CAUSES AND CONSEQUENCES OF DELAY IN VASCULAR SURGERY

To my family, in memory of Opa

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CAUSES AND CONSEQUENCES OF DELAY IN VASCULAR SURGERY

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ACADEMIC DISSERTATION

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CONTENTS

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This thesis is based on the following publications:

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III Noronen K, Laukontaus S, Kantonen I, Lepäntalo M, Venermo M. The natural course of abdominal aortic aneurysms that meet the treatment criteria but not the operative requirements. Eur J Vasc Endovasc Surg. 2013 Apr;45(4):326-31.

IV Noronen K, Laukontaus S, Kantonen I, Aho P, Albäck A, Venermo M. Quality assessment of elective abdominal aortic aneurysm repair from referral to surgery. Vasa 2015 Mar;44(2):115-21.

The publications are referred to in the text by their Roman numerals.

ABBREVIATIONS

AAA	abdominal aortic aneurysm
ABI	ankle brachial index
AFX	amaurosis fugax
AFS	amputation-free survival
BMT	best medical therapy
bEVAR	branched endovascular aortic repair
CAD	coronary artery disease
CAS	carotid artery stenting
CEA	carotid endarterectomy
CFA	common femoral artery
CT	computed tomography
CTA	computed tomography angiogram
DEB	drug-eluting balloon
DFU	diabetic foot ulcer
ECST	European Carotid Surgery Trial
ESRD	end-stage renal disease
ESVS	European Society for Vascular Surgery
EVAR	endovascular aortic repair
EVAS	endovascular aortic sealing
ET	endovascular treatment
fEVAR	fenestrated endovascular aortic repair
ICU	intensive care unit
IFU	instructions for use
i.e.	id est
IWGDF	International Working Group on the Diabetic Foot
HUH	Helsinki University Hospital
LS	limb salvage
MRI	Magnetic resonance imaging
MRA	Magnetic resonance angiogram
NASCET	North American Symptomatic Carotid Surgery Trial
OS	open surgery
PAD	peripheral artery disease
PTA	percutaneous transluminal angioplasty
RAAA	ruptured abdominal aneurysm
SVS	Society for Vascular Surgery
Tcp02	transcutaneous partial oxygen pressure
TP	toe pressure
TIA	transient ischaemic attack

ABSTRACT

Background: Timing of surgery signifies a decision of fundamental importance for the vascular patient whether with symptomatic carotid stenosis, a diabetic foot ulcer (DFU) or an abdominal aortic aneurysm (AAA). In general, all elective procedures should take place in time to prevent the condition from progressing beyond the treatment possibilities. For the vascular patients in question, the obvious goals are: to operate on patients with symptomatic carotid stenosis before major stroke, to revascularise the limbs of patients with DFUs before amputation is required and to operate patients with AAAs before aneurysm rupture.

Carotid surgery is the one area in vascular surgery where guidelines for the timing of surgery have been established even if the optimal time for surgery remains unclear. For symptomatic carotid stenosis, the risk of ischaemic stroke is the highest in the two weeks following the ischaemic symptoms and carotid surgery is hence recommended within the two weeks, a goal achieved for only 11% of the patients at Helsinki University Hospital (HUH) during 2007–2008.

For patients with diabetic foot ulcers, the optimal timing of revascularisation based on the current literature is unclear.

Furthermore, based on available data, the optimal timing, i.e. the acceptable delay of elective AAA repair, is yet to be defined, and whether to treat certain patients at all remains unresolved.

Aim of the study: The aim of this study was to investigate the timing of treatment and the concurrent impact on the outcome in the three major patient cohorts of vascular surgery: patients with symptomatic carotid stenosis, diabetic foot ulcers and large abdominal aortic aneurysms.

Patients and methods: The study consisted of patients referred to elective surgical evaluation for symptomatic carotid stenosis in 2010, for DFUs in 2010–2011 and for large AAAs in 2000–2010. The patient cohorts were all retrospectively analysed, focusing on the timing of treatment and possible causes for delay. The outcomes of our elective treatment processes were also analysed with the main interest in the consequences arising from a delay.

Main Results: For carotid surgery, the organisational changes made in 2009 resulted in 37% of the symptomatic patients being treated within two weeks, and the median time from symptom to surgery shortened from 47 (3–368) to 19 (1–236) days. In the treatment of diabetic foot ulcers, a delay of more than two weeks from referral to revascularisation was associated with inferior limb salvage. The elective treatment

process of AAAs comprised 21 (5.8%) emergency operations and 11 (3.0%) aneurysm ruptures. Of the patients excluded from surgical treatment, 33 % died of an aneurysm rupture, and 5 out of 12 patients undergoing an emergency operation survived.

Conclusions: In carotid surgery, reaching the two-week target time is an achievable goal, provided that, in addition to the institutional changes, efforts are also made to improve public awareness.

Diabetic foot ulcers always require diagnostics to detect the possible underlying ischaemia and rapid revascularisation once ischaemia is detected.

Guidelines for the timing of the elective AAA treatment process are important in order to minimise the amount of aneurysm ruptures and emergency operations that occur while waiting for surgery. Exclusion from elective aortic repair is a decision requiring careful consideration and collaboration between different specialities.

INTRODUCTION

The timing of surgery is important in vascular surgery, as delaying treatment jeopardises the future of the patient, with potential irreversible outcomes described for the three major vascular patient groups as follows: stroke for patients with symptomatic carotid stenosis, amputation for patients with DFUs and death due to aneurysm rupture for patients with AAAs.

In carotid surgery, the aim is to reduce the risk of stroke after a cerebrovascular event, i.e. to maintain the current condition. Guidelines for the timing of surgery have been established by Rothwell et al. (2004) based on data derived from large randomised trials, the North American Symptomatic Carotid Endarterectomy Trial and the European Carotid Surgery Trial. Rothwell and collaborators concluded carotid endarterectomy (CEA) to be highly beneficial in patients with symptomatic stenosis of over 50% when the patient undergoes an operation within two weeks from the ischaemic symptom. According to an observational study by Vikatmaa et al. (2011), only 11 % of patients with symptomatic carotid stenosis were treated within two weeks in Helsinki University Hospital (HUH), and the median time from symptom to surgery was 47 (3–368) days, heavily affected by the 25 (2–202) days of surgical delay, i.e. the time between consultation and surgery.

For patients with DFUs, the optimal timing of treatment has not been defined. The aim of treatment for DFUs differs from carotid surgery, for the aim is in achieving wound healing in order to sustain limb salvage. A DFU affects approximately 25% of the patients with diabetes in their lifetime (Gregg et al. 2004). Of these ulcers 50%–60% have been considered to be of ischaemic origin (Prompers et al. 2008). With the increasing numbers of patients with diabetes worldwide, this signifies a growing burden on the healthcare system, Finland included (King et al. 1998). Defining the optimal timing of revascularisation once ischaemia is detected presents a challenge, for it is ethically problematic to investigate delay prospectively. Therefore, conclusions are bound to be drawn from retrospective analyses and observational studies and treatment policies today are mainly based on practical experience.

For patients with AAAs meeting the generally excepted treatment criteria of an aneurysm diameter of >55 mm, the aim of treatment is to avoid aneurysm rupture. The risk of rupture is related to the size of the aneurysm. According to Lederle et al. (2002), the annual rupture risk is 9.4% for aneurysms of 55–59 mm in size, 10.2% for aneurysms of 60-69 mm and 32.5% for aneurysms of >70 mm. These estimations, however, are directional as the data is based on the surveillance of patients excluded from surgical treatment. The rupture data is, for the most part, extracted from death certificates without an autopsy confirming the finding, for the autopsy rate worldwide is in steep decline (Pompilio et al. 2008). Especially when a person is found deceased, pronouncing the cause of death without autopsy leaves plenty of room for speculation.

The timing of elective aortic surgery is based on estimations of the risk of rupture, and the aim is hence to treat larger aneurysms sooner; in HUH, the target time for the surgical delay, i.e. from decision on operative treatment to surgery, has been less than one month for aneurysms of > 65mm and 3 months for smaller aneurysms. Before the decision is reached, additional diagnostic imaging might be needed and the patient's overall health and the perioperative risks need to be evaluated. These processes may take time and delay surgery further.

REVIEW OF THE LITERATURE

1 CAROTID SURGERY

1.1 INDICATIONS FOR SURGERY

1.1.1 Symptomatic stenosis

The most important indication for carotid surgery is symptomatic internal carotid artery (ICA) stenosis, which is a stenosis detected after a cerebrovascular event; a transient ischaemic attack (TIA); amaurosis fugax (AFX); or stroke. Large-artery thrombosis accounts for 19%–21% of first strokes (Ward et al. 1988, O'Donnel et al. 2010), and carotid stenosis can be detected in 10%–16% of patients after a TIA or stroke (Kolominsky-Rabas et al. 2001, Poisson et al. 2011). All treatment aims at reducing the risk of future cerebrovascular events. So far the most important factor predicting the risk of a new cerebrovascular event is the degree of stenosis in ICA. Today's guidelines are based on two large randomised trials, the North American Symptomatic Carotid Endarterectomy Trial (NASCET 1998) by Barnett et al. and the European Carotid Surgery Trial (ECST 1998) by the European Carotid Surgery Trialists' Collaborative Group, which have provided the information on the benefits of surgery according to the degree of stenosis. After re-measurements to unify the definition of the stenosis degree and adjustment to obtain comparable results, the pooled analysis of these trials by Rothwell et al. (2003) revealed that carotid endarterectomy (CEA) is highly beneficial in symptomatic patients with a stenosis degree of 70%–99% and moderately beneficial with a stenosis degree 50%–69%.

1.1.2 Asymptomatic stenosis

The benefit for the patient from operating on asymptomatic stenoses continues to be under debate. In North America, the randomised ACAS trial (Asymptomatic Carotid Atherosclerosis Study) showed a significantly lower risk of stroke or death for patients with stenosis of > 60% when compared with patients treated only medically – 5.1% and 11.0%, respectively (Executive committee for ACAS 1995). These results contributed to the increase in operations on asymptomatic patients in North America, where 48% of leading experts would recommend CEAs for an asymptomatic patient in comparison to 28% of leading experts in Western Europe (Masuhr et al. 1998). In

2004, the international multicentre Asymptomatic Carotid Surgery Trial (ACST) published results pointing in a similar direction: at 5 years, the stroke risk was 6.4% for patients undergoing CEA with stenosis of >70% and 11.8% for their medically treated counterparts (Halliday et al.). These trials share the same flaws, patient selection being the first, since patients with higher perioperative risks were excluded from the studies. Also, the best medical treatment has changed with more effective antihypertensive medications and new anti-platelets such as clopidogrel. Furthermore, statin medication was not in common use at the time of the studies, and it has been argued later that these results do not transfer as such to modern times.

1.2 SURGICAL TREATMENT

1.2.1 Carotid endarterectomy

CEA is the gold standard in the treatment of symptomatic carotid artery stenosis. In the operation, carotid vessels are dissected carefully, applying a non-touch technique to the affected internal carotid artery to avoid disturbing the plaque causing the stenosis. Carotid arteries are clamped and, through longitudinal incision or using eversion technique, the affected intima is removed, i.e. endarterectomised. If a longitudinal incision is used, patch closure is recommended (Hobson et al. 2008, Liapis et al. 2009). Operating on the ICA and clamping it during the procedure leads to the constant presence of a risk of perioperative stroke or death, and this risk is what the expected benefit is weighed against. According to results from NASCET, ECST, ACAS and ACST, CEAs should be performed only in centres that carry a <6% perioperative risk of stroke or death for symptomatic stenosis and a <3% risk for asymptomatic stenosis.

1.2.2 Stenting

Carotid artery stenting (CAS) is an option to open surgery. Via a puncture site typically in the common femoral artery (CFA), a stent is introduced through a long sheath or guiding catheter to the ICA. A protection device against distal embolisation is commonly used and recommended by guidelines (Hobson et al. 2008, Liapis et al. 2009).

1.2.3 CEA vs. CAS

Randomised studies, the ICSS (International Carotid Stenting Study) with 1713 symptomatic patients and the CREST (Carotid Revascularization Endarterectomy vs. Stenting Trial) with 1321 symptomatic and 1181 asymptomatic patients, presented CEA in 2010 as the safer choice since CAS was associated with a higher risk of perioperative stroke, whereas CEA carried a higher risk of perioperative myocardial infarction (Brott et al.). The 10-year results from ICSS by Bonatti et al. (2015) recognise the higher immediate risk of perioperative stroke related to CAS, but determine both CAS and CEA to be beneficial and durable options. This fairly novel treatment method takes time to master; according to Smout et al. (2010), the learning curve is almost two years in an active centre before the complication rate of under 5 % is obtained. In the hope of improving techniques and advances in the materials, great expectations are cast on CAS. However, according to the literature, it seems that CEA is superior to CAS, a position reinforced by a recent systematic review on contemporary administrative dataset registries by Paraskevas et al. (2015). In 13 of the 18 registries (72%), the 30-day stroke or death risk after CAS for a symptomatic patient with an "average risk" of CEA exceeded the 6% limit set by American Heart Association (AHA) and American Stroke Association (ASA) guidelines. CAS remains the alternative for patients with high perioperative risks and certain anatomical conditions such as hostile neck post radiation or previous surgery.

1.3 CONSERVATIVE TREATMENT

For all symptomatic as well as asymptomatic patients, operated or not, the best medical treatment (BMT) is recommended. It has been shown that even though asymptomatic stenosis carries a low annual risk for stroke of 1%, the annual cardiac and all-cause mortality is significantly higher, 3.3% and 5.2 %, respectively (Giannopoulos et al. 2015). In long-term follow-up of up to 15.2 years, patients undergoing CEA had a 4.4-fold risk of acute myocardial ischaemia compared with age- and sex-matched population controls (Nuotio et al.2015), hence the conservative treatment of cardiovascular risk factors is essential, including anti-platelet, statin and antihypertensive treatment as well as smoking cessation.

1.3.1 Anti-platelet treatment

Aspirin reduces the risk of stroke and cardiovascular death with a dosage of 75–150mg per day (Antithrombotic Trialists' Collaboration 2002) and is recommended as primary and secondary prevention by the European Stroke Organisation (ESO) and the AHA/ASA. If the cerebrovascular symptom occurs while a patient is on aspirin medication, the policy has been to combine aspirin with dipyramidol or change aspirin to clopidogrel, alterations that have been shown to be equally effective in preventing recurrent stroke (Sacco et al 2008). Two randomised trials, the CARESS in 2005 and the CLAIR in 2010, investigated the relation of aspirin and clopidogrel combined with asymptomatic microembolisation among patients with recently diagnosed symptomatic cerebral or carotid artery stenosis and discovered that the combination of aspirin and clopidogrel is more effective than aspirin alone in reducing the microemboli (Markus et al., Wong et al.). This dual antiplatelet therapy is also showing clinically promising results, as was reported in the recently published prospective audit by Batchelder et al. (2015), with reduction of recurrent symptoms from 13% to 3% after implementing a strategy where clopidogrel was combined with aspirin at a TIA clinic immediately after intracranial haemorrhage had been ruled out and continued through and after the perioperative period.

