Abdominal Aortic Aneurysms

Pharmacoepidemiological Studies

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THE THREE ORIGINAL PAPERS ARE

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II. Wemmelund H, Høgh A, Hundborg HH, Johnsen SP, Lindholt JS. Preadmission use of renin–angiotensin blockers and rupture of abdominal aortic aneurysm: a nationwide, population-based study. Pharmacoepidemiol Drug Saf 2016; 25:141-50.
III. Wemmelund H, Jørgensen T, Høgh A, Behr-Rasmussen C, Johnsen SP, Lindholt JS. Low-dose aspirin and rupture of abdominal aortic aneurysm. J Vasc Surg 2017;65:616-25.

INTRODUCTION

ABDOMINAL AORTIC ANEURYSM

Abdominal aortic aneurysm (AAA) is a common disease in the elderly. The prevalence of AAA has been reported to be between 1-5% among men above 65 years and increases with age[1-6]. AAA is 5-6 times more prevalent in men than in women[7,8].

AAA is characterized by a bulging or enlargement of the abdominal aorta. No rigid definition exists, but common definitions include an enlargement of the infrarenal aorta to a diameter of 3.0 cm or a 50% increase in diameter relative to the suprarenal aorta[9,10]. AAA is most often asymptomatic and is commonly discovered as an incidental finding when a patient is under investigation for other diseases. The major risk of having an AAA is sudden rupture, resulting in death due to massive hemorrhaging. The risk of rupture is closely related to the AAA diameter, with a substantial increase in risk of rupture when the diameter exceeds 5.5 cm[11-13]. Women have an up to 4-fold higher risk of ruptured AAA (rAAA) than men[14].

At present, the definitive treatment for AAA is either open surgical or endovascular repair. When a small AAA (< 5.5 cm) is detected, the current practice is to watch and wait, i.e., enroll the patient for imaging surveillance of the AAA until the risk of rupture and subsequent complications equals or exceeds the risk of the complications of elective treatment. The average growth of an AAA depends on its size and has been reported to range between 2-5 mm/year in AAAs smaller than 5 cm[15]. Elective repair is recommended when the aneurysm reaches a size of 5.5 cm (women: 5.0 cm), or earlier if the aneurysm has a growth rate at or above 1.0 cm per year[16].

In 2012, the 30-day mortality in Denmark after elective surgical repair for AAA was 4% (95% confidence interval (CI): 2-7%), whereas the 30-day mortality rate after surgical repair for rAAA was almost 10-fold higher, 33% (95% CI: 30-36%)[17]. Consequently, it may seem rational to systematically search for patients with AAA and offer repair before rupture occurs. National AAA screening programs have been implemented in Sweden and in the UK. In Denmark, a national screening program has been proposed but has not been implemented[18].

AAA DEVELOPMENT

The mechanisms of AAA development are complex and have been extensively studied. Still, the exact mechanisms that lead to aneurysmal development, growth and, ultimately, rupture, are not fully understood. AAA was long regarded an atherosclerotic manifestation; however, histopathological studies have revealed complex degrading and weakening processes of the aortic vascular wall. The relevant processes involve mural inflammation, neovascularization, matrix degradation, and thrombus formation.

Inflammatory cells found in the aortic wall are thought to migrate from the aorta and from neovascularization of the media. These cells, as well as local smooth muscle cells and fibroblasts, in the media and adventitial layers promote proteolytic destruction of the aortic wall, resulting in a loss of normal aortic elasticity and tensile strength. Matrix metalloproteinases and plasmin synthesized by infiltrating inflammatory cells and macrophages are believed to be crucial in the degradation of elastin and collagen in the connective tissue matrix of the aortic wall. In the majority of patients with an AAA of ≥ 4.0 cm, the AAA is associated with the development of an intraluminal or mural thrombus. The thrombus is biologically active, promotes activation of platelets and inflammatory factors and has been suggested to be an active participant in further aneurysmal dilatation when the AAA and thrombus are established[19-25].

RISK OF RUPTURE

Risk is traditionally understood as “the possibility of something bad happening at some time”[26]. In the context of medicine, risk is defined as the probability of developing a disease[27]. Throughout this thesis, the risk of rAAA is defined as the risk of presenting with a rAAA in contrast to the risk of presenting with an intact AAA on hospital admission.

A risk factor is a characteristic associated with an increased risk of developing a disease[27]. Risk factors for the development of an AAA include both unmodifiable and modifiable factors. Unmodifiable risk factors include race, male sex, increasing age, cardiovascular disease, a history of tobacco smoking, and a family history of AAA. Potentially modifiable risk factors comprise current tobacco use, overweight, hypercholesterolemia, atherosclerosis, and hypertension. Diabetes is negatively associated with the risk of AAA and therefore seems somewhat protective[28-30].

The predominant predictor for rAAA is, as previously mentioned, the size of the AAA, with a substantial increase in risk of rupture when the AAA reaches a diameter of 5.0 cm for women and 5.5 cm for men (Table 1)[14,21,31]. The risk factors for rAAA are generally unmodifiable, i.e., female sex, advanced age (>80), a family history of AAA; however, other factors include current smoking, renal failure, and high blood pressure[12,32-34].

Table 1. *12-month AAA rupture risk by diameter. Adapted from Moll et al., Eur J Vasc Endovasc Surg, 2011*[31]

AAA Diameter (mm)	Rupture Risk (% / year)
30-39	0
40-49	1
50-59	1.0-11
60-69	10-22
> 70	30-33

PROGNOSIS AFTER RUPTURE

Prognosis is the prediction of the outcome of a disease[27]. Throughout this thesis, prognosis is considered as the short-term outcome after rAAA, i.e., the 30-day mortality or the 30-day case fatality. Prognostic factors are characteristics or conditions related to the outcome.

In Denmark, an overall 30-day mortality rate of 75% has been reported for patients with a hospital diagnosis of rAAA[35]. However, the true 30-day mortality for rAAA is unknown given that probably fewer than 50% of patients survive to reach the hospital[36]. Consequently, a very important prognostic factor when experiencing a rAAA is the ability to reach the hospital alive, which again depends on a variety of other factors, including anatomic location of the rupture, clarity of symptoms, prehospital emergency capabilities, geographical distance to the hospital and infrastructure.

Inherent patient-related prognostic factors include not only age and sex but also the overall preadmission comorbidity. In elective AAA surgery, advanced age, female sex, compromised cardiopulmonary status and renal function have been suggested to be associated with a worse prognosis[37]. The same factors may influence the prognosis after rAAA. In-hospital or perioperative prognostic factors include aneurysm morphology, hemodynamic stability, coagulation status and advanced postoperative intensive care capabilities, among others [38].

BACKGROUND AND EXISTING LITERATURE

STATINS

Statins, or 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, are a class of lipid-lowering drugs. Their primary mechanism of action is the inhibition of the rate-limiting enzyme, HMG-CoA reductase, in the endogenous biosynthetic pathway of cholesterol (i.e., the mevalonate pathway). In this way, statins lower,in particular, the production of LDL-cholesterol[39]. However, the mevalonate pathway provides substrates for intracellular processes throughout the human organism. These processes involve intracellular signaling, growth mediation and cellular differentiation. As statins partially inhibit this pathway, statin therapy has been suggested to exert effects beyond cholesterol lowering. These so-called pleiotropic effects include enhanced endothelial function and attenuation of both vascular wall inflammation and atherosclerosis[40,41].

The first statins were introduced in the late 1980s, but wide implementation of statin therapy into clinical practice was not instituted until the mid-1990s. By this time, large and well-designed randomized controlled trials (RCTs) had proven statins to be both safe and highly effective in reducing LDL-cholesterol and also effective in reducing major cardiovascular events (i.e., myocardial infarction, need for coronary re-vascularization and cardiovascular death)[39,42-44].

Today, statins are indicated for hypercholesterolemia and both the primary and secondary prevention of coronary heart disease. However, indications and recommendations for statin use have widened to encompass documented cardiovascular diseases, including AAA[31,45]. In Denmark, statins are available by prescription only.

Statins and AAA

In rodent studies, statins have been suggested to attenuate AAA growth by reducing matrix degradation in the vascular wall of experimentally induced AAAs[46,47]. These findings led to a number of studies investigating the potential effect of statins on AAA growth in humans. A summary of the existing literature on growth and rupture as well as the search strategy is provided in Table 2.

In trauma-related hemorrhagic shock, severe sepsis, and noncardiac surgery, preadmission statin use has been associated with lower mortality[48-51]. Likewise, statins have been suggested to play a role in improving the outcome after rAAA repair. Table 3 provides a summary of the literature examining the association between statin use and mortality after repair for AAA or rAAA. The table includes three studies on the association between statin use and mortality after elective surgery and one study on the mortality after rupture and emergency surgery.

Limitations of the literature on statins and AAA

Studies on the association between statin use and rAAA are sparse. In our review, we were only able to identify one study[34] with published data on this association, published after Study I. However, several studies investigated the association between statin use and AAA growth[52-63]. All of the identified studies were observational studies, and the majority of these were based on prospectively registered data. None of the three large growth studies (i.e., N > 500) found an association between statin use and AAA growth[52,56,57], whereas the relatively large study on statin use and rAAA[34] found a reduced risk of rAAA.

Generally, the studies were small and, except for two studies, limited to observations from single centers. This potentially limits

external validity given that the study populations may not be representative of the general population of patients with AAA. Seven of the 12 studies did not consider the effects of statin use as the main study objective; thus, the findings are secondary[34,52,55,57-59,61]. Four of the studies relied on patient self-reporting when statin use was defined, leaving a potential for recall bias[53,54,61,63]. In five studies, the definition of statin use was rather unclear and, consequently, the results were difficult to compare[52,58-60,62]. Additionally, four of the studies only presented univariate estimates, with a potential for substantial residual confounding of the results[55,59,60,62]. A meta-analysis by Sweeting and colleagues[64], not identified in the literature search, was based on analyses of individual data from several published and unpublished AAA surveillance studies. These studies were not individually designed to examine the influence of drug use on AAA growth and risk of rAAA. Nevertheless, six of the included studies (N=4,621) had data on the association between statin use and AAA growth (and, to a lesser extent, the risk of rAAA), but no association between the use of statins and AAA growth or the risk of rAAA were found.

The literature on short-term mortality after rAAA is even more limited. We only identified one small, single-center study concerning in-hospital mortality after rAAA[65]. This study was limited primarily by its size; however, unclear reporting of statin exposure and restrictive inclusion criteria also limited the external validity of the study. The remaining studies investigated 30-day mortality after elective aneurysm repair and are, as such, unfortunately not comparable[66-68]. Still, these latter studies were included in the review as containing the best available knowledge in the field.

