Cardiovascular comorbidity in patients with abdominal aortic aneurysmal disease

Nicolajsen, Chalotte Winther

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EPIDEMIOLOGY, PROGNOSIS AND TREATMENT OPTIONS

BY
CHALOTTE WINTHER NICOLAJSEN

DISSERTATION SUBMITTED 2023

AALBORG UNIVERSITY
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Chalotte Winther Nicolajsen

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PhD supervisor: Professor Torben Bjerregaard Larsen,
Department of Cardiology, Aalborg University Hospital
Department of Clinical Medicine, Aalborg University

Assistant PhD supervisors: Associate Professor, MD, PhD, Nikolaj Eldrup
Department of Vascular Surgery, Rigshospitalet
Institute of Clinical Medicine, Copenhagen University

Associate Professor, MSc, PhD Peter Brønnum Nielsen
Department of Cardiology, Aalborg University Hospital
Department of Clinical Medicine, Aalborg University

Associate Professor, DVM, PhD Mette Søgaard
Department of Cardiology, Aalborg University Hospital
Department of Clinical Medicine, Aalborg University

PhD committee: Clincal Professor Bodil Steen Rasmussen (chair)
Aalborg University, Denmark

Professor Jes Sanddal Lindholt
Odense University Hospital, Denmark

Associate Professor Birgitta Sigvant
Örebro University, Sweden

PhD Series: Faculty of Medicine, Aalborg University

Department: Department of Clinical Medicine

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ENGLISH SUMMARY

Abdominal aortic aneurysms, defined as a more than 1.5 times dilatation of the infrarenal aorta, are associated with risk of aortic rupture. Moreover, the disease is associated with a high burden of cardiovascular comorbidity and a higher risk of incident cardiovascular events and premature death than the general population, regardless of aneurysm-repair. The elevated risk of cardiovascular comorbidity and ischemic events is well described in the literature, yet a comprehensive insight of the cardiovascular burden among patients with abdominal aortic aneurysms in the Danish population is still lacking. The high cardiovascular risk implies a benefit of medical cardioprotective treatment. However, the evidence to guide current recommendations on treatment in patients with abdominal aortic aneurysms, especially antithrombotic therapy in those without concurrent symptomatic atherosclerotic disease, is sparse.

The overall aim of this thesis was to investigate the burden of concurrent cardiovascular comorbidity, the cardiovascular prognosis, and associated efficacy of medical cardioprotective treatment on prognosis in the Danish population of patients with abdominal aortic aneurysmal disease. The thesis is based on three epidemiological studies using data from the nationwide Danish health registries.

Study I describe temporal trends in cardiovascular comorbidity and concurrent medical cardioprotective therapy in patients with incident abdominal aneurysmatic disease. Over a 20-year period, the prevalence of atherosclerotic cardiovascular comorbidity and incidence of new ischemic events decreased, while the proportion of patients in medical prophylactic treatment with antiplatelets and statins increased. Despite these improvements, the burden of prevalent and incident cardiovascular atherosclerosis remained high, and half of the patients diagnosed with abdominal aortic aneurysms did not receive medical cardioprotective therapy within recent years. These findings indicate room for further optimization of preventive strategies.

Study II investigate the associated effect of new-onset atrial fibrillation on risk of ischemic events in patients with prevalent abdominal aortic aneurysms. In these patients, the cardiovascular prognosis also improved over time, in concordance with increasing implementation of relevant anticoagulant therapy. Despite observed improvements, the risk of suffering an ischemic stroke or myocardial infarction was still doubled after incident atrial fibrillation compared with before.

Study III compare the effectiveness of antiplatelet therapy vs no antiplatelet therapy on the risk of ischemic events and bleeding in patients with abdominal

aortic aneurysmal disease and no other manifestations of atherosclerotic vascular disease. Analyses revealed that antiplatelet therapy was associated with a trend towards lower risk of myocardial infarction and ischemic stroke, but also a higher risk of bleeding. Yet, the differences in event-free survival were minimal (less than 1%), indicating no clinically meaningful difference among patients treated with antiplatelet therapy vs no antiplatelet therapy.

The results from the studies included in this thesis, contributes to the existing knowledge on the burden of atherosclerotic comorbidity, as well as trends in and effect of medical cardioprotective treatment among patients with abdominal aortic aneurysmal disease. Our findings of an increasing proportion of patients with aneurysmatic disease without prevalent symptomatic atherosclerotic indicate a need of further investigations of potential differences in disease manifestation and prognosis in patients with and without symptomatic atherosclerosis. Further, the observed lack of clinical benefit of antiplatelet therapy in patients without symptomatic atherosclerotic disease, warrants caution in prescribing antiplatelets to all patients with abdominal aortic aneurysms, and highlights the necessity of a dedicated clinical trial investigating the effect of antiplatelet therapy in this patient group.

DANSK RESUME

Abdominal aorta aneurisme sygdom eller udposning på legemspulsåren i maven, defineres som en halvanden gange udvidelse på legemspulsåren under nyrearterierne. Sygdommen er ikke bare associeret med risiko for ruptur, men også med forøget risiko for konkurrerende hjerte-kar-sygdom, nye arterielle blodpropper og tidlig død, uanset om udposningen behandles eller ej. Selvom den øgede kardiovaskulære risiko er velbeskrevet i litteraturen, mangler der fortsat en tilbundsgående afdækning af omfanget af hjerte-kar-sygdom blandt patienter med udposningssygdom i den danske befolkning. Den forøgede kardiovaskulære risiko indikerer et behov for hjertemedicinsk forebyggende behandling. Evidensen bag de nuværende anbefalingerne er dog sparsom, især for blodfortyndende behandling til patienter med udposning, som ikke samtidig har påvist symptomgivende åreforkalkning.

Formålet med denne afhandling er at klarlægge omfanget af og prognosen for konkurrerende hjerte-kar-sygdom og medicinsk forebyggende behandling, samt at undersøge den associerede effekt af forebyggende blodfortyndende behandling med trombocythæmmer blandt patienter med udposningssygdom i Danmark. Afhandlingen er baseret på tre epidemiologiske studier udført på data fra de landsdækkende danske sundhedsregistre.

Studie I beskriver udvikling over tid i omfanget af hjerte-kar-sygdom og brug af medicinsk forebyggende behandling blandt patienter med ny-diagnosticeret udposning på legemspulsåren. Over en 20-årig periode observeredes forekomsten af konkurrerende hjerte-kar-sygdom at falde, mens andelen af personer i medicinsk forebyggende behandling med trombocythæmmer og statin var stigende over tid. På trods af forbedringer i medicinsk behandling var forekomsten af hjerte-kar-sygdom stadig meget høj, og halvdelen af de inkluderede patienter modtog fortsat ikke hjertemedicinsk forebyggende behandling i den seneste tidsperiode. Disse fund indikerer, at indsatser til at øge forebyggelsen af hjerte-kar-sygdom synes relevante for denne patientgruppe.

Studie II undersøger sammenhængen mellem ny-diagnosticeret forkammer flimren og risikoen for blodpropper blandt patienter med kendt udposningssygdom. Hos disse patienter fandt vi en forbedring af den kardiovaskulære prognose over tid, samtidig med en større andel af patienterne blev opstartet i relevant blodfortyndende behandling. Dog fordobledes risikoen for at få en blodprop i både hjerne og hjerte fortsat, efter at forkammer flimmer-diagnosen blev givet, sammenlignet med perioden inden diagnosen.

Studie III sammenligner virkningen af trombocythæmmende behandling mod ingen trombocythæmmende behandling på risikoen for blodpropper og blødning blandt

patienter med udposningssygdom uden samtidige symptomer på åreforkalkning. Undersøgelserne viste en association mod lavere risiko for blodpropper samt større risiko for blødning blandt patienter i behandling med pladehæmmer. Dog var forskellene mellem grupperne i event-fri overlevelse minimale (mindre end 1%), hvorfor forskellene ikke kan tillægges nogen klinisk relevant betydning.

Resultaterne fra studierne i denne afhandling, udbygger den eksisterende viden om omfanget af hjerte-kar-sygdomme samt udviklingen over tid og effekt af den medicinske forebyggende behandling blandt patienter med udposningssygdom. Den observerede stigende andel af patienter med udposning uden samtidig symptomgivende åreforkalkning, indikerer et behov for yderligere undersøgelser af potentielle forskelle i sygdomspræsentation og prognose mellem patienter som præsenterer sig med og uden samtidig symptomgivende åreforkalkning. Derudover bør resultaterne for effekt og risiko associeret til trombocythæmmende behandling give anledning til forsigtighed i brug af netop disse præparater hos patienter med udposning uden samtidig symptomgivende åreforkalkning, samt til yderligere forskning med dedikerede klinisk forsøg, som kan afdække en klinisk relevant fordel af behandlingen eller ej.

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"We cannot create observers by saying 'observe', but by giving them the power and the means for this observation and these means are procured through education of the senses."

Maria Montessori (1870-1952) Italian doctor and writer

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ABBREVIATIONS

AAA	Abdominal Aortic Aneurysmal disease
IHD	Ischemic Heart Disease
CeVD	Cerebrovascular Disease
PAD	Peripheral occlusive Arterial Disease
MI	Myocardial Infarction
AF	Atrial Fibrillation
OAC	Oral Anticoagulant therapy
DOAC	Direct Oral Anticoagulation therapy
CHA_2DS_2-VASc	Cardiac failure or dysfunction, hypertension, age > 75 years (doubled), diabetes, stroke (doubled)-vascular disease (atherosclerotic, excluding aneurysmatic disease), age 65 to 74 years, and sex category (female)
ICD-10	International Classification of Disease, version 10
ATC	Anatomical Therapeutic Chemical classification
CPR	Civil Personal Registration System
DNPR	Danish National Patient Registry
IR	Incidence Rate
OR	Odds Ratio
HR	Hazard Ratio
CI	Confidence Interval
IQR	Interquartile Range
DD	Daily Dose
ITT	Intention to Treat
OT	On Treatment

LIST OF PAPERS

This thesis is based on the following papers:

I

Temporal trends in abdominal aortic aneurysmal disease - A nationwide cohort study on cardiovascular morbidity and medical cardioprotective therapy. Nicolajsen CW, Søgaard M, Eldrup N, Jensen M, Larsen TB, Goldhaber SZ, Nielsen PB. European Journal of Preventive Cardiology, Volume 29, Issue 15, October 2022, p. 1957-64

II

Stroke and Myocardial Infarction in Patients with Abdominal Aortic Aneurysms and New-Onset Atrial Fibrillation. Nicolajsen CW, Nielsen PB, Jensen M, Eldrup N, Larsen TB, Lip GYH, Goldhaber SZ, Søgaard M. Thrombosis & Hemostasis, epub ahead of print January 2023

III

Antiplatelet therapy in patients with abdominal aortic aneurysm without symptomatic atherosclerotic disease: A target trial emulation of national observational data. Nicolajsen CW, Søgaard M, Jensen M, Eldrup N, Larsen TB, Goldhaber SZ, Behrendt CA, Nielsen PB. Submitted February 2023

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CHAPTER 1. THESIS STRUCTURE

This dissertation investigates the impact of concurrent cardiovascular and cerebrovascular comorbidity, cardiovascular prognosis, and associated medical cardioprotective treatment on prognosis in the Danish population of patients with abdominal aortic aneurysmal (AAA) disease. It is based upon three epidemiologic research studies, which are discussed in detail throughout the dissertation and are referred to by their Roman numerals (I, II, and III) in the text.

