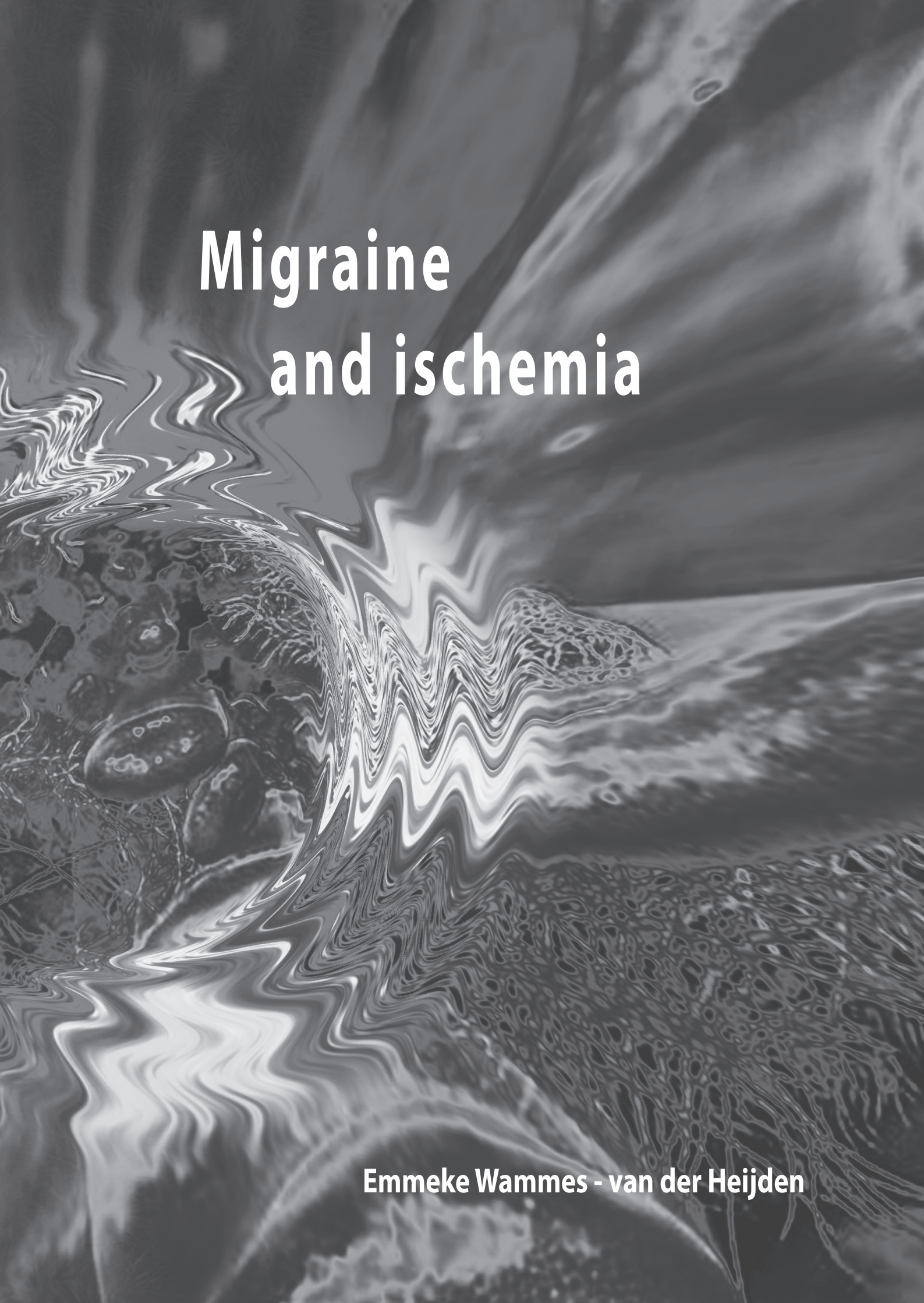

Migraine and ischemia

Emmeke Wammes - van der Heijden

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MIGRAINE AND ISCHEMIA

MIGRAINE EN ISCHEMIE
(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. J.C. Stoof, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op donderdag 11 juni 2009 des middags te 2.30 uur

door

ELISABETH ANNEMIEK VAN DER HEIJDEN

geboren op 19 april 1972 te Gemert

PROMOTOR: Prof.dr. A.C.G. Egberts

CO-PROMOTOR: Dr. C.C. Tijssen

“MAMA, IS HET KLAAR?”

“JA, HET IS KLAAR!!!”

CONTENTS

1

INTRODUCTION

MIGRAINE

Migraine is a very common paroxysmal headache disorder, characterized by various combinations of neurological, gastrointestinal, and autonomic changes. One year migraine prevalences in the general population for Western countries vary from 4% to 9% in men and from 11% to 25% in women. Non-Western countries report lower figures.[1,2] Prevalence continues to increase through middle life until approximately 40 years of age, after which it declines.[2,3] Migraine greatly affects quality of life and has a high socio-economic impact. The World Health Organization ranks migraine amongst the world's 20 most disabling medical illnesses.[4]

The word migraine is derived from the Greek word *hemicrania* (one-sided headache), introduced by the Roman doctor Galenus in the second century. This degenerated to *megrim* and subsequently, due to the French writer Rabelais, to *migraine*, which means grenade explosion. The diagnosis is based on the headache's characteristics and associated symptoms, i.e. the clinical phenotype. The International Headache Society (IHS) diagnostic criteria for headache disorders (1988)[5] have been revised in 2004. This second edition of the International Classification of Headache Disorders (ICHD-II) provides criteria for seven subtypes of migraine.[6] The two major subtypes are migraine without aura (MA-) and migraine with aura (MA+). The recurrent headache attacks last 4 – 72 hours. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or photophobia and phonophobia. MA+ is primarily characterized by the focal neurological symptoms that usually precede or sometimes accompany the headache. Most auras consist of transient visual symptoms, but also sensory, aphasic, or motor disturbances may occur.[6]

Treatment of migraine begins with making a diagnosis, explaining it to the patient, and developing a treatment plan that takes into account coincidental or comorbid conditions. Headache calendars are useful to record headache frequency, duration, severity and treatment response.[7] Pharmacotherapy can be acute (abortive) or preventive (prophylactic); patients may need both approaches. Acute treatment can be specific (ergotamine and triptans [$5HT_{1B/D}$ agonists]) or non-specific (e.g. acetaminophen and nonsteroidal anti-inflammatory drugs [NSAIDs]). The choice of treatment depends on the severity and frequency of the attacks, associated symptoms, coexistent disorders, previous treatment response, patient preference, and the drug characteristics such as efficacy, potency for overuse, and adverse events. A non-oral route of administration and an anti-emetic can be considered in case of severe nausea or vomiting. For a long period of time the pharmacologically unspecific ergot alkaloids were the only specific abortive migraine drugs available, the fear and risk of ischemic complications limiting their use. Currently, triptans,

with sumatriptan as their first representative introduced in 1991, are first-line drugs for severe attacks and for less severe attacks that do not adequately respond to standard analgesics. Early intervention prevents escalation and can increase the effectiveness of migraine treatment.[7] Preventive drugs reduce attack frequency, duration, or severity. Choice is based on effectiveness, adverse events, and coexistent and comorbid conditions. Preventive drugs with the best documented effectiveness are the β-adrenergic blockers propranolol and metoprolol, valproic acid and topiramate.[7]

Although recent advances in treatment, especially the introduction of triptans, have increased the scientific, medical and social interest and attention for migraine, this disorder still remains underdiagnosed and undertreated.[8-10] This is in part due to underrecognition of migraine by patients themselves and lack of a simplified diagnostic test.

PATHOPHYSIOLOGY

Although family and twin studies show that there is a genetic component to migraine, no genes predisposing to common forms of the disorder have yet been identified. The most encouraging findings have emerged from the identification of genes causing rare Mendelian traits that phenotypically resemble migraine. These studies have pointed migraine research towards ion-transport genes; however, currently there is no direct evidence of the involvement of these genes in common forms of migraine.[11]

For many years migraine was considered primarily a vascular phenomenon. The migraine aura was thought to be caused by cerebral vasoconstriction and the headache by reactive vasodilatation,[12] which explained the headache's throbbing quality and its relief by ergots. However, headache often begins while cortical blood flow is reduced,[13,14] thus, headache is not caused by simple reflex vasodilatation. Moreover, considering the associated features of the attack such as nausea, vomiting, photophobia and phonophobia, the vascular hypothesis as an isolated phenomenon, seems unattractive.

Cortical spreading depression (CSD) is now generally accepted to be the underlying mechanism of the aura.[15] CSD induces the release of hydrogen ions, potassium ions and other agents, including arachidonic acid and nitric oxide, in the extracellular space of the neocortex. These agents diffuse towards local blood vessels and depolarize perivascular trigeminal terminals, which, in turn, causes activation of the trigeminal nucleus complex in the brainstem.[16] The aura is associated with an initial hyperaemic phase followed by reduced cortical blood flow, persisting from

30 minutes to six hours, then slowly returning to baseline or increase.[7] Headache probably results from activation of meningeal and blood vessel nociceptors combined with a change in central pain modulation. Headache and its associated neurovascular changes are subserved by the trigeminal system. Trigeminal sensory neurons contain neuropeptides. Stimulation results in release of these peptides and neurogenic inflammation. The neuropeptides interact with the blood vessel wall, producing dilatation, plasma protein extravasation, and platelet activation. Neurogenic inflammation sensitizes nerve fibres (peripheral sensitization) that respond to previously innocuous stimuli, such as blood vessel pulsations, causing, in part, the pain of migraine. Central sensitization can also occur.[7] CSD activates the trigeminovascular system, linking the aura and headache mechanisms.[7,16] These findings support the current view that migraine is fundamentally a disorder of brain function, not of blood vessels.

Although considerable knowledge is available on the mechanisms once the attack has started, it is to a large extent unclear what triggers an attack to begin. It might be that these triggers vary between persons and between different subtypes of migraine. One of the suggested triggers has been ischemia.[17,18]

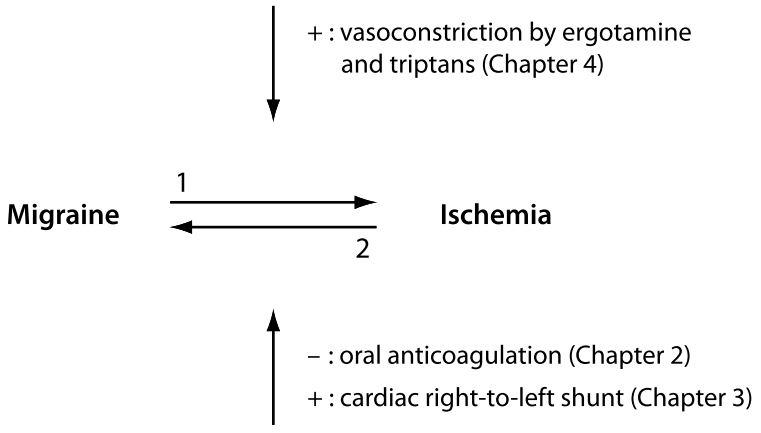
MIGRAINE AND ISCHEMIA

An association between migraine and ischemic events has been debated for many years. Whether migraine is a risk factor for ischemic events (Figure 1, arrow 1) or ischemia triggers migraine (Figure 1, arrow 2), or both, is still unclear.

The vascular component of migraine and the clinical observation of a close association between migraine and ischemic stroke among young women started a debate concerning whether or not migraine is a risk factor for ischemic stroke (arrow 1).[19] Nowadays, migraine, and particularly MA+, has been consistently associated with an increased risk of ischemic stroke in several studies of various designs.[20-23] The risk is especially increased in younger women with MA+, but is also apparent in older individuals. Moreover, results from imaging studies indicate that migraine is associated with clinically silent brain lesions, mostly in the white matter.[24] The Dutch population-based CAMERA (Cerebral Abnormalities in Migraine, an Epidemiological Risk Analysis) study found that migraine patients had a significantly higher prevalence of white matter hyperintense lesions and infarct-like lesions in the cerebellar region of the posterior circulation (PC) territory of the brain, notably in patients with aura.[25] Clinical and neuroimaging characteristics of migraine patients from the CAMERA study with these PC infarct-like lesions suggest that a combination of (possibly migraine attack-related) hypoperfusion

and embolism is the likeliest mechanism for these infarctions in migraine, and not atherosclerosis or small-vessel disease.[26] Recent data from two prospective cohort studies also suggest an association between migraine and ischemic cardiovascular disease.[27,28] Findings from the Women's Health Study, in which information on migraine aura was recorded, indicate that this association is limited to migraineurs with aura.[27]

Figure 1 Possible relationships between migraine and ischemia



The biological mechanisms by which migraine may cause ischemic vascular events (arrow 1) are currently unclear and likely to be complex. Potential mechanisms include: a higher prevalence of cardiovascular risk factors among patients with migraine, interrelationship between migraine and existing vascular pathologies, hypercoagulability, and shared genetic factors.[29,30] The vasoconstrictive properties of specific antimigraine drugs such as ergotamine and triptans might also influence the relationship between migraine and ischemic events.[31,32]

However, the relationship between migraine and ischemia might be bi-directional: migraine may be cause (arrow 1) or consequence (arrow 2) of ischemia, or both. As mentioned above, hypercoagulability may be a factor in the ischemic risk in migraine.[30,33] In an alternative scenario, hypercoagulability-related cerebral ischemia may induce cortical spreading depression, i.e. symptomatic migraine (arrow 2). The results of a study in 1993 show that ischemia-induced migraine attacks may be more frequent than migraine-induced ischemic insults.[17] This hypothesis is supported by reports in the literature about improvement of migraine during treatment with oral anticoagulants.[34-40] Furthermore, there is increasing evidence

that migraine, and particularly MA+, is associated with increased prevalence of cardiac right-to-left shunts (RLS), like patent foramen ovale (PFO) and atrial septal aneurysm.[41-47] The basis for this association is uncertain, but there is evidence for dominant inheritance of atrial shunts, which is linked to inheritance of MA+ in some families.[48] Since these interatrial septal abnormalities are demonstrated risk factors for ischemic stroke,[49,50] this coexistence of RLS and migraine may, at least partly, explain the increased risk for ischemic stroke in patients with MA+ (arrow 1). On the other hand, observations of improvement and even disappearance of migraine symptoms after closure of the PFO suggest a causal relationship.[44,51-57] It is hypothesized that RLS may lead to subtle emboli entering the central circulation and subsequently may trigger a migraine attack (arrow 2).[51] An increased prevalence of migraine has also been shown in patients with pulmonary right-to-left shunts, due to pulmonary arteriovenous malformations (PAVM).[58,59] One study showed a decrease in prevalence of migraine after embolization of PAVM in patients with hereditary hemorrhagic telangiectasia, suggesting that the presence of a right-to-left shunt rather than the localization of this shunt plays a causative role in the pathogenesis of migraine.[60]

OBJECTIVES OF THE THESIS

The central theme of this thesis is the possible relationship between migraine and ischemia. The main objectives are to gain insight in:

- the effect of anticoagulants on migraine;
- the possible relationship between cardiac right-to-left shunts and migraine;
- the use of antimigraine drugs in relation to ischemic complications and cardiovascular disease.

Different research principles and methods were applied to attain these objectives: a case series, a randomized clinical trial, a systematic review, diagnostic research, a retrospective nested case-control study, and a retrospective observational drug utilization study.

OUTLINE OF THE THESIS

This thesis contains five chapters. In this introductory chapter (Chapter 1) the scope, objectives and outline are provided. Next, the individual research projects of the thesis are described in three chapters: the effect of anticoagulants on migraine (Chapter 2); cardiac right-to-left shunts and migraine: a causal relationship?

(Chapter 3); antimigraine drug use, ischemic complications and cardiovascular disease (Chapter 4). The results and future perspectives are discussed in Chapter 5.

The effect of anticoagulants on migraine (Chapter 2)

As outlined above, there is some evidence that a prothrombotic tendency may be involved in the pathogenesis of migraine.[33] The positive effect of anticoagulants on migraine has been described in case reports and observational studies.[34-40] This has not been studied in a randomized, controlled fashion. In addition, it remains unclear whether a positive effect, if any, concerns only a select group of migraineurs with certain common characteristics. Chapter 2.1 describes the results of an open study, which involved four patients with migraine who reported a substantial decrease in the frequency of their migraine attacks during previous therapeutic use of oral anticoagulants. The presence of thromboembolic risk factors and the effect of low-intensity acenocoumarol treatment on migraine were investigated in these patients. Based on the results of this study and other mainly observational evidence, we conducted a randomized, open, crossover study in migraine patients investigating the effect of low-intensity acenocoumarol treatment on the frequency and severity of migraine attacks compared with propranolol (Chapter 2.2).

Cardiac right-to-left shunts and migraine: a causal relationship? (Chapter 3)

Both cardiac RLS and MA+ are known risk factors for ischemic stroke.[49,50] Several studies have shown that the prevalence of a cardiac RLS in patients with MA+ is significantly higher than in patients without migraine.[41-47] To assess the strength of the possible relationship between RLS and migraine, the literature concerning this subject was systematically reviewed (Chapter 3.1).

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a rare hereditary disease characterized by recurrent transient ischemic attacks, strokes, cognitive decline, and MA+. A very high prevalence of RLS (4/5, 80%) was found in an Italian family with CADASIL. All patients with CADASIL and MA+ (4/4) showed RLS.[61] We investigated the prevalence of RLS in patients with CADASIL with MA+ and compared it with the prevalence of RLS in CADASIL patients without migraine (Chapter 3.2).

Antimigraine drug use, ischemic complications and cardiovascular disease (Chapter 4)

Due to their vasoconstrictive properties ergotamine and triptans can cause serious complications such as myocardial infarction, ischemic stroke, and ischemic colitis, mostly in patients with cardiovascular disease or risk factors.[62-68] The incidence

of ischemic complications is low when the specific antimigraine drugs are used appropriately.[69-72] However, it remains unclear whether overuse of triptans or ergot alkaloids is associated with an increased risk of ischemic events. In a retrospective nested case-control study we investigated whether the intensity of triptan and ergotamine use, in specific overuse, is associated with the risk of serious ischemic complications that require hospitalization (Chapter 4.1). Prescribers' concerns about the cardiovascular safety may limit the use of specific antimigraine drugs. Due to growing evidence that the incidence of triptan-associated serious cardiovascular adverse events in both clinical trials and clinical practice appears to be extremely low, this concern may change over time. It is presently unclear to what extent triptans and ergotamine are prescribed to patients with a low or high cardiovascular risk profile. Chapter 4.2 describes the baseline cardiovascular risk profile among new users of specific antimigraine drugs and its change over time.

General discussion

Finally, in Chapter 5 the studies presented in this thesis are put in a broader perspective.

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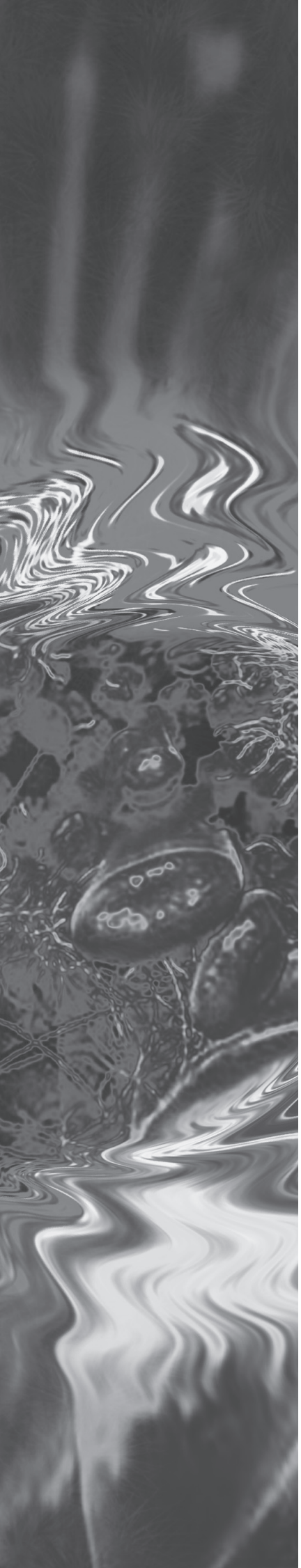
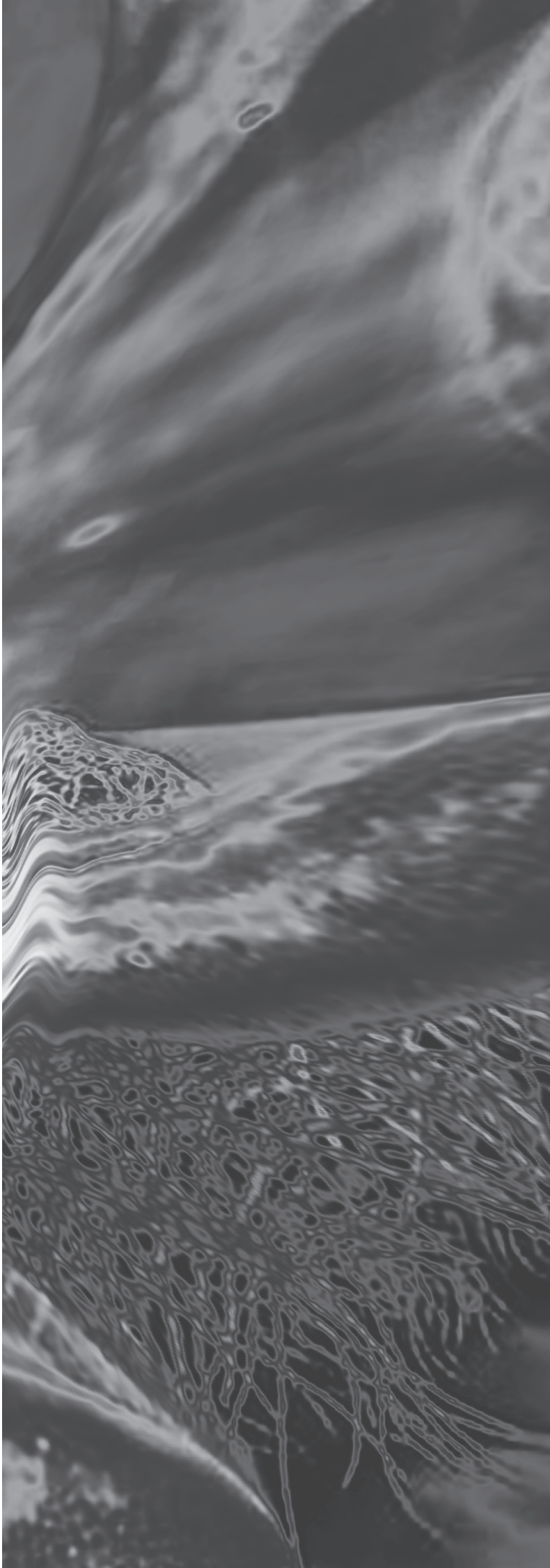
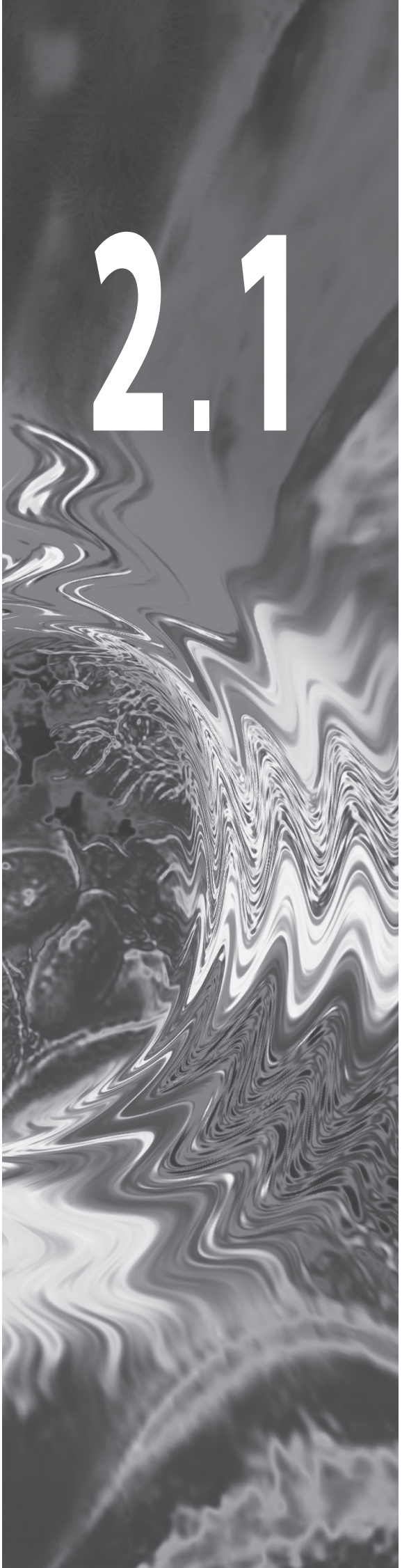


2

THE EFFECT OF ANTICOAGULANTS ON MIGRAINE





2.1

A THROMBOEMBOLIC PREDISPOSITION AND THE EFFECT OF ANTICOAGULANTS ON MIGRAINE

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ABSTRACT

Objective

To investigate the presence of thromboembolic risk factors and the effect of low-intensity acenocoumarol therapy on migraine in patients who spontaneously reported a reduction of their migraine attacks during previous therapeutic use of anticoagulants.

Background

The positive effect of anticoagulants on migraine has been described in case reports and observational studies. It remains unclear whether this concerns only a select group of migraineurs with certain common characteristics.

Methods

In four migraineurs with a self-reported reduction of attack frequency during previous use of anticoagulants (international normalized ratio [INR] 2.5 to 4.0), the presence of thromboembolic risk factors and the effect of low-intensity acenocoumarol therapy (INR 1.5 to 2.0) on migraine attacks were prospectively investigated in an open study.

Results

All patients had one or more thromboembolic risk factors. Two patients, both with factor V Leiden heterozygosity, experienced a clear improvement of migraine during low-intensity acenocoumarol therapy.

Conclusions

Our findings support the hypothesis that migraine, as a phenotype, has different underlying mechanisms, amongst which a thromboembolic tendency. In this group of patients, oral anticoagulants may be a suitable form of migraine prophylaxis, but this needs further clinical investigation.

INTRODUCTION

During the last decade, attention has been given to the increased risk for ischemic events in patients with migraine. Crassard et al. reviewed the contribution of hemostasis to the ischemic risk in patients with migraine, particularly with regard to platelet hyperaggregability, antiphospholipid antibodies, and congenital thrombophilia.[1] They concluded that all three factors might contribute to the ischemic risk of migraine.

Much less attention, however, has been focused on the effect of anticoagulation in migraineurs. Since 1979, five case reports have been published describing patients with migraine in whom the frequency of migraine attacks clearly decreased during treatment with an oral anticoagulant.[2-6] In addition, a questionnaire study among 400 patients treated with the oral anticoagulant, acenocoumarol (for nonneurologic indications), reported an improvement of headache in 63% of patients with migraine and 38% of patients with nonmigraineous headaches.[7] Furthermore, a recent, observational, retrospective, follow-up study showed a clear decrease in sumatriptan and ergotamine use during acenocoumarol therapy.[8]

Although no randomized clinical trials have been conducted so far and the mechanism has not been fully elucidated, these observational findings suggest that coumarin therapy may offer beneficial prophylactic effects for the migraineur. It may well be that only a select group of migraineurs, with certain common characteristics, will respond to treatment with anticoagulants.

This study investigated the presence of thromboembolic risk factors in four patients who spontaneously reported a decrease in migraine attacks during previous use of oral anticoagulants. The effect of low-intensity acenocoumarol (target international normalized ratio [INR] 1.5 to 2.0) in these patients also was evaluated.

PATIENTS AND METHODS

An open study was performed, which involved four patients with migraine (diagnosed according to the criteria of the International Headache Society [IHS]) who reported a substantial decrease in the frequency of migraine attacks during previous use of oral anticoagulants.

Two patients spontaneously reported improvement of their migraine to a nurse at the Thrombosis Services during therapeutic use of oral anticoagulants (for a deep venous thrombosis after a broken ankle without thrombosis prophylaxis in one patient and atrial fibrillation in the other). The third patient noticed a remarkable decrease in attack frequency (one attack in six months) during use of oral anticoagulants (for a posterior inferior cerebellar artery infarction after a vertebral

dissection), which subsequently returned to the normal attack frequency of about one attack per month after discontinuation of the oral anticoagulant. He spontaneously reported this experience to his general practitioner. The fourth patient recalled a time without migraine during anticoagulation (for placement of a spondylodesis) when reading about an ongoing trial with low-intensity acenocoumarol as migraine prophylaxis. All patients were referred to a neurologist.

The patients were informed about the nature of the study by a neurologist and by written information. The Ethics Committee for Medical Research of the hospital approved the study protocol. All patients gave informed consent before enrollment.

We took blood from the patients to screen for thrombotic risk factors including anticardiolipin antibodies (aCL), lupus anticoagulant (LA), protein C/S deficiency, factor V Leiden, antithrombin III deficiency, prothrombin G20210A, hyperhomocysteinemia, factor VIII, von Willebrand factor, and thrombocythemia. An independent cardiologist performed a transesophageal echocardiography to screen for patent foramen ovale (PFO) and atrial septal aneurysm, both risk factors for ischemic stroke. Magnetic resonance imaging (MRI) was performed to look for ischemic brain lesions.

Before we allowed the patient to start acenocoumarol, it was necessary for the following parameters to be within the reference range: bleeding time (INR and activated partial thromboplastin time), complete blood count, liver function, renal function, and sodium and potassium levels.

After a run-in period of eight weeks, the patients received low-intensity acenocoumarol during twelve weeks (target INR 1.5 to 2.0). During this period, the INR was checked at the Thrombosis Services at least once every two weeks. There was continuous surveillance of possible interactions with comedication. After discontinuation of acenocoumarol, the patients were followed for another eight weeks. Throughout the entire study, patients kept diary cards on which they registered attack characteristics. Patients were allowed to use the following symptomatic medications: metoclopramide, domperidone, acetaminophen, and triptans. Use of prophylactic treatment of migraine other than the study medication was not allowed during the study. Each month the patient visited the outpatient clinic of neurology for evaluation.

The primary endpoint was the difference in attack frequency between the treatment period and the run-in period. Secondary endpoints were number of hours with migraine, use of drugs for symptomatic relief, patient preference, and adverse events.

RESULTS

All four patients had one or more thromboembolic risk factors (Table 1). None of the MRI scans showed ischemic abnormalities other than known from former clinical diagnosis.

Patient 1, with factor V Leiden heterozygosity, showed 71% fewer migraine attacks during low-intensity acenocoumarol therapy than during the run-in period (Figure 1). In both patients with factor V Leiden heterozygosity (patients 1 and 4), the attack duration in hours was reduced by 84% in patient 1 and by 73% in patient 4. After discontinuation of acenocoumarol, the observed improvement disappeared and both patients preferred to restart low-intensity acenocoumarol. Patients 2 and 3 discontinued treatment, because, in contrast to previous use, no improvement of migraine was observed (Figure 1). No serious adverse events were noted.

Table 1 Results of screening for thromboembolic risk factors

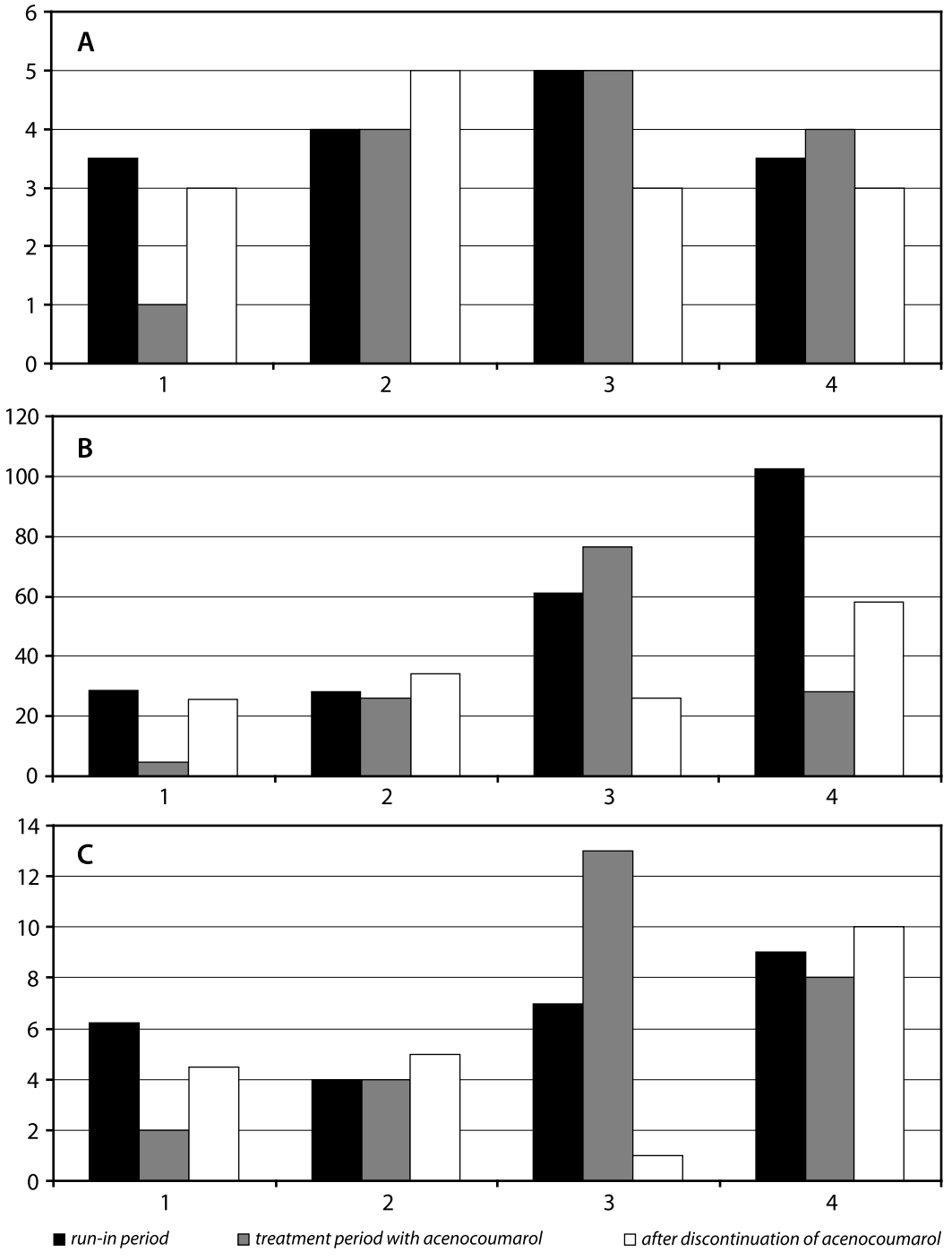
Patient	Sex, Age (y)	Age (y) at first migraine attack	Indication for therapeutic anticoagulation	Blood tests	TEE	MRI
1	F, 29	23	deep venous thrombosis	Factor V Leiden heterozygote	no abnormality	no abnormality
2	F, 69	54	atrial fibrillation, brainstem infarction	Factor VIII 197% vWF antigen 161% vWF activity 178%	PFO	pons infarct
3	M, 29	23	vertebral dissection with PICA infarction	Factor VIII 186% vWF antigen 203% vWF activity 150% LA positive aCL negative	no abnormality	PICA infarct
4	F, 46	40	surgery for spondylodesis	Factor V Leiden heterozygote homocysteine 22 µmol/L	not performed	no abnormality

TEE = transesophageal echocardiography; MRI = magnetic resonance imaging; vWF = von Willebrand factor; PFO = patent foramen ovale; PICA = posterior inferior cerebellar artery; LA = lupus anticoagulant; aCL = anticardiolipin antibodies

DISCUSSION

All four patients who experienced a decrease in attack frequency during previous use of anticoagulants had one or more thromboembolic risk factors. During repeated anticoagulation with a lower target INR, two patients experienced, again, a clear improvement of their migraine.