Table 2. *Summary of literature; the effect of statins on AAA growth and rupture risk*

Author, year, country	Study design	Study population	N	Exposure	Outcome	Results	Comments
Lederle et al., 2015, USA[52]	Cohort Prospective data	Multicenter 1994-2010	2,428	Statin use n=1,013 (42%)	AAA-growth	Multivariate estimated difference in growth rate (mm/year): 0.1 (95% CI: -0.2;0.5)	Propensity score matched cohort. Unclear statin exposure.
Gokani et al., 2015, UK[34]	Case control Prospective data	Single-center 2004-2010	983	Statin use n=226 (23%)	AAA-rupture	Rupture risk: Adjusted OR: 0.50 (95% CI: 0.32;0.77) for statin use compared to no statin use	No data on concomitant drug use.
Periard et al., 2012, Switzerland[53]	Cohort Prospective data	Single-center 2000-2007	94	Statin use n=50 (53%)	AAA-growth	Mean AAA-growth (mm/year): Statin: 2.91 (95% CI: 2.33;3.49) No-statin: 4.37 (95% CI: 3.35;5.39) Multivariate estimated difference in growth rate (mm/year): -1.06 (95% CI: -2.17;0.04)	AAA-definition > 25 mm. Overall high growth rate.
Karrowni et al., 2011, USA[54]	Cohort Retrospective data	Single-center 2001-2005	211	Statin use n=136 (64%)	AAA-growth	Median AAA-growth (mm/year): Statin: 0.9 (iqr: -1.0;1.0) No-statin: 3.2 (iqr: 2.0;4.9), p<0.0001 Adjusted mean change in diameter (%/year): Statin: -0.7 (95% CI: -2.8;1.5) No-statin: 7.5 (95% CI: 5.4;9.6)	Mean follow-up: 1 year. Different imaging modalities. Alternative reporting (%/year).
Badger et al., 2011, UK[55]	Cohort Retrospective data	Single-center 2005-2006	143	Statin use n=92 (64%)	AAA-growth	Average growth rate (%/year): Statin: 4.5 No-statin: 7.5, p=0.005	Alternative reporting (%/year). Univariate analysis.
Ferguson et al., 2010, Australia & NZ[56]	Cohort Prospective data	Multicenter Median follow-up: 5 years	652	Statin use n=349 (54%)	AAA-growth	Growth above median growth: Adjusted OR: 1.23 (95% CI: 0.86;1.76) for statin use compared to no statin use	Very small AAAs (mean diameter 33.2 mm). Incomplete medication history.
Thompson et al., 2010, UK[57]	Cohort Prospective data	Single-center 1984-2007	1,269	Statin use n=357 (28%)	AAA-growth	Multivariate estimated difference in growth rate (mm/year): -0.07 (95% CI: -0.45;0.32)	25 year cohort – historic change in prescription patterns.
Sweeting et al., 2010, UK[58]	Cohort Prospective data	Multicenter 1991-1995	1,701	Statin use n=21 (1.2%)	AAA-growth	Multivariate estimated difference in growth rate (mm/year): -0.90 (se: 0.55), p=0.106	Mean follow-up: 1.9 years.
Karlsson et al., 2009, Sweden.[59]	RCT	Multicenter 2002-2005	211	Statin use n=84 (40%)	AAA-growth	AAA-growth (mm/year): Statin: 1.6 No statin: 2.5, p=0.008.	Post-hoc analysis, primary exposure: Azitromycin. Univariate analysis.
Mosorin et al., 2008, Finland[60]	Cohort Retrospective data	Single-center 1993-2005	121	Statin-use n=34 (28%)	AAA-growth	AAA-growth (mm/year): Statin: 1.9 ±1.8 No-statin: 2.6 ±2.4	Data collection undescribed. Univariate analysis, residual confounding.

Author, year, country	Study design	Study population	N	Exposure	Outcome	Results	Comments
Schlösser et al., 2008, The Netherlands[61]	Cohort Prospective data	Single-center 1996-2007	147	Lipid-lowering drugs n=63 (43%)	AAA-growth	Univariate estimated difference in growth rate (mm/year): -1.2 (95% CI: -2.2;-0.19) Multivariate estimated difference in growth rate (mm/year): -1.2 (95% CI: -2.3;-0.06)	Unclear exposure definition (lipid lowering drugs dosage - estimated 98% statins).
Sukhija et al., 2006, USA[62]	Cohort Prospective data	Single-center	130	Statin use n=75 (58%)	AAA-growth	Statin use: Baseline: 4.6 ±0.6 cm Follow-up: 4.5 ±0.6 cm No-statin: Baseline: 4.5 ±0.6 cm Follow-up: 5.3 ±0.6 cm	Short report. Study design and aim not clearly specified. Unadjusted estimates.
Schouten et al., 2006, The Netherlands[63]	Cohort Prospective data	Single-center 2002-2005	150	Statin use n=59 (39%)	AAA-growth	Multivariate estimated difference in growth rate (mm/year): -1.16 (95% CI: -1.99;-0.33)	

Abbreviations: AAA, abdominal aortic aneurysm; CI, confidence interval; OR, odds ratio; HR, hazard ratio; iqr, interquartile range; se, standard error; RCT, randomized controlled trial.

Search strategy: Papers were identified in PubMed (only papers written in English and only including humans) using the following queries: ("Aortic Aneurysm, Abdominal"[Mesh] OR "aortic rupture"[mesh]) AND ("Hydroxymethylglutaryl-CoA Reductase Inhibitors"[Mesh]), (("Aortic Aneurysm, Abdominal"[Mesh]) AND ("expansion rate" OR "growth")) AND ("Hydroxymethylglutaryl-CoA Reductase Inhibitors"[Mesh]), and from searching ClinicalTrials.gov for "abdominal aortic aneurysm | Interventional Studies | expansion OR growth OR rupture". Additional relevant papers were identified in the reference lists of the included papers and from reviews on the topic. Last search: March 14, 2016.
Relevant PubMed.org hits: 9/112. Relevant ClinicalTrials.gov hits: 0/27. Other relevant papers: 4. Total number of papers reviewed: 9+0+4=13.

Table 3. *Summary of literature; the effect of statins on short-term mortality after rAAA*

Author, year, country	Study design	Study population	N	Exposure	Outcome	Results	Comments
McNally *et al.*, 2010, USA[66]	Cohort Retrospective data	Single-center 2004-2007	401	Statin use n= 181 (45%)	30-day mortality (or in-hospital) *after* elective OAR or EVAR.	30-day/in-hospital mortality rate: OAR: (n=228, 57%) Statin use: 0% No-statin: 5.9% (OR: 0.89, p=0.04) EVAR: (n=173, 43%) Statin use: 0% No-statin: 3.6% (OR: 0.21, p=0.02)	Research question not predefined; analysis based on multivariate analysis to identify possible covariates with an association. Unclear mortality definition.
Feeney et al., 2009, USA[65]	Cohort Retrospective data	Single-center 2000-2008	81	Statin use n=23 (28%)	In-hospital mortality *after* rAAA	In-hospital mortality rate: Statin use: 34.8% No-statin: 63.8%	Only ICU-admitted patients Mix of EVAR and OAR. No precise time frame. Univariate model.
Leurs et al., 2006, The Netherlands[67]	Cohort Prospective data	Multicenter 1997-2004	5,892	Statin use n=731 (12%)	30-day mortality *after* elective EVAR	30-day mortality rate: statin use: 1.5% No-statin: 2.6%	Incomplete follow-up. Univariate model. Multivariate model only for long-term survival.
Kertai et al., 2004, The Netherlands[68]	Cohort Retrospective data	Single-center 1991-2001	570	Statin use n=162 (28%)	30-day mortality or MI *after* elective OAR	30-day mortality or MI: Statin use vs. No-statin: Univariate model OR: 0.31 (95% CI: 0.13;0.74) Multivariate model: OR: 0.24 (95% CI: 0.10;0.70)	Composite endpoint.

Abbreviations: rAAA, ruptured abdominal aortic aneurysm; OAR, open aortic repair; EVAR, endovascular aortic repair; OR, odds ratio; MI, myocardial infarction; CI, confidence interval.

Search strategy: Papers were identified in PubMed (only papers written in English and only including humans) using the following query: ("Aortic Aneurysm, Abdominal"[Mesh] OR "aortic rupture"[mesh]) AND ("Hydroxymethylglutaryl-CoA Reductase Inhibitors"[Mesh]) and from searching ClinicalTrials.gov for "abdominal aortic aneurysm | Interventional Studies | mortality OR death OR survival". Last search: March 14, 2016.
Relevant PubMed.org hits: 4/112. Relevant ClinicalTrials.gov hits: 0/59. Total number of papers reviewed: 4+0=4.

RENIN–ANGIOTENSIN SYSTEM AND RENIN–ANGIOTENSIN SYSTEM BLOCKERS

The renin-angiotensin system (RAS) is an important endogenous hormonal system that regulates blood pressure in addition to the balance of salt and water in the body. Renin is an enzyme that is primarily excreted to the blood from the kidneys. Renin facilitates the cleavage of angiotensinogen (from the liver) to the inactive peptide, angiotensin I, which in turn is converted by angiotensin-converting enzyme (ACE) to the potent vasoconstrictor, angiotensin II. Angiotensin II exerts its vasoconstricting effect on the arterioles by binding to the angiotensin receptor (AT_1), thereby increasing the systemic blood pressure. Furthermore, angiotensin II regulates the release of aldosterone, which is responsible for salt and water retention[69-71]. The regulatory mechanisms of the RAS are complex; however, thorough coverage of this topic is beyond the scope of this thesis.

Drugs that block different pathways of the RAS are referred to as RAS-blockers and consist of a number of drugs. Among these compounds, angiotensin-converting enzyme inhibitors (ACE-inhibitors) and angiotensin II receptor type AT_1 blockers (ARBs) are the most important and, consequently, the RAS-blockers considered in this thesis.

ACE-inhibitors act by decreasing the production of angiotensin II by inhibiting the conversion of angiotensin I to angiotensin II. In contrast, ARBs likely exert a more direct action by blocking the binding of angiotensin II to the effector receptor, the angiotensin receptor (AT_1). The multiple effects of ACE-inhibitors and ARBs include blood pressure reduction, protection of the kidneys in diabetes and hypertensive disease, and improved systolic function in heart failure[69,70]. The survival benefits of ACE inhibitor and ARB treatment among patients with previous myocardial infarction and/or left ventricular dysfunction are well documented[72-78].

ACE-inhibitors were discovered in the late 1970s and ARBs in the mid-1980s. Both classes of drugs were introduced into clinical practice some 10 years later[71]. Their use has been growing ever since; however, the use of ACE-inhibitors has been decreasing slightly in recent years compared to ARB use, likely because of the more favorable profile of adverse effects of ARBs[79]. Today, RAS-blockers are indicated for the treatment of hypertension, heart failure and diabetic nephropathy. RAS-blockers are, like statins, available by prescription only.

RAS-blockers and AAA

Angiotensin II has been shown to promote AAA growth in experimental rodent models, and RAS-blockade has been shown to attenuate aneurysmal dilatation in mice[80-83]. Additionally, angiotensin II levels have been found to be higher in aneurysmal aortas compared to normal aortas in human aortic specimens[84]. Thus, RAS-blockers have been suggested to decrease AAA growth rates and the risk of rupture. Table 4 provides an overview of the existing literature and the search strategy used.

As RAS-blockers have shown to improve survival in patients with hypertension and heart failure, conditions that are prevalent among many patients with AAA, treatment with RAS-blockers may be associated with a better outcome after rupture. Table 5 summarizes the literature examining the association between use of RAS-blockers and 30-day mortality after repair for AAA.