The dissertation is organized into nine chapters. The first chapters provide an overview of the existing knowledge on AAA and the associated risks and prognosis of cardiovascular disease, including atrial fibrillation (AF), along with current evidence and recommendations on medical cardioprotective therapy. The subsequent chapters provide a detailed outline of the studies, including objectives, methods, results, and discussion of the methodology in relation to the existing literature. The last chapters describe future perspectives, references, and appendixes.

CHAPTER 2. BACKGROUND

2.1. AAA – DEFINITION, PRESENTATION, AND BURDEN OF DISESASE

A true arterial aneurysm is defined as a permanent dilatation of an artery to more than one and a half times the normal size.[1] The infrarenal aorta is by far the most common anatomical location of an arterial aneurysm, here defined as a dilatation of more than three centimeters.[2] The formation of an AAA is attributed to age, gender, and a number of risk factors, such as smoking, hypertension, hypercholesterolemia, cardiovascular atherosclerotic disease, chronic obstructive pulmonary disease, and genetic predisposition. The strongest association is determined to be male gender, age above 65 years, and former or current tobacco use.[3–6]

AAA disease presents as a significant health concern, also in future perspective. Current estimates of prevalence of AAA among males 65 years and older in the western world range from 1%-5.5%, highest among smokers.[7,8] Within recent years, a decline has been observed in some countries, with the lowest prevalence of AAA (0.97%-1.7%) occurring in countries with established screening programs for AAA, such as Sweden and the UK .[9,10] The prevalence of AAA in the Danish population appears to remain constant at around 4%.[11]

Most AAA cases are asymptomatic and will be identified either incidentally during tests for other conditions or through screening.[10] If referred to a vascular unit, as recommended in the European guidelines[7], the patient will be offered enrolment in a surveillance program with regular ultrasound scans every 3 to 24 months, depending on AAA diameter. If the diameter of the AAA exceeds 5-5.5cm, the patient will be evaluated for prophylactic AAA repair.[2] Previous randomized trials and screening-based studies have demonstrated that patient are followed with ultrasound surveillance for an average of four years after diagnosis, and that 30%-60% of patients diagnosed with AAA will eventually reach the threshold for aneurysm repair.[12–14] A decreasing percentage of patients (from 9.2/100,000 during 1994 to 1999 to 6.9/100,000 during 2010 to 2014) present with symptoms of aneurysm expansion or actual rupture such as: sudden onset hypotension, abdominal or back pain, and/or a pulsatile abdominal mass.[15] If verified, it is a life-threatening condition necessitating immediate surgical intervention.[2,10]

2.2. AAA AND CARDIOVASCULAR COMORBIDITY

AAA and cardiovascular atherosclerosis share several risk factors, such as age, gender, smoking, and hypertension, leading to speculations of a possible causal relationship between the two.[16] However, there are also some significant discrepancies in risk profiles, in particular when it comes to the role of diabetes.

While diabetes is strongly associated with atherosclerosis, the association with the development of AAA appears to be neutral or even negative, with some studies suggesting this association may be attributed to treatment with Metformin.[17–20] A summary of the main similarities and differences are presented in Table 1. Generally, cardiovascular atherosclerosis and AAA are now considered distinct disease entities; yet, the presence of atherosclerosis is still thought to promote the degenerative process causing AAA formation.[18,19,21]

Table 1. Similarities and differences between atherosclerosis and AAA (modified from Golledge et al. Arteriosclerosis, thrombosis, and vascular biology, 2010[17])

Characteristics	Similarities	Differences
Clinical risk factors	Common risk factors; smoking, hypertension, hypercholesterolemia.[17, 18,22]	Diabetes; no or protective association with AAA, but strong negative association with atherosclerosis, male gender and smoking are more dominant risk factors for AAA[17,18,22]
Circulating risk factors	Similar biomarkers; fibrinogen, CRP, HDL (negative), apolipoprotein status[23]	LDL; strong association with atherosclerosis, but not AAA[24]
Genetic risk factors	Family history; strongly associated with AAA and atherosclerosis.[18] A locus on chromosome 9p21 is associated with IHD, stroke and AAA[25]	Several genetic determinants of atherosclerosis that have no association with AAA, e.g. apolipoprotein E genotype[18,26]
Histology	Presence of intimal atheroma and thrombosis[18,27]	Marked elastin fragmentation and adventitial chronic inflammation are mainly restricted to AAA[18]

Abbreviations: AAA, abdominal aortic aneurysm; CRP indicates C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; IHD, ischemic heart disease.

Given the associations between AAA and the number of comorbidities (defined as two or more simultaneous medical conditions), atherosclerotic cardiovascular comorbidity is a natural focus in the management of AAA and in the modification of risk factors.[22,28–30] Compared with people without AAA, the prevalence of several cardiovascular risk factors and comorbidities are twice as high, when AAA is diagnosed, as shown in a screening study from the United Kingdom (UK) (Table 2).[31]

The range of cardiovascular comorbidity among AAA patients varies between studies. Data from UK primary care between 2000 and 2012 indicated a high prevalence of ischemic heart disease (IHD) of 32.0%, cerebrovascular disease (CeVD) 16.6%, and peripheral arterial occlusive disease (PAD) 24.3%, registered among patients diagnosed with AAA.[28] However, a lower prevalence was reported in 2013-2015 among men aged 65 years or older with screening-detected AAA in the UK, with patient-reported IHD at 20.0% and CeVD at 6.3% (Table 2).[31] In Denmark, a 2014-2017 screening cohort of 65-75 year old men with AAA showed a patient-reported IHD prevalence of 24.3%, CeVD at 12.9%, and PAD at 5.0%.[32] Additionally, an increasing prevalence of cardiovascular comorbidity was observed compared to earlier populations with similar AAA screening criteria.[33] Variations in reporting standards and target populations, may account for some of these differences. Yet, comprehensive insights of the cardiovascular burden in the AAA population are still lacking.

Other concomitant health conditions also impact the cardiovascular outcome and survival of these patients. Much like atherosclerotic disease, AAA share several common risk factors with atrial fibrillation (AF), including age, smoking habits, and hypertension.[34,35] A recent cohort study found a link between AF and AAA.[36] Furthermore, a positive association between AAA and a higher risk of AF was noticed, although it was uncertain whether this relationship was in fact due to other existing risk factors or to the AAA diagnosis itself.[36,37] AF and atherosclerotic cardiovascular disease are strongly related, with the presence of both conditions leading to an elevated risk of ischemic cardiovascular outcomes, for instance ischemic stroke and myocardial infarction (MI).[38,39] Potentially, the same holds true for patients with AAA, although this association has not been previously studied in-depth.

Table 2. Differences in cardiovascular risk factors and comorbidity status in a UK screening population, the United Kingdom Aneurysm Growth Study (modified from Bath et al., Eur J Vasc Endovasc Surg 2017[31]).

	Non-aneurysmal group	AAA group	p-value
N (all male)	4871	384	-
Mean age (95% CI)	69.8 (69.7-69.9)	71.9 (71.4-72.5)	<.0001
Smoking (current)	5.2% (249/4788)	15.3% (56/366)	<.0001
Smoking (ever)	57.1% (2614/4580)	84.1% (270/321)	<.0001
Hypertension	37.8% (1769/4677)	57.8% (203/351)	<.0001
Hypercholesterolemia	31.5% (1456/4615)	53.2% (185/348)	<.0001
Diabetes	10.4% (478/4580)	17.7% (62/350)	<.0001
IHD	5.8% (279/4778)	20.0% (73/366)	<.0001
CeVD	3.1% (146/4773)	6.3% (23/363)	.0007

Prevalence displayed as % (n/N), Abbreviations: AAA – abdominal aortic aneurysm; IHD – ischemic heart disease; CeVD – cerebrovascular disease.

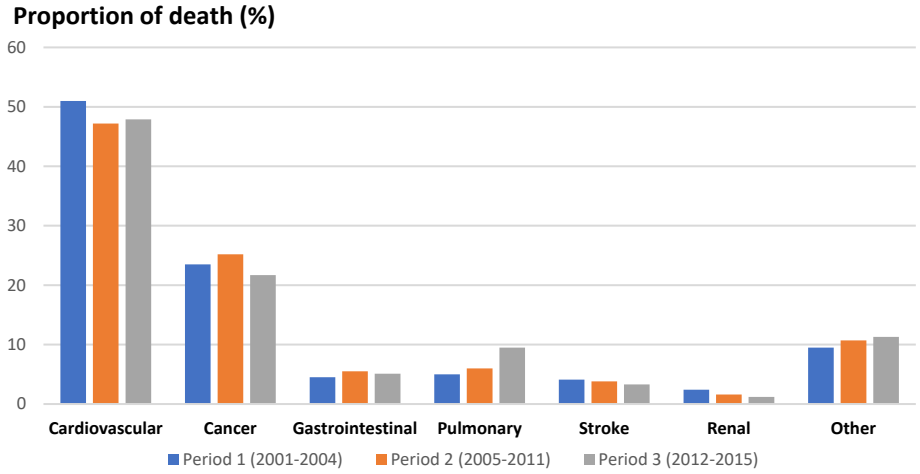
2.3. AAA AND CARDIOVASCULAR PROGNOSIS

AAA disease comes with an inherent increase in risk of cardiovascular ischemic events and mortality. In comparison to a population without AAA, matched on sex and age, the risk of first-time MI and stroke is 50-70% higher post-diagnosis, and the long-term risk of ischemic events after AAA repair is almost doubled.[29,40,41] Additionally, the annual cardiovascular mortality risk among patients with AAA is 3% from time of diagnosis, compared with 0.8% in the general population.[29]

