al. Effect of implementing routine early invasive strategy on one-year mortality in patients with acute myocardial infarction. The American journal of cardiology. 2010;105(1):36-42.

22. Ravn-Fischer A, Karlsson T, Santos M, Bergman B, Johanson P, Herlitz J. Chain of care in chest pain--differences between three hospitals in an urban area. International journal of cardiology. 2013;166(2):440-7.

23. Ruigomez A, Masso-Gonzalez EL, Johansson S, Wallander MA, Garcia-Rodriguez LA. Chest pain without established ischaemic heart disease in primary care patients: associated comorbidities and mortality. The British journal of general practice : the journal of the Royal College of General Practitioners. 2009;59(560):e78-86.

24. Webster R, Norman P, Goodacre S, Thompson A. The prevalence and correlates of psychological outcomes in patients with acute non-cardiac chest pain: a systematic review. Emergency medicine journal : EMJ. 2012;29(4):267-73.

25. Willemsen RT, Kietselaer BL, Kusters R, Buntinx F, Dinant GJ. [Diagnostic tools for acute coronary syndrome (ACS): a challenge for general practitioners and cardiologists]. Nederlands tijdschrift voor geneeskunde. 2014;158:A8078.

26. Marshall GA, Wijeratne NG, Thomas D. Should general practitioners order troponin tests? The Medical journal of Australia. 2014;201(3):155-7.

27. Backus BE, Six AJ, Kelder JC, Mast TP, van den Akker F, Mast EG, et al. Chest pain in the emergency room: a multicenter validation of the HEART Score. Critical pathways in cardiology. 2010;9(3):164-9.

28. Ishak M, Ali D, Fokkert MJ, Slingerland RJ, Tolsma RT, Badings E, et al. Fast assessment and management of chest pain patients without ST-elevation in the pre-hospital gateway (FamouS Triage): ruling out a myocardial infarction at home with the modified HEART score. European heart journal Acute cardiovascular care. 2017:2048872616687116.

29. Andersson PO, Karlsson JE, Landberg E, Festin K, Nilsson S. Consequences of high-sensitivity troponin T testing applied in a primary care population with chest pain compared with a commercially available point-of-care troponin T analysis: an observational prospective study. BMC research notes. 2015;8:210.

30. Bandstein N, Ljung R, Holzmann MJ. Risk of revisits to the emergency department in admitted versus discharged patients with chest pain but without myocardial infarction in relation to high-sensitivity cardiac troponin T levels. International journal of cardiology. 2016;203:341-6.

31. Nilsson S, Andersson A, Janzon M, Karlsson JE, Levin LA. Cost consequences of point-of-care troponin T testing in a Swedish primary health care setting. Scand J Prim Health Care. 2014;32(4):241-7.

Chapter 7

Non-cardiac chest pain: Prognosis and secondary health care utilisation

Accepted by Open Heart

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ABSTRACT

Objective

Presentations of non-cardiac chest pain (NCCP) to the emergency department (ED) is increasing. More knowledge of prognosis and health care utilisation of NCCP patients is necessary to optimize their management.

Methods

This study is a prospective, observational, prevalence-based cohort study conducted from September 2015 to February 2016 with one-year follow-up including all patients 18 years and older referred to the ED with chest pain. Discharge diagnoses, mortality, major adverse cardiac events (MACE), re-presentations to the ED, hospitalisations, cardiac interventions and out-patient monitoring were assessed.

Results

More than 60% of the 1239 patients presenting with chest pain were discharged with NCCP. The all-cause one-year mortality rate of NCCP patients was 2.3% compared to 7.2% in cardiac chest pain (CCP) patients ($p<0.001$) and the occurrence of MACE was 5.1% versus 8.3% respectively ($p=0.026$). Previous history of coronary artery disease (CAD) in NCCP patients was identified as a predictive factor for MACE (OR 4.30 [95% CI 1.24-14.89], $p=0.021$). NCCP patients had more non-invasive interventions than CCP patients (proportion of 0.225 vs 0.165 per patient, $p<0.001$) and 13.7% of NCCP patients re-presented at the ED within one year.

Conclusion

The majority of patients referred to the ED with chest pain are discharged with NCCP. The prognosis of NCCP patients is better than CCP patients, however they are at risk for MACE due to a history of CAD. NCCP patients moreover utilise a substantial amount of medical resources, stressing the importance of good triage to minimize unnecessary health care utilisation while still preventing MACE.

INTRODUCTION

Non-cardiac chest pain (NCCP) has grown in clinical significance both in primary and secondary health care. There has been an increase in admissions with NCCP over the past decades, whereas the amount of presentations with acute coronary syndrome (ACS) has decreased.[1] Population based studies have estimated the prevalence of NCCP to range between 23-33%[1, 2], accounting for 2-5% of all emergency presentations and more than 50% of all chest pain cases presenting at the emergency department (ED).[1, 3] Due to the heterogeneous nature of the condition, diagnosing the underlying cause of NCCP is challenging.[1, 4, 5] NCCP is defined as chest pain not attributed to underlying ischemic heart disease and may be of gastro-intestinal, musculoskeletal, respiratory, or psychological origin.[1, 3, 4, 6] Moreover, there may be an overlap in the underlying conditions causing NCCP.[1] As a consequence of these diagnostic challenges, the cost of NCCP has increased tremendously.[1] In addition, there is a considerable persistence of symptoms resulting in continued utilisation of medical resources, with signs of over-investigation in every tenth patient with persisting chest pain, despite the good prognosis.[1, 7]

The primary aim of this study is to gain insight into the prognosis of NCCP patients presenting at the emergency department (ED) compared to patients with cardiac chest pain (CCP), in terms of mortality and occurrence of major adverse cardiac events (MACE). Secondly, the study aims to identify baseline variables in NCCP patients that increase the risk for developing a MACE. Finally, it provides an overview of the utilisation of secondary health care at the cardiology department by patients with chest pain. These insights will contribute to the optimal management of patients with NCCP.

METHODS

Study design

This study is a prospective, observational, prevalence-based cohort study conducted from the 1st of September 2015 to the 28th of February 2016 with a year follow-up until the 28th of February 2017.

Study sample and setting

All patients 18 years or older with chest pain who were referred to the ED suspected of ACS were included in this study. This included all patients with non-traumatic chest pain and other symptoms that can rise the suspicion of ACS. This study investigated patients referred from outside the hospital and thus excluded patients referred by specialists. The ED is located at Vie-Curi Medical Centre, a medium sized teaching hospital and an off-site percutaneous coronary intervention (PCI) centre in the Netherlands.

Data collection

Data was collected by the attending physician and retrieved through medical files. A questionnaire was given to patients with additional questions not readily available in the medical files to minimize missing data. Collected data included demographics, history, symptoms, medication, discharge diagnosis made by the attending physician, mortality, occurrence of MACE, re-presentations at the ED, hospitalisations and cardiac interventions.

Ethical approval was waived by medical ethical review commission Utrecht, protocol number 15/382.

Data analysis

Statistical analyses were performed using IBM SPSS version 24. Descriptive statistics are summarized as proportions for categorical variables and mean with standard deviation (SD) for continuous variables. Comparison between patients with NCCP and CCP were performed using the Students-*t*-test, Mann Whitney *U* test or chi-square test, as appropriate. Possible factors in the NCCP subset related to the occurrence of MACE were investigated using logistic regression analysis. Factors with a p-value <0.10 in univariate models were considered for further investigation by means of a multivariate model and expressed as odds ratios (ORs) and 95% confidence intervals (CIs). A *p*-value <0.05 was considered to be statistically significant. Patients with missing values were included, with exception of their missing values.

Definitions

Patients with CCP included patients with ACS and non-ischaemic heart disease. ACS was subdivided as ST-elevation myocardial infarction (STEMI), non-STEMI (NSTEMI), or unstable AP (UAP).[8] Non-ischaemic heart disease included (myo-) pericarditis, heart rhythm problems, valvular disease and cardiomyopathies.

NCCP was defined as chest pain not attributed to underlying (ischemic) heart disease and subdivided in NCCP of known origin (NCCP-K) and NCCP of unknown origin (NCCP-U). NCCP-K comprised of patients who were discharged from the index admission with a non-cardiac diagnosis for their chest pain. This group included severe conditions such as pneumonia, pulmonary embolism, pneumothorax, aortic dissection and severe gastro-intestinal disorders, but also benign conditions such as gastroesophageal reflux disease, musculoskeletal disorders and psychological disorders. NCCP-U are patients who were discharged with chest pain not otherwise specified.

MACE included any STEMI, NSTEMI, UAP, PCI and coronary artery bypass grafting (CABG) after discharge. An ACS diagnosis and its corresponding treatment at initial admission was not considered a MACE.[8]

RESULTS

During the study period 1322 patients, with a total of 1469 presentations, were referred to the ED with suspected ACS. Patients referred by specialists (n=66) and patients who were referred with an out-of-hospital cardiac arrest (n=17) were excluded from further analysis. There were 25 patients loss to follow-up due to them not living in the Netherlands or due to an unknown GP. GPs referred 1001 (80.8%) patients and the remaining 238 (19.2%) patients were referred by EMT or were self-referrals. CCP was diagnosed in 490 (39.5%) patients and NCCP in 749 (60.5%) patients. Further differentiations are shown in Figure 1.

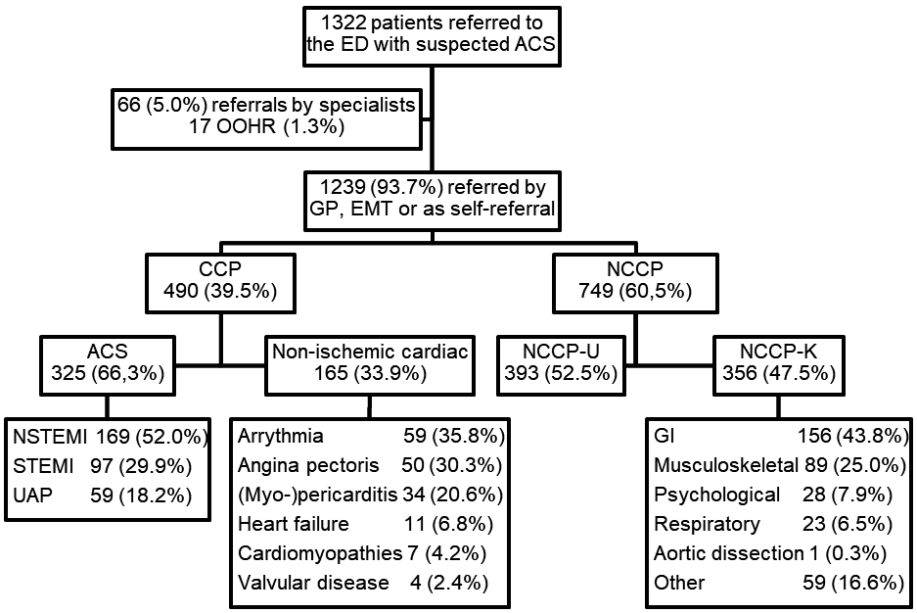

Figure 1. Study flow chart and diagnosis at discharge from ED

ED: emergency department, ACS: acute coronary syndrome, GP: general practitioner, EMT: emergency medical transport, CCP: cardiac chest pain, NCCP: non-CCP, ACS: NCCP-K: NCCP of known origin, NCCP-U: NCCP of unknown origin, STEMI: ST-elevated myocardial infarction, NSTEMI: non-STEMI, UAP: unstable angina pectoris, GI: gastro-intestinal disorders

Baseline characteristics

Characteristics at baseline differed between the NCCP and CCP/ACS patients in mean age (60.6 vs 66.1/66.6 years, p<0.001/p<0.001), male gender (45.3% vs 66.5/66.8%, p<0.001/p<0.001) and history of hypercholesterolemia (39.3% vs 47.6/49.1%, p=0.004/p=0.003). Baseline differences between NCCP and CCP patients (but not ACS patients) were seen for cardiovascular disease (CVD) (42.9% vs 48.6, p=0.048) and coronary artery disease (CAD) (29.1% vs 35.8%, p=0.014) (Table 1). The NCCP-K and NCCP-U subsets did not differ in baseline characteristics, with the exception of history of CVD (37.4% vs 47.8%, p=0.004) and CAD (23.9% vs 33.9%, p=0.003), which were both more prevalent in the NCCP-U subset.