Limitation of the literature on RAS-blockers and AAA

The association between RAS-blockers and AAA growth has been investigated in a number of studies[52,56-58,85-88]. The use of ACE-inhibitors was the predominant exposure and was investigated in all eight studies, with ARBs being examined in three studies. All of the studies identified in our literature review were observational studies based on prospectively collected data, except for one, with reported post hoc analyses from a RCT that primarily considered doxycycline and AAA growth[87]. Additionally, we identified two ongoing RCTs that are expected to report on the effects of an ACE-inhibitor (Perindopril)[89] and an ARB (Telmisartan) on AAA-growth [90]. The literature on the association between RAS-blockers and rAAA is, however, limited to a single large population-based study[91]. A large, Danish population-based study reported on the association between use of RAS-blockers and an alternative outcome, namely, the risk of surgery for AAA[85].

The results of the identified studies are not consistent. The large population-based case control study by Hackam *et al.* included more than 15,000 patients with AAA and reported an approximately 20% reduced risk of rAAA in current users of ACE-inhibitors[91]. Discontinuation of ACE-inhibitor use was associated with a small increased risk of rAAA. A multicenter study by Sweeting and colleagues reported an increased growth rate among users of ACE-inhibitors[58]. However, in the later meta-analysis on individual data from seven studies (N=4,826), Sweeting *et al.* reported no association between ACE-inhibitor use and the risk of rAAA or AAA growth[64]. The study on RAS-blockers and the risk of surgery for AAA reported a lower risk of surgery among ACE-inhibitor users, whereas ARB use did not yield any protective association[85]. Additionally, a single-center study reported reduced AAA growth in ARB users[57]. The remaining studies among patients with AAA did not report any association between the use of RAS-blockers and AAA growth.

Differences in design, exposure, and mode of outcome reporting make direct comparison among the studies difficult. A limitation in five of the studies was a different or unclear definition of RAS-blocker use (e.g., baseline use, “on ACE-inhibitors”, drug history, received medical therapy > 1 year)[56,58,86-88]. Four of the studies did not state RAS-blocker use as the primary exposure of interest, and the reported results were thus from sub-analyses[56,57,87,88]. As in the reviewed statin studies, three of the studies relied on self-reported drug use[58,86,88].

The examined outcomes have also varied between studies. The outcome of the Danish study[85], risk of AAA-surgery, was not directly comparable to the outcome of the other studies. A proportion of patients with large aneurysms, who are not considered fit for surgery due to either comorbidity or anatomical inability, would not be able to contribute risk to the outcome under the study. Thus, a selection bias toward a seemingly more favorable outcome could have been introduced. One study measured aortic diameters in non-AAA patients and found reduced infrarenal aortic diameters at baseline in patients on chronic RAS-blockade. Additionally, a tendency toward reduced aortic growth in patients on RAS-blockade was reported. However, these results may not be comparable to AAA growth in patients with AAA 86.
No studies on short-term prognosis after rAAA and the use of RAS-blockers were found during our literature review. Still, we identified two studies reporting on AAA-mortality (ACE-inhibitor or ARB use improved prognosis)85 and 30-day mortality after elective open aortic repair (RAS-blockade was associated with a

worse prognosis)92. Additionally, one of the aforementioned ongoing RCTs will report on AAA-related death89. However, these studies were only included in the review to illustrate the sparse data available within this area of research.

Table 4. *Summary of literature; the effect of ACE-inhibitors and ARBs on AAA growth and rupture risk*

Author, year, country	Study design	Study population	N	Exposure	Outcome	Results	Comments
Lederle et al., 2015, USA[52]	Cohort Prospective data	Multicenter 1994-2010	2,428	ACE-inhibitor use n=994 (41%) ARB use n=115 (5%)	AAA-growth	Multivariate estimated difference in growth rate (mm/year): ACE inhibitor use: 0,1 (95% CI: -0.3;0.4) ARB use: -0.2 (95% CI: -1.3;0.9)	Propensity score matched cohort. Unclear ACE-inhibitor and ARB exposure.
Kristensen et al., 2015, Denmark[85]	Cohort Prospective data	Population-based 1995-2011	9,441	ACE-inhibitor use n=1,186 (13%) ARB use n=467 (5%)	Surgery for AAA	ACE-inhibitor use: HR 0.86 (95% CI: 0.74;0.99) ARB use HR: 1.02 (95% CI: 0.84;1.23)	AAA-patients who died within 60 days of diagnosis were excluded.
Silverberg et al., 2014, Israel[86]	Cohort Prospective data	Single-center 2012	122	ACE-inhibitor use n=45 (37%) ARB use n=45 (37%) No ACE-inhibitor or ARB use n=32 (26%)	AAA-growth	Uni- / multivariate mean growth (mm/8 month): ACE-inhibitor use: 0.47 (se: 0.19) / 0.36 (se: 0.20) ARB use: 0.51 (se: 0.16) / 0.56 (se: 0.17) No ACE-inhibitor or ARB use: 0.89 (se: 0.22) / 0.95 (se: 0.24)	Not patients with AAA (!) May not be applicable on AAA-patients with manifest vascular lesions. Only 8 months follow-up. Incomplete follow-up.
Kortekaas et al., 2014, The Netherlands[87]	RCT sub-study	Single-center 2008-2011	286	ACE-inhibitor use n=82 (29%)	AAA-growth	Multivariate estimated difference in growth rate (mm/18 month): -0.24 (95% CI: -0.90;0.45)	Post-hoc analysis. Primary exposure: Doxycycline. Alternative reporting: 18 months growth rate
Dalman et al., 2012-2016, USA[90]	RCT reg. 2012	Multicenter 2012-2016	300	ARB use (Telmisartan)	AAA-growth	Pending	Estimated study completion in August 2016
Poulter et al., 2011-2015, UK[89]	RCT, reg. 2011.	Multicenter 2011-2015	227	ACE inhibitor use (Perindopril)	AAA-growth	Pending	Three-armed study: Perindopril, amlodipine, or placebo. Study completed.
Sweeting et al., 2010, UK[58]	Cohort Prospective data	Multicenter 1991-1995	1,701	ACE-inhibitor use n=169 (10%)	AAA-growth	Multivariate estimated difference in growth rate (mm/year): 0.63 (se: 0.24), p=0.009	Mean follow-up: 1.9 years
Thompson et al., 2010, UK[57]	Cohort Prospective data	Single-center 1984-2007	1,269	ACE-inhibitor use n=265 (21%) ARB use n=73 (6%)	AAA-growth	Multivariate estimated difference in growth rate (mm/year): ACE-inhibitor use: -0.28 (95% CI: -0.67;0.12) ARB use: -0.91 (95% CI: -1.78;-0.03)	25 year cohort – historic change in prescription patterns.

Table 5. *Summary of literature; the effect of ACE-inhibitors and ARBs on short-term mortality after rAAA*

Author, year, country	Study design	Study population	N	Exposure	Outcome	Results	Comments
Kristensen et al., 2015, Denmark[85]	Cohort Prospective data	Population-based 1995-2011	9,441	ACE-inhibitor use n=1,186 (13%) ARB use n=467 (5%)	1. AAA-specific mortality 2. All-cause mortality	ACE-inhibitor use 1. HR 0.64 (95% CI: 0.51;0.80) 2. HR 0.63 (95% CI: 0.55;0.71) ARB use 1. HR: 0.65 (95% CI: 0.48;0.88) 2. HR: 0.58 (95% CI: 0.48;0.70)	Broad definition of AAA-death (DI71). AAA-specific mortality, censored after surgery. AAA-patients who died within 60 days of diagnosis were excluded
Poulter et al., 2011-2015, UK[89]	RCT, reg. 2011.	Multicenter 2011-2015	227	ACE inhibitor use (Perindopril)	AAA-related death	Pending	3 armed study: Perindopril, amlodipine, or placebo. Secondary outcome. Study completed.
Railton et al., 2010, Canada[92]	Cohort Retrospective data	Multicenter (2 centers) 1998-2005	883	RAS-blockade n=359 (41%)	30-day mortality *after* OAR	OR for 30-day mortality associated with RAS-blockade: Univariate analysis OR: 3.2 (95% CI: 1.5;6.7) Propensity score matched analysis OR: 5.0 (95% CI: 1.4;27)	Propensity score matched subjects were unbalanced on hypertension. No measures made to adjust for hypertension.

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; AAA, abdominal aortic aneurysm; HR, hazard ratio; CI, confidence interval; RAS, renin angiotensin system; OAR, open aortic repair; OR, odds ratio.

Search strategy: Papers were identified in PubMed (only papers written in English and only including humans) using the following query: ("Aortic Aneurysm, Abdominal"[Mesh] OR "aortic rupture"[mesh]) AND ("Angiotensin-Converting Enzyme Inhibitors"[Mesh] OR "Angiotensin Receptor Antagonists"[Mesh]) and from searching ClinicalTrials.gov for "abdominal aortic aneurysm | Interventional Studies | mortality OR death OR survival". Additional relevant papers were identified in the reference lists of the included papers and from reviews on the topic. Last search: March 14, 2016.

Relevant PubMed.org hits: 1/31. Relevant ClinicalTrials.gov hits: 1/59. Other relevant papers: 1. Total number of papers reviewed: 1+1+1=3.

LOW-DOSE ASPIRIN

Aspirin belongs to the group of non-steroidal anti-inflammatory drugs (NSAIDs). The active compound is acetylsalicylic acid, a synthetic preparation of salicin. This compound, an extract from willow bark, has been known since ancient times to relieve fever, pain and inflammation. Aspirin was introduced by Bayer in 1899 as an analgesic. The mechanism of action was, however, first described in the early 1970s [93]. Acetylsalicylic acid inhibits the synthesis of prostaglandin and thromboxane (TxA_2) by non-selectively blocking the enzymes cyclooxygenase (COX)-I and COX-II. The inhibition of TxA_2 formation attenuates platelet activation, platelet aggregation, and several other complex processes[94]. Treatment with low-dose aspirin (ASA) has been shown to reduce mortality in suspected acute myocardial infarction as well as the incidence of serious vascular events (e.g., non-fatal myocardial infarction, non-fatal stroke, and vascular death) in high-risk patients[95,96]. Thus, ASA is indicated for the acute treatment of acute coronary syndrome and recommended for the secondary prophylaxis in coronary heart disease, cerebrovascular disease, and peripheral vascular disease[31,97]. In Denmark, ASA is available both by prescription and over the counter.

Low-dose aspirin and AAA

AAAs of significant size tend to have an intraluminal thrombus. Studies of the characteristics and activity of the thrombus in experimental models have suggested that inhibition of platelet activity could possibly influence the development of the thrombus, attenuate AAA growth and reduce the risk of rAAA[98,99]. In Table 6, a summary of the existing literature on ASA use and AAA growth and rAAA is provided.

No comparable literature was found considering ASA use and mortality after rAAA. Thus, no separate table is provided. However, the search strategy is summarized below in Table 6.