Over the past decades, short-term and aneurysm-related survival have seen significant improvements, mainly driven by advances in AAA repair techniques and screening.[2,30,42] However, long-term survival has not seen a similar level of improvement.[43] In comparison to a non-AAA population, survival remain lower (HR

0.89 (95% CI: 0.86–0.91)) and have not changed since the early 2000.[30] Cardiovascular risk factors and comorbidity has a greater impact on prognosis, than the AAA disease itself, along with age, gender and other serious comorbidities, such as end-stage pulmonary and renal disease.[43] Further, cardiovascular death remains the primary cause of death in the patient group, as displayed in Figure 1.[30]

Figure 1. Causes of death after AAA repair in Sweden (modified from Bulder et al. Ann Vasc 2020[30])



2.4. AAA AND CARDIOPROTECTIVE MEDICAL THERAPY

Several clinical trials have attempted to find a method to slow the pace of AAA expansion through utilization of different drugs (statins, doxycycline, beta-blockers and angiotensin converting enzyme inhibitors).[2] Yet until now, no particular medical therapy has been demonstrated to modify AAA growth, aside from smoking cessation.[2]

Given the burden of cardiovascular atherosclerotic comorbidity and the increased risk of cardiovascular events among patients with AAA, cardiovascular risk modification are recommended at time of diagnosis to improve life expectancy and disease-free survival.[7,44,45] Modifications may include advice on smoking cessation, exercise, and medical treatment of elevated blood pressure and cholesterol levels.[7] The use of cardioprotective medications, such as statins, antiplatelets, and antihypertensive agents, have been associated with a 15-35% improvement in overall long-term survival.[28,46–48] However, no dedicated randomized trials have been

performed to evaluate the effects of cardioprotective drugs in the AAA population specifically, and evidence are based on observational studies, that may be prone to confounding and selection bias.[47–50] Additionally, a recently published metanalysis, regarding the consequences of antithrombotic treatment, based on these observational data, failed to provide evidence for an effect on cardiovascular outcomes, nor any positive association with survival in patients with AAA under surveillance.[48] Consequently, absolute indications for initiation of statin and antiplatelet therapy are only given in patients with AAA and concomitant peripheral arterial occlusive disease.[2,44,45] Notwithstanding, international guidelines for AAA management still recommend considering medical cardioprotective therapy to all patients with AAA (Level B/C evidence).[2,51] The most recent consensus document (2021) on antithrombotic therapy from the European Society of Cardiology even suggests antiplatelet therapy to all patients with AAA with no contraindications for treatment, based on the same evidence.[52] For patients requiring oral anticoagulant (OAC) therapy (e.g., AF and a CHA_2DS_2-VASc score > 1 (>2 for females)), it is advisable to refrain from dual pathway inhibition with OAC and antiplatelet therapy if possible, due to a high risk of bleeding.[52,53]

2.5. GAPS IN EXISTING LITERATURE

Cardiovascular atherosclerotic comorbidity is a risk factor for AAA development, as well as a major contributor to excess morbidity and mortality in this patient group.[18,21] An excessive burden of cardiovascular comorbidity is consistently reported in population-based AAA studies. However, the exact prevalence of comorbidity varies between studies and up-to-date data is missing.

The efficacy of medical cardioprotective treatments for patients with AAA is not straightforward, and there is not much evidence to guide practitioners in providing recommendations to AAA patients without concurrent symptomatic atherosclerotic comorbidity. Speculations on the beneficial effect of antiplatelet and statin therapy in patients with no concurrent atherosclerosis, have likely led to initiation of medical cardioprotective therapy in asymptomatic patients.[51,52] However, the exact implementation of medical preventive therapy in the Danish AAA population is not known. Despite intensified recommendations, primary prophylaxis with antiplatelets for those with AAA but no manifestations of atherosclerotic disease is still controversial, due to the increased risk of bleeding and limited evidence of benefits of treatment in asymptomatic atherosclerosis.[52,54,55] To strengthen future recommendations on medical cardioprotective treatment, more studies are needed to enforce the role of antiplatelet agents in AAA patients.

Therefore, this dissertation investigated the temporal changes in the prevalence of cardiovascular comorbidity, the use of medical cardioprotective therapy and the cardiovascular prognosis in the AAA population at time of diagnosis (Study I), the

influence of new-onset AF on cardiovascular prognosis and medical antithrombotic treatment (Study II), and the influence of antiplatelet therapy on cardiovascular prognosis in AAA patients without symptomatic atherosclerotic disease (Study III).

CHAPTER 3. SPECIFIC AIMS

The three sub-studies were conducted with the following specific aims:

Study I

To provide updated nationwide data on temporal trends in cardiovascular comorbidity, medical cardioprotective treatment and cardiovascular outcomes after AAA diagnosis.

Study II

To investigate associations between incident AF and risk of stroke and MI in patients with prevalent AAA disease. A second objective was to ascertain changes in antithrombotic therapy associated with the AF diagnosis.

Study III

To estimate the effect of antiplatelets on risk of ischemic events (MI, stroke) and bleeding in patients with AAA and no manifestations of atherosclerotic vascular disease, we designed a target trial and emulated the trial using nationwide observational healthcare data.

Table 3. Summary of methods

	Study I	Study II	Study III
Objectives	To examine temporal trends in cardiovascular comorbidity, medical cardioprotective treatment and cardiovascular outcomes after AAA diagnosis	To investigate associations between incident AF, risk of stroke and MI and antithrombotic treatment in patients with prevalent AAA	To estimate the effect of antiplatelets on risk of ischemic events (MI, stroke) and bleeding patients with AAA and no other manifestations of atherosclerotic vascular disease
Design	Population-based cohort study	Cohort and exposure-crossover study	Target trial emulation of observational data
Study period	January 1999 – December 2018	January 1997 – December 2018	January 2010 - August 2021
Study population	Patients with a first diagnosis of AAA (n=33,296)	Patients with prevalent AAA and subsequent incident AF (n=3,035)	Patients with prevalent AAA and no history of atherosclerotic vascular disease who were naïve for antiplatelet therapy (n=6,344 / 131,047 trial cases)
Exposure	Incident diagnosis of AAA Analyses stratified according to year of diagnosis by four periods: 1 "1999-2003", 2 "2004-2008", 3 "2009-2013" and 4 "2014-2018"	Incident diagnosis of AF	Antiplatelet (Aspirin or Clopidogrel) use
Outcomes	1. Incidence of AAA 2. Cumulative incidence rates of atherosclerotic cardiovascular disease (CeVD, IHD and PAD)	1. MI and ischemic stroke 2. Antithrombotic therapy (antiplatelets and oral anticoagulants)	1. Ischemic events (MI and ischemic stroke) 2. Major bleeding
Follow-up	2 years	1 year	5 years
Covariates	Age, sex, type of AAA, atherosclerotic cardiovascular comorbidity (IHD, CeVD, PAD), hypertension, chronic pulmonary disease, chronic kidney disease, heart failure, atrial fibrillation, venous thromboembolism, heart valve replacement, diabetes mellitus, rheumatic disorders, malignancy, cardioprotective therapy (aspirin, statins, antihypertensives and OAC).	Age, sex, CeVD, MI, PAD, congestive heart failure, diabetes, chronic pulmonary disease, renal insufficiency, venous thromboembolism), hypertension, CHA_2DS_2-VASc score, and comedications use of anticoagulants, antiplatelets, statins, antihypertensives and antiarrhythmics	Age, sex, calendar year of inclusion, CeVD, IHD, PAD, recent major bleeding, major liver- or renal-impairment, cancer, hypertension, diabetes, atrial fibrillation, and heart failure, medical treatment with cardioprotective agents (antiplatelets, OAC, statins and antihypertensive therapy), and a proxy for smoking status (diagnosis of smoking related COPD, tobacco abuse/ registered smoking, smoking cessation advice and medicine).
Statistics	Calculation of age- and sex-standardized incidence rates, time-to-event analyses, Kaplan-Meier and Aalen-Johansen estimates	Time-to-event analysis with Aalen-Johansen estimates, McNemar's test for matched pairs	Pooled logistic regression Observational analogue to ITT and OT treatment effect
Confounder control	Stratification, restriction	Stratification, self-controlled/crossover analyses, induction period	Directed acyclic graph, Inverse probability weights of propensity scores
Subgroups	+/- Presence of atherosclerotic cardiovascular disease (CeVD, IHD and PAD) at the time of AAA diagnosis	Groups according to year of AF diagnosis (1997-2010, 2011-2018)	+/- concurrent treatment with statins, >80 years of age, type of antiplatelet (aspirin or clopidogrel), excluding prevalent cancer patients
Sensitivity analyses		Length of the induction interval (4, 8, 16 and 24 weeks before AF diagnosis and 0 and 2 weeks after AF diagnosis), restricted to those surviving until end of observation period.	prolonging the discontinuation gap to 90 days and restricted to patients diagnosed with AAA < 6 months prior to inclusion.