1.3.2 Statins

Statins are known to be effective in the prevention of cardiovascular events in large randomised trials such as the Scandinavian Simvastatin Survival Study (4S 1994) and the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID study group 1998), which both also implied statin medication's association to stroke risk reduction. This matter was addressed in the CARE (Cholesterol And Recurrent Events) study by Plehn et al. (1999), and pravastatin was determined effective in reducing stroke and TIA incidence after a myocardial infarction. In secondary prevention, statins have been shown to reduce the incidence of cerebrovascular events and mortality among patients undergoing CEA (McGirt et al. 2005). The SPARCL (The Stroke Prevention by Aggressive Reduction in Cholesterol) trial by Amarenco et al. (2006) established that atorvastatin 80 mg taken once a day following a stroke or TIA resulted in a reduction of the incidence of stroke or cardiovascular events, a finding that has led to the use of high-dose statins as secondary prevention in general practice. In primary stroke prevention, the role of statins has been controversial, even though the effect on cardiovascular events has been established. For patients with asymptomatic carotid stenosis gathered from the prospective ACES (Asymptomatic Carotid Emboli Study) trial and followed for 2 years, statins had no effect on reducing the risk of stroke or cardiac death (King et al. 2013). However, asymptomatic stenosis of > 50% predisposes the patient for a high risk of atherosclerotic cardiovascular disease events within 10 years and, according to the guidelines by the American College of Cardiologists and the American Heart Association (ACC/AHA), statin medication is therefore recommended (Giannopoulos et al. 2015).

1.3.3 Antihypertensive medication

Hypertension is linked with cardiovascular and overall mortality, and according to the guidelines by the ESO, lowering blood pressure to 140/85 mmHg or below serves as primary prevention of stroke as well coronary events. As secondary prevention, antihypertensive medication also has an important role in preventing stroke recurrence and hyperperfusion syndrome after CEA (Naylor et al. 2013).

1.3.4 Smoking cessation

Smoking is an independent risk factor for stroke, with a relative risk of 1.67. (Wolf et al. 1988, King et al. 2013). Smoking cessation reduces the risk significantly, bringing it down to the same level as for non-smokers in 1–5 years (O'Donnl et al. 2010, Wolf et el. 1988). All patients with carotid stenosis should be guided towards smoking cessation and offered supportive medication.

1.4 TIMING OF SUGERY

1.4.1 The Past

In the 1980s, it was considered beneficial to wait for 6 weeks before surgery, especially if the onset symptom was stroke. This waiting period was deployed in the fear of a fatal complication, cerebral haemorrhage. The evidence base for this fear was, however, weak and based only on a few publications (Wylie 1964) at a time when diagnostics were performed without the imaging methods of today, namely computed tomography (CT) and magnetic resonance imaging (MRI). Even before the NASCET and ERCT trials, it was shown that the 6-week wait is pointless and CEA can be performed safely (Dosick 1985, Piotrowski 1990), but delayed surgery still remained in practice past the turn of the century.

1.4.2 The Present

In a further pooled subgroup analysis of NASCET and ECST by Rothwell et al. (2004), the timing of surgery was taken into account, and in both trials, the benefit of stroke risk reduction rapidly declined after two weeks from the last symptom to CEA. Since then, two weeks has been the widely adopted goal from symptom to surgery. Initially, the median times exceeded this goal markedly, with results like 82 days in the UK (Dellagrammaticas et al. 2007) and 48 days in Sweden (Johansson et al. 2008). Various efforts have been made and the delay has dramatically decreased during the last decade – according to the national vascular registries, it has been reduced to 13 days in the UK, 7 days in Sweden and 12 days in Denmark (UK National Vascular Registry, Swedvasc, Karbase).

A notable issue is how the index symptom is defined. Some institutions determine the index symptom as the first symptom that results in an operation, whereas others conceive it as the last symptom before the operation, thus excluding the possible recurrent symptoms. Recurrent ischaemic symptoms are reported to occur in 3.1%–5.2% of patients within 2 days after the index symptom, increasing to up to 11.2% within 2 weeks (Giles et al. 2007, Johansson et al. 2013). The difference in the definition of index symptom meant 4–8 more days in median delay according to the observational study by den Hartog et al. (2014), emphasising the importance of this definition when reporting and analysing delays.

The relatively high risk of recurrence has steered the discussion today towards operating even sooner, within in the first 48 hours. CEA has been shown to be safe during this hyperacute period, with a similar risk of stroke or death when compared to patients operated on in 2–14 days (Sharpe et al. 2013, Tsivgoulis et al. 2014). However, according to the Swedish vascular registry Swedvasc, the combined stroke or death rate was 11.5% for patients operated on within 2 days of the onset symptom as opposed to the stroke or death rate of 3.6%–4.0% among patients operated within 2–14 days and 5.4% for patients operated within 15–180 days. (Stromberg et al. 2012), so the matter of optimal timing remains under debate.

Expedited surgical treatment requires distinguishing the patients at the greatest risk of a recurrence of TIA or stroke. Clinical risk prediction tools have been established to help in this task, and the most commonly used one is the ABCD2 score (Johnston et al. 2007, Ehsan et al. 2008), in which 1 point per character is gained from Age over 60, Blood pressure above 140/90 mmHg, Clinical presentation of speech impairment, a Duration of 10–59 minutes and having Diabetes. Weakness of a unilateral limb adds 1 point and a duration of symptoms of over 60 minutes another. A score of >6 points indicates high risk and <3 low risk. The sensitivity of the ABCD2 score has been questioned and demonstrated to be poor in a large meta-analysis by Wardlaw et al. (2015). By adding Dual events (recurrence of symptoms within 7 days) to the score with 2 points produces the ABCD3 score, which has been shown to be more accurate in predicting stroke risk but does not exclude the need for imaging studies (Purroy et al. 2012, Johansson et al. 2013). These imaging studies are also currently of great interest concerning carotid plaque morphology. An ulcerated plaque surface in an angiogram (Lovett et al. 2004) as well as the presence of intraplaque haemorrhage in MRI (Saam et al. 2013) have been associated with an increased risk of stroke recurrence. Positron emission tomography (PET) imaging has also yielded promising results on identifying the vulnerable plaques (Graebe et al. 2010, Pedersen et al. 2015). Hence, imaging may play a major role in the future in distinguishing the patients at highest risk of recurrent symptoms and stroke.

1.4.3 Timing of carotid surgery in the Helsinki and Uusimaa region

According to an observational study by Vikatmaa et al. (2011), in Helsinki University Hospital with catchment area of approximately 1.5 million inhabitants, the median delay from first symptom to surgery was 47 days in 2008, and only 11% of the patients were operated on within two weeks. A recurrence or progression of symptoms was experienced by 10% of the patients while waiting for CEA in a median of 8.5 days from the index symptom, and 40% had had recurrence or progression prior to hospital contact (Sairanen et al. 2012).

1.5 GUIDELINES FOR THE TIMING OF SURGERY

Both the European Society for Vascular Surgery (ESVS) in 2009 (Liapis et al.) and the Society for Vascular Surgery (SVS) in 2008 (Hobson et al.) have published guidelines for carotid interventions, with similar recommendations. For symptomatic patients with >50% stenosis, the recommended treatment is CEA. The ESVS guidelines state that the operation should take place within 2 weeks of the last symptom. The timing of surgery was not addressed in the SVS guidelines of 2008, but in the update (Ricotta et al. 2011), the timing is discussed and the conclusion is that a carotid intervention is preferably performed within 2 weeks rather than delayed until 4–6 weeks.

Neurologists have also taken a stand concerning the timing of surgery. The ESO established in their guidelines (ESO executive committee 2008) for the management of ischaemic stroke and transient ischaemic attack that CEA should be performed as soon as possible, preferably within 2 weeks from the last symptom, and the same position was taken by the AHA/ASA guidelines: "surgery within 2 weeks is reasonable rather than delaying surgery if there are no contraindications to early revascularisation"(Brott et al. 2013). In the UK, the National Institute for Health and Care Excellence (NICE) have guidelines from 2008 also stating that a patient expressing TIA or stroke symptoms should undergo surgery within a maximum of 2 weeks, whereas the UK National Stroke Strategy by the Department of Health has taken a more active position and recommends a carotid intervention for high-risk patients (ABCD >4) within 48 hours.

1.6 DELAY IN THE TREATMENT PROCESS

1.6.1 Pre-hospital delay

1.6.1.1 Patient-related delay

A patient-related delay is the time from the symptom until the patient seeks help from a health care professional. The countdown for the delay starts with the patient's reaction to the onset of symptoms. The awareness of the need for urgent evaluation of ischaemic cerebral symptoms remains relatively low (Parahoo et al. 2003, Dombrowski et al. 2015, Ntaios et al. 2015), and even if the symptoms are recognised, the willingness to seek help immediately often seems to be lacking. By-standers (family, friends or passers-by) have an important role in the first crucial minutes when the course is set for the treatment process (Mellor et al. 2015, Wolters et al. 2015). Several ways to improve public awareness have been introduced ranging from printed materials, lectures and courses to the use of mass media (Martin 2014). The mass media reaches the largest amount of the population, and significant results have been achieved after such campaigns in raising public awareness, but the effect on publics behaviour has remained meagre (Marx et al. 2008, Hartigan et al. 2014). One of the largest campaigns using television with promising results is the FAST (face-arm-speech-time) campaign, which educates the public about the alarm symptoms (face-arm-speech), in addition to encouraging people to act quickly (time) and call for help immediately (Flynn et al. 2014). This campaign, first launched in the US (Kleindorfer et al. 2007), is currently in use in several countries. In the UK, after a television campaign, the median time to seeking attention fell from 53 to 31 minutes and the median time to hospital arrival from 185 to 119 minutes (Wolters et al.2015). In Japan, after a FAST-based TV campaign, the pre-hospital delay fell from a median of 13.5 hours to 12 hours and the proportion of patients arriving within 3 hours of the symptoms rose from 46.5% to 55.7% (Nishijima et al. 2015). It is one thing to raise public awareness, but quite another to maintain the knowledge. The effect of awareness campaigns seems to fade in 5 months, and continuous campaigning is therefore needed in order to uphold public awareness (Hodgson et al. 2007).

1.6.1.2 Referral delay

Referral delay is the time from the patient's first healthcare contact to the evaluation by a neurologist or vascular surgeon. The first health care contact is often a general practitioner (GP) (Vikatmaa et al. 2011). According to a Swiss questionnaire study, the referring GPs seemed to have a fairly good perception of the importance of TIA symptoms to the risk of stroke, even to the point of overestimation, but many of them still did not consider emergency referral necessary if encountered by a TIA patient (Streit et al. 2015).

The foundation of TIA clinics has played an important role in shortening referral delay, making the first contact and evaluation possible in 24 hours (Lavallee et al. 2007,Rothwell et al. 2007, Salem et al. 2011). Even though it has been reported that 50% of patients referred are in fact TIA mimics, the effect on stroke risk reduction is still evident, with a decline in reported stroke risks at 90 days from 7.5%–9.4% to 1.3%–2.9% after the implementation of TIA clinics (Dutta et al. 2015).

1.6.2 In-hospital delay

1.6.2.1 Imaging delay

Imaging delay is the time it takes to image the carotid arteries. Imaging is rarely delayed if the previous steps of the treatment process have gone fluently and the patient arrives on an emergency basis to a centre where immediate diagnostics and care are available. Computed tomography (CT) is widely available around the clock and therefore used as the first imaging method with the advantage of fast imaging and the possible inclusion of imaging the carotid vessels. Magnetic resonance imaging (MRI) has been shown to be more accurate in detecting small ischaemic lesions after a TIA or minor stroke (Moreau et al. 2013, Sidorov et al. 2014), and if availability will increase in future, MRI could replace CT as the first-line imaging study.

1.6.2.2 Neurological delay

The delay from evaluation by a neurologist to vascular surgeon is usually not the problem, since the need for surgery is usually established at this point and a vascular surgeon consulted accordingly. The patient's overall condition may delay the consultation, which bears little relevance, however, since the patient in such a case is usually not fit for surgery. In Helsinki, the neurological delay was a median of 7 days, including the imaging studies (Vikatmaa et al 2011).

1.6.2.3 Surgical delay

Surgical delay is the time from the decision to operate until the operation takes place. When the decision on CEA is reached, the goal for the vascular surgeon is to schedule the operation within two weeks from the index symptom, which is possible only if the two weeks has not already passed. Surgical delay has contributed considerably to the delay from symptom to surgery in the earlier reports, and reducing this component has also shortened the overall delays remarkably. (Johansson et al. 2008, den Hartog et al. 2014) The long median delay of 47 days from symptom to surgery in Helsinki was also heavily influenced by the surgical delay of median 25 days (Vikatmaa et al. 2011). Reducing the surgical delay as well as other elements of in-hospital delays is more easily achieved than the reduction of the pre-hospital delay, but it does require resources to achieve, mainly operating hours and the accessibility of an operating room on an emergency basis if needed.

2 DIABETIC FOOT ULCERS

2.1 INCIDENCE AND PREVALENCE OF DFUS

The prevalence of diabetes is on the rise from an estimated 284 million worldwide in 2010 to up to 439 million or even more by the year 2030 (Shaw et al.2009, Danaei et al. 2011). In Finland, approximately 400 000 patients had diagnosed diabetes in 2007 according to Ikonen et al. (2010). With undiagnosed patients included, the number of patients with diabetes has been suggested to rise to up to almost 1 million in the next decade (Sund et al. 2009).

Foot ulcerations affect up to 25% of patients with diabetes in their lifetime (Gregg et al. 2004, Singh et al. 2006) – therefore, in Finland, we can expect close to a quarter of a million diabetic foot ulcers (DFUs) in the future.

2.2 DEVELOPMENT OF DFU

The formation of a DFU is a multifactorial process, most often including neuropathy, deformity and trauma (Reiber et al. 1999). Diabetic peripheral neuropathy (DPN) embodies sensorial, motor and autonomic sympathetic components. The clinical findings are loss of sensation in a stocking-like distribution, small muscle loss and joint immobility, deformities like claw toes and hallux valgus as well as reduced sweating, which can lead to dry skin and callus formation (Bowling et al. 2015). For the majority of the patients, DPN commences the pathway to ulcer formation; sensory loss leads to the absence of pain as a warning signal, while small muscle loss and joint immobility predispose to deformity and altered pressure distribution, all of which combined with callus formation easily result in an ulcer after minor trauma.

2.3 DIABETIC FOOT AND PAD

Peripheral artery disease (PAD) affects 9%–23% of patients with diabetes and, according to the prospective Eurodiale study, ischaemia is present in 50%–60% of DFUs, raising the annual major amputation and mortality rate from 2% to 8% and from 3% to 9%, respectively (Prompers et al. 2007,2008). The manifestation of PAD in diabetes has distinctive features; mainly the infra-popliteal arteries are affected diffusely and, in the artery wall, the sclerosis affects the tunica media rather than the intima (Faglia et al. 1998). The profunda femoris artery has also been shown to present with worse disease compared to patients with no diabetes (Jude et al.2001).

2.3.1 Investigations for PAD in patients with diabetes

All DFUs should be evaluated for the presence of PAD, starting with the palpation of the pedal pulses. Palpable pulses are considered a sign of adequate blood flow. However, palpation findings have been shown to be unreliable (Lundin et al. 1999) and, on the other hand, the presence of pedal pulses does not conclusively exclude PAD (Rivers et al. 1990, Collins et al. 2006). Ankle Brachial Index (ABI) measurement is in routine use for detecting ischaemia, though for patients with diabetes it has been proven to be directional at best due to medial sclerosis (Aerden et al. 2011, Alvaro-Afonso et al. 2015). Further information may be gained from toe pressure (TP) and transcutaneous oxygen pressure (TcPO2) measurements, which have demonstrated superior reliability in the examination of patients with diabetes (Brownrigg et al. 2015, Sonter et al. 2015).