Figure 1 **Efficacy parameters in four patients with migraine during the run-in period, treatment period, and after discontinuation of acenocoumarol**



The run-in period (mean per month of eight weeks) is compared with the last four weeks of the treatment period and the last four weeks of the evaluation period (taking a washout period into account).
Duration of treatment period: patient 1, 12 weeks; patient 2, 11 weeks; patient 3, 7 weeks; patient 4, 12 weeks.
A. Attacks per month. A succesfully treated attack which returns within 24 hours is considered as one attack.
B. Hours with migraine per month.
C. Defined daily dose for symptomatic treatment per month.

The positive effect of anticoagulants on migraine, as described in case reports and observational studies,[2-8] also has been observed in two specific groups of patients with thromboembolic risk factors. Cuadrado et al. observed a dramatic improvement of migraine during treatment with warfarin in eight patients with the antiphospholipid syndrome (caused by aCL, LA, or both) and subsequent stroke.[9]
In patients with a right-to-left shunt, migraine, especially migraine with aura (MA+), may improve after anticoagulant therapy. In a study that investigated the frequency of PFO and MA+ in 74 patients admitted for acute stroke, five of six patients having PFO and MA+ who were treated with anticoagulants in order to prevent recurrent stroke, noticed complete disappearance of their MA+ attacks.[10]
The presence of thromboembolic risk factors in all four of our patients suggests that improvement of migraine during treatment with anticoagulants may be applicable to a select group of patients with a prothrombotic predisposition or PFO. Only two of the patients showed improvement of migraine during treatment with low-intensity acenocoumarol, suggesting that the effect may be dependent on the degree of anticoagulation. We used the low INR target range for ethical reasons.
The small number of patients and lack of controls limited our study. Nevertheless, when randomly screening four patients with migraine for thrombotic risk factors, it is unlikely to find a prothrombotic state in all four. The open study limits the interpretation of the results. The strong reduction found in two patients, however, is probably not only due to a placebo effect, which is normally not more than about 30%. Moreover, initially all patients spontaneously reported improvement of their migraine before entering the study. Initially, worsening of migraine after discontinuation of previous use of anticoagulants could bias the results. The period between discontinuation of previous use of anticoagulants and the start of the run-in period of the current study, however, was eight, seven, and four months and six years – long enough to assume the normal attack frequency to return.
Our findings support the hypothesis that migraine, as a phenotype, has different underlying mechanisms, amongst which a thromboembolic tendency. In this group of patients, oral anticoagulants may be a suitable form of migraine prophylaxis. Use of oral anticoagulants for migraine prophylaxis, however, needs further investigation, raising the question whether the potential benefit of a better health-related quality of life outweighs the potential risk of bleeding complications.

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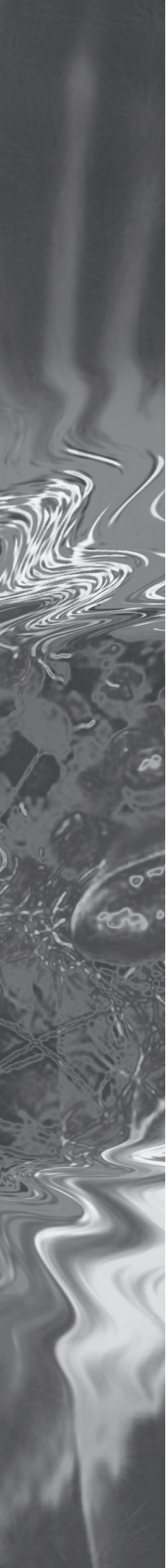

2.2

EFFECT OF LOW-INTENSITY ACENOCOUMAROL ON FREQUENCY AND SEVERITY OF MIGRAINE ATTACKS

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ABSTRACT

Objective

To investigate the effect of low-intensity acenocoumarol treatment (target international normalized ratio [INR] 1.5 to 2.0) on the frequency and severity of migraine attacks.

Background

The positive effect of anticoagulation on migraine has been described in case reports and observational studies.

Methods

We conducted a randomized, open, crossover study in migraine patients. After a run-in period of eight weeks, all patients received acenocoumarol or propranolol during a period of twelve weeks and, after a washout period of two weeks, propranolol or acenocoumarol during a second period of twelve weeks.

Results

Nineteen patients fulfilling the criteria were included. In twelve patients with complete data collection, only one good responder could be noted. In the other patients, treatment with low-intensity acenocoumarol did not show improvement of migraine symptoms compared with the run-in period. Treatment with propranolol showed a trend towards improvement compared with the run-in period. No serious adverse events were observed.

Conclusions

Overall, low-intensity acenocoumarol treatment has no prophylactic effect in migraine patients.

INTRODUCTION

The drugs recommended for prophylactic therapy of migraine show a limited effectiveness and a great interindividual variability. In addition, some of these drugs may cause troublesome, sometimes severe, adverse effects, which can contribute to noncompliance.

There is some evidence that a prothrombotic tendency may be involved in the pathogenesis of migraine.[1] Positive effects of anticoagulation as migraine prophylaxis have only been described in observational reports. In 1977, Thonnard Neumann showed that administration of heparin (injected or inhaled) reduced the frequency and severity of migraine attacks.[2] Since 1979, five case reports have been published that described a remarkable reduction of the frequency and severity of migraine attacks during treatment with phenprocoumon,[3] acenocoumarol,[4] and warfarin.[5-7] After discontinuation of the treatment, the attacks returned. A patient questionnaire study among 400 trial subjects treated with acenocoumarol for nonneurological indications revealed that treatment with oral anticoagulants produced improvement of headache in 63% of patients with migraine versus 38% of patients with nonmigraineous headache.[8] Recently, an observational retrospective follow-up study was performed, showing that treatment with coumarins when compared to low-dose acetylsalicylic acid led to a significant reduction in the consumption of specific abortive migraine drug use.[9]

The abovementioned observational findings indicate that coumarin therapy may offer beneficial prophylactic effects to the migraineur. No controlled trials have been conducted so far. Therefore we performed a randomized, controlled, crossover study to investigate the effect of low-intensity acenocoumarol therapy (international normalized ratio [INR] 1.5 to 2.0) on the frequency and severity of migraine attacks compared to the run-in period and propranolol therapy.

PATIENTS AND METHODS

Setting and study population

The study started in March 2001 at the outpatient clinic of the Department of Neurology, St. Elisabeth Hospital Tilburg, serving a catchment population of approximately 200 000 persons in the Southern part of the Netherlands. Potential study patients were informed about the study by their neurologist while consulting the outpatient clinic of the Department of Neurology of the St. Elisabeth Hospital or the TweeSteden Hospital in Tilburg, by their general practitioner or local pharmacist in the area Midden-Brabant, and by an advertisement in the paper of the Dutch Federation of Headache patients.

Inclusion criteria were diagnosis of migraine with and without aura according to the criteria of the International Headache Society, men and women aged between 18 and 60 years, onset of migraine before the age of 50 years, and attacks occurring three to eight times a month during last year. Patients already had to have tried at least one drug for migraine prophylaxis without sufficient effectiveness. Exclusion criteria were use of other prophylactic drugs for migraine during the study period, interval headaches not clearly differentiated from migraine, > 6 interval headaches per month, overuse of analgesics, ergotamin or triptans, use of estrogens for < 6 months, hypersensitivity or contraindications for coumarin derivatives or propranolol, use of heparin or low molecular weight heparin during the study period, use of any drug that inhibits the platelet aggregation (eg, nonsteroidal anti-inflammatory drugs [NSAIDs], [low-dose] aspirin, selective serotonin reuptake inhibitors, clopidrogel, dipyridamol), pregnancy, lactation, inability to maintain adequate birth control, increased risk of bleeding (history of, or current hemostatic or platelet disorder, thrombocytopenia [platelet count < 120 000/µl], thrombopathy, cerebrovascular accident, gastrointestinal bleeding), decreased renal or hepatic function, hypertension, recent myocardial infarction, or diabetes mellitus type I or II.

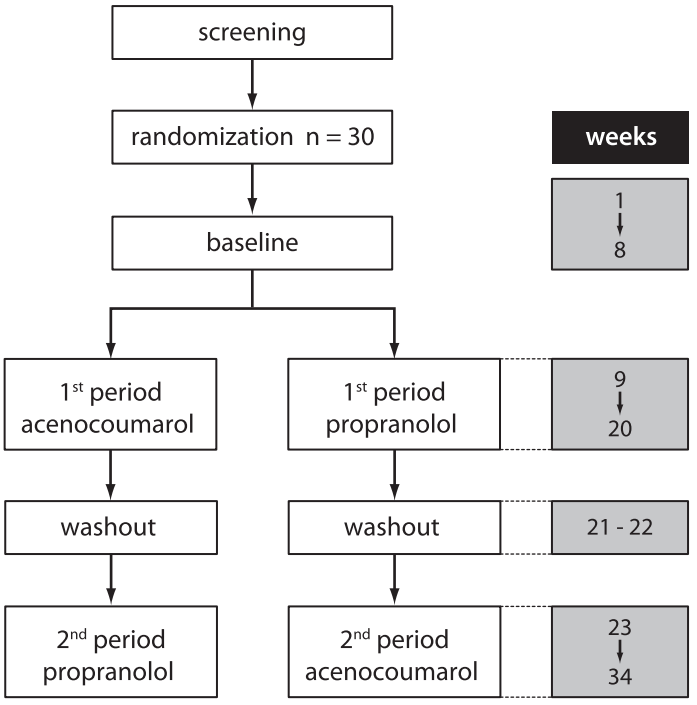
The Ethics Committee for Medical Research of the St. Elisabeth Hospital approved the study protocol. All patients had to give written informed consent before enrollment.

Study design

We conducted a randomized, open, crossover study (Figure 1). Patients who fulfilled the inclusion criteria were allocated to treatment according to a randomization procedure with five consecutive blocks of six patients (three with acenocoumarol during first period, three with propranolol during first period). Throughout the study period, the patients kept diary cards on which they recorded the characteristics of their migraine attacks. Patients started with a run-in period of eight weeks, followed by the first treatment period of twelve weeks during which acenocoumarol (INR 1.5 to 2.0) or propranolol was used. Propranolol (retard capsule) was started with a dosage of 80 mg once daily, if possible increased to 80 mg twice daily after two weeks. After a washout period of two weeks, the second treatment period of twelve weeks followed. Patients visited the neurologist or study nurse once a month throughout the study period. During treatment with acenocoumarol, the INR was measured at least once every two weeks at the Thrombosis Services. Patients were allowed to use triptans and acetaminophen for symptomatic treatment.

Primary endpoint variable was the intraindividual change in the number of migraine attacks per month during the treatment period with acenocoumarol

Figure 1 Study design



compared to the run-in period. Secondary endpoint variables were intraindividual changes in the number of hours with migraine and defined daily doses (DDDs) of triptans; comparison with propranolol; adverse events (especially bleeding); and preference of the patient.

A reduction in attack frequency compared to the run-in period of ≥ 50% was considered to be clinically relevant. Assuming at least three attacks per month during the run-in period and a standard deviation of two, which is the extreme estimate for a crossover trial,[10] with a given power of 90% and $\alpha = 5\%$, 21 evaluable patients were needed to detect the defined, clinically considered reduction in attack frequency. An interim analysis was done after twelve patients.

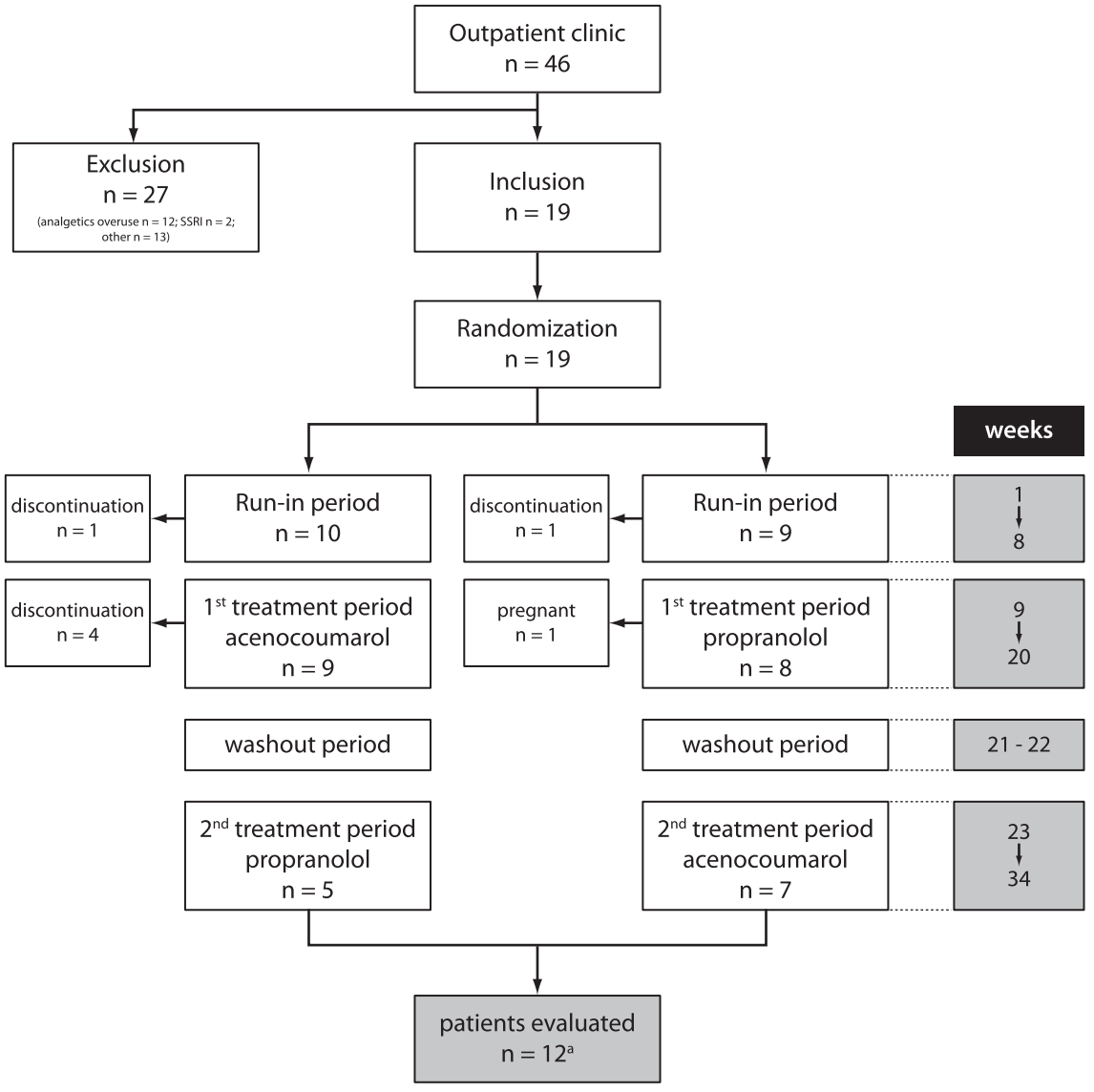
Statistical analysis

The Wilcoxon signed rank test was used to compare endpoint variables with the run-in period and the treatment period with propranolol. Treatment periods were considered to be statistically significantly different if $p < 0.05$. The statistical package SPSS for Windows (version 10.0) was used for data-analysis.

RESULTS

Since March 2001, 46 candidate patients were seen at the outpatient clinic of the Department of Neurology (details are provided in Figure 2). Up to November 2002, 18 women and one man were included who fulfilled all criteria. The main reason for exclusion of other patients was medication overuse (n = 12). Of these 19 patients, two patients discontinued during the baseline period for private reasons. One patient discontinued during her first treatment period with propranolol because

Figure 2 Trial profile



SSRI = selective serotonin reuptake inhibitor

a) One of the twelve patients discontinued treatment with acenocoumarol (second treatment period) after ten weeks.

she became pregnant. Four patients discontinued during the treatment period with acenocoumarol. In three of these patients, the reason for discontinuation was no improvement of migraine after three, six, and seven weeks of treatment with acenocoumarol. The fourth patient discontinued after four weeks of treatment with acenocoumarol for private reasons. Twelve patients completed the study. Mean age was 41.5 years (range 24 – 59). Four patients had migraine with aura, eight patients had migraine without aura (Table 1).

Table 1 Baseline characteristics (n = 12)

Characteristic	
Mean age in years (range)	41.5 (24 – 59)
Gender (men:women)	0:12
Migraine with aura	4
Migraine without aura	8
Mean age of first migraine attack (range)	18.5 (8 – 33)
Mean duration of migraine in years (range)	23.0 (6 – 39)
Mean attack frequency per month during the run-in period (range)	3.6 (2 – 7.5)
Mean hours with migraine per month during the run-in period (range)	87 (28.5 – 228.5)
Mean DDDs triptans per month during the run-in period (range)	6.8 (1.5 – 13)

DDDs = defined daily doses

The interim analysis pointed out that it was not possible to reach statistically significant improvement for low-intensity acenocoumarol treatment compared with the run-in period with the calculated number of 21 patients. Therefore the trial was discontinued prematurely.

Treatment with low-intensity acenocoumarol did not show improvement of migraine symptoms compared with the run-in period (Table 2). A reduction of at least 50% (for attack frequency, hours with migraine and DDDs triptans) was seen in two patients during acenocoumarol treatment compared with the run-in period. However, only one of these patients experienced this improvement herself and preferred low-intensity acenocoumarol therapy.

Treatment with propranolol showed a not statistically significant improvement compared with the run-in period (Table 2). In comparison with the run-in period, a reduction of at least 50% was seen in five patients for attack frequency and hours with migraine and seven patients for DDDs triptans during treatment with propranolol. Six patients preferred to continue with propranolol prophylaxis at the end of the trial.

Table 2 **Intraindividual change in twelve patients during the run-in period (mean per month during eight weeks) compared with the last four weeks (week 9 to 12)[a] of the treatment period with acenocoumarol and the last four weeks of the treatment period with propranolol**

	Acenocoumarol		Propranolol	
	Mean change % (range)	p-value	Mean change % (range)	p-value
Attack frequency per month [b]	+18.3 (-78 – 200)	0.42	-22.0 (-100 – 67)	0.14
Hours with migraine per month	+7.2 (-84 – 129.5)	0.88	-27.7 (-100 – 114)	0.14
DDDs triptans per month	+11.4 (-90.5 – 140)	0.58	-31.6 (-100 – 166.7)	0.08

a) One patient discontinued treatment with acenocoumarol after ten weeks. For this patient the efficacy parameters of week 7 to 10 were used for the analysis.
b) A migraine attack treated successfully with medication but with relapse within 24 hours counts as one attack.

Comparison of the treatment period with acenocoumarol to the treatment period with propranolol showed a (not statistically significant) deterioration of migraine to the disadvantage of acenocoumarol. Mean intraindividual changes of +1.4 attacks per month ($p = 0.08$), +24.2 hours with migraine per month ($p = 0.14$), and +2.8 DDDs triptans per month ($p = 0.10$) were observed.
No serious adverse events were observed (Table 3).

DISCUSSION

During treatment with low-intensity acenocoumarol, only one of twelve patients experienced a clinically relevant improvement of migraine compared to the run-in period. No major bleedings occurred.
In designing this study, we faced a major ethical dilemma, namely answering the question whether a better quality of life and new knowledge about targets for the development of drugs for migraine prophylaxis on the one hand weighs against the risk of major bleeding complications in patients with a disabling though not life-threatening disease on the other hand.
Major bleeding[a] is the most important complication of coumarin therapy. From several studies regarding this subject, it is possible to estimate the risk of bleeding complications during anticoagulation therapy. Using the results of a study that

[a] Major bleeding complications are usual defined as intracranial hemorrhage, bleedings that cause death, that require blood transfusion, admission to a hospital or surgery, and all muscle and joint bleedings

Table 3	Adverse events in migraine patients treated with acenocoumarol and propranolol	
	Acenocoumarol (n = 12)	**Propranolol (n = 12)**
Menorrhoea	5	-
Hematoma after injection	1	-
Nose bleeding	1	-
Fatigue	1	7
Dizziness	-	2
Bradycardia (≤ 56 per minute)	-	1
Cold/tingling extremities	-	5
Nightmares/restless sleeping	-	4
Weight gain	-	1

investigated the frequency of bleeding complications in patients treated by the Leiden Thrombosis Service in the Netherlands,[11,12] we calculated that the probability to observe one major bleeding in our study is maximal 0.06%. Although often perceived differently, this risk is in the same order of magnitude as serious complications with the chronic use of NSAIDs. The risk is probably further reduced by exclusion of high-risk patients, a low-target INR, and strict control of the INR. As is common in the Netherlands there was continuous surveillance of possible interactions with comedication. Based on these considerations and the severity of migraine of the included patients, we felt it justified to perform the study.

The guidelines for controlled trials of drugs in migraine recommend to perform double blind placebo controlled trials for migraine prophylaxis.[13] For practical difficulties, as for example three-months INR control during placebo treatment requiring unnecessary venapunctures and placebo dosage advices, we chose to set up an open crossover study. Furthermore, we chose a comparison with baseline as our primary endpoint and as base of our sample size calculation. Given the limited observational evidence concerning anticoagulants and migraine, we considered a small trial more justified. A trial to prove equivalence with propranolol requires far more patients.

It was hard to find eligible patients, largely depending upon the strict inclusion and exclusion criteria that were maintained. For instance, 22% of the patients did not use properly a prophylactic drug for migraine before. Another 26% of the patients used analgesics and triptans excessively; this group is not suitable for drug trials in migraine prophylaxis.[13] Due to the small number of patients who completed the trial, the results did not reach statistical significance.

During treatment with acenocoumarol, we did not observe the expected placebo response of about 30%. Though we cannot explain this observation, it does not influence the interpretation of our results.

Contradictory to previous observational findings, no improvement of migraine symptoms was observed during use of acenocoumarol compared to baseline. It remains unclear whether the low-target INR (1.7) plays part in this. It may also be that only in a subgroup of migraine patients, symptoms are reduced by treatment with anticoagulants. This theory is supported by the observation of Cuadrado who mentioned improvement of intractable headache or migraine during treatment with low molecular weight heparin or warfarin in patients with the antiphospholipid syndrome.[14,15] Secondly, four migraine patients were described who all had thromboembolic risk factors, with a self-reported strong reduction of their migraine during previous therapeutic use (INR 2.5 to 4.0) of anticoagulants. In two patients, both with factor V Leiden heterozygosity, the attack duration in hours reduced by 84% and 73%, respectively, during treatment with low-intensity acenocoumarol treatment.[16] Furthermore, there is evidence that migraine in patients with a right-to-left shunt (RLS) might improve after closure of the atrial defect or after anticoagulant therapy.[17-19]

Thromboembolic tendency is not the only possible target for anticoagulants in migraine prophylaxis. Inhibition of the production of nitric oxide (NO), a molecule that seems to be involved in the initiation and maintenance of migraine attacks,[20,21] is another postulated mechanism for this action. The oral anticoagulants phenprocoumon and dicoumarol inhibit the production of NO.[22]

It is unclear to what extent the low-target INR is responsible for our results. The question remains whether anticoagulation may still be a suitable form of migraine prophylaxis in a selected group of patients, such as patients with coagulation disorders or RLS.

In conclusion, low-intensity acenocoumarol treatment is not generally applicable as migraine prophylaxis. The mechanism behind the positive effects in individual patients needs elucidation.

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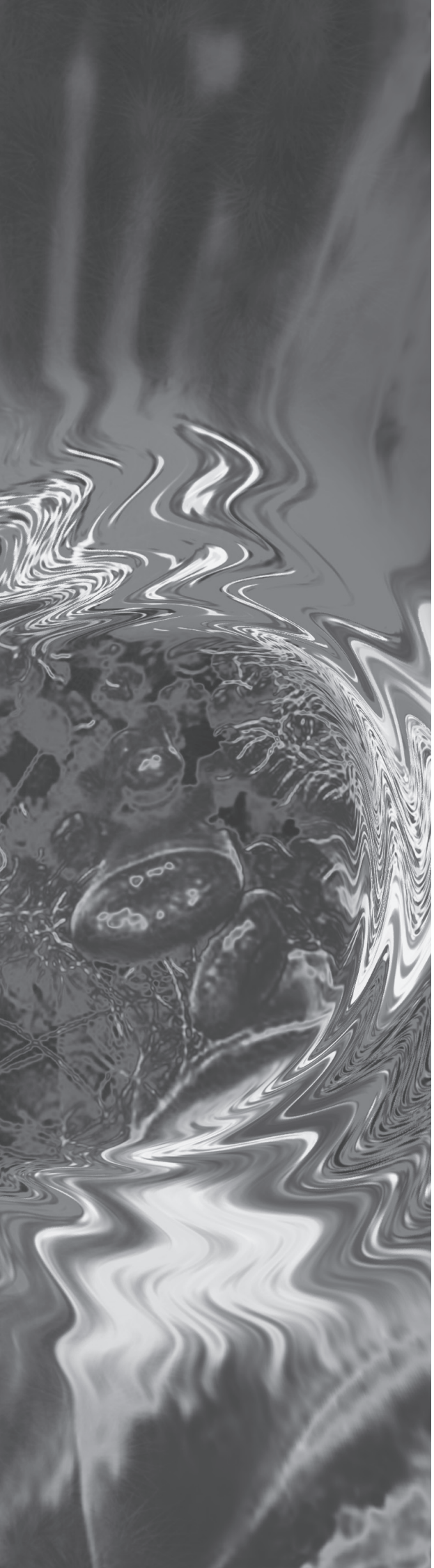
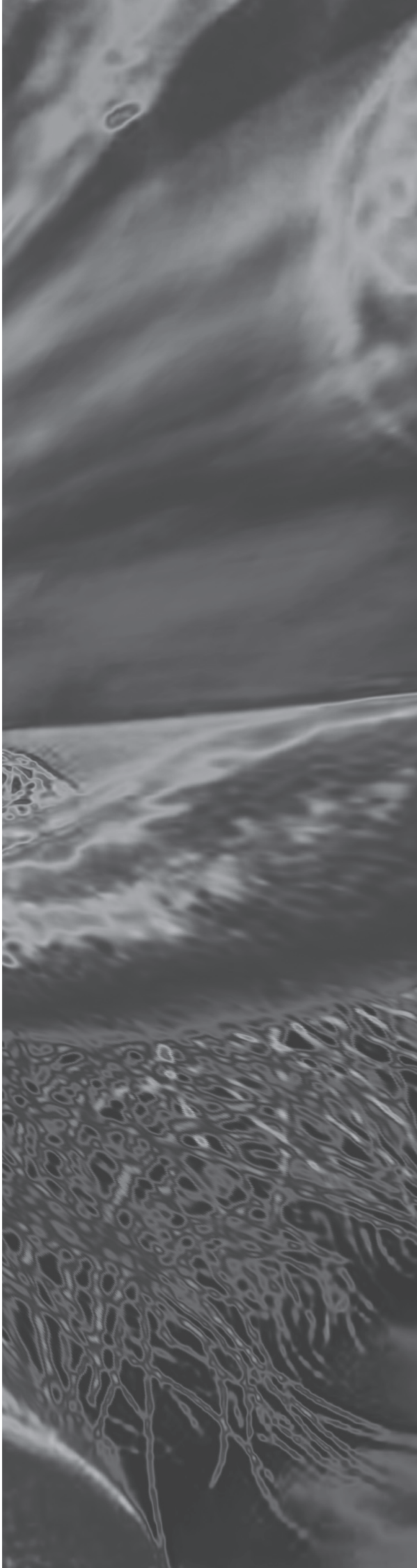
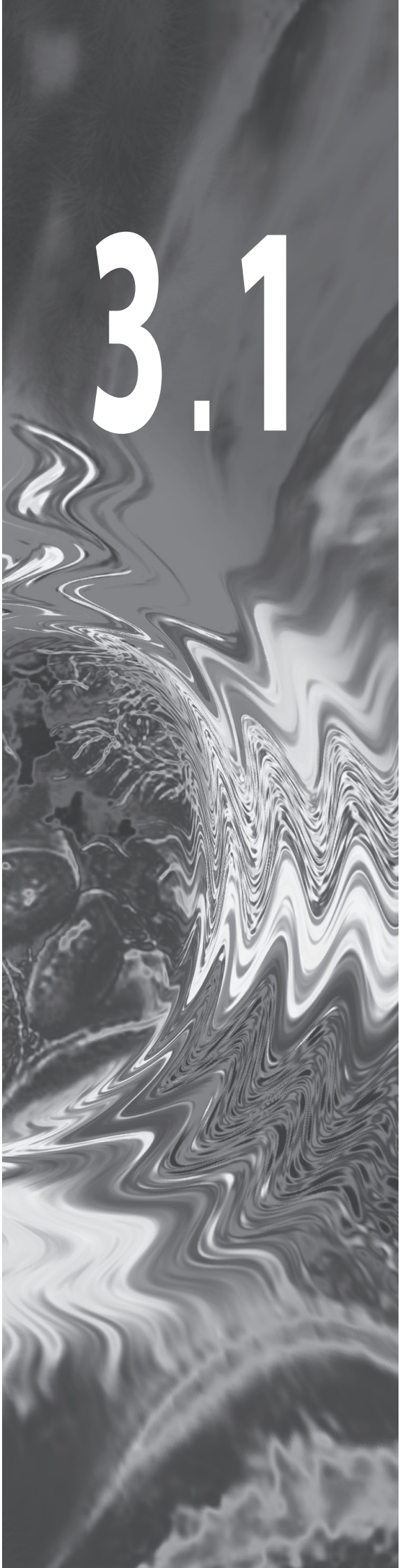


3

CARDIAC RIGHT-TO-LEFT SHUNTS AND MIGRAINE: A CAUSAL RELATIONSHIP?





3.1

RIGHT-TO-LEFT SHUNT AND MIGRAINE: THE STRENGTH OF THE RELATIONSHIP

Elisabeth A Wammes – van der Heijden

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Cephalalgia 2006;26:208-13

ABSTRACT

Objective

To assess the strength of the possible relationship between right-to-left shunt (RLS) and migraine.

Background

Several studies have shown that the prevalence of a cardiac RLS in patients with migraine with aura is significantly higher than in patients without migraine.

Methods

The literature concerning the subject was systematically reviewed.

Results

We identified seven relevant studies. Among patients with RLS migraine with aura was 3.5 times more prevalent than among subjects without RLS (Mantel-Haenszel odds ratio [OR_{MH}] 3.5; 95% confidence interval [CI] 2.1 – 5.8). In patients with ischemic stroke migraine was more than two times more prevalent in patients with RLS than in patients without RLS (OR_{MH} 2.1; 95% CI 1.6 – 2.9).

Conclusions

Our review shows that there is a clear association between RLS and migraine, especially migraine with aura. The relationship between RLS and migraine is further substantiated by the observations of disappearance and improvement of migraine symptoms after closure of the foramen ovale. However, the mechanism as well as the question about causality of this association has to be further elucidated.

INTRODUCTION

A recent meta-analysis showed that interatrial septal abnormalities - patent foramen ovale (PFO) and atrial septal aneurysm (ASA) - are risk factors for ischemic stroke (IS) in patients younger than 55 years.[1] PFO, with or without ASA, may cause right-to-left shunting of blood. Recently it was found that the prevalence of a cardiac right-to-left shunt (RLS) in patients with migraine with aura (MA+), another risk factor for IS in the young, was about 2.5 times higher compared with a group of patients without migraine,[2,3] and that this association between RLS and MA+ is independent of sex.[4] This higher prevalence of RLS may, at least partly, explain the increased risk for IS in patients with MA+, as first postulated by Ries et al. in 1996.[5]

We systematically reviewed the available literature to quantify the strength of the relationship between RLS and migraine in patients with and without IS.