Table 1. Patient demographics

	Diagnosis at discharge					*P-value*		
	CCP[a] (N=490)	ACS (N=325)	NCCP[b] (N=749)	NCCP-K (N=356)	NCCP-U (N=393)	CCP vs NCCP	ACS vs NCCP	NCCP-K vs NCCP-U
Age, yrs (SD)	66.1 (14.1)	66.6 (12.9)	60.6 (15.5)	60.3 (16.0)	60.8 (15.1)	<0.001	<0.001	0.681
Male, n(%)	315 (66.5)	217 (66.8)	339 (45.3)	159 (44.7)	180 (45.8)	<0.001	<0.001	0.755
Caucasian, n(%)	464 (94.9)	305 (94.1)	709 (94.8)	341 (96.1)	368 (93.6)	0.937	0.666	0.137
DM, n(%)	90 (18.4)	56 (17.2)	113 (15.1)	54 (15.2)	59 (15.1)	0.130	0.380	0.964
HC, n(%)	232 (47.6)	159 (49.1)	292 (39.3)	128 (36.4)	164 (41.9)	0.004	0.003	0.120
BMI >25, n(%)	318 (65.8)	214 (66.9)	479 (65.9)	220 (64.3)	259 (67.3)	0.986	0.756	0.403
Hyperten-sion, n(%)	231 (47.1)	153 (47.1)	322 (43.0)	150 (42.3)	172 (43.8)	0.156	0.222	0.677
Smoking, n(%)	172 (36.2)	124 (39.5)	251 (34.3)	108 (31.2)	143 (37.1)	0.505	0.111	0.092
Family history of CVD, (%)	178 (38.7)	125 (40.1)	255 (37.5)	118 (36.5)	137 (38.4)	0.683	0.440	0.620
History of CVD, n(%)	238 (48.6)	148 (45.5)	321 (42.9)	133 (37.4)	188 (47.8)	0.048	0.416	0.004
History of CAD, n(%)	175 (35.8)	108 (33.2)	218 (29.1)	85 (23.9)	133 (33.9)	0.014	0.181	0.003
History of renal disease, n(%)	2 (0.4)	1 (0.3)	2 (0.3)	0 (0)	2 (0.5)	0.668	0.909	0.177

CCP: cardiac chest pain, ACS: acute coronary syndrome, NCCP: non-CCP, NCCP-K: NCCP of known origin, NCCP-U: NCCP of unknown origin, DM: diabetes mellitus, HC: hypercholesterolemia, BMI: body mass index, CVD: cardiovascular disease, CAD: coronary artery disease, SD: standard deviation

[a] CCP group includes ACS patients

[b] NCCP group is a sum of the patients of the NCCP-K and NCCP-U groups

Changes in discharge diagnosis during one year follow-up

A number of the initial diagnoses were revised within the one year follow-up. In the ACS patients, all STEMI and NSTEMI diagnoses remained unchanged, whereas 74.6% of the UAP diagnoses remained the same. In the latter group 9 (15.2%) patients received a diagnosis of non-ischaemic heart disease, and 6 (10.2%) diagnoses became NCCP-K. In the group of patients with chest pain caused by non-ischaemic heart disease 145 (88.0%) diagnoses remained unchanged, the remaining cases were adjusted into ACS (0.6%), NCCP-K (1.2%) and NCCP-U (10.2%). In the NCCP-K group 6 (1.7%) diagnoses were adjusted into non-ischaemic heart disease and 136 (38.2%) diagnoses into NCCP-U, when all other diagnoses were excluded. The remaining 215 (60.4%) diagnoses remained NCCP-K .

The majority of the NCCP-U diagnoses, namely 336 (85.5%), remained unchanged. Of the remaining patients, 2 (0.5%) diagnoses were adjusted into UAP, 31 (7.9%) into non-ischaemic heart disease, and 24 (6.1%) into NCCP-K.

Prognosis

A total of 52 patients died during the follow-up of one year. Kaplan-Meier survival plots are presented in Figure 2 and mortality rates per group are summarized in Table 2.

CCP patients had a one year mortality rate of 7.2% and ACS patients of 8.1%, both higher compared to the NCCP group with a one year mortality rate of 2.3% (p<0.001).

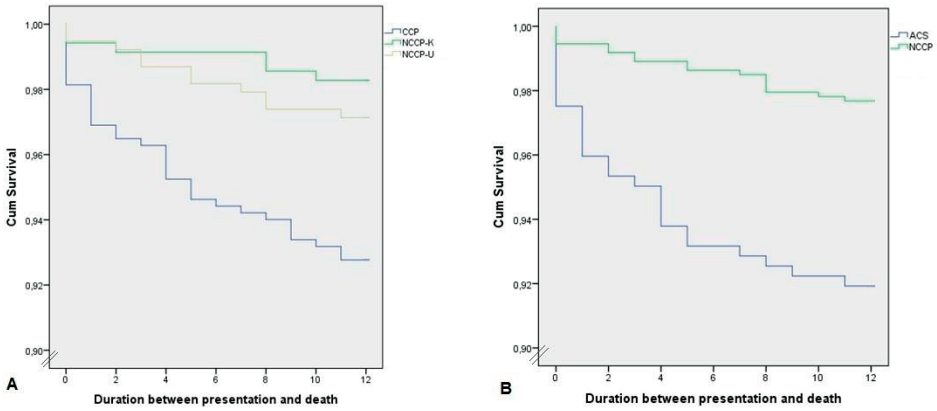

Figure 2. Overall survival

A: Survival in cardiac chest pain (CCP) group compared to non-CCP (NCCP) of known (K) and unknown (U) origin; CCP vs NCCP p<0.001 (log-rank test); NCCP-K vs NCCP-U p=0.41 (log-rank test). B: Survival in the acute coronary syndrome (ACS) group compared to the NCCP group; P<0.001 (log-rank test)

Table 2. Mortality rate

	Diagnosis at discharge					P-value		
	CCP[a] (N= 490)	ACS (N= 325)	NCCP[b] (N= 749)	NCCP-K (N= 356)	NCCP-U (N= 393)	CCP vs NCCP	ACS vs NCCP	NCCP-K vs NCCP-U
In hospital mortality rate, n(%)	10 (2.0)	9 (2.8)	4 (0.5)	2 (0.6)	2 (0.5)	0.014	0.002	0.921
6 Month mortality rate, n(%)[c]	27 (5.6)	22 (6.8)	10 (1.4)	3 (0.9)	7 (1.8)	<0.001	<0.001	0.263
1 Year mortality rate, n(%)[c]	35 (7.2)	26 (8.1)	17 (2.3)	6 (1.7)	11 (2.9)	<0.001	<0.001	0.306

CCP: cardiac chest pain, NCCP: Non-CCP, ACS: acute coronary syndrome, NCCP-K: NCCP of known origin, NCCP-U: NCCP of unknown origin

[a] CCP group includes ACS patients

[b] NCCP group is a sum of the patients of the NCCP-K and NCCP-U groups

[c] 7, 6, 9, and 9 patients loss of follow-up in the CCP, ACS, NCCP-K and NCCP-U groups respectively

The occurrence of MACE during follow-up was higher in the CCP and ACS groups compared to the NCCP group (8.3% and 8.7% vs 5.1% respectively, p=0.026) as portrayed in Table 3. There was no difference between NCCP-K and NCCP-U subsets in the occurrence of MACE, except for the incidence of UAP which was more frequent in the NCCP-U subset (0.0% vs 1.3%, p=0.04). We also analysed the effect of a known history of CAD in the NCCP-U subset. The most striking difference was found in the occurrence of MACE (15.3% with known CAD vs 1.6% without, p<0.001). This was also seen when comparing patient with known CVD and without CVD (occurrence of MACE in 10.8% vs 2.0%, p<0.001). The mortality did not differ in NCCP-U patients with or without CAD or CVD.

Possible predictors for the occurrence of MACE in the NCCP group were analysed. After correction for possible confounders, we identified one predictor, namely a history of CAD (OR 4.30 [95% CI 1.24-14.89], p=0.021) as shown in Table 4.

Table 3. Major adverse cardiac events during one year follow-up

	Diagnosis at discharge					P-value		
	CCP[a] (N= 471)[c]	ACS (N= 310)[c]	NCCP[b] (N= 729)[c]	NCCP-K (N= 345)[c]	NCCP-U (N= 383)[c]	CCP vs NCCP	ACS vs NCCP	NCCP-K vs NCCP-U
MACE, n(%)	39 (8.3)	27 (8.7)	37 (5.1)	13 (3.8)	24 (6.3)	0.026	0.026	0.123
STEMI, n(%)	15 (3.2)	12 (3.9)	19 (2.6)	8 (2.3)	11 (2.9)	0.555	0.273	0.636
NSTEMI, n(%)	15 (3.2)	8 (2.6)	12 (1.6)	5 (1.4)	7 (1.8)	0.079	0.316	0.685
UAP, n(%)	8 (1.7)	6 (1.9)	5 (0.7)	0 (0)	5 (1.3)	0.098	0.072	0.033
CABG or PCI, n(%)	12 (2.5)	9 (2.9)	16 (2.2)	7 (2.0)	9 (2.3)	0.692	0.495	0.764

MACE: Major adverse cardiac events defined as a combinations of the following: STEMI: ST-elevation myocardial infarction, NSTEMI: non-STEMI, UAP: unstable angina pectoris, CABG: coronary artery bypass graft, PCI: percutaneous coronary intervention, CCP: cardiac chest pain, NCCP: non-CCP, NCCP-K: NCCP of known origin, NCCP-U: non-cardiac chest pain group of unknown origin (NCCP-U).

[a] CCP group includes ACS patients

[b] NCCP group is a sum of NCCP-K and NCCP-U patients

[c] Exclusion of 19, 15, 20, 10, and 10 patients from analysis in the CCP, ACS, NCCP, NCCP-K and NCCP-U groups respectively; in total 25 due to loss-to-follow-up and 14 due to in-hospital death.

Utilisation of secondary health care in the cardiology department

Table 5 shows the utilisation of secondary health care in the cardiology department during the one-year follow-up after discharge from the index admission. CCP patients had a higher utilisation of medical resources compared to NCCP patients. The duration of rehospitalisation of NCCP patients at the cardiology department was however similar to that of CCP patients and a proportion of 13.7% of NCCP patients re-presented at the ED.

Patients of the NCCP-U subset had a longer duration of hospitalisation, more re-presentations at the ED, more rehospitalisation, more out-patient department visits, more consultations by phone and a longer out-patient department monitoring than the NCCP-K subset.

Table 4. Predictors for occurrence of major adverse cardiac events within one year in the non-cardiac chest pain group

	Univariate analysis			*Multivariate analysis*		
	OR	95% CI	P value	OR	95% CI	P value
Age (per year)	1.01	0.99-1.04	0.229			
Male gender	1.59	0.81-3.12	0.178			
Caucasian race	1.87	0.25-14.00	0.545			
Diabetes Mellitus	1.93	0.88-4.22	0.100			
Hypercholesterolemia	2.85	1.42-5.72	0.003	1.16	0.52-2.56	0.719
BMI >25	1.13	0.54-2.34	0.752			
Hypertension	2.76	1.36-5.60	0.005	1.85	0.85-4.02	0.123
Smoking	1.28	0.64-2.54	0.489			
Family history of CVD	2.20	1.12-4.33	0.023	1.59	0.78-3.24	0.200

Table 4. Predictors for occurrence of major adverse cardiac events within one year in the non-cardiac chest pain group (continued)

	Univariate analysis			*Multivariate analysis*		
	OR	95% CI	P value	OR	95% CI	P value
History of CVD	7.07	2.91-17.22	<0.001	1.96	0,47-8.11	0.354
History of CAD	8.04	3.71-17.42	<0.001	4.30	1.24-14.89	0.021
History of renal disease	0.00	0.00-0.00	0.99			

BMI: body mass index, CVD: cardiovascular disease, CAD: coronary artery disease.

Table 5. Utilisation of secondary health care at the cardiology department during one year

	Diagnosis at discharge					P-value		
	CCP[a] (N= 484)[c]	ACS (N= 322)[c]	NCCP[b] (N= 732)[c]	NCCP-K (N= 347)[c]	NCCP-U (N= 384)[c]	CCP vs NCCP	ACS vs NCCP	NCCP-K vs NCCP-U
Re-presentations, n(SD)	0.43 (0.85)	0.44 (0.85)	0.23 (0.72)	0.18 (0.68)	0.27 (0.75)	<0.001	<0.001	0.013
Re-presentations of patients with re-presentations, n(SD)[d]	1.53[e] (0.93)	1.55[e] (0.906)	1.67[e] (1.16)	1.72[e] (1.34)	1.64[e] (1.06)	0.628	0.918	0.960
Hospitalisations, n(SD)	1.02 (0.78)	1.21 (0.713)	0.23 (0.57)	0.17 (0.46)	0.30 (0.65)	<0.001	<0.001	0.001
Duration of hospitalisation, hours(SD)	142.56 (165.30)	148.32 (165.99)	72.75 (127.82)	74.64 (73.24)	71.76 (148.76)	<0.001	<0.001	0.157
Re-hospitalisations, n (SD)	0.32 (0.65)	0.34 (0.66)	0.13 (0.46)	0.09 (0.35)	0.17 (0.54)	<0.001	<0.001	0.024
Duration of re-hospitalisations, hours(SD)	109.18 (213.44)	102.61 (213.36)	112.43 (229.11)	34.80 (21.25)	155.60 (278.60)	0.582	0.697	0.312
Duration of out-patient department monitoring, days(SD)	311.42 (120.37)	329.50 (102.14)	159.78 (167.56)	134.78 (163.65)	182.41 (168.05)	<0.001	<0.001	<0.001
Out-patient department visits, n(SD)	1.91 (1.07)	1.98 (1.07)	1.05 (1.05)	0.90 (1.01)	1.19 (1.07)	<0.001	<0.001	<0.001
Consultations by phone, n(SD)	0.14 (0.46)	0.12 (0.39)	0.12 (0.52)	0.09 (0.55)	0.14 (0.48)	0.123	0.357	0.035

CCP: cardiac chest pain, NCCP: non-CCP, NCCP-K: NCCP of known origin, NCCP-U of unknown origin, Re-presentations: average number of re-presentations per patient, Re-presentations excluding: average number of re-presentations per patient, excluding patients without re-presentations, SD: standard deviation

[a] CCP includes ACS patients

[b] NCCP group is a sum of NCCP-K and NCCP-U patients

[c] 7, 6, 9, and 9 loss of follow-up in the CCP, ACS, NCCP-K and NCCP-U groups respectively

[d] Excludes patients without re-presentations

[e] n=136, 28.0%; n=92, 28.6%; n=100, 13.7%; n=36, 10.4%; n=64, 16.7% in the CCP, ACS, NCCP-K and NCCP-U groups respectively

Table 6. Diagnostic and treatment interventions performed during first admission and during one year of follow-up

	CCP[a] (N= 490)[c]	*ACS (N= 325)[c]*	*NCCP[b] (N= 749)[c]*	*NCCP-K (N= 356)[c]*	*NCCP-U (N= 393)[c]*	*CCP vs NCCP*	*ACS vs NCCP*	*NCCP-K vs NCCP-U*
CABG/PCI n (prop)[d]	293 (0.598)	280 (0.862)	35 (0.047)	9 (0.025)	26 (0.066)	<0.001	<0.001	0.008
CAG/FFR, n (prop)[d]	123 (0.251)	71 (0.218)	89 (0.119)	26 (0.073)	63 (0.160)	<0.001	<0.001	<0.001
Non-invasive imaging, n (prop)[d]	81 (0.165)	38 (0.117)	217 (0.290)	80 (0.225)	137 (0.349)	<0.001	<0.001	<0.001
Referral to other specialism n (prop)[d]	1 (0.002)	1 (0.003)	47 (0.063)	42 (0.118)	5 (0.013)	<0.001	<0.001	<0.001
No inter-vention, n (%)[e]	121 (24.7)	31 (9.5)	296 (39.5)	130 (36.5)	166 (42.2)	<0.001	<0.001	0.110

CCP: cardiac chest pain, ACS: acute coronary syndrome, NCCP; non-cardiac chest pain, NCCP-K: NCCP of known origin, NCCP-U: NCCP of unknown origin, CABG: coronary artery bypass graft, PCI: percutaneous coronary intervention, prop: proportion, CAG: coronary angiography without PCI intervention, FFR: functional flow reserve without PCI intervention, Non-invasive imaging included computed tomography scans, single photon emission computed tomography scans, and magnetic resonance imaging.