Limitations of the literature on low-dose aspirin and AAA

The literature on ASA and rAAA is just as scarce as the literature on the association between rAAA and statins or RAS-blockers. An American study obtained data on ASA use and rAAA but reported on the composite endpoint of dissection and rupture[99]. However, the majority of studies investigated AAA growth rates and consisted merely of observational studies[24,54,56-59,100]. Only two of the identified studies specified the use of ASA as the primary study objective[99,100]. Thus, we included studies of antiplatelet use in the review given that ASA was believed to be the predominantly used drug in these studies[57,58]. We lastly identified an ongoing RCT investigating the effect of the new and potent antiplatelet drug Ticagrelor on AAA growth rate[101].

The aforementioned American study suggested a reduced risk of dissection or rupture in ASA users[99]. However, the study included patients with thoracic and thoracoabdominal aneurysms, and the reported results were imprecise. The remaining identified studies all considered ASA use in relation to AAA growth. Two of the studies, based on surveillance data from two different Danish screening programs, reported a lower AAA growth rate in ASA users compared to non-users[24,100]. No other studies found an association between ASA use and AAA growth[54,56-59]. Direct comparison of the studies was difficult because of differences in the exposure and the outcomes reported.

We found no studies on ASA-use and short-term mortality after hospitalization with AAA or rAAA. However, a RCT was identified that aimed to evaluate 30-day mortality after pre-operative platelet administration in rAAA patients[102]. The estimated study completion was scheduled for March 2015. It is unclear whether this study was terminated or is still ongoing.

The meta-analysis of individual patient data by Sweeting *et al.* also considered anti-platelet use (most likely ASA, but not specified) in six studies (N=4,137) but found no association between anti-platelet use and AAA growth or the risk of rAAA[64]. During our literature review, we additionally located a Taiwanese population-based study reporting on ASA use and the composite endpoint of all-cause mortality, aortic dissection, rupture, admission without rupture, or surgical repair[103]. The study population included a mixture of patients with AAA and patients with thoracoabdominal aneurysms. A null result was reported, but the methodology was very unclearly specified; thus, this study was not considered meaningful for summarization of its data in a table. Furthermore, a paper from Kurzencwyg and colleagues examined the association between in-hospital mortality and preadmission use of statins, ACE-inhibitors and ASA[104]. However, similar to the aforementioned study, the results were not clearly reported and the data could not be compared to other results in the present context.

Table 6. *Summary of literature; the effect of ASA on AAA growth and rupture risk*

Author, year, country	Study design	Study population	N	Exposure	Outcome	Results	Comments
Owens et al., 2015, USA[99]	Cohort Retrospective data	Single-center	1,578	ASA use n=unavailable	Dissection or rupture (227 dissections, 124 ruptures)	Dissection or rupture of AAA, ASA-use compared to no ASA use. Univariate analysis HR: 0.28 (95% CI: 0.18;0.43) Multivariate analysis: HR 0.47 (95% CI: 0.22;1.00)	Study period not specified Unclear methodology. Mix of TAA (17.7%), TAAA (59.5%), AAA (22.7%). Dissection (64.6%), rupture (35.4%).
Wanhainen et al., 2014-2017, Sweden[101]	RCT, reg. 2014	Single-center 2014-2017	140	Ticagrelor	AAA-growth	Pending	Not ASA but newer antiplatelet drug. Estimated study completion, February 2017.
Behr-Rasmussen et al., 2014, Denmark.[24]	Cohort Prospective data	Multicenter 2008-2011	416	1. ILT n=256 (62%) 2. ASA use, n=209 (50%)	1. ILT-size 2. AAA-growth	1. A 10% increase in relative ILT size was associated with increased growth of 0.15 mm/year. 2. Growth rate (mm/year): ASA use: 2.42 No ASA use: 3.01, p=0.033.	1. Multivariate analysis. 2. Univariate analysis.
Karrowni et al., 2011[54]	Cohort Retrospective data	Single-center 2001-2005	211	ASA use n=145 (69%)	AAA-growth	Mean change in lesion size (%): ASA use: 3.9 (95% CI: 2.0;5.8) No ASA use: 2.8 (95% CI: 0.5;5.1)	Univariate analysis.
Ferguson et al., 2010, Australia NZ[56]	Cohort Prospective data	Multicenter Median follow-up: 5 years	652	ASA use n=363 (56%)	AAA-growth	Growth above median growth: Adjusted OR: 1.10 (95% CI: 0.78;1.56) for ASA use compared to no ASA use.	Very small AAA (mean diameter 33.2 mm). Non-comparable measures of growth (OR). Incomplete medication history (only upon entry). Study period not specified.
Sweeting et al., 2010, UK[58]	Cohort Prospective data	Multicenter 1991-1995	1,701	Antiplatelet use n=501 (29%)	AAA-growth	Multivariate estimated difference in growth rate (mm/year): 0.16 (se: 0.14)	Mean follow-up: 1.9 years. Type of antiplatelet therapy not specified; most likely ASA.
Thompson et al., 2010, UK[57]	Cohort Prospective data	Single-center 1984-2007	1,269	Antiplatelet use n=757 (60%)	AAA-growth	Multivariate estimated difference in growth rate (mm/year): -0.19 (95% CI: -0.53;0.12)	25 year cohort – historic change in prescription patterns. Type of antiplatelet therapy not specified; most likely ASA.
Karlsson et al., 2009, Sweden.[59]	RCT, Azithromycin	Multicenter 2002-2005	211	ASA use n=101 (48%)	AAA-growth	Growth rate (mm/year): ASA use: 1.8 No ASA use: 2.6, p=0.004.	Post-hoc analysis, primary exposure: Azitromycin. Univariate analysis.

Author, year, country	Study design	Study population	N	Exposure	Outcome	Results	Comments
Lindholt et al., 2008, Denmark[100]	Cohort Prospective data	Single-center 1994-2005	148	ASA use n=62 (42%)	AAA-growth	Multivariate estimated difference in growth rate (mm/year): AAA < 40 mm: 0.44 (95% CI: -0.17;1.06) AAA 40-49 mm: -2.13 (95% CI: -3.68; -0.58)	Baseline medication. Not adjusted for different observation times among users and non-users.

Abbreviations: ASA, acetylsalicylic acid; AAA, abdominal aortic aneurysm; HR, hazard ratio; CI, confidence interval; TAA, thoracic aortic aneurysm; TAAA, thoracoabdominal aortic aneurysm; ILT, intraluminal thrombus; OR, odds ratio; se, standard error.

Search strategy: Papers were identified in PubMed (only papers written in English and only including humans) using the following queries: ("Aortic Aneurysm, Abdominal"[Mesh] OR "aortic rupture"[mesh]) AND ("Aspirin"[Mesh]), (abdominal aortic aneurysm[MeSH Terms] AND (expansion OR growth)) AND (("Aspirin"[Mesh]) OR (intraluminal thrombus)), and from searching ClinicalTrials.gov for "abdominal aortic aneurysm | Interventional Studies | expansion OR growth OR rupture". Additional relevant papers were identified in the reference lists of the included papers and from reviews on the topic. Last search: March 14, 2016.
Relevant PubMed.org hits: 2/48. Relevant ClinicalTrials.gov hits: 1/27. Other relevant papers: 6. Total number of papers reviewed: 2+1+6=9

Search strategy for the effect of ASA on short-term mortality after rAAA (no table): Papers were identified in PubMed (only papers written in English and only including humans) using the following query: ("Aortic Aneurysm, Abdominal"[Mesh] OR "aortic rupture"[mesh]) AND ("Aspirin"[Mesh]) and from searching ClinicalTrials.gov for "abdominal aortic aneurysm | Interventional Studies | mortality OR death OR survival". Additional relevant papers were identified in the reference lists of the included papers and from reviews on the topic. Last search: March 14, 2016.
Relevant PubMed.org hits: 1/15. Relevant ClinicalTrials.gov hits: 1/59.

AIMS

The review of the literature revealed several studies on AAA growth and association with the use of statins, RAS-blockers and ASA. However, studies were generally small and results were not consistent. Additionally, important weaknesses in study design and methodology were present in the existing studies. Literature considering rAAA as the endpoint and literature on the short-term prognosis following rAAA are lacking.

Given the very high mortality rates after rAAA, a drug to halt AAA growth or decrease the risk of rAAA is needed for the treatment of patients with small AAAs detected either incidentally or by screening. To address this need, we conducted three studies with the following aims:

Study I: To examine the clinical impact of preadmission statin use on the risk of rAAA and subsequent case fatality.

Study II: To examine the possible impact of preadmission RAS-blockade on the risk of rAAA and case fatality following rAAA.

Study III: To examine the association between ASA use and the risk of rAAA and short-term mortality after rAAA.

METHODS

SETTING

The Danish national healthcare system is tax-financed and covers the entire Danish population (approximately 5.6 million in 2012[105]) with free, unrestricted public healthcare. This care includes access to free hospital care, free visits to general practitioners and partial reimbursement for most prescribed drugs, including statins, RAS-blockers and ASA. We conducted three population-based studies using data from national healthcare registries. Study I was conducted on national data obtained between 1996 and 2008, whereas Study II and III additionally included data from 2009-2012.

DATA SOURCES

The Civil Registration System

A unique Civil Person Register (CPR) number is assigned to every Danish citizen at birth and to residents at immigration. This ten-digit identifier enables unambiguous individual-level linkage of records across multiple nationwide healthcare and administrative registries. The Civil Registration System retains daily updated individual-level information on migration, marital status and vital status for all persons living in Denmark[106].

The Danish National Registry of Patients

The Danish National Registry of Patients (DNRP) retains comprehensive information on all somatic admissions and surgical procedures performed in Danish hospitals since 1977, including outpatient visits since 1995. Discharge diagnoses are coded by the discharging doctor according to the *International Classification of Diseases* (8th edition until 1993 and 10th edition from 1994 onwards) and procedural codes according to the *NOMESCO Classification of Surgical Procedures*[107].

The Register of Medicinal Product Statistics

Also known as the Danish National Prescription Registry, this register holds individual-level information on all prescribed drugs dispensed from Danish pharmacies, including statins, RAS-blockers and ASA. Data on drug type (coded according to the Anatomical Therapeutic Chemical classification system), package size (dose unit and number of dose units in package), and date of dispensing are recorded. The register is considered complete since 1995[108].

The Integrated Database for Labor Market Research

The Integrated Database for Labor Market Research retains annually updated labor market data including detailed individual-level and household income data supplied from the tax authorities. This register was established in 1980[109].

The National Health Insurance Service Registry
The National Health Insurance Service Registry stores data on services provided and covered by the primary healthcare system, including all contacts to general practitioners, since 1990. This registry is assumed to have a high level of completeness as its information is gathered as part of the healthcare provider's reimbursement of invoices related to the service provided[110].

AAA-database
We recently built a population-based AAA-database in Jutland, Denmark. The database is based on a review of medical records from 1996-2008 and comprises data from 4,128 patients diagnosed with either AAA or rAAA. In the database, patients are categorized as rAAA patients if a rupture is described radiologically or during surgery. Similarly, patients are categorized as AAA patients if there is radiological evidence of an AAA with a maximum diameter of at least 3 cm. Furthermore, the database contains baseline information on AAA size.

STUDY DESIGN
All three of the studies were designed as combined case-control and follow-up studies.