METHODS

A Medline search (accessed through Pubmed, most recent search April 2005) was performed for the words (all fields) patent foramen ovale, PFO, cardiac abnormalities, right-to-left shunt, RLS, atrial septal aneurysm or atrial septal defect and migraine. Other papers of potential interest were sought from the reference lists of the retrieved papers. Only studies with quantitative data about the relationship RLS – migraine were included. There were no restrictions with respect to the design and quality of the studies. Unpublished data were not sought. We evaluated the strength of the association between RLS as the determinant (independent variable) and migraine as the outcome (dependent variable). Since RLS is a risk factor for IS, we stratified the results for patients with IS and patients without IS. Mantel-Haenszel odds ratios (OR_{MH}) with 95% confidence intervals (CI) of pooled data were calculated.

RESULTS

The Medline search identified 76 papers. Cross-referencing did not result in additional papers. Of these, seven studies provided quantitative data concerning the relation between RLS and migraine. One of these studies[6] appeared to be an extension of an earlier study, so the data of this latest study were used (see also Table 1). The investigators of these reports studied the relationship between RLS and migraine in cross-sectional studies either by determining the prevalence of

Table 1 Patients without ischemic stroke			
Study	**RLS+**	**RLS-**	**OR (95% CI)**
Anzola 1999	54 / 59	59 / 79	3.7 (1.3 – 10.4)
Angeli 2001 [a]	32 / 40	48 / 90	3.5 (1.5 – 8.4)
Domitrz 2004	33 / 49	29 / 78	3.5 (1.6 – 7.4)
Total	119 / 148	136 / 247	OR_{MH} = 3.5 (2.1 – 5.8)

Comparison: right-to-left shunt (RLS) versus no RLS. Outcome: migraine with aura (versus no migraine)
OR = odds ratio; OR_{MH} = Mantel-Haenszel odds ratio
a) Part of the results of this study were formerly published: Del Sette et al., 1998.[2]

migraine in samples of patients with and without RLS[7,8] or by determining the prevalence of RLS in patients with and without migraine.[2,3,6,9,10]

Patients without IS

In a consecutive unselected cohort of migraine patients a prevalence of RLS of 48% (54/113) was found in patients with MA+ compared with 23% (12/53) in patients with migraine without aura (MA-) and 20% (5/25) in control subjects (age-matched nonmigraine members of the hospital staff).[3] Del Sette et al. found a prevalence of RLS of 40% in 80 consecutive patients with MA+ compared with 16% in 50 healthy control subjects without migraine.[2,6] Domitrz et al. found a prevalence of RLS of 53% (33/62) in patients with MA+ compared with 25% (15/60) in patients with MA- and 25% (16/65) in healthy age-matched controls.[10] These three studies consistently show that, in patients without IS, MA+ was more prevalent (OR_{MH} 3.5; 95% CI 2.1 – 5.8) in patients with RLS than in those without RLS (Table 1).

Patients with IS

Using data from a prospective stroke registry to determine the characteristics of acute IS in patients with active migraine, it was shown that patients with first-ever IS and migraine (with and without aura) had a RLS almost twice as often as patients with first-ever IS without migraine: 18.5% (24/130) compared with 10.1% (121/1195).[9] In 581 patients (18 – 55 years) with a cryptogenic stroke, 27.3% of the patients with a PFO had migraine (with and without aura) compared with 14.0% of the patients without a PFO.[7] In a series of 74 consecutive patients presenting with an acute stroke of undetermined origin, PFO was found in 44 of 74 patients, of whom 36% (16/44) had MA+, compared with 13% (4/30) of the patients without PFO.[8] This difference was not observed for MA-. The combined results of these three studies show that in patients with IS, migraine (with and without aura) was twice as prevalent (OR_{MH} 2.1; 95% CI 1.6 – 2.9) in patients with RLS as in patients without RLS (Table 2).

Table 2 Patients with ischemic stroke			
Study	**RLS+**	**RLS-**	**OR (95% CI)**
Milhaud 2001	24 / 145	106 / 1180	2.0 (1.2 – 3.3)
Lamy 2002	73 / 267	44 / 314	2.3 (1.5 – 3.5)
Sztajzel 2002	27 / 44	14 / 30	1.8 (0.7 – 4.6)
Total	124 / 456	164 / 1524	OR_{MH} = 2.1 (1.6 – 2.9)

Comparison: right-to-left shunt (RLS) versus no RLS. Outcome: migraine (versus no migraine)
OR = odds ratio; OR_{MH} = Mantel-Haenszel odds ratio

DISCUSSION

Among patients with RLS, MA+ is clearly more prevalent than among persons without RLS. The prevalence of RLS found in the control groups without migraine is comparable to the prevalence of PFO in the general population, i.e. about 25%.[11] Several limitations of our analysis should be mentioned. First, the applied diagnostic procedures and diagnostic criteria for PFO, ASA or RLS were not the same in all studies, which may explain the differences between studies in the reported prevalence of RLS. Transcranial Doppler sonography with contrast medium,[2,3,6,10] transesophageal echocardiography with contrast medium (gold standard),[7] transthoracic echocardiogram with contrast medium or a combination of these techniques[8,9] were used to diagnose cardiac abnormalities. Although this may have influenced the absolute prevalence of interatrial septal abnormalities found in each individual study, this does not influence the relative risk estimates (OR), as within each study there were no diagnostic differences between the various groups of patients that were compared. Bias towards a positive finding of migraine was unlikely since, in both studies which determined the prevalence of migraine (outcome) in patients with and without RLS, a blinding procedure[7] or independent observers[8] were used to establish the diagnosis. Although migraine was diagnosed according to the criteria of the International Headache Society in all studies, misclassification with respect to migraine cannot be ruled out. Besides, in two of the three studies with IS patients no distinction was made between MA+ and MA-.[7,9] This might explain the lower odds ratio for the relationship between RLS and migraine found in IS patients, since up to now no relationship between RLS and MA- has been established.[3,8,10,12] Second, we did not put restrictions on the design and quality criteria of the studies, since there were only a few studies with quantitative data. Third, the studies included in our analysis were relatively small and were all non-randomized. Within both subgroups, the odds ratios of the individual studies were, however, remarkably consistent. Fourth, given the

observational design of the included studies and the fact that it was not possible to take into account the presence of thromboembolic risk factors in our analysis, we cannot eliminate confounding and therefore could not state that the found association is causal in nature. However, in five of six studies the age, a major confounder, of the cases was comparable to the ages of control subjects.[2,6,8-10] Furthermore, the study of Lamy et al. showed that patients with PFO were less likely to have traditional risk factors of stroke than patients without PFO.[7] This means that in case the prevalence of migraine was higher in patients with these risk factors, the found association between RLS and migraine would be even stronger. Finally, we sought only published data, which due to publication bias may have overestimated our results. Despite these limitations, we believe that an association between RLS and MA+ does exist.

Further evidence that substantiates the relationship between RLS and migraine is found in three patient groups. First, in patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), Angeli et al. found a prevalence of RLS of 80% (4/5).[6] All patients with CADASIL and migraine (4/4) showed RLS. However, this concerns a report of only one Italian family and needs confirmation.

Second, in a group of divers with decompression illness, MA+ in daily life unconnected with diving was found in 47.5% of divers with a large RLS at rest and 13.8% of divers with no shunt.[12] The prevalence of MA- was the same in both groups. In divers with RLS, decompression illness is probably caused by paradoxical gas embolism.[13]

Finally, though all based on uncontrolled studies, the observation of improvement or even disappearance of migraine after closure of the PFO supports the association between RLS and migraine (Table 3).[8,14-20] Based on their design, these studies have several limitations which have to be mentioned. First of all, there can be a clear placebo effect in migraine treatment. However, in two studies patients were unaware of a potential benefit of the intervention on migraine outcome.[15,18] Furthermore, the study of Schwerzmann et al. showed no reduction of nonmigrainous headaches.[15] Although a placebo effect cannot be excluded, it is unlikely to have produced such consistent results. Second, all data on headache frequency before the closure procedure were retrospective, which can introduce recall bias. Finally, most of the patients received antiplatelet therapy after the closure procedure for a period of six months. However, the mean follow-up time of these patients was ≥ 12 months and sustained migraine relief was observed after antiplatelet therapy was discontinued. Additionally, it has to be mentioned that new-onset migraine has also occurred in patients (immediately) after closure of a PFO or an atrial septal defect.[18,20-22]

Table 3 Changes of migraine after closure of cardiac right-to-left shunts

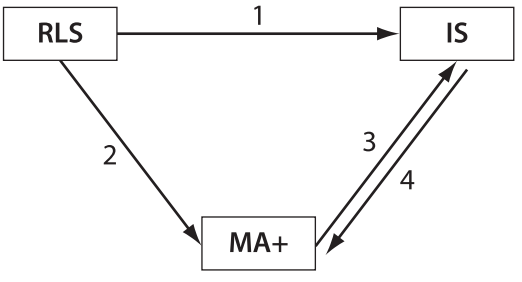
Study	Reason for closure	Intervention	Migraine before closure	(n)	Changes of migraine after closure	
Sztajzel 2002	Not mentioned	Surgical PFO closure	MA+	1	Disappearance of aura attacks in 2 (of 3) MA+/- patients	
			MA+/-	3		
			MA-	2		
Morandi 2003	Stroke or TIA	Transcatheter PFO closure	MA+	8	Six months after closure: - disappearance aura	6
			MA-	9	- disappearance M	5
					- improvement M	10
Schwerzmann 2004	Presumed PFO mediated paradoxical embolism	Percutaneous PFO closure	MA+	37	- reduction attack frequency MA+	54%
			MA-	11	- reduction attack frequency MA-	62%
					- no total disppearance of MA+ and MA-	
Post 2004	Stroke or peripheral embolism	Percutaneous PFO closure	MA+	12	Two months after closure: - disappearance MA+	8
			MA-	14	- disappearance MA-	10
Reisman 2005	Prevent recurrent stroke or TIA in patients with presumed paradoxical embolism	Transcatheter PFO closure	MA+	38	- disappearance MA+	21
					- ≥ 50% improvement MA+	5
			MA-	12	- disappearance MA-	7
					- ≥ 50% improvement MA-	2
Wilmshurst 2000	Resumption of diving after decompression illness, stroke with suspected paradoxical embolism or a large ASD	Transcatheter PFO or ASD closure	MA+	16	- disappearance MA+	7
					- improvement MA+	8
			MA-	5	- disappearance MA-	3
					- fortification spectra direct after closure	11
Azarbal 2005	Not mentioned	Transcatheter PFO or ASD closure	MA+	24	- disappearance MA+	18
					- improvement MA+	1
			MA-	13	- disappearance MA-	4
					- improvement MA-	5
Mortelmans 2005	Not mentioned	Percutaneous ASD closure	MA+	8	≥ six months after closure: - disappearance MA+	4
					- new-onset MA+	7
			MA-	14	- disappearance MA-	8
					- new-onset MA-	3

PFO = patent foramen ovale; MA+ = migraine with aura; MA+/- = migraine with and without aura; MA- = migraine without aura; M = migraine (unspecified with or without aura); TIA = transient ischemic attack; ASD = atrial septal defect

The underlying mechanism of the possible relation between RLS and migraine remains speculative. Wilmshurst et al.[18] postulated that RLS allows trigger substances in the venous circulation such as vasoactive chemicals and microemboli to bypass the pulmonary filter and reach the brain, inducing a migraine attack. Interestingly, paradoxical emboli seems to have a particular propensity for the posterior circulation,[23] the area in which hypoperfusion occurs during the aura phase. It has also been mentioned that emboli may be formed within the atrial septal defect itself.[24] Finally, it has been suggested that a particular genetic substrate might determine both atrial septal abnormalities and migraine.[2,7] Wilmshurst et al. showed that there is dominant inheritance of atrial shunts, which is linked to inheritance of MA+ in some families.[25]

The question whether the risk of migraine varies with the degree of shunting is controversial. Such a relationship was found in persons with decompression illness,[12] though was not observed in patients with a cryptogenic stroke; MA+ was found in 22.2%, 29.2%, and 28.1% of the patients with small (three to nine microbubbles), moderate (10 – 30 microbubbles) and large (> 30 microbubbles) shunts, respectively.[7]

Figure 1 **Relationships between right-to-left shunt (RLS), ischemic stroke (IS) and migraine with aura (MA+) as reported in literature**



1. Interatrial septal abnormalities are potential risk factors for stroke in patients younger than 55 years.[1]
2. Patients with RLS have a higher risk for having MA+ compared with normal controls.[3,6,8,10] The observation of improvement or even disappearance of migraine after closure of the RLS supports this relationship.[8,14-20] Wilmshurst et al. showed that there is dominant inheritance of atrial shunts, which is linked to inheritance of MA+ in some families.[25]
3. MA+ is a risk factor for getting an IS.[26]
4. Ischemic events, for example caused by paradoxical embolization, might be a trigger for cortical spreading depression causing migrainous aura.[18]

What does this all mean for the various relationships between RLS, MA+ and IS that have been reported in the literature (Figure 1)? The studies that have shown that MA+ is a risk factor for IS (arrow 3) did not take the presence of RLS as a

potential confounder into account. This means that RLS may explain at least a part of the increased ischemic risk in patients with MA+. In those patients arrow 3 can be replaced by the hypothesis that RLS may lead to subtle emboli entering the central circulation (arrow 1) and subsequently may trigger a migraine attack, especially MA+ (arrow 4), and arrow 2 will be crossed out.

In conclusion, the current evidence indicates that there is an association between RLS and MA+. However, the mechanism, as well as the question whether this association is also causal in nature, have to be further elucidated. This knowledge may shed new light over the pathogenesis of migraine in special cases, possibly with new therapeutic options in the distant future.

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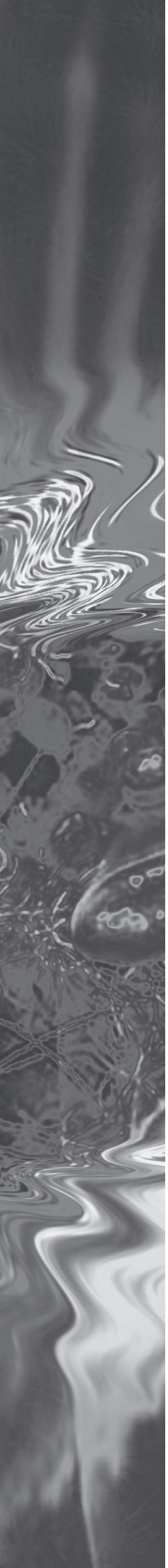

3.2

PREVALENCE OF CARDIAC RIGHT-TO-LEFT SHUNTS IN PATIENTS WITH CEREBRAL AUTOSOMAL DOMINANT ARTERIOPATHY WITH SUBCORTICAL INFARCTS AND LEUKOENCEPHALOPATHY (CADASIL) WITH AND WITHOUT MIGRAINE

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ABSTRACT

Objective

To investigate the prevalence of cardiac right-to-left shunt (RLS) in patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) with migraine with aura (MA+) and without migraine.

Background

There is increasing evidence that migraine, particularly MA+, is associated with increased prevalence of RLS. A high prevalence of RLS was found in a CADASIL family and all patients with RLS suffered from MA+.

Methods

Seventeen CADASIL patients, nine with MA+ and eight without migraine, underwent a transesophageal echocardiography with gaseous contrast to assess the presence of cardiac RLS.

Results

Three out of 17 CADASIL patients (18%) showed a cardiac RLS. The prevalence of cardiac RLS was 33% (3/9) in CADASIL patients with MA+ and 0% (0/8) in CADASIL patients without migraine.

Conclusions

The overall prevalence of cardiac RLS in our group of CADASIL patients was comparable with the prevalence of RLS found in the general population. The prevalence of RLS was higher, though not statistically significant, in CADASIL patients with MA+ than in CADASIL patients without migraine, confirming previous small studies. Given the small sample sizes and the striking results in another small prevalence study, the possible relationship between RLS and MA+ in CADASIL patients should be further evaluated.

INTRODUCTION

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a hereditary small vessels disease caused by mutations in the Notch3 gene.[1] The course of CADASIL varies between and within families. The reasons for the extreme variability in presentation and clinical progression are still not understood. Clinical hallmarks of CADASIL are recurrent stroke and cognitive decline.[2] Up to 40% of mutation carriers suffer from migraine, accompanied by aura in over 85% of these patients.[2] The question how this high prevalence of migraine with aura (MA+) is associated with the vasculopathy of CADASIL, still has to be answered.

There is increasing evidence that migraine, particularly MA+, is associated with increased prevalence of right-to-left shunts (RLS) in the general population.[3-9] The basis for this association is uncertain, but dominant inheritance of atrial shunts, which is linked to inheritance of MA+ in some families, has been shown.[10] We formerly confirmed that among patients with RLS MA+ was 3.5 times more prevalent than among subjects without RLS.[11]

Almost a decade ago, a very high prevalence of RLS (4/5; 80%) was found in an Italian family with CADASIL compared to 40% (32 of 80) in patients with MA+ and 16% (8/50) in control subjects without migraine. All patients with CADASIL and RLS had MA+ (4/4).[12] Recently, two studies investigated RLS as a possible comorbidity factor in CADASIL patients.[13,14] The first study showed a RLS prevalence of 50% (3/6) in CADASIL patients with MA+ compared to 11% (1/9) in CADASIL patients without migraine.[13] The second study showed a high prevalence of RLS in CADASIL patients (15/21; 71%), but no difference was found between patients with MA+ (4/6; 67%) and without migraine (11/15; 73%).[14]

We investigated the prevalence of cardiac RLS in CADASIL patients with MA+ and without migraine in a Dutch population.

PATIENTS AND METHODS

Setting and study population

The study started in May 2004. Potential patients were acquainted of the study by a letter (written by the investigators) sent by the department of Neurology and Clinical Genetics of the Leiden University Medical Centre, Leiden (patients who gave permission to be approached on clinical research during participation in former trials in this hospital), or the letter was handed to CADASIL patients visiting the outpatient clinic of these departments, by information of the study on the Dutch website for CADASIL patients, or by their own neurologist who was informed

about the study by one of the investigators. During a visit at the outpatient clinic of the Department of Neurology of the St. Elisabeth Hospital, Tilburg, the investigator further informed eligible patients about the nature of the study. Before this visit all patients had received written patient information. Inclusion criteria were men and women 18 years and older who had previously been diagnosed with CADASIL and either had no migraine or MA+. MA+ was diagnosed according to the diagnostic criteria of the International Headache Society.[15] Diagnosis of CADASIL was based on Notch3 mutation carriership, determined by direct sequencing analysis, according to previously described techniques.[16]

Information on the occurrence of stroke, transient ischemic attack (TIA) and cognitive impairment were, after approval by the patient, derived from The Leiden University Medical Center (eight patients who participated in a clinical trial performed in this hospital [17]), or from their neurologist in attendance.

Based on the known prevalence of patent foramen ovale (PFO) in the general population which is about 25%,[18] and assuming a prevalence of 80% in patients with CADASIL with MA+, with a given power of 90% and $\alpha = 5\%$, 17 CADASIL patients with MA+ were needed to detect the defined clinically considered difference in prevalence of 55%. An interim analysis was done after nine CADASIL patients with MA+ and eight CADASIL patients without migraine were included, and data of two other prevalence studies were published.

The Ethics Committee for Medical Research of the St. Elisabeth Hospital approved the study protocol. All patients gave written informed consent before enrollment.

Study procedures of assessment of presence of RLS

All patients who fulfilled the inclusion criteria underwent a contrast transesophageal echocardiographic examination (TEE) performed by a trained cardiologist, at the Department of Cardiology of the St. Elisabeth Hospital, Tilburg, using 5-MHz omniplane transducers to screen for cardiac RLS caused by interatrial septal abnormalities. The patients were examined in fasting state, and received topical anaesthesia of the oropharynx when necessary. A bicaval view (vertical plane) of the atrial septum was obtained before the injection of contrast agent. The contrast agent is a mixture of 0.9% sodium chloride (6-8 ml), air (1 ml) and blood of the patient (1 ml), agitated vigorously in a syringe. To obtain a good bolus of air microbubbles, the contrast solution was injected immediately after preparation rapidly through a 18-gauge catheter placed into a right antecubital vein. This procedure was performed once during normal breathing and once or more during the end phase of a Valsalva manoeuvre. The cardiologist was blinded for the diagnosis of MA+ or no migraine.

A cardiac RLS was defined as the passage of more than three microbubbles from the right atrium to the left atrium within the first three cardiac cycles after opacification of the right atrium with contrast. Positive contrast studies were classified into three grades by counting the maximum number of microbubbles in the left atrium within three heart cycles after the contrast media filling of the right atrium. A small shunt was defined as a count of less than six microbubbles, a moderate shunt was defined as a count between six and 25 microbubbles and a large shunt was considered to be present if the count was over 25 microbubbles. Atrial septal aneurysm, not causing atrial shunting itself, appears as a redundant, highly mobile membranous portion of the atrial septum and was defined as a billowing or localized outpouching greater than 11 mm from the plane of the septum, with a base of 1.5 cm.

Data analysis

The differences in prevalence of cardiac RLS between CADASIL patients with MA+ and without migraine were tested for significance by a Fisher's exact test. Calculations were carried out using SPSS statistical package (version 14.0 for windows). Differences were considered to be statistically significantly different if $p < 0.05$.

RESULTS

Seventeen CADASIL patients, nine with MA+ and eight without migraine, underwent a TEE for RLS assessment. The clinical characteristics of the patients and findings from the TEE are shown in Table 1. One patient showed a mild cardiac RLS during Valsalva procedure, and two related patients showed a large cardiac RLS. Three of the nine (33%) CADASIL patients with MA+ had RLS, none of the eight (0%) CADASIL patients without migraine ($p = 0.21$).

DISCUSSION

In our study 18% (3/17) of CADASIL patients, with a range of eleven different Notch3 mutations, displayed a cardiac RLS on contrast-enhanced TEE examination. We found a higher RLS prevalence in CADASIL patients with MA+ (33%) than in patients without migraine (0%). This difference in RLS between CADASIL patients with MA+ and those without migraine was also found by Mazzucco et al (50% vs. 11%),[13] though not by Zicari et al (67% vs. 73%).[14]

Table 1	Characteristics of the patients and results from the transesophageal echocardiography								
Patient [a]	**Sex**	**Age (yrs)**	**Exon**	**Amino acid change**	**Migraine**	**Stroke**	**TIA**	**Cognitive decline**	**TEE findings**
1	F	51	19	Cys1015Arg	–	+	+	+	no abnormalities
2	M	50	19	Cys1015Arg	–	+	–	+	no abnormalities
3	F	42	4	Arg141Cys	–	–	+	–	no abnormalities
4	M	56	20	Arg1076Cys	–	+	–	–	no abnormalities
5	F	56	4	Arg153Cys	–	–	–	+	no shunt; hypermobile IAS but no ASA
6	M	61	8	Cys446Phe	–	+	+	–	no abnormalities
7	M	33	3	Arg110Cys	–	–	–	+	no abnormalities
8	M	48	11	Arg544Cys	–	+	–	+	no abnormalities
9	F	51	4	Arg141Cys	MA+	+	+	+	moderate R/L shunt with Valsalva (6 microbubbles)
10	M	46	19	Cys1015Arg	MA+	+	–	–	no abnormalities
11	M	42	4	Arg182Cys	MA+	–	–	–	large R/L shunt with Valsalva (> 25 microbubbles)
12	M	35	4	Arg182Cys	MA+	+	–	–	large R/L shunt (>> 25 micro-bubbles) due to ASD; also L/R shunt
13	M	44	4	Cys162Trp	aura without migraine	+	–	+	no shunt; hypermobile IAS but no ASA
14	F	63	19	Cys1015Arg	MA+	–	–	+	no shunt; hypermobile IAS but no ASA
15	F	51	4	Arg153Cys	MA+	+	+	+	no abnormalities
16	M	37	4	Arg182Cys	MA+	–	–	–	no abnormalities
17	M	46	11	Arg578Cys	MA+	–	–	+	no septal abnormalities

TIA = transient ischemic attack; TEE = transesophageal echocardiography; IAS = interatrial septum; ASA = atrial septal aneurysm; MA+ = migraine with aura; R/L = right-to-left; ASD = atrial septal defect
a) Siblings: 1, 2 and 10 are sister and brothers; 3 and 9 are sisters; 11 and 12 are brothers.

The overall prevalence of 18% matches with the prevalence of 25% (4/16) in CADASIL patients found by Mazzucco et al.[13] From these figures we would conclude that RLS is not overrepresented in CADASIL patients, but matches with the prevalence in the general population, which is about 25%.[18] The other Italian

study showed a RLS in 71% of their CADASIL patients.[14] The authors stated that the high prevalence might not be coincidence and suggested a common genetic origin of CADASIL and the cardiac septal defect, though did not rule out other genetic or environmental factors. With a known PFO prevalence of about 25% in the general population,[18] the presence of other factors, like for instance dominant inheritance of atrial shunts, seems more probable. Unfortunately, no information about sibship was given. Using transcranial Doppler (TCD) instead of TEE might also explain part of the higher prevalence, since TCD lacks specificity in differentiating atrial shunts versus pulmonary shunts.[19] However, Mazzucco et al also used TCD to detect RLS.[13]

It has been suggested that specific Notch3 mutations, such as Arg141Cys, could induce a higher prevalence of RLS.[13] Our data cannot confirm this hypothesis; two related patients had a Arg141Cys mutation, one showing a mild RLS during Valsalva manoeuvre. In the study of Zicari et al,[14] none of the patients had a Arg141Cys mutation.[20] Again, with a known PFO prevalence of about 25% in the general population,[18] a causal relationship between this specific mutation and RLS is not probable.

Cardiac RLS – mainly caused by PFO – is a risk factor for ischemic stroke (IS).[21,22] Potential mechanisms of stroke in patients with cardiac RLS include paradoxical embolism from a venous source and direct embolization from thrombi formed within the aneurysm.[23] These emboli seem to have a particular propensity for the posterior circulation (PC).[24,25] Also migraine, and particularly MA+, has been consistently associated with an increased risk of IS in several studies of various designs.[26-29] Furthermore, brain imaging studies found that migraine patients, especially patients with aura, had a significantly higher prevalence of white matter hyperintense lesions and infarct-like lesions. Notably, these infarct-like lesions mainly occurred in the PC territory.[30] Whether migraineurs with PC infarction had a cardiac RLS was not investigated. Since cardiac RLS are demonstrated risk factors for ischemic stroke, the coexistence of RLS and migraine may, at least partly, explain the increased risk for ischemic stroke in patients with MA+, as first postulated in 1996.[31] On the other hand, observation of total disappearance and improvement of migraine symptoms after surgical closure of the foramen ovale supports the hypothesis of a causal relationship between RLS and migraine.[3,32-38] It is hypothesized that RLS may lead to subtle emboli entering the cerebral circulation and subsequently may trigger cortical spreading depression and migrainous aura.[32] A trial of closure of RLS in migraine patients, however, did not result in relief of headache.[39]

In case of the hypothesis that RLS triggers MA+ via paradoxical embolism, we should reverse the direction of the relationship and look at the prevalence of MA+

(outcome) in CADASIL patients with and without RLS (dependent). We as well as Mazzucco et al.[13] found a high prevalence of MA+ in patients with RLS: 100% (3/3) and 75% (3/4) of the CADASIL patients with RLS had MA+, compared to 43% (6/14) and 27% (3/11) of the patients without RLS. However, these results could not be confirmed by the data from the study of Zicari et al, in which only four of 15 (27%) CADASIL patients with RLS showed MA+, compared to 33% (2/6) of the patients without RLS.[14] Therefore, from the pooled data (Table 2) we cannot conclude RLS to be a risk factor for MA+ in CADASIL patients (Mantel-Haenszel odds ratio [OR_{MH}] 3.0; 95% confidence interval [CI] 0.7 – 12.4).

Table 2 **CADASIL patients. Comparison: right-to-left shunt (RLS) versus no RLS. Outcome: migraine with aura (versus no migraine)**

Study	RLS+	RLS-	Odds Ratio (95% CI)
Zicari 2008	4/15	2/ 6	0.7 (0.1 – 5.6)
Mazzucco 2009	3/ 4	3/11	8.0 (0.6 – 110.3)
Wammes 2009	3/ 3	6/14	9.2 (0.4 – 210.3)
Total	10/22	11/31	OR_{MH} = 3.0 (0.7 – 12.4)

OR_{MH} = Mantel-Haenszel odds ratio

The lack of clear genotype – phenotype correlations in CADASIL patients has led to the suggestion that factors, genetic or environmental, may modulate the disease process. Both former prevalence studies showed no relation between RLS and clinical features as stroke, TIA and cognitive impairment.[13,14] At a glance, we can see that also in our CADASIL population cardiac RLS is not a comorbidity factor for these features, the low prevalence of RLS limiting the value of this observation.
In conclusion, two studies showed that the prevalence of RLS in CADASIL patients is comparable with the prevalence of RLS in the general population, and therefore not linked to CADASIL. The finding that 86% (6/7) of the CADASIL patients with RLS in these two studies had MA+, may lead to the suggestion that, as in the general population, RLS is a risk factor for MA+ in CADASIL patients. In this case, future recommendations from studies investigating the association between RLS and MA+ in the general population, could probably be extrapolated to CADASIL patients with RLS and MA+. However, since both studies were small, and another small study showed striking results with a much higher RLS prevalence, both in CADASIL patients with MA+ and CADASIL patients without migraine, more data are still needed.

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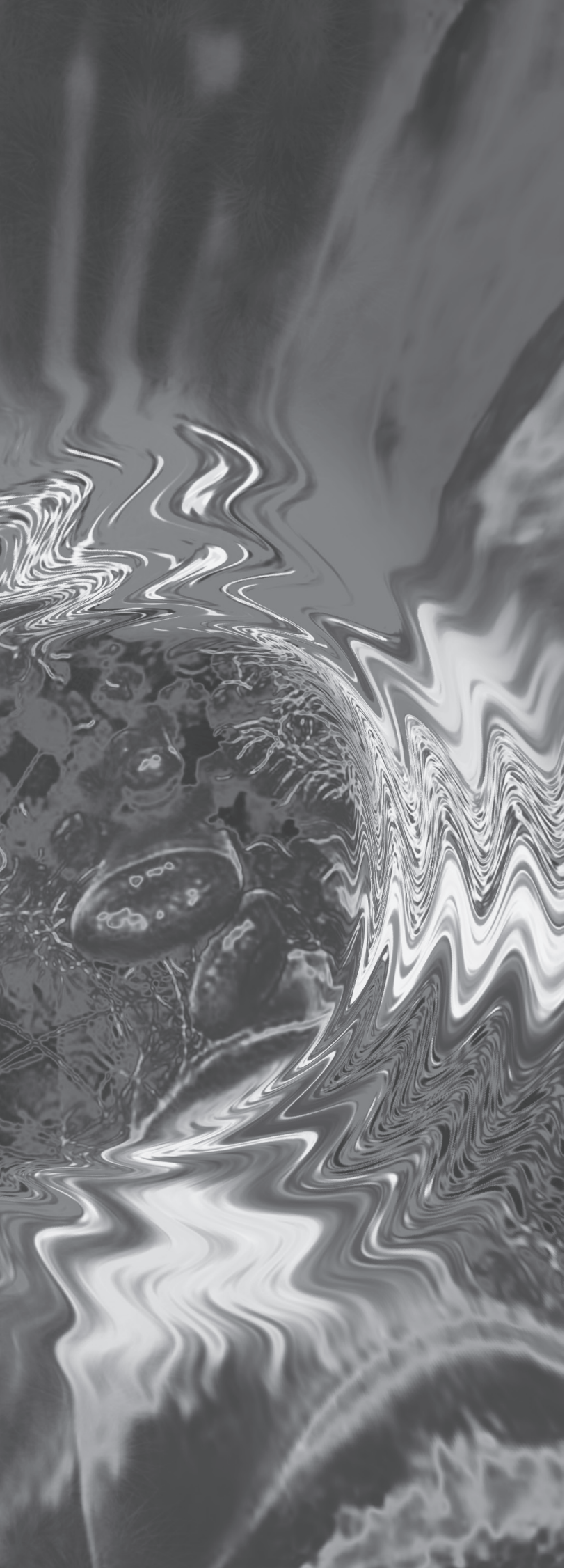
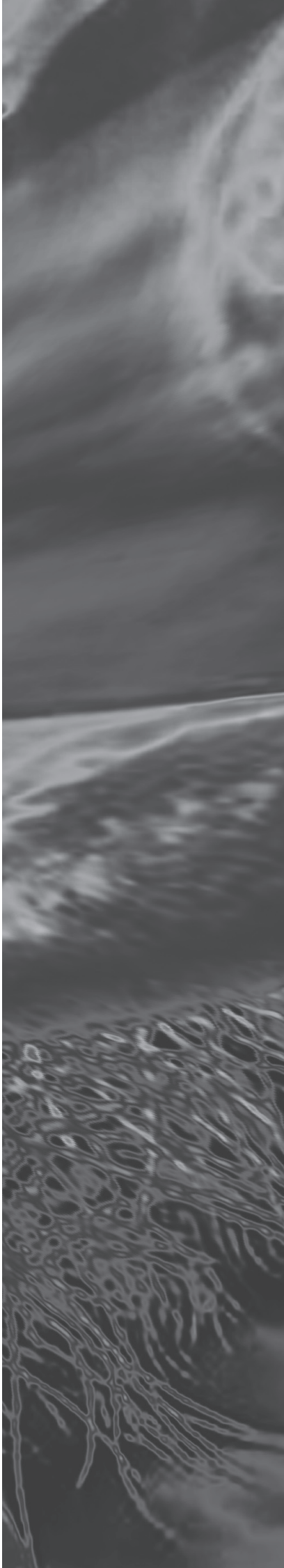
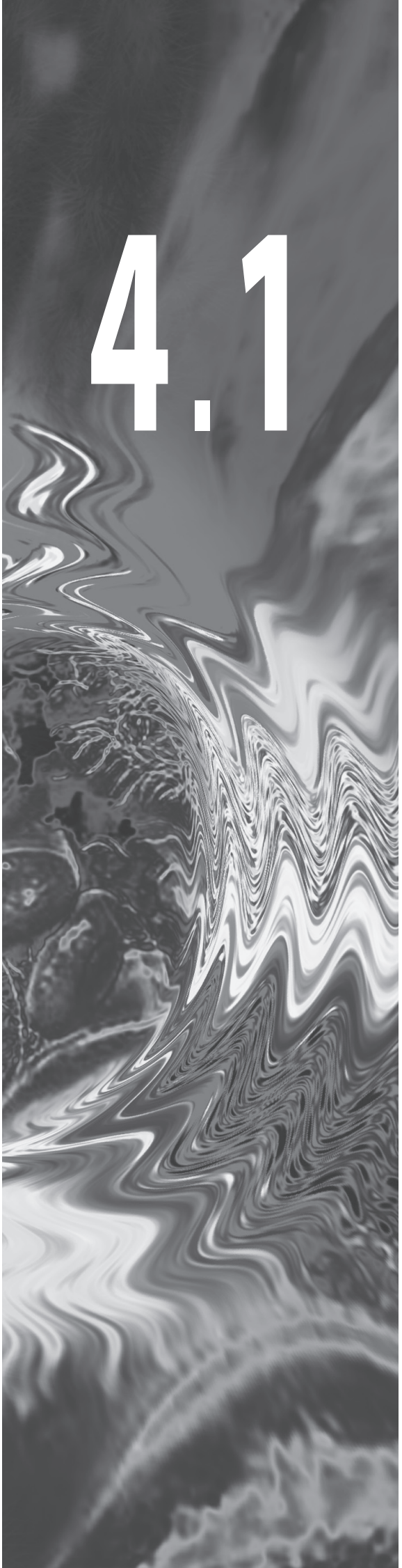


4

ANTIMIGRAINE DRUG USE, ISCHEMIC COMPLICATIONS AND CARDIOVASCULAR DISEASE





4.1

RISK OF ISCHEMIC COMPLICATIONS RELATED TO THE INTENSITY OF TRIPTAN AND ERGOTAMINE USE

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ABSTRACT

Objective

To investigate whether the intensity of triptan and ergotamine use, in specific overuse, is associated with the risk of ischemic complications.