[a] CCP includes ACS patients

[b] NCCP group is a sum of NCCP-K and NCCP-U patients

[c] 7, 6, 9, and 9 loss of follow-up in the CCP, ACS, NCCP-K and NCCP-U groups respectively

[d] Some patients had more than one intervention, thus proportion of interventions is given

[e] Patients with no intervention, thus percentage over group is given

Cardiac Interventions

We analysed the amount of interventions performed within the patient groups (Table 6). We present proportions as some patients have undergone more than one intervention within the follow-up period. CCP patients and in particular ACS patients underwent more PCIs or CABG (0.598/0.862 vs 0.047, p<0.001/p<0.001) and more CAG without intervention (0.251/0.218 vs 0.119, p<0.001/p<0.001) than NCCP patients. NCCP patients and in particular NCCP-U patients, underwent more non-invasive interventions such as CT-scans, SPECT or MRI's (0.165 in CCP group vs 0.290 in NCCP group, p<0.001 and 0.349 in NCCP-U group, p<0.001). The NCCP group was the group with the most patients without any intervention (24.7% in CCP group, 39.5% in NCCP group, p<0.001).

DISCUSSION

Prognosis

The majority of the patients (60.5%) referred to the ED with chest pain are discharged with NCCP. The prognosis of NCCP patients is better in terms of survival (one-year mortality of 2.3% vs 7.2% and 8.1% respectively, p<0.001) and occurrence of MACE (5.1% vs 8.3% and 8.7% respectively, p=0.026) compared to CCP and ACS groups. Previous studies showed similar results with one-year mortality rates ranging from 1.4-4.2% for NCCP patients and 14-19.9% for ACS

patients.[4] Our reported one-year mortality rate in the ACS group was lower than earlier studies, which may be related to the introduction of new sensitive markers combined with the more sensitive assays for troponins allowing more accurate diagnosis and earlier treatment of ACS.[4] The mortality of the NCCP, of known and unknown origin, patients is comparable to the mortality of the general population, however the occurrence of MACE in the NCCP, and in particular the NCCP-U patients is considerably high, namely 5.1% and 6.3% respectively in one year. Moreover despite the lower occurrence of MACE in the NCCP group, the amount of STEMIs, NSTEMIs, UAP, and even PCIs or CABG was not statistically significantly lower compared to the CCP group, though this could be due to the low incidence. The relatively high MACE in NCCP patients may be a consequence of the overlapping cardiovascular risk factors at baseline in the NCCP and CCP groups. A history of CAD was identified as a predictive factor for the occurrence of MACE in the NCCP patients. We also found that patients with NCCP-U with a history of CAD (or CVD) had a higher risk of developing a MACE in the follow-up. This is in line with previously reported findings by Ruddox et al,[4] wherein it was stated that the prognosis of NCCP patients is not necessarily benign due to the pre-existing CAD in approximately 40% of these patients. These findings suggest that patients with chest pain and a history of CAD should be monitored closely and might benefit more from a follow-up to prevent frequent re-presentations, re-hospitalisations and MACE.

Consultations and interventions

NCCP patients did not exceed the amount of visits for medical care compared to patients with ischaemic heart disease. In the organization of the Dutch health care system general practitioners (GPs) also play an important role in the management of NCCP and thereby decrease the health care utilisation in secondary health care. Health care utilisation in the primary health care setting was not included in this study.

NCCP patients, in particular the NCCP-U patients, do utilise a substantial amount of medical resources at the cardiology department. The mean amount of re-presentations at the ED, duration of out-patient department monitoring and visits to the cardiologist of NCCP-U patients exceeds that of NCCP-K patients. Moreover the amount of cardiac interventions including PCI, CABG, CAG and non-invasive imaging are also higher in the NCCP-U vs the NCCP-K group. It is believed that a lack of explanation for their symptoms may lead to psychological distress which drives patients with NCCP-U to seek medical advice,[3] whereas patients who are given a specific diagnosis for their chest pain utilise less health care.[6] The higher amount of PCI in the NCCP group may be due to incidental findings of coronary artery stenosis that is not related to the chest pain complaints. In the process, NCCP patients are exposed to risk and stress by unnecessary referral or admission to the hospital and the consequential interventions, posing a psychological burden on them as well as their families.[9, 10] In order to combat the issues of overcrowding at the ED, the costs of health care, and the exposure of patients to unnecessary

hospital admissions and diagnostics, it is important to improve triage and follow-up of patients with chest pain.[9]

Strengths and limitations

All patients 18 years and older with chest pain referred from primary health care were included in this study, making it an unselected study population with a good representation of daily practice at the ED. However, this may result in a rather heterogeneous study population.

Furthermore, the study was a single-centre study and set at the ED, making it vulnerable for selection bias, with patients mostly referred after contact with a GP. In the Netherlands GPs have a gatekeeper role and patients are advised to initially consult their GP for most symptoms. Therefore, the patients that are referred to the ED are more likely to have cardiovascular risk factors and prior history of CAD. As a consequence, our study population may have had a higher occurrence of MACE than the general population and patients in primary health care and even than in countries without GPs as gate keepers.

This single-centre study did include all patients referred from the region. A selection bias through expertise of the centre was not a factor.

CONCLUSION

The majority of patients referred to the ED with chest pain are discharged with a non-cardiac diagnosis. The prognosis in NCCP patients is better than CCP patients, however they are nevertheless at risk for the occurrence of MACE due to the presence of cardiovascular risk factors and prior history of CAD at baseline. NCCP, and in particular NCCP-U, patients moreover utilise a substantial amount of medical resources. Triage during the first presentation with chest pain should be improved to minimize unnecessary hospital admissions and the consequential health care utilisation of NCCP patients while still preventing MACE.

REFERENCES

1. Eslick G, Coulshed D, Talley N. The burden of illness of non-cardiac chest pain. Alimentary pharmacology & therapeutics. 2002;16(7):1217-23.
2. Eslick G, Jones MP, Talley N. Non-cardiac chest pain: prevalence, risk factors, impact and consulting—a population-based study. Alimentary pharmacology & therapeutics. 2003;17(9):1115-24.
3. Mourad G, Alwin J, Strömberg A, Jaarsma T. Societal costs of non-cardiac chest pain compared with ischemic heart disease-a longitudinal study. BMC health services research. 2013;13(1):403.
4. Ruddox V, Mathisen M, Otterstad JE. Prevalence and prognosis of non-specific chest pain among patients hospitalized for suspected acute coronary syndrome-a systematic literature search. BMC medicine. 2012;10(1):58.
5. Ruigómez A, Massó-González EL, Johansson S, Wallander M-A, García-Rodríguez LA. Chest pain without established ischaemic heart disease in primary care patients: associated comorbidities and mortality. Br J Gen Pract. 2009;59(560):e78-e86.
6. Leise MD, Locke GR, Dierkhising RA, Zinsmeister AR, Reeder GS, Talley NJ, editors. Patients dismissed from the hospital with a diagnosis of noncardiac chest pain: cardiac outcomes and health care utilization. Mayo Clinic Proceedings; 2010: Elsevier.
7. Glombiewski JA, Rief W, Bösner S, Keller H, Martin A, Donner-Banzhoff N. The course of nonspecific chest pain in primary care: symptom persistence and health care usage. Archives of internal medicine. 2010;170(3):251-5.
8. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). European heart journal. 2015.
9. Mol K, Rahel B, Meeder J, van Casteren B, Doevendans P, Cramer M. Delays in the treatment of patients with acute coronary syndrome: Focus on pre-hospital delays and non-ST-elevated myocardial infarction. International journal of cardiology. 2016;221:1061-6.
10. Webster R, Norman P, Goodacre S, Thompson A. The prevalence and correlates of psychological outcomes in patients with acute non-cardiac chest pain: a systematic review. Emerg Med J. 2011:emermed-2011-200526.

Chapter 8

A prospective cohort study to improve the AccUracy of Referrals to the emerGency departmEnt of patieNts with chesT pain: to decrease the delay in acute coronary syndrome patients and rule out non-cardiac chest pain patients (URGENT):

Feasibility study

Submitted

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ABSTRACT

Background

The challenge for general practitioners (GPs) to refer chest pain patients with acute coronary syndrome (ACS) and rule out non-cardiac chest pain in a timely manner is considerable. The primary objective is to refer chest pain patients more promptly and accurately to the emergency department.

Methods

This study is a prospective, observational, prevalence based, cohort. GPs evaluated low to intermediate risk patients with the HEART score at the GP cooperation (GPC). The accuracy of the URGENT trial was intended to be analysed by comparison to a baseline registry of referred patients and aspired to include 175 patients. After six months the Philips Minicare, the troponin tester used in this trial, was taken off the market. This was due to financial issues, with no reflection on safety. Therefore, we present the first 40 patients as a pilot study.

Results

Of the 40 patients included within the URGENT trial, 23 (62.2%) patients had low HEART scores and were not referred. None of these patients developed major adverse cardiac events in the six week follow-up. Four patients were, in spite of HEART scores higher than 3, not referred (protocol violation). One of these patients has ACS in follow-up. The referred patients were diagnosed with ACS, angina pectoris, (myo-)pericarditis and non-cardiac diagnoses.

Conclusion

The URGENT trial pilot data suggests that use of the HEART score at the GPC is safe and feasible. This trial should be expanded to prove the efficacy and further support GPs in the triage of chest pain patients.

INTRODUCTION

Chest pain is a common symptom among patients contacting the primary care physician.[1] Acute coronary syndrome (ACS) with its inherent high risk is only one of the more than forty diagnoses that can cause chest pain.[1] Diagnosing a patient with ACS among this group is therefore a great challenge for general practitioners (GPs). Patients with ACS should be referred promptly to the hospital to reduce mortality and morbidity.[2, 3] Referring all patients with chest pain to the emergency department (ED), is not feasible as up to 80% of the patients with chest pain in the primary care do not have ACS.[4] Patients with non-cardiac chest pain (NCCP) have a low mortality, only slightly higher than the mortality of the general population.[5] Referring these patients to the ED induces great stress on the patients and their families as well as on the ED.[6] Moreover, patients unnecessarily referred to the hospital have an increased risk of adverse events contributed to unnecessary diagnostics and are more likely to re-present at the ED.[7]

Symptoms, history, risk factors and even electrocardiograms (ECGs) can not differentiate ACS from NCCP adequately.[8, 9] Troponin testing in the primary health care is not recommended, due to logistics.[10] GPs are thus in need of an efficient way to exclude low risk patients.[11]

The HEART score has been validated to exclude low risk patients at the ED, and in a modified version, within the emergency medical transport (EMT).[12, 13] It uses history, ECG, age, risk factors and troponin testing within two hours to differentiate between patients with a low, intermediate or high risk of a cardiac event.[12] Recently available point-of-care (POC) testers boast a minimal wait for accurate troponin testing, an asset for GPs.[14]

In this study we investigated the feasibility of the HEART score combined with a POC troponin tester to exclude low risk patients from referral to the ED by GPs.

METHODS

The URGENT trial was designed as a prospective, observational, prevalence based, cohort study aiming to accurately triage patients for referral to the ED. The primary objective was to be achieved by training triage nurses at the out-of-hours GP cooperation (GPC) and assisting the GPs at the GPC with the HEART score, using a point-of care (POC) troponin tester, the Philips Minicare cardiac troponin-I (cTnI) (Table 1 and Figure 1).

Six months after the start of the trial, the Philips Minicare cTnI was taken off the market. This was due to financial issues of the company, with no reflection on the safety of the Minicare or the URGENT trial. Therefore, we present the first 40 patients included within the URGENT trial as a pilot study.

The URGENT pilot has a follow-up of six weeks to detect the occurrence of any major adverse cardiac event (MACE), defined as any ACS, percutaneous coronary intervention (PCI),

coronary artery bypass grafting or cardiac death. A six week follow-up has been chosen, as any MACE beyond six weeks, is not expected to be related to the index presentation.