AAA; abdominal aortic aneurysm, CeVD; cerebrovascular disease (ischemic stroke and transitory ischemic attack), IHD; ischemic heart disease (angina and myocardial infarction), PAD; peripheral arterial disease (intermittent claudication, rest pain, ischemic ulcers and gangrene), OAC; oral anticoagulant therapy, AF; atrial fibrillation, MI; myocardial infarction, CHA_2DS_2-VASc score; cardiac failure or dysfunction, hypertension, age > 75 years (doubled), diabetes, stroke (doubled)-vascular disease (atherosclerotic, excluding aneurysmatic disease), age 65 to 74 years, and sex category (female)[1], ITT; Intention-to-treat, OT; On-treatment

CHAPTER 4. METHODS

Methods used for each study is summarized in Table 3

4.1. SETTING

Data utilized for the analyses presented in this dissertation was extracted from the unified health registries covering the entire Danish population. The Danish Health Services routinely collect and document these data, and all hospitals in Denmark are mandated to follow a registry policy, which translates to near-total enrolment of the entire Danish population.[56] This individual-level linkage of registry data is enabled by the unique personal registration system number (CPR), assigned to all citizens upon birth or immigration.[57] All Danish citizens are entitled to free and equal access to general practitioners, hospitals and partial reimbursement for prescribed medications, such as aspirin taken for cardioprotection.[56,58]

4.2. DATASOURCES

We used data collected from three national population-based administrative and medical registries as visualized in Figure 2.[59]

The Civil Registration System

The Civil Registration System tracks all legal residents through the CPR number and records contact with the official authorities, and contains information on date of birth, sex, marital and vital status for all residents since 1968. Information is updated on a daily basis.[57]

The Danish National Patient Registry

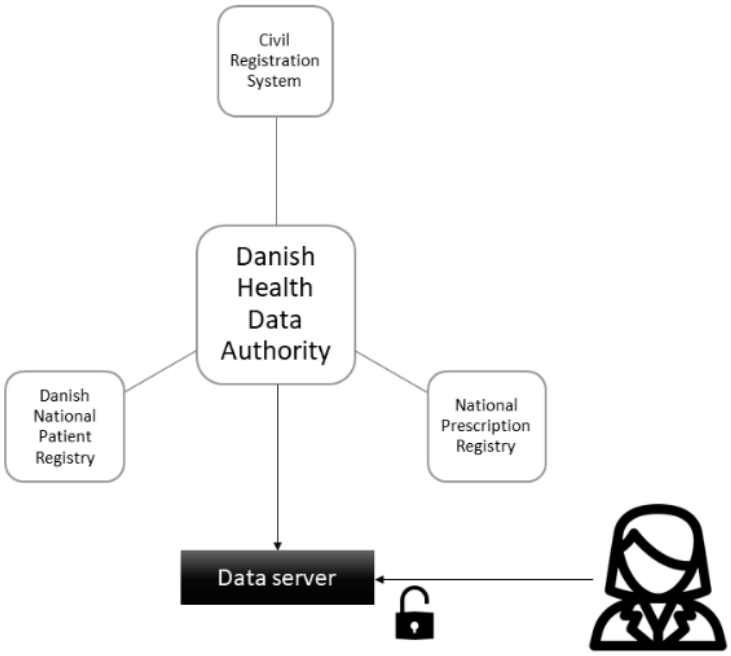
The Danish national patient registry (DNPR) covers all in- and outpatient hospital registrations. The DNPR has stored information on hospitalizations since 1977, and outpatient and emergency department visits at all hospitals in Denmark since 1995.[56,60] Data include Civil Personal Registry numbers, dates of admission and discharge, and up to 20 diagnoses coded by the International Classification of Diseases (ICD-10).[60]

The National Prescription Registry

All pharmacies in Denmark use electronic accounting systems, with the primary purpose of securing reimbursement from the National Health Services.[61] Data on every redeemed prescription is electronically transferred to the Danish Health Data

authorities and are available for research through the Danish National Prescription Registry, which stores detailed information on purchase dates, Anatomical Therapeutic Chemical (ATC) classification code, package size, and dose for every prescription claim, with national coverage since 1994.[62]

Figure 2. Data linkage and flow of data from Danish health registries used in Study I-III



4.3. STUDY DESIGNS

In the setting of the Danish population-based healthcare system, we conducted two cohort studies (Study I and II), a combined cohort and self-controlled exposure-crossover study (Study II), and a target trial emulation of observational data (Study III) (see Table 3. Summary of study design).

4.4. STUDY POPULATION

All three studies were nested within the population of patients registered with a diagnosis of AAA in the DNPR. Study I included all patients diagnosed with incident AAA between January 1999 and December 2018. Study II included those with any diagnosis of AAA registered between January 1997 and December 2018, while Study III was restricted to patients registered with a diagnosis of AAA from January 2010 until August 2021.

The diagnosis of AAA was identified either by a primary or secondary discharge diagnosis (in- and outpatient ICD-10 codes: I713, I714) in the DNPR. A previous validation study have reported a positive predictive value of the AAA diagnosis in the DNPR of >98%.[63] Patients who had not been resident in Denmark within the year before AAA diagnosis were excluded. Patients aged <50 years were excluded to account for patients with potential erroneous diagnosis of AAA and to exclude patients with severe connective tissue disease, which has a different aetiology than degenerative AAA.[64]

Study II was further restricted to patients with no history of prevalent AF, but with concurrent new-onset AF after the AAA diagnosis. The study population in Study III was restricted to patients without any previous diagnosis of atherosclerotic vascular disease (IHD, PAD or CeVD) and no previous prescription record of antiplatelet therapy.

4.5. EXPOSURES, OUTCOMES AND CONFOUNDING FACTORS

The exposure of interest in Study I was the incident diagnosis of AAA, as described in the previous section.

Atrial fibrillation

In Study II, the exposure was defined as a diagnosis of new-onset AF registered as a primary or secondary discharge diagnosis (in- and outpatient ICD-10 code: I48) in the DNPR. Previous validation studies have reported a positive predictive value of the AF diagnosis in the DNPR of 92.6%.[65]

Antithrombotic therapy

We used the Danish National Prescription Registry to identify prescription claims for antithrombotic drugs, classified as antiplatelet therapy; aspirin, clopidogrel and other thienopyridines (ATC codes: B01AC06, B01AC04, B01AC24 and B01AC22) and OAC therapy; coumarins including warfarin, phenprocoumon, rivaroxaban, apixaban, dabigatran and fondaparinux (ATC codes: B01AA03, B01AA04, B01AE07,

B01AF01, B01AF02, B01AF03 and B01AX05). In Denmark, aspirin is also available as an over-the-counter drug, sold from pharmacies, and was thus potentially not registered in the Danish National Prescription Registry in all cases. Yet, with an estimated proportion of total sales of low-dose aspirin (75-150 mg) dispensed by prescription of 92% in 2012, over-the-counter use of low-dose aspirin is not common in Denmark.[66]

In Study I and II, the use of any antithrombotic drugs was an outcome measure, stratified on at least one prescription claim of antiplatelet therapy or OAC therapy. In Study I, prescriptions claimed within 365 days before and up to 90 days after AAA diagnosis was used as a descriptive measure, while in Study II records of prescriptions claimed after the AF-diagnosis was analysed as an outcome measure.

In Study III, the exposure of interest was initiation vs no initiation of antiplatelet therapy, here restricted specifically to aspirin or clopidogrel (ATC codes: B01AC06 or B01AC04). Discontinuation dates for on-treatment (OT) analyses were calculated using daily dose (DD) and number of pills provided in each prescription.

All-cause mortality

All-cause mortality was a secondary outcome measure in Study I and a sensitivity outcome in Study III. The exact date of death was ascertained through the Danish Civil Registration System.

Ischemic events and admissions

Cardiovascular outcomes or ischemic risk was the main outcome of interest throughout the three studies.

For Study I, the main outcome was new in-hospital admissions for atherosclerotic cardiovascular disease (IHD, CeVD and PAD), with separate outcome analyses for the specific outcomes of MI and ischemic stroke.

In Study II and III, outcome analyses were restricted to the specific outcomes of MI and ischemic stroke (Study II) and as combined effect estimate (Study III), since they have the highest predictive values (MI; ICD-10 code I21, PPV 92.4%-97%[63,67], ischemic stroke; ICD-10 code I63, PPV 79%-87%[68,69]) in the DNPR.

Bleeding

Bleeding was defined as any bleeding (except nosebleed) requiring hospital-admission and was assessed as a safety outcome in Study III.

Confounding factors

To characterize the study populations, adjusted for confounding, and to perform subgroup analyses, we obtained information on demographic data, comorbidities, and medical treatment from in- and outpatient medical history as well as prescription data history. If possible, we combined prescription and hospital data to increase sensitivity for covariates such as diabetes and hypertension.

See further specifications on variables and codes in Appendix I-III.

4.6. STATISTICAL ANALYSES

Design of the specific studies are described in detail in appendices I-III and are summarized in Table 3 under Summary of study methods, while study methods potentially new to the readers of this dissertation are specified in this section.

4.6.1. STRATIFICATION

To illustrate changes over time as well as changes in medical cardioprotective treatment patterns, patient inclusion was stratified into four time periods in Study I; 'Period 1' (1999–2003), 'Period 2' (2004–2008), 'Period 3' (2009-2013), and 'Period 4' (2014–2018), and in two time periods in Study II: 1997-2010 and 2011-2018. For the same purposes analyses was stratified in two time periods in Study II; 1997-2010 and 2011-2018.

4.6.2. TIME-TO-EVENT ANALYSES

Time-to-event analyses were applied to calculate incidence rates of outcomes in Study I and II. Kaplan-Meier estimates were used to describe the risk of all-cause mortality (Study I). Further, competing risk analysis was performed, with a competing risk defined as an event whose occurrence precluded the primary event of interest. Assuming independent censoring, crude Aalen-Johansen estimates were used to depict cumulative incidence curves for each outcome with death as a competing risk. Outcomes were reported as cumulative incidence proportions (Study I and Study II), and incidence rates (IR) (events per 100 person-years) (Study I).

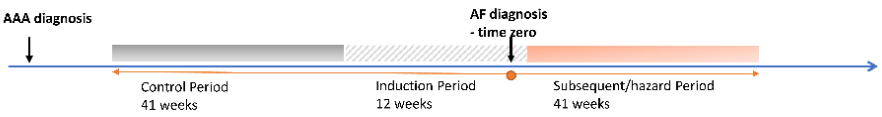
4.6.3. SELF-MATCHING ANALYSES (STUDY II)

In study II, we aimed to analyse the changes in risk of ischemic events associated with AF in patients with AAA. However, patients with AAA and AF may differ from AAA patients without AF with respect to several clinical characteristics, demographic factors, and lifestyle habits, which were not all accessible through health registry data. Additionally, patients with prevalent AF would be a heterogenous group of patients affected by the same factors, as well as affected by differences in time interval between AF and AAA diagnoses. Therefore, an observational study including

patients with prevalent AF, could be susceptible to confounding by factors potentially related to our outcome of interest. Consequently, we chose to apply a self-matched study design with incident AF as the exposure of interest. This exposure-crossover analysis by design minimizes both measured and unmeasured confounding that does not vary over time, such as genetics, education level, and lifestyle.[70] In our study, case self-matching consisted of a within-patient comparison of ischemic outcome events occurring in a predefined period after AF diagnosis (the "subsequent interval") compared with outcome events occurring in a matched period before AF (the "baseline interval"), Figure 3 illustrates the exposure-crossover study design.[71] This design allowed for analyses of the changes in risk of ischemic events associated specifically to the AF diagnosis.[70]

Specifications on time-intervals compared are provided in Appendix II. In the exposure-crossover analyses we estimated the relative odds (matched odds ratio (OR) of primary outcomes in the subsequent interval after AF diagnosis compared with the baseline interval before AF by using McNemar's test for matched pair's data.