Background

Due to their vasoconstrictive properties triptans and ergotamine have been associated with serious complications as myocardial infarction, ischemic stroke and ischemic colitis in case reports.

Methods

We conducted a retrospective nested case-control study using data from the PHARMO Record Linkage System. All patients with more than one prescription for either a triptan or ergotamine were initially identified. Cases were all patients who were admitted to the hospital for an ischemic complication. Matched controls were assigned the same index date as the cases. The determinant was the intensity of use of triptans and ergotamine during one year preceding the index date. Overuse was defined as use of ≥ 90 defined daily doses during that year. Conditional logistic regression was used to estimate odds ratios (OR), adjusting for confounders. Stratified analysis was used to estimate the risk for both patients using and those not using cardiovascular drugs.

Results

A total of 17 439 patients received more than one prescription. A total of 188 cases and 689 controls were identified. Triptan overuse was not associated with an increased risk of ischemic complications (OR 0.96; 95% confidence interval [CI] 0.49 – 1.90). Overuse of triptans in patients concomitantly using cardiovascular drugs did not increase this risk. Overuse of ergotamine turned out to be a risk factor for ischemic complications (OR 2.55; 95% CI 1.22 – 5.36). Patients overusing ergotamine and concomitantly using cardiovascular drugs were at highest risk (OR 8.52; 95% CI 2.57 – 28.2).

Conclusions

In general practice, triptan overuse does not increase the risk of ischemic complications. Overuse of ergotamine may increase the risk of these complications, especially in those simultaneously using cardiovascular drugs.

INTRODUCTION

The ergot alkaloids were the first specific antimigraine therapy available. Intermittent, chronic, and excessive use of ergotamine can lead to serious ischemic adverse effects such as peripheral ischemia, arterial stenosis, myocardial infarction, and cerebral ischemia,[1-3] probably due to its broad pharmacological activity involving serotonin ($5HT_1$ and $5HT_2$), dopamine, and α-adrenoceptors. Sumatriptan and the other second-generation serotonin $5HT_{1B/1D}$-receptor agonists (triptans) have improved the quality of acute migraine treatment by providing a higher degree of efficacy and a more favorable side effect profile vs ergotamine. However, due to their $5HT_1$ agonist activity, triptans can also cause coronary, craniovascular, and peripheral vasoconstriction possibly leading to serious complications such as myocardial infarction,[4-7] ischemic stroke,[8,9] and ischemic colitis,[10-12] mostly in patients with cardiovascular disease or risk factors. Therefore, the use of triptans, like ergotamine, is contraindicated in these patients.

The incidence of ischemic complications is extremely low when triptans are used appropriately.[13-16] However, some patients use triptans more frequently than recommended, which may lead to medication overuse headache (MOH).[17] One study examined the relationship between the intensity of triptan and ergot alkaloid use and the risk of stroke, but found no dose-response relationship.[16] However, the overall intensity of use in this study was low and no category of overuse was defined. It remains unclear whether overuse of triptans or ergot alkaloids is associated with an increased risk of ischemic events.

Therefore, we conducted a retrospective nested case-control study to investigate whether the intensity of triptan and ergotamine use, in specific overuse, is associated with the risk of serious ischemic complications that require hospitalization.

METHODS

Setting

We received data from the PHARMO Record Linkage System, which includes pharmacy dispensing records from community pharmacies linked to hospital discharge records of all 950 000 community-dwelling residents of 25 population-defined areas in the Netherlands from 1985 onwards.[18] Because virtually all patients in the Netherlands are registered with a single community pharmacy, independent of prescriber, pharmacy records are virtually complete with regard to prescription drugs. Participants of the PHARMO population enter the database with the first prescription filled in a PHARMO community pharmacy and are followed until the last prescription.

The computerized drug-dispensing histories contain information concerning the dispensed drug, dispensing date, the prescriber, amount dispensed, prescribed dose regimen, and the estimated duration of use. The duration of use of each dispensed drug is estimated by dividing the number of dispensed units by the prescribed number of units to be used per day. Patient information per prescribed medicine includes gender and date of birth. The database does not provide information concerning the indications for use of the medicines, in this case, the diagnosis of migraine vs. cluster headache, or accurate registration of nonprescription medicines (e.g. use of over-the-counter salicylates, nonsteroidal anti-inflammatory drugs [NSAIDs], paracetamol).

The hospital discharge records were obtained from the Dutch Medical Register (LMR) from PRISMANT, an institute that collects all hospital discharge records nationwide in the Netherlands since the 1960s in a standardized format.[19] These records include detailed information concerning the primary and secondary discharge diagnoses, diagnostic, surgical and treatment procedures, type and frequency of consultations with medical specialists, and dates of hospital admission and discharge. All diagnoses are coded according to the International Classification of Diseases, 9th edition (ICD-9-CM).

Study base population

For this study, all patients with more than one prescription for either a triptan or ergotamine, alone or in combination with caffeine and cyclizine, from 1 January 1990 to 31 December 2002, were initially identified. Patients with only one prescription for a triptan or ergotamine during the study period were excluded, as this pattern of use is partially indicative of diagnostic uncertainty for migraine.[20] The date of the first presented prescription for a triptan or ergotamine during the study period was termed the start date antimigraine drug and the last ever presented prescription for one of these drugs was termed the stop date antimigraine drug.

Case and control definition

In order to investigate the association between the intensity of triptan and ergotamine use, in specific overuse and hospitalization due to ischemic complications, we performed a case- control study, nested within the study base population.

Cases were defined as all patients from the study base population who were hospitalized for the first time for a primary or secondary diagnosis that could be attributed to or exacerbated by the coronary, peripheral, or cerebral vascular side effect profile of triptans or ergotamine during the study period. These diagnoses were ischemic heart disease (ICD-9-CM codes 410, 411, and 413), Raynaud syndrome (ICD-9-CM code 443.0), unspecified peripheral vascular disease (ICD-9-CM

code 443.9), vascular insufficiency of intestine (ICD-9-CM code 557.0 and 557.9), gangrene (ICD-9-CM code 785.4), and cerebral ischemia (ICD-9-CM codes 433 to 436 and 437.0, 437.1, and 437.6). The date of hospital admission was termed the index date. Further inclusion criteria for both cases and controls were at least one year of observation in PHARMO before the index date, the start date antimigraine drug had to be before the index date, the stop date antimigraine drug had to be not longer ago than one year before the index date (current and recent use), the last dispensing date of any drug in the PHARMO database had to be after the index date, and patients had to be 18 years or older at the index date. Consequently, those patients who had their first dispensing of a specific antimigraine drug after the index date were excluded because it is not clear whether these patients already had migraine before the index date. Likewise, past users (the stop date antimigraine drug was more than one year before the index date) were excluded because it is not clear whether these patients still had migraine.

For each case patient, four age- (± five years) and sex-matched control patients were randomly sampled from the noncases (no hospitalization due to an ischemic event during the study period) of the study base population from the same geographic area. Controls were assigned the same index date as the corresponding case. Each control could be included only once.

Exposure definition

The determinant of interest was the intensity of triptan and ergotamine use during the observation period of one year preceding the index date for both cases and controls. For each patient, the total consumption of these two drugs was estimated by the sum of defined daily doses (DDDs) of triptans and ergotamine dispensed in the year preceding the index date. One DDD was defined as 6 mg sumatriptan parenterally, 50 mg sumatriptan orally, 25 mg sumatriptan rectally, 20 mg sumatriptan nasally, 2.5 mg naratriptan, 2.5 mg zolmitriptan, 10 mg rizatriptan, 12.5 mg almotriptan, 40 mg eletriptan, 4 mg ergotamine single preparation by any route, and 2 mg ergotamine combination preparation by any route. Patients were subsequently categorized according to the intensity of use: 0, > 0 to < 30, 30 to < 90, and ≥ 90 DDDs. Given the definition of our study base population in which we nested our case-control study, this implies that the patients assigned to the category no use (no DDDs) were not dispensed ergotamine or triptans during the year before the index date, but were dispensed antimigraine drugs before the year prior to the index date and during the years after the index date.

The revised International Classification of Headache Disorders (ICHD-II) defines MOH for triptans and ergotamine as use on ten or more days per month on a regular basis of at least three months.[21] The quantity of medicine taken per month

is no longer regarded as the main criterion of overuse. From our data, we were not able to calculate the number of days on which antimigraine drugs were used. Therefore, we defined overuse as use of ≥ 90 DDDs during one year.

Potential confounding factors

In order to adjust for factors that may confound the association between antimigraine drug use and the occurrence of ischemic complications, the following covariates were studied as potential confounders: prior hospitalization one year prior to the index date and comedication use one year prior to the index date (benzodiazepines, antidepressants, antidiabetics, gastrointestinal drugs [proton pump inhibitors, H_2-antagonists], migraine prophylaxis [propranolol, atenolol, metoprolol, valproic acid, clonidine, methysergide, pizotifen, flunarizine], NSAIDs, and hormones [oral anticonceptives and hormone replacement therapy]).

Data analysis

For both cases and controls, the prevalence of each characteristic during the period one year prior to the index date was determined. Differences between cases and controls were examined using the χ^2-test for categorical variables and independent-sample t-test for continuous variables. Conditional logistic regression was used to estimate the strength of the association between the intensity of use of triptans and ergotamine and ischemic complications requiring hospitalization, expressed as crude and adjusted odds ratios (OR) with 95% confidence intervals (CIs). The overall logistic regression model included all univariately associated (at $p < 0.1$) risk factors for ischemic complications requiring hospitalization. Stratified analysis was used to estimate the risk both of patients with and without concomitant cardiovascular drug use. Cardiovascular drug use was defined as use of one or more of the following drugs during one year prior to the index date: angiotensin-converting enzyme inhibitors, β-blockers (except propranolol, atenolol, and metoprolol), calcium antagonists, diuretics, nitrates, digoxin, vitamin K antagonists, antiplatelet therapy, and lipid-lowering therapy.

In order to distinguish the outcome with individual drugs, the analysis was also performed separately for triptans and ergotamine. In this analysis, the matching factors age and gender were added to the multivariate logistic regression model.

Microsoft Access, a relational database software package, was used for database management and internal quality procedures. All statistical analyses were performed with SPSS statistical software (version 11.5).

Table 1 Baseline characteristics of cases (ischemic event) and controls (no ischemic event)

Characteristics	Cases n = 188 (100%)	Controls n = 689 (100%)	p-value [a]
Gender			0.45
female	127 (67.6%)	485 (70.4%)	
male	61 (32.4%)	204 (29.6%)	
Age in years; mean (sd)	56.7 (11.8)	56.0 (11.3)	0.45
18 – 40	12 (6.4%)	52 (7.5%)	
> 40 – 65	136 (72.3%)	505 (73.3%)	
> 65	40 (21.3%)	132 (19.2%)	
Antimigraine drug			0.68
triptan	74 (39.3%)	285 (41.3%)	
ergotamine	78 (41.5%)	256 (37.2%)	
both	5 (2.7%)	26 (3.8%)	
no use	31 (16.5%)	122 (17.7%)	
Prescriber			0.22
general practitioner	153 (81.4%)	525 (76.2%)	
neurologist	3 (1.6%)	20 (2.9%)	
other	1 (0.5%)	13 (1.9%)	
unknown	0 (0.0%)	9 (1.3%)	
no use	31 (16.5%)	122 (17.7%)	
Mean duration to index date in years (sd)	4.36 (3.14)	4.19 (2.95)	0.49
Prior hospitalization	40 (21.3%)	85 (12.3%)	< 0.01
Comedication			
antidepressants	23 (12.2%)	77 (11.2%)	0.69
benzodiazepines	90 (47.9%)	236 (34.3%)	< 0.01
cardiovascular	77 (41.0%)	152 (22.1%)	< 0.01
antidiabetics	7 (3.7%)	11 (1.6%)	0.07
gastrointestinal	50 (26.6%)	78 (11.3%)	< 0.01
migraine prophylaxis	59 (31.4%)	144 (20.9%)	< 0.01
nonsteroidal anti-inflammatory drugs (NSAIDs)	100 (53.2%)	291 (42.2%)	< 0.01
oral contraceptives	17 (9.0%)	72 (10.4%)	0.57
hormonal replacement therapy (HRT)	16 (8.5%)	63 (9.1%)	0.79

a) χ^2-test ($p < 0.1$) for comparison of proportions, and independent samples t-test ($p < 0.1$) for comparisons of means between cases and controls.

RESULTS

A total of 29 672 patients had commenced a triptan or ergotamine during the study period 1990 to 2002, of whom 17 439 (59%) had presented more than one prescription. Overall, 446 (2.6%) patients had experienced 697 hospitalizations

Table 2 Characteristics of ischemic events of the cases					
Diagnosis	**Number**	**Triptan use**	**Ergotamine use**	**Ergotamine & triptan use**	**No use**
	n = 188	**n = 74**	**n = 78**	**n = 5**	**n = 31**
Cerebrovascular	**50**	**25**	**18**	**1**	**6**
Occlusion and stenosis of precerebral arteries	1	0	0	0	1
Occlusion of cerebral arteries	11	7	4	0	0
Transient cerebral ischemia	22	7	10	0	5
Acute, but ill-defined, cerebrovascular disease	12	8	3	1	0
Cerebral atherosclerosis	1	1	0	0	0
Other generalized ischemic cerebrovascular disease	3	2	1	0	0
Cardiovascular	**124**	**46**	**56**	**3**	**19**
Acute myocardial infarction	43	17	16	1	9
Other acute and subacute forms of ischemic heart disease	26	10	13	0	3
Angina pectoris	55	19	27	2	7
Peripheral	**14**	**3**	**4**	**1**	**6**
Peripheral vascular disease, unspecified	10	2	2	1	5
Acute vascular insufficiency of intestine	1	1	0	0	0
Gangrene	3	0	2	0	1

with a primary or secondary diagnosis representing ischemic events. Patients with less than one year of medication history (n = 39), patients who had their first dispensing of a specific antimigraine drug after the index date (n = 54), and past users (last dispensing date of an antimigraine drug was more than one year before the index date; n = 157), were excluded. Further inclusion criteria resulted in a final case population compromising 188 patients. A total of 689 controls could be identified. Characteristics of the study population at the index date are described in Table 1. Table 2 gives further specification of the ischemic events. Most of the events were of cardiovascular nature: 66.0% (124/188) of the whole study population, 62.2% (46/74) of the triptan users, and 71.8% (56/78) of the ergotamine users. Cerebrovascular events occurred in 26.6% (50/188) of the whole study population, in 33.8% (25/74) of the triptan users, and in 23.1% (18/78) of the ergotamine users.

Considering the whole study population, overuse of antimigraine drugs, defined as use of ≥ 90 DDDs in one year, did not increase the risk of hospitalization due to

Table 3 Association between intensity of antimigraine drug use and the risk of hospitalization due to ischemic events: DDDs of triptans and ergotamine dispensed during one year prior to the index date

Intensity of use (DDDs)	Cases n = 188 (100%)	Controls n = 689 (100%)	Crude OR (95% CI)	Adjusted [a] OR (95% CI)
Whole population				
0	31 (16.5%)	122 (17.7%)	1.0 (reference)	1.0 (reference)
> 0 to < 30	75 (39.9%)	295 (42.8%)	1.00 (0.63 – 1.60)	0.92 (0.57 – 1.50)
30 to < 90	43 (22.9%)	170 (24.7%)	1.00 (0.59 – 1.67)	0.88 (0.51 – 1.50)
≥ 90	39 (20.7%)	102 (14.8%)	1.51 (0.88 – 2.58)	1.43 (0.82 – 2.49)
Without cardiovascular drug use				
0	19 (10.1%)	94 (13.6%)	1.0 (reference)	1.0 (reference)
> 0 to < 30	45 (23.9%)	227 (32.9%)	0.98 (0.55 – 1.77)	0.93 (0.51 – 1.70)
30 to < 90	25 (13.3%)	130 (18.9%)	0.95 (0.50 – 1.83)	0.94 (0.48 – 1.83)
≥ 90	22 (11.7%)	86 (12.5%)	1.27 (0.64 – 2.50)	1.28 (0.64 – 2.56)
With cardiovascular drug use				
0	12 (6.4%)	28 (4.1%)	2.12 (0.92 – 4.90)	1.99 (0.83 – 4.76)
> 0 to < 30	30 (16.0%)	68 (9.9%)	2.18 (1.14 – 4.20)	1.86 (0.92 – 3.74)
30 to < 90	18 (9.6%)	40 (5.8%)	2.23 (1.06 – 4.68)	1.69 (0.76 – 3.75)
≥ 90	17 (9.0%)	16 (2.3%)	5.26 (2.27 – 12.2)	4.36 (1.78 – 10.7)

DDDs = defined daily doses; OR = odds ratio

a) Adjusted for prior hospitalization and use of comedication (benzodiazepines, antidiabetics, gastrointestinal drugs, migraine prophylaxis, and nonsteroidal anti-inflammatory drugs). In the analysis stratified to cardiovascular drug use, also adjusted for age and gender.

ischemic events (Table 3). Stratified results according to cardiovascular drug use showed that patients using cardiovascular drugs, but not using antimigraine drugs in the year prior to the index date, had a (nonsignificant) two times higher risk of these events (OR 1.99; 95% CI 0.83 – 4.76). Overuse of antimigraine drugs in those patients simultaneously using cardiovascular drugs more than doubled this risk of ischemic complications: OR 4.36 (95% CI 1.78 – 10.7).

Stratified analysis according to triptan and ergotamine use (Table 4 and 5) showed that this increased risk in patients with overuse of antimigraine drugs and use of cardiovascular drugs was clarified by overuse of ergotamine and not triptans. Considering all triptan users (Table 4), triptan overuse did not increase the risk of ischemic complications (OR 0.96; 95% CI 0.49 – 1.90). Stratified results showed that patients using cardiovascular drugs, but not using triptans in the year prior to the index date, had an almost (nonsignificant) two times higher risk of these events vs. patients not using cardiovascular drugs and not using triptans (OR 1.94;

Table 4	Association between intensity of triptan use and the risk of hospitalization due to ischemic events: DDDs of triptans dispensed one year before the index date			
	Triptan users (n = 359) and no antimigraine drug use (n = 153)			
Intensity of use (DDDs)	**Cases n = 105 (100%)**	**Controls n = 407 (100%)**	**Crude OR (95% CI)**	**Adjusted [a] OR (95% CI)**
All patients				
0	31 (29.5%)	122 (30.0%)	1.0 (reference)	1.0 (reference)
> 0 to < 30	36 (34.3%)	137 (33.6%)	1.03 (0.60 – 1.77)	0.86 (0.49 – 1.53)
30 to < 90	19 (18.1%)	81 (19.9%)	0.92 (0.49 – 1.74)	0.78 (0.40 – 1.53)
≥ 90	19 (18.1%)	67 (16.5%)	1.12 (0.59 – 2.13)	0.96 (0.49 – 1.90)
Without cardiovascular drug use				
0	19 (18.1%)	94 (23.1%)	1.0 (reference)	1.0 (reference)
> 0 to < 30	28 (26.7%)	103 (25.3%)	1.35 (0.71 – 2.57)	1.17 (0.60 – 2.30)
30 to < 90	12 (11.4%)	66 (16.2%)	0.90 (0.41 – 1.98)	0.80 (0.35 – 1.81)
≥ 90	12 (11.4%)	58 (14.3%)	1.02 (0.46 – 2.26)	0.94 (0.41 – 2.13)
With cardiovascular drug use				
0	12 (11.4%)	28 (6.9%)	2.12 (0.92 – 4.90)	1.94 (0.79 – 4.76)
> 0 to < 30	8 (7.6%)	34 (8.3%)	1.16 (0.47 – 2.91)	0.76 (0.28 – 2.04)
30 to < 90	7 (6.7%)	15 (3.7%)	2.31 (0.83 – 6.43)	1.61 (0.53 – 4.88)
≥ 90	7 (6.7%)	9 (2.2%)	3.85 (1.28 – 11.6)	2.28 (0.68 – 7.65)

DDDs = defined daily doses; OR = odds ratio

a) Adjusted for age, gender, prior hospitalization, and use of comedication (benzodiazepines, antidiabetics, gastrointestinal drugs, migraine prophylaxis, and nonsteroidal anti-inflammatory drugs). Combined use of triptans and ergotamine was excluded in the analysis.

95% CI 0.79 – 4.76). Overuse of triptans in patients using cardiovascular drugs did not further increase this risk (OR 2.28; 95% CI 0.68 – 7.65).

Considering all ergotamine users (Table 5), it was shown that overuse of ergotamine is a risk factor for ischemic complications (OR 2.55; 95% CI 1.22 – 5.36). Overuse of ergotamine by those patients without cardiovascular drug use slightly increased the risk of ischemic complications without reaching significance (OR 2.19; 95% CI 0.84 – 5.68). Patients using cardiovascular drugs during the year prior to the index date, but not using ergotamine, had a (nonsignificant) two times higher risk of these complications (OR 2.20; 95% CI 0.90 – 5.36). Overuse of ergotamine in patients simultaneously using cardiovascular drugs increased this risk almost fourfold: OR 8.52; 95% CI 2.57 – 28.2).

Table 5 Association between intensity of ergotamine use and the risk of hospitalization due to ischemic events: DDDs of ergotamine dispensed one year before the index date

	Ergotamine users (n = 334) and no antimigraine drug use (n = 153)			
Intensity of use (DDDs)	**Cases n = 109 (100%)**	**Controls n = 378 (100%)**	**Crude OR (95% CI)**	**Adjusted [a] OR (95% CI)**
All patients				
0	31 (28.4%)	122 (32.3%)	1.0 (reference)	1.0 (reference)
> 0 to < 30	38 (34.9%)	149 (39.4%)	1.00 (0.59 – 1.71)	1.00 (0.57 – 1.72)
30 to < 90	21 (19.3%)	78 (20.6%)	1.06 (0.57 – 1.98)	1.01 (0.52 – 1.95)
≥ 90	19 (17.4%)	29 (7.7%)	2.58 (1.28 – 5.19)	2.55 (1.22 – 5.36)
Without cardiovascular drug use				
0	19 (17.4%)	94 (24.9%)	1.0 (reference)	1.0 (reference)
> 0 to < 30	17 (15.6%)	116 (30.7%)	0.73 (0.36 – 1.47)	0.77 (0.38 – 1.58)
30 to < 90	11 (10.1%)	56 (14.8%)	0.97 (0.43 – 2.19)	1.10 (0.47 – 2.53)
≥ 90	9 (8.3%)	22 (5.8%)	2.02 (0.81 – 5.07)	2.19 (0.84 – 5.68)
With cardiovascular drug use				
0	12 (11.0%)	28 (7.4%)	2.12 (0.92 – 4.90)	2.20 (0.90 – 5.36)
> 0 to < 30	21 (19.3%)	33 (8.7%)	3.15 (1.51 – 6.58)	3.26 (1.45 – 7.36)
30 to < 90	10 (9.2%)	22 (5.8%)	2.25 (0.92 – 5.51)	2.21 (0.81 – 6.05)
≥ 90	10 (9.2%)	7 (1.9%)	7.07 (2.39 – 20.9)	8.52 (2.57 – 28.2)

DDDs = defined daily doses; OR = odds ratio

a) Adjusted for age, gender, prior hospitalization and use of comedication (benzodiazepines, antidiabetics, gastrointestinal drugs, migraine prophylaxis, and nonsteroidal anti-inflammatory drugs). Combined use of ergotamine and triptans was excluded in the analysis.

DISCUSSION

Our research shows that overuse of triptans (defined as use of ≥ 90 DDDs per year), neither in the general population nor in those using cardiovascular drugs, increases the risk of cerebral, cardiovascular, or peripheral ischemic complications requiring hospitalization. Ergotamine overuse in patients simultaneously using cardiovascular drugs, on the contrary, increases the risk of these ischemic complications almost fourfold vs. patients using cardiovascular drugs but not using ergotamine.

Our results correspond with in vitro pharmacologic data that show that, at therapeutically relevant concentrations, triptans have little potential to cause clinically relevant constriction of nondiseased coronary arteries.[22] As shown recently by in vivo data, this might also be applied to diseased coronary arteries.[23]

We had too few cases on which to perform a separate analysis for cerebral, coronary, and peripheral ischemic events. Therefore, we do not know whether (over)use of triptans, being powerful vasoconstrictors of the cerebral arteries, increases the risk of ischemic stroke. However, the absolute risk of this potential adverse event of triptans remains low. Furthermore, all triptans produce substantially less potent arterial constriction than ergotamine.[22]

Two comparable studies have been published recently. The first study investigated the incidence of stroke, cardiovascular events and death in a migraine cohort, stratified by triptan prescription, and found that in general practice triptan treatment did not increase the risk for these events.[14] However, in this study, the intensity of triptan use and the differential risk of ergotamine use were not taken into account. These two aspects were (partly) studied in the second study, investigating the rates of vascular events in relation to dispensing of triptans and ergotamine among migraineurs.[16] Overall, in the group of migraineurs, neither current nor recent triptan or ergotamine use was associated with an increased risk of myocardial infarction, unstable angina, serious ventricular arrhytmia, stroke, or transient ischemic attack compared with no use. Intensity of triptan and ergotamine use was only investigated in relation to the occurrence of stroke. No association was found for triptan use. Recent use of ergotamine showed an increased risk of stroke in only one category of use (11 to 28 days supplied in the past six months) compared with no use (OR 4.54; 95% CI 2.26 – 9.10). In the highest category of use (ergotamine supplied ≥ 61 days in the past six months), no increased risk of stroke was found. No distinction was made of whether cardiovascular drugs were used.

Several limitations of our analysis should be mentioned. First, different validity studies indicate that certain conditions may not be accurately reflected by discharge ICD-9 codes. One study investigated the sensitivity and the positive predictive value (PPV) of the ICD-9 codes 434 and 436 in a general hospital in Italy.[24] They found a sensitivity of 82% and a PPV of 76%. An administrative database of five academic medical centers in the United States found a PPV of 85% for ICD-9 code 434, and 77% for the ICD-9 codes 435 and 436.[25] Dutch validity studies for the ICD-9 discharge codes that we used have not been published so far. However, a low sensitivity rate means that among controls one could find some cases (false negatives), which would have diluted our results. A low PPV means that not all our cases truly are cases (false positives). Because there is no reason to assume that these false positives would have used more antimigraine drugs, this would not have overpowered, but probably rather diluted, our estimates.

Second, the duration of exposure had to be estimated because the PHARMO database contains only data about the dates and quantities of drug dispensing and not information about the actual moments of drug intake by the patient. However,

estimation of drug overuse not need be a problem because prescriptions repeated consistently can serve as strong evidence of drug use by patients.[26] We admit that our cutoff of ≥ 90 DDDs per year is somewhat arbitrary. Therefore, we performed an additional analysis in which we divided the last category (≥ 90 DDDs) into two categories: 90 to < 150 DDDs and ≥ 150 DDDs. The observed pattern (increasing risk of ischemic complications with increasing dispensing of ergotamine, but not triptans) was comparable with the pattern using a cutoff of ≥ 90 DDDs (data not shown). However, the extra category meant loss of power because only a few patients were in these last two categories (90 to < 150 DDDs and ≥ 150 DDDs). Therefore, we chose not to split the category ≥ 90 DDDs and defined this last category as overuse.

Furthermore, a recent meta-analysis showed the association between migraine and ischemic stroke.[27] Therefore, it is possible that an increased intensity in use reflects an increased severity of migraine, being the actual cause of the ischemic stroke. However, in this case, one would expect that for both triptans and ergotamine, a higher percentage of overuse in the case group compared with the control group. Triptan overuse was about equal in both cases and controls.

Although adjusted for potential confounders, residual confounding may exist because a few factors known to be associated with increased risk of coronary and cerebrovascular complications such as smoking, family history, obesity, and fitness were unknown. Despite these limitations, we believe that our research contributes to the confirmation of the safety of triptans and emphasizes the risk of ischemic complications due to ergotamine overuse, so far only described in case reports.

We also determined whether increasing use of triptans and ergotamine shortly before the index date was associated with the risk of hospitalization. Therefore, we computed the distribution of the total number of DDDs dispensed across the year preceding the index date in monthly intervals for each eligible patient, expressed as the pattern score. This method was adapted from a study that investigated the intensity of β-agonist inhaler therapy.[28] The pattern score may range from 1 to 12. The score 1 indicates that the total DDDs were dispensed during the first monthly interval and none in the remaining intervals and the score 12 indicates that all DDDs were concentrated in the 12th month interval and none in the previous intervals. Contrary to our expectations, the pattern score (expressed as categorized pattern scores: 0, > 0 to ≤ 5, > 5 to < 7, ≥ 7) did not differ significant between the cases and controls. Based on the pharmacologic properties of triptans and ergotamine, we expected that increased use of these drugs shortly before the ischemic event would be a risk factor for the occurrence of this event. Apparently it was not.

Due to their vasoconstrictive pharmacodynamic properties, triptans and ergotamine are contraindicated in patients with cardiovascular risk factors. Therefore, as one

would expect, it was previously found that triptans were prescribed to those at less risk of cardiovascular events.[14] Remarkably, in our population, we found that the percentage of patients who did not use specific antimigraine drugs during the study period was 17.5% (40/229) in those using cardiovascular drugs vs. 17.4% (113/648) in those not using cardiovascular drugs. Also patients who used cardiovascular drugs were dispensed as much specific antimigraine drugs as patients who did not use cardiovascular drugs (mean DDDs per year [excluding no use]: 56.0 vs. 56.2). It has to be noted that we did not categorize the number of different cardiovascular drugs used, and therefore no distinction was made between patients at high and patients at low cardiovascular risk. This might probably explain part of the finding that patients using cardiovascular drugs (but not using antimigraine drugs) showed only a nonsignificant two times higher risk of ischemic complications vs. patients not using cardiovascular drugs (and not using antimigraine drugs). Furthermore, we found that more than 60% (114/188) of the cases were still dispensed a specific antimigraine drug after their ischemic event. Notably, this did not result in a higher risk of a second ischemic event: 28.1% (32/114) of those who continued to use triptans or ergotamine had a second event compared with 29.7% (22/74) of those who discontinued use. A possible explanation for these striking results could be that antimigraine drugs were in particular discontinued in those who were at high risk for another event.

Interactions between ergotamine and comedication may predispose to ergot toxicity. One of the most reported interactions with ergotamine is coadministration with the macrolide antibiotics erythromycin and clarithromycin, causing increased bioavailability due to inhibition of cytochrome P-450 3A4.[29-32] Protease inhibitors may also interact with ergotamine.[33-35] Only six of our cases used ergotamine in combination with erythromycin or clarithromycin during the period one year before the index date. In all cases, the dispensing date was ≥ 1 month prior to the index date (1, 2, 3, 5, 10 and 11 months) and therefore less likely related to the ischemic event. Protease inhibitors were not used by our study population during one year prior to the index date. Because also other drugs (strongly) inhibit CYP3A4, these drugs may also have interfered with ergotamine. We did not study all these possible interfering drugs. However, if these kind of drug interactions played a role in our data, it would have diluted our results.

Overall, we provided evidence that, regarding the occurrence of ischemic complications requiring hospitalization, triptan use and even triptan overuse are safe in general practice. Possibly due to its stronger vasoconstrictive properties, overuse of ergotamine may increase the risk of these complications, especially in those simultaneously using cardiovascular drugs. Moreover, because we did not distinguish between patients with low and patients with high cardiovascular risk,

we did not investigate the attributable risk of specific antimigraine drugs to the occurrence of ischemic complications in specific populations as those with a high cardiovascular risk profile. Therefore, this conclusion cannot be extended to such a population, and when prescribing specific antimigraine drugs to these patients, one still should take the contraindications into account.