STUDY POPULATION
For all three of the studies, we included all patients aged 50 years or above with a first time-registered (incident) hospital discharge diagnosis of AAA or rAAA. All patients with a previous hospital history of rAAA, AAA or any other aortic pathology (i.e., aortic dissection, thoracic or thoracoabdominal aortic aneurysm, any dilatation of the aorta, Marfan syndrome or Ehlers-Danlos syndrome) were thus excluded.

Study I included all incident rAAA patients (cases) recorded in the DNRP from 1 January 1996 until 31 December 2008. For each rAAA case, one age- and sex-matched AAA patient (control) was selected using risk set sampling; i.e., the AAA control had to be alive and at risk of rAAA at the time the corresponding case was diagnosed. The controls were age-matched within ± 1 year of age and were to be diagnosed with AAA within 179 days of the corresponding rAAA case.

Study II included all incident rAAA cases recorded in the DNRP from 1 January 1996 until 31 December 2012. For each rAAA case, up to five age- and sex-matched AAA controls were selected using the same definitions as in Study I. The eligible control patients were allowed to be selected as controls for more than one rAAA case.

Study III included all incident rAAA cases recorded in the DNRP from 1 January 1996 until 31 December 2012. For each rAAA case, one age- and sex-matched AAA control was selected using the same definitions as in Study I.

EXPOSURE
Statins (Study I)
The exposure in Study I was preadmission statin use, defined as the filling of at least two statin prescriptions before hospital admission (index date). The cases and controls were categorized on the basis of filled statin prescriptions into current users, former users or never users. Current use was defined as the filling of a statin prescription within 90 days of the index date. Former use was defined as the filling of at least two statin prescriptions more than 90 days before the index date. Never users never filled a statin prescription. The amount of prescribed statins was quantified for the individual patients as the cumulative number of filled defined daily doses (DDDs), and patients were further categorized into quartiles of increasing use.

RAS-blockers (Study II)
The exposure in Study II was preadmission use of an ACE-inhibitor or an ARB. We used the same user definitions and quantified the intensity of the treatment in cumulative filled DDDs as in Study I.

Low-dose aspirin (Study III)
In Study III, preadmission ASA use was the exposure of interest. The cases and controls were categorized based on filled ASA prescriptions into ASA users, who were defined as having filled at least one ASA prescription before the index date, and non-users, defined as having no filled ASA prescriptions before the index date. The extent of ASA use was quantified in usage years from the first filled prescription until the last filled prescription before the index date. Additionally, the percentage of ASA coverage was computed as years of ASA use divided by the total observation time and grouped in quartiles of increasing ASA coverage.

OUTCOMES
Risk of rupture (Study I, II, III)
The outcome of interest in the case-control studies was the association between the use of statins, RAS-blockers and ASA and the risk of presenting with rAAA compared to presenting with AAA on hospital admission.

30-day case fatality (Study I, II, III)
For the follow-up studies, the outcome of interest was the association between the use of statins, RAS-blockers and ASA and 30-day case fatality after hospital admission with rAAA.

Data validity (Study III)
In Study III, we additionally assessed the validity of rAAA and AAA diagnoses and the validity of ASA use in the registries compared to data from the AAA-database based on information from medical records.

POTENTIAL CONFOUNDING FACTORS
We included a number of variables in our studies that could be associated with the exposures and outcomes under study and thus could potentially confound the results of the analyses. We acquired data on age, sex and marital status from the Civil Registration System. The DNRP provided data on relevant comorbidities that were diagnosed before the index date. Additionally, the DNRP provided data on surgery performed on AAA-patients within 180 days of the index date. From the Register of Medicinal Product Statistics, we created a medication history for each individual patient, including drug use that could possibly affect the risk of rupture, the rate of AAA growth or 30-day mortality. Drug use that could indicate or unveil important comorbidities not necessarily leading to hospitalization was also considered. Additionally, we obtained data on individual gross-income in the year before the index date from the Integrated Database for Labor Market Research. Lastly, data on all contacts to general practitioners in the year before the index date were attained from the National Health Insurance Service Registry.

In Study I, we additionally obtained external data on tobacco smoking among patients with AAA (Lindholt J, Høgh A, and Thomsen MD, unpublished data, 2013) and data on the risk of rAAA in smokers compared to non-smokers (Sweeting and colleagues, 2012[64]) to compute the magnitude of impact from this unmeasured possible confounding factor. Lastly, for Study III, we had available data on AAA size for a subgroup of the AAA controls from the AAA database.

STATISTICAL ANALYSES

The statistical analyses are summarized below. A full description of the analyses for each study is provided in the appendices. All of the analyses were performed using STATA® (StataCorp LP, College Station, TX, USA), Release 12, 13, and 14 for studies I, II and III, respectively. All of our studies were approved by the Danish Data Protection Agency (record number 2007-58-0010). Medical record review was approved by the Danish National Board of Health (record number 7-604-04-2/170/EHE). No ethical approvals are necessary for registry-based studies in Denmark.

Conditional logistic regression analyses (Studies I, II, III)

In all three of the studies, the cases and controls were matched on sex and age. Thus, we used conditional logistic regression analyses to compute odds ratios (ORs) with 95% confidence intervals (CIs) of the association between preadmission drug use (statins, RAS-blockers and ASA) and the risk of rAAA. As the controls were sampled using risk set sampling, the ORs estimate the corresponding incidence rate ratios. We used multivariable conditional regression analyses to control for potential confounding factors.

Cox proportional hazards regression analyses (Studies I, II, III)

The rAAA cases were followed from date of admission until death or end of follow-up (30 days), whichever came first. We used Cox proportional hazards regression analyses to compute 30-day mortality rate ratios (MRRs) with 95% CIs. The analyses were repeated in multivariable Cox proportional hazards regression analyses to control for potential confounding. The proportional hazards assumption was assessed visually by inspection of log-log plots.

Subgroup analyses (Studies I, II, III)

All of our studies included repeated analyses conducted across strata of age, sex and calendar year. Further analyses were performed in subgroups of patients based on cumulative drug use. We also conducted subgroup analyses among AAA controls, who had AAA repair within 6 months of the index date, and their corresponding rAAA cases. We computed separate estimates of both risk and 30-day case fatality for the use of the most common statins (I). Additional analyses were performed among subgroups of patients with different markers of frailty (I, II), patients with combined RAS-blocker use (II), rAAA cases stratified according to repair status (±surgery) (II, III), and AAA patients with AAA diameters ≥ 5.5 cm (III).

Sensitivity analyses (Studies I, II, III)

In Study I, we performed an external adjustment for unmeasured confounding by tobacco smoking using a Microsoft® Excel spreadsheet (Microsoft, Redmond, Washington, USA) from Lash and colleagues[111,112]. Furthermore, to supplement to the analyses mentioned above, we systematically repeated the statistical analyses with different definitions of drug use (Studies I, II), different inclusion and exclusion criteria (Study I, II), and among patients with a leading diagnosis of rAAA or AAA (III).

Propensity score matched analysis (Study II)

To examine the robustness of the primary analyses in Study II, we used a propensity score-matched design in a supplementary analysis. We used propensity score matching (1:1) without replacement (nearest neighbor method with a caliper of 0.2 standard deviations of the logit of the predicted propensity score) to sample controls with balanced baseline predictors for either ACE-inhibitor or ARB use[113]. We used multivariable logistic regression to compute propensity scores for all of the individual patients included in the primary study. The balance between cases and controls was assessed, and we adjusted for imbalanced variables (standardized differences > 0.1) in the following conditional logistic regression analysis[114].

Validation (Study III)

In Study III, we compared the diagnostic coding in the DNRP to the clinical findings of rAAA or AAA in the medical records, as reflected in the AAA database. We analyzed the concordance between the diagnostic coding in the DNRP and the information from medical records, with estimates of positive predictive values (PPVs) with 95% CIs.

RESULTS

STUDY I: STATINS AND RAAA

Characteristics

From the DNRP, we identified 3,691 rAAA cases that fulfilled the inclusion criteria in the study period (1996-2008). For the risk analysis, it was possible to match 3,584 rAAA cases (97.1%) to 3,584 AAA controls. The male: female ratio was nearly 5:1, and the median age was 74.4 years (interquartile range, IQR, 11.8 years). Among the rAAA cases and AAA controls, we found 13.4% to be current statin users at the time of hospital admission. Simvastatin was the most used statin, comprising almost three quarters of the total use, followed by atorvastatin, pravastatin and other statins. Selected baseline characteristics are shown in Table 7 (also see Supplementary tables S1 and S3, Study I).

Risk of rAAA (case-control study)

The results of the risk analyses are presented in Table 8. We found current statin use to be associated with a lower risk of presenting with rAAA at hospital admission compared to never using statins, adjusted OR: 0.73 (95% CI: 0.61;0.86). Additionally, former use of statins was associated with a comparable lower risk, adjusted OR: 0.74 (95% CI: 0.59;0.94).

Thirty-day case fatality (follow-up study)

Thirty-day case fatality was 46.1% in current statin users and 54.8% in former statin users, compared to 59.3% among never users. Compared to never statin users, this corresponded to adjusted mortality rate ratios (MRRs) of 0.80 (95% CI: 0.68;0.95) for current users and 0.98 (95% CI: 0.78;1.22) for former users (Table 9).

Subgroup analyses

In both the case-control and the follow-up study, subgroup analyses across strata of age, sex and calendar year did not reveal any

systematic deviations from the primary results. Likewise, subgroup analyses of different types of statins and cumulative statin use yielded comparable results (Supplementary tables S2 and S4, Study I). In the case-control study, the results were equally consistent for a subgroup of AAA controls who had AAA repair in the first 6 months after admission and their corresponding rAAA cases (data not shown). In the follow-up study, we conducted analyses that were restricted to patients with and without markers of frailty (age >80 years, any malignancy or any liver disease). Additionally, we repeated analyses in a group of patients with comorbidity, suggesting an indication for statin therapy. Neither of these sub-analyses substantially changed the estimates (Table 9).

Sensitivity analyses

In the case-control study, sensitivity analyses among different groups of former statin users revealed a slightly lower risk reduction for former users, who discontinued statin use more than 2 years before admission, compared to more recent users (Table 8). Adjustment for unmeasured tobacco smoking was conducted in the risk analysis using external data and did not considerably change the primary result, adjusted OR: 0.78 (95% CI: 0.66;0.92).

STUDY II: RAS-BLOCKERS AND RAAA

Characteristics

We identified 4,052 rAAA cases and 10,549 AAA controls from the DNRP in the study period (1996-2012). For the risk study, we aimed to match the rAAA cases 1:5 to age- and sex matched AAA controls. It was possible to find matched controls for 3,586 (88%) of the rAAA cases. For these cases, we found five matched controls for 3,292 (92%) of the cases, leaving the remaining 294 (8%) rAAA cases with between one and four AAA controls. Thus, for the case-control study, there were 17,271 AAA controls (Fig. 1, Study II).

The median age among the included patients was 74.5 years (IQR: 11.5 years), and the vast majority were males (85.6%). Compared to the rAAA cases, a slightly higher proportion of the AAA controls had congestive heart failure and diabetes mellitus registered. In contrast, the rAAA cases had more peripheral arterial diseases and renal diseases registered (Table 1, Study II).