Figure 3. Exposure-crossover study design



4.6.4. TARGET TRIAL EMULATION (STUDY III)

In Study III, we sought to compare the effect of antiplatelet therapy vs no antiplatelet therapy on the risk of ischemic events and bleeding in patients with AAA and no other manifestations of atherosclerotic vascular disease. The ideal method for estimating the efficacy and safety of treatment would be a randomized controlled trial. Yet, given the ethical issues concerning randomization of antiplatelet therapy considering current treatment recommendations, as well as conjectured difficulties raising funding for such a trial, we imagine such a trial to be highly unlikely. Hence, with the comprehensive and high quality of Danish health registry data, an appropriate alternative for analyses could be a target trial emulation using observational data.[72] We therefore specified a target trial protocol for estimation of the average treatment effect of antiplatelet therapy vs no treatment on the incidence of ischemic events (MI and ischemic stroke) and major bleeding in antiplatelet-naïve patients with prevalent AAA disease. Specifications of trial components are listed in Table S1 and Supplement A in Appendix III. We emulated

the target trial using data from the Danish national health registries and mirrored the target trial components whenever possible, with modifications required to accommodate the use of observational data. Participants could potentially meet the eligibility criteria for the target trial multiple times during the study period. For statistical efficiency and to enable inclusion of patients eligible more than once, we emulated the target trial as a sequence of trials, with a new trial starting at each of the possible 140 months new trial months in the predefined study period.[73] This allowed individuals to contribute information to multiple trials, depending on status of eligibility.[74,75] Screening for inclusion was assessed in the first (baseline) month of each of the sequential trials, and eligible individuals were assigned to a treatment group and followed from the end of baseline month until censoring or end of follow-up. We emulated target trial randomization assuming exchangeability conditional on the propensity for receiving the observed treatment, considering baseline covariates; age, sex, relevant comorbidity (hypertension, diabetes, atrial fibrillation, renal insufficiency, and heart failure), medical treatment with other cardioprotective agents (statins and antihypertensive therapy), and smoking status. We analysed data by fitting pooled logistic regression models of each effect estimate of interest (Intention-to-treat; ITT and On-treatment; OT) and pooled the emulated trials. The statistical analyses accounted for the repeated use of individuals by clustering in the logistic regression models. We estimated the average treatment effect as the difference in 5-year risk of outcomes, expressed as hazard ratios (HR) and event-free survival-curves conditional on baseline covariates defined in Appendix III.[76] We used nonparametric bootstrapping with 500 samples to calculate 95% confidence intervals (CI).

OT analyses were performed with censoring at discontinuation of antiplatelet therapy in the treatment arm and initiation of antiplatelet therapy in the non-treatment arm. Discontinuation was defined based on daily dose (DD) calculations from date of initiation of antiplatelet therapy and with a maximum gap between DDs of 60 days. On-treatment analysis was performed with adjustments for baseline covariates, as well as time-varying post-baseline covariates (described in Appendix III) associated with adherence and with the outcome of interest.

4.7. ETHICAL CONSIDERATIONS

In Denmark, registry-based studies in which specific individuals cannot be identified are not required to receive approval from an ethics committee. The study was conducted in accordance with the General Data Protection Regulation and the North Denmark Region's record of Processing Activities (project no. 2017-40). The data were provided by the Danish Health Data Authority.

CHAPTER 5. RESULTS

The main findings of included studies are summarized in the following sections.

5.1. TEMPORAL TRENDS IN AAA – CARDIOVASCULAR CO-MORBIDITY AND CARDIOPROTECTIVE TREATMENT (STUDY I)

A total of 33,296 individuals were diagnosed with AAA in Denmark during 1999 to 2018, increasing from 6,009 individuals in Period 1 (1999-2003) to 9,998 in period 4 (2014-2018). Median age at diagnosis was approximately 73 years and consistent throughout the study periods, and approximately 25% were females (Table 5).

5.1.1. CARDIOVASCULAR COMORBIDITY – PREVALENCE AND PROGNOSIS

The proportion of patients with a history of any atherosclerotic cardiovascular disease decreased continuously over time (from 41.5% in Period 1 to 32.6% in Period 4), mainly driven by a lower proportion of patients with prevalent IHD (24.3% to 19.2%) and PAD (17.2% to 11.0%), Table 5. With regards to other comorbidities, the proportion of patients with a diagnosis of hypertension (17.9% to 30.8%), diabetes (5.2% to 8.7%), AF (9.6% to 12.5%), and cancer (8.8% to 13.9%) increased over time.

The incidence of atherosclerotic vascular disease and ischemic events requiring admission after AAA diagnosis was high but decreased over time for each successive time period. A more than 50% reduction in IR of all ischemic events was observed from Period 1 to 4, also for CeVD. Details are described in Table 3 in Appendix I. The same reduction was observed for all-cause mortality at two-year follow-up (IR 24.3 (CI 95%; 23.2-25.3) in Period 1 decreasing to IR 12.4 (CI 95%; 11.9-13.0) in Period 4).

Table 5. Prevalence of comorbidities in patients diagnosed with AAA between 1999 and 2018, stratified by time period (modified from Table 1 in Study I, Nicolajsen et al., Eur J Prev Cardio 2022[64])

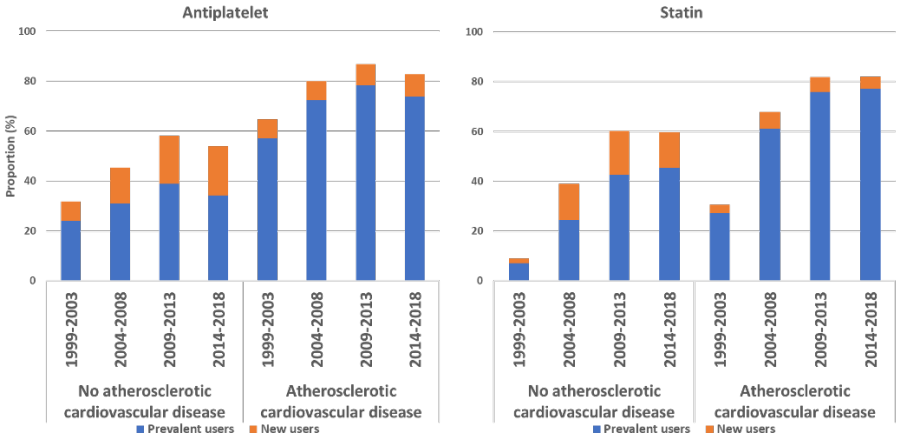
	Period 1 1999-2003	Period 2 2004-2008	Period 3 2009-2013	Period 4 2014-2018	Stand. Diff
Demographics, % (N)					
N	6009	7784	9602	9998	
Age, median (IQR)	73 (67-79)	73 (68-79)	74 (68-79)	74 (69-80)	0.13
Female	24.7 (1458)	25.1 (1950)	23.8 (2281)	23.5 (2351)	0.04
Any atherosclerotic cardiovascular disease	41.5 (2456)	40.7 (3169)	36.3 (3487)	32.6 (3264)	0.19
Cerebrovascular disease	10.4 (613)	10.7 (832)	9.1 (875)	8.9 (887)	0.06
- Ischemic stroke	7.8 (459)	8.0 (620)	6.4 (617)	6.4 (635)	0.06
Ischemic heart disease	24.3 (1439)	24.5 (1910)	21.7 (2080)	19.2 (1916)	0.13
- Myocardial infarction	7.8 (459)	7.0 (546)	6.0 (575)	5.3 (531)	0.10
Peripheral arterial occlusive disease	17.2 (1017)	15.0 (1168)	12.9 (1239)	11.0 (1102)	0.18
Comorbidity, other					
Hypertension	17.9 (1059)	26.8 (2084)	30.1 (2889)	30.8 (3084)	0.31
Diabetes	5.2 (308)	7.3 (571)	8.5 (819)	8.7 (867)	0.14
Heart Failure	9.9 (585)	9.6 (744)	8.1 (773)	7.9 (774)	0.07
Atrial Fibrillation	9.6 (559)	11.5 (892)	11.6 (1112)	12.5 (1251)	0.10
Chronic Pulmonary Disease	12.5 (740)	13.2 (1025)	13.4 (1288)	14.4 (1440)	0.06
Chronic Renal Disease	4.9 (290)	5.2 (405)	5.9 (571)	6.2 (617)	0.06
Cancer	8.8 (522)	10.8 (844)	12.8 (1233)	13.9 (1394)	0.16
Venous Thromboembolism	2.4 (141)	2.6 (201)	3.0 (285)	3.8 (381)	0.08

Abbreviations: AAA –abdominal aortic aneurysm; N – number; IQR – Inter quartile range; Stand.Diff. - Standardized difference between time periods (SD > 0.1 = significant difference)

5.1.2. MEDICAL CARDIOPROTECTIVE TREATMENT

A general increase in the use of all cardioprotective drugs was observed. The proportion of patients using antiplatelets went up from 45.6% in Period 1 to 68.7% in Period 3, yet with a minor decrease to 63.3% in Period 4. When including OAC use, the utilization of any antithrombotic medication plateaued in Period 3. The utilization of statins increased from 17.9% in Period 1 to 66.9% in Period 4, with a plateau in Period 3. When stratifying based on the history of atherosclerotic disease (CeVD, IHD and PAD), the same trends emerged, though medication usage was the highest in patients with comorbid atherosclerotic disease (Figure 4). Amongst those, who initiated cardioprotective treatment after AAA diagnosis (new users) the largest proportion of new users was observed among those without any record of atherosclerotic disease (Figure 4).

Figure 4. Proportion of patients in medical cardioprotective treatment with antiplatelet and statin therapy at time of AAA diagnosis according to time period and history of atherosclerotic vascular disease (modified from Nicolajsen et al. Eur J Prev Cardio 2022[64])



5.2. AAA AND INCIDENT ATRIAL FIBRILLATION (STUDY II)

A total of 3035 patient with prevalent AAA and subsequent AF were included in Study II. The study population were older, and a larger proportion had a record of one or more simultaneous comorbidities at time of AF diagnosis, compared to the total AAA population described in Study I (Table 5. Prevalence of comorbidities (Study I)). The median age was 78 (IQR; 73-83) and 18% had a history of prior ischemic stroke,

23.9% had prior MI, and 38.5% had PAD. The median CHA_2DS_2-Vasc score was 4 (IQR: 3-5) (see details in Table 1 in Appendix II).