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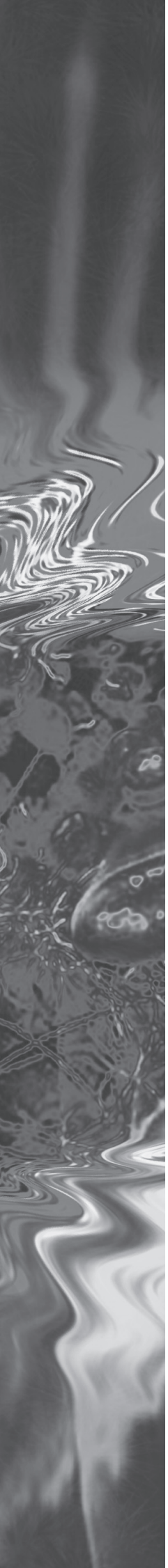

4.2

TREATMENT CHOICES AND PATTERNS IN MIGRAINE PATIENTS WITH AND WITHOUT A CARDIOVASCULAR RISK PROFILE

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ABSTRACT

Objective

To characterize the baseline cardiovascular risk profile of new users of specific abortive migraine drugs, and to investigate treatment choices and patterns in patients with and without a known cardiovascular risk profile.

Background

Treatment patterns in migraine patients with cardiovascular risk factors are largely unknown.

Methods

A retrospective observational study using data from the PHARMO Record Linkage System was conducted. New users of a triptan, ergotamine or Migrafin® from 1 January 1990 to 31 December 2006 were included. The cardiovascular risk profile was determined at the start of the antimigraine drug.

Results

The study population included 36 839 new users of specifice abortive migraine drugs. Approximately 90% of all new users did not have a clinically recognized cardiovascular risk profile. The percentage of new users with a cardiovascular risk profile did not differ between new users of a triptan, ergotamine or Migrafin® and also did not change during the study period of 17 years. During the year preceding the first prescription of an abortive migraine drug, patients with a cardiovascular risk profile used 2.3 (95% confidence interval [CI] 2.1 – 2.5) times more often drugs for migraine prophylaxis and 1.4 (95% CI 1.3 – 1.5) times more often nonsteroidal anti-inflammatory drugs compared to patients without a cardiovascular risk profile. Switch to a triptan was less often seen in patients with a cardiovascular risk compared to those without a cardiovascular risk (odds ratio [OR] 0.7; 95% CI 0.6 – 0.8).

Conclusions

Since 1991, almost 90% of new users of triptans and ergotamine in the Netherlands have no clinically recognized cardiovascular risk profile. Differences in treatment choices and patterns between migraine patients with and without a known cardiovascular risk profile reveal a certain reticence in prescribing vasoconstrictive antimigraine drugs to patients at cardiovascular risk.

INTRODUCTION

It is well known that ergotamine can lead to serious ischemic adverse effects such as peripheral ischemia, arterial stenosis, myocardial infarction and cerebral ischemia,[1-4] probably due to its broad pharmacologic activity involving serotonin ($5HT_1$ and $5HT_2$), dopamine and α-adrenoceptors. For a long time ergotamine was the only specific migraine abortive drug available, and the potential for these complications has always been a limitation to its use, especially in patients with a cardiovascular risk profile. The selective 5-$HT_{1B/1D}$ agonists, known as triptans and available from the 1990s onwards, have improved the quality of acute migraine treatment by providing a higher degree of efficacy and a more favourable side effect profile than ergotamine. However, soon after the introduction of sumatriptan, reports began to appear of angina-like chest symptoms.[5,6] Data from long-term open-label clinical trials and large post marketing studies suggested that the vast majority of triptan-related chest symptoms were non-cardiac in origin.[7-9] Nevertheless, case reports of serious ischemic complications such as myocardial infarction,[10-13] ischemic stroke [14,15] and ischemic colitis [16-18] were published related to triptan use, mostly in patients with cardiovascular disease risk factors. Therefore, the use of triptans, like ergotamine, is contraindicated in these patients.

Subsequent observational evidence has shown that the incidence of cardiovascular adverse events is low when triptans are used appropriately.[19-21] A recent case-control study has shown that regarding vasoconstrictive complications, triptan use and even its overuse did not increase the risk for these complications, even in patients simultaneously using cardiovascular drugs. Overuse of ergotamine, however, significantly increased the risk for these complications, especially in those simultaneously using cardiovascular drugs.[22]

Prescribers' concerns about the cardiovascular safety of ergotamine and triptans may lead them to choose other treatment options first, such as nonsteroidal anti-inflammatory drugs (NSAIDs) or migraine prophylaxis, before prescribing the specific migraine abortive drugs to patients at cardiovascular risk. In addition, treatment patterns of antimigraine drugs themselves, such as the intensity of use, may differ. Due to growing evidence that the incidence of triptan-associated serious cardiovascular adverse events in both clinical trials and clinical practice appears to be extremely low, this concern, and therefore also prescribing behaviour, may have changed over time. However, treatment patterns in migraine patients with cardiovascular risk factors remain largely unknown.

This retrospective observational study was conducted to characterize the baseline cardiovascular risk profile of new users of specific abortive migraine drugs and its change over time. Treatment choices and patterns were investigated in patients with and without a clinically recognized cardiovascular risk profile.

METHODS

Setting

We reviewed data from the PHARMO Record Linkage System, which includes several databases and links drug dispensing records and hospital records from currently more than two million individuals in defined areas in the Netherlands.[23] The pharmacy database consists of a sample of > 200 pharmacies in > 50 regions scattered over the Netherlands and is representative of the Netherlands with respect to age, gender and healthcare consumption. Currently, it covers data of more than two million residents regardless of type of insurance, corresponding to 12% of the Dutch population.[24] Since virtually all patients in the Netherlands are registered with a single community pharmacy, independent of prescriber, pharmacy records are virtually complete with regard to presciption drugs. Members of the PHARMO population enter the database with the first prescription filled in a PHARMO community pharmacy and are followed until the last prescription.

The computerized drug dispensing histories contain information concerning the dispensed drug, dispensing date, the prescriber, amount dispensed, prescribed dosage regimen and the estimated duration of use. The duration of use of each dispensed drug is estimated by dividing the number of dispensed units by the prescribed number of units to be used per day. All drugs are coded according to the Anatomical Therapeutic Chemical Classification. Patient information per prescribed medicine includes gender and date of birth. The database does not provide information concerning the indications for use of the medicines, in this case the diagnosis of migraine vs. cluster headache, or accurate registration of non-prescription medicines (e.g. over-the-counter [OTC] use of salicylates, NSAIDs or paracetamol).

The hospital discharge records were obtained from PRISMANT, previously known as the Dutch Center for Healthcare Information (LMR database), an institute that collects nationwide all hospital discharge records in the Netherlands since the 1960s in a standardized format.[24] These records include detailed information concerning the discharge diagnoses, diagnostic, surgical and treatment procedures, type and frequency of consultations with medical specialists and dates of hospital admission and discharge. All diagnoses are coded according to the International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM).

Study population

For this study, all patients with at least one dispensed prescription for either a triptan, ergotamine (alone or in combination with caffeine and/or cyclizine), or Migrafin® (a combination drug of 900 mg acetylsalicylic acid and 10 mg metoclopramide, approved for acute migraine treatment since 1996 in the Netherlands) from 1

January 1990 to 31 December 2006, were initially identified from the PHARMO system. To identify 'new users' of these specific migraine abortive drugs the date of the first dispensed prescription for a triptan, ergotamine or Migrafin® in that time period was termed the 'start date'. Patients were only included in the present study if, at the start date, the patient had at least one year's history in PHARMO and if the patient was ≥ 18 years old.
The following characteristics were evaluated at the start date: gender, age, prescriber, use of NSAIDs during the year preceding the start date, and use of migraine prophylactics (propranolol, metoprolol [since in the Netherlands propranolol and metoprolol are the only β-blockers mentioned in guidelines for migraine prophylaxis], valproic acid, clonidine, methysergide, pizotifen, flunarizine, topiramate) during the year before the start date.
Patients who used both ergotamine and triptans or Migrafin® were categorized as 'switchers' only if the last dispensing date of the drug type (ergotamine, triptan or Migrafin®) dispensed on the start date was before the first dispensing date of the drug type were one switched to. Therefore, during the period before switching, only one drug type (ergotamine, triptan or Migrafin®) was used. For switchers the date of the first presented prescription of the drug, were one switched to, was termed the 'switch date'.

Cardiovascular risk profile

The determinant of interest was a clinically recognized cardiovascular risk profile at the start of the treatment with migraine abortive drugs. This was determined on the basis of the use of cardiovascular drugs as well as hospitalizations for cardiovascular reasons.
The use of cardiovascular drugs was assessed during the six months before the start date. This window was set to indicate simultaneous use of the various types of drugs. A six-month time window is long enough to observe at least one dispensing in chronic medication, but not too long for drugs used sequentially, rather than simultaneously.
Dispensing of the following drugs during the six months before the start date was identified: renin-angiotensin-aldosterone system inhibitors, β-blockers – except propranolol and metoprolol – calcium channel blockers, diuretics, nitrates, cardiac glycosides, oral anticoagulants, antiplatelet therapy, lipid-lowering therapy and oral antidiabetics. Except for dispensing of the individual drugs, combination therapy was be identified: zero, one, two, three and four or more drugs in the abovementioned categories.
In addition, hospitalizations due to a cardiovascular event during one year preceding the start date were assessed. The included discharge diagnoses were:

hypertensive disease (essential hypertension [ICD-9-CM code 401], hypertensive heart disease [ICD-9-CM code 402], secondary hypertension [ICD-9-CM code 405]), ischemic heart disease (ICD-9-CM codes 410-414), heart failure (ICD-9-CM code 428), cerebral ischemia (ICD-9-CM codes 433-436, 437.0, 437.1 and 437.6) and atherosclerosis (ICD-9-CM code 440).
For switchers, in the same way, the cardiovascular risk profile was also determined preceding the switch date.

Treatment choices and patterns

Different treatment patterns between new users were identified, all stratified to patients with and without a cardiovascular risk profile. The use of other migraine treatment options before the start of a specific abortive migraine drug, was assessed by determining the use of NSAIDs or migraine prophylactics (see section on Study population) during the year before the start date.
After the start date we looked at different patterns of specific abortive migraine drug use. First, the prevalence of single use (only one prescription) was determined. Second, for non-incident users (repeated prescriptions) with at least one year's follow-up after the start date, the intensity of triptan, ergotamine and Migrafin® use during the first year after the start of the antimigraine drug was determined. To express the intensity of use, for each patient the total consumption of drugs was estimated by the sum of defined daily doses (DDDs) of triptans, ergotamine and Migrafin® dispensed during this first year.[25] One DDD was defined as 6 mg sumatriptan parenteral, 50 mg sumatriptan oral, 25 mg sumatriptan rectal, 20 mg sumatriptan nasal, 2.5 mg naratriptan, 2.5 mg zolmitriptan, 10 mg rizatriptan, 12.5 mg almotriptan, 40 eletriptan, 2.5 mg frovatriptan, 4 mg ergotamine single preparation by any route, 2 mg ergotamine combination preparation by any route and one tablet Migrafin®. Patients were subsequently categorized according to the intensity of use: > 0 – < 12, 12 – < 36, 36 – < 72 and ≥ 72 DDDs dispensed during this year. Finally, we assessed switch behaviour of new users: switch from ergotamine or Migrafin® to a triptan, switch from a triptan or Migrafin® to ergotamine and switch from ergotamine or a triptan to Migrafin®. For definition of 'switchers' we refer to the section on Study population.

Data analysis

For all new users of antimigraine drugs the prevalence of each characteristic was determined on the start date. Logistic regression was used to estimate the strength of the differences in treatment characteristics between migraine patients with and without cardiovascular risk, expressed as odds ratios (ORs), crude and adjusted for age, with 95% confidence interval (CI). Microsoft Access, a relational

database software package, was used for database management and internal quality procedures. All statistical analyses were performed with SPSS statistical software (version 14.0) (SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 72 743 patients had been dispensed a triptan, ergotamine or Migrafin® during the study period 1990 – 2006. Patients with < 1 year of medication history (n = 33 432), patients < 18 years old (n = 2376) and patients who started two types of drug (e.g. ergotamine and a triptan) on the same date (n = 96) were excluded, resulting in a final study population of 36 839 new users of specific abortive migraine drugs. Characteristics of the study population at the start date are described in Table 1. There were no remarkable differences between new users of triptans, ergotamine

Table 1 Baseline characteristics of new users (n=36 839) of triptans, ergotamine or Migrafin® [a]

	Triptan n = 26 318 (100%)	Ergotamine n = 5 364 (100%)	Migrafin® n = 5 157 (100%)
Gender			
male	5 623 (21.4%)	1 027 (19.1%)	978 (19.0%)
female	20 695 (78.6%)	4 337 (80.9%)	4 179 (81.0%)
Age; mean (sd) in years	40.6 (12.8)	42.1 (13.5)	39.8 (13.5)
18 – 40	13 764 (52.3%)	2 571 (47.9%)	2 871 (55.7%)
> 40 – 65	11 428 (43.4%)	2 472 (46.1%)	2 038 (39.5%)
> 65	1 126 (4.3%)	321 (6.0%)	248 (4.8%)
Prescriber first prescription			
neurologist	1 776 (6.7%)	111 (2.1%)	202 (3.9%)
general practitioner	23 745 (90.3%)	5 060 (94.3%)	4 840 (93.8%)
other	350 (1.3%)	107 (2.0%)	24 (0.5%)
unknown	438 (1.7%)	86 (1.6%)	91 (1.8%)
History of NSAID use			
yes	11 003 (41.8%)	2 121 (39.5%)	2 282 (44.3%)
no	15 315 (58.2%)	3 243 (60.5%)	2 875 (55.7%)
History of migraine prophylactics			
yes	2 290 (8.7%)	544 (10.1%)	331 (6.4%)
no	24 028 (91.3%)	4 820 (89.9%)	4 826 (93.6%)

NSAID = nonsteroidal anti-inflammatory drug

a) A combination drug of 900 mg acetylsalicylic acid and 10 mg metoclopramide, approved for acute migraine treatment in 1996 in the Netherlands.

Table 2a	Cardiovascular risk profile of new users (n = 36 839) of triptans, ergotamine or Migrafin® [a]		
	Triptan	**Ergotamine**	**Migrafin®**
	n = 26 318 (100%)	**n = 5 364 (100%)**	**n = 5 157 (100%)**
Treatment with drugs for cardiovascular risk management			
RAAS – inhibitors	904 (3.4%)	138 (2.6%)	172 (3.3%)
β-blockers	756 (2.9%)	124 (2.3%)	175 (3.4%)
Ca-channel blockers	436 (1.7%)	79 (1.5%)	91 (1.8%)
diuretics	974 (3.7%)	227 (4.2%)	212 (4.1%)
nitrates	148 (0.6%)	42 (0.8%)	50 (1.0%)
cardiac glycosides	48 (0.2%)	13 (0.2%)	6 (0.1%)
oral anticoagulants	173 (0.7%)	36 (0.7%)	19 (0.4%)
antiplatelet therapy	675 (2.6%)	74 (1.4%)	163 (3.2%)
lipid-lowering therapy	878 (3.3%)	76 (1.4%)	169 (3.3%)
oral antidiabetics	252 (1.0%)	42 (0.8%)	80 (1.6%)
none	23 179 (88.1%)	4 823 (89.9%)	4 545 (88.1%)
any 1 category [b]	1 874 (7.1%)	343 (6.4%)	334 (6.5%)
any 2 categories	741 (2.8%)	128 (2.4%)	141 (2.7%)
any 3 categories	313 (1.2%)	41 (0.8%)	70 (1.4%)
any 4 or more categories	211 (0.8%)	29 (0.5%)	67 (1.3%)
Prior hospitalization due to a cardiovascular event			
yes	64 (0.2%)	19 (0.4%)	21 (0.4%)
no	26 254 (99.8%)	5 345 (99.6%)	5 136 (99.6%)

RAAS = renin-angiotensin-aldosterone system

a) A combination drug of 900 mg acetylsalicylic acid and 10 mg metoclopramide, approved for acute migraine treatment in 1996 in the Netherlands.

b) Category: one of the abovementioned groups of drugs for cardiovascular risk management (e.g. RAAS-inhibitors).

or Migrafin® with respect to age distribution, gender, prescriber and history of prescription NSAID use or history of migraine prophylaxis.

Table 2a shows that 88 – 90% of all new users did not have a clinically recognized cardiovascular risk profile; 6.4 – 7.1% used one drug and 3.7 – 5.4% used more than one drug for cardiovascular risk management during the period of six months before the start date. Only 0.2 – 0.4% of all new users had experienced a hospitalization due to a cardiovascular event during one year preceding the start date. For switchers the cardiovascular risk profile was determined preceding the switch date: 2408 persons switched from ergotamine or Migrafin® to a triptan, 137 switched to ergotamine and 545 switched to Migrafin®. Cardiovascular risk profiles of these switchers were comparable to the profiles of new users (data not

Table 2b Treatment with drugs for cardiovascular risk management of new users (n = 36 839) of triptans, ergotamine or Migrafin® [a] stratified for age

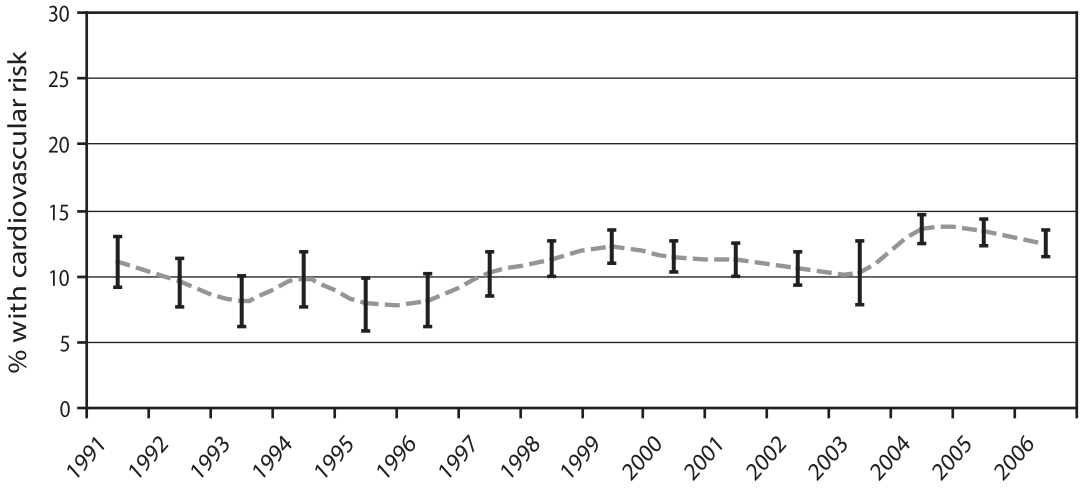
	Triptan (n = 26 318)	Ergotamine (n = 5 364)	Migrafin® (n = 5 157)
Patients < 40 years	12 952 (100%)	2 428 (100%)	2 731 (100%)
none	12 491 (96.4%)	2 352 (96.9%)	2 632 (96.4%)
any 1 category [b]	366 (2.8%)	61 (2.5%)	80 (2.9%)
any 2 categories	72 (0.6%)	12 (0.5%)	14 (0.5%)
any 3 categories	18 (0.1%)	3 (0.1%)	2 (0.1%)
any 4 or more categories	5 (0.0%)	0 (0.0%)	3 (0.1%)
Patients 40 – 60 years	11 542 (100%)	2 392 (100%)	2 035 (100%)
none	9 819 (85.1%)	2 124 (88.8%)	1 728 (84.9%)
any 1 category	1 105 (9.6%)	191 (8.0%)	170 (8.4%)
any 2 categories	401 (3.5%)	54 (2.3%)	72 (3.5%)
any 3 categories	144 (1.2%)	15 (0.6%)	40 (2.0%)
any 4 or more categories	73 (0.6%)	8 (0.3%)	25 (1.2%)
Patients > 60 years	1 824 (100%)	544 (100%)	391 (100%)
none	869 (47.6%)	347 (63.8%)	185 (47.3%)
any 1 category	403 (22.1%)	91 (16.7%)	84 (21.5%)
any 2 categories	268 (14.7%)	62 (11.4%)	55 (14.1%)
any 3 categories	151 (8.3%)	23 (4.2%)	28 (7.2%)
any 4 or more categories	133 (7.3%)	21 (3.9%)	39 (10.0%)

a) A combination drug of 900 mg acetylsalicylic acid and 10 mg metoclopramide, approved for acute migraine treatment in 1996 in the Netherlands.
b) Category: one of the groups of drugs for cardiovascular risk management mentioned in Table 2a.

shown). Table 2b shows that the use of drugs for cardiovascular risk management was age dependent. There were no major differences between the three treatment groups, except that in the group > 60 years old ergotamine users had 1.3 times more frequently no use of drugs for cardiovascular risk management than starters of triptans or Migrafin®.

Figure 1 shows that the percentage of new users with a known cardiovascular risk profile at the moment a triptan, ergotamine or Migrafin® was started did not change over calender time. This was also the case when these three groups were observed separately (figures not shown). The average age of patients starting one of the study drugs remained constant over the entire study period (38.8 – 42.8 years). During the years we observed an almost complete substitution from ergotamine to triptans. In 1991 28.2% of the new users started with a triptan, 71.8% with ergotamine and 0% with Migrafin®, compared with, respectively, 94.9, 0.4 and 4.7% in 2006. After its introduction in 1996, Migrafin® showed in 1997 and 2000 a maximum of 28% market share, declining rapidly afterwards to < 5% in 2006.

Figure 1 Percentage new users of specific abortive migraine drugs with a known cardiovascular risk profile: change over time



I : upper 95% CI / lower 95% CI

Treatment choices and patterns are shown in Table 3. During the year preceding the first prescription of an abortive migraine drug, patients with a cardiovascular risk profile used 2.3 (95% CI 2.1 – 2.5) times more often drugs for migraine prophylaxis and 1.4 (95% CI 1.3 – 1.5) times more often NSAIDs than patients without a known cardiovascular risk profile. Single use of an abortive migraine drug was more frequently seen in patients with cardiovascular risk. The intensity of use of abortive migraine drugs was not different between patients with and without cardiovascular risk. Switch to a triptan was less often seen in patients with cardiovascular risk than in patients without cardiovascular risk (OR 0.67; 95% CI 0.56 – 0.79).

DISCUSSION

Our research shows that since the introduction of sumatriptan in 1991 in the Netherlands, almost 90% of new users of triptans and ergotamine have no clinically recognized cardiovascular risk profile. This pattern did not change during the study period. Comparing treatment choices and patterns between patients with and without a cardiovascular risk profile, the more frequent history of use of drugs for migraine prophylaxis and NSAIDs in patients with cardiovascular risk factors during the year preceding the start of an abortive migraine drug reveals a certain reticence in prescribing vasoconstrictive antimigraine drugs to these patients.

Table 3 Treatment choices and patterns of migraine patients with and without a known cardiovascular risk profile

	Cardiovascular risk	No cardiovasular risk	Crude	Adjusted [a]
	n = 4 312 (100%)	n = 32 527 (100%)	OR (95% CI)	OR (95% CI)
Before start abortive migraine drug				
Migraine prophylaxis	771 (17.9%)	2 394 (7.4%)	2.74 (2.51 – 2.99)	2.30 (2.08 – 2.54)
NSAID	2 127 (49.3%)	13 279 (40.8%)	1.41 (1.32 – 1.50)	1.38 (1.29 – 1.48)
After start abortive migraine drug				
Single use [b]	2 284 (53.0%)	14 084 (43.3%)	1.48 (1.38 – 1.57)	1.29 (1.20 – 1.38)
DDDs during first year (n = 17 664)				
> 0 – < 12	502 (29.1%)	4 867 (30.5%)	0.93 (0.84 – 1.04)	0.93 (0.82 – 1.04)
12 – < 36	697 (40.3%)	6 480 (40.7%)	0.99 (0.89 – 1.09)	1.01 (0.91 – 1.12)
36 – < 72	308 (17.8%)	2 866 (18.0%)	0.99 (0.87 – 1.13)	1.00 (0.88 – 1.15)
≥ 72	221 (12.8%)	1 723 (10.8%)	1.21 (1.04 – 1.41)	1.14 (0.97 – 1.33)
Switch to ergotamine	18 (0.4%)	119 (0.4%)	1.14 (0.70 – 1.88)	1.43 (0.84 – 2.42)
Switch to triptan	167 (3.9%)	2 241 (6.9%)	0.54 (0.46 – 0.64)	0.67 (0.56 – 0.79)
Switch to Migrafin® [c]	57 (1.3%)	488 (1.5%)	0.88 (0.67 – 1.16)	1.04 (0.77 – 1.40)

OR = odds ratio; NSAID = nonsteroidal anti-inflammatory drug; DDDs = defined daily doses, intensity of use of non-incident users (repeated prescriptions) is presented

a) Adjusted for age.
b) Single use is defined as delivery of just one prescription (first prescription = last prescription).
c) A combination drug of 900 mg acetylsalicylic acid and 10 mg metoclopramide, approved for acute migraine treatment in 1996 in the Netherlands.

Once the treatment with a specific antimigraine drug was accepted by the doctor and patient, the intensity of use did not differ between patients with and without a cardiovascular risk profile.

Our data about prescribing triptans to patients with a clinically recognized cardiovascular risk profile are of the same order as findings from a population-based study in the UK: 5.9% hypertension, 3.1% cardiac disease and 0.8% diabetes among triptan-treated migraine patients.[21] A population-based study in France showed a higher percentage: 16% of new triptan users had known cardiovascular risk factors.[26] The study from the UK also showed that triptans were selectively prescribed to those less at risk for cardiovascular events.[21] No difference in intensity of use after accepting the treatment was also seen in a recent nested case-control study, which showed that patients who used cardiovascular drugs were dispensed as much specific antimigraine drugs as those without cardiovascular drug use.[22]

Our analysis is limited by the fact that, due to several reasons, the cardiovascular risk profile in our population may be underestimated. First, we considered only

clinically recognized cardiovascular risk, since cardiovascular disease unknown to the treating physician cannot influence treatment decisions. Population-based studies show that a great part of cardiovascular disease – such as hypertension and diabetes – are undetected and untreated.[27,28] Other cardiovascular risk factors such as smoking, family history, obesity and physical condition were unknown. However, this misclassification is likely to be non-differential over time and non-differential between different exposure groups. Furthermore, different validity studies indicate that certain conditions may not be accurately reflected by discharge ICD-9 codes. However, studies investigating the sensitivity and the positive predictive value (PPV) of ICD-9 codes 434 and 436 have found sensitivity rates of 76 and 82% and PPVs between 71 and 85%.[29,30] ICD-9 code 433 showed a low PPV of 15%.[30] In our final study population only three patients showed hospitalization for an event diagnosed by code 433 one year before the start of an antimigraine drug. Considering our low hospitalization percentages, this means that, at least for these ICD-codes, our data are hardly influenced by this degree of invalidity. Dutch validity studies for the ICD-9 discharge codes we used have not been published so far.

Second, due to fact that our database does not contain information about the indication for use of medicines, in a proportion of patients propranolol and metoprolol will be used as cardiovascular drugs and incorrectly categorized as migraine prophylactics. This might have led to overestimation of prophylactic use in both the cardiovascular and non-cardiovascular group (propranolol and metoprolol monotherapy). Therefore, the OR of 2.3, indicating a reticence in prescribing vasoconstrictive antimigraine drugs to migraine patients with a cardiovascular risk profile, has to be interpreted carefully. Furthermore, since the PHARMO Record Linkage System is based upon dispensings from community pharmacies, it does not provide an accurate registration of non-prescription (i.e. OTC) NSAIDs. This means that the frequency of NSAID use in both the cardiovascular and the non-cardiovascular group will be underestimated. It is, however, unlikely that this misclassification is differential. We believe therefore that the risk estimate is still valid.

Another limitation is the fact that our study population consisted of patients who started with a specific abortive migraine drug. One should be aware of this when comparing the results with data concerning migraineurs clinically diagnosed in accordance with International Headache Society standardized diagnostic criteria for migraine with and without aura. Furthermore, due to the selection of 'new users', our study cannot give information about the cardiovascular risk profile in migraineurs who are not treated with specific abortive migraine drugs. This was the main reason for including the group Migrafin® users as a control group, since the components of this drug have no vasoconstrictive properties and therefore the

official label does not contraindicate the use in patients with known or suspected coronary artery disease.

Recently, in the Netherlands, the GEM (Genetic Epidemiology of Migraine) population-based study has shown that migraineurs, particularly with aura, have a higher cardiovascular risk profile than individuals without migraine.[31] Among migraineurs, the prevalence of high total cholesterol was 16%, total cholesterol: high-density lipoprotein ratio > 5 was 22%, history of diagnosed hypertension 33% and hypertension at examination 18%. This study did not investigate whether these patients with cardiovascular risk factors were treated with triptans or ergotamine. However, these higher prevalences of cardiovascular risk factors, compared with our data, also suggest reticence in prescribing these specific antimigraine drugs to migraineurs with these risk factors, or underestimation due to underdiagnosis of hypercholesterolemia and hypertension. In our study we were not able to distinguish between migraineurs with and without aura. Therefore we do not know if prescribing patterns differ between these two forms of migraine.

Recent data from two prospective cohort studies suggest also an association between migraine and ischemic cardiovascular disease.[32,33] Findings from the Women's Health Study, in which information on migraine aura was recorded, indicate that this association is limited to migraineurs with aura.[32] From this point of view, it is very important to investigate thoroughly the cardiovascular safety of triptans, since withholding these drugs from migraine patients with a cardiovascular risk profile may influence the quality of life.

Most clinical trials and clinical practice data on triptans are derived from patients without known coronary artery disease. The lack of information about cardiovascular safety of triptans in this specific population probably explains the observed constant prescribing pattern of triptans to patients with known cardiovascular risk. No consensus exists among family practitioners or headache specialists about when to avoid using a triptan due to excessive cardiac risk factors.[34] Cardiovascular risk assessment should be applied to decisions for prescribing triptans.

Apparently prescribers did not choose Migrafin® as the first alternative for patients with cardiovascular risk factors. We would then have seen a higher percentage of patients with cardiovascular risk in new Migrafin® users compared with triptans and ergotamine, which was not the case. One might wonder if NSAIDs are attractive alternative drugs for triptans in patients with cardiovascular disease. Due to adverse effects on cardio-renal function, use of NSAIDs is not without risk in patients with cardiovascular disease. There are complications arising from alteration of renal hemodynamics such as worsening of congestive heart failure, oedema and increased blood pressure.[35,36] In combination with platelet aggregation inhibitors or oral anticoagulants, the bleeding risk increases.[37-39] Moreover, use of NSAIDs at

high frequency or dose has been associated with a significantly increased risk for major cardiovascular events.[40]

Single use of an abortive migraine drug, indicating non-acceptance of the treatment, was more frequently seen in patients with cardiovascular risk. A questionnaire study has shown that fear of side effects and occurrence of side effects are the main reasons for non-acceptance (single prescription) of selective serotonin reuptake inhibitor treatment.[41] Although non-cardiac in origin, it might be the case that patients with cardiovascular disease receive more information about chest symptoms such as burning, tingling or tightness. This information may cause fear of side effects, preventing patients from starting or continuing therapy. Fear itself may even cause side effect like symptoms. This, of course, does not mean that information on side effects should not be disclosed to the patient.

In conclusion, during the past 16 years the percentage of migraine patients with known cardiovascular risk factors to whom ergotamine or triptans were prescribed remained low and constant. Growing evidence that the incidence of triptan-associated serious cardiovascular adverse events in both clinical trials and clinical practice appears to be extremely low did not change prescribing patterns over time. Available evidence that concerns about cardiovascular safety of triptans are unwarranted suggests that a prospective trial of triptans is justified in patients who would previously have been excluded from treatment.[42] An earlier choice for optimal treatment in these patients might improve their quality of life.