A systematic review of the effectiveness of bedside investigations was recently conducted by the International Working Group on the Diabetic Foot (IWGDF), with a conclusion of insufficient evidence to support a single non-invasive diagnostic modality for the detection of PAD among patients with diabetes (Brownrigg et al. 2015). Therefore, in the case of DFU, regardless of the measurements, imaging to determine the anatomical distribution of the disease should be performed if any doubt concerning blood supply to the ulcerated foot exists. The imaging methods most often used today are magnetic resonance angiography (MRA) and computed tomography angiography (CTA) instead of digital subtraction angiography (DSA), with the advantage of non-invasiveness and better availability for CTA and avoidance of iodinated contrast and radiation exposure for MRA (Meyersohn et al. 2015). Doppler ultrasound scanning can also be used and is undoubtedly the least-invasive imaging method, but it can be time-consuming and requires a skilled professional to obtain reliable and DSA-comparable results, especially on the crural arteries (Eiberg et al. 2010).

2.4 FACTORS INFLUENCING THE OUTCOME OF DFU

2.4.1 Renal function

Impaired renal function complicates the diagnostics and treatment of DFUs, as iodinated contrast is not recommended in patients who still have some renal function left. Patients with end-stage renal disease (ESRD), on the other hand, can undergo these procedures as long as they attend dialysis afterwards. Diabetic nephropathy is the leading cause of ESRD and dialysis treatment (Bjornstad et al. 2015). ESRD is also a risk factor for the development of DFU (Lewis et al. 2012), and it has a negative effect on ulcer healing and is associated with a higher risk of limb loss and mortality (Ndip et al. 2010, Lepäntalo et al. 2012).

2.4.2 Wound characteristics

Diabetic ulcers are very heterogeneous, ranging from superficial abrasions with good healing potential to bone penetrating infectious ulcers needing surgical revision and to gangrene a step away from amputation, hence the expectations for wound healing are bound to vary also.

2.4.2.1 Wound classifications

Classification systems for wound characteristics have been established in order to predict the outcome of DFUs. In 1976, the Meggit classification was first introduced, but it was taken into wider use in 1981 after reintroduced by Wagner. This Wagner-Meggitt classification disregards possible infection and ischaemia and categorises the wounds by depth in 6 grades (0–5) from pre- or post-ulcerative lesion to whole foot gangrene. In 1996, Lavery et al. presented the University of Texas wound classification (Table 1), which includes the evaluation of ischaemia and infection and is therefore considered more applicable in estimating DFUs (Oyibo et al. 2001).

Table 1 The University of Texas Wound classification modified from Lavery et al.1996 with permission.

	0	I	II	III
A	Pre- or postulcerative lesion completely epithelialized	Superficial wound, not involving tendon, capsule or bone	Wound penetrating to tendon or capsule	Wound penetrating to bone or joint
B	Pre- or postulcerative lesion, completely epithelialized with infection	Superficial wound, not involving tendon, capsule or bone with infection	Wound penetrating to tendon or capsule with infection	Wound penetrating to bone or joint
C	Pre- or postulcerative lesion, completely epithelialized with ischemia	Superficial wound, not involving tendon, capsule or bone with ischemia	Wound penetrating to tendon or capsule with ischemia	Wound penetrating to bone or joint with ischemia
D	Pre- or postulcerative lesion, completely epithelialized with infection and ischemia	Superficial wound, not involving tendon, capsule or bone with infection and ischemia	Wound penetrating to tendon or capsule with infection and ischemia	Wound penetrating to bone or joint with infection and ischemia

More recently, wound classifications have been developed with further consideration also for ulcer area and neuropathy, such as the classifications S(AD)SAD (Size [Area, Depth], Sepsis, Arteriopathy, Denervation) and the PEDIS (Perfusion, Extent, Depth, Infection and Sensation) by IWGDF, both showing promising results (Treece et al. 2014, Chuang et al. 2015), but none of these classifications have proven to be completely adequate; for example, the degree of ischaemia is not defined in detail and the inter-observer agreement grading the classifications is demonstrated to be only moderate (Santema et al. 2015).

The Society for Vascular Surgery (SVS) introduced in 2014 the WIfI (Wound, Ischemia, foot Infection) classification (Mills et al. 2014), which takes into account the severity of ischaemia according to ABI, TP or TcpO2 and estimates the risk of amputation at 1 year in four clinical categories ranging from very low risk to high risk of amputation (Table 2). The correlation of the classification system with wound healing and limb salvage has been validated, but further efforts are still needed in order to incorporate this classification into wider clinical use (Cull et al. 2014, Zhan et al. 2015). The use of the same classification in common practice would simplify clinical work and enable the collection of comparable data, thus benefitting both the clinician and the researcher.

Table 2 Risk of amputation at 1 year. W=wound, I=Ischaemia, fI=foot infection. 0=none, 1=mild, 2=moderate, 3=severe. VL=Very low, L=Low, M=Moderate, H=High. Modified from Mills et al. 2014 with permission.

W	Ischaemia -0				Ischaemia -1				Ischaemia - 2				Ischaemia - 3			
0	VL	VL	L	M	VL	L	M	H	L	L	M	H	L	M	M	H
1	VL	VL	L	M	VL	L	M	H	L	M	H	H	M	M	H	H
2	L	L	M	H	M	M	H	H	M	H	H	H	H	H	H	H
3	M	M	H	H	H	H	H	H	H	H	H	H	H	H	H	H
fI	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3

2.4.2.2 Wound location

The location of the ulcer has not conclusively been shown to affect wound healing (Ince et al. 2007), but higher recurrence rates for ulcers on the plantar surface have been reported (Dubsky et al. 2013). On the other hand, a recent large cohort study by Örneholm et al. (2015) consisting of 701 patients with plantar ulcers demonstrated a 79% healing rate in a median of 17 weeks. The location of the wound can be categorised according to the angiosome concept, which has been used in plastic surgery ever since it was first introduced by Taylor and Palmer in 1987. Vascular surgeons became interested in the concept after Attinger et al. (2006) presented the concept with the division of the foot and ankle area into 6 angiosomes according to the artery supplying vascularisation. The major flaw with the angiosome concept, however, is the fact that there is often more than one ulcer and the ulcer, or ulcers, is rarely located in only one angiosome area. In a recent study by Spillerova et al. (2015) on 161 patients (66.5% with diabetes) with critical limb ischaemia and a foot ulcers, only 24% of the ulcers were located in one angiosome.

2.4.3 Previous ulcer or minor amputation

Of all the risk factors for DFUs, a previous ulcer or amputation is the most predictive (Boulton 2004, Monteiro-Soares et al. 2012). After a minor amputation, the greatest risk of further amputation is in the first six months (Izumi et al. 2006).

2.5 TREATMENT

2.5.1 Preventive methods

The prevention of ulcer formation is pivotal in the treatment of diabetes. Repeated education in foot care and guidance in daily foot inspections should be provided for all patients with diabetes (Schaper et al. 2015). The recommendation is general knowledge among health care professionals, but awareness among patients with diabetes worldwide remains insufficient (Basu et al. 2004, Saurabh et al. 2014, Lamchahab et al. 2011).

In 2010, Lavery et al. demonstrated in two high-risk patient cohorts of diabetic patients in dialysis and patients with previous DFUs that only 1.3% of the patients received formal education and 30% preventive podiatric care. Well-fitting shoes are an important factor in ulcer prevention as ill-fitting shoes have been shown to be associated with a 29% causality for ulcer formation (Connolly et al. 2004). Connolly et al. (2004) also showed in a study of 200 male veterans visiting a podiatry clinic that the shoe size increased by at least 1 shoe size in 48% of the study patients during adulthood, a plausible risk factor for ulcer formation. They recommend controlling the shoe size regularly after the age of 50 years.

The IWGDF recommends the evaluation of diabetic feet annually by a healthcare professional. This evaluation should include the palpation of pedal pulses, a sensory examination with monofilament from the plantar surface and with a tuning fork from the dorsal side of the distal phalanx of the first toe. (Hinchcliffe et al. 2015.)

2.5.2 Conservative treatment

All cardiovascular risk factors worsen the outcome of DFUs, and, therefore, smoking cessation, which is also an independent risk factor of ulcer formation and gangrene (Al-Rubeaan et al. 2015), as well as the control of hypertension and dyslipidemia along with adequate treatment of diabetes are the basis of conservative treatment (Heikkinen et al. 2007). Medical treatment usually includes anti-platelet therapy, even though lower effects in patients with diabetes have been reported for the two most commonly used drugs, aspirin (Sacco et al. 2003, Watala et al. 2004) and clopidogrel (Angiolillo et al. 2005). The diminished anti-platelet activity is suggested to be influenced by dyslipidemia, for which statin treatment is nearly always initiated. The beneficial role of statin use in patients with diabetes has shifted from being a hypothesis (Gulcan et al. 2007) to reducing the risk of major amputation (Sohn et al. 2013) and, when combined with angiotensin-converting enzyme (ACE) inhibitors, mortality as well (Faglia et al. 2014).

Of other medications, iloprost has been suggested as being beneficial in wound healing for DFUs (Altstaedt et al. 1993), but according to a Cochrane review (Ruffolo et al. 2010) based on 20 eligible trials out of 111 potential ones, no conclusive evidence exists for the long-term effectiveness and safety of different prostanoids, even if some positive results concerning rest-pain relief, ulcer healing and amputations have been achieved.

2.5.3 Revascularisation

After ischaemia is detected and arterial imaging performed, the revascularisation strategy is selected as either endovascular treatment (ET) or open surgery (OS) according to the findings of the imaging study. Traditionally, long total occlusions are considered best-suited for bypass surgery and shorter lesions for ET, but with evolving materials and methods, ET has become more applicable, shifting the balance within the last decade towards most patients undergoing endovascular treatment. (Skrepenk et al. 2013.) The outcomes of both strategies are of great interest and have been widely investigated, but legitimate results are scarce mainly due to the diversity of clinical features of the patients with DFUs and the versatile manifestations of the arterial disease, making the standardisation of study patients nearly impossible.

2.5.3.1 Endovascular Treatment (ET)

Endovascular treatment is usually performed via an antegrade puncture in the common femoral artery (CFA) or the superficial femoral artery (SFA) as the target lesions in patients with diabetes are mainly below the knee. Faglia et al. (2002) demonstrated in their multicentre study consisting of 219 patients with DFUs infrapopliteal angioplasty to be feasible and safe with an 87.2% technical success rate, with one case of temporary renal failure managed medically as the only complication. The limb salvage rate during a median of 12 months' follow-up was 94.8%. According to DeRubertis et al. (2008), limb salvage after ET is similar in patients with and without diabetes, but primary patency at one year is inferior in diabetics. The study, however, included patients with indications for treatment varying from claudication to limb-threatening ulcers, and the latter were significantly more common among patients with diabetes ($p < 0.004$), thus rendering the relevance of the finding questionable.

The majority of endovascular procedures performed for DFUs include the recanalisation of the stenosis or occlusion and balloon angioplasty, i.e. percutaneous transluminal angioplasty (PTA). Stents have been used only if absolutely necessary as a bail-out alternative (Randon et al. 2010); today, however, drug-coated stents are also an option, with some promising results (Antoniou et al. 2013, Fusaro et al. 2013). Drug-eluting balloons (DEB) are also of great interest currently – in a randomised trial comparing below-the-knee paclitaxel-coated DEBs to conventional PTA among diabetic patients with critical limb ischaemia, Liistro et. al. (2013) demonstrated reduced rates of restenosis, target lesion revascularisation and target vessel occlusion at one year. The second study with the same DEB, the IN.PACT Amphirion, however, resulted in the withdrawal of the device from the market at 12 months due to a trend (non-significant) towards an increased major amputation rate among the patients treated with the DEB (Zeller et al. 2014). Further studies are therefore needed, but, potentially, these novel methods are the methods of the future (Jaff et al. 2015).

In a retrospective study by Acin et al. (2014), 101 infrapopliteal endovascular procedures were performed for diabetic feet with ulcers. The ulcer healing rate at one year was 55.0%, reflecting the slow healing process, while the limb salvage rate at two years was still 74.9% and amputation-free survival 63.3%, results that can be considered to be fairly good.

Restenosis is common after infrapopliteal ET, and several procedures are often needed to achieve wound healing and limb salvage. The re-intervention rate has been reported to be 5%–26% (Faglia et. al 2002, Giles et al. 2008, Fossaceca et. 2013, Söderström et al. 2013).

2.5.3.2 Open Surgery (OS)

Open surgery is selected when endovascular treatment is expected to fail or has already failed, and the treatment plan is usually bypass to the crural or pedal arteries, since the affected arteries are mainly below the knee.

The outcome of bypass surgery in patients with diabetes has previously been considered to be inferior compared to patients with no diabetes. Virkkunen et al. (2004) demonstrated in the Finnvasc study with 5709 patients undergoing surgery for critical limb ischaemia that diabetes is an independent risk factor for below-knee amputation (OR 1.7), cardiac complications (OR 1.5) and wound infection (OR 1.3). Diabetes was also associated with major cardiac events (OR 2.5) in a study by Roghi et al. (2001). Furthermore, in a retrospective review by Wallaert et al. (2012), diabetes was found to be a significant contributor to the risk of postoperative complications after bypass surgery. Insulin dependence was associated with higher risk. The comorbidities of patients with diabetes therefore require special attention when invasive interventions are planned. The results of the revascularisation, on the other hand, have been shown to be equal after bypass surgery concerning graft patency and limb salvage among patients with and without diabetes. (Schantzer et al. 2008, Oberhuber et al. 2013.) .

2.5.3.3 Endo vs. open

The "endovascular first" approach has gained a strong foothold in today's practice, with several studies advocating the strategy (Arvela et al. 2011, Garg et al. 2014, May et al. 2014, Katib et al. 2015). Therefore, OS is performed on many after failed ET. Contradictory results from secondary bypass surgery have been reported; a study by Uhl et al. (2014) determined no negative effect on the outcome of patients undergoing pedal bypass surgery after failed ET, whereas Nolan et al. (2011) described higher amputation and graft occlusion rates at one year for bypasses after ipsilateral PTA. Other reports have also emerged in opposition to the "endovascular first" strategy – Spinelli et al. 2015 reported significantly inferior limb salvage rates at 1 month and 1 year among patients undergoing bypass surgery after failed ET. In a study by Jones et al. (2013) comparing 1154 patients undergoing secondary bypass surgery with 2350 patients undergoing primary surgery, the freedom from major adverse limb events was significantly inferior in patients undergoing secondary surgery after primary endovascular treatment but also after prior surgery, emphasising the importance of the first revascularisation plan. Most reports, pro and con, have assumed a similar perspective on the entire endo vs. open debate to rather disregard the confrontational set up altogether and focus on the individual needs of the patient with an optimised treatment process including a tailored revascularisation plan according to the vascular morphology (Dick et al. 2007, Garg et al. 2014, Spinelli et al. 2015).

2.5.3.4 Angiosome-targeted revascularisation

In the analyses of wound healing, the angiosome concept is currently often taken into account and the comparison is made between direct revascularisation (DR) and indirect revascularisation (IR), describing the achieved blood flow to the angiosome of the ulcer. In a systematic review and meta-analysis of 15 studies comparing these approaches, DR was associated with improved wound healing and limb salvage, but no difference was found in mortality or re-intervention rates (Bosanquet et al. 2014). One of the fifteen studies included in the review was conducted in HUH by Söderström et al. (2013) on 250 consecutive diabetic feet with ulcers undergoing infra-popliteal PTA, with significantly better ($p<0.001$) wound healing after DR (72%) than IR (45%). In a study by Spillerova et al. (2015) on 744 consecutive patients undergoing any infra-popliteal revascularisation, DR was also found superior in regard to wound healing and limb salvage, but bypass surgery surpassed ET in wound healing even if performed indirectly. The importance of an intact pedal arch might partly explain the finding, for it has been shown to be more important as regards wound healing in bypass surgery than the direct angiosome revascularisation (Rashid et al. 2013).