In total, 3,137 (15%) of the studied patients were current users of ACE-inhibitors and 1,409 (6.8%) were current ARB users. The three most used ACE-inhibitors, comprising 75% of the total use, were enalapril (40%), ramipril (23%), and trandolapril (12%). Among the ARB users, the three most used drugs (85%) were losartan (60%), candesartan (17%), and valsartan (9%).

Risk of rAAA (case-control study)

We found no association between current use of ACE-inhibitors or ARBs and the risk of rAAA, adjusted ORs: 0.96 (95% CI: 0.85;1.07) and 0.93 (0.79;1.09), respectively (Table 10). However, former use of either ACE-inhibitors or ARBs was associated with a reduced risk of presenting with rAAA (Table 10).

Propensity score matched analyses

In the propensity score matched analyses, we were able to identify one matched AAA control for each rAAA case (N=3,586). The balance of the baseline characteristics were assessed graphically, and any unbalanced variables were adjusted for in a multivariable conditional logistic regression analyses. The results of the propensity score matched analyses for both ACE-inhibitors and ARBs were virtually similar to the results of the main risk analyses (Table 11).

Thirty-day case fatality (follow-up study)

For the follow-up study, 4,039 rAAA cases were followed from hospital admission until death or the end of follow-up (30-days) (Table 3, Study II). The cumulative 30-day mortality rate was 61.0% in current ACE-inhibitor users and 58.6% in current ARB users compared to 59.4% and 59.9% in never users of ACE-inhibitors and ARBs, respectively. The corresponding adjusted MRRs suggested no association between former or current use of RAS-blockers and 30-day case fatality (Table 12).

Subgroup analyses

In the repeated analyses across strata of age, sex and calendar year, we found no systematic differences compared to the principal results. We found no substantial deviations in the subgroup analyses of cumulative use of ACE-inhibitors and ARBs (Table 2 and Table 4, Study II). Analyses allowing one-prescription users to be classified as users did not alter the results (data not shown). Additionally, the subgroup analyses among AAA-controls with presumably large AAAs (surgery within 6 months of hospital admission) produced estimates close to the primary results (ACE-inhibitors, adjusted OR: 0.96 (95% CI: 0.75;1.24) and ARBs, adjusted OR: 0.77 (95% CI: 0.54;1.09)).

In the follow-up study, analysis stratified on repair status revealed no marked differences for the rAAA patients who were currently on RAS-blockers and who underwent surgical repair. However, former users of RAS-blockers had a higher 30-day mortality following rAAA, (ACE-inhibitors, adjusted MRR: 1.34 (95% CI: 1.10;1.64) and ARBs, adjusted MRR: 1.43 (95% CI: 1.09;1.87)).

STUDY III: LOW-DOSE ASPIRIN AND RAAA

Characteristics

We identified 4,055 rAAA cases from the DNRP who were eligible for the study. For the risk analysis, we found one age- and sex matched AAA control for 4,010 rAAA cases (Fig. 1, Study III). The median age among the studied individuals was 74.6 years (interquartile range, IQR, 11.8 years). Males comprised 83.4% of the study population (Table 1, Paper 3).

Risk of rAAA (case-control study)

Preadmission ASA use was found in 1,815 (45.3%) of the rAAA cases, compared to 2,111 (52.6%) of the AAA controls. These data corresponded to a crude OR of 0.72 (95% CI: 0.66;0.79) for presenting with rAAA for ASA users compared to non-users. However, when we adjusted for potential confounding factors, we found no association between ASA use and the risk of rAAA, adjusted OR: 0.97 (95% CI: 0.86;1.08)(Table 13).

Thirty-day case fatality (follow-up study)

ASA use was associated with an unfavorable 30-day case fatality. We found a cumulated 30-day mortality rate of 60.0% for ASA users and 56.8% for non-users. The corresponding crude MRR of 1.24 (95% CI: 1.15;1.35) did not change a great deal upon adjustment for potential confounding factors, adjusted MRR 1.17 (95% CI: 1.06;1.28)(Table 14).

Subgroup analyses

Results of both the case-control study and the follow-up study were robust in repetitive analyses stratified by sex, age, calendar

year and visits to a GP in the year before hospital admission. Additionally, subgroup analyses among AAA controls with large AAA diameters or surgery within 6 months of hospital admission did not deviate substantially from the primary results (Table 13). The stratified analysis on repair status after hospital admission did not change the higher 30-day case fatality among the rAAA cases who underwent immediate repair. However, unsurprisingly, no association between ASA use and 30-day mortality was found in rAAA cases in whom surgery was not performed (Table 14).

Validation of AAA coding in the DNRP compared to medical records

To assess the validity of the AAA and rAAA diagnoses, coding in the DNRP was compared to information from the AAA database, which comprised information from medical records. An incident rAAA diagnosis was considered valid if surgical or radiological evidence of rupture was described upon hospital admission. An incident diagnosis of AAA was confirmed if the first ultrasound or computer tomography scan described an infrarenal AAA of ≥ 3.0 cm. Table 15 provides the result of the medical record review.

The positive predictive value for a rAAA diagnosis was 854/996 = 85.7% (95% CI: 83.4;87.9). For an AAA diagnosis, the PPV was 2,523/2,620= 96.3% (95% CI: 95.5;97.0).

Table 7. *Characteristics at hospital admission for 3,584 rAAA cases and 3,584 age- and sex-matched AAA controls, Denmark 1996-2008. Adapted from Wemmelund et al., Br J Surg, 2014*[115]

	rAAA cases, n (%)		AAA controls, n (%)	
Statin use				
Current use	418	(11.7)	539	(15.0)
Former use (>90 days)	158	(4.4)	198	(5.5)
Sex				
Female	601	(16.8)	601	(16.8)
Male	2,983	(83.2)	2,983	(83.2)
Age, years				
50-64	550	(15.3)	552	(15.4)
65-69	544	(15.2)	544	(15.2)
70-74	771	(21.5)	780	(21.8)
75-79	764	(21.3)	770	(21.5)
80+	955	(26.6)	938	(26.2)
Preadmission hospital-diagnosed comorbidities				
Hypertension	720	(20.1)	708	(19.8)
Myocardial infarction	541	(15.1)	564	(15.7)
Congestive heart failure	359	(10.0)	369	(10.3)
Peripheral vascular disease	696	(19.4)	533	(14.9)
Cerebrovascular disease	614	(17.1)	586	(16.4)
Chronic pulmonary disease	528	(14.7)	425	(11.9)
Diabetes mellitus	131	(3.7)	174	(4.9)
Moderate/severe renal disease	214	(6.0)	141	(3.9)
Preadmission medications				
ACE-inhibitors	430	(12.0)	491	(13.7)
Angiotensin II receptor blockers	157	(4.4)	158	(4.4)
Beta blockers	524	(14.6)	627	(17.5)
Calcium antagonists	629	(17.6)	709	(19.8)
Low-dose aspirin	885	(24.7)	967	(27.0)
Non-steroidal anti-inflammatory drugs	197	(5.5)	169	(4.7)
Oral corticosteroids	282	(7.9)	167	(4.7)

Table 8. *Associations between preadmission statin use and risk of rAAA, Denmark 1996-2008. From Wemmelund et al., Br J Surg, 2014*[115]

Statin use	rAAA cases, n (%)	AAA controls, n (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
Never	3,008 (83.9)	2,847 (79.4)	1.00 (reference)	1.00 (reference)
Former (>90 days)	158 (4.4)	198 (5.5)	0.73 (0.59;0.91)	0.74 (0.59;0.94)
> 90 days to 2 years*	130 (3.6)	168 (4.7)	0.71 (0.56;0.90)	0.72 (0.56;0.93)
> 2 years†	28 (0.8)	30 (0.8)	0.87 (0.52;1.45)	0.84 (0.49;1.46)
Current	418 (11.7)	539 (15.0)	0.70 (0.60;0.81)	0.73 (0.61;0.86)

* Former statin use, terminated 90 days to 2 years before the index date.
† Former statin use, terminated more than 2 years before the index date.

Table 9. *Thirty-day mortality and adjusted mortality rate ratios (MRRs) after admission with rAAA, Denmark 1996-2008. Adapted from Wemmelund et al., Br J Surg, 2014*[115]

	Never statin user		Former statin user		Current statin user	
	30-day mortality, n (%)	Adjusted MRR (95% CI)	30-day mortality, n (%)	Adjusted MRR (95% CI)	30-day mortality, n (%)	Adjusted MRR (95% CI)
All	1,837 (59.3)	1.00 (reference)	89 (54.8)	0.98 (0.78;1.22)	197 (46.1)	0.80 (0.68;0.95)
≥ 1 frailty marker*	861 (73.3)	1.00 (reference)	35 (72.2)	1.01 (0.70;1.45)	55 (60.4)	0.78 (0.58;1.05)
No frailty markers†	976 (50.7)	1.00 (reference)	54 (47.4)	0.97 (0.72;1.29)	142 (42.3)	0.84 (0.68;1.03)
Indication for statins‡	832 (64.6)	1.00 (reference)	68 (57.4)	0.97 (0.75;1.26)	143 (45.4)	0.76 (0.62;0.94)

*Model restricted to patients with ≥1 frailty marker or relative contraindication to statin treatment (defined as >80 years, any malignancy or any liver disease). † Restricted model without frailty markers or relative contraindication to statin treatment (defined as ≤80 years, any malignancy or any liver disease). ‡ Patients with a history of previous myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease or diabetes mellitus.

Table 10. *Associations between preadmission ACE-inhibitor and ARB use and risk of rAAA, Denmark 1996–2012.*

	rAAA cases, n (%)	AAA controls, n (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
ACE-inhibitor use				
Never	2,679 (74.7)	12,242 (70.9)	1.00 (reference)	1.00 (reference)
Former (>90 days)	393 (11.0)	2,406 (13.9)	0.74 (0.65;0.83)	0.79 (0.70;0.90)
Current	514 (14.3)	2,623 (15.2)	0.89 (0.80;0.99)	0.96 (0.85;1.07)
ARB use				
Never	3,185 (88.8)	14,982 (86.7)	1.00 (reference)	1.00 (reference)
Former (>90 days)	171 (4.8)	1,110 (6.4)	0.72 (0.61;0.85)	0.72 (0.61;0.86)
Current	230 (6.4)	1,179 (6.8)	0.92 (0.79;1.07)	0.93 (0.79;1.09)

Table 11. *Propensity score matched analysis of associations between preadmission ACE-inhibitor and ARB use and risk of rAAA, Denmark 1996–2012.*

	rAAA cases, n (%)	AAA controls, n (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
ACE-inhibitor use				
Never	2,679 (74.7)	2,501 (69.7)	1.00 (reference)	1.00 (reference)
Former (>90 days)	393 (11.0)	577 (16.1)	0.68 (0.59;0.78)	0.73 (0.63;0.86)
Current	514 (14.3)	508 (14.2)	1.01 (0.87;1.17)	1.02 (0.88;1.19)
ARB use				
Never	3,185 (88.8)	3,146 (87.7)	1.00 (reference)	1.00 (reference)
Former (>90 days)	171 (4.8)	225 (6.3)	0.66 (0.55;0.81)	0.71 (0.57;0.88)
Current	230 (6.4)	215 (6.0)	1.02 (0.85;1.25)	1.02 (0.83;1.26)