Table 1. HEART score[12]

History (Anamnesis)	Highly suspicious	2	
	Moderately suspicious	1	
	Slightly suspicious	0	
ECG	Significant ST-deviation	2	
	Non-specific repolarisation disturbance / LBBB / PM	1	
	Normal	0	
Age	≥ 65 years	2	
	45 – 65 years	1	
	≤ 45 years	0	
Risk factors	≥ 3 risk factors *or* history of atherosclerotic disease	2	
	1 or 2 risk factors	1	
	No risk factors known	0	
Troponin	≥ 3x normal limit	2	
	1-3x normal limit	1	
	≤ normal limit	0	
		Total	

Risk factors for atherosclerotic disease:

Hypercholesterolemia	Cigarette smoking
Hypertension	Positive family history
Diabetes Mellitus	Obesity (BMI>30)

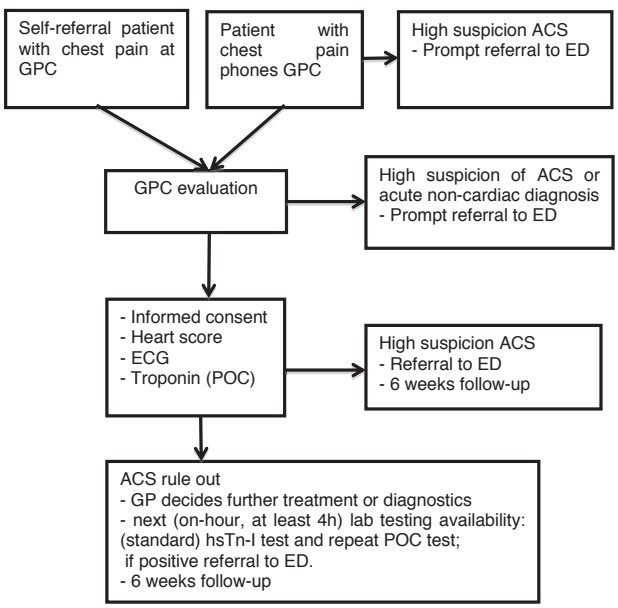

Figure 1. Flowchart of the URGENT trial study design.
GPC: general practitioner cooperative; ACS: acute coronary syndrome; ED: emergency department; POC: point-of-care; GP: general practitioner; hsTn-I: high sensitive troponin-I.

Study design

The study design of the URGENT trial is pictured within Figure 1. GPs at the GPC were able to evaluate patients with a low to intermediate suspicion of ACS with the HEART score (Table 1). High suspicion of ACS excluded the patient of inclusion and were referred to the ED promptly.

The HEART score is calculated by the GP with evaluation of the ECG by a cardiology resident and if needed, supervising Cardiologist. Troponin testing at the GPC was carried out with the POC Minicare I-20 analyser of Philips, which gave troponin results within 10 minutes. The POC test was executed by the supporting nurse at the GPC using capillary blood. The Philips Minicare cTnI has a specificity of 98% and a sensitivity of 92% when patients are tested twice with two to four hours between tests.[15] In this study patients were analysed with the HEART score and not only troponin testing. As the HEART score advises in further follow-up of the patient after initial evaluation, no patients needed to be excluded as a result of chest pain duration.

Patients with an intermediate to high HEART score (>3) were referred to the ED and patients with a low HEART score (0-3) could be excluded from referral (further evaluation was at the GPs own discretion). The patients with low HEART scores had a follow-up high sensitive troponin-I (hsTn-I) test (VieCuri Medical Centre uses the Abbott architect hsTn-I test) and a POC troponin test between four to 24 hours after initial blood test to confirm rule-out. Patients referred to the ED after evaluation with the HEART score received standard care and a POC troponin test at least four hours after first blood test with hsTn-I for follow-up purposes.

Referral to the ED was ultimately left to the discretion of the GP. The GPs were free to refer the patient to the ED despite low HEART scores.

In- and exclusion criteria:

All patients 18 years or older with chest pain or other symptoms suspect of ACS in which the GP was in need of further diagnostics to make a decision of referral, could be included in the URGENT trial. Exclusion criteria were a typical history and/or physical examination resulting in a high suspicion of ACS and requiring immediate referral or symptoms in which a non-coronary emergency was suspected, e.g. pulmonary embolism, thoracic aortic dissection etc.

Sample size calculation

The initial aim of the study was to evaluate the efficacy of using the HEART score by reviewing all patients referred by the GPC to the ED with suspected ACS. We planned to compare the accuracy of diagnosis with the accuracy of diagnosis measured in a baseline registry. The baseline registry showed that 74.5% of the patients with suspected ACS referred by the GPC to the ED, did not have ACS. With a power of 80% and a two-tailed type I error of 5%, to detect a reduction of 10% in not accurately referred patients, we calculated that 329 patients needed to be enrolled within this study. We aspired to enrol 350 patients within the URGENT study to evaluate the effectiveness of the URGENT trial, and account for any loss-to-follow-up. As a substantial amount of patients are referred directly after telephone contact we moreover

aspired to achieve a minimum of 175 patients evaluated at the GPC with the HEART score (50% of the aspired patient goal) to be able to analyse the HEART score use at the GPC.

Data analysis

Data were analysed using SPSS version 24. Baseline characteristics are given per patient. Categorical data are presented as number and percentages of patients or presentations when applicable. Continuous data are presented as means and standard deviation (SD) or as median and range (in case of a non-normal distribution). Patients with missing values are included, with exception of their missing values. Percentages are calculated with respect to the available data, thus excluding missing values. Due to the low inclusion number we have not performed any statistical analyses to compare groups.

Ethical statement

The URGENT trial has been approved by the Medical Ethics Committee of Zuyderland and Zuyd Hogeschool (METC Z, number NL60045.096.16) and is registered at Clinical trials (https://clinicaltrials.gov; trial number NCT03115190).

RESULTS

Inclusion

The sample size of at least 175 patients evaluated at the GPC by a GP has not been achieved. The URGENT trial was terminated prematurely with only 40 patients evaluated at the GPC between 18th of April and the 18th of October 2017 due to the retraction of the Philips Minicare POC tester as well as a low inclusion rate at the GPC.

Baseline characteristics

Baseline characteristics from patients evaluated with the HEART score by the GP are given in Table 2. Patient not referred to the ED, i.e., patients with low HEART scores, were younger (55.2 vs 65.6 years) and had less risk factors compared to patients who were referred to the ED. The time from first medical contact (contact with the GPC) to ECG was 69 vs 97 minutes for patients not referred and referred to the ED respectively.

Table 2. Baseline characteristics of patient evaluated with the HEART score by the GP

	URGENT trial referred (n=10)	*URGENT trial not referred (n=27)*
Caucasian, No.(%)	10 (100.0)	24 (88.9)*
Age, mean (SD), yrs	65.5 (16.9)	55.2 (15.7)
Male gender, No.(%)	7 (70.0)	14 (51.9)

Table 2. Baseline characteristics of patient evaluated with the HEART score by the GP (continued)

	URGENT trial referred (n=10)	*URGENT trial not referred (n=27)*
Smoker, No.(%)	2 (20.0)	5 (25.0)*
Diabetes mellitus, No.(%)	1 (10.0)	0 (0.0)*
Hypercholesterolemia, No.(%)	3 (30.0)	6 (31.6)*
Hypertension, No.(%)	5 (50.0)	5 (26.3)*
Positive family history, No.(%)	3 (30.0)	1 (5.3)*
History of atherosclerotic disease, No.(%)	2 (20.0)	3 (11.1)
Delay to ECG, mean of min (SD)	97 (56.5)	69 (39.1)*

SD: standard deviation.

* 8 patients with missing data

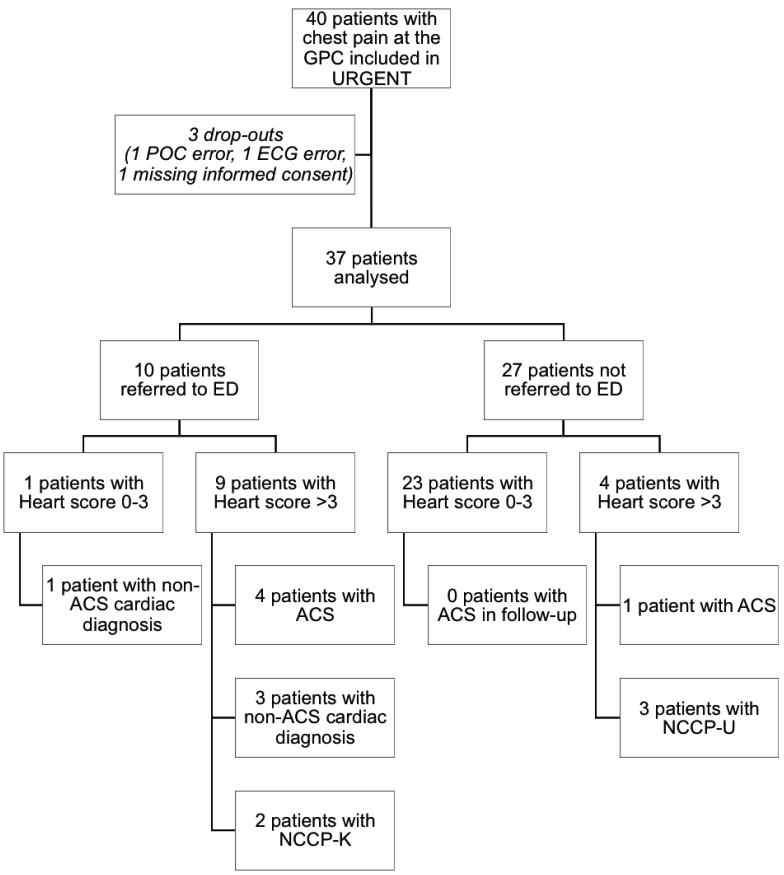

Figure 2. Flowchart of URGENT trial

GPC: general practitioner cooperation, POC: point-of-care troponin tester, ECG: electrocardiogram, ED: emergency department, ACS: acute cardiovascular syndrome, NCCP-U: non-cardiac chest pain of unknown origin, NCCP-K: NCCP of known origin

Outcomes and follow-up

The outcome of the 40 patients included within the URGENT trial is summarized in Figure 2. Three patients have been withdrawn because of one error in POC troponin results, one ECG error and one missing informed consent registry.

Twenty-three patients (62.2%) had a HEART score between 0-3 and were not referred to the ED. None of these patients had ACS in the follow-up.

Despite trial protocol emphasizing that patients with a HEART score of more than 3 should be referred to the ED, this was not followed in all cases. Of the 27 patients that were not referred to the ED, four patients had a HEART score of higher than 3. Three of these patients did not have ACS in follow-up. Their HEART scores were 4 (ECG 1, age 2, risk factors 1), 4 (history 1, age 2 and risk factors 1) and 5 (history 2, age 2, risk factors 1). One patient however had a HEART score of 5 (history 1, ECG 1, age 2 and risk factors 1) with a follow-up troponin test the next day marginally positive. The patient was admitted to the hospital with ACS, namely non-ST-elevated myocardial infarction (NSTEMI). A coronary angiogram (CAG) revealed three-vessel disease for which the patient received multi-vessel PCI.

In the referred patient group, one patient was referred with a HEART score of lower than 4, namely 2 for troponin results. This patient received a CAG which showed no coronary artery disease and was diagnosed with myopericarditis.

Nine patients were referred to the ED with HEART scores higher than three (HEART score ranging from 4 to 9). Of these patients, four had a NSTEMI, two had angina pectoris, one had pericarditis and two had gastroesophageal reflux disease.

DISCUSSION

The pilot data of the URGENT trial suggests that the use of the HEART score within the GPC is feasible and safe. Our study is the first study to demonstrate the feasibility of the HEART score use by GPs in patients with low to intermediate suspicion of ACS.

No patients with ACS were missed within the study protocol of the URGENT trial and no patients within the follow-up period developed MACE. One ACS diagnosis was, regrettably, missed due to protocol breach.

Including patients with a low to intermediate suspicion of ACS resulted in 23 (62.2%) patients not referred to the ED due to low HEART scores. These patients were successfully deferred from referral to the ED, with its inherent risks and stress.

In the group with low suspicion of ACS by the GP, 10 (27.0%) patients were nonetheless referred to the ED. These patients consisted of nine patients with high HEART scores (contradicting the suspicions of the GP) and one patient with a low HEART score but high troponin values. Four patients had ACS, another four patients had non-ACS cardiac diagnoses and only two patients were diagnosed as NCCP. This suggests once more that it is not reliable to diagnose

a patient with ACS solely on patient history and physical examination,[9] as GPs concluded a low to intermediate risk of ACS in these patients before HEART score calculation. It furthermore demonstrates the GPs need for triage tools, such as the HEART score, and POC troponin tests to evaluate patients with chest pain.

Regrettably there was a protocol breach in which patients with high HEART scores were not referred to ED. In four cases this did not result in any morbidity, however one patient did have ACS, found by follow-up troponin testing as dictated by protocol. GPs were thus not compliant within the protocol, as the protocol clearly dictated that patients with a HEART score of higher than 3 should be referred to the ED.

In this study 24 patients (64.9%) had a HEART score of 0-3, much more compared to the original HEART study at the ED (36.4%)[16] or the FAMOUS trial (35.8%), which analysed the HEART score at the EMT.[13] This was expected as the study protocol dictated the inclusion of patients with a low to intermediate suspicion of ACS and excluded patients with a high suspicion of ACS. Patients reviewed at the GPC have already been triaged as patients with a low suspicion, as all patients with a high suspicion of ACS are referred by EMT directly after (telephone) contact with the GPC to the ED.

Strengths, limitations and further research

This study indicates that it is feasible and safe to use the HEART score at the GPC to exclude low risk patients from referral to the ED. More research needs to be done to evaluate the efficacy of HEART score use in the primary care.

This trial's strength is mostly the practical research which represents the real world. The GPs calculated the HEART score with use of a POC troponin tester at the GPC, with the ECG evaluation supported from the Cardiology department. The HEART score including a POC troponin tester allows GPs to triage patients with chest pain with more than only history and physical examination without resulting in long delays. The problems faced in this study should however be addressed in further research.

First of all the POC tester used in this study, which is no longer available, can be substituted with another available POC troponin tester, as the HEART score has been validated without specification on troponin tester.[14]

Secondly the GPs need a simplified method to include patients to amplify inclusion and lower delays. Inclusion was left to the discretion of the GPs, resulting in low inclusion rates. Due to the low inclusion rates, the GPs, as well as their staff, could not easily gain experience with the execution of this protocol. This resulted in longer delays in these patients than necessary.

We believe that if these problems are tackled, that patients with low chance of ACS can be saved the stress and risk of unnecessary referral to the ED.