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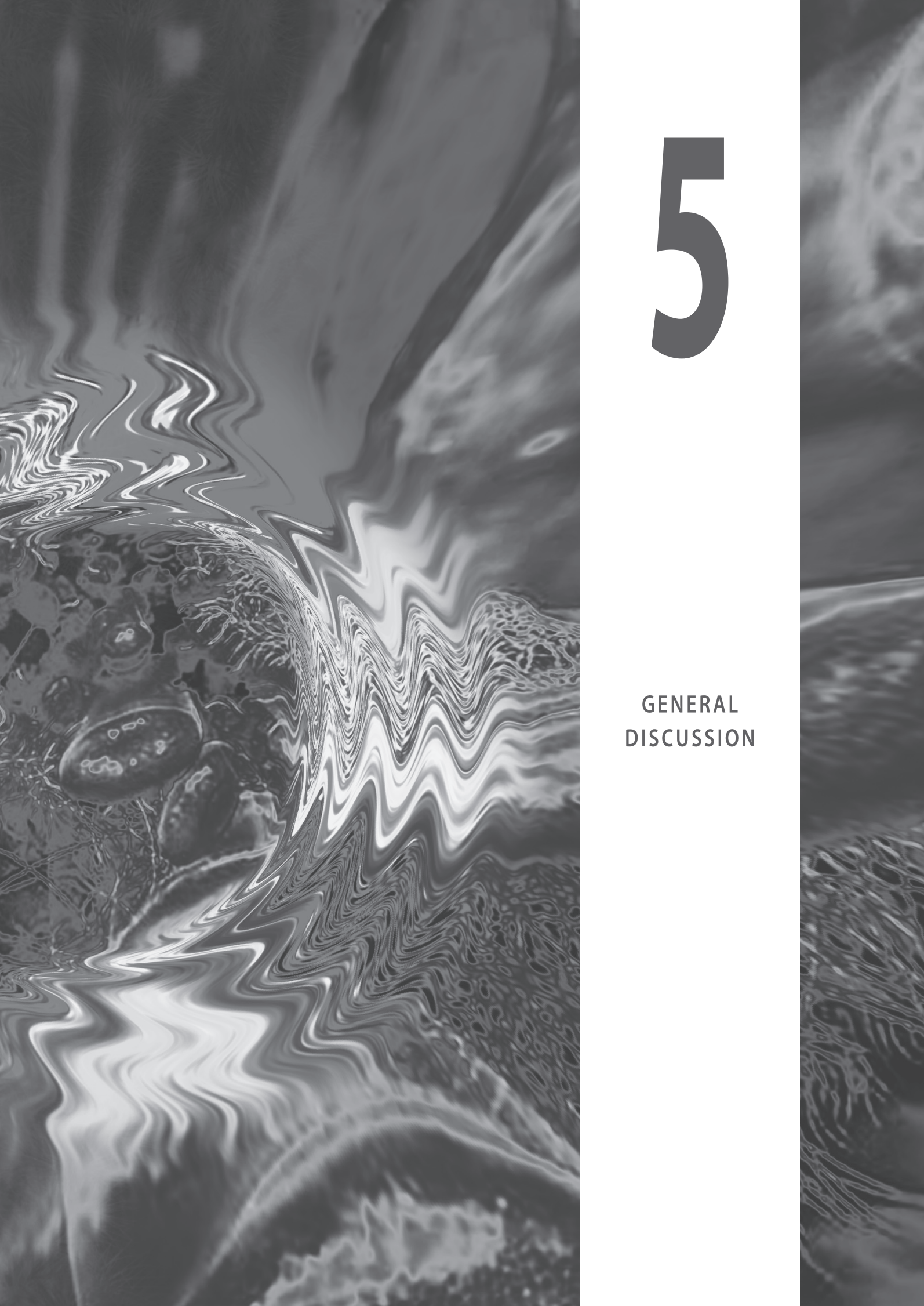


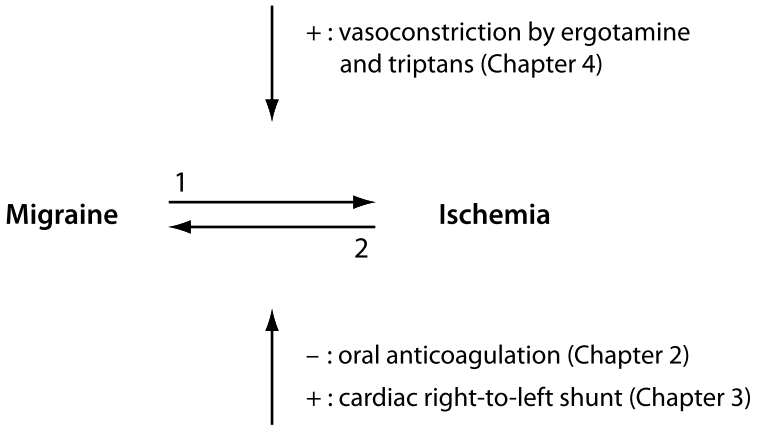
5

GENERAL DISCUSSION

Migraine has received considerable attention in the past 15 years as it has become better understood and recognized as a clinically relevant brain disorder with new treatment strategies. During recent years, the possible relationships between migraine and ischemia have become a hot topic. One of the first questions raising on this subject is about the direction of the relationship (Figure 1). Is migraine a cause or consequence of ischemia, or both? Or is it only a matter of coexistence, possibly caused by the same environmental or genetic factors?

Specifying the word ischemia in its relationship with migraine, one first concentrated on the higher risk of ischemic stroke in migraine patients,[1-5] but currently much attention is paid to the possible relationship between migraine and cardiovascular disease, including myocardial infarction.[6-8] And one wonders if migraine is associated with a systemic, possibly progressive, vascular disorder.[9,10] However, since the absolute risk of these ischemic vascular events in migraine patients is low, it is possible that this only concerns a particular subset of patients, rather than being a general principle. But who are those patients? Does it, for example, only concern migraine patients with aura?

Figure 1 Possible relationships between migraine and ischemia



What is the link between migraine and ischemia? Could it be (partly) due to prothrombotic factors,[11,12] hyperhomocysteinemia,[13,14] endothelian dysfunction,[15] atrial septal abnormalities like patent foramen ovale (PFO) and atrial septal defects,[16-19] pulmonary arteriovenous malformations,[20] a more risky cardiovascular profile,[13,21] vasospasm,[15] or the vasoconstrictive properties of specific antimigraine drugs?[22-24] Do patients need to be actively screened for these factors? What is their

relevance? Do these features have consequences for treatment options? And what are the recommendations for clinical practice?
This thesis provides some answers to the abovementioned questions. Not surprisingly, new questions for the future are raised as well.

THE EFFECT OF ANTICOAGULANTS ON MIGRAINE

The positive effect of therapeutic use of anticoagulants on migraine as experienced by our patients (Chapter 2.1) and other patients described in literature,[25-30] supports the hypothesis that migraine might be triggered by ischemia. However, the evidence is weak. The role of low-dose aspirin, a platelet inhibitor, as migraine prophylaxis is unclear. Results from small trials have been inconsistent. Two large randomized controlled trials show an effect comparable with placebo.[31,32] Therefore, if ischemia triggers migraine, it is not likely that this ischemia is due to atherosclerosis. So far, with coumarins only one open, controlled clinical trial has been performed, showing no effect of low-intensity acenocoumarol on migraine (Chapter 2.2). It remains unclear to what extent the low target international normalized ratio (INR) is responsible for these results. Due to the risk of major bleeding, which is the most important complication of treatment with anticoagulants, clinical research on this subject probably will not be performed on a large scale in the future. Even after showing effect, in clinical practice this treatment would only be used in unique cases for the same reason.
The intriguing finding that all our four patients with a clear self-reported reduction of migraine during previous therapeutic use of anticoagulants showed one or more thromboembolic risk factors (Chapter 2.1), points out that a thromboembolic predisposition might be one of the conditions in those cases. For future research into the possible relationships between migraine and ischemia, it is recommended to also look for the presence of thromboembolic risk factors, among which hemostatic abnormalities, helping to understand the underlying mechanisms. Furthermore it might help to predict those cases in which ischemia may play a role in migraine. In the meantime, in general practice there is no justification for systematic screening for hemostatic abnormalities in migraine patients.

CARDIAC RIGHT-TO-LEFT SHUNTS AND MIGRAINE: A CAUSAL RELATIONSHIP?

Cardiac right-to-left shunt (RLS) – mainly caused by PFO – is a risk factor for ischemic stroke (IS).[33,34] Potential mechamisms of stroke in patients with cardiac RLS include paradoxical embolism from a venous source and direct embolization from thrombi formed within the aneurysm.[35] These emboli seem to have a particular propensity for the posterior circulation (PC).[36,37] Stroke patients with a larger PFO show more brain imaging features of embolic infarcts than those with a small PFO.[37] Also migraine, and particularly migraine with aura (MA+), has been consistently associated with an increased risk of IS in several studies of various designs.[38-41] Furthermore, brain imaging studies found that migraine patients, especially patients with aura, had a significantly higher prevalence of white matter hyperintense lesions and infarct-like lesions. Notably, these infarct-like lesions mainly occurred in the PC territory.[42] As shown by our systematic review (Chapter 3.1), cardiac RLS have a higher prevalence in patients with MA+. Moreover, shunt size appears to be larger in migraineurs compared to controls.[43] These intriguing similarities leads to the question whether migraineurs with aura and PC infarction have a high prevalence of (a moderate to large) RLS, a question so far not investigated.

The remarkably high prevalence of RLS in a family with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) suggested a possible relationship between CADASIL and RLS.[44] Although further data did not show RLS to be a comorbidity factor in CADASIL,[45-47] the high prevalence of MA+ found in CADASIL patients with RLS (Chapter 3.2) may suggest that, as in the general population, RLS may be an independent risk factor for MA+ in CADASIL patients. However, due to limited data and striking results in literature, the evidence is weak and more data are still needed.

A recent study, which screened 185 consecutive patients with MA+ for white matter lesions (WMLs) and RLS, found no difference in the total volume and number of WMLs in the group with and without RLS.[48] As mentioned above, paradoxical emboli and the brain infarcts found in migraineurs usually occur in the brain posterior circulation, whereas deep WMLs prevail in the anterior circulation. Therefore the authors conclude that the deep WMLs detected in MA+ patients are unlikely caused by brain embolism, even when a RLS is present.[48] However, in migraineurs with a large PFO and subclinical brain lesions at magnetic resonance imaging (MRI), a significant reduction in frequency and severity of migraine recurrence was established by PFO closure when compared with controls without PFO closure.[49] The open design of this study is one of the limiting factors. As mentioned above, it would be interesting to study whether in these patients there is also a link between RLS, PC infarction and improvement of migraine after PFO

closure. Apart from this, it is not yet known whether these subclinical changes have any clinical meaning or consequence.

Coinheritance has been proposed as an explanation for the increased RLS prevalence in migraineurs.[50] It may offer an explanation why RLS is more often encountered in MA+, but not in migraine without aura, assuming that only gene defects promoting aura phenomena are coinherited with gene defects predisposing to atrial shunts. However, coinheritance alone is not compatible with improvement of migraine after shunt closure. Currently, it is still unknown whether this relationship between RLS and migraine is causal in nature. Paradoxical embolism of small thrombi has been proposed as a migraine-provoking event caused by cardiac shunts.[51] Thereby, the occurrence of exacerbation of migraine aura or new-onset aura in patients undergoing PFO closure,[52] may be related to the fact that transcatheter closure of PFO is associated with significant activation of the coagulation system.[53] Whether suture closure of PFO will become a safe procedure, possibly improving these complications, has yet to be shown by future investigation.[54] Additionally, it has been hypothesized that cardiac shunts, but also pulmonary shunts, could allow vasoactive substances such as atrial natriuretic peptide, platelet factors, amines and serotonin to bypass the pulmonary filter, triggering cortical spreading depression.[51,55]

Whereas there may be feasible mechanisms that support a speculative causal association between RLS and MA+, the proof and the issue germane to patients and clinicians is whether repair or closure of a PFO leads to improvement in clinical migraine outcomes. Observational studies and an open intervention study showed that PFO closure resulted in migraine cessation or improvement of migraine, supporting a causal link between RLS and migraine.[18,49,51,56-60] However, up to now, only one randomized, double blind, sham-controlled trial has been completed: Migraine Intervention with STARFlex Technology (MIST) trial.[61] Patients who suffered from MA+, experienced frequent migraine attacks, had previously failed ≥ 2 classes of prophylactic treatments, and had moderate or large RLS consistent with the presence of a PFO, were randomized to transcatheter PFO closure with the STARFlex implant or to a sham procedure (anaesthesia and groin puncture without catheterization). Although this trial confirmed the high prevalence of RLS in patients with MA+, no significant effect was found for primary or secondary endpoints. On exploratory analysis, excluding two outliers, the implant group demonstrated a greater reduction in total migraine headache days, supporting further investigation. In the spring of 2006 this trial was presented as a positive clinical trial at a high profile international meeting. However, almost two years later, after independent review it was published as a completely negative study, which generated a lot of discussion in the world. Questions were raised on the quality

of echocardiographic screening, the higher than expected procedural complication rate (6.8%) and a high percentage of large residual shunts. Especially the issue concerning procedural complications, with one case each of cardiac tamponade and retroperitoneal bleed, both potentially life threatening, brings us to the central question: does the potential benefit justify the risk of a serious or potentially life threatening procedural complication? The Food and Drug Administration (FDA) required MIST II, one of the three randomized controlled trials approved by the FDA to further study the effect of PFO closure on migraine, to be powered for a safety outcome, rather than an efficacy outcome.[62] Therefore over 500 subjects would have been needed. However, MIST II was discontinued early in 2008 due to recruitment difficulties as a consequence of strict enrollment requirements. We are left in a mist, with two randomized controlled trials currently underway, both with cardiac catheterization in the sham arm (also insisted on by the FDA), and both powered for safety. Hopefully, they are successful in recruiting patients and will clear our sight by answering the question whether the association of RLS and migraine is causal, and not just casual.

So, before we consider application of PFO-closure devices as a migraine treatment in clinical practice, we first have to confirm the causal relationship between RLS and migraine, have to explore if there is a certain subset of migraine patients (e.g. those with PC infarction and a large PFO) in which causality is more prone, and need to evaluate the risk and benefit of using device closure compared with alternative approaches. At the moment there are no reasons for routinely screening migraine patients for RLS. Not to mention off-label PFO closure in migraine patients.

ANTIMIGRAINE DRUG USE, ISCHEMIC COMPLICATIONS AND CARDIOVASCULAR DISEASE

Recent prospective data suggest an association between MA+ and ischemic vascular events, including cardiovascular disease.[7,8,39,40,63] The absolute risk of these events is low, the relative risk 2-4 times higher compared to patients without migraine. The biological mechanisms linking migraine to these ischemic events are currently unclear and likely to be complex. Besides, it is still questioned whether the biological mechanisms leading to ischemic stroke differ from the mechanisms leading to myocardial infarction. Remarkably, the increased risk of ischemic stroke is most apparent in young migraineurs without cardiovascular risk factors,[1,3,39,41,64] with the exception of smoking and use of oral contraceptives,[3,41] whereas the risk for myocardial infarction in women with MA+ seems to be related to a high vascular risk status.[64] The high prevalence of RLS would be a possible mechanism for the

increased risk of stroke in migraine patients, though cannot clarify the association found between MA+ and ischemic cardiovascular events. Does genetics play a part? It has been shown that the increased risk for ischemic stroke among migraineurs with aura is magnified for MTHFR 677TT genotype carriers (677C>T polymorphism of the methylenetetrahydrofolate reductase (MTHFR) gene).[65] This increased risk was not apparent for myocardial infarction.[65] The mechanisms by which the TT genotype confers additional risk for ischemic stroke among migraineurs with aura remains to be established. So far, common biomarkers of cardiovascular disease showed only a modest association with migraine, not supporting a strong biological relationship.[21] Considering the shown safety of triptans in clinical practice, even in those with overuse and simultaneous use of cardiovascular drugs (Chapter 4.1), it is unlikely that the vasoconstrictive properties of these drugs explain the observed increased risk of ischemic vascular events. Moreover, these drugs are used by all migraineurs, not just those with MA+. Besides unravelling the mechanism of potential links between migraine and ischemic events, future studies have to demonstrate whether specific migraine features, such as migraine frequency, intensity and type, influence the risk of the ischemic events. Recently, predilection sites of brain abnormalities in migraineurs were identified and it was shown that both attack frequency and disease duration are indicators for brain damage in migraine.[66] A logical question which has to be answered in the future, is whether this damage can be prevented by migraine prophylaxis.

Identifying migraineurs at highest risk for ischemic stroke and heart disease will be the first step towards prevention, though currently impossible. In addition to discouraging smoking and use of oral contraceptives in MA+ patients, it is recommendable to be alert for treatable cardiovascular risk factors like hypertension or hyperlipidemia in migraine patients.[64] However, diagnosing cardiovascular risk factors in migraine patients will possibly increase the number of patients in whom triptans are contraindicated. From this point of view it is important that in the near future good clinical research will be performed on the cardiovascular safety of triptans, also in migraine patients with known cardiovascular risk. Withholding the most effective abortive migraine treatment would be of influence on quality of life. Furthermore, we look forward to the development of the promising novel calcitonin gene-related peptide (CGRP) receptor antagonists, which appear to be effective in the treatment of moderate and severe migraine attacks,[67-69] with lack of direct vasoconstrictor activity.[70,71] However, it must be highlighted that CGRP has a protective function during coronary ischemia, which was blocked by the CGRP receptor antagonist olcegepant in a rat heart model.[72] Thus, if these findings hold for humans as well, CGRP receptor antagonists, like triptans, may also be contraindicated in patients with coronary artery disease.

STUDY DESIGN ISSUES: FOCUS ON THE STUDY POPULATION

Different research principles and methods, each with their own strengths and limitations, were applied to gain insight into the intriguing relations between migraine and ischemia: a case series, a randomized clinical trial, a systematic review, diagnostic research, a retrospective nested case-control study, and a retrospective observational drug utilization study. Nowadays, the evidence-based movement strongly emphasizes the randomized clinical trial (RCT) and meta-analysis. Perhaps more by accident than by intent, the observational study has been made to appear the 'poorer' form of evidence when compared with the RCT. However, most frontline clinical medical journals continue to devote the majority of their space to the publication of observational data from case series, case-control, and cohort studies.[73,74] One may not forget the limitations of a randomized clinical trial. For example strict inclusion and exclusion criteria may cause a strongly selected study population, not being representative for the population in clinical practice.[75,76] This was also concluded in a report conducted by the Chronic Disease Prevention & Control Research Center at Baylor College of Medicine, Houston.[77] This report, being a part of the EDICT project (started to develop tools to help Eliminate Disparities in Clinical Trials), claims that clinical trials routinely excluded or underrepresented many populations, like women, older people, and disabled people, undermining the quality of evidence. Likewise, for ethical reasons, the study population in our randomized clinical trial (Chapter 2.2) included only those migraine patients with attacks occurring at least three to eight times a month during last year, and who had already tried at least one drug for migraine prophylaxis without sufficient effectiveness. This means a selected group of moderate to severe migraine patients. In the MIST trial even stricter inclusion criteria were used, leading to a selected group of severe migraine patients.[61]

In general, observational data reflect common daily clinical practice. Triptans are contraindicated in migraine patients with cardiovascular risk factors, and therefore these patients are normally excluded in clinical trials with triptans. However, as shown by our observational studies (Chapter 4.1 and 4.2), in clinical practice doctors sometimes do prescribe these drugs to patients with a clinically recognized cardiovascular risk. The findings from our nested case-control study (Chapter 4.1), which show safety of triptans in clinical practice, also with concomitant use of cardiovascular drugs, has led to an editorial in which the authors conclude that a prospective trial of triptans is justified in patients who would previously have been excluded from treatment.[78] Although we agree with this comment, we also remark that the conclusion of safety can currently not be extended to a population with a high cardiovascular risk profile. Simply because we did not distinguish between patients with low and patients with high cardiovascular risk. The intriguing finding

of prescribing triptans to patients with concomitant cardiovascular drug use, led us to our retrospective observational study of treatment choices and patterns in migraine patients with and without a cardiovascular risk profile. These findings indeed showed that in clinical practice triptans are selectively prescribed to those at lowest cardiovascular risk. Only 2% of the patients used more than two drugs for cardiovascular risk management when a triptan was started, confirming our remark not to extend the conclusion about safety to patients with high cardiovascular risk. Selective prescribing of drugs to a relatively polluted population,[79] is an important reason why observational evidence also has to be carefully interpreted. Pharmacoepidemiologic research has provided many examples of this channelling problem during the past 20 years.

A select population can also arise from other causes. Remarkable was the finding in our case series that all four patients with a self-reported reduction of migraine during previous therapeutic use of anticoagulants showed one or more thromboembolic risk factors (Chapter 2.1). This population, however, probably did not correspond with the twelve patients receiving low-intensity acenocoumarol for migraine in our clinical trial (Chapter 2.2), and therefore may partly clarify the negative results. A comparable problem may play a role in the population of the much-discussed MIST trial. The patients in observational studies (Chapter 3.1) concerning the possible link between migraine and RLS, frequently involved specific populations: cryptogenic stroke [18,19,56-59] and decompression illness.[51] These patients may be different from the patients with severe and frequent migraine included in the MIST trial, possibly partly explaining the disappointing results. So, if observational findings are only applicable for a certain group of patients, it is important to take this into account in future research.

The question remains: what explains the link between migraine and ischemia? Is there a specific condition, or, more likely, are there more different mechanisms explaining this link? It seems likely that many pathways may lead to the same phenotype called 'migraine', with a hypothesizing role for ischemia, due to different causes, in triggering migraine, especially MA+. However, to answer this important question, future trials should incorporate brain imaging, hemostatic abnormalities, and biomarkers for ischemic vascular events, not only to unravel the mechanism but also to distinguish subgroups in the migraine phenotype and to help direct treatment to those who are most likely to respond.

This thesis about migraine and ischemia has led to concrete implications for practice and implications for research, which are shown below.

Implications for practice

- There is no justification for routinely screening for hemostatic abnormalities or right-to-left shunts in migraine patients.
- Since, so far, there is only observational evidence of improvement of migraine during use of oral anticoagulants and after closure of an open foramen ovale, it is not justified using either of these therapies outside of clinical trials.
- Reassure patients who are concerned about the cardiovascular safety of triptans: triptans have been proven to be safe in daily practice.
- Since the safety of triptans is not quantified in low versus high cardiovascular risk patients, triptan prescription still has to be carefully evaluated for the individual patient.
- Do not prescribe ergotamine to migraine patients with a cardiovascular risk profile.

Implications for research

- Future research into the possible relationships between migraine and ischemia should incorporate hemostatic abnormalities, brain imaging, and biomarkers for ischemic vascular events to unravel the mechanism explaining the link and to distinguish subgroups in the migraine phenotype.
- The question whether migraineurs with aura and posterior circulation (PC) infarction have a high prevalence of (a moderate to large) right-to-left shunt (RLS), has to be investigated.
- Future research has to confirm the causal relationship between RLS and migraine, has to explore if there is a certain subset of migraine patients (e.g. those with PC infarction and a large patent foramen ovale) in which causality is more prone, and needs to evaluate the risk and benefit of using device closure compared with alternative approaches in migraine patients with a cardiac RLS.
- To show cardiovascular safety of triptans in migraine patients with known cardiovascular risk, a prospective trial is needed.
- Defining the study population for a clinical trial, one should carefully identify the evaluated patients in observational research and be aware of the limitations due to (too) strict inclusion criteria.
- Future studies have to demonstrate whether specific migraine features, such as migraine frequency, intensity and type, influences the risk of the ischemic events and whether this risk can be reduced by migraine prophylaxis.

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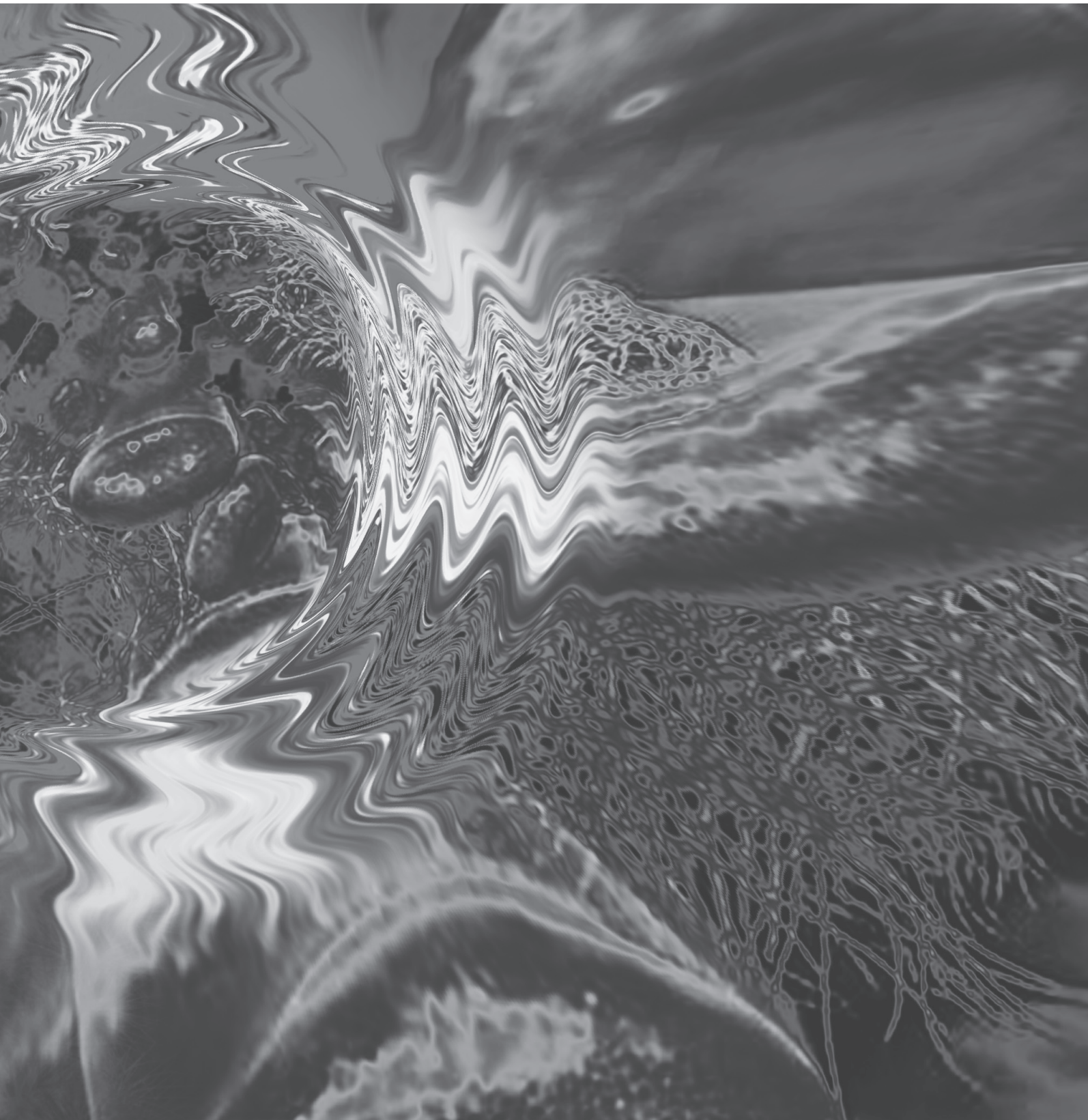
SUMMARY



INTRODUCTION

Migraine is a very common paroxysmal headache disorder, characterized by various combinations of neurological, gastrointestinal, and autonomic changes. One-year migraine prevalences in the general population for Western countries vary from 4% to 9% in men and from 11% to 25% in women. Migraine greatly affects quality of life and has a high socio-economic impact. Diagnosis is based on the headache's characteristics and associated symptoms. The two major subtypes are migraine without aura and migraine with aura (MA+). Pharmacotherapy can be acute (abortive) or preventive (prophylactic); patients may need both approaches.
For many years migraine was considered primarily a vascular phenomenon. The current view is that migraine is fundamentally a disorder of brain function, not of blood vessels. Although considerable knowledge is available on the mechanisms once the attack has started, it is to a large extent unclear what triggers an attack. It has been suggested that ischemia is one of these triggers. An association between migraine and ischemic events has been debated for many years. Whether migraine is a risk factor for ischemic events or ischemia triggers migraine, or both, is still unclear.
The central theme of this thesis is the possible relationship between migraine and ischemia. The main objectives are to gain insight in:

- the effect of anticoagulants on migraine;
- the possible relationship between cardiac right-to-left shunts and migraine;
- the use of antimigraine drugs in relation to ischemic complications and cardiovascular disease.

CHAPTER 1

In **Chapter 1** the scope, objective and outline of this thesis are described. This introductory chapter gives an overview on migraine in general, its pathophysiology, and the different relationships between migraine and ischemia.

CHAPTER 2

Chapter 2 of this thesis is entitled **'The effect of anticoagulants on migraine'**. The positive effect of anticoagulants on migraine has been described in case reports and observational studies. Furthermore, there is some evidence that a prothrombotic tendency may be involved in the pathogenesis of migraine.

It remains unclear if a positive effect of anticoagulants, if any, concerns only a select group of migraineurs with certain common characteristics. In *Chapter 2.1* we investigated the presence of thromboembolic risk factors in four patients who spontaneously reported a decrease in migraine attacks during previous use of oral anticoagulants. The effect of low-intensity acenocoumarol (target international normalized ratio [INR] 1.5 to 2.0) in these patients was also evaluated. All four patients had one or more thromboembolic risk factors. One patient, with factor V Leiden heterozygosity, showed 71% fewer migraine attacks during low-intensity acenocoumarol therapy than during baseline. In both patients with factor V Leiden heterozygosity, the attack duration in hours was reduced by 84% and 73% respectively. After discontinuation of acenocoumarol, the observed improvement disappeared and both patients preferred to restart low-intensity acenocoumarol. The other two patients discontinued treatment, because, in contrast to previous use, no improvement of migraine was observed. No serious adverse events were noted. These findings support the hypothesis that migraine, as a phenotype, has different underlying mechanisms, amongst which a thromboembolic tendency. In this group of patients, oral anticoagulants may be a suitable form of migraine prophylaxis.

The effects of anticoagulants on migraine has not been studied in a randomized controlled fashion. In *Chapter 2.2* we conducted a randomized, open, crossover study in migraine patients investigating the effect of low-intensity acenocoumarol treatment on the frequency and severity of migraine attacks compared to the run-in period and propranolol. Patients started with a run-in period of eight weeks, followed by the first treatment period of twelve weeks during which acenocoumarol (INR 1.5 to 2.0) or propranolol was used. Propranolol (retard capsule) was started with a dosage of 80 mg once daily, if possible increased to 80 mg twice daily after two weeks. After a washout period of two weeks, the second treatment period of twelve weeks followed. Forty-six candidate patients were seen at the outpatient clinic of the Department of Neurology. Eighteen women and one man were included who fulfilled all criteria. Twelve patients completed the study. Only one good responder could be noted. In the other patients, treatment with low-intensity acenocoumarol did not show improvement of migraine symptoms compared with the run-in period. Treatment with propranolol showed a trend towards improvement compared with the run-in period. No serious adverse events were observed. Overall, low-intensity acenocoumarol treatment has no prophylactic effect in migraine patients.

CHAPTER 3

In **Chapter 3** we tried to answer the question **'Cardiac right-to-left shunt and migraine: a causal relationship?'**

Several studies have shown that the prevalence of a cardiac right-to-left shunt (RLS) in patients with MA+ (both risk factors for ischemic stroke [IS] in the young) is significantly higher than in patients without migraine. In *Chapter 3.1* we systematically reviewed the available literature to quantify the strength of the relationship between RLS and migraine in patients with and without IS. We identified seven relevant studies. Among patients with RLS (without IS) MA+ was 3.5 times more prevalent than among subjects without RLS (Mantel-Haenszel odds ratio [OR_{MH}] 3.5; 95% confidence interval [CI] 2.1 – 5.8). In patients with IS migraine was more than two times more prevalent in patients with RLS than in patients without RLS (OR_{MH} 2.1; 95% CI 1.6 – 2.9). The prevalence of RLS found in the control groups without migraine was comparable to the prevalence of patent foramen ovale in the general population, i.e. about 25%. This review shows that there is a clear association between RLS and migraine, especially MA+. The relationship between RLS and migraine is further substantiated by the observations of disappearance and improvement of migraine symptoms after closure of the foramen ovale. However, the mechanism as well as the question about causality of this association has to be further elucidated.

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a rare hereditary disease characterized by recurrent transient ischemic attacks, strokes, cognitive decline, and MA+. Almost a decade ago, a high prevalence of RLS was found in a CADASIL family and all patients with RLS suffered from MA+. In *Chapter 3.2* we investigated the prevalence of cardiac RLS in CADASIL patients with MA+ and without migraine. Seventeen CADASIL patients, nine with MA+ and eight without migraine, underwent a transesophageal echocardiography with gaseous contrast to assess the presence of cardiac RLS. One patient showed a mild cardiac RLS during Valsalva procedure, and two related patients showed a large cardiac RLS. Three of the nine (33%) CADASIL patients with MA+ had RLS, none of the eight (0%) CADASIL patients without migraine ($p = 0.21$). We compared our limited data with two other small prevalence studies. The overall prevalence of cardiac RLS in our group of CADASIL patients was 18% (3/17) which was comparable with the prevalence of RLS found in another small prevalence study and in the general population, and therefore not linked to CADASIL. The finding that 86% (6/7) of the CADASIL patients with RLS in these two studies had MA+, may lead to the suggestion that, as in the general

population, RLS is a risk factor for MA+ in CADASIL patients. However, since both studies were small, and another small study showed striking results with a much higher RLS prevalence, both in CADASIL patients with MA+ and CADASIL patients without migraine, more data are still needed.

CHAPTER 4

Recent prospective data suggest an association between MA+ and ischemic vascular events, including cardiovascular disease. Due to their vasoconstrictive properties, the specific antimigraine drugs ergotamine and triptans may play a role in this association. In **Chapter 4** we explored the association between '**Antimigraine drug use, ischemic complications and cardiovascular disease**'.

The incidence of ischemic complications, like myocardial infarction and ischemic stroke, is low when specific antimigraine drugs are used appropriately. However, it remains unclear whether overuse of triptans or ergotamine is associated with an increased risk of ischemic events. In *Chapter 4.1* we conducted a retrospective nested case-control study using data from the PHARMO Record Linkage system, to investigate whether the intensity of triptan and ergotamine use, in specific overuse, is associated with the risk of serious ischemic complications that require hospitalization. All patients with more than one prescription for either a triptan or ergotamine were initially identified. Cases were all patients who were admitted to the hospital for an ischemic complication. Matched controls were assigned the same index date as the cases. The determinant was the intensity of use of triptans and ergotamine during one year preceding the index date. Overuse was defined as use of ≥ 90 defined daily doses during that year. Conditional logistic regression was used to estimate odds ratios (OR), adjusting for confounders. Stratified analysis was used to estimate the risk for both patients using and those not using cardiovascular drugs. A total of 17 439 patients received more than one prescription. A total of 188 cases and 689 controls were identified. Triptan overuse was not associated with an increased risk of ischemic complications (OR 0.96; 95% CI 0.49 – 1.90). Overuse of triptans in patients concomitantly using cardiovascular drugs did not increase this risk. Overuse of ergotamine turned out to be a risk factor for ischemic complications (OR 2.55; 95% CI 1.22 – 5.36). Patients overusing ergotamine and concomitantly using cardiovascular drugs were at highest risk (OR 8.52; 95% CI 2.57 – 28.2). In general practice, triptan overuse does not increase the risk of ischemic complications. Overuse of ergotamine may increase the risk of these complications, especially in those simultaneously using cardiovascular drugs.