The aim according to the IWGDF guidelines is to restore direct flow to at least one of the foot arteries, preferably the artery supplying the area of the ulcer (Hinchcliffe et al. 2015), i.e. angiosome-targeted revascularisation is recommended. This aim, however, is jeopardised by the fact that there is rarely a choice between DR and IR, but rather revascularisation is performed at the site possible.

2.5.4 Topical treatment

There are numerous topical agents and dressings on the market for the treatment of DFUs. Reliable and unbiased data is hard to come by as the products are constantly evolving. No superiority has been determined in favour of certain topical agents (Jude et al. 2007, Jeffcoate et al. 2009, Dumville et al. 2013).

The effectiveness of hyperbaric oxygen therapy on wound healing was evaluated in a recent Cochrane review (Kranke et al. 2015), with ten out of the twelve studies included focusing on diabetic feet. Short-term wound healing was improved, but no long-term effect on wound healing was seen and the impact on limb salvage remains unclear.

The strongest, though not conclusive, evidence seems to be for the positive effect of negative pressure wound therapy in assisting wound closure and limb salvage (Lavery et al. 2007, Garwood et al. 2015, Hasan et al. 2015), and this therapy method is widely utilised today.

Topically applied growth factors are being studied in prospective randomised settings, and promising results have been reported on connective tissue growth factor (Henshaw et al. 2015), whereas platelet-derived growth factor does not seem to improve the healing of DFUs (Ma et al. 2015). Further studies in order to substantiate the role of growth factors are needed.

2.6 GUIDELINES ON THE TIMING OF REVASCULARISATION

2.6.1 IWGDF

The International Working Group on the Diabetic Foot was established in 1996, and the latest recommendations for the prevention and management of diabetic foot were established in 2015. Evaluation for the presence of PAD is recommended for all DFUs by measuring ABI and TP, and TCPo2 may also be used. Urgent imaging should be considered with an ABI of < 0.5, ankle pressure of < 50mmHg, TP of < 30mmHg or a TcPo2 of < 25 mmHg. If the DFU does not show improvement within 6 weeks, vascular imaging needs to be considered irrespective of the measurement results.

2.6.2 Finnish guidelines

The Finnish Current Care guidelines from 2009 and the update from 2013 are in accordance with the IWGDF guidance, also including recommendations for the urgency of the referrals from primary care. All ischaemic DFUs should be referred for vascular investigations, with the aim of 1–8 days. Emergency referral should be written for patients with an infectious DFU and systemic symptoms regardless of the presence of ischaemia.

2.7 DELAY IN THE TREATMENT PROCESS

2.7.1 Patient-related delay

As discussed earlier, the prevention of ulcer formation is a priority in the treatment of DFUs, but when preventive methods fail and an ulcer appears, patient awareness defines the course that the ulcer treatment takes. Due to neuropathy, the detection of the wound may be delayed, and daily check-ups are therefore recommended. (Bus et al. 2015.) According to a cohort study on referral trajectories by Sanders et al. (2013), once an ulcer was detected, a median of 3 (0–243) days passed before the patient contacted a health care professional and a further 7 (0-279) days before a podiatrist was consulted. In a retrospective study by Yan et al. (2013) on 270 patients with diabetic foot problems, the pre-hospital delay was a median of 46.5 days. The longest delays were independently associated with poor diabetic foot education and a lack of knowledge concerning foot lesion warning signs.

2.7.2 Referral delay

The delay between the first health care professional and an evaluation by a vascular surgeon when ischaemia is suspected has not been investigated; the previously mentioned 6 weeks of conservative treatment before considering vascular procedures is widely adopted as common practice.

2.7.3 Imaging delay

The time it takes to have the necessary imaging carried out for the planning of the revascularisation may increase the delay and affect the outcome of the DFUs, but no data currently exists on this issue.

2.7.4. Surgical delay

For the time being, no guidelines have been established for the timing of non-urgent procedures. When a vascular surgeon first examines a DFU, a considerable amount of time has already passed. Due to this highly variable pre-hospital delay, determining the optimal time for revascularisation presents a challenging task, and no studies had previously addressed the issue. In a recent retrospective study by Elzgyri et al. (2014) on 478 ischaemic DFUs, the median time from first presentation at a multidisciplinary diabetic foot centre to revascularisation was 8 (3–18) weeks including imaging, which was conventional angiography during the study period of 1984–2006. A delay of less than 8 weeks was associated with a higher probability of healing.

3 ABDOMINAL AORTIC ANEURYSMS

3.1 PREVALENCE OF AAAS

The prevalence of abdominal aortic aneurysms (AAA) determined as an enlargening of the aorta by over 30 mm has been reported to vary from 1.3% to 8.9% in men and from 1.0% to 2.2% in women (Sakalihasan et al. 2005, Zankl et al. 2007). The prevalence has changed in the recent decades according to data obtained from screening studies. When the Veterans Affairs Cooperative Study Group published the results of the Aneurysm Detection And Management (ADAM) trial, the overall prevalence of AAAs was 4.6% among the study population of 73,451 veterans and, after validation with a second cohort consisting of 52,745 veterans, 3.6% (Lederle et al. 1997 and 2000). Also, in the Multicentre Aneurysm Screening Study (MASS), the prevalence among patients screened was 4.9% (Ashton et al. 2002), whereas in a recent study by Benson et al. (2015) on men participating in the National Abdominal Aortic Aneurysm Screening Program (NAAASP), the reported prevalence was only 1.18%.

3.2 RISK FACTORS FOR AAA

A well-known risk factor is male sex, as is evident in the difference in prevalence between the sexes. In a screening trial by Scott et al. (2002), an AAA was found in 1.3% of women and in 7.6% of men. Age is also a notable risk factor, for the prevalence of AAAs has been shown to increase after the age of 65 years from 2.7 % to 4.4% in ten years (Vardulaki et al. 2000).

A family history of AAAs raises the risk of aneurysm formation. In a study focusing on the siblings of patients undergoing surgical aneurysm repair, the overall prevalence of AAAs was 6.1%, but for male siblings over 65 years of age, the prevalence was as high as 16.7% (Ogata et al. 2005).

In a systematic review by Cornuz et al. (2004), smoking, previous myocardial infarction and peripheral artery disease were all moderately associated and hypertension weakly associated with AAA, whereas in a more recent prospective cohort study including 18,782 patients, smoking was determined as the strongest risk factor, and myocardial infarction was negatively associated with AAA incidence (Jahangir et al. 2015). The role of smoking as the most significant risk factor for AAA is undisputed, but for hypertension and coronary artery disease (CAD), the association is not unequivocally substantiated. Blanchard et al. (2000) found both smoking and elevated diastolic pressure to be independent risk factors. Madaric et al. (2005) determined the AAA prevalence to be significantly higher in men with CAD, 14% versus 3%, but smoking among them was also more common. In a Finnish review study, the prevalence of AAA among men with CAD was found to be 9.5% (Hernesniemi et al. 2015), and in a screening study, the incidence of AAA was 5.7% in male patients with CAD (Vänni et al. 2015).

3.3 FACTORS INFLUENCING ANEURYSM GROWTH

3.3.1 Patient characteristics

The annual growth rate of an aneurysm has been reported to be a mean of 2.2 mm according to a meta-analysis by Sweeting et al. (2012) consisting of the results from 18 studies including 15,475 subjects. The growth rate has been shown to accelerate with the size of the aneurysm (Brady et al. 2004) as well as with increasing age (Chang et al. 1997). Men may have the higher prevalence of AAAs and present with larger aneurysms (Lederle et al. 1997), but women tend to have aneurysms that grow faster. In a study by Solberg et al. (2005), the mean growth rates were 2.43 mm for women and 1.65 mm for men per year. In this study, the median initial diameter was 31 mm for women and 34 mm for men, accounting for the lower overall growth rates compared to studies with an annual growth rate of 2.6 mm in patients with an initial mean diameter of 42–43mm (Brady et al. 2004, Bhak et al. 2015).

3.3.2 Smoking and hypertension

Like for the prevalence, active smoking is the most important risk factor also for aneurysm growth, with a 0.35–0.5 mm increase in the annual growth rate (Sweeting et al. 2012, Bhak et al. 2015). The role of hypertension as the cause of increased growth has not been conclusively established (Chang et al. 1997, Brady et al. 2004, Sweeting et el. 2012), but according to a recent study by Bhak et al. (2015), it would seem that especially elevated diastolic pressure increases aneurysm growth.

3.3.3 Thrombus formation

It has been suggested that the proportion of an intraluminal thrombus in the aneurysm is associated with growth rate (Behr-Rasmussen et al. 2014). Thrombus location may also play a role, for it has been reported that a thrombus in the posterior part of the aneurysm is associated with a significantly lower growth rate when compared to an anterior location (Metaxa et al. 2015). In a prospective follow-up study on thrombus consistency, Nguyen et al. (2014) demonstrated an association between an unorganised loose thrombus detectable by MRI with faster aneurysm growth.

3.4 RUPTURE RISK AND MORTALITY

The risk of aneurysm rupture can easily also be perceived as the risk of death, since without intervention, a rupture is affiliated with close to 100% mortality. The rupture risk is in concordance with the size of the aneurysm, and according to the ADAM trial in the US and the UK Small Aneurysm Trial (1998), an aneurysm smaller than 55mm carries a rupture risk of 0.6%–1% per year in men and no benefit in terms of survival is gained by operating on these smaller aneurysms (Lederle et al. 2002, Powell et al. 2007). Women, however, have been reported to have three times the rupture risk compared to men (Brown L. et al. 1999). Women also tend to have smaller aneurysms at the time of rupture (50±8mm vs. 60±14mm) and a 3.9% risk of rupture at 50mm, according to a long-term follow-up report by Brown P. et al. (2003). Of the other risk factors, smoking and hypertension have also been associated with higher rupture rates (Sweeting et al. 2012).

The decision on operative treatment is based on the risk of rupture and, following the findings of the large trials, the criteria used commonly today are an aneurysm diameter of at least 55 mm for men and 50mm for women. For the larger aneurysms, i.e. aneurysms exceeding the threshold for surgical repair, the risk of rupture has not been defined conclusively, for studies are mainly based on mortality data and have been conducted on unfit patients excluded from surgical treatment.

3.4.1 Unfit patients

In a study on patients considered unfit for AAA surgery, Jones et al. (1998) presented the risk of rupture to be 28% within 3 years for aneurysms of 50–59mm and 41% for aneurysms larger than 60mm, with a median time of 18 (1–38) months from diagnosis to rupture. The conclusion drawn in this study, however, was that unfit patients are more likely to die of other illnesses than aneurysm rupture. These other illnesses were determined as a cause of death mainly according to the patient records, for the autopsy rate was 14.0%.

Conway et al. (2001) concluded in their study that, for unfit patients, a ruptured abdominal aortic aneurysm (RAAA) was the cause of death in 36% of the patients, an AAA of 55–59 mm being the culprit in 50% of the patients with an AAA of 60–70 mm and in 55% of the patients with an AAA larger than 70 mm. However, the autopsy rate was also low in this study, 15.7%. In a study with a 46% autopsy rate, Lederle et al. (2002) demonstrated the 1-year incidence of probable rupture to be 9.4% for an AAA of 55–59 mm, 10.2% for an AAA of 60–69 mm and 32.5% for an AAA of 70 mm or more.

3.4.2 Mortality data

The reliability of mortality data is questionable, for the autopsy rate has declined rapidly in recent decades from 50%–80% to 3%–30% in the Western countries (Petri 1993, Lindström et al 1997, Chariot et al. 2000,Brinkmann et al.2002, Shojania et al. 2008). Multiple factors have contributed to this decline. Physicians today are speculated to be less interested in autopsy due to improved antemortem diagnostics, even if it has been demonstrated that there is an approximately 10% discrepancy in significant findings between antemortem diagnoses and autopsy (Tejerina et al. 2012, Liisanatti et al. 2015). Furthermore, for medical autopsies, as opposed to medico-legal ones, permission from the family is required and asking for permission after delivering the fatal news might be difficult. In the United States, according to Harrington et al. (2010), the decline from 50% to 7% in autopsy rate was provoked by the removal of the minimum autopsy rate requirement in 1971 and also influenced considerably by economic factors. In comparison to other Western countries, Finland is well represented with an autopsy rate of 25%–30% (Ylijoki-Sorensen et al. 2014).

3.5 TREATMENT

3.5.1 Conservative treatment

For patients who smoke, giving up the habit is the most important form of conservative treatment. Mani et al. (2011) demonstrated that a smoking cessation intervention cost-effectively increases long-term survival and decreases the need for operative repair in patients with small AAAs identified at screening, findings that further encourage physicians to promote a non-smoking lifestyle for all AAA patients.

As for medical management, due to the connection with other cardiovascular disorders, the treatment of cardiovascular risk factors as a line of secondary prevention, including anti-platelet therapy, antihypertensive medication and lipid-lowering medication, is usually commenced, even though convincing data on the reduction of cardiovascular events and mortality is lacking according to current literature (Robertson et al. 2014). The effects of these drugs on aneurysm growth and rupture rate have been implied but remain to be established, although some evidence exists for a reduction of growth rate in patients using low-dose aspirin (Lindholt et al. 2008) as well as patients taking statins (Sukhija et al. 2006, Schlösser et al. 2008). For statin medication, contradictory findings with no connection to aneurysm growth rate have also been reported (Ferguson et al. 2010). According to a Cochrane review on medical management of small AAAs, roxithromycin has a small but significant protective effect on aneurysm expansion and propanolol a minor insignificant protective effect (Rughani et al. 2012).

3.5.2 Open surgery (OS)

In open surgical repair, the aneurysmatic part of the aorta is typically replaced with a prosthetic graft through a midline incision laparotomy. The alternative is the retroperitoneal approach through a left-sided oblique incision (Conway et al. 2015). General anaesthesia is required for the operation. Depending on the aneurysmal morphology, the aorta is cross-clamped either above or below the renal arteries, a decision crucial to renal circulation. Suprarenal clamping is associated with a higher risk of renal failure, as demonstrated in a retrospective study on 242 pararenal aneurysm repairs by West et al. (2006) with 22.3% of the patients developing renal insufficiency and 3.7% requiring dialysis. In a study by Wartman et al. (2014) on 69 patients undergoing open repair with suprarenal clamping, perioperative renal dysfunction was diagnosed in 30.4% and 5.8% required dialysis, while late renal dysfunction was found in 17.5%. However, infrarenal clamping also affects the kidneys. In a study by Hertzer et al. (2002) with 1135 patients undergoing infrarenal repair, renal insufficiency was found in 1.7% postoperatively, whereas in a smaller study by Tallgren et al. (2007), acute renal dysfunction was discovered in 22% of patients after infrarenal clamping of the aorta, with 4% requiring dialysis. The incidence results on post-operative renal function vary notably due to diversity in terminology ranging from renal impairment, dysfunction, injury and insufficiency to failure, added to alternating definitions of these terms, thus complicating the interpretation and comparison of different studies.

Postoperatively, the patient is monitored in the intensive care unit (ICU) usually for 2 days, and the average in-hospital recovery time has been reported to be 7.9–8.8 days (Schwartze et al. 2009, Huang et al. 2015). Follow-up usually consists of a single visit approximately one month after the operation. The European and American guidelines, however, recommend ultrasound control at 5-year intervals to detect a possible para-anastomotic aneurysm (Chaikof et al. 2009, Moll et al. 2011).

As a late complication, an incisional hernia after midline laparotomy is detected relatively frequently after open AAA repair in comparison to aortic repair due to aorto-occlusive disease. In a systematic review of seven studies, the incidence of an incisional hernia after AAA repair was 21% and after aorto-occlusive repair 9.8% (Takagi et al. 2007).