CONCLUSION

The URGENT trial pilot data suggests that the use of the HEART score at the GPC is safe and feasible. Better triage of chest pain patients at the GPC with the HEART score is needed to improve the accuracy of referrals, reducing the stress on the ED as well as on the patients. This trial should be expanded to prove the efficacy and further help the GPs evaluate patients with chest pain and reducing the amount of NCCP patients referred to the ED.

REFERENCES

1. Verdon F, Herzig L, Burnand B, Bischoff T, Pecoud A, Junod M, et al. Chest pain in daily practice: occurrence, causes and management. Swiss medical weekly. 2008;138(23-24):340-7.
2. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). European heart journal. 2016;37(3):267-315.
3. Steg PG, James SK, Atar D, Badano LP, Blomstrom-Lundqvist C, Borger MA, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. European heart journal. 2012;33(20):2569-619.
4. Bosner S, Becker A, Haasenritter J, Abu Hani M, Keller H, Sonnichsen AC, et al. Chest pain in primary care: epidemiology and pre-work-up probabilities. The European journal of general practice. 2009;15(3):141-6.
5. Ruddox V, Mathisen M, Otterstad JE. Prevalence and prognosis of non-specific chest pain among patients hospitalized for suspected acute coronary syndrome - a systematic literature search. BMC medicine. 2012;10:58.
6. Webster R, Norman P, Goodacre S, Thompson A. The prevalence and correlates of psychological outcomes in patients with acute non-cardiac chest pain: a systematic review. Emergency medicine journal : EMJ. 2012;29(4):267-73.
7. Weinstock MB, Weingart S, Orth F, VanFossen D, Kaide C, Anderson J, et al. Risk for Clinically Relevant Adverse Cardiac Events in Patients With Chest Pain at Hospital Admission. JAMA internal medicine. 2015;175(7):1207-12.
8. Chan L, Willemsen, R, Konings, K. Elektrocardiografie in de huisartsenpraktijk. Huisarts & Wetenschap. 2014(4):57.
9. Fanaroff AC, Rymer JA, Goldstein SA, Simel DL, Newby LK. Does This Patient With Chest Pain Have Acute Coronary Syndrome?: The Rational Clinical Examination Systematic Review. Jama. 2015;314(18):1955-65.
10. Marshall GA, Wijeratne NG, Thomas D. Should general practitioners order troponin tests? The Medical journal of Australia. 2014;201(3):155-7.
11. Mol KA, Rahel BM, Meeder JG, van Casteren BC, Doevendans PA, Cramer MJ. Delays in the treatment of patients with acute coronary syndrome: Focus on pre-hospital delays and non-ST-elevated myocardial infarction. International journal of cardiology. 2016;221:1061-6.
12. Backus BE, Six AJ, Kelder JC, Mast TP, van den Akker F, Mast EG, et al. Chest pain in the emergency room: a multicenter validation of the HEART Score. Critical pathways in cardiology. 2010;9(3):164-9.
13. Ishak M, Ali D, Fokkert MJ, Slingerland RJ, Tolsma RT, Badings E, et al. Fast assessment and management of chest pain patients without ST-elevation in the pre-hospital gateway (FamouS Triage): ruling out a myocardial infarction at home with the modified HEART score. European heart journal Acute cardiovascular care. 2017:2048872616687116.
14. Amundson BE, Apple FS. Cardiac troponin assays: a review of quantitative point-of-care devices and their efficacy in the diagnosis of myocardial infarction. Clin Chem Lab Med. 2015;53(5):665-76.

15. Kemper DW, Semjonow V, de Theije F, Keizer D, van Lippen L, Mair J, et al. Analytical evaluation of a new point of care system for measuring cardiac Troponin I. Clin Biochem. 2017;50(4-5):174-80.
16. Backus BE, Six AJ, Kelder JC, Bosschaert MA, Mast EG, Mosterd A, et al. A prospective validation of the HEART score for chest pain patients at the emergency department. International journal of cardiology. 2013;168(3):2153-8.

Chapter 9

General discussion

GENERAL DISCUSSION

This dissertation has two aims, namely to review interventions that aim to shorten the pre-hospital delays of ST-elevated myocardial infarction (STEMI) patients and to improve the accuracy of chest pain referrals from the pre-hospital network.

Acute coronary care (ACS) patients, and in particular STEMI patients, need to be treated within a timely manner to decrease mortality and major adverse cardiac events (MACE) (Figure 1). To achieve the guideline recommended delays in our region, North and Middle Limburg, two interventions were initiated and then analysed in **part I**. First an ACS focus group consisting of Cardiologists, general practitioners (GPs) and emergency medical transport (EMT) personnel was formed. Secondly an off-site percutaneous coronary intervention (PCI), a centre without in-hospital cardiac surgery back-up, was launched.

In the effort to achieve the guideline recommendations in the delays of STEMI patients many patients with chest pain are referred readily to the emergency department (ED) to neither miss nor delay any patients with ASC. This leads, however, to a high referral of non-cardiac chest pain (NCCP) patients. These patients without a cardiac diagnosis have a low mortality and MACE incidence. The referral of these patients leads to psychological stress, high health care consumption and corresponding costs. In **part II** we analysed the scope of the problem in the pre-hospital triage. Secondly we analysed the benefit of a clinical decision rule (CDR) to improve the accuracy of pre-hospital referrals of chest pain patients.

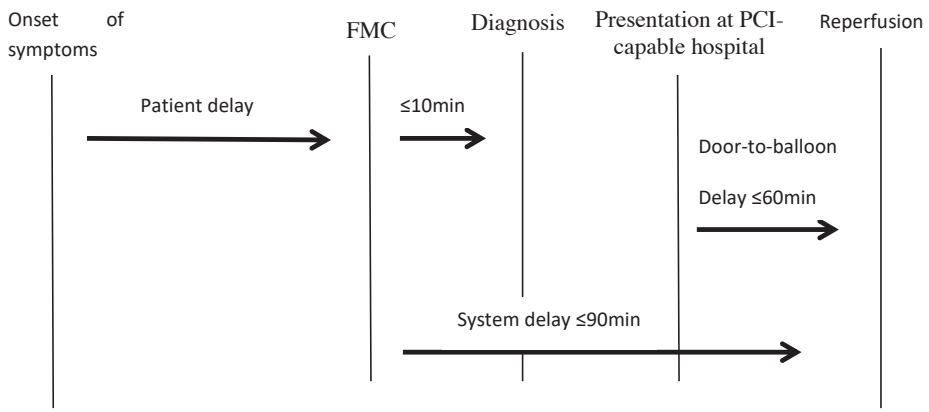

Figure 1. Guideline recommended delays.
FMC: first medical contact, any contact with a (para)medic about cardiac symptoms, PCI: percutaneous coronary intervention, min: minutes

PART I: PRE-HOSPITAL DELAYS

In **chapters 1 and 2** we showed that the guideline recommended delays regarding STEMI patients, were not met globally.[1, 2] These delays are pictured in Figure 1 and explained in more detail in **chapters 1, 2 and 5**. Improvements have mostly been made in door-to-balloon (DTB) and EMT delays, disregarding a substantial part of the pre-hospital delays. The *first aim* of this thesis was therefore to review methods that were designed to shorten the pre-hospital delays of STEMI patients: the start of an ACS focus group and an off-site PCI centre.

Off-site PCI centre

The start of the off-site PCI centre in 2011 was described and analysed in **chapters 3, 4 and 5**. We showed in **chapter 3** that (semi-) elective PCIs in the off-site PCI centre were safe with a procedural complication rate of 5.7% and no procedure related mortality, comparable to off-site centre Alkmaar.[3] Following the promising start of the elective PCIs in the region, a primary PCI program with 24 hour / 7 day coverage was launched in 2013. We compared our off-site PCI centre data with regards to primary PCI for STEMI patients with data from an on-site PCI centre in **chapter 4**. The patients treated at the on-site centre were also patients from our region treated before the primary PCI program at the off-site centre was launched and thus included before 2013. The difference between these patients was the transportation time, as the on-site PCI centre was 60 km away from our region. This delay, was significantly longer in patients treated at the on-site PCI centre resulting in a significantly longer system delay when compared to the patients treated at the off-site PCI centre (101 vs 76 minutes, P<.001). The 'improved' system delay of 76 minutes when treating patients at the regional off-site PCI centre is comparable to the 75 minutes reported by the National Cardiovascular Data Registry (NCDR) in the Netherlands.[4] In this study patients were collected in "snapshot" weeks in 2013, 2014 and 2015, the same period as our analyses in **chapter 4.** In **chapter 4** we found that the procedural complications (8.4% vs 12.3%, p=0.065), 30-day MACE (7.9% vs 8.1%, p=0.797), and mortality (3.2% vs 1.8%, p=0.723) were not significantly different between the off-site and on-site patient groups respectively. We concluded that the off-site PCI centre in our region is safe and effective.

Delays

In **chapter 5** we analysed the differences in delays between the patients treated at the on-site and off-site PCI centres in more depth. The patients treated at the on-site PCI centre had substantial delays with a median system delay of 80 minutes. Only 73.3% of the patients were treated within 90 minutes from first medical contact (FMC) to PCI start (for definitions see **chapter 1** and Figure 1 above). We showed that the start of the off-site PCI (and focus group, see below) resulted in vast improvement to a median system delay of 65 min (p<0.001). Moreover 85.3% of patients were treated within 90 minutes after FMC (p=0.004) and 93.0% were treated within 90 minutes after ECG registration.

While the delays had improved, mortality remained similar (2.6% on-site vs 2.6% off-site, p=0.578), as stated in **chapter 4.** This lack of improvement in mortality despite improvements in the delays of STEMI patients has been found in other studies. These studies, reporting on DTB-delays without the pre-hospital delays, show the lack of improvement in mortality despite decreases from 16 up to 53 min.[5-8] A possible explanation is the increased incidence of PCIs over the years, which includes more patients with high risk profiles.[7, 9]

In **Chapter 5**, we did not find any differences in the thrombolysis in myocardial infarction (TIMI) risk scores between the on- and off-site groups (2.2 vs 2.2 p=0.310), however the TIMI risk score does not include all confounding factors. The TIMI risk score estimates the mortality for patients with ACS. We found a significant, albeit small, difference in age (62.0 on-site vs 63.3 years off-site, p=0.036) between the groups, and there are undoubtedly other factors we did not take in account. High risk patients also frequently have higher (DTB) delays as a result of the need for haemodynamic stabilization before PCI.

A second explanation for the lack of improvement in mortality is that longer pre-hospital delays tend to be overlooked. As these delays and subsequent longer total ischemic times do not shorten with the initiated programs mortality remains stable.[6, 7, 10] As the pre-hospital delays did improve in our study, other explanations might be considered. The incidence of mortality remains relatively low (n=6, 2.6% on-site vs n=7, 2.1% off-site patients), resulting in a numerical challenge in proving a statistically significant difference. Secondly the off-site centre in North Limburg was initiated to achieve the guideline recommended delays. Our studies are observational studies reviewing this initiation and thus not powered to analyse mortality differences.

All studies reporting on delay times in STEMI patients have limitations. Due to obvious ethical considerations none of the studies were randomized.[5-10] Patients with longer delays were compared to patients who had shorter occurring delays naturally, either through the years,[5] after specific programs or after the start of an off-site PCI centre. There are many possible confounders in studies which compare patients with improved delays in longitudinal studies due to great improvements in pharmacological and interventional therapies over the years.[11] Almost all researchers raise the concern of possible unmeasured or even unknown confounding factors as an important limitation to their conclusions.[9]

When taking these limitations in account and reviewing other studies that do show improvements in STEMI patients with shorter delays, we believe that shortening the delays is still an important factor in ACS patients.[12, 13] Further research should be performed to achieve the guideline recommended delays and reduce the risks in ACS patients.

Focus group

We acknowledge that the start of an off-site PCI centre is not feasible in all regions. There are institutional and operator volumes to be met.[14] Therefore improving the delays in regions with a small incidence of STEMI patients will arguably not improve the quality of treatment. Besides

the start of an off-site PCI centre a focus group was initiated in our region to improve the treatment and delays of ACS patients. We believe that a focus group is feasible, and perhaps necessary, in all regions.

In **chapter 5** we showed that this focus group included all (para-) medics within the ACS network and consisted of Cardiologists, GPs and EMTs in the region. The guidelines indicate that patients with chest pain should bypass GPs and contact the EMTs directly to shorten delays and lengthen the time of rhythm observation,[1] after many studies had proven the benefits of EMT use in ACS patients. In the Netherlands, however, many patients with chest pain contact their GP as the FMC. **Chapter 5** showed that almost 50% of STEMI patients contact a GP first in our region, while in other countries the participation of GPs is found to be between 16.3 to 28%.[15, 16] The contact with GPs increases the delays in STEMI patients, through an added doctor or diagnosis delay, up to 25.6 min.[15] We found a much lower increase of only 10 minutes if the patients contacted the GP instead of the EMT first in **chapter 5**.

Below, in **part II,** we show that GPs play a vital part in the management of chest pain patients and can therefore not simply be bypassed, as guidelines suggest.[17] We believe that GPs can play an important part in the diagnosis of chest pain patients if they are a part of a focus group. The whole network in ACS benefits from a collaboration between (para-) medics. These focus groups should continuously evaluate and update the guideline-recommended processes to improve the network and tackle any problems. To achieve the quality control standards, as recommended by the European Society of Cardiology guidelines, they should establish measurable quality indicators to analyse strategies that ensure that ACS patients receive the best possible care.[17] In the Netherlands this has been supported by the Dutch Cardiac Society, the "Nederlandse Vereniging voor Cardiologie (NVVC)", through the initiation of the Connect ACS program. The goal of this program is to ensure a high quality of care in a safe environment and to improve the health care network through optimal coordination between all (para-) medics and the chance to learn from each other.[18] This is extremely important as regions have different protocols to manage STEMI patients and decrease their delays.[19, 20]

CONCLUDING PART I: GUIDELINE ADHERENCE

In **part I** we showed that the off-site PCI centre in our region is safe and effective. The guideline advised goals in STEMI patients can be achieved through the start of an off-site PCI centre and a focus group involving all (para-) medics associated with the ACS network.