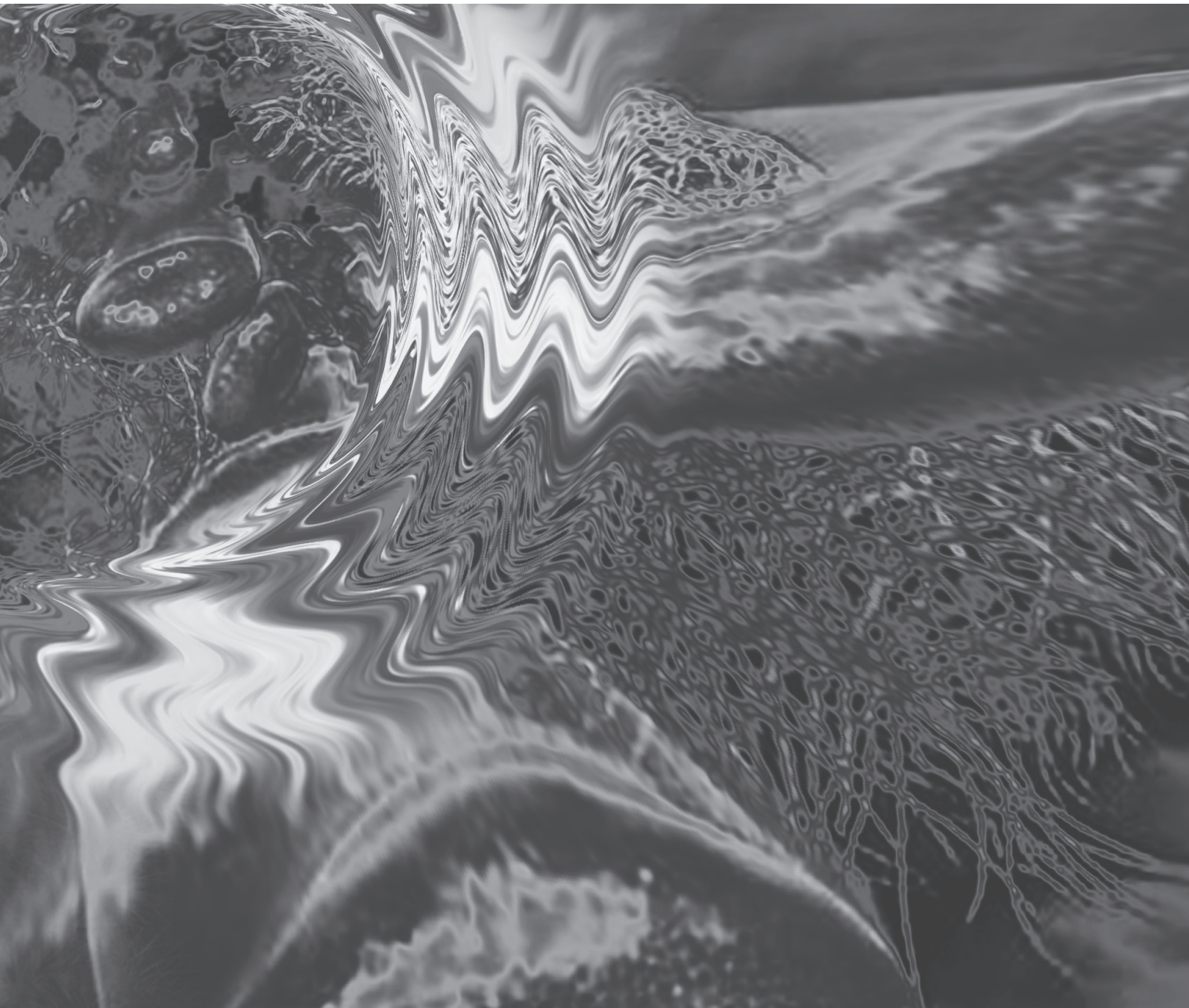
Prescribers' concerns about the cardiovascular safety may limit the use of specific antimigraine drugs. Due to growing evidence that the incidence of triptan-associated serious cardiovascular adverse events in both clinical trials and clinical practice appears to be extremely low, this concern may change over time. It is presently unclear to what extent triptans and ergotamine are prescribed to patients with a low or high cardiovascular risk profile. In *Chapter 4.2* we conducted a retrospective observational study using data from the PHARMO Record Linkage System to characterize the baseline cardiovascular risk profile of new users of specific abortive migraine drugs, and to investigate treatment choices and patterns in patients with and without a known cardiovascular risk profile. New users of a triptan, ergotamine or Migrafin® (a combination drug of 900 mg acetylsalicylic acid and 10 mg metoclopramide, approved for acute migraine treatment in 1996 in the Netherlands) from 1 January 1990 to 31 December 2006 were included. The cardiovascular risk profile was determined at the start of the antimigraine drug. The study population included 36 839 new users of specifice abortive migraine drugs. Approximately 90% of all new users did not have a clinically recognized cardiovascular risk profile; 6.4 – 7.1% used one drug and 3.7 – 5.4% used more than one drug for cardiovascular risk management during the period of six months before the start date. The percentage of new users with a cardiovascular risk profile did not differ between new users of a triptan, ergotamine or Migrafin® and also did not change during the study period of 17 years. During the year preceding the first prescription of an abortive migraine drug, patients with a cardiovascular risk profile used 2.3 (95% CI 2.1 – 2.5) times more often drugs for migraine prophylaxis and 1.4 (95% CI 1.3 – 1.5) times more often nonsteroidal anti-inflammatory drugs compared to patients without a cardiovascular risk profile. Switch to a triptan was less often seen in patients with a cardiovascular risk compared to those without a cardiovascular risk (OR 0.7; 95% CI 0.6 – 0.8). In conclusion, during the past 17 years the percentage of migraine patients with known cardiovascular risk factors to whom ergotamine or triptans were prescribed remained low and constant. Differences in treatment choices and patterns between migraine patients with and without a known cardiovascular risk profile reveal a certain reticence in prescribing vasoconstrictive antimigraine drugs to patients at cardiovascular risk.

CHAPTER 5

In **Chapter 5** the individual studies regarding the association between migraine and ischemia are put in a broader perspective. Different mechanisms possibly explaining the association are discussed. Implications for clinical practice and for research are

given. To unravel the intriguing link between migraine and ischemia, future trials should incorporate brain imaging, hemostatic abnormalities, and biomarkers for ischemic vascular events. Hopefully this will lead to the identification of subgroups in the migraine phenotype and helps to direct treatment to those who are most likely to respond.

SAMENVATTING



Migraine is een veelvoorkomende neurologische aandoening met aanvalsgewijs optredende hoofdpijn. In de Westerse landen heeft ongeveer 4 tot 9% van de mannen en 11 tot 25% van de vrouwen minimaal eenmaal per jaar last van migraine. Ondanks de huidige behandelmogelijkheden kan migraine uitermate belastend zijn voor de patiënt en zijn directe omgeving, en heeft migraine een grote economische impact door onder andere ziekteverzuim.

De diagnose migraine wordt gesteld op basis van de kenmerken van de hoofdpijn en de bijkomende verschijnselen. In haar meest typische vorm wordt migraine gekenmerkt door terugkerende aanvallen van heftige, bonzende hoofdpijn, die vaak aan één zijde van het hoofd gelokaliseerd is, en gepaard gaat met misselijkheid, braken en overgevoeligheid voor licht en geluid. De duur van de aanval varieert van 4 tot 72 uur. Bij ongeveer een derde van de patiënten kunnen deze hoofdpijnverschijnselen voorafgegaan worden door auraverschijnselen (migraine met aura). Dit zijn meestal stoornissen van het zien, zoals schitteringen, flikkeringen of lichtflitsen, of een gedeeltelijke uitval van het gezichtsveld. Er kunnen ook andere neurologische uitvalsverschijnselen optreden, zoals tintelingen, krachtsverlies en het onvermogen om te spreken. De meeste auraverschijnselen ontwikkelen zich gedurende vijf tot twintig minuten en duren meestal korter dan één uur.

Er zijn verschillende mogelijkheden om migraine met medicijnen te behandelen: de behandeling van een aanval, de preventieve behandeling, of een combinatie van beide. Bij de aanvalsbehandeling worden medicijnen pas ingenomen als de aanval begonnen is. De klachten en verschijnselen worden onderdrukt met pijnstillers en eventueel medicijnen tegen de misselijkheid. Er kunnen niet-specifieke pijnstillers gebruikt worden (zoals paracetamol, ibuprofen en naproxen), of specifieke antimigrainemiddelen (ergotamine en triptanen). Tot 1991 was alleen ergotamine beschikbaar voor het specifiek onderdrukken van migraineuze hoofdpijn. Dit middel kan echter ernstige bijwerkingen geven zoals ergotamine-afhankelijke hoofdpijn en ergotisme (het afsterven van weefsel tengevolge van ernstige vaatvernauwing). Na de introductie van de triptanen in de jaren negentig (zoals sumatriptan [Imigran®], rizatriptan [Maxalt®], naratriptan [Naramig®] en zolmitriptan [Zomig®]), welke veiliger zijn en een betere werkzaamheid hebben dan ergotamine, is er nauwelijks meer reden om ergotamine voor te schrijven.

Wanneer een patiënt twee of meer aanvallen per maand heeft, die minder goed reageren op aanvalsbehandeling, kan overwogen worden om naast de aanvalsbehandeling ook preventieve medicijnen te nemen (migraineprofylaxe). Bij migraineprofylaxe worden dagelijks medicijnen ingenomen om te voorkomen dat aanvallen optreden of om het aantal aanvallen, en de ernst ervan, te verminderen. Vrijwel alle middelen voor migraineprofylaxe zijn middelen die ook gebruikt worden voor andere aandoeningen. Zo zijn propranolol en metoprolol middelen

die bij hoge bloeddruk gegeven worden en ~~zijn~~ valproïnezuur en topiramaat middelen tegen epilepsie. Bij toeval is ontdekt dat bij gebruik ervan het aantal migraineaanvallen kan verminderen of worden voorkomen.

Jarenlang werd migraine gezien als een primaire aandoening van de bloedvaten in de hersenen. Het optreden van de auraverschijnselen zou het gevolg zijn van het samenknijpen van de bloedvaten, de hoofdpijn het gevolg van de daaropvolgende verwijding van bloedvaten. Tegenwoordig wordt migraine beschouwd als een primaire aandoening van de hersenen, waarbij de bloedvaten weliswaar een rol spelen. Als de migraineaanval op gang is gekomen, wordt een bepaald deel van de hersenen, het zogenaamde trigeminovasculaire systeem, geactiveerd. Activatie van dit systeem leidt tot verwijding van de bloedvaten in de hersenvliezen waardoor de zenuwuiteinden rondom die bloedvaten geprikkeld worden. Dit veroorzaakt pijn en het vrijkomen van allerlei stoffen. Deze stoffen veroorzaken een steriele ontstekingsreactie (zonder bacteriën en virussen), hetgeen onder andere verdere verwijding van de bloedvaten en ophoping van vocht rondom de bloedvaten als gevolg heeft. Hierdoor blijven zenuwuiteinden geprikkeld, wat de langdurige hoofdpijn verklaart. Volgens de huidige theorie worden de auraverschijnselen veroorzaakt door een spreidende uitdoving van de hersenactiviteit in de hersenschors. Meestal begint deze uitdoving in het achterste deel van de hersenen, dat verantwoordelijk is voor het zien. De spreidende uitdoving activeert het trigeminovasculaire systeem, hetgeen de aura en de hoofdpijn met elkaar verbindt.

Ondanks dat er momenteel veel kennis is over wat er in de hersenen gebeurt tijdens een migraineaanval, is het grotendeels onduidelijk hoe een migraineaanval begint. Waarom krijgt iemand herhaaldelijk migraineaanvallen? Dit is voor een deel erfelijk bepaald. Daarnaast spelen lichaams- en omgevingsfactoren een rol. Deze factoren kunnen ervoor zorgen dat een patiënt gevoeliger wordt voor het optreden van migraine (prikkeldempelverlagende factoren; bijvoorbeeld extreme moeheid) of een aanval kunnen uitlokken (uitlokkende factoren; bijvoorbeeld het drinken van wijn [alhoewel dit nooit wetenschappelijk is aangetoond]). Ischemie, oftewel onvoldoende doorbloeding, is een van de veronderstelde uitlokkende factoren. De relatie tussen migraine en ischemische gebeurtenissen, zoals het optreden van een herseninfarct, wordt al jaren bediscussieerd. Of migraine het risico op het optreden van deze ischemische gebeurtenissen verhoogt, of dat ischemie een migraineaanval kan uitlokken, of beide, is nog steeds onduidelijk.

In dit proefschift worden verschillende relaties tussen migraine en ischemie bestudeerd. Er wordt gekeken naar:

- het effect van bloedverdunners op migraine;
- de mogelijke relatie tussen een 'gaatje in het hart' en migraine;
- het gebruik van specifieke antimigrainemiddelen in relatie tot het optreden van ischemische complicaties en hart- en vaatziekten.

HOOFDSTUK 1

Hoofdstuk 1 is een **algemene inleiding** waar wordt ingegaan op migraine in het algemeen en de verschillende mogelijke relaties tussen migraine en ischemie. De inhoud van het proefschrift wordt in hoofdlijnen beschreven.

HOOFDSTUK 2

Hoofdstuk 2 van dit proefschrift is getiteld **'Het effect van bloedverdunners op migraine'**. In de literatuur zijn verschillende patiënten beschreven die merkten dat hun migraine minder werd op het moment dat ze bloedverdunners gebruikten. Daarnaast zijn er aanwijzingen dat stollingsafwijkingen in het bloed die tot gevolg hebben dat er sneller een bloedstolsel gevormd wordt, een rol spelen bij het ontstaan van migraine.

Het is nog onduidelijk of het positieve effect van bloedverdunners alleen bij een selecte patiëntengroep optreedt, die bepaalde, nog onbekende, eigenschappen heeft. In *Hoofdstuk 2.1* hebben we het bloed onderzocht van vier migrainepatiënten die tijdens eerder gebruik van bloedverdunners merkten dat hun migraineaanvallen sterk verminderden of zelfs wegbleven. Bij alle vier de patiënten werden afwijkingen in het bloed gevonden die de kans op de vorming van een bloedstolsel vergroten (verhoogde stollingsneiging). Daarnaast werd aan deze patiënten een lage dosering van de bloedverdunner acenocoumarol gegeven. De dosering werd laag gehouden zodat de kans op bloedingen verwaarloosbaar was. Bij twee patiënten met dezelfde stollingsafwijking in het bloed (factor V Leiden heterozygoot) werd tijdens het gebruik van acenocoumarol een duidelijke vermindering van de migraine waargenomen. Na het staken van acenocoumarol verdween deze verbetering en beide patiënten zouden, als ze de keuze hadden, ervoor kiezen te herstarten met de lage dosering van de bloedverdunner. De andere twee patiënten staakten vroegtijdig de behandeling met een lage dosering acenocoumarol omdat er, in tegenstelling tot eerdere behandeling met een hogere dosering acenocoumarol, geen verbetering van de migraine optrad. Er traden geen ernstige bijwerkingen op. Deze

bevindingen steunen de hypothese dat er verschillende factoren tot het ziektebeeld migraine kunnen leiden. Bij een bepaalde groep patiënten zou een verhoogde stollingsneiging van het bloed een rol kunnen spelen. Bij deze patiënten zou het gebruik van bloedverdunners het aantal migraineaanvallen kunnen verminderen.

Het effect van bloedverdunners op migraine is nooit onderzocht in een vooraf opgezet klinisch onderzoek. In *Hoofdstuk 2.2* hebben we een klinisch onderzoek uitgevoerd om bij migrainepatiënten het effect van een lage dosering van de bloedverdunner acenocoumarol te bestuderen. Eerst moesten de migrainepatiënten gedurende acht weken opschrijven hoeveel migraineaanvallen ze hadden en hoelang deze aanvallen duurden. Dit werd de 'basislijn periode' genoemd. Daarna werd gestart met medicijnen die dagelijks werden ingenomen om het optreden van de migraineaanvallen te verminderen of te voorkomen (de eerste behandelperiode). De ene groep patiënten kreeg gedurende twaalf weken een lage dosering van de bloedverdunner acenocoumarol, de andere groep startte met propranolol (een middel dat in de dagelijkse praktijk gegeven wordt voor migraineprofylaxe). Na deze periode kregen de patiënten gedurende twee weken geen acenocoumarol of propranolol (de 'uitwasperiode'). Hierna startte de tweede behandelperiode. Patiënten die in de eerste behandelperiode acenocoumarol kregen startten nu met propranolol, de andere groep startte met acenocoumarol. Tijdens het gehele onderzoek hielden de patiënten in een hoofdpijndagboek bij hoeveel migraineaanvallen er optraden en hoelang deze aanvallen duurden. Er werden 46 migrainepatiënten gezien op de polikliniek van de afdeling Neurologie van het St. Elisabeth Ziekenhuis in Tilburg. Eén man en 18 vrouwen voldeden aan alle eisen die gesteld werden om aan het onderzoek mee te mogen doen. Uiteindelijk rondden twaalf patiënten het onderzoek af. Slechts één van de twaalf patiënten gaf aan dat tijdens gebruik van een lage dosering acenocoumarol de migraine sterk verbeterde ten opzichte van de basislijn periode. De andere elf patiënten merkten geen verbetering van de migraine. Behandeling met propranolol gaf wel enige verbetering van migraine ten opzichte van de basislijn periode. Er traden geen ernstige bijwerkingen op. Er kan dus gesteld worden dat bij migrainepatiënten in het algemeen de behandeling met een lage dosering van de bloedverdunner acenocoumarol geen effect heeft op migraine.

HOOFDSTUK 3

In **Hoofdstuk 3** hebben we geprobeerd een antwoord te vinden op de vraag: **'Cardiale rechts-links shunt en migraine: een oorzakelijk verband?'**

Na de geboorte, als de baby zelf gaat ademen, sluit de verbinding tussen de linker- en rechterboezem van het hart. De kleine bloedsomloop (van en naar de longen) en de grote bloedsomloop (van en naar de rest van het lichaam) worden dan van elkaar gescheiden. Bij ongeveer een kwart van de mensen, is de sluiting niet volledig en blijft er een klein gaatje tussen de bovenste harthelften bestaan. Normaliter stroomt het zuurstofrijke bloed vanuit de longen naar de linker harthelft, waarna het bloed het lichaam (inclusief de hersenen) wordt ingepompt. Na zuurstof te hebben afgegeven aan het lichaam stroomt het zuurstofarme bloed via de rechterhelft van het hart weer naar de longen om opnieuw zuurstof op te nemen. Bij personen met een 'gaatje in het hart' kan er in bepaalde omstandigheden een fractie van het zuurstofarme bloed vanuit de rechterboezem naar de linkerboezem van het hart stromen. Dit wordt een cardiale (betreffende het hart) rechts-links shunt (RLS) genoemd.

Door dit gaatje kunnen ook kleine bloedstolsels meegevoerd worden die vervolgens in de hersenen terecht kunnen komen. Het blijkt dat het hebben van een 'gaatje in het hart' de kans op het krijgen van een herseninfarct vergroot. Uit onderzoek is gebleken dat migrainepatiënten, met name migrainepatiënten met auraverschijnselen, ook een enigszins vergrote kans hebben op het krijgen van een herseninfarct. Daarnaast is recent aangetoond dat bij migrainepatiënten, met name migraine met aura, een RLS vaker voorkomt dan bij personen zonder migraine. Men vraagt zich dus af of de hogere kans op het krijgen van een herseninfarct bij migrainepatiënten deels verklaard kan worden door het vaker voorkomen van een RLS (die immers ook de kans op het krijgen van een herseninfarct vergroot). En als er een relatie is tussen RLS en migraine, is er dan sprake van een oorzakelijk verband? In *Hoofdstuk 3.1* hebben we systematisch de gepubliceerde onderzoeken over dit onderwerp bestudeerd. We vonden zeven relevante onderzoeken. We hebben onderscheid gemaakt tussen patiënten met een herseninfarct en mensen zonder een herseninfarct. Het blijkt dat bij patiënten met een RLS (maar zonder een herseninfarct) migraine met auraverschijnselen ongeveer 3,5 keer zo vaak voorkomt als bij patiënten zonder een RLS. Bij patiënten die een herseninfarct hadden doorgemaakt kwam migraine twee keer zo vaak voor bij patiënten met een RLS als bij patiënten zonder RLS. Bij de groep patiënten zonder een herseninfarct was in de onderzoeken geen onderscheid gemaakt tussen migraine met of zonder auraverschijnselen. In de groep patiënten zonder migraine (controlegroep) kwam een RLS net zo vaak voor als in de algehele bevolking, ongeveer 25%. Ons overzicht bevestigt dat migraine, met name migraine met aura, vaker voorkomt bij mensen met een RLS (ten gevolge van een 'gaatje in het hart') dan bij mensen zonder een RLS. Deze relatie wordt bevestigd door het feit dat uit onderzoek is gebleken dat sluiten van het gaatje kan leiden tot minder migraineklachten. Desondanks

dienen zowel het mechanisme van deze relatie als de vraag of er sprake is van een oorzakelijk verband verder onderzocht te worden.

CADASIL is een erfelijke vorm van herseninfarcten en dementie. De afkorting staat voor Cerebraal (betreffende de hersenen) Autosomaal Dominante (wijze van overerven) Arteriopathie (ziekte van de slagaders) met Subcorticale infarcten (infarcten in een bepaald gedeelte van de hersenen) en Leukoencephalopathie (ziekte van de witte hersenstof). Ongeveer 45% van de CADASIL patiënten heeft ook migraine met auraverschijnselen.
Ongeveer tien jaar geleden werd in een familie met CADASIL bij vier van de vijf personen een RLS aangetoond. Alle vier deze personen hadden migraine met aura. In *Hoofdstuk 3.2* hebben we onderzocht hoe vaak een RLS bij CADASIL patiënten met migraine en bij CADASIL patiënten zonder migraine voorkomt. Bij 17 CADASIL patiënten, waarvan negen met migraine met aura en acht zonder migraine, werd via de slokdarm een echo van het hart gemaakt (transoesophageale echo) om te kijken of er een 'gaatje in het hart' zat waardoor er bloed van de rechterhelft van het hart naar de linkerhelft kan stromen (een RLS). Bij één patiënt werd een kleine RLS aangetoond, bij twee broers werd een grote shunt aangetoond. Drie van de negen (33%) CADASIL patiënten met migraine met aura hadden een RLS. Geen van de acht (0%) CADASIL patiënten zonder migraine had een RLS.
Omdat wij slechts een klein aantal patiënten hebben onderzocht, hebben wij onze resultaten vergeleken met de resultaten van twee andere kleine vergelijkbare onderzoeken. In ons onderzoek kwam RLS bij 18% (3/17) van de CADASIL patiënten voor. Dit was vergelijkbaar met de resultaten van één van de twee andere onderzoeken en met het voorkomen van RLS in de algehele bevolking. Daaruit zouden we kunnen concluderen dat RLS niet gerelateerd is aan CADASIL. Als we de resultaten van dit eerdere onderzoek en ons onderzoek optellen, blijkt 86% (6/7) van de CADASIL patiënten met RLS migraine met aura te hebben. Hieruit zou de suggestie kunnen ontstaan dat bij CADASIL patiënten, net als in de algehele bevolking, RLS een risicofactor is voor het krijgen van migraine met aura. Echter, aangezien het totaal aantal onderzochte patiënten klein is, en men in een tweede onderzoek vond dat RLS bij wel 70% van de CADASIL patiënten voorkwam, zowel bij patiënten met als zonder migraine met aura, zijn er meer gegevens nodig om uitspraken te kunnen doen over de relatie tussen RLS en migraine bij CADASIL patiënten.

HOOFDSTUK 4

Er zijn veel onderzoeksgegevens die suggereren dat er een relatie tussen migraine met aura en ischemische (onvoldoende doorbloeding) vasculaire (betreffende de bloedvaten) gebeurtenissen, zoals het optreden van een herseninfarct, bestaat. Dit betreft ook hart- en vaatziekten in het algemeen. Door hun eigenschap bloedvaten te kunnen samenknijpen (vernauwen) zouden de specifieke antimigrainemiddelen ergotamine en triptanen hierbij mogelijk een rol kunnen spelen. In de literatuur zijn enkele patiënten beschreven waarbij direct na gebruik van ergotamine of een triptan een ischemische complicatie, zoals bijvoorbeeld een hart- of herseninfarct, optrad. Ergotamine en triptanen mogen dan ook niet gebruikt worden (zijn gecontraïndiceerd) bij patiënten die bekend zijn met hart- en vaatziekten. In **Hoofdstuk 4** onderzochten we de relatie tussen **'Specifieke antimigrainemiddelen, ischemische complicaties en hart- en vaatziekten'**.

Ischemische complicaties, zoals een hart- en herseninfarct, komen maar zeer weinig voor indien ergotamine en triptanen op de juiste manier, dit wil zeggen niet te veel, gebruikt worden. Het is echter nog onduidelijk of het veelgebruik of overmatig gebruik van deze middelen wel de kans op een hart- of herseninfarct vergroot. In *Hoofdstuk 4.1* hebben we onderzocht of het gebruik, en met name overmatig gebruik, van ergotamine en triptanen het risico op ernstige ischemische complicaties (waarvoor ziekenhuisopname noodzakelijk is) vergroot. Dit hebben we gedaan met behulp van een database met aflevergegevens uit apotheken en opname- en ontslaggegevens van ziekenhuizen. Alle patiënten met meer dan één recept voor ergotamine of een triptan werden geselecteerd. De patiënten die ooit waren opgenomen in het ziekenhuis voor een ischemische complicatie noemden we de 'cases'. De dag van de ziekenhuisopname noemden we de 'index datum'. Bij de cases zochten we personen in de database die ongeveer even oud waren en in hetzelfde gebied woonden als de cases: de 'controlegroep'. De controle kreeg dezelfde indexdatum toegekend als de case. We onderzochten hoeveel ergotamine en triptanen patiënten gebruikt hadden gedurende het jaar vóór de indexdatum (voor de cases dus het jaar vóór de ziekenhuisopname). Overmatig gebruik werd gedefinieerd als ≥ 90 dagdoseringen gedurende dat ene jaar. We hebben onderscheid gemaakt tussen mensen die wel en mensen die geen medicijnen gebruikten voor hart- en vaatziekten, zoals bijvoorbeeld medicijnen die de bloeddruk verlagen. De eerste groep is namelijk in meer of mindere mate belast met hart- en vaatziekten, en heeft daardoor reeds een grotere kans op het krijgen van een hart- of herseninfarct, dan mensen die geen hart- en vaatziekten hebben.
In de database selecteerden we 17 439 patiënten die meer dan één recept voor ergotamine of een triptan hadden gekregen. Er waren 188 patiënten die een

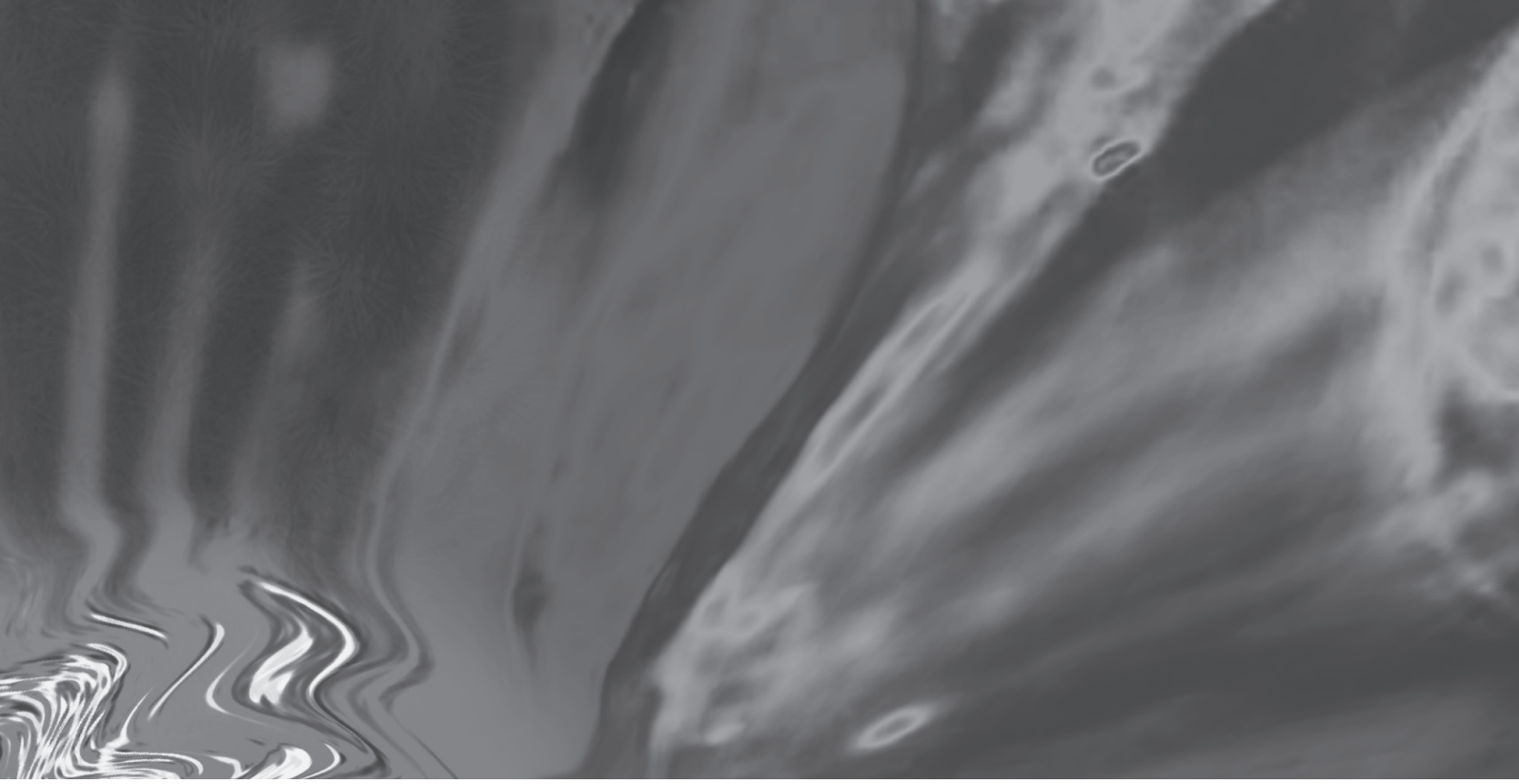
ziekenhuisopname voor een ischemische complicatie hadden gehad. Hier werden 689 controles bij gezocht, die geen ischemische complicatie hadden gehad. Het overmatig gebruik van triptanen bleek het risico op ischemische complicaties niet te verhogen. Ook niet indien er tegelijkertijd medicijnen voor hart- en vaatziekten gebruikt werden. Overmatig gebruik van ergotamine bleek het risico op ischemische complicaties 2,5 keer te verhogen. Patiënten met overmatig gebruik van ergotamine die gelijktijdig medicijnen voor hart- en vaatziekten gebruikten hadden het grootste risico op ischemische complicaties (8,5 keer zo groot als mensen zonder ergotamine en zonder medicijnen voor hart- en vaatziekten). We concluderen uit dit onderzoek dat in de dagelijkse praktijk het overmatig gebruik van triptanen het risico op ischemische complicaties niet verhoogd. Overmatig gebruik van ergotamine verhoogt deze kans op complicaties wel, met name bij patiënten die gelijktijdig middelen voor hart- en vaatziekten gebruiken.