The mortality associated with open AAA repair has remained unchanged. According to a vascular registry study consisting data from 9 different countries (Australia, Denmark, Finland, Hungary, Italy, Norway, Sweden, Switzerland and the UK), the 30-day mortality after elective open repair is 3.5% and after an emergency operation due to a ruptured aneurysm 32.6% (Mani et al. 2011).

3.5.3 Endovascular aortic repair (EVAR)

In basic EVAR, the aneurysm sac is excluded from circulation with a stent graft typically extending from the infra-renal aneurysm neck to both common iliac arteries. CTA is the imaging method most often used preoperatively, providing information on the morphology of the aneurysm and the suitability for EVAR, therefore enabling the selection of an appropriately fitting stent graft. The assessment of suitability for EVAR is based on the length, diameter and angulation of the aortic neck as well as thrombus formation at the proximal sealing site and the tortuosity and diameters of the iliac arteries. (Harkin et al. 2007.) According to the instructions for use (IFU), 49.4% of the infra-renal aneurysms are suitable for basic aorto-bi-iliac EVAR (Kristmundsson et al. 2014).

In the procedure, both common femoral arteries (CFA) are cannulated. From one side, the main body of the stent graft is introduced into the aorta extending to the ipsilateral common iliac artery. The location of the main body in relation to the renal arteries as well as aortic and iliac bifurcation is verified with an X-ray using contrast medium. Thereafter, the contralateral limb of the stent graft is introduced from the other CFA and additional limbs to the stent graft from both sides if needed. The procedure can be performed with local anaesthesia, provided that the patient is co-operative. In a multicentre trial by Broos et al. (2015) with 1261 patients, no difference was found in perioperative morbidity and mortality between general, regional and local anaesthesia, but the ICU and overall hospital stays were longer among patients undergoing general anaesthesia. On the other hand, in the randomised IMPROVE trial, the use of local anaesthesia was associated with reduced 30-day mortality compared to general anaesthesia (Powell et al. 2014).

Renal dysfunction may also develop after EVAR as a result of the use of contrast medium and the possible interference with renal circulation caused by an unfavourable placement of the stent graft. In a meta-analysis consisting of 11 studies with 1974 patients, clinically relevant renal impairment at one year was found in 18 % of the patients (Karthikesalingam et al. 2015).

Post-procedural follow-up in an ICU is not necessary, and the average time spent in hospital is approximately 3 days (Schwartze et al. 2009, Huang et al. 2015). Re-interventions are more common after EVAR than after OR, but they are usually managed by endovascular means. In a retrospective analysis of 623 patients undergoing EVAR by Johnson et al. (2013), the re-intervention rate was 13%, with a mean follow up of 29 months.

Follow-up after EVAR is life-long in order to detect possible endoleaks causing continuous aneurysm sac growth, device migration or structural failures. The guidelines recommend CTA at 1 and 12 months and, if nothing abnormal is detected, ultrasound annually thereafter (Chaikof et al. 2009, Moll et al. 2011). According to the Vascunet registry data by Mani et al. (2011), the 30-day mortality for EVAR was 1.4% after an elective procedure and 19.7% after emergency repair.

3.5.4 Novelties of endovascular treatment

The newest method in treating infra-renal AAAs, endovascular sealing (EVAS), is, according to the IFU, also applicable in shorter and wider necks as compared to conventional stent grafts (Karthikesalingam et al. 2013). Sealing of the aneurysm is performed with a device consisting of two covered stents with surrounding polyurethane pouches – the aneurysmal sac, i.e. the possible site of endoleaks, is sealed by filling these endobags with a polymer solution. So far, promising but only short-term results of this technique are available (Carpenter et al 2015).

The basic EVAR and EVAS are designed for infra-renal aneurysms, but with evolving materials and techniques, para- and suprarenal aneurysms are today also treated with endovascular methods. These include fenestrated (fEVAR) and branched (bEVAR) devices as well as the chimney technique, with alternative ways of securing the blood supply to the kidneys and visceral organs through either fenestrations in the main body of the stent graft or through separate branches. In the treatment of complex AAAs, fEVAR and bEVAr have been demonstrated to be useful options with relatively low peri-operative morbidity and mortality of 2.4%–6.3% at 30 days. (Wilson et al. 2013.Glebova et al. 2015, Martin-Gonzalez et al. 2015.) Nevertheless, these methods require expensive custom-made devices (Osman et. al 2015). The attempt to analyse the cost-effectiveness of fEVAR and bEVAR in a systematic review setting failed, as no clinical trials with unbiased patient selection exist (Armstrong et. al 2014).

3.5.5 OS vs. EVAR

Four large randomised trials have been published to date comparing elective OR and EVAR: the British EVAR-1 trial, the American OVER trial, the Dutch DREAM trial and the French ACE trial (Greenhalgh et al. 2004, Lederle et al. 2009, De Bruin et al. 2010, Becquemin et al. 2011). According to these trials, the 30-day mortality has been established to be lower with EVAR, but in long-term follow up of a minimum of 3 years, no superiority could be established for EVAR (Paravastu et al. 2014). Moreover, no significant difference was found in renal function after OR vs. EVAR (Brown L. et al. 2010). Epstein et al. (2014) analysed the cost-effectiveness of EVAR compared to OR based on these randomised trials without being able to make a clear distinction between the two methods; only the OVER trial indicated EVAR as more cost-effective. The authors, however, discourage comparisons between countries regarding economic issues.

The inclusion criterion for all these randomised trials was an aneurysm suitable for both OR and EVAR, but this is rarely the case in reality. The practice has shifted towards treating patients with EVAR when possible and with an open procedure when EVAR is not an option. Obviously, this policy leads to more complex open surgery with fewer capable vascular surgeons, as residents today rarely have the opportunity to participate in open abdominal surgery (Aziz et al. 2013).

In the last ten years, EVAR has taken over the position as the first line of treatment in many centres worldwide, Helsinki included, due to the clear benefits arising from the less strenuous procedure, shorter hospital stay and lower perioperative mortality (Kontopodis et al. 2015). That said, the technical aspects as well as the materials and equipment required inevitably make EVAR unavailable in smaller centres. European guidelines also recommend that only centres with at least 50 elective AAA repairs should perform aortic repair to begin with (Moll et al. 2011). Self-evidently, a certain number of procedures is needed to acquire the skills in endovascular repair and, in order to sustain these skills, a steady patient flow is also necessary. In Finland, the matter of centres with a low volume of AAA procedures was recognised quite early on – in 1997, a feasibility study conducted after the first EVARs were performed in Finland in three university hospitals reached the speculative conclusion that centralisation of EVAR would be wise (Lepäntalo et al. 1997).

3.6 SCREENING

Since aneurysms are usually asymptomatic and ruptures occur without warning signals, leading to a likely fatal result, screening for AAAs has understandably been of interest, especially since detecting an AAA by ultrasound is simple and fast with reliable results (McGregor 1977, Graham et al.1988).

Table 3 Overview of the randomised population-based screening trials. Modified from Svensjö et al. 2014 with permission.

STUDY	Chichester, UK	Viborg, Denmark	MASS, UK	Western Australia
Patients (n)	15,775	12,628	67,800	41,000
Gender	Men and women	Men	Men	Men
Age (years)	65–80	65–73	65–74	65–79
Recruitment	1988–1990	1994–1998	1997–1999	1996–1998
AAA repair at	6 cm	5 cm	5.5 cm	–
Attendance	68 %	76 %	80 %	70 %
Prevalence of AAA	4% (7.6% in men)	4 %	4.9%	7.2%

In the 1990s, large randomised population screening trials were initiated in the UK, Denmark and Australia, with fairly similar prevalence results presented in Table 3 (Scott et al. 1995, Lindholt et al. 1998, Ashton et al. 2002, Norman et al. 2004).

The benefits expected from the screening programmes included a decrease in rupture rate, emergency repairs and aneurysm-related mortality. Screening overall is considered to be worthwhile when a level of cost-effectiveness is established, expressed in most studies as cost per life year saved. Prior to the publication of results from any randomised screening studies, Frame et al. (1993) concluded that screening men with ultrasound once between the ages of 60 and 80 years may be cost-effective and modestly beneficial. At four years of follow-up, the Multicentre Aneurysm Screening Study Group (2002) demonstrated a level of cost-effectiveness defined as at the margin of acceptability, whereas Lindholt et al. (2006) concluded, according to the Vyborg study, that is seemingly cost-effective with a 75% reduction in emergency procedures and a 67% decrease in aneurysm-related mortality. For both studies, the expectation was that, during the following years, the level of cost-effectiveness would rise as the cost per life year saved decreases over time, and the Vyborg study group substantiated this in a later report with remarkably low incremented cost at 157 € per life year saved (Lindholt et al. 2010). In a Cochrane review, the cost-effectiveness of screening was recognised based on these four trials, but, at the same time, further analyses were still called for (Cosford et al. 2011).

A decline in the prevalence of AAAs due to the general public's improved, non-smoking lifestyle has raised doubts on the benefits of screening programmes. Svensjö et al. (2014), however, demonstrated one-time screening for men over 65 years still to be cost-effective today. Screening programmes are currently in use in the UK, USA, Australia, New Zealand, Italy, Sweden, Denmark and Norway (Stather et al. 2013). In 2011, the National Institute for Health and Welfare published a report by a joined task force investigating the benefit of screening in Finland. The cost-effectiveness was established, but implementing the screening programme would require extra resources (Mäklin et al. 2011).

3.7 TIMING OF ELECTIVE AORTIC REPAIR

Even though the goal is clear – elective aortic repair should take place before the aneurysm ruptures – the optimal timing remains unclear. Determining the right timing is difficult, for it is based on the estimated risk of rupture mainly derived from studies on patients turned down from operative treatment.

3.7.1 Guidelines

The European Society for Vascular Surgery (ESVS) published clinical practice guidelines for the management of AAAs in 2011 (Moll et al.). The timing of elective surgery regarding the whole treatment process is not discussed in the guidelines, but it is recommended that a vascular surgeon reviews the patient within 2 weeks of the aneurysm reaching 55mm. Preoperative evaluation and treatment of risk factors prior to surgery are recommended. Statin treatment is suggested to be started one month prior to the operation, a statement perhaps describing the viewpoint on timing.

In North America, the Society for Vascular Surgery (SVS) has published their guidelines on the care of patients with a AAA in 2009 (Chaikof et al.). The timing of elective surgery is addressed in the guidelines, recognising the necessity of preoperative evaluations as well as the possibility of aneurysm rupture prior to the operation. However, no recommendations are declared, except for the inclusion of the patient and the family in the process so that they understand and accept the small risk of rupture while waiting for the operation.

3.8 DELAY IN AAA TREATMENT

3.8.1 Pre-hospital delay

AAA formation is usually an asymptomatic process, an a patient-related delay is therefore rare. One might be aware of an enlarging pulsating abdominal mass, but for the most part, AAA diagnoses are accidental side products of other imaging studies in countries like Finland with no active screening programme. When an aneurysm is detected by the patient or primary health care professional, referral to the vascular unit, is presumably made promptly; however, there is no data to confirm this assumption.

3.8.2 In-hospital delay

When a patient with a large AAA fulfilling the treatment criteria is diagnosed, the planning of the elective treatment begins. The treatment method, open or endovascular, needs to be determined, a process that may take some time, as can the acquisition of custom-made endografts, possible delays in the process that are rarely reported. Patients undergoing aortic repair require overall health assessment for the perioperative risks (Moll et. al 2011). Additional investigations and treatment of other illnesses may also be required, delaying the AAA repair further. Studies on the delay in aortic repair are scarce; Sobolev et al. (2000) reported the waiting times in their institution in Ontario, Canada, for all vascular procedures, and even though their aim was to treat AAAs within a maximum of 4 weeks, the median time to the operation was 7 weeks. Oram et al. (2008) reported the results of 54 patients exiting the screening programme due to a large aneurysm and for whom elective surgery was considered. Eleven patients were excluded from treatment, 3 were operated on an emergency basis due to a symptomatic aneurysm, and 2 patients died due to a RAAA while waiting for an operation, which took place in a median of 6 months. To date, no reports on the delay across the entire treatment process and the repercussions thereof have been published.

AIMS OF THE PRESENT STUDY

The purpose of this study was to explore and analyse the treatment processes of the essential patient cohorts in vascular surgery – patients with symptomatic carotid stenoses, DFUs or large AAAs.

The specific aims were to:

1. Establish the impact of the organisational changes made in 2009 on the delay in carotid surgery. (I)
2. Investigate the treatment process of DFUs and define the impact of delay on the outcome. (II)
3. Determine the natural course of large AAAs by investigating the patients excluded from operative treatment. (III)
4. Investigate the elective treatment of AAAs and the possible delaying factors as well as consequences arising from the delay. (IV)

MATERIAL AND METHODS

Approval for all studies was granted by the Institutional Review Board of Helsinki University Hospital (HUH).

1 PATIENTS AND STUDY DESIGN

The patients and data for this study were retrospectively gathered from the hospital records. Statistics Finland provided the data on causes of death. The prospective HUSVASC registry provided the demographics (Table 4) with specific features for each study as follows:

Table 4 The patient demographics for studies I–IV.

	Study I	Study II		Study III	Study IV
		Diabetes	No Diabetes		
Number of patients	144	242	152	154	361
Age (mean)	68.9	77.0	79.1	79.6	72
Male (%)	63.9	58.3	42.1	68.8	83.9
Smoking (%)	43.8	21.9	29.6	-	47.1
Hypertension (%)	66.7	82.6	60.5	-	81.9
Diabetes (%)	29.9	100.0	0	30.6	14.7
Cardiac disease (%)	31.9	47.5	32.9	60.4	53.1
Statin medication (%)	59.0	50.4	28.3	-	54.0
Anti-platelet treatment (%)	61.8	65.7	55.2	-	51.0

I

All 144 consecutive patients with a combined 145 symptomatic carotid stenoses undergoing CEA in 2010 were included in the study. The index symptom was categorised by a neurologist as TIA, AFX, or minor or major stroke according to the modified Ranking Scale (mRS). The degree of the carotid stenosis and the possible contralateral stenosis were recorded according to the NASCET criteria. The first health care contact was determined.

II

The study population comprised all DFUs (n=273) referred to a vascular surgeon's evaluation during 2010–2011. The demographic data included the patients' mobility and living conditions, previous amputations and revascularisations as well as the duration and location of the ulcer.

III

The study comprised all 154 patients with large AAAs who were excluded from operative treatment during 2000–2010. The patients were analysed in subgroups according to the diameter of the aneurysm: 55–60mm, 61–70mm and >70mm. The demographics included pulmonary disease, PAD and malignancy. The evaluation of suitability for EVAR was noted.

IV

In this study, 361 patients assigned for elective AAA repair during 2005–2010 were analysed in aneurysm size groups, < 60mm, 61–70mm and >70mm, and also according to the treatment method used, OS and EVAR. We determined our success in reaching the target times, that were applied in our institution during the study period, from the decision on operative treatment to the operation, 1 month for an aneurysm of >65mm and 3 months for smaller ones.

2 DELAY ANALYSIS AND END POINTS

The delay analysis started from the symptom (I) or referral to a vascular surgeon (II, IV). The delays in the various steps of the treatment process were analysed: referral delay occurring before the first evaluation by a vascular surgeon, radiological delay for the time spent on imaging, the delay in reaching the decision on treatment and surgical delay from the decision to the intended treatment. In addition, each study had their distinctive features and focuses:

I

The delay analysis included the patient-related delay for the time it took for the patient to seek medical attention after the index symptom. Perioperative complications and the postoperative recovery were determined. Follow-up at 30 days was routinely carried out by a vascular nurse over the telephone.