5.2.1. CARDIOVASCULAR PROGNOSIS IN ASSOCIATION WITH ATRIAL FIBRILLATION

Over time, the risk of experiencing an ischemic event after incident AF decreased. During 1997-2010, the cumulative risk of ischemic stroke was 5.9% (95% CI; 4.6%-7.5%) after one-year follow-up, while it was 4.5% (95% CI; 3.7-5.5%) during 2011-2018. For MI, the cumulative risk was 5.4% (95% CI; 4.2%-6.9%) during 1997-2010, and 4.0% (95% CI; 3.2%-4.9%) during 2011-2018. However, when examining the within-individual risk of ischemic events associated with the AF diagnosis, we found a substantially higher risk regardless of time period. Matched OR for ischemic stroke was 2.8 (95% CI; 1.6-5.2) in 1997-2010 and OR 2.4 (95% CI; 1.5-3.9) in 2011-2018, and the OR for MI was 3.5 (95% CI; 1.7-7.5) and 1.5 (95% CI; 0.9-2.4) within the same time periods respectively (Table 6). All sensitivity analyses conducted to ascertain of the robustness of the results of the within-individual comparisons showed similar results (Appendix II, Supplemental Figure 3).

Table 6. Matched OR of ischemic event (stroke and myocardial infarction) after incident AF compared to before in patients with AAA, stratified according to time of AF diagnosis (modified from Nicolajsen et al. Thromb Hemo 2023[77])

	Total N	No of events (subsequent/ baseline interval)	Matched OR	95% CI
Stroke				
1997-2010	1040	53/20	2.8	1.6-5.2
2011-2018	1995	62/26	2.4	1.5-3.9
Myocardial Infarction				
1997-2010	1040	40/13	3.5	1.7-7.5
2011-2018	1995	47/33	1.5	0.9-2.4

Abbreviations: OR- odds ratio; AAA – abdominal aortic aneurysm; AF – atrial fibrillation; CI – confidence interval

5.2.2. MEDICAL ANTITHROMBOTIC THERAPY IN ASSOCIATION WITH ATRIAL FIBRILLATION

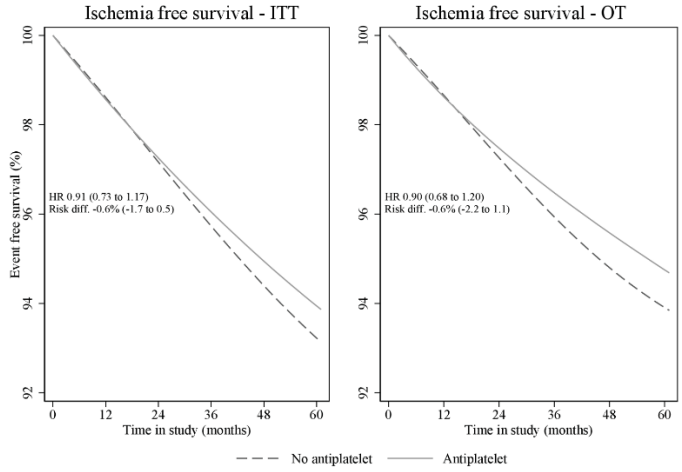
As expected, the medical antithrombotic therapy changed over time and in association with the incident AF diagnosis. The cumulative proportion of patients claiming a prescription of antiplatelet therapy in the year after AF diagnosis changed from 80.8% (78.2%-83.1%) in 1997-2010 to 60.9% (58.6%-63.0%) in 2011-2018. In contrast, cumulative prescription claims of anticoagulant therapy (OAC) at one-year increased from 66.1% (63.1%-68.9%) in 1997-2010 to 82.6% (80.8%-84.2%) in 2011-2018.

5.3. AAA AND ANTIPLATELET THERAPY – COMPARATIVE EFFECTIVENESS AND SAFETY IN PATIENTS WITHOUT SYMPTOMATIC ATHEROSCLEROSIS (STUDY III)

Among 25,326 patients identified with AAA, 6,344 patients fulfilled the inclusion criteria for the target trial and had no record of atherosclerotic vascular disease or previous antiplatelet use. According to the study design, they contributed a total of 131,047 trial cases to the pooled analyses. Of these, 3,363 participants were initiators of antiplatelet therapy and 127,684 were non-initiators (Figure S1, Flowchart of inclusion in Appendix III, Supplementals). Emulation of the target trial with randomization conditional on baseline covariates, as described in detail in the methods section, resulted in an equally weighted distribution of baseline characteristics among initiators and non-initiators of antiplatelet therapy (Table 1 and Figure S3 in Appendix III).

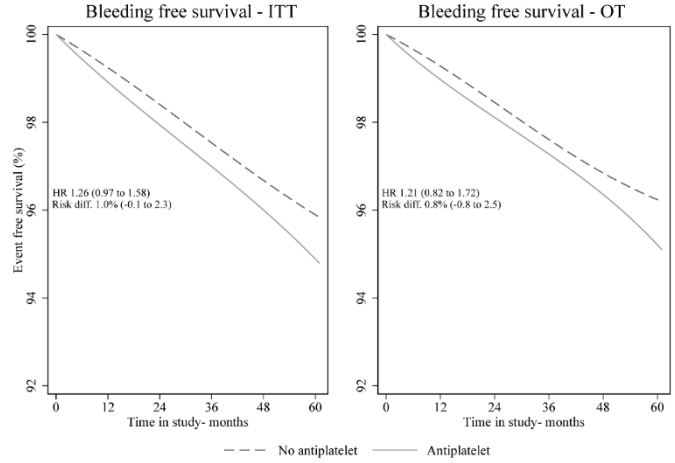
After 5-years of follow-up (total 5,011,227 person-months of follow-up, median follow-up 24 months (IQR 11 to 40 months) for initiators and 23 months (IQR 11 to 38 months) for non-initiators), we found an ITT HR of 0.91 (95% CI 0.73 to 0.1.17) for ischemic events, corresponding to an event free survival difference of -0.6% (95% CI -1.7% to 0.5%), in favour of antiplatelet therapy (Figure 5). After censoring non-adherent person-time, the estimated OT HR was 0.90 (95% CI 0.68 to 1.20), with a difference in event-free survival of -0.6% (95% CI -2.2 to 1.1). For the safety outcome of bleeding, we found an ITT HR of 1.26 (95% CI 0.97 to 1.58) (event free survival difference 1.0% (95% CI -0.1% to 2.3%)), while the estimated OT HR was 1.21 (95% CI 0.90 to 1.82) (event free survival difference 0.8% (95% CI -0.5 to 2.8)) (Figure 6).

Figure 5. Estimated event free survival curves for Ischemic events (MI and/or ischemic stroke) (reuse of figure from Nicolajsen et al. Submitted February 2023[78])



Abbreviations: ITT- intention-to-treat, OT – on-treatment, HR – hazard ratio, Risk. Diff. – estimated difference in event-free survival

Figure 6. Estimated event free survival curves for major bleeding (reuse of figure from Nicolajsen et al. Submitted February 2023[78])



Abbreviations: ITT- intention-to-treat, OT – on-treatment, HR – hazard ratio, Risk. Diff. – estimated difference in event-free survival

CHAPTER 6. DISCUSSION

In this section, the findings from Study I-III are discussed, considering both the existing evidence at the time of publication, as well as any subsequent research published.

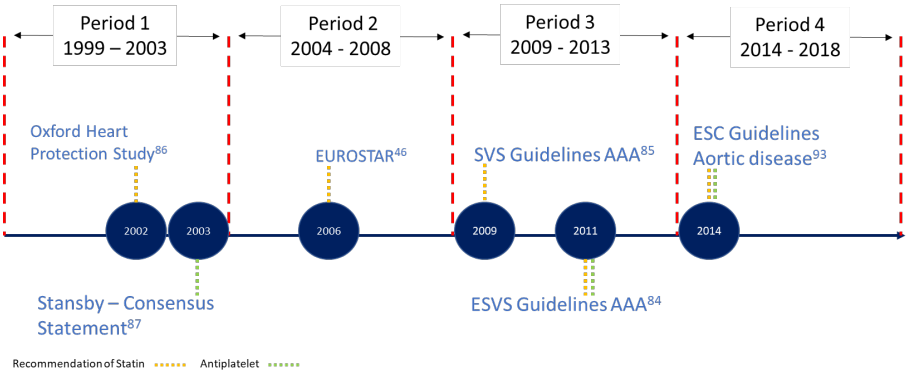
6.1. PREVALENCE OF CARDIOVASCULAR COMORBIDITY

In Study I, we described trends over time in cardiovascular comorbidity in the full AAA-population at time of diagnosis. We found a decreasing and consistently lower prevalence of concomitant atherosclerotic cardiovascular disease affecting a maximum of 43% of patients, compared to a prevalence of up to 60% previously reported.[28,29,33] Differences could partially be explained by differences in reporting standards (registered diagnoses vs. self-reported comorbidity) and target populations. Further, none of the studies, reporting a higher prevalence of comorbidity, used data or patient inclusion with national coverage. Nonetheless, these differences do not explain the decreases observed in prevalence of cardiovascular comorbidity over time. A similar trend has been described in the general population aged 55 and older in Denmark and in other Western European countries.[79,80] Additionally, the increasing prevalence of other comorbidities, such as cancer and atrial fibrillation in the general population was reflected in the AAA population.[81–83] Whether these increases are caused by intensified screening for these specific diseases or other factors, requires further analyses.

6.2. CURRENT PRACTICE OF MEDICAL CARDIOPROTECTIVE THERAPY

The importance of medical cardioprotective treatment in AAA disease has gained growing attention during the last decades, and the AAA guidelines from the International Vascular Societies have included a formalized recommendation on medical cardioprotective management with statins and antihypertensive therapy since 2009, and antiplatelet therapy since 2011, to all patients diagnosed with AAA (Figure 6).[84,85]

Figure 6. Timeline for pivotal studies and guidelines on medical cardioprotective therapy in 1999-2018 (modified from Nicolajsen et al. Eur J Prev Cardio 2022[64])



Oxford Heart Protection Study[86], Stansby – Consensus Statement[87], Eurostar 2006[46], SVS (Society of Vascular Surgery) guidelines 2009[85], ESVS (European Society of Vascular Surgery) guidelines 2011[84], ESC (European Society of Cardiology) guidelines 2014[88], Abbreviations: AAA - Abdominal Aortic Aneurysm.