PART II: ACCURACY

When improving the delays in ACS patients, the referrals of patients with symptoms suspect of ACS increases. Medical professionals, such as GPs, refer patients with chest pain readily to miss nor delay any patients. Referring all patients with chest pain to the emergency department (ED) is not beneficial to the health care system nor the patients. The *second aim* of this dissertation was therefore to improve the accuracy of referrals from the pre-hospital network and in particular the GPs. We analysed the scope of non-cardiac chest pain (NCCP) referrals and investigated the use of the HEART score in the GP cooperation (GPC) to decrease NCCP referrals while maintaining low delay times and a low risk of misdiagnosis.

Referrals and health care consumption

The increased referral rate of chest pain patients results in a high number of referred patients without ACS, as we showed in **chapter 6** with a NCCP incidence of 76% in referred patients with suspected ACS. This high rate causes higher in-hospital mortality, psychological distress and higher costs in NCCP patients.[21-24] The costs include healthcare costs, but also indirect costs associated with productivity loss and sick leave.[24] NCCP patients use a great amount of health care, as shown in **chapter 7.** Though patients with NCCP did not exceed the amount of visits compared to ACS patients, they did utilize a substantial amount of medical resources at the Cardiology department. Testing NCCP patients, patients without evidence of ischemia, has not been associated with a reduction in subsequent ACS admission.[25] Moreover, the presence of coronary artery calcification, proven by testing, in NCCP patients does not significantly differ from the general, asymptomatic population.[26] As shown in **chapter 7** NCCP patients have a low mortality (1-year mortality of 2.3% vs 8.1% in ACS patients), which is comparable to the general population.

A possible explanation for the high health care consumption and the high amount of sick leave, despite the mild prognosis is the lack of explanation for the chest pain leading to psychological distress.[24] Patients are also not easily convinced that their diagnosis is of a non-cardiac origin.[27]

The contradictive higher MACE found in NCCP patients in **chapter 7** is explained by the presence of coronary artery disease (CAD), with 15.3% MACE in 1-year in patients with CAD and 1.6% in patients without CAD, $p<0.001$. Therefore we do advise, despite not referring patients to ED, to treat their cardiac risk factors aggressively.

ACS vs NCCP

The increase in referrals, subsequent health care consumption and low mortality for NCCP patients encourages further research into the pre-hospital triage of patients with symptoms suspect of ACS. GPs and EMT personnel could benefit from a supplementary test or tool based on anamnesis, physical examination and on-hand diagnostics as they frequently have to assess

patients with chest pain. The incidence of chest pain at the primary care department is 1.26% in the Netherlands and Belgium. GPs refer 5.7% of these patients to a cardiac ED, 8.5% to the "general" ED and another 21.4% to the out-patient clinic.[28]

As stated in **chapter 1**, the 'typical' symptoms of ACS such as a tight, squeezing, heavy or pressure-like chest pain with radiation to the jaw, neck, throat, left arm or shoulder do not discriminate between the presence of ACS or NCCP. In **chapter 6**, we aimed to find symptoms that do differ between ACS and NCCP patients.

We found that the presence of symptoms such as dizziness, chest pain reproducible by palpation and symptoms induced by exercise to differ statistically significantly between ACS and NCCP patients. The clinical relevance remains to be questioned however, as no symptoms excluded ACS completely. Other characteristics between patients, such as age and risk factors were higher in ACS patients, but also frequently seen in NCCP patients. As the patients analysed by us were referred to the ED, they were frequently referred for complaints combined with risk factors, explaining the higher amount of risk factors in all patients.

Clinical decision rules

As we do not as of yet have any symptoms or characteristics that definitely differentiate between ACS and NCCP patients,[29] there is a need for a CDR. Such a CDR would take into account a combination of factors in order to differentiate between ACS and NCCP in the pre-hospital setting. CDRs which only require symptoms or characteristics of patients would be a perfect tool for the pre-hospital setting.

Many studies have developed and subsequently analysed these "anamnesis only" CDRs, using varying combinations of characteristics, risk factors and symptoms of chest pain patients, [30-34] nearly the same symptoms and characteristics that were found in **chapter 6** to be significantly different between ACS and NCCP patients. Regrettably they either have not shown to be better in classifying chest pain patients than GPs without the CDRs or when improving the decisions they still do not exclude ACS sufficiently.[30-32]

In **chapter 1** we stated that while ECGs alone can help diagnose a STEMI, NSTEMI and UAP are not distinguished by ECG abnormalities.[35] Relying solely on troponin testing will misdiagnose patients with UAP.[36] Studies that combine symptoms and characteristics, such as the factors mentioned in the CDRs above, with diagnostics in the form of an ECG and cardiac biomarker testing have proven to be more specific and sensitive.[21] The (new) Vancouver Chest Pain Rule and the HEART score were designed to evaluate patients presenting to the ED with chest pain.[37, 38] Established risk scores such as the TIMI risk score and the GRACE ACS risk score were developed as clinical predictions tools, but have been used in studies to help guide the diagnostic challenge of chest pain patients.[39, 40] The TIMI risk score has for example been included in an accelerated decision protocol (ADP) with ECG and 0- and 2-hour troponin testing to identify ED patients suspected of having ACS who are suitable for safe early discharge,[30] though it is also used independently . In studies comparing the use of these scores at the ED the HEART

score outperforms the TIMI and the GRACE ACS risk scores, as well as the other, less used tools such as the Vancouver Chest Pain Rule.[41]

CDRs and/or risk factors could potentially support the triage in the pre-hospital setting as they have shown to have a better sensitivity and specificity in the evaluation of chest pain patients at the ED. However cardiac biomarker testing is problematic in the pre-hospital setting. Troponin testing has not been recommended due to logistical as well as safety reasons.[36] Using a troponin test without taking the history and risk factors does not improve triage.[42] A risk score or CDR validated in the pre-hospital setting combining symptoms, characteristics, ECG *and* troponin testing, possibly could.

After resolving the safety issues, the logistics of troponin testing would still be an issue. Generally patients need to be referred to a laboratory and testing takes over an hour. A possible solution to these issues are Point-Of-Care (POC) troponin testers. The use of these testers yields quick results and do not require a laboratory referral. There are different kind of POC testers available with results available after 7 to 20 min.[43] They have shown to have comparable sensitivity and specificity to standard troponin testers[44, 45] GPs are interested and see the benefit of POC troponin testers if the results come back within 10 minutes and testing of capillary blood is sufficient.[46] However, just like in laboratory based troponin tests, the results by themselves are not sufficient to reliably exclude ACS and should be placed in context or incorporated in a CDR.

Willemsen et al developed a health economic model to review the impact of the use of CDR with incorporated POC test in the primary care. This model was based on a literature review and registration studies and showed a potential to improve the exclusion of ACS patients. This would result in a considerable reduction in annual healthcare costs as compared to current practice.[47]

URGENT trial

In **chapter 8** we initiated the URGENT trial. This trial combined the HEART score with a POC troponin tester from Philips, the Minicare cTnI, to analyse a reliable and rapid CDR for use at the GPC. The Philips Minicare cTnI was a POC troponin tester which used capillary blood and gave results within 10 minutes.[48] It had a specificity of 98% and a sensitivity of 92% when patients were tested twice with two to four hours between tests. Regrettably our trial was cut short as the Philips Minicare cTnI was taken off the market within six months of the start of the trial. This was due to financial issues of the company, with no reflection on the safety of the Minicare or the URGENT trial. We presented the first 40 patients included within the URGENT trial as a pilot study. No patients with ACS were missed within the protocol, suggesting that the use of the HEART score at the GPC is safe and feasible. Naturally more research should be performed to evaluate the safety and feasibility of the HEART score incorporating another POC troponin tester for the improvement of the triage in the pre-hospital setting. We are confident that this has a high potential, after our pilot study and after the results of the FAMOUS trial. This trial has retrospectively evaluated the use of the HEART score in the EMT, with favourable results.[49]

CONCLUDING PART II: PRE-HOSPITAL TRIAGE

In the pre-hospital triage of chest pain patients the (para-) medics are in need of diagnostic tools to further aid their decisions. Chest pain patients are hard to diagnose without additional testing and have high health care consumption. CDRs incorporating ECGs and troponin testing have shown promising results, however in the prehospital triage there is a need for a fast and reliable POC troponin tester to incorporate within these CDRs.

CONCLUSION

Improving the delays in ACS patients, and particularly in STEMI patients, to guideline standards is achievable through regional improvements. In our region, North and Middle Limburg, this included the start of an off-site PCI centre and a focus group including all (para-) medics involved in the ACS network. The average travel distance for STEMI patients to a PCI-centre has decreased to 45 km in our region, resulting in 85% of patients treated within a system delay of 90 minutes. We achieved this through a substantial decrease in pre-hospital delays, an aspect generally ignored in studies and guidelines.

Decreasing the delays in ACS patients, however, results in a high amount of NCCP referrals. These patients have high health care consumption without an increased mortality risk. It results in psychological distress for patients and high cost for society. Despite the low mortality risk, the MACE in these patients is high due to the accompanying risk factors, therefore there is still a need for adequate treatment of cardiac risk factors.

The dilemma between referring patients in a timely manner to maintain low delays and not referring an excess of NCCP patients, but still treating their cardiac risk factors is great. Mostly because a clear distinction between ACS and NCCP patients can not be made with anamnesis and physical examination alone. This pre-hospital triage challenge can be supported and improved by CDRs which incorporate ECG and troponin testing, such as the HEART score. The emergence of POC troponin testers show promising results for further improvement within the pre-hospital triage of chest pain patients.

REFERENCES

1. Steg PG, James SK, Atar D, Badano LP, Blomstrom-Lundqvist C, Borger MA, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. European heart journal. 2012;33(20):2569-619.
2. Widimsky P, Wijns W, Fajadet J, de Belder M, Knot J, Aaberge L, et al. Reperfusion therapy for ST elevation acute myocardial infarction in Europe: description of the current situation in 30 countries. European heart journal. 2010;31(8):943-57.
3. Peels JO, Hautvast RW, de Swart JB, Huybregts MA, Umans VA, Arnold AE, et al. Percutaneous coronary intervention without on site surgical back-up; two-years registry of a large Dutch community hospital. International journal of cardiology. 2009;132(1):59-65.
4. Hoedemaker NP, Ten Haaf ME, Maas JC, Damman P, Appelman Y, Tijssen JG, et al. Practice of ST-segment elevation myocardial infarction care in the Netherlands during four snapshot weeks with the National Cardiovascular Database Registry for Acute Coronary Syndrome. Netherlands heart journal : monthly journal of the Netherlands Society of Cardiology and the Netherlands Heart Foundation. 2017;25(4):264-70.
5. Flynn A, Moscucci M, Share D, Smith D, LaLonde T, Changezi H, et al. Trends in door-to-balloon time and mortality in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention. Archives of internal medicine. 2010;170(20):1842-9.
6. Mallidi J, Visintainer P, Pallekonda I, Fisher D, Barringhaus K, Kugelmass A, et al. Clinical Outcomes of Transferred Versus Onsite Primary Percutaneous Coronary Intervention for Patients With STEMI: Time to Look Beyond Door to Balloon Time. Critical pathways in cardiology. 2018;17(1):13-8.
7. Menees DS, Peterson ED, Wang Y, Curtis JP, Messenger JC, Rumsfeld JS, et al. Door-to-balloon time and mortality among patients undergoing primary PCI. The New England journal of medicine. 2013;369(10):901-9.
8. Nallamothu BK, Normand SL, Wang Y, Hofer TP, Brush JE, Jr., Messenger JC, et al. Relation between door-to-balloon times and mortality after primary percutaneous coronary intervention over time: a retrospective study. Lancet. 2015;385(9973):1114-22.
9. Foo CY, Bonsu KO, Nallamothu BK, Reid CM, Dhippayom T, Reidpath DD, et al. Coronary intervention door-to-balloon time and outcomes in ST-elevation myocardial infarction: a meta-analysis. Heart. 2018.
10. Solhpour A, Chang KW, Arain SA, Balan P, Loghin C, McCarthy JJ, et al. Ischemic time is a better predictor than door-to-balloon time for mortality and infarct size in ST-elevation myocardial infarction. Catheter Cardiovasc Interv. 2016;87(7):1194-200.
11. Fox KA, Steg PG, Eagle KA, Goodman SG, Anderson FA, Jr., Granger CB, et al. Decline in rates of death and heart failure in acute coronary syndromes, 1999-2006. Jama. 2007;297(17):1892-900.
12. Gibson CM, Pride YB, Frederick PD, Pollack CV, Jr., Canto JG, Tiefenbrunn AJ, et al. Trends in reperfusion strategies, door-to-needle and door-to-balloon times, and in-hospital mortality among patients with ST-segment elevation myocardial infarction enrolled in the National Registry of Myocardial Infarction from 1990 to 2006. American heart journal. 2008;156(6):1035-44.
13. Terkelsen CJ, Sorensen JT, Maeng M, Jensen LO, Tilsted HH, Trautner S, et al. System delay and mortality among patients with STEMI treated with primary percutaneous coronary intervention. Jama. 2010;304(7):763-71.

14. Kolh P, Windecker S. ESC/EACTS myocardial revascularization guidelines 2014. European heart journal. 2014;35(46):3235-6.

15. Trimmel H, Bayer T, Schreiber W, Voelckel WG, Fiedler L. Emergency management of patients with ST-segment elevation myocardial infarction in Eastern Austria: a descriptive quality control study. Scand J Trauma Resusc Emerg Med. 2018;26(1):38.