II

The delay analysis was continued after revascularisation in order to include all re-interventions as well as wound healing, one of the main end points of the study. During the treatment process, emergency operations were taken into account as were major amputations and deaths during the entire follow-up extending until the end of 2013.

III

The process of evaluation and exclusion from elective treatment was analysed, including the effect of the preoperative clinic established in 2005 and consisting of specialists in anaesthesiology and internal medicine. After the exclusion decision, follow-up continued until 30 April 2012, during which aneurysm ruptures and deaths were noted, focusing on rupture-related deaths.

IV

In the delay analysis, the time spent on patient assessment in the preoperative clinic and other possible instances were also regarded. Emergency repairs and deaths while waiting for treatment were the main focuses. Post-operative follow up extended until the end of 2012.

2.1 Statistical analysis

Statistical analyses were performed by SPSS 19.0 (I-III) and MS Excel 2003 (IV). Student's t-test was used in the comparison of the subgroups for continuous variables (I, II, IV) and Pearson's χ test for discrete variables (I). A Cox proportional hazards model was employed in multivariate analysis (II) and Kaplan Meier estimate curves to determine survival and freedom from RAAA (III). In the delay analysis, the times spent on each step of the treatment process were expressed in median days with ranges (R) (I,II,IV) and interquartile ranges[IQR] (II,IV).

RESULTS

1 SHORTENING THE DELAY FOR PATIENTS WITH SYMPTOMATIC STENOSIS (I)

The changes made in 2009, two additional time slots per week in the operating schedule for CEAs and the possibility to assign emergency treatment when an elective time was not available, resulted in a significant decrease in delay, with a median time reduction from 47 (3–368) to 19 (1–236) days (p<0.001; Figure 1) The changes made mostly affected the surgical delay, which decreased from 25 (2–202) to 8 days (0–80). Patients (55.2%, n=80) who arrived in HUH on an emergency basis had a median delay of 13 (1–148) days from symptom to surgery compared to the 36 (6–326) days for patients referred electively.

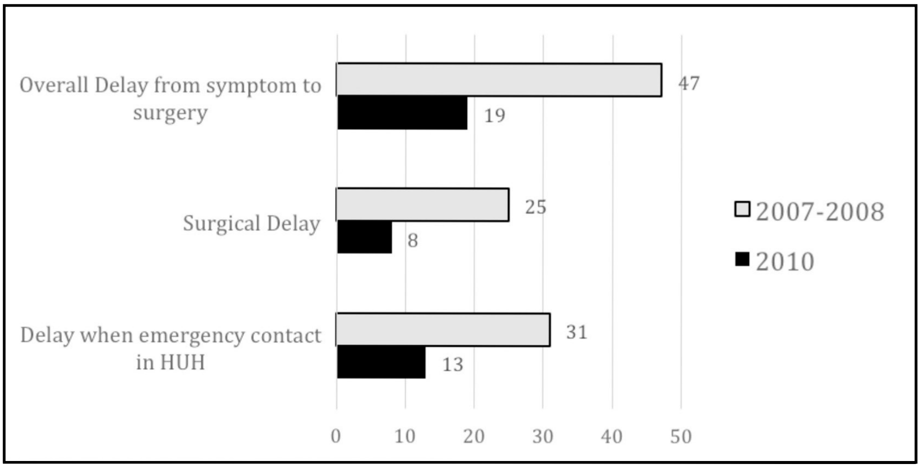

Figure 1 The median delays in 2007–2008 and in 2010. Reproduced from Noronen et al. 2012 with permission.

When the patients were operated on changed significantly after the organisational changes (Figure 2). Previously, most (68%) patients were operated on in more than 4 weeks and, in 2010, the same proportion (67%) was treated within 4 weeks. The goal of 2 weeks from symptom to surgery was achieved for 37% of the patients in comparison to the 11% during the previous study period.

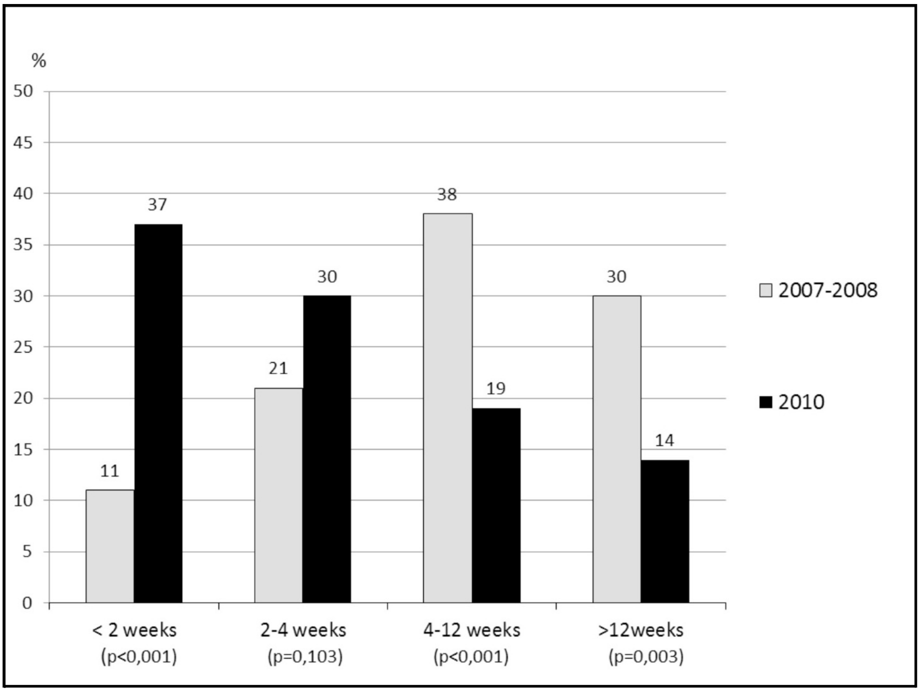

Figure 2 Operations taking place at time intervals 2,4 and 12 weeks in comparison to 2007–2008. Reproduced from Noronen et al. 2012 with permission.

Twenty (13.8%) patients had recurrent symptoms prior to surgery – nine of them suffered a TIA, six had AFX and five fluctuating minor stroke symptoms. In addition, one patient's minor stroke progressed into a major stroke. (Table 5)

Table 5 The occurrence of recurrent symptoms while waiting for CEA according to the index symptom and time after symptom. * One progression into a major stroke.

Index symptom	1-2 days	3-7 days	7-14 days	14-21 days	>21 days
TIA	4	3	1	0	1
AFX	1	0	0	2	3
Minor stroke	3*	1	0	0	1

The patients whose surgical delay exceeded 2 weeks (n=32) were investigated more closely to discover areas of further improvement in our own work. For nearly half (48%) of these patients, no specific reason was found for the prolonged waiting time and, on the other hand, for 43% of these patients, there were reasons for the delay beyond the surgeons' influence, such as another illness that required treatment, an unexpected staff shortage in the OR and a delay of > 2 weeks at the time of the consultation.

A closer analysis of the patients (n=21) with the longest delay (> 12 weeks) revealed a substantially longer patient-related delay of a median of 43(0–139) days compared to the 0(0–139) days for the entire study population. These patients were more often female and their index symptom was more likely to be AFX and not minor stroke. The long patient-related delay was also associated with a longer neurological and surgical delay of 21(0–81) days and 16(1–80) days, respectively.

2 THE IMPACT OF DELAY ON DIABETIC FOOT ULCERS (II)

DFUs formed the majority (n=273, 60.5%) of the suspected ischaemic ulcers evaluated in the vascular outpatient clinic by a senior consultant during the study period of 2010–2011. Cardiovascular manifestations such as coronary disease and hypertension were more common, and the use of statins was also more frequent among patients with diabetes. (Table 3)

Revascularisation was planned for 56.0% (n=153) of the diabetic limbs, and as primary revascularisation, ET was performed for 85.5% (n=136) and OS for 14.6%(n=23). An additional 28 diabetic limbs underwent OS due to failed ET, resulting in 67.9%(n=108) endovascular and 32.1% (n =51) open procedures. The decision on conservative treatment was made for 44.0% (n=120) of the patients with diabetes and was more often based on the expectation of spontaneous healing, whereas for patients with no diabetes, their overall condition was more often the reason for refraining from revascularisation. (Table 6)

Table 6 Diabetic foot ulcers assigned for conservative treatment compared with other ischaemic ulcers.

	DM (n=120)	**No DM** (n=75)	
Reasons	%	%	
Wound likely to heal...			
...spontaneously	59.2	32.0	p<0.001
... after minor amputation/revision	11.7	14.7	ns
Major amputation needed	7.5	4.0	ns
Poor overall condition	13.3	46.7	p<0.001
Revascularisation not considered possible	6.7	2.7	ns
Patient refuses treatment	1.7	0	ns
Outcome			
Later Revascularization	17.5	13.3	ns
Major Amputation	17.5	17.3	ns
Death	60.0	70.7	ns
Amputation free survival	34.2	22.7	ns

After revascularisation, 84.3% (n=134) of the patients with diabetes were followed, as were 77.8% (n=84) of the patients with no diabetes. In a median of 78(16–877) days, wound healing was achieved in 61.6 % of the revascularised diabetic limbs, in 53.7% (n=58) of the patients who received ET and in 78.4% (n=40) of those who underwent OS (p=0.003). A conversion of the initial treatment plan from ET to OS had no effect on the wound healing rate. For patients with no diabetes, the overall wound-healing rate was 43.5%(n=47) – 37.7% (n=29) after ET and 19.4 % (n=6) after OS.

At one year from revascularisation, the limb salvage (LS) rate was 86.4% for patients with diabetes and 79.5% for patients with no diabetes (p=0.053), and the AFS was 63.5% and 62.0% (p=0.805), respectively.

The structure of delay, as presented in Figure 3 for all 159 diabetic limbs undergoing revascularisation, did not differ from patients with no diabetes, with a median delay from referral to revascularisation of 43(29–66) days. There were 29 urgent revascularisations during the treatment process.

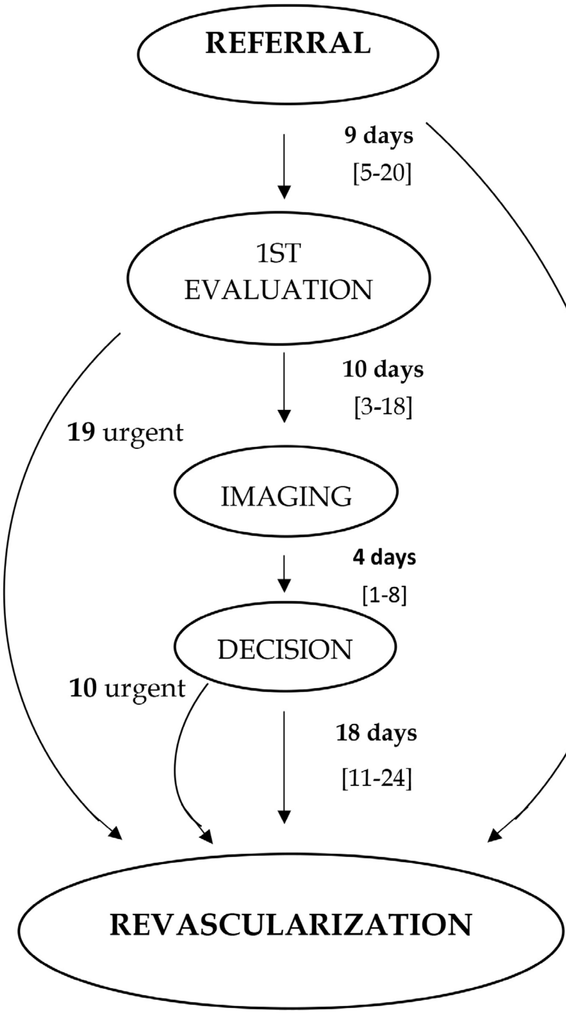

Figure 3 Median delays from referral to revascularisation with interquartile ranges [ ] for DFUs in HUH in 2010–2011.

When the delay from referral to surgery was less than 2 weeks, there was no difference between patients with diabetes and no diabetes in limb salvage (100% vs. 92.9% at 30 days, 86.5% vs. 85.1% at 12 months). However, when the delay exceeded 2 weeks, limb salvage was significantly ($p<0.001$) inferior among patients with diabetes (Figure 4). In multivariate analysis, diabetes was significantly associated with major amputation when the delay exceeded 2 weeks (OR 3.1, 95% CI 1.4–6.9),

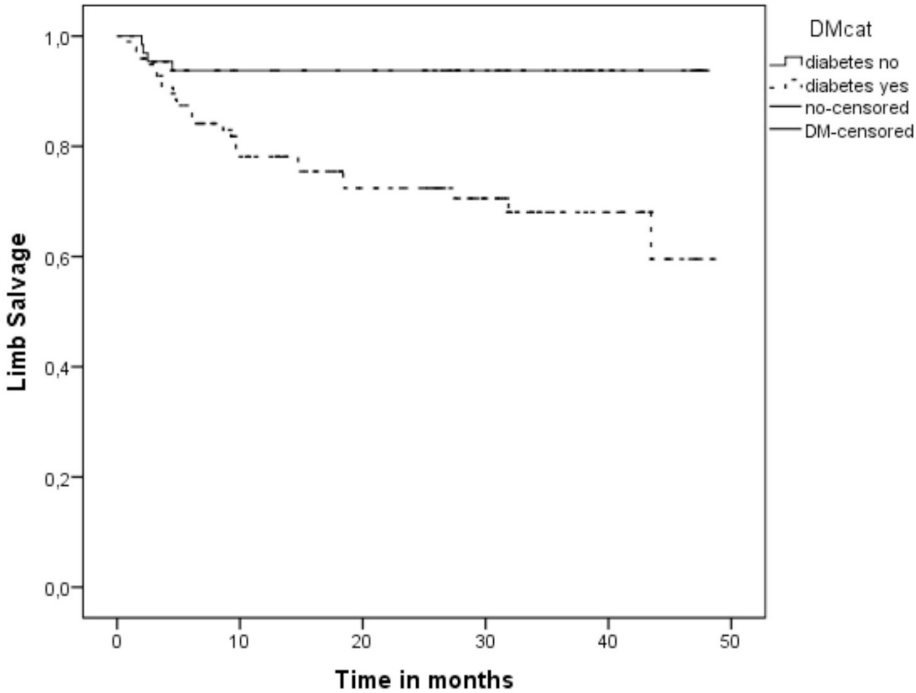

Figure 4 Limb salvage for patients with diabetes and no diabetes undergoing revascularisation with a delay > 2 weeks from referral to revascularisation.

The median follow-up time was 25.9 months ending on 31 December 2013. The overall amputation-free-survival (AFS) after revascularisation was 41.5% for patients with diabetes and 38.0% for patients with no diabetes (p=0.562). For patients with diabetes undergoing OS, the AFS was 45.1%, and for those undergoing ET, 39.8% (p=0.528).