In support of the development in recommendations, we found a higher proportion of AAA patients receiving medical cardioprotective treatment at time of diagnosis in Study I.[64] Our observations extends the insights on the medical management of patients with AAA, where an increasing trend was reported in patients diagnosed with AAA from 2000-2012 in the UK.[28] However, the observed unchanged proportion of AAA patients taking antiplatelet and statin therapies during the most recent study period (2014-2018) has not been reported previously. As the recommendations on both statin and antiplatelet therapy has been intensified within recent years, this finding is somewhat disturbing.[7,44,52] A similar trend has been observed in other patient groups with cardiovascular disease, along with an indication of a more general trend in use of cardiovascular preventive medicine.[89–91] Given the paucity of high-level evidence, supporting treatment with antiplatelets in patients with AAA without symptomatic atherosclerotic vascular disease, the observed stagnation in trends could also be attributed to weak recommendations.[2,51]

In patients with AAA and concurrent AF, the guidelines on medical antithrombotic treatment are more concise.[53] At this point, the increasing proportion of patients initiating OAC and not antiplatelet therapy after AF diagnosis during 2011-2018 compared with 1997-2010, reflected improvements in implementation of AF treatment recommendations, as also observed in other studies describing the use of OAC in patients with AF.[77,92,93]

6.3. CARDIOVASCULAR PROGNOSIS AND MORTALITY

Since the early 2000, we found a continuous improvement in the cardiovascular prognosis of patients diagnosed with AAA, with a lower rate of all adverse atherosclerotic cardiovascular events leading to hospitalization as well as all-cause mortality.[64] Nevertheless, the cardiovascular admission-rate was still markedly higher among AAA patients, than in the general population of same age and sex (males, age group 65-74 years).[94] Thus, disregarding improvements, atherosclerotic cardiovascular disease continues to be an important cause of long-term morbidity in patients with AAA.[64] Despite a 50% decrease over the last two decades, all-cause mortality was still significant. One in five patients diagnosed with AAA between 2014 and 2018 died within two years after diagnosis, also after excluding patients with a diagnosis of AAA rupture.[64] The evidence of an excess mortality in the AAA population compared with the general population is convincing, based on these and previous findings.[30,41,95,96] Cardiovascular comorbidity is considered one of the main attributes to the high risk of ischemic events and excess mortality.[29,30,40,95] An explanation also supported by the fact that cardiovascular death is the most common cause of death in patients with AAA, while cancer is the most common cause of death among those without AAA. [30,95] The concurrent decline in both prevalent an incident cardiovascular morbidity as well as mortality observed in Study I supports these hypotheses.[64]

The risk of cardiovascular ischemic events and survival is well described in the general AAA population, and efforts to improve the cardiovascular prognosis has therefore been directed towards the AAA population as a whole. However, subgroups of AAA patients, such as those with atherosclerotic cardiovascular comorbidity or AF, potentially have worse prognosis than other subgroups and could therefore theoretically benefit to a higher extent from intensified management of risk factors. However, the evidence describing the ischemic risk and benefits of medical cardioprotective therapy in these subgroups is less well examined.

6.3.1. RISK OF ISCHEMIC EVENTS CONFERRED BY ATRIAL FIBRILLATION

A diagnosis of AF confers an increased risk of thromboembolic events in general[97,98], and the cardiovascular prognosis is further compromised in patients with AF and concomitant cardiovascular atherosclerotic disease.[39,99,100] In patients with AAA, evidence suggest that both prevalent and incident AF is associated with increased peri- and postoperative risk of cardiovascular events and death after AAA repair.[101,102] Our findings from Study II extends this knowledge to the AAA population as a whole, irrespective of intervention. We observed a higher incidence of both stroke and MI after incident AF (4-6% after one-year follow-up), compared with the AAA population as a whole (2-4% after 2-year follow-up).[64,77] Furthermore, we demonstrated higher (within-patient) odds of both stroke and MI after incident AF diagnosis.[77] Results were comparable to patients with AF and concomitant

atherosclerotic vascular diseases[39,99,103], indicating that patients with AAA and AF also represent a frail subgroup of patients at high risk of subsequent ischemic outcomes, in the pre-, peri- and postoperative setting.[77,102] The increased odds of MI associated with incident AF diminished over time, in concordance with increasing use of OAC therapy, while improvements in OAC use over time did not reflect any changes in the odds of stroke.[77] Potentially, this finding may be explained by the high residual risk of stroke in older, multimorbid patients, such as the AAA population, despite optimal anticoagulation.[104,105] This highlights the importance of attention also on AF in the cardiovascular risk assessment in patients with AAA.

6.3.2. RISK OF ISCHEMIC EVENTS AND PROTECTIVE EFFECT OF ANTIPLATELET THERAPY IN PATIENTS WITH AAA WITHOUT SYMPTOMATIC ATHEROSCLEROSIS

As demonstrated previously, AAA is associated with higher risk of ischemic events in general.[29,41,64] However, risk differences between AAA patients with and without a history of atherosclerosis are sparsely described. This also applies to differences in the effects of cardioprotective medical therapy. In patients with symptomatic atherosclerotic cardiovascular disease in general, the evidence supporting antiplatelets as secondary prevention of ischemic events is substantial.[55,106] In patients without symptomatic atherosclerosis however, recommendations have changed and antiplatelet prophylaxis are no longer recommended routinely to all, but limited to patients at very high cardiovascular risk and with minimal risk of bleeding.[55,107] These changes in recommendations are based on results from several large randomized controlled trials, and meta-analyses, revealing no or moderate ischemic risk reduction at the expense of an increased risk of bleeding in patients without symptomatic atherosclerotic disease.[108–111] In line with results from these RCTs, the findings from Study III suggests a limited benefit of antiplatelets on risk of cardiovascular events combined with a trend towards increased risk of major bleeding.

Based on the recent changes in guidelines, the results from Study III, and the decreased prevalence and improved prognosis of cardiovascular morbidity seen in Study I[64], it seems reasonable to question, if all patients presenting with AAA should be considered for antiplatelet prophylaxis.[7,52] Instead, antiplatelet therapy might be limited to those with AAA and associated symptomatic atherosclerotic cardiovascular disease and/or other important risk factors.[55] Clinical trials focusing on evaluating the effect of antiplatelet prophylaxis in AAA patients with and without atherosclerotic vascular disease is warranted, in order to improve the quality of guideline recommendations.

CHAPTER 7. MAIN CONCLUSIONS

Based on the results of Studies I-III, the following conclusions have been drawn:

7.1. STUDY I

The prevalence of concomitant atherosclerotic cardiovascular disease and the incidence of new atherosclerotic admissions after AAA diagnosis declined over the 20-year study period. However, the burden of prevalent and incident IHD and PAD remained high. Despite improvements, half of AAA patients did not receive medical therapy with statin and antiplatelets in the most recent period. These findings suggest that a potential for improving implementation of medical cardioprotective therapy exists, which may lead to further reductions in morbidity and improved survival in patients with AAA.

7.2. STUDY II

Among patients with AAA and incident AF, the cardiovascular prognosis also improved over time, in agreement with the increasing implementation of relevant anticoagulant therapy. Nevertheless, a diagnosis of AF is still associated with a 50-100% higher risk of stroke and MI compared with the period before AF. These findings indicate a need to focus on detecting co-existent AF in the management and medical optimization of high-risk patients with AAA.

7.1. STUDY III

In patients with AAA and no symptoms of manifest atherosclerotic cardiovascular disease, antiplatelet therapy was associated with limited difference in risk of MI and ischemic stroke, and a trend towards a higher risk of bleeding, compared with patients who did not receive antiplatelet therapy. However, the differences in event-free survival were minimal (less than 1%), indicating no clinically meaningful difference. Consequently, our findings do not support the utilization of antiplatelet prophylaxis in patients with AAA without symptomatic atherosclerotic cardiovascular disease.

CHAPTER 8. METHODOLOGICAL CONSIDERATIONS

The studies, forming the basis of this dissertation, were all observational cohort studies, but with study designs specifically related to the research question of interest. Observational studies can be prone to random error (e.g., lack of precision) and systematic errors (e.g., bias), affecting the interpretation of estimated associations.[112] In this chapter, the potential methodological issues related to the sources of information (the national Danish health registries) and the study designs used are therefore discussed. Further, the internal validity or accuracy of the outcomes obtained, with regards to bias related to selection, information, and confounding issues will be evaluated, as well as the external validity of results. A description of the registries used to obtain data are provided in the methods section (Chapter 4).

8.1. PRECISION

The precision of the estimated associations was evaluated using 95% CIs in all included studies.[64,77] To avoid misconception of associations, we did not use significance testing or p-values[113], as the span of the CI gives a better indication of the amount of random error and level of precision in a given estimate.[112] The use of Danish administrative health care data in a national setting, enabled the inclusion of large and unselected study populations. The large numbers of outcomes and cases yielded statistically precise estimates with narrow CI's, that were unlikely to have occurred by pure chance.[112] Due to restrictions in inclusion criteria and definition of study population, the numbers of events per type of outcome were smaller in Study II, and the precision of estimates therefore slightly lower.[77] The precision of estimates could have been increased by the use of combined effect estimates, as done in Study III.[78] Yet, the increase in precision comes at the expense of greater uncertainty in the interpretation of results.[114] As the associated effect of incident AF on risk of MI and ischemic stroke respectively, potentially run through different causal mechanisms, we therefore chose not to combine the outcomes in Study II.[77,115]

8.2. BIAS

8.2.1. SELECTION BIAS

Selection bias is defined as systematic errors associated with the selection of study participants. The bias occurs, when the association between exposure and outcome is different between the study population and those not included in the study, but otherwise eligible.[112,116] For Study I-III [64,77,78], the study populations were recruited from the largest possible source population (the entire Danish population). Further,

since both AAA and AF can be asymptomatic, and is often diagnosed incidentally, we used a combination of in- and outpatient records as well as primary and secondary diagnoses registered in the DNPR, to ensure identification of all individuals potentially relevant to be included in the study population. Selection bias based on exposure status, was thus not considered an issue.[116] Selection bias can also occur in case of differential loss-to–follow up. In the included studies, we used data exclusively retrieved from national health registries of high validity with virtually complete information on vital status and registration of outcome events leading to hospital admission.[60] Loss-to-follow up was therefore considered negligible.