Kort na de introductie van sumatriptan (Imigran®) werden er bijwerkingen gemeld als een beklemmend, drukkend, zwaar, warm of pijnlijk gevoel op de borst, lijkend op angina pectoris (pijn op de borst ten gevolge van verminderde doorbloeding van het hart). Uit onderzoek is inmiddels gebleken dat deze klachten, die kunnen ontstaan tijdens het gebruik van triptanen, niets met het hart te maken hebben. Als artsen zorgen hebben over de cardiovasculaire (betreffende het hart en de vaten) veiligheid van specifieke antimigrainemiddelen, zou dit terughoudendheid in het voorschrijven van deze middelen tot gevolg kunnen hebben. Aangezien de laatste jaren ook steeds meer is aangetoond dat het optreden van ischemische complicaties na gebruik van triptanen vrijwel niet voorkomt en triptanen in de dagelijkse praktijk dus veilig blijken te zijn, zou het voorschrijfgedrag van artsen in de loop van de jaren veranderd kunnen zijn. Tot op heden was het onduidelijk in welke mate ergotamine en triptanen werden voorgeschreven aan mensen met een laag of een hoog cardiovasculair risicoprofiel. In *Hoofdstuk 4.2* hebben we het cardiovasculair risicoprofiel van patiënten bestudeerd op het moment dat wordt gestart met ergotamine of een triptan. Daarnaast hebben we de behandelkeuzes en patronen tussen patiënten met en patiënten zonder een bekend cardiovasculair risicoprofiel met elkaar vergeleken. We hebben hierbij gebruik gemaakt van een database met aflevergegevens van apotheken. Alle personen die tussen 1 januari 1990 en 31 december 2006 startten met ergotamine, een triptan of Migrafin® (een combinatiepreparaat met de niet specifieke pijnstiller acetylsalicylzuur en metoclopramide, een middel tegen misselijkheid, welke in 1996 in Nederland in de handel kwam voor de acute behandeling van migraine) werden geselecteerd. Migrafin® heeft niet de eigenschap bloedvaten te vernauwen en werd daarom als controlegroep beschouwd. Het cardiovasculair risicoprofiel werd vastgesteld op

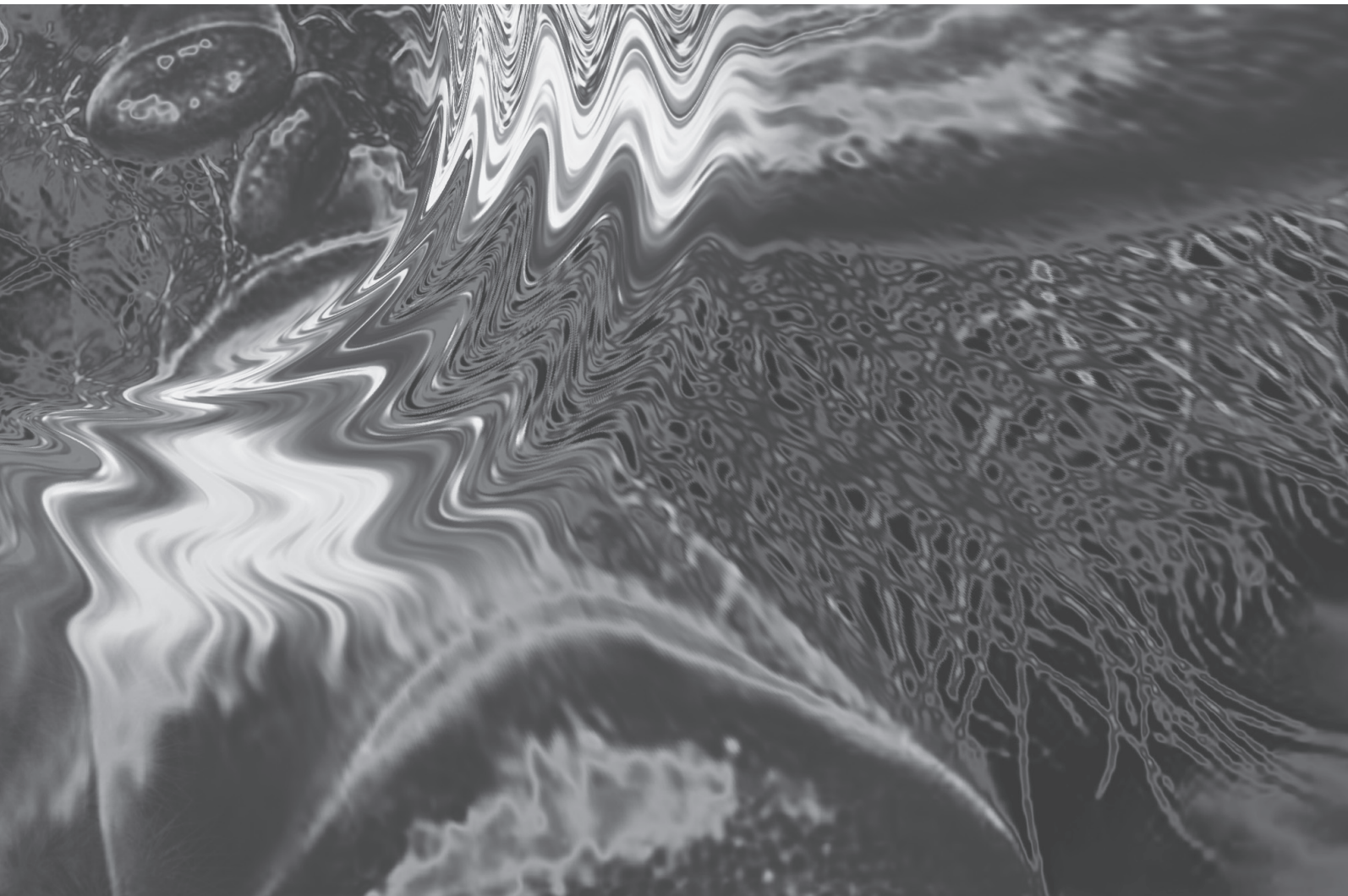
het moment dat het specifieke antimigrainemiddel werd gestart. Er werd daarbij gekeken naar het gebruik van medicijnen voor hart- en vaatziekten gedurende de zes maanden voorafgaande aan de start van het antimigrainemiddel. Er werden 36 839 starters van specifieke antimigrainemiddelen geselecteerd. Ongeveer 90% van de starters had geen bekend cardiovasculair risicoprofiel; 6.4 – 7.1% van de starters gebruikte één medicijn voor hart- en vaatziekten en 3.7 – 5.4% van de starters gebruikten twee of meer medicijnen voor hart- en vaatziekten. Er was hierbij geen verschil tussen starters met ergotamine, een triptan of Migrafin®. Dit patroon veranderde ook niet gedurende de studieperiode van 17 jaar. Gedurende het jaar voorafgaand aan het eerste recept van een specifiek antimigrainemiddel, gebruikten patiënten met een cardiovasculair risicoprofiel ruim twee keer zo vaak een middel voor migraineprofylaxe en bijna anderhalf keer zo vaak een niet specifieke pijnstiller (NSAID) vergeleken met patiënten zonder cardiovasculair risicoprofiel. Patiënten met een cardiovasculair risicoprofiel veranderden minder vaak van ergotamine of Migrafin® naar een triptan dan patiënten zonder cardiovasculair risicoprofiel.
Samenvattend concluderen wij dat gedurende de laatste 17 jaar het percentage migrainepatiënten met een bekend cardiovasculair risicoprofiel aan wie ergotamine of een triptan werd voorgeschreven laag en constant bleef. Verschillen in behandelkeuzes en patronen tussen patiënten met en patiënten zonder een cardiovasculair risicoprofiel lieten een zekere mate van terughoudendheid zien om specifieke (vaatvernauwende) antimigraine middelen voor te schrijven aan cardiovasculair belaste patiënten.

HOOFDSTUK 5

In **Hoofdstuk 5** zijn de afzonderlijke onderzoeken, allen gericht op de relatie tussen migraine en ischemie, in een bredere context geplaatst. Verschillende mechanismen die de relatie mogelijk kunnen verklaren worden bediscussieerd. Er worden aanbevelingen gedaan voor de dagelijkse praktijk en voor verder wetenschappelijk onderzoek. Om de intrigerende relatie tussen migraine en ischemie in de toekomst te kunnen ontrafelen, zal toekomstig onderzoek ook moeten kijken naar stollingsafwijkingen, risicofactoren voor ischemische vasculaire gebeurtenissen en beeldvorming (MRI) van de hersenen. Hopelijk leidt dit tot het identificeren van subgroepen van patiënten waarbij ischemie een rol speelt bij hun migraine, en kan behandeling ingezet worden bij die patiënten die er, op basis van hun eigenschappen, het meest waarschijnlijk baat bij zullen hebben.



DANKWOORD



En dan, ik kan het zelf bijna niet geloven, de allerlaatste, en waarschijnlijk meest gelezen woorden die ik op ga schrijven voor dit boek. Alle mensen die op hun eigen manier hebben bijgedragen aan dit proefschrift wil ik hierbij graag bedanken. Laat ik bij het begin beginnen…..

In Tilburg, bij mijn promotor Toine Egberts. Beste Toine, tijdens mijn opleiding tot ziekenhuisapotheker, toen je mij begeleidde bij mijn zoektocht naar een onderwerp voor wetenschappelijk onderzoek, zei jij: "Ik heb een goed gevoel bij migraine en antistolling". Nu, zo'n negen jaar later, is 'migraine and ischemia' een veelbesproken onderwerp in de internationale literatuur en ook nog de titel van dit proefschrift. Jij hebt mij als geen ander geleerd een onderzoeksvraag kort en bondig te formuleren, wetenschappelijke artikelen kritisch te beoordelen en vooral ook de klinische praktijk nooit uit het oog te verliezen ("wat is je advies aan de dokter?"). Dankzij jou enthousiasme, je enorme drive en kwaliteiten 'to teach' en de vele uren aan goede begeleiding, heb ik deze jaren met veel plezier heel veel geleerd! Heel erg bedankt.

Mijn co-promotor, Cees Tijssen, beste Cees, jij durfde het aan om antistolling te geven als migraineprofylaxe. Al die jaren heb je vertrouwen in mij en het onderzoek gehad. Je hebt me met enthousiasme begeleid en je kritische klinische blik geworpen op alle onderzoeksvoorstellen ("waarom wil de dokter dit weten?"). Daarnaast heb je ervoor gezorgd dat ik ook in de 'wereld der neurologen' mijn verhaal kon doen. Dank je wel voor je inzet!

Eén promotor en één co-promotor die mij soms beide het gevoel gaven hun enige promovenda te zijn….. Toine en Cees, beiden ook bedankt voor jullie enorm snelle en gerichte reacties op alle stukken die ik jullie heb gemaild!

Voor de onderzoeken naar het effect van antistolling op migraine gaat mijn speciale dank uit naar Annelies van 't Hoff en José de Bont.
Beste Annelies, je zult waarschijnlijk verrast zijn als dit proefschrift op je deurmat valt. Als medisch leider van de trombosedienst was je meteen enthousiast over het onderzoek naar het effect van antistolling op migraine. Je selecteerde patiënten, zorgde voor een strakke INR controle en wist je medewerkers erbij te betrekken. Dank hiervoor!
Beste José, als trialverpleegkundige heb je mij enorm geholpen! Je hebt veel geduld, bent zeer precies en waarschijnlijk het meest belangrijk, je hebt een luisterend oor voor de patiënt. Dank je wel.

Verder wil ik graag alle medewerkers van de Trombosedienst Midden–Brabant bedanken, de openbare apothekers in de regio Midden–Brabant die hebben bijgedragen aan de selectie van geschikte migrainepatiënten en last but not least, de co-auteurs Martijn Smidt en mijn opleider Bertil Lenderink.

Het diagnostisch onderzoek van het hart had niet uitgevoerd kunnen worden zonder de medewerking van de cardiologen Walter Hermans en Wally Wonnink – de Jonge. Ik heb met veel plezier gekeken naar het enthousiasme waarmee jullie de echobeelden beoordeelden. Beste Wally, ik heb bewondering voor de manier waarop jij je rust wist over te brengen op alle patiënten. De TEE's werden zeer kundig uitgevoerd. Beiden bedankt!
Joost Haan wil ik bedanken voor zijn medewerking als deskundige op het gebied van CADASIL. Ook wil ik de artsen van het Leids Universitair Medisch Centrum bedanken, die eraan dachten (en hopelijk denken) informatie over ons onderzoek aan CADASIL patiënten mee te geven. In het bijzonder Saskia Lesnik ‑ Oberstein, met name ook voor haar medewerking aan het doorgeven van patiëntgegevens.

Alle patiënten die mee hebben gedaan aan de klinische onderzoeken, wil ik graag bedanken voor hun deelname en vertrouwen.

Bij mijn database onderzoeken heb ik de nodige hulp gehad. Speciale dank gaat uit naar Patrick Souverein. Beste Patrick, bedankt voor het aanvragen en in het juiste format aanleveren van alle data en voor het pijlsnel reageren op mijn vragen.
Hamid Rahimtoola, beste Hamid, ik mocht jouw oorspronkelijke idee over antimigrainemiddelen en vasoconstrictieve complicaties opnieuw vormgeven. Dank voor je steun daarbij en voor het wegwijs maken in de wereld van databaseonderzoek.
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Een aantal jaren was ik 'dagjesmens' op de achtste verdieping van het Wentgebouw. Elke keer werd ik er weer door iedereen hartelijk ontvangen. Ineke, Addy of Suzanne zocht een heerlijk rustige werkplek voor me en ik had een tijd lang zelfs een vaste werkplek en eigen kamergenoten, Pearl en Hedi. Het was er gewoon gezellig! Iedereen bedankt daarvoor.

Bij tijd en wijlen kwam ik weer 'ns binnen wandelen in de apotheek van het St. Elisabeth Ziekenhuis, mijn opleidingsplek. Dames, bedankt dat ik altijd enthousiast

werd begroet en onder het genot van een kopje koffie in een mum van tijd werd bijgepraat. Nu kunnen jullie eindelijk een borrel komen drinken!
Ook op het secretariaat van de afdeling Neurologie was ik altijd welkom. Beste Noor, Anja en Heidi, dank hiervoor en ook voor jullie administratieve hulp. Het is af! Komen jullie ook?

Beste Hans-peter en Christian, bedankt dat jullie mij de ruimte hebben gegund om een tijd lang maar twee dagen in de week in de apotheek te zijn, zodat ik twee dagen per week aan onderzoek kon besteden. Daarnaast hebben jullie mij nog wat vaker moeten missen….. gelukkig was Janneke de reddende engel!

Lieve Vivian, dank je wel voor het corrigeren van het Engels van de Introduction en Summary. Redelijk taaie kost die je toch met interesse hebt gelezen.

De leden van de beoordelingscommissie, Prof.dr. L.J. Kappelle, Prof.dr. M.D. Ferrari, Prof.dr. P.R. Saxena, Prof.dr. J.A.M. Raaijmakers en Prof.dr. A. de Boer wil ik bedanken voor het doornemen van mijn manuscript.

Beste Francis, hoe kon je toch denken dat ik de lay-out zelf zou doen? Dit is vakwerk! Dank je wel, ik ben er heel blij mee.

Mijn paranimfen, lieve Kris en Marieke, tijdens onze opleidingsperiode in Tilburg hebben we samen een bijzondere tijd gehad. De ups en downs werden altijd uitgebreid met elkaar besproken. Bij elkaar thuis, op het werk, al carpoolend in de auto, op de parkeerplaats, aan de telefoon,….. urenlang! Veel meer als vrienden dan als collega's. We kunnen het nog steeds en komen altijd tot dezelfde conclusie: we zouden een goed team vormen. Laten we dat dan 11 juni doen! En Kris, bedankt voor je eindeloze geduld om mij op zeer didactische wijze de principes van het databaseonderzoek met Access uit te leggen. Je ziet het, het heeft resultaat gehad. Maar wanneer gaan we nou eten?

En dan prijs ik mij gelukkig met mijn twee lieve broers Dirk en Joris, met mijn lieve familie en lieve vrienden. De afgelopen jaren hebben we het vooral ook níet over promoveren gehad. Dat we nog maar veel gezellige, leuke en ontspannende dingen mogen doen!

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Lieve Camiel, wat een groot geluk dat wij in ons zevende jaar samen practicum mochten doen! Dank je wel voor alles wat je voor mij en voor onze jongens bent. Je bent míjn Lief. Van nu af aan geen wijntjes meer op zolder, maar samen met jou op de bank!

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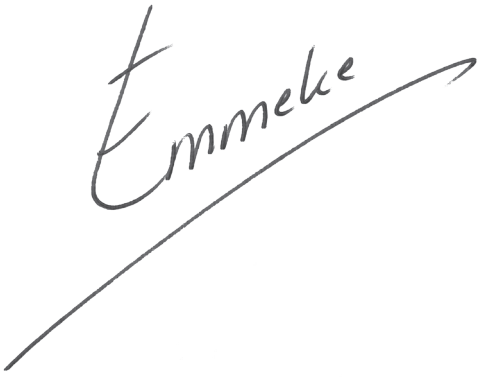
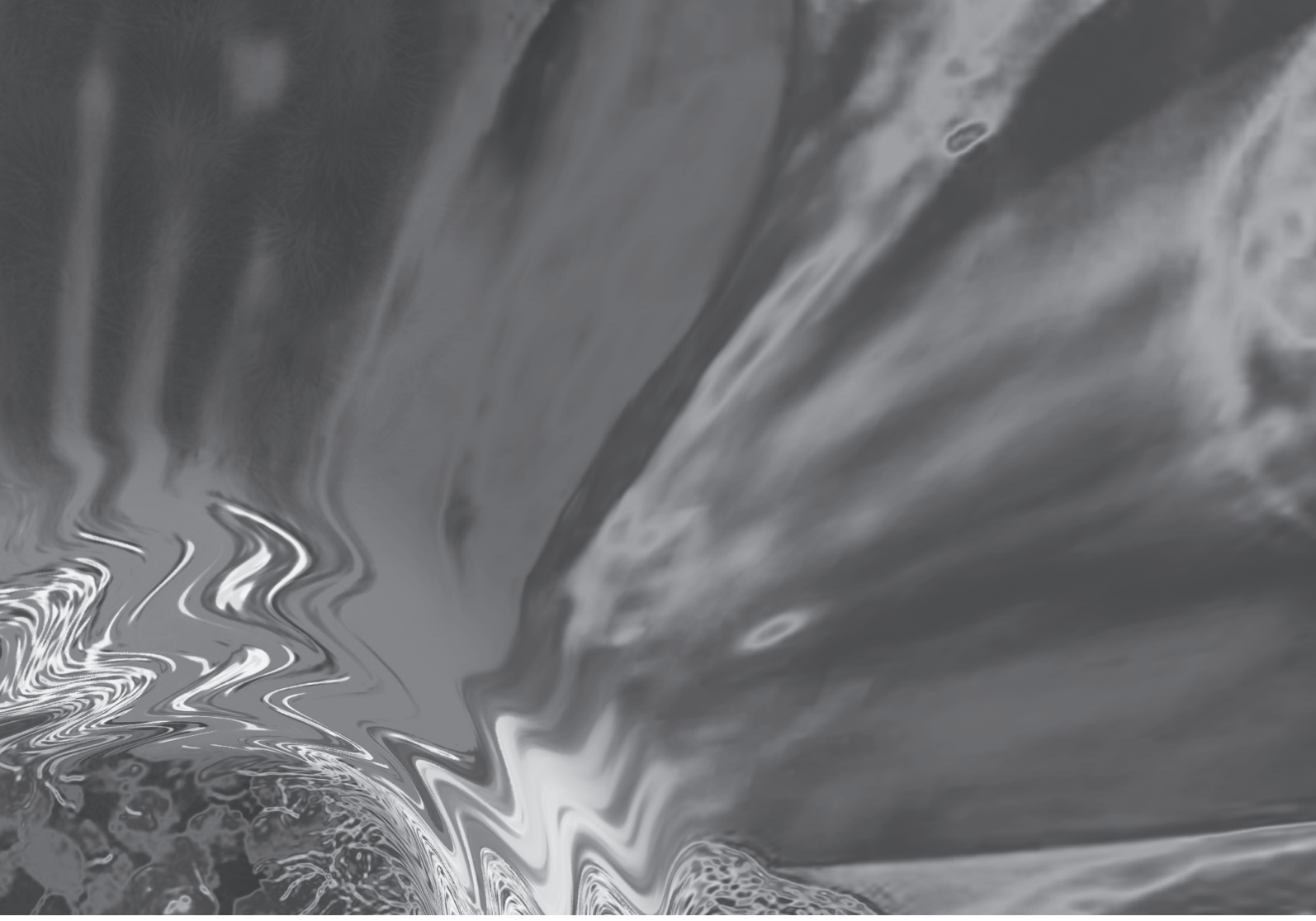
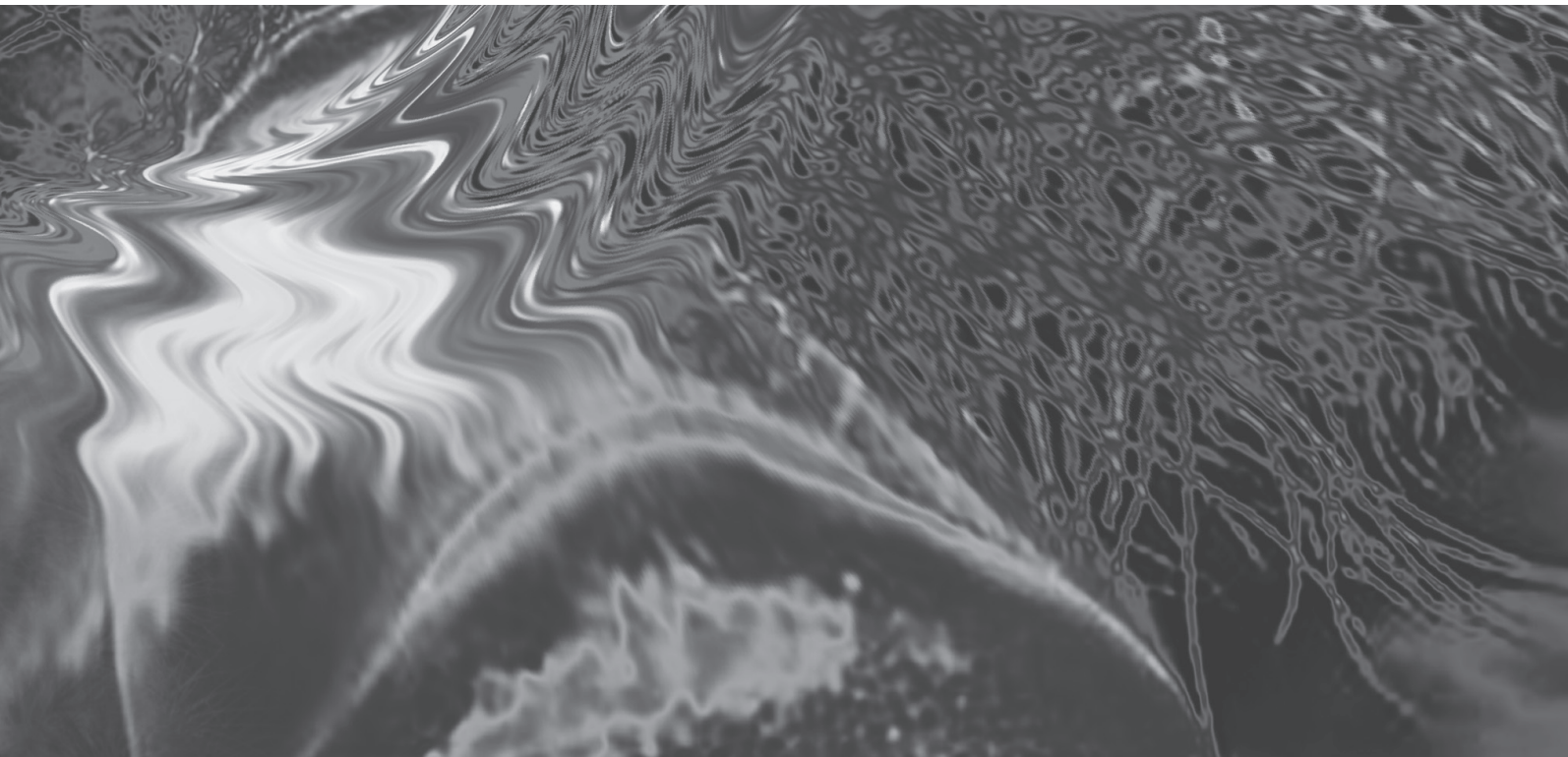




LIST OF CO-AUTHORS



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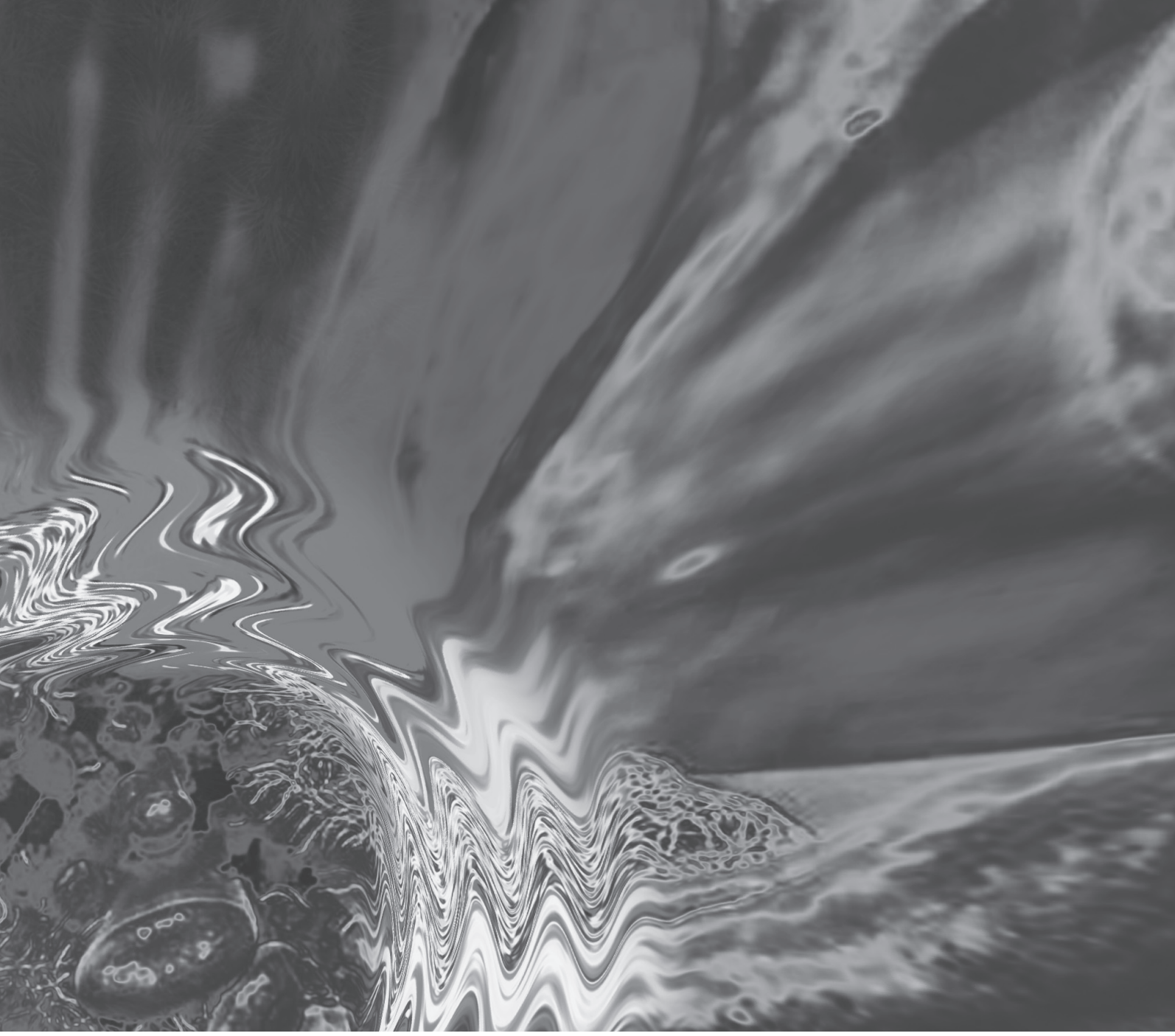

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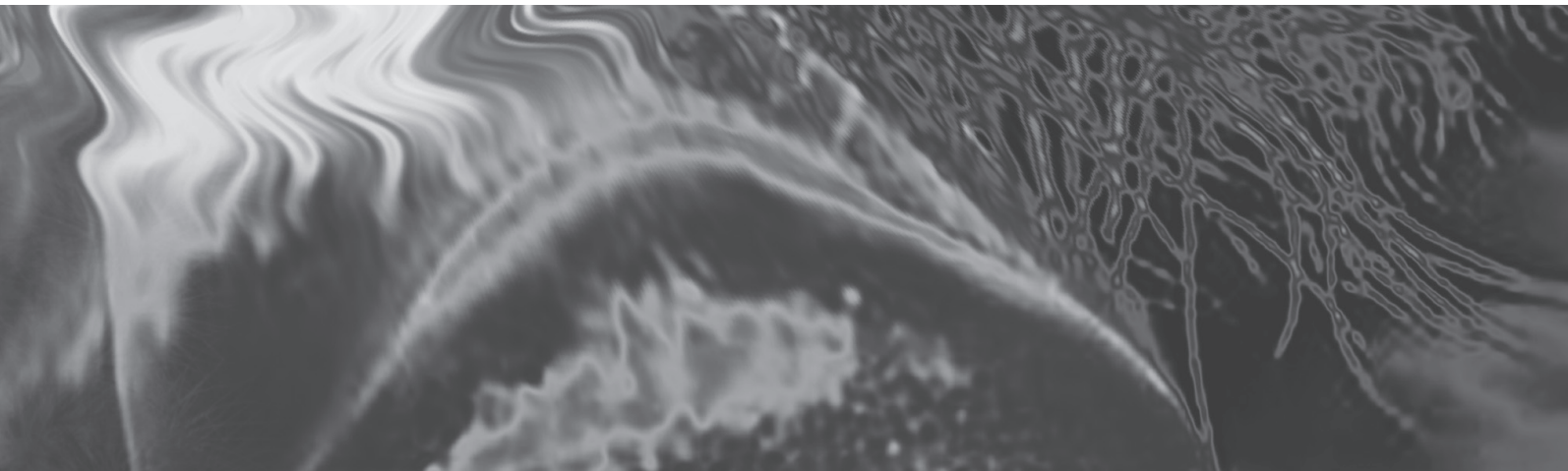

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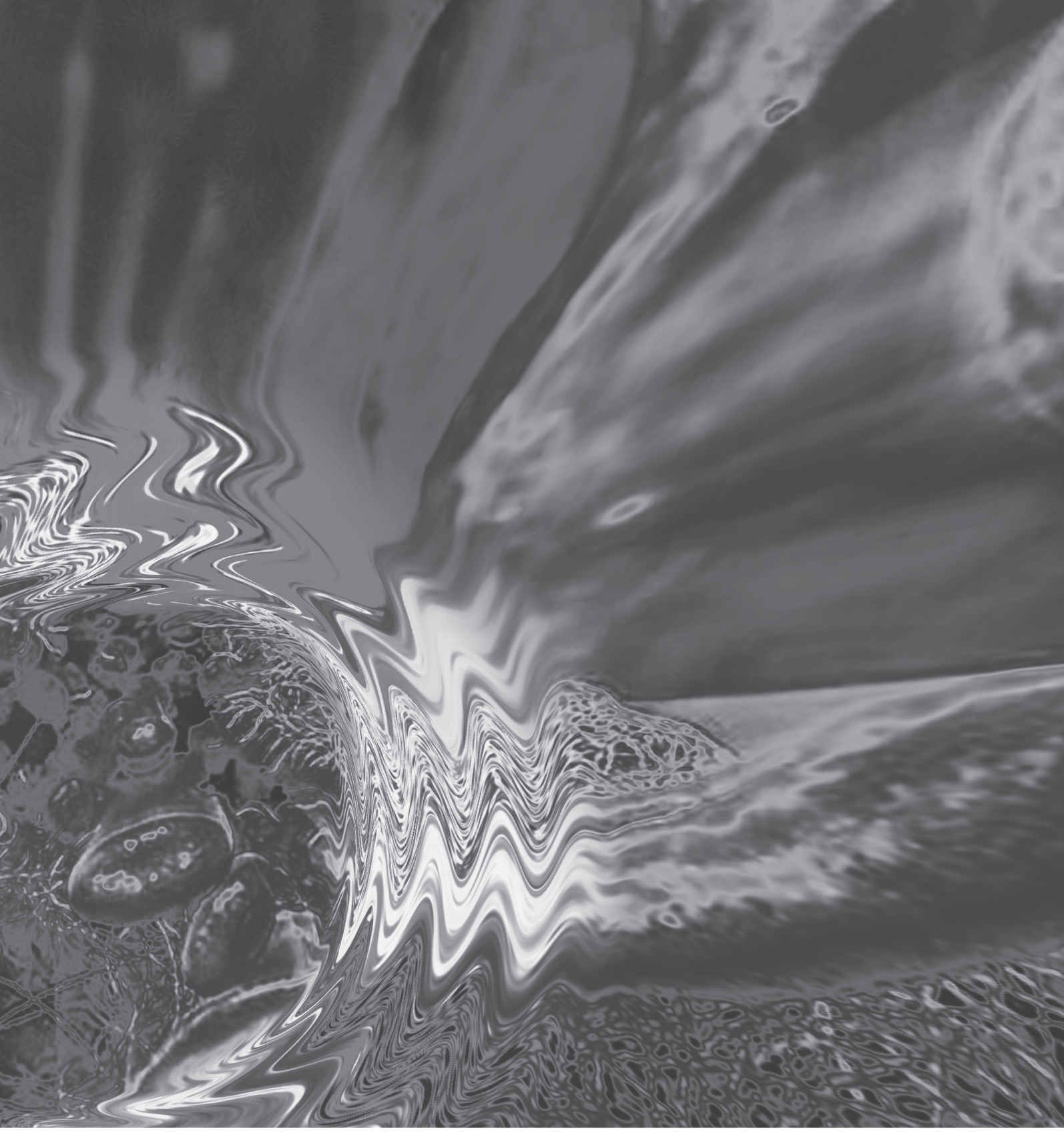

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Emmeke Wammes – van der Heijden was born on 19 April 1972 in Gemert, the Netherlands. After finishing secondary school (VWO) at the Macropedius College in Gemert in 1990, she started her pharmacy study at the Utrecht University. In 1996, she obtained her Master's degree in Pharmacy, followed by her Pharmacist degree in 1998.

Thereafter she started her training to become a hospital pharmacist at the Hospital Pharmacy Midden–Brabant, TweeSteden Hospital and St. Elisabeth Hospital, Tilburg. In 2002 she worked as a hospital pharmacist in the Máxima Medisch Centrum in Eindhoven and Veldhoven. At the same time she started with her PhD research at the Department of Clinical Pharmacy of the University Medical Center Utrecht in affiliation with the Department of Pharmacoepidemiology & Pharmacotherapy of the Utrecht Institute for Pharmaceutical Sciences of Utrecht University. From November 2002 she holds a position as a hospital pharmacist at the Department of Clinical Pharmacy at the St. Anna Zorggroep in Geldrop.

Emmeke is married to Camiel Wammes. They are the proud parents of their four sons Thomas, Joost, Lucas and Klaas.