3 THE FATE OF THE UNFIT AAA PATIENTS (III)

The patients who were denied operative treatment consisted of 74 patients with an aneurysm of 55–60mm, 57 patients with an aneurysm of 61–70mm and 23 patients with an aneurysm of > 70mm. During the study period 2000–2010, the number of excluded patients increased, mainly in the category of aneurysms sized 55–70m. (Figure 5)

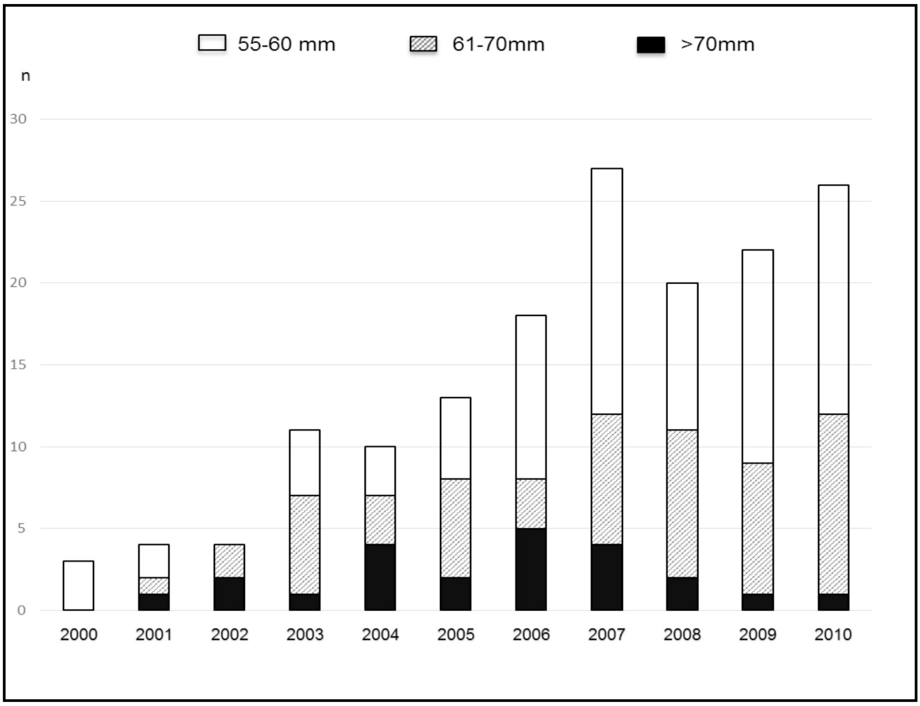

Figure 5 Patients with AAAs > 55mm and excluded from operative treatment in HUH in 2000–2010. Modified from Noronen et al. 2013 with permission.

Over the study period, the preoperative evaluation system changed into a more organised assessment by the preoperative clinic established in 2005. Prior to that, 37.9% of the excluded patients were evaluated by an internist, but the exclusion decision was mostly based on a vascular surgeon's opinion, whereas later 61.6% of the patients underwent an evaluation at the preoperative clinic and the decision was reached in co-operation with an anaesthesiologist and an internist. The reasons for exclusion are presented in Table 7. The suitability for EVAR was analysed for 82.5% of the patients, 22.3% of whom were found suitable.

After the exclusion decision, the patients were followed until the end of 2012, yielding a median follow-up time of 18 months (2 days–6 years and 7 months). Mortality among the study population was high; the overall survival was 22.1%, and the larger the aneurysm, the shorter the survival.

Table 7 The reasons for exclusion from operative care. Modified from Noronen et al. 2013 with permission.

Reasons for exclusion (%)	55-60mm	61-70mm	>70mm
Cardiorespiratory condition	39.2 %	43.8 %	17.4 %
Malignancy	5.1 %	8.8 %	8.7 %
Overall condition	26.6 %	24.6 %	47.8 %
Patient's choice	22.8 %	19.3 %	21.7 %

Of the patients who died during follow-up, 33% died of aneurysm rupture. Across the size groups, RAAA was the most common cause, accounting for 42%–44% of the deaths (Figure 6).

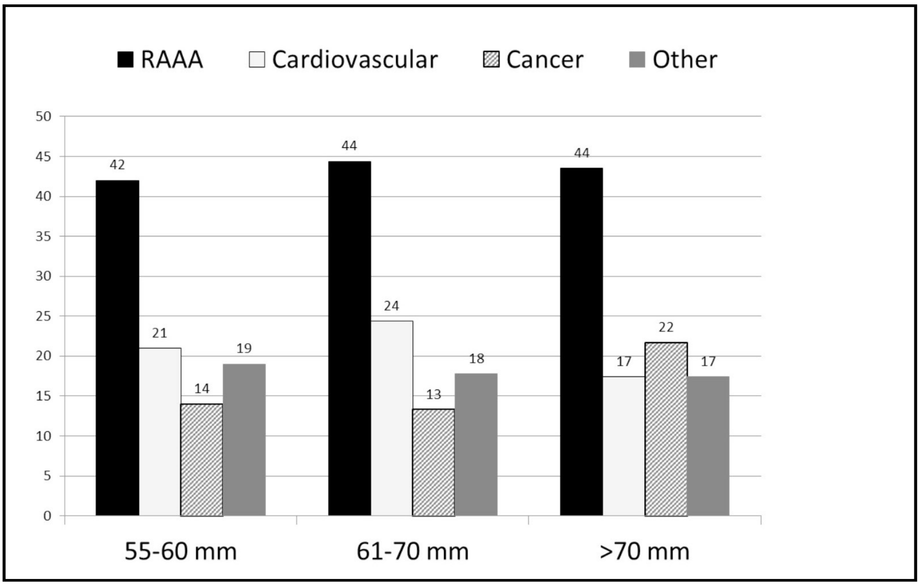

Figure 6 The causes of death for the 120 patients who died during follow-up. Reproduced from Noronen et al. 2013 with permission.

In this study, the overall autopsy rate was 23%. For RAAA deaths, the autopsy rate was 35%, and 41% of them were confirmed in hospital with ultrasound or CT. (Figure 7) Death certificates for the rest of the deceased patients were reviewed and, accordingly, the causes of death were classified as either likely to be accurate or not certain.

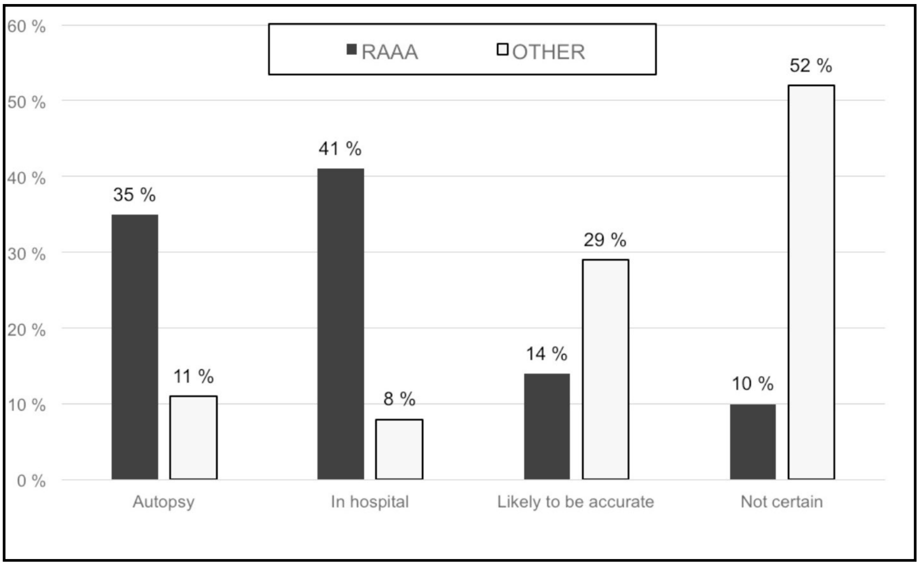

Figure 7 The determination of causes of death for RAAA (n=51) and other (n=65) causes. Reproduced from Noronen et al. 2013 with permission.

During the median follow-up of 19 months ranging from 2 days to 6 years and 7 months, 56 (36.4%) aneurysms ruptured. Twelve patients underwent emergency repair at the time of aneurysm rupture and of those, 5 survived the 30-day postoperative period. (Figure 8)

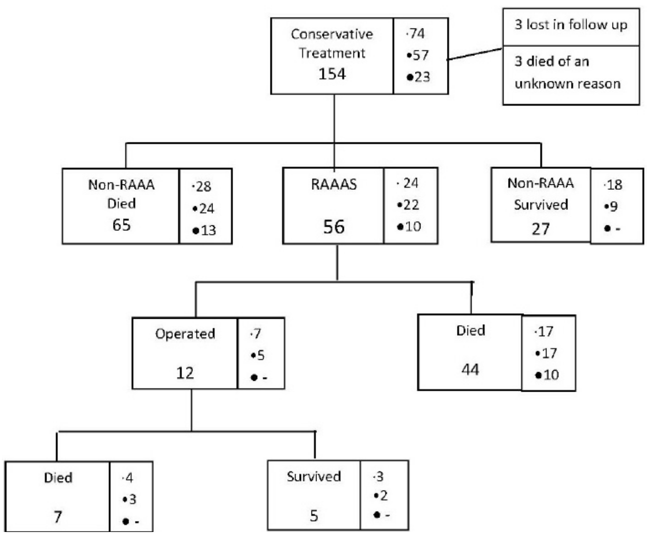

Figure 8 The outcome of the patients treated conservatively in HUH in 2000–2010. Modified from Noronen et al. 2013 with permission.

4 ANALYSIS OF THE ELECTIVE AAA TREATMENT PROCESS (IV)

For the 361 patients with AAAs meeting the treatment criteria, the first visit to the vascular outpatient clinic took place in a median of 12 (0–176) days after the referral. The treatment decision was made for 26.1% of the patients instantly, and the rest were referred to further preoperative evaluations. Evaluations by an anaesthesiologist and internist were the most common, the others including a cardiologist's consultation for 27.1%. The patients for whom EVAR was planned had more preoperative assessments – 44.8% of them had more than 2 assessments, while this was the case for 31.7% of the patients assigned to OR.

The median time from referral to surgery was 101(IQR: 53–159) days for all cases, 98(IQR: 52–159) days for OR and 110(IQR: 63–156) days for EVAR. For the aneurysm size groups – <60mm, 61-70mm and >70mm – the delays from referral to surgery were 112 (IQR: 79–225) days, 91 (IQR:52–119) days and 46 (IQR: 26–65) days, respectively. (Figure 9)

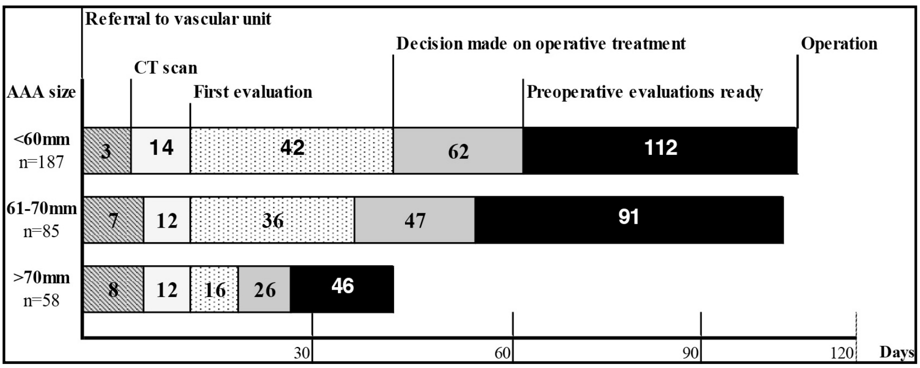

Figure 9 The cumulative median delays in 2005–2010 for AAAs according to size. Modified from Noronen et al. 2015 with permission.

The target time of 1 month from decision on operative treatment to surgery was reached for 58% (n=72) of the patients undergoing OS and 45% (n=27) of those undergoing EVAR. The 3-month target was achieved for 52% (n=48) and 63 % (n=33), respectively. The patients (n=129) exceeding the intended target times were analysed more closely. For the majority (77%) of them, no reason for the delay could be determined.

There were 11 patients whose aneurysms ruptured during the preoperative period, yielding rupture rates of 2.7% (5/187) for aneurysms of < 60mm, 3.5% (3/85) for aneurysms of 61–70mm and 5.2% (3/58) for aneurysms of >70mm during a median follow-up of 70(38–1190) days (Figure 10). Five patients died of a RAAA without an operation, six patients underwent an emergency operation, and two survived the operation, resulting in 2.5% (9/361) preoperative rupture-related mortality. An emergency operation was also performed for 17 further patients due to a symptomatic aneurysm (n=12), an aneurysm diameter of 85–120mm (n=3), acute limb ischaemia (n=1) and a suspicious CT finding (n=1). They all survived the emergency operation. The 30-day post-operative mortality was 3.6% for OR and 1.8%for EVAR.

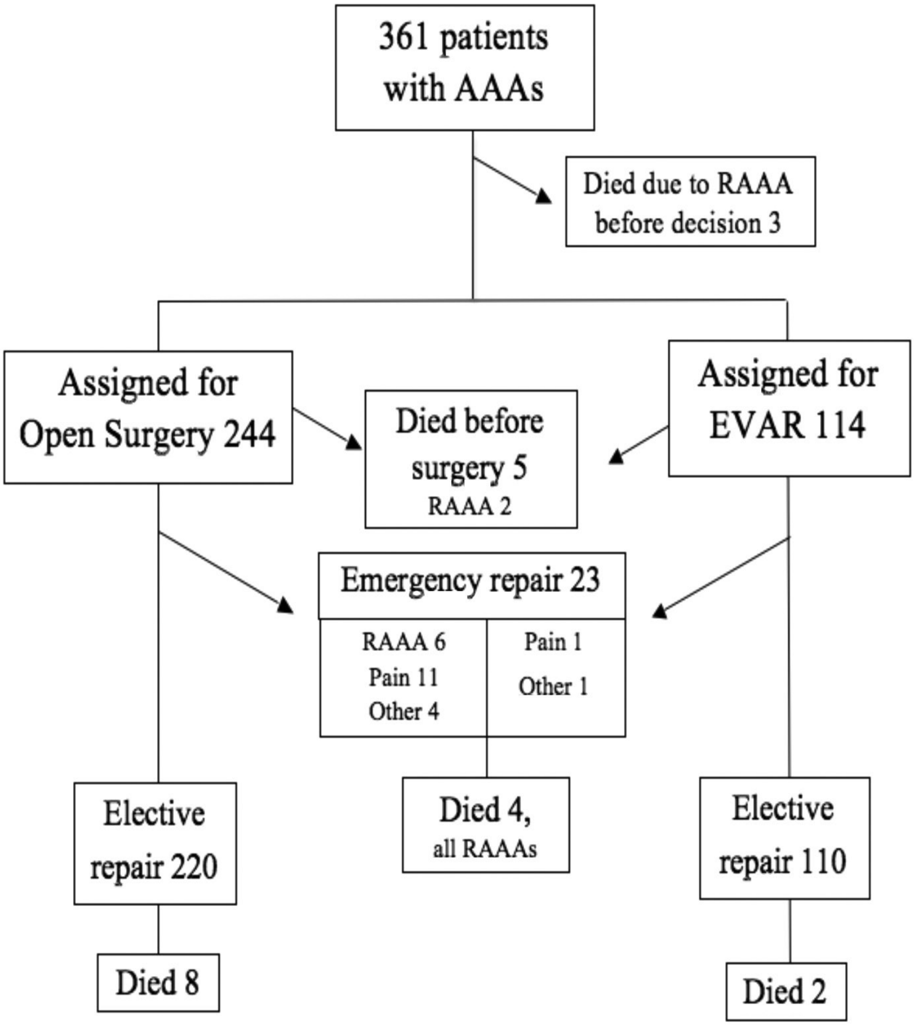

Figure 10 The outcome of 361 patients with large AAAs in HUH in 2005–2010. Modified from Noronen et al. 2015 with permission.

DISCUSSION

LIMITATIONS OF THE STUDY

Investigating delay in surgical treatment is largely limited by the lack of a possibility to engineer a study in prospective settings, for deliberately causing delay or withholding treatment from patients threatened by stroke, amputation or death would be highly unethical. Hence, all the studies (I–IV) are retrospective with a common goal: to learn from the past for the benefit of the future.