16. Vafaie M, Hochadel M, Munzel T, Hailer B, Schumacher B, Heusch G, et al. Guideline-adherence regarding critical time intervals in the German Chest Pain Unit registry. European heart journal Acute cardiovascular care. 2018:2048872618762639.

17. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). European heart journal. 2017.

18. NVVC Connect [Available from: http://www.nvvcconnect.nl/.

19. Tra J, van der Wulp I, de Bruijne MC, Wagner C. Exploring the treatment delay in the care of patients with ST-elevation myocardial infarction undergoing acute percutaneous coronary intervention: a cross-sectional study. BMC health services research. 2015;15:340.

20. Adams R, Appelman Y, Bronzwaer JG, Slagboom T, Amoroso G, van Exter P, et al. Implementation of a prehospital triage system for patients with chest pain and logistics for primary percutaneous coronary intervention in the region of Amsterdam, the Netherlands. The American journal of cardiology. 2010;106(7):931-5.

21. Fanaroff AC, Rymer JA, Goldstein SA, Simel DL, Newby LK. Does This Patient With Chest Pain Have Acute Coronary Syndrome?: The Rational Clinical Examination Systematic Review. Jama. 2015;314(18):1955-65.

22. Eslick GD, Coulshed DS, Talley NJ. Review article: the burden of illness of non-cardiac chest pain. Alimentary pharmacology & therapeutics. 2002;16(7):1217-23.

23. Webster R, Norman P, Goodacre S, Thompson A. The prevalence and correlates of psychological outcomes in patients with acute non-cardiac chest pain: a systematic review. Emergency medicine journal : EMJ. 2012;29(4):267-73.

24. Mourad G, Alwin J, Stromberg A, Jaarsma T. Societal costs of non-cardiac chest pain compared with ischemic heart disease--a longitudinal study. BMC health services research. 2013;13:403.

25. Sandhu AT, Heidenreich PA, Bhattacharya J, Bundorf MK. Cardiovascular Testing and Clinical Outcomes in Emergency Department Patients With Chest Pain. JAMA internal medicine. 2017;177(8):1175-82.

26. Ilangkovan N, Mogensen CB, Mickley H, Lassen AT, Lambrechtsen J, Sand NPR, et al. Prevalence of coronary artery calcification in a non-specific chest pain population in emergency and cardiology departments compared with the background population: a prospective cohort study in Southern Denmark with 12-month follow-up of cardiac endpoints. BMJ open. 2018;8(3):e018391.

27. . !!! INVALID CITATION !!! {}.

28. Hoorweg BB, Willemsen RT, Cleef LE, Boogaerts T, Buntinx F, Glatz JF, et al. Frequency of chest pain in primary care, diagnostic tests performed and final diagnoses. Heart. 2017;103(21):1727-32.

29. Swap CJ, Nagurney JT. Value and limitations of chest pain history in the evaluation of patients with suspected acute coronary syndromes. Jama. 2005;294(20):2623-9.

30. Than M, Flaws D, Sanders S, Doust J, Glasziou P, Kline J, et al. Development and validation of the Emergency Department Assessment of Chest pain Score and 2 h accelerated diagnostic protocol. Emergency medicine Australasia : EMA. 2014;26(1):34-44.

31. Bruins Slot MH, Rutten FH, van der Heijden GJ, Geersing GJ, Glatz JF, Hoes AW. Diagnosing acute coronary syndrome in primary care: comparison of the physicians' risk estimation and a clinical decision rule. Family practice. 2011;28(3):323-8.

32. Haasenritter J, Donner-Banzhoff N, Bosner S. Chest pain for coronary heart disease in general practice: clinical judgement and a clinical decision rule. The British journal of general practice : the journal of the Royal College of General Practitioners. 2015;65(640):e748-53.

33. Bosner S, Becker A, Haasenritter J, Abu Hani M, Keller H, Sonnichsen AC, et al. Chest pain in primary care: epidemiology and pre-work-up probabilities. The European journal of general practice. 2009;15(3):141-6.

34. Gencer B, Vaucher P, Herzig L, Verdon F, Ruffieux C, Bosner S, et al. Ruling out coronary heart disease in primary care patients with chest pain: a clinical prediction score. BMC medicine. 2010;8:9.

35. Rutten FH, Kessels, A.G.H, Willems, F.F, Hoes, A.W. Is elektrocardiografie in de huisartsenpraktijk nuttig? Huisarts & Wetenschap. 2001;44:179-83.

36. Marshall GA, Wijeratne NG, Thomas D. Should general practitioners order troponin tests? The Medical journal of Australia. 2014;201(3):155-7.

37. Cullen L, Greenslade JH, Than M, Brown AF, Hammett CJ, Lamanna A, et al. The new Vancouver Chest Pain Rule using troponin as the only biomarker: an external validation study. The American journal of emergency medicine. 2014;32(2):129-34.

38. Backus BE, Six AJ, Kelder JC, Bosschaert MA, Mast EG, Mosterd A, et al. A prospective validation of the HEART score for chest pain patients at the emergency department. International journal of cardiology. 2013;168(3):2153-8.

39. Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, Papuchis G, et al. The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. Jama. 2000;284(7):835-42.

40. Fox KA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, Van de Werf F, et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). BMJ. 2006;333(7578):1091.

41. Liu N, Ng JCJ, Ting CE, Sakamoto JT, Ho AFW, Koh ZX, et al. Clinical scores for risk stratification of chest pain patients in the emergency department: an updated systematic review. Journal of Emergency and Critical Care Medicine. 2018;2:16.

42. Nilsson S, Andersson A, Janzon M, Karlsson JE, Levin LA. Cost consequences of point-of-care troponin T testing in a Swedish primary health care setting. Scand J Prim Health Care. 2014;32(4):241-7.

43. Amundson BE, Apple FS. Cardiac troponin assays: a review of quantitative point-of-care devices and their efficacy in the diagnosis of myocardial infarction. Clin Chem Lab Med. 2015;53(5):665-76.

44. Venge P, van Lippen L, Blaschke S, Christ M, Geier F, Giannitsis E, et al. Equal clinical performance of a novel point-of-care cardiac troponin I (cTnI) assay with a commonly used high-sensitivity cTnI assay. Clin Chim Acta. 2017;469:119-25.

45. Andersson PO, Karlsson JE, Landberg E, Festin K, Nilsson S. Consequences of high-sensitivity troponin T testing applied in a primary care population with chest pain compared with a commercially

available point-of-care troponin T analysis: an observational prospective study. BMC research notes. 2015;8:210.

46. Kip MMA, Noltes AM, Koffijberg H, MJ IJ, Kusters R. Improving early exclusion of acute coronary syndrome in primary care: the added value of point-of-care troponin as stated by general practitioners. Prim Health Care Res Dev. 2017;18(4):386-97.

47. Willemsen RTA, Kip MMA, Koffijberg H, Kusters R, Buntinx F, Glatz JFC, et al. Early health technology assessment of future clinical decision rule aided triage of patients presenting with acute chest pain in primary care. Prim Health Care Res Dev. 2018;19(2):176-88.

48. Kemper DW, Semjonow V, de Theije F, Keizer D, van Lippen L, Mair J, et al. Analytical evaluation of a new point of care system for measuring cardiac Troponin I. Clin Biochem. 2017;50(4-5):174-80.

49. Ishak M, Ali D, Fokkert MJ, Slingerland RJ, Tolsma RT, Badings E, et al. Fast assessment and management of chest pain patients without ST-elevation in the pre-hospital gateway (FamouS Triage): ruling out a myocardial infarction at home with the modified HEART score. European heart journal Acute cardiovascular care. 2017:2048872616687116.

Appendix

SUMMARY

Acute coronary syndrome (ACS) is a life threatening disease with high morbidity. In ACS the oxygen requirements of the myocardium is not met due to a sudden reduction of blood flow, typically resulting in chest pain. ACS consists of ST-elevated myocardial infarction (STEMI), non-STEMI (NSTEMI) and unstable angina pectoris. The duration of coronary artery occlusion and the extent of myocardial necrosis are directly linked. Delays in diagnosis and treatment of patients suspected of ACS should therefore be kept as short as possible to reduce complications and mortality. Cardiac guidelines have specific recommendations about the delays of STEMI patients. The system delay (from first medical contact to start of percutaneous coronary intervention (PCI)) should be less than 90 minutes and at least 90% of patients should be treated within these 90 minutes. To decrease delays in STEMI patients and achieve the guideline recommendations many researchers in the past have focussed on in-hospital delays, neglecting the pre-hospital delays. This dissertation focusses on the pre-hospital delay and the network of ACS patients.

In **chapter 2** we discuss several themes within the pre-hospital phase of ACS diagnosis and treatment. These subjects include the pathophysiology of ACS, chest pain prevalence, patient delay, general practitioner (GP) role in ACS and their delays, (nurse) triage, and the role of the emergency medical transport (EMT) and their delays within the ACS network.

The patient delay is among the longest in the pre-hospital chain of ACS patients. Interventions such as mass media campaigns or individual education programs have not shown much improvement. Patients with chest pain most often contact the GP instead of the recommended EMT, increasing delays as well.

Referring all chest pain patients without restriction to the emergency department (ED) with the EMT to reduce pre-hospital delays and achieve guidelines recommended delays is not feasible. Chest pain is a common symptom and non-cardiac chest pain (NCCP) is diagnosed in up to 80% of patients referred to the ED. As the mortality of NCCP patients is low and unnecessary referral to the ED causes stress for the patients and their family as well as on the ED, triage is imperative. GPs need (validated) tools to help them distinguish patients with ACS for rapid referral from patients without ACS.

In **part I** of this dissertation we reviewed interventions that aimed to shorten the pre-hospital delays of STEMI patients. These interventions included the start of an off-site PCI centre, a PCI centre without in-hospital surgical back-up, and the start an ACS focus group involving Cardiologists, GPs and EMT.

In **part II** we analysed the scope of NCCP referrals. We investigated the use of the HEART score, a triage tool for chest pain patients, in the GP cooperation to decrease NCCP referrals while maintaining low delay times and a low risk of misdiagnosis.

Part I Prehospital delays

At VieCuri Medical Centre for Northern Limburg in Venlo an off-site PCI program was initiated to meet the increased demands in PCIs, due to an increase of ACS patients, and to decrease the delays in STEMI patients. In **chapter 3** we analysed the first results of the off-site PCIs at VieCuri Medical Centre. We found that 5.7% of patients had a procedural complication and a major adverse cardiac event (MACE) had occurred in 13.1% of the patients. There were no deaths or emergency surgery related to the PCI procedures. These results are comparable to the results of Medical Centre Alkmaar, the first off-site PCI centre of the Netherlands. In conclusion we demonstrated that the off-site PCI program at VieCuri Medical Centre is safe.

After the success of the elective procedures, a primary PCI program, capable op 24/7 (emergency) PCIs, ensued. In **chapter 4** we analysed the first results of these procedures and compared them to on-site PCI centre Catharina Hospital Eindhoven. The occurrence of procedural complications was low in both groups with 8.4% at VieCuri Medical Centre versus 12.3% at Catharina Hospital Eindhoven. At 30 days 17 (7.9%) patients in the VieCuri group and 9 (8.1%) patients in the Catharina Hospital group had a MACE. We concluded that performing primary PCIs in the off-site PCI centre is safe and effective as the results were comparable to the on-site PCI centre.

We evaluated the effect of the off-site centre on the pre-hospital delays of STEMI patients in **chapter 5**. In addition to the start of the off-site PCI centre a focus group was set up to improve the network of STEMI patients. This focus group consisted of Cardiologists, GPs and EMTs from the region. The median system delay decreased significantly from 80 to 65 minutes. The median electrocardiogram (ECG)-to-PCI delay decreased from 64 to 48 minutes. The percentage of patients with a system delay of less than 90 minutes improved from 73% to 85% and the percentage with an ECG-to-PCI delay of less than 90 minutes improved from 92% to 96%. With these results we showed that the guideline recommended delays can be achieved with the start of an ACS focus group and off-site PCI centre.

In conclusion in **part I** we show that an off-site PCI centre is safe and effective. The guideline advised goals in STEMI patients can be achieved through the start of an off-site PCI centre and a focus group involving all (para-) medics associated with the ACS network.

Part II Accuracy

The consequence of referring patients with chest pain rapidly via EMT to the ED to reduce delays, is the excess referral of patients with NCCP. In **chapter 6** we investigated the triage system of chest pain patients referred to the hospital with suspected ACS and analysed the difference in on- and off-hour GPs. We found that the role of the GP is important with 76% of chest pain patients at the ED were referred by the GP. Most patients referred by on-hour GPs were examined by the GP, whereas off-hour GPs mostly referred patients directly via EMT. The accuracy of referrals was low and significantly lower in the off-hour GP group. ACS was diagnosed in 27.1% of patients referred by on-hour GPs and 20.1% referred by off-hour GPs.

We did not identify any symptoms, history or risk factors that could differentiate adequately between ACS and NCCP. This once more demonstrates the need for triage tools for chest pain patients, especially in the GP practice.

To quantify the burden of NCCP patients we analysed the prognosis and health care utilisation of NCCP patients in **chapter 7**. We found that the all-cause one year mortality rate of NCCP patients was 2.3% compared to 7.2% in cardiac chest pain (CCP) patients and the occurrence of MACE was 5.1% versus 8.3%. A history of coronary artery disease in NCCP patients was identified as a predictive factor for the occurrence of MACE. The utilisation of secondary health care within the cardiology department by NCCP patients was high. Patients with NCCP of unknown origin utilized more health care than NCCP of known origin. We concluded that the prognosis of NCCP patients exceeds that of CCP patients, however their prognosis is not benign due to the presence of cardiovascular risk factors and a history of coronary artery disease. The majority of patients presenting at the ED with chest pain were discharged with NCCP. These patients nonetheless utilized substantial medical resources at the Cardiology Department during the one-year follow-up. This research corresponds with **chapter 6** and stresses the importance of triage and (validated) triage tools in patients with chest pain.