Table 12. *Thirty-day mortality and adjusted mortality rate ratios (MRRs) after admission with rAAA, Denmark 1996-2012.*

	Never user		Former user		Current user	
	30-day mortality, n (%)	Adjusted MRR (95% CI)	30-day mortality, n (%)	Adjusted MRR (95% CI)	30-day mortality, n (%)	Adjusted MRR (95% CI)
ACE-inhibitor	1,783 (59.4)	1.00 (reference)	284 (63.7)	1.07 (0.94-1.22)	359 (61.0)	1.06 (0.94-1.20)
ARB	2,145 (59.9)	1.00 (reference)	128 (65.8)	1.12 (0.94-1.34)	153 (58.6)	0.96 (0.82-1.14)

Table 13. *Preadmission use of low-dose aspirin and risk of rAAA, Denmark 1996-2012*

ASA use	Crude OR (95% CI)	Adjusted OR (95% CI)
ASA non-user	1.00 (reference)	1.00 (reference)
ASA user	0.72 (0.66-0.79)	0.97 (0.86-1.08)
Years from first to last ASA prescription		
< 1	0.65 (0.57-0.76)	0.81 (0.69-0.96)
1-2	0.72 (0.62-0.84)	1.00 (0.84-1.19)
3-5	0.72 (0.62-0.83)	0.94 (0.79-1.12)
6-10	0.77 (0.65-0.90)	1.01 (0.84-1.22)
> 10	0.66 (0.54-0.81)	1.06 (0.83-1.35)
ASA coverage (% of observation period in quartiles)		
1. quartile (lowest)	0.66 (0.58-0.77)	0.85 (0.72-1.00)
2. quartile	0.68 (0.59-0.78)	0.92 (0.78-1.08)
3. quartile	0.82 (0.71-0.94)	1.06 (0.89-1.25)
4. quartile (highest)	0.67 (0.58-0.78)	0.94 (0.80-1.12)
Controls with large AAAs		
AAA ≥ 5.5 cm	0.69 (0.51-0.95)	0.77 (0.51-1.17)
Elective AAA repair	0.75 (0.62-0.90)	0.89 (0.71-1.11)

Table 14. *Preadmission use of low-dose aspirin and 30-day mortality after rAAA, Denmark 1996–2012*

ASA use	Crude MRR (95% CI)	Adjusted MRR (95% CI)
ASA non-user	1.00 (reference)	1.00 (reference)
ASA user	1.24 (1.15-1.35)	1.17 (1.06-1.28)
Years from first to last ASA prescription		
< 1	1.39 (1.22-1.57)	1.30 (1.14-1.48)
1-2	1.19 (1.04-1.36)	1.11 (0.96-1.28)
3-5	1.20 (1.05-1.37)	1.09 (0.94-1.25)
6-10	1.25 (1.09-1.43)	1.16 (1.00-1.34)
> 10	1.17 (0.98-1.39)	1.09 (0.89-1.33)
ASA coverage (% of observation period in quartiles)		
1. quartile (lowest)	1.35 (1.19-1.52)	1.30 (1.15-1.48)
2. quartile	1.13 (0.99-1.29)	1.09 (0.95-1.25)
3. quartile	1.23 (1.09-1.40)	1.13 (0.99-1.29)
4. quartile (highest)	1.27 (1.12-1.44)	1.11 (0.97-1.27)
Surgical status after admission		
Open or endovascular repair	1.26 (1.12-1.43)	1.20 (1.03-1.38)
No repair	1.03 (0.93-1.14)	1.07 (0.96-1.21)

Table 2. *Medical record review for 3,616 patients with a registered incident diagnosis of rAAA or AAA in the DNRP, Denmark 1996-2008.*

		Medical records		
		rAAA	AAA	Total
DNRP	DI713 (cases)	854	142	996
	DI714 (controls)	97	2,523	2,620
	Total	951	2,665	3,616

DISCUSSION

MAIN CONCLUSIONS

Study I: Statins

Preadmission statin use was associated with an approximately 25% lower risk of presenting with rAAA on hospital admission. Additionally, preadmission statin use was associated with 20% lower 30-day all-cause case fatality following hospital admission with rAAA.

Study II: RAS-blockers

Preadmission use of RAS-blockers was neither associated with a lower risk of presenting with rAAA on hospital admission or with a lower 30-day all-cause case fatality following hospital admission with rAAA.

Study III: Low-dose aspirin

Preadmission ASA use was not associated with a lower risk of presenting with rAAA on hospital admission. However, preadmission ASA use was associated with an approximately 20% higher 30-day all-cause case fatality following hospital admission with rAAA.

METHODOLOGICAL CONSIDERATIONS

Selection bias

Selection bias has been defined as "a systematic error in a study that stems from the procedures used to select subjects and from factors that influence study participation"[116]. Thus, selection bias can occur if an association between exposure and outcome is different in study participants compared to non-participants.

The studies presented in this dissertation were population-based and included almost all registered incident rAAA cases and age- and sex-matched controls. Moreover, we had virtually complete follow-up data for the studied individuals. Although the risk of selection bias was therefore minimized, it cannot be totally excluded.

A potential source of selection bias may arise from the unknown proportion of rAAA patients who fail to reach the hospital and consequently are ineligible for study inclusion. If sudden death due to rAAA is associated with use of the drug under study, selection bias could be introduced. However, we believe that an association of this kind would be unlikely, in particular for statins and RAS-blockers. In Study III, the proportion of those receiving ASA among rAAA cases is quite similar to the proportion among the AAA controls. This fact, in combination with the apparent modest harmful effect postoperatively after rupture, suggests that use of ASA did not influence the probability of arrival to the hospital with rupture.

Another potential source of selection bias could be the so-called healthy user bias. Past studies considering the effect of statin use have suggested statin users to be healthier than non-users and to exhibit more beneficial health behavior. However, data from a recent Danish study showed that, in general, statin users in Denmark were neither healthier nor exhibited any more beneficial health behavior than non-users[117]. Additionally, in studies I and II, we considered frailty (defined as advanced age, registered cancer or liver disease) as a source of selection bias that would potentially influence both exposure and outcome. The subgroup analyses among frail patients did not, however, reveal any substantial changes in the estimates.

Information bias

Information bias can occur if "the information collected about or from study subjects is erroneous"[116] and this incorrect information in unevenly distributed among the groups under study.

In all three of the studies, we had access to comprehensive data regarding preadmission drug use. However, even though the Register of Medicinal Product Statistics has a high degree of completeness, it only reflects filled prescriptions and is thus a proxy-measure of the actual "pill in the mouth". This limitation introduces possible information bias in terms of misclassifying subjects as being current users, former users or non-users of the drug under study. The partial reimbursement of many drugs (including statins, RAS-blockers, and ASA) requires patients to provide some of the payment for the drug. In studies I and II, we made the restriction that only users who had filled at least two prescriptions were represented as users of either statins or RAS-blockers. As we considered it unlikely that patients will continue to pay for a drug they did not use, the restriction should at least in part reduce the extent of information bias. The results were virtually unchanged in our repeated analyses without the above restriction. In Study III, however, the drug under study (ASA) was available as an over-the-counter drug in addition to by prescription. Consequently, with no need for prescription and definite registration of ASA use, a major source for information bias could be introduced. The extent of this bias may have decreased during the study period, however, given that the percentage of ASA prescription sales increased from 62% to 92% from 1999-2012[118]. Still, a misclassification of this kind would most likely be non-differential and thus bias our results toward a null association.

Another source of information bias is the potential misclassification of rAAA cases. The implausibility of surviving > 30 days after rAAA admission without surgical repair led us to exclude these cases. However, these patients could still have undergone surgery. As we were not able to rule out whether this was due to incorrect coding of the surgery performed, we chose to err on the side of caution. Exclusion strategies evolved slightly during the

course of the studies, with 111 cases excluded from Study I, 526 cases from Study II, and 477 from Study III. The PPV for a diagnosis of rAAA (85%) found in our validation of rAAA and AAA diagnoses correlates well to the percentage of excluded cases (roughly 15% in Study II and III). Still, the magnitude of this potential information bias is likely to be rather small as repeated analyses with inclusion of these patients left the primary results in all three of the studies unchanged.

Confounding

Confounding bias can arise "if the effect of the exposure is mixed with the effect of another variable"[116]. By definition, a confounding factor needs to be associated with both exposure and outcome without being on the casual pathway from exposure to outcome. Furthermore, the confounding factor needs to be imbalanced in the exposure groups under study. Dealing with confounding is an essential issue in observational studies. Potential confounding can be controlled by restriction and matching during the study design and stratification and adjustment in the analyses[116].

In the three presented studies, we used restriction in the study design by including incident rAAA cases and AAA controls only. The restriction was primarily performed to limit the extent of potential confounding by indication as well as to limit other potential actions from attending doctors after diagnosis. Furthermore, we chose a matched design to limit potential confounding by sex and age, which are known risk factors for AAA. During the analyses, we used both stratification and multivariable logistic regression, conditioned on the matched factors. We adjusted for a range of potential confounding factors using comprehensive data from the registries, including comorbidity, concomitant drug use, primary health care utilization and socioeconomic factors.

In Study I, we additionally performed an external adjustment to control for unmeasured confounding by tobacco smoking, leading to a small decrease in the risk estimate. In Study II, we attempted to balance the potential confounding factors between rAAA cases and AAA controls by propensity score matching in a sub-study. The results remained virtually unchanged. In Study III, we analyzed the association between preadmission ASA use and rAAA in a small subgroup with known large AAAs (≥ 5.5 cm). AAA size is an important predictor for rAAA; however, in our study, AAA size was more likely an intermediate step between exposure and outcome rather than a confounding factor. Still, AAA size has been considered a confounding factor in previous studies focusing on AAA growth, and these studies thus controlled for baseline AAA-diameter[24,56,58,100]. We sought to explore whether the different baseline risks of rAAA in the case group compared to the control group influenced our estimates. The analysis did not suggest that differences in baseline AAA size substantially influenced our ever, the lower risk of rAAA could also be a result of a stabilizing, retained anti-inflammatory effect of earlier statin therapy in the aortic wall. A protracted effect of atorvastatin has previously been described[119]. However, this interpretation remains speculative, and further studies on the causal mechanisms will be required to support this hypothesis.

Only one study examined the association between preadmission statin use and short-term mortality after rAAA[65]. The finding of a reduced in-hospital mortality rate is in accordance with our results. However, the studies are not directly comparable given that only patients admitted to the ICU after rAAA surgery were considered in the small single-center study. Additionally, patients (20% of eligible cases) with a living will or an advance directive against life-sustaining treatment were excluded from the study. Both measures leave potential for selection bias among the studied cases given that both patients who died in the immediate perioperative period as well as potentially frail patients were excluded. The finding of lower 30-day mortality in statin-treated patients was also reported in a RCT examining fluvastatin treatment and the risk of perioperative myocardial ischemia in non-cardiac vascular surgery; in this previous study, half of the analyzed patients underwent AAA repair[120]. A reduced 30-day mortality (HR: 0.47, 95% CI: 0.24;0.94) from cardiovascular causes, including nonfatal myocardial infarction, was found as a secondary outcome. Although this previous analysis is not directly comparable to our study, with respect to mortality following rAAA, this study

estimates. The subgroup analyses among AAA controls with presumably large AAAs (Study I, II, III) yielded comparable results.