Certain additional limitations concerning the study design, data collection and outcome analysis are recognised. Patients with symptomatic carotid stenosis undergoing CEA were not compared to patients possibly denied CEA or assigned to BMT, for these patients were not considered in the study design (I). Collecting data on ulcers and analysing the wound healing retrospectively presents a challenge and, unavoidably, some of this data is missed (II). In the analysis of unfit patients with an AAA, no definite exclusion criteria existed and, for most of them, the decision was based on multiple co-morbidities (III). In all natural history studies, as in study III, a common limitation is the inaccuracy of the causes of death. Death certificates provided the information for 56% of the deceased as there were no hospital records or an autopsy confirming the diagnosis. Most of these uncertain causes had been documented as not aneurysm-related, including six death certificates proclaiming coronary deaths but still describing the typical symptoms related to a RAAA. Therefore, the number of aneurysm-related deaths might be underestimated, and no conclusions can be drawn for the other causes of death.

In the assessment of elective AAA treatment, the conclusions drawn from the analysis on reasons for delay are bound to be based partly on speculation since for 77% of the patients, the reason for delay could not be specified from the patient records (IV).

ESTABLISHING DELAY

Delay in the treatment of vascular patients can lead to higher morbidity and mortality. Therefore, investigating and knowing whether a delay exists is, or at least ought to be, of utmost importance in units performing vascular surgery. In order to improve the treatment process by decreasing delay, it is necessary to first establish the existence of delay.

When this study commenced, a delay had been established for carotid surgery by Vikatmaa et al. (2011), but not for patients with DFUs or AAAs. Areas for improvement were discovered for all three patient cohorts. For carotid patients, the delay had shortened significantly after the organisational changes made in 2009. The pre-hospital delay still played a major role in the delay, even if patients referred to HUH on an emergency basis now reached the two-week target time from symptom to surgery with a median of 13 days as opposed to the 31 days in the previous report.

For patients with DFUs, the delay from referral to revascularisation was discovered to be too long, with a median of 43 days. The in-hospital delay of 28 days was a notable finding, as was the 9 days from referral to first evaluation.

The delay from referral to AAA repair depended on the size of the aneurysm in accordance with the risk of rupture. Patients with the largest aneurysms were treated the fastest in a reasonable time, but the aneurysms of ≤ 60mm had a fairly long delay, with the in-hospital delay constituting most of the delay.

CAUSES OF DELAY

Determining the causes behind the delays is a complex task. Patient-related factors have been suggested to influence the delay the most (Dombrowski et al. 2015) in carotid patients as well as patients with DFUs (Yan et al. 2013), but rarely in the case of large AAAs. Patient-related delay is also the most difficult part of the delay to manage, for it requires co-operation and motivation from the patient.

For the in-hospital delay, the causes were fairly similar in carotid surgery and elective AAA repair (Table 6).

Table 8 Reasons for the longest delays among symptomatic carotid and AAA patients.

Reasons for long delays	Carotid surgery (n= 32)	AAA repair (n=129)
No specific reason	48 %	77 %
Other illness	15 %	14 %
Staff shortage/cancellation	15 %	1 %
Delay prior to surgical delay	12 %	1 %
Complication on operating day	3 %	4 %
Patient’s choice	3 %	1 %
Classification error	3 %	1 %

The preoperative evaluations for AAAs were not associated with the longest delays, contrary to what was somewhat expected as open surgery requires thorough investigation of patient’s overall condition. On the other hand, EVAR may require further analysis of the aneurysmal morphology and sometimes also custom-made devices. For most patients, 48% of the carotid and 77% of the AAA patients, no obvious reason for the delay could be determined, implying the underlying lack of resources, i.e. operating times and also an attitude that the scheduled time was considered satisfactory to the patient and the surgeon even if it surpassed the intended target time.

The long in-hospital delay in the treatment of DFUs included approximately 2 weeks for the imaging and decision-making and nearly 3 weeks from decision to revascularisation. Imaging delay was mainly caused by the limited availability of MRA. Like for the majority of the carotid and AAA patients, no specific reason was also found for diabetic patients in regard to the waiting time between decision and revascularisation, implying the unavailability of elective times in the operating room or angiography suite.

CONSEQUENCES OF DELAY

The consequences of a delay in the treatment process vary among the vascular patients with symptomatic carotid stenosis, DFUs or AAAs. Nevertheless, they all share the fear of a grave outcome arising from the delay: stroke for patients with symptomatic carotid stenosis, amputation for patients with DFUs and death due to rupture for patients with large AAAs.

Of the symptomatic patients with carotid stenosis, 14% had a recurrence or progression of ischaemic symptoms, including one minor stroke progressing into a major stroke, which can be considered as consequences arising from the delay, even if ten of them occurred within one week and the median time from symptom to surgery for all patients with a recurrence was 11 days. Of the CEAs, 8.3% were performed on an emergency basis due to the lack, or suspected lack, of available operating times, a figure that would probably have been higher had the surgeons been more meticulous in placing patients on the emergency operation waiting list whenever an available time within two weeks was not found.

Due to the rapid deterioration of the ischaemic diabetic foot with an ulcer, the delay often translates into emergency procedures. Indeed, 12% of our patients were assigned in the first visit to emergency revascularisation, reflecting the pre-hospital delay, and 6.5% while waiting for elective treatment as a sign of the in-hospital delay. There was no difference in limb salvage for patients with diabetes undergoing emergency procedures compared to elective revascularisations, though the small number of these patients diminishes the meaning of this finding. One of the original aims of study II was to evaluate the success of the intended treatment in relation to the delay. However, performing such an evaluation proved too difficult a task and reliable results were impossible to obtain mostly due to the heterogeneous presentation of the arterial disease and alternating expectations on the revascularisation at the time of the decision. Many centres, including ours, advocate the "endovascular first" strategy (Garg et al. 2014, May et al. 2014, Katib et al. 2015), according to which ET is assigned as the first treatment even when success seems unlikely, especially for elderly patients with co-morbidities raising the risks involved with open surgery. For patients with DFUs, the ET failure rate resulting in OS was a notable 21%, with no statistically significant difference compared to patients with no diabetes.

Delay from referral to revascularisation was associated with inferior limb salvage for patients with DFUs ($p<0.001$), underlining the importance of rapid revascularisation. When the delay before revascularisation was less than 2 weeks, including emergency procedures, there was no difference in the outcome between patients with and without diabetes. The diabetic foot is often compromised by infection and neuropathy, both of which potentially contribute to the inferior outcome. In a prolonged delay, the tissue lesion and infection may progress silently, whereas without neuropathy, the patient usually notices the deterioration and seeks help urgently.

The consequence of delay in the treatment of AAAs may be fatal. During the treatment process of large AAAs (IV), there were 11 (3.0%) aneurysm ruptures, three before the final decision on treatment and 8 while waiting for the operation. The annual risk of rupture varied between 3.0% (95%CI 1.2–6.4%) for the aneurysms of <60 mm and 39.7%(95%CI 28.1–52.5%) for the aneurysms of >70 mm, which is in line with previous publications (Lederle et al. 2002, Brown et al.2003). The fate of patients deemed unfit for elective repair supports this as the overall rupture rate was high: 32.4% for aneurysms of 55–60mm, 38.6% for aneurysms of 61–70mm and 43.5% for aneurysms of >70mm (III). Aneurysm rupture was also the most common cause of death in all size groups. Considering the generally low autopsy rates, such as the 23% in study III, the achieved 76% accuracy for RAAA mortality can be conceived as a notable accomplishment rarely attained in studies addressing the rupture and mortality risk of AAAs.

While waiting for elective AAA repair, 6.4% of the patients underwent an emergency operation, suggesting that the intended schedule for the operation was not adequate (IV). Emergency operations for intact as well as ruptured AAAs are associated with higher perioperative morbidity and mortality (Leo et al. 2005, Mani et al. 2011), which was confirmed in study IV with 17.4% mortality after an emergency operation and 66.7% mortality after a RAAA operation. During the study period, EVAR was not routinely performed on an emergency basis in HUH, but today it is the method more commonly used and expectations are high on the improved prognosis of RAAAs in the future.

DECREASING DELAY

In carotid surgery, the changes in our own system resulted in a substantial decrease in the in-hospital delay with a median of 19 days from symptom to surgery and 37% of patients being operated on within 2 weeks, a result that can be considered commendable. Since then, no further follow-up studies have been reported, but the conception is that well past 50% of the symptomatic patients with carotid stenosis are currently operated within 2 weeks, since if an elective time is not available, the patient is put on the waiting list for an emergency operation within 48 hours. Hence, out of all vascular emergency procedures, CEA has become one of the most frequently performed. While certainly not a favourable outcome, it is, with today's resources, the only option in order to reach the two-week target time. Challenges can be expected if the aim is set on operating even sooner, as has been suggested by the UK National Stroke Strategy guidelines with a goal to operate within 48 hours. In the current study, this would have prevented 10 of the recurrent or fluctuating symptoms and, possibly, the one progression from minor to major stroke occurring on the second day after the index symptom. Before we start assigning all symptomatic carotid patients to expedited surgery, the contradictory results of previous reports for (Sharpe et al.2013) and against (Stromberg et al. 2012) urgent CEA should be kept in mind. The potential means to distinguish the patients at greatest risk for recurrent symptoms and stroke ought to be explored, even if the possibilities at present are limited. Perhaps, in the years to come, with the aid of risk assessment tools such as the ABCD3 score and novel imaging methods, the distinction will become clearer. In addition, to achieve better results on operating delays, public awareness needs to be improved, a task unfortunately proven difficult (Hodgson et al. 2007). In Finland, campaigning for the recognition of cerebrovascular incidents has been launched by the Finnish Brain Association.

For DFUs, the pre-hospital delay also has an important role. Educating patients with diabetes on daily check-ups is important, as is foot care by a podiatrist. Whenever tissue loss is detected, vascular evaluation by the primary care physician is needed. The guideline by the IWGDF to wait 6 weeks of healing assumes that the need for urgent care due to ischaemia or an infection is ruled out by primary care measures. Underlying ischaemia, however, is not that easily detected due to the insufficient information provided by the non-invasive methods. (Brownrigg et al. 2015) Therefore, 6 weeks of waiting seems rather long in the light of the results of the current study II. The NICE guideline of evaluation within in 48 hours seems sensible in order to initiate the investigations rapidly, for in HUH the median delay from referral to first evaluation was a median of 9 days. The imaging mostly relied on MRA, whose availability is unfortunately limited, hence the two-week delay between the first visit and decision on treatment. If MRA was more accessible, the decision could certainly be reached sooner, ideally at the first visit if imaging was scheduled and performed according to the referral. An attempt to improve this imaging delay has already been made in HUH after the current study period, with 2 time slots a day twice a week reserved for MRA the same day as the first visit of ulcer patients with critical limb ischaemia. However, these 4 times a week are not even close to covering all patients with ischaemic ulcers. Results are yet to be established regarding the effectiveness of this reformation, but, unfortunately, the initial perception is that it does not cover the patients who benefit from the immediate imaging the most, mostly due to the inadequate information in the referrals. DFUs are generally regarded as their own entity, and the poor wound healing and prognosis are well recognised according to previous studies (Roghi et al. 2001, Söderström et al. 2013). Whenever possible, the aim for DFUs has been rapid diagnostics and imaging, and after the results of the current study undoubtedly even more so. In 2015 a reception for DFUs by a multidisciplinary team including vascular and plastic surgeons, and a diabetologist, have been moved from diabetology to vascular surgery in order to increase the number of patients reached with this specialised team.

In the treatment of AAAs, after the results of study IV, we re-assessed the target times observed during the study period and set goals for the entire preoperative period from referral to surgery: 3 months for aneurysms of <60mm, 2 months for aneurysms of 61–70mm and 1 month for aneurysms of 70–90 mm. Aneurysms of >90mm in size are operated on an emergency basis. Including the time prior to the final decision on operative treatment is important in order to guarantee treatment in a time with reasonable risks, for the longer the delay prior to AAA repair, the more likely is rupture to occur (III, IV). For the unfit patients, the exclusion from elective AAA treatment can be considered as a lethal decision, but for 5 patients in study III, this was not the case. At the time of rupture, they survived emergency repair, resulting in a surprising 41.7% survival rate, comparable to all RAAA operations, even if these patients were already considered unfit for elective procedure. Since the study, EVAR has become the more common procedure overall, in both elective and emergency settings. The perioperative risks are therefore lower, especially when most of the procedures are performed under local anaesthesia. The intention is also to make the decision on abstaining from operative treatment jointly with the different specialists and the patient.

DELAY IN THE FUTURE

The prevalence of vascular disorders such as carotid stenosis, peripheral arterial disease and aortic aneurysms all increase with age, as does the prevalence of diabetes. The diagnostics are also constantly evolving, leading to more patients being diagnosed. Inevitably, we will have more patients to treat. The resources for treatment, however, are not likely to proliferate at the same pace. Therefore, prioritising and patient selection will become necessary. Both are tedious tasks, but should already be considered today.

Prioritising should be primarily conducted within the patient cohorts with the following goals in mind: Distinguishing the carotid patients at the highest risk of recurrent symptoms and stroke, prioritising the patients with diabetes in diagnostics and treatment amongst patients with limb ischaemia and tissue loss, and, for AAA patients, ensuring that operating dates are assigned according to the size of the aneurysm, waiting time included.

Prioritising is strongly linked with the timing of treatment. Deciding who needs to be treated first requires the comprehension of optimal timing for each patient. According to the current thesis, the optimal times to treat the patients being discussed are: 2 weeks from the symptom for patients with symptomatic carotid stenosis, 2 weeks from the first visit for patents with DFUs and 1–3 months from referral for patients with large AAAs.

When deciding on the order patients are treated in, ideally only patients requiring the same procedure are compared. Seldom does anything constructive arise from comparing CEA to lower limb bypass, i.e. debating on whether a patient who had a TIA a week ago or one with a DFU should be operated first, nor is the decision based on evidence. Unfortunately, the described situation is where we currently, but hopefully not permanently, often find ourselves in when faced with the mounting emergency operating lists due to the lack of available elective times. In such a situation, the decision is reached by considering the disease-specific aspects as well as the patient's condition and capacity to wait. For all patients, it is also important to consider the treatment altogether, mainly when the overall condition of the patient is severely compromised. The sometimes difficult but best decision for the patient is to withhold surgical treatment. The complexity of this decision is well-described by the old proverb, "Good surgeons know how to operate, better ones when to operate, and the best when not to operate."

The importance of timing for three major patient cohorts in vascular surgery is established in the current thesis. As a noteworthy observation, the timing of vascular procedures is demonstrated to depend on several matters, starting with the patient and the caring physician, but also ranging from the availability of diagnostics and reception times at the outpatient clinic to the capacity in the operating room and the ward. Furthermore, an important conclusion arising from this thesis is the vascular surgeons' limited power to decrease the delay alone. Communication and collaboration between specialities involved in the patient's care in order to manage the in-hospital delay is fundamental. And lest we forget, the timing of treatment is not the only thing affecting the patient's outcome. The patient's pre-existing condition and the professional skills of the personnel at each step of the treatment process are all as important. Therefore, timing is not everything, but it is a vital thing.

CONCLUSIONS

1. In-hospital reforms facilitate decreasing the delay for patients with symptomatic carotid stenosis. Emergency evaluation leads to the best results, and minimising the pre-hospital delay is therefore required to meet the current guidelines.
2. For patients with DFUs, revascularisation should be organised rapidly once ischaemia is confirmed, preferably within two weeks.
3. Aneurysm rupture is a significant cause of death among patients determined unfit for surgery regardless of the size of the aneurysm.
4. Establishing guidelines for the timing of elective AAA repair is important, as is evaluating the fulfilment of these guidelines in order to avoid aneurysm ruptures while waiting for treatment.

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