In **chapter 8** we analysed a tool for the triage of chest pain patients by GPs in the URGENT trial. We assisted the GPs with the HEART score, a chest pain risk score and acronym based on History, ECG, Age, Risk factors and Troponin. As standard troponin testing is not recommended in the GP practice due to logistics, we used a point-of-care (POC) troponin tester. During the trial the POC tester was taken off the market due to financial company issues with no reflection on the safety of the POC tester or the URGENT trial. We presented the first 40 patients included within the trial as a pilot study. No patients included within the URGENT trial developed a MACE within the follow-up of six weeks. The accuracy of referrals did not improve, most likely due to the low inclusion. The URGENT trial proves the safety and feasibility of the HEART score use at the GP cooperative. The trial needs further expansion to prove the efficacy and further aid the GPs with the triage of patients with chest pain.

In conclusion, in **part II** we show the need for tools in the pre-hospital triage of chest pain patients. Differentiating between chest pain patients without additional testing is difficult resulting in high health care consumption. The HEART score, a risk score incorporating ECGs and troponin testing, shows promising results, however in the pre-hospital triage there is a need for a fast and reliable POC troponin tester to incorporate with this risk score.

NEDERLANDSE SAMENVATTING

Acuut coronair syndroom (ACS) is een levensbedreigende aandoening met een hoge morbiditeit. De oorzaak van ACS is een plotseling reductie in de coronaire doorbloeding met te weinig zuurstof in het myocard als gevolg. Het meest voorkomend symptoom hierbij is pijn op de borst. ACS wordt onderverdeeld in ST-elevatie myocard infarct (STEMI), non-STEMI (NSTEMI) en instabiele angina pectoris. De duur van kransslagader occlusie is direct gerelateerd aan de grootte van myocardnecrose. Snelle diagnostiek en behandeling van ACS patiënten is cruciaal om het aantal complicaties en de mortaliteit te verminderen. Concreet advies ten aanzien van de duur tot behandeling van STEMI patiënten is geformuleerd in de Europese en Amerikaanse Cardiale richtlijnen. De "systeem delay" (de tijd van het eerste medische contact tot de start van de percutane coronaire interventie (PCI)) moet minder dan 90 minutes zijn en minstens 90% van de patiënten moet binnen deze 90 minuten behandeld zijn. De eerste onderzoeken om de tijden in het ACS netwerk te verbeteren hebben zich vooral gericht op de tijden binnen het ziekenhuis. Hierbij lieten ze veelal de pre-hospitale tijden buiten beschouwing. Het speerpunt van dit proefschrift zijn deze pre-hospitale tijden in het ACS netwerk.

In **hoofdstuk 2** introduceren wij verscheidene thema's binnen het pre-hospitale netwerk van ACS: de pathofysiologie van ACS, de prevalentie van pijn op de borst, de "patiënt delay" (de tijd van symptomen tot het inroepen van medische hulp), de rol van de huisarts binnen ACS en de bijbehorende delays, de triage van pijn op de borst patiënten, al dan niet door dokters assistenten, en de rol van de ambulance dienst en de bijbehorende delays.

De patiënten delay is een groot onderdeel binnen de pre-hospitale keten van ACS patiënten. Interventies zoals media campagnes of individuele training hebben weinig verbeteringen laten zien. Patiënten met pijn op de borst contacteren veelal de huisarts in plaats van, zoals geadviseerd, de ambulance dienst. Dit vergroot de vertraging in het pre-hospitale traject.

Het halen van de tijdslimieten door prompt alle patiënten met pijn op de borst naar de spoedeisende hulp te sturen is geen werkbare oplossing. Pijn op de borst is een veel voorkomend symptoom, waarbij 80% van de patiënten die verwezen worden naar de spoedeisende hulp geen cardiale diagnose hebben. De mortaliteit van niet cardiale pijn op de borst (NPOB) patiënten is laag en onnodige verwijzingen veroorzaken stress bij de patiënten, hun familie en op de spoedeisende hulp. Triage van deze patiënten is dus essentieel. Huisartsen hebben (gevalideerde) triage hulpmiddelen nodig om patiënten met ACS, die snel ingestuurd moeten worden, te onderscheiden van patiënten zonder ACS.

In **deel I** van dit proefschrift analyseren we interventies die de pre-hospitale delays in STEMI patiënten verminderen. Deze interventies zijn de start van een off-site PCI centrum, een PCI centrum zonder on-site chirurgische back-up, en een ACS focusgroep bestaande uit Cardiologen, huisartsen en ambulance personeel uit de regio.

In **deel II** bestuderen wij de omvang van de NPOB verwijzingen. Daarnaast evalueren we het gebruik van de HEART score, een triage middel voor patiënten met pijn op de borst, in de

huisartsenpost. Hierbij is het doel om NPOB verwijzingen te verminderen terwijl we de delays niet vergroten en een lage risico voor misdiagnose nastreven.

Deel I: Pre-hospitale tijden

Om de geadviseerde delays in STEMI patiënten, bij minstens 90% van de patiënten moet binnen 90 minuten de behandeling gestart zijn, te halen is er een off-site PCI programma in VieCuri Medisch Centrum voor Noord Limburg in Venlo gestart. In **hoofdstuk 3** hebben we de eerste resultaten van dit off-site PCI centrum geanalyseerd. Hierbij hadden 5.7% van de patiënten een aan de procedure gerelateerde complicatie en in 13.1% van de patiënten was er een ernstige cardiale bijwerking (major adverse cardiac event (MACE)). Er zijn geen patiënten overleden noch waren er patiënten die een spoed operatie nodig hadden. Deze resultaten zijn vergelijkbaar met de resultaten van Medisch Centrum Alkmaar, het eerste off-site PCI centrum van Nederland. Het onderzoek van **hoofdstuk 3** laat dus zien dat het off-site PCI programma in VieCuri Medisch Centrum veilig is.

Na het succes van de electieve procedures volgde er een primair PCI programma waarbij 24/7 spoed PCIs mogelijk zijn. In **hoofdstuk 4** zijn de eerste resultaten van deze procedures geanalyseerd en vergeleken met on-site PCI centrum Catharina Ziekenhuis Eindhoven. De incidentie van procedurele complicaties was laag in beide groepen met 8.4% in VieCuri Medisch Centrum versus 12.3% in Catharina Ziekenhuis Eindhoven. In de follow-up van 30 dagen hadden 17 (17.9%) patiënten in de VieCuri groep en 9 (8.1%) patiënten in de Catharina Ziekenhuis groep een MACE. Wij concludeerde hierbij dat primaire PCIs uitgevoerd in het off-site PCI centrum vergelijkbaar zijn met het on-site PCI centrum en daarom veilig en effectief.

In **hoofdstuk 5** hebben we het effect van het off-site PCI centrum op de pre-hospitale tijden van STEMI patiënten geanalyseerd. Naast de initiatie van het off-site PCI centrum is er een focus groep opgezet om het netwerk van ACS patiënten te verbeteren. De focus groep bestond uit cardiologen, huisartsen en ambulance dienst uit de regio. De mediane systeem delay daalde significant van 80 naar 65 minuten. De mediane elektrocardiogram (ECG)-tot-PCI delay daalde van 64 naar 48 minuten. Het percentage patiënten met een systeem delay van minder dan 90 minuten verbeterde van 73% naar 85% en het percentage van ECG-tot-PCI delay van minder dan 90 minuten verbeterde van 92% naar 96%. Met deze resultaten laten we zien dat de geadviseerde tijden in de richtlijnen haalbaar zijn met behulp van een ACS focus groep en het starten van een off-site PCI centrum.

Concluderend laten wij in **deel I** van dit proefschrift zien dat een off-site PCI centrum veilig en effectief is. De door de richtlijnen geadviseerde tijden in STEMI patiënten kunnen gehaald worden met behulp van de start van een off-site PCI centrum en een focus groep, waarbij alle (para-)medici in het ACS netwerk samenwerken.

Deel II: Nauwkeurigheid

Het gevolg van het prompt insturen van patiënten met pijn op de borst via de ambulance dienst naar de spoedeisende hulp om de delays te verbeteren is de overmaat aan verwijzingen van patiënten met NPOB. In **hoofdstuk 6** onderzoeken wij het triage systeem van pijn op de borst patiënten die verwezen zijn naar de spoedeisende hulp met verdenking van ACS. Daarnaast analyseerde we de verschillen tussen de verwijzingen vanuit de huisartsenpraktijken, binnen kantoortijden, met de verwijzingen vanuit de huisartsenpost, buiten kantoortijden. Op de spoedeisende hulp ware 76% van de patiënten met pijn op de borst verwezen door een huisarts. Patiënten verwezen vanuit huisartsenpraktijken worden vaker gezien door een huisarts, terwijl patiënten die de huisartsenpost hebben gebeld, vaker meteen doorgestuurd zijn naar de spoedeisende hulp. De nauwkeurigheid van de verwijzingen was laag en significant lager vanuit de huisartsenpost in vergelijkingen met de huisartsenpraktijken. ACS werd gediagnosticeerd in 27.1% van de patiënten verwezen door de huisartsenpraktijken en 20.1% in de verwijzingen vanuit de huisartsenpost. De diagnostische waarde van symptomen, voorgeschiedenis of risicofactoren om te differentiëren tussen ACS en NPOB is laag. Hiermee tonen we nogmaals de nood voor hulpmiddelen in de triage van patiënten met pijn op de borst, in het bijzonder voor huisartsen.

In **hoofdstuk 7** hebben we, om de impact van het probleem van NPOB te kwantificeren, de prognose en zorgconsumptie van NPOB patiënten geanalyseerd. De één-jaars mortaliteit van NPOB patiënten was 2.3% vergeleken met 7.2% in patiënten met cardiale pijn op de borst (CPOB) en de incidentie van MACE was 5.1% versus 8.3%. Een voorgeschiedenis van coronaire aandoeningen in NPOB patiënten werd als een voorspellende waarde gevonden voor een MACE. De zorgconsumptie door NPOB patiënten binnen de cardiologische afdeling was hoog. Patiënten met NPOB van onbekende oorzaak, hadden daarbij een grotere zorgconsumptie in vergelijking met NPOB patiënten met een bekende oorzaak. We concludeerde dat de prognose van NPOB patiënten gunstiger is dan die van CPOB patiënten. De prognose van deze patiënten is echter slechter ten opzichte van de algehele populatie door de aanwezigheid van risicofactoren en een voorgeschiedenis van coronaire aandoeningen. Dit onderzoek komt overeen met het onderzoek van **hoofdstuk 6** en benadrukt het belang van triage en (gevalideerde) triage hulpmiddelen voor patiënten met pijn op de borst.

In **hoofdstuk 8** analyseren we een triage hulpmiddel voor de triage door huisartsen van pijn op de borst patiënten in de URGENT trial. Hierbij ondersteunen wij de huisartsen met de HEART score, een risicoscore voor patiënten met pijn op de borst. Het is een Engels acroniem wat staat voor History (anamnese), ECG, Age (leeftijd), Risk factors (risicofactoren) en Troponine. Gezien een reguliere troponine test in de huisartsenpraktijk niet geadviseerd wordt vanwege logistieke knelpunten, hebben wij een point-of-care (POC) troponine tester gebruikt. Gedurende het onderzoek werd om economische redenen de POC tester van de markt gehaald. Dit was niet te wijten aan de veiligheid van de POC tester of de URGENT trial. De 40 geïncludeerde patiënten zijn als pilot studie geanalyseerd. Geen patiënten hebben een MACE opgelopen binnen de

follow-up van zes weken. De nauwkeurigheid van de verwijzingen verbeterde niet, waarschijnlijk als gevolg van de lage inclusie. De URGENT trial toont dat het gebruik van de HEART score op de huisartsenpost veilig en uitvoerbaar is. Het onderzoek heeft een verder vervolg nodig om de effectiviteit te bewijzen en huisartsen verder te ondersteunen met de triage van patiënten met pijn op de borst.

Concluderend laten we in **deel II** de noodzaak voor hulpmiddelen in de pre-hospitale triage van pijn op de borst patiënten zien. Het onderscheid maken tussen pijn op de borst patiënten zonder aanvullende onderzoeken is lastig en resulteert in een hoge zorgconsumptie. De HEART score, een risicoscore met gebruik van een ECG en een troponine test, lijkt veilig en haalbaar. Voor de pre-hospitale triage is er echter een snelle en betrouwbare POC troponine tester nodig om deze scorelijst te gebruiken.

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CURRICULUM VITAE

Karen Mol is geboren op 14 februari 1988 te Terneuzen als tweede dochter van Bernard en Linda Mol-Morgan. Op jonge leeftijd wist ze al dat zij arts wou worden en heeft daarvoor Gymnasium gedaan met het profiel Natuur en Gezondheid. In 2006 heeft zij haar eindexamen gehaald, echter werd zij helaas het eerste jaar uitgeloot voor de studie Geneeskunde. Na een jaar Biomedische Wetenschappen aan de Universiteit van Amsterdam is zij het tweede jaar wel ingeloot voor de studie Geneeskunde aan de Universiteit Maastricht. Haar eerste coschap was een keuze coschap Cardiologie te Maastricht Universitair Medisch Centrum. Dit beviel haar zo goed dat ze haar wetenschaps- en semi-arts stage heeft gedaan bij de Cardiologie in VieCuri Medisch Centrum voor Limburg Noord in Venlo. Vanuit haar wetenschapsstage is er een promotietraject gegroeid met als promotor Prof. Dr. P.A.F.M. Doevendans van het Universitair Medisch Centrum Utrecht en als copromotoren Dr. B.M Rahel en Dr. J.G. Meeder van VieCuri Medisch Centrum. Daarnaast was er ook een grote weggelegd voor Dr. M.J. Cramer van het Universitair Medisch Centrum. Begin 2018 is zij begonnen in Universitair Medisch Centrum Utrecht waar zij nog met veel plezier werkt. Ze woont samen met Tomas in Utrecht.