Despite the control of a wide range of confounding factors, we cannot exclude the possibility that unknown or unmeasured factors may have confounded the estimates. Notably, tobacco smoking could still be an important residual confounding factor, even though we attempted to control for this factor by external adjustment in Study I and indirectly through adjustment for chronic pulmonary disease in the adjusted analyses (Study I, II, III).

Precision

The width of 95% confidence intervals presented throughout the thesis and in the three studies reflects the statistical precision. The statistical precision was high in most of the main analyses of the large population-based studies. However, caution must be taken when interpreting the findings of the sub-analyses, where the precision was lower and the results were more susceptible to chance.

COMPARISON WITH THE EXISTING LITERATURE

Study I: Statins

To our knowledge, Study I is the largest study to assess the impact of preadmission statin use on the risk of rAAA and 30-day case fatality after rAAA. The Study I findings of a reduced risk of rAAA in statin users are in concordance with the recently published study from UK, which analyzed risk factors for rAAA among patients admitted for elective AAA-surgery and emergency rAAA surgery[34]. The reported rAAA risk reduction among preadmission statin users (adjusted OR: 0.50, 95% CI: 0.32;0.77) is comparable to our findings. The remaining published studies investigated statin use and AAA growth (see section 2.1.2). Four of the small studies suggested a decreased AAA growth in statin users and thus appear supportive of our results[54,55,61,63]. However, our results do not seem to agree with the large studies, as none of these found a reduction in AAA growth with statin use[52,56,57]. Additionally, the meta-analysis of individual data by Sweeting *et al.* did not indicate a lower AAA growth rate in statin users or a lower risk of rAAA[64]. However, differences in the definitions of exposure and outcome and heterogeneity among the studies included in the meta-analysis make a direct comparison to our study results challenging. Furthermore, the reduced risk of rAAA may be unrelated to growth or potential growth retardation and may rather reflect a stabilization of the AAA, which could render the AAA less likely to rupture. The comparable lower risk of rAAA found in former and current users of statins could be interpreted as supporting a non-causal association. How

and the remaining three studies in our literature review[66-68] all point to a reduced short-term mortality in statin users after AAA repair. The exact magnitude of the effect and the underlying mechanisms eliciting this association are, however, unknown.

Study II: RAS-blockers

As discussed in section 2.2.2, previous studies on RAS-blockers and rAAA and AAA growth have reported contrasting results. The largest and most comparable study from Canada reported a reduced risk of rAAA in current users of ACE-inhibitors and a slightly increased risk of rAAA in former users of ACE-inhibitors[91]. These results are in contrast to our findings that current use of ACE-inhibitors was not associated with the risk of rAAA and that former use was associated with a lower risk of presenting with rAAA. The two studies are comparable in their population-based design and size, and the available data from the utilized registries share common characteristics. However, some important differences exist; i.e., the AAA controls in the Canadian study were younger and had undergone more extensive cardiovascular investigation (including cholesterol testing, electrocardiography, echocardiography and aortic imaging) than the rAAA cases. Although Hackam and colleagues adjusted for health care use in their analyses, a degree of confounding by indication cannot be excluded as a possible explanation of the results.

None of the remaining studies that evaluated RAS-blockade and AAA growth are directly comparable to our study[56-58,86-88]. The predominant finding that AAA-growth is not associated with the use of RAS-blockers may support our findings of a null association. Still, the measures of AAA growth and rAAA may not represent the same pathophysiological entity given that not all large AAAs rupture and not all ruptured AAAs are (very) large.

A Danish follow-up study using the exact same registries with almost the same time span found a decreased risk of surgery for AAA in patients treated with ACE-inhibitors. However, this study reported no association between the use of ARBs and risk of AAA surgery[85]. Although investigating largely the same population, the methods and outcome measures differed significantly between the studies. The study by Kristensen *et al*. included both AAAs and thoracoabdominal aneurysms. It is, however, not clear whether these diseases share the exact same pathophysiology; thus, a direct comparison is difficult if not impossible.

We found no association between the use of RAS-blockers and case fatality following rAAA. To the best of our knowledge, no other studies examined the same association. A retrospective Canadian cohort study found that RAS-blockade is associated with increased 30-day mortality following elective open aortic repair[92]. Furthermore, the aforementioned Danish cohort study found that the use of ACE-inhibitors or ARBs was associated with a favorable AAA-specific and all-cause mortality after an AAA diagnosis[85]. Patients with AAA were included 60 days after an AAA diagnosis and followed until death, surgery or emigration. However, as patients with AAA were censored at surgical intervention, a comparison to our study was unfortunately rendered unfeasible.

Study III: Low-dose aspirin

In our large population-based study, we found no association between preadmission ASA use and the risk of rAAA. The only other study concerning ASA use and rupture risk included a mixture of patients with AAA and thoracic and thoracoabdominal aneurysms, and the outcome included aortic dissection[99]. However, a marked reduced risk of both dissection and rupture was found in ASA users. Still, the methodology of the study was very unclearly described, and as both the study population and outcome were different, a firm comparison with our study was not possible.

The majority of studies on AAA growth in ASA users found no association between AAA growth and the use of ASA[54,56-59]. As previously addressed, three of these studies did not exclusively consider ASA use but considered antiplatelet use as the exposure[57,58]. However, this difference was not considered a major limitation given that ASA is believed to be the predominantly used antiplatelet drug. Additionally, the hypothesis of ASA action was linked to thrombocyte inhibition. The two Danish surveillance studies found a reduced AAA growth rate in ASA users[24,100]. These findings were proposed to be linked to an attenuated activity of the intraluminal thrombus, which in turn led to the hypothesis that more direct-acting anti-platelets would be beneficial[121]. The ongoing RCT examining the effect of Ticagrelor on AAA-growth is expected to shed light on this hypothesis [101].

Our finding of an adverse outcome in ASA users following rAAA was not confirmed in any previous studies. The mechanism of this adverse outcome could be explained by a disturbed coagulative status due to thrombocyte blockade in ASA users following rAAA. However, a RCT studying ASA use and perioperative mortality in non-cardiac surgery reported an increased risk of major bleeding in ASA-users, but no excess in 30-day mortality was found[122]. In an observational follow-up study among vascular surgery patients, reduced 30-day and 5-year mortalities were suggested for patients who were treated with anti-platelet therapy compared to those receiving no such therapy [123].

PERSPECTIVES

The reported AAA prevalence and rAAA mortality has been declining in recent years[4,124]. However, AAA and rAAA in particular remain significant causes of mortality and morbidity in the elderly, predominantly male, population.

The studies in this thesis extends current knowledge regarding the risk of rAAA and case fatality following rAAA among patients with the preadmission use of commonly used cardiovascular drugs, namely, statins, RAS-blockers and low-dose aspirin. We were able to show a lower risk of rAAA and a lower 30-day case fatality in statin-treated patients. Furthermore, we found an adverse 30-day case fatality following rAAA in ASA-treated patients.

The results of our studies support current guidelines[31,125], recommending the initiation of statin therapy in patients with AAA. The study on RAS-blockers do not indicate any beneficial effect in relation to the risk of rAAA, neither do they seem to cause any harm. RAS-blockers should thus be initiated or continued if otherwise indicated. Our results do not provide sufficiently strong evidence to recommend against the use of ASA in patients with asymptomatic AAAs given that the anticipated general cardiovascular protective effect is considered more important than the risk of an adverse outcome if the patient should suffer a rAAA.

The uniformly organized Danish health care system and the possibilities of linking health care and administrative registries provide excellent settings for large population-based studies that examine both the risk of rAAA and the prognosis of patients with AAA. Furthermore, the implementation of a national screening program in Denmark with prospective registration of standardized AAA measurements and the surveillance of AAA patients at risk of rAAA would facilitate studies of the association of AAA growth, AAA rupture risk, and potentially beneficial drug therapy. However, given the complex and still not fully understood pathophysiology of AAA, in combination with the results presented in

this thesis, no "wonder-drug" that eliminates the risk of rupture exists or is expected. For now, the results of three ongoing RCTs investigating the effects of ACE-inhibitor, ARB and antiplatelet treatments on AAA-growth are awaited[89,90,101].

Until this time, the care for patients with detected small AAAs should continue to be surveillance (watchful waiting), evaluation of the need for and the possible initiation of cardiovascular prophylactic treatment to prevent adverse cardiovascular outcomes in this population, which is at a high risk of concomitant cardiovascular disease[126].

SUMMARY

An abdominal aortic aneurysm (AAA) is an enlargement of the abdominal aorta. It is a common disease in the elderly, with a prevalence of 1-5%. An AAA is normally asymptomatic, and the diagnosis is often incidental, identified when a patient is examined for other conditions. The major risk of having an AAA is sudden rupture and death caused by massive hemorrhaging. As rupture risk increases with increasing AAA diameter, the current management strategies include regular imaging surveillance and elective repair before rupture occurs.

Ruptured AAA (rAAA) carries high mortality, and an identification of a drug or compound with the potential to halt the growth of an AAA and/or reduce the risk of a rAAA is needed. Thus, the aims of this thesis were to examine the clinical impact of treatment with statins (Study I), renin-angiotensin system (RAS) blockers (Study II), and low-dose aspirin (ASA)(Study III) on the risk of rAAA and case fatality following rAAA. The thesis is based on three nation-wide, combined case-control and follow-up studies using data from Danish population-based health-care and administrative registries.

In Study I (1996-2008), we included 3,691 patients with an incident diagnosis of rAAA (cases). For the risk analyses, we matched 3,584 rAAA cases to 3,584 age- and sex-matched patients with an incident diagnosis of AAA (controls). Current statin use was associated with a lower risk of rAAA, adjusted odds ratio (OR): 0.73 (95% CI: 0.61;0.86), compared to never use of statins. Furthermore, current statin use was associated with a lower 30-day case fatality following rAAA, adjusted mortality rate ratio (MRR): 0.80 (95% CI: 0.68;0.95).

In Study II (1996-2012), we identified 4,052 rAAA cases and 10,549 AAA controls. We were unable to demonstrate any association between the current use of either angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers and the risk of rAAA, adjusted ORs: 0.96 (95% CI: 0.85;1.07) and 0.93 (95% CI: 0.79;1.09), respectively. The results were robust in supplemental propensity score matched analyses. Likewise, no association between current use of RAS-blockers and 30-day case fatality was found.

In Study III (1996-2012), 4,055 rAAA cases were included. The adjusted OR for the risk of rAAA in ASA users compared to non-users was 0.97 (95% CI: 0.86;1.08). However, ASA use was associated with an unfavorable 30-day case fatality, adjusted MRR 1.17 (95% CI: 1.06;1.28), corresponding to an excessive rAAA case fatality in ASA users of nearly 20%.

In conclusion, we found an approximately 25% lower risk of rAAA and 20% lower 30-day case fatality in statin-treated patients. Furthermore, we found an almost 20% higher 30-day case fatality following rAAA in ASA treated patients. No association between the use of RAS-blockers and the risk of rAAA or case fatality following rAAA was found. Similarly, we found no association between the use of ASA and the risk of rAAA.

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