Selection bias due to competing risks (also known as informative censoring) is particularly relevant in an older population with high mortality rates, such as the AAA population, where death is the main competing risk.[117] Accordingly, the risk of non-fatal events can be overestimated in especially time-to-event analyses using the Kaplan-Meier estimate.[118] To account for the competing risk of death, analyses were performed with censoring at time of death, and using cumulative incidence functions with Aalen-Johansen estimates in time-to-event analyses in Study I and II.[64,77,119] In Study III pooled logistic regression analyses with estimation of cumulative event-free-survival was performed. [76,78,119] Another way of handling death as a competing risk, is by including death as a composite endpoint together with outcome of interest. However, as previously mentioned, this approach comes with difficulties in the interpretation of results. Since the mortality rate by far exceeds the rate of any ischemic outcome of interest, as illustrated in Study I[64], a combined effect estimate including all-cause death would reflect the associated effects of death, more than the effects of the ischemic outcomes of interest.[120]

In Study II immortal-time bias was a special concern when conducting the exposure-crossover analyses, since study participants has to survive until the subsequent comparison period, potentially leading to an underestimation of the exposure effect.[70] However, the overall agreement between the main results, and sensitivity analyses conducted on those surviving until the end of the study period, supports the robustness of our findings.

8.2.2. MISCLASSIFICATION / INFORMATION BIAS

Misclassification of disease, exposure, and outcome status leading to incorrect categorization of study participants may lead to biased results.[112,116] Misclassification can be either non-differential; when the misclassification is equally likely to occur in all subgroups, and are independent of other study variables, or differential; when misclassification is not equally distributed in subgroups of the study population.[112,116] In case of non-differential misclassification, the estimates will most often be biased towards the null, while the direction of bias is less predictable in differential misclassification.[112,116] Exposure and outcome data were identified through the

DNPR and the Danish National Prescription Registry in Study I–III[64,77,78], and the risk of misclassification thus dependent on the completeness and accuracy of the recorded diagnoses. Since data in these health registries are prospectively collected, inaccuracies in recording of data will most likely lead to non-differential misclassification, while data are less prone to differential misclassification, since self-reporting of health information and medicine use is avoided.[112]

In Study I-III[64,77,78], the study population was defined by patients with a first (in Study III; any) diagnosis of AAA, while the exposure status was further defined by a first diagnosis of AF in Study II. The positive predictive value of the AAA and AF diagnosis in the DNPR are both considered high (>90%), and are unlikely to be associated with the exposure status in the included studies.[65,121] In Study III, exposure status was defined as initiation or non-initiation of antiplatelet therapy, including prescription claims of clopidogrel and aspirin registered in the Danish National Prescription Registry.[78] As the recording of drug prescriptions are virtually complete in the Danish health registries, aside from in-hospital administration, any misclassification of exposure status would pertain mainly to over-the-counter use of aspirin among participants classified as non-initiators.[122] Although the over-the-counter use of aspirin is considered minimal in Denmark (approximately 8%)[66], it could potentially have biased the results towards the null, leading to an underestimation of differences of effect between antiplatelet initiators and non-initiators.

Ischemic events were the primary measure of outcome in all included studies. Study I described outcomes for CeVD, IHD and PAD in broad terms as well as the specific outcomes of MI and ischemic stroke also used in Study II and III.[64,77,78] The positive predictive value of all ischemic diagnoses have previously been validated against medical record review, and was found to be approximately 94% for CeVD[123], 42% (for angina specifically) to 92% for IHD[67], 69%-99% for PAD[121,123,124], 79%-97% for ischemic stroke[68,69,125], and 74%-97% for MI.[67,121,126] We classified unspecified stroke as ischemic stroke and thereby misclassified some intracerebral haemorrhages (approximately 6%).[125] Mortality data were virtually complete.[57] Potential misclassifications caused by coding errors of outcomes would be unlikely to differ between study groups, and would thus be non-differential. Given the overall high validity of recorded outcomes, any coding errors seems unlikely to have had influenced the estimated outcomes to an extent where the interpretation should be changed.

8.2.3. CONFOUNDING

Confounding relates to studies examining causality, and occurs when the effect of other risk factors is mixed with the causal effect of an exposure on the outcome, leading to differential effect across exposed and non-exposed study groups, also referred to as lack of exchangeability.[112,116] Observational studies are particularly

prone to confounding due to the non-randomized nature of exposure. As previously stated, we aimed to reduce potential confounding both by choice of study design and through methods of analyses (Table 3, methods section).

In Study II, we used a self-matched comparison to examine the associated effects related to incident AF in an effort to reduce bias related to both measured and unmeasured confounding from factors that are constant over time.[70,77] Given the relatively short time span between periods of comparison (less than two years from the beginning of the baseline period to the end of the hazard/subsequent period), bias related to increasing age and accumulating comorbidity was also accounted for.

In Study III, we emulated randomization by balancing measured baseline variables with potential influence on exposure status and outcome between study groups based on the inverse probability weights derived from the propensity scores.[78,127,128] Further, we used marginal structural models and pooled logistic regression to estimate the effect of the intervention on the outcome, while controlling for a wide variety of both baseline and time-varying confounding factors.[76]

Regardless of study design, control for confounding was limited to covariates available from the Danish health registries, and differences in unmeasured confounding, cannot be ruled out. We lacked information on potential confounding factors such as tobacco use, which is not recorded in a uniform manner.[129] In Study III, we therefore constructed a proxy for smoking. However, the quality of the proxy confounding factor was still dependent of the strength of the association with the true confounder (smoking status). Thus, despite the efforts to limit confounding, it is an untestable assumption and the potential risk of residual an unmeasured confounding due to the observational nature of data, can never be ruled out.

8.3. GENERALIZABILITY

Assuming high internal validity, our results are likely generalizable to the AAA population in most Western countries with comparable lifestyle, risk factor prevalence, and treatment regimens, though differences in prevalence of AAA between countries, may affect characteristics in the AAA populations, such as comorbidity status.[9,10] The Danish population is very homogenous with regards to ethnicity, and results may therefore not be generalizable to more ethnic diverse populations.[113]

We chose to include all patients registered with a diagnosis of AAA, not just those under surveillance or those registered with AAA repair. This approach was chosen, based on evidence that cardiovascular risk management is important from time of diagnosis, regardless of aneurysm size and time to repair.[31,95] Consequently, the study population also included frail patients and patients with an anticipated short

life-expectancy, potentially deemed unfit or non-eligible for AAA repair, making comparisons to studies on cardiovascular disease prevalence and prognosis after AAA repair difficult.

CHAPTER 9. CLINICAL IMPLICATIONS

This dissertation contributes to the existing knowledge on the prevalence of atherosclerotic comorbidity, as well as trends in and effect of medical cardioprotective treatment among patients with AAA.

We provided data describing a decreasing prevalence of comorbid atherosclerosis at the time of AAA diagnosis, and, although still high, a continuous decrease in the risk of developing new atherosclerotic manifestations after diagnosis.[64] With symptomatic atherosclerosis present in only one third of AAA patients diagnosed within most recent years, our findings support suggestions on AAA and atherosclerosis as distinct disease entities, more than AAA being a manifestation of atherosclerosis and thrombosis.[18,19,21] With this in mind, potential differences in disease manifestations and prognosis in patients, with and without atherosclerotic comorbidity, should be further explored.

In support of previous studies and current recommendations, we found an increasing implementation of medical cardiopreventive therapy with statin and antiplatelets in all patients with AAA, also in the more than 60 % of AAA patients without manifest comorbid atherosclerosis.[2,28,52,64] However, our findings of a lack of clinical benefit of antiplatelet therapy in patients with AAA without atherosclerotic manifestations, does not support the recommendation of antiplatelet therapy to all patients with AAA, as most recent recommendations advocate.[52,78] Given these findings and the limited (observational) evidence guiding current recommendations, there is an urgent need for a dedicated randomized clinical trial, investigating the efficacy of antiplatelet therapy in patients with AAA with and without atherosclerotic vascular disease. Until then, clinicians should carefully weigh the risk of ischemic events against the risk of bleeding, and patient preferences, before prescribing prophylactic antiplatelets to AAA patients without manifestations of atherosclerosis.

Besides contributions regarding atherosclerotic comorbidity, we provided data indicating a high and increasing prevalence of AF in patients with AAA, which has not previously been recognized.[64] The risk of ischemic stroke is increased in the majority of patients with AF.[97,98] Our results suggest, that not only the risk of ischemic stroke but also the risk of MI increases by 50-100% after incident AF, in patients with AAA.[77] Further investigations are necessary, evaluating the effect of AF in the AAA population and its impact on prognosis. Clinicians should be aware of the prognostic effect of AF on ischemic risk, regardless of correct implementation of anticoagulant therapy.[77,105]

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APPENDICES

Appendix 1.

Study 1: Nicolajsen CW, Søgaard M, Eldrup N, et al. Temporal trends in abdominal aortic aneurysmal disease : a nationwide cohort study on cardiovascular morbidity and medical cardioprotective therapy. *Eur J Prev Cardiol* 2022; 29: 1957–1964. DOI: 10.1093/eurjpc/zwac105

Appendix 2

Study 2: Nicolajsen CW, Brønnum Nielsen P, Jensen M, et al. Stroke and myocardial infarction in patients with abdominal aortic aneurysms and new-onset atrial fibrillation. *Thromb Haemost*. Epub ahead of print 10 January 2023. DOI: 10.1055/a-2009-8954

Appendix 3.

Study 3: Nicolajsen CW, Søgaard M, Jensen M, et al. Antiplatelet therapy in patients with abdominal aortic aneurysm without symptomatic atherosclerotic disease: A target trial emulation of national observational data. *Submitted February 2023*.

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FULL RESEARCH PAPER
Aortic and peripheral vascular disease

Temporal trends in abdominal aortic aneurysmal disease: a nationwide cohort study on cardiovascular morbidity and medical cardioprotective therapy

Chalotte W. Nicolajsen [1,2]*, Mette Søgaard[1,2], Nikolaj Eldrup[3], Martin Jensen[1], Torben B. Larsen[1,2], Samuel Z. Goldhaber[5,6], and Peter B. Nielsen[1,2]

[1]Department of Clinical Medicine, Faculty of Health, Aalborg Thrombosis Research Unit, Aalborg University, Sdr. Skovvej 15, 9000 Aalborg, Denmark; [2]Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark; [3]Department of Vascular Surgery, Rigshospitalet, Copenhagen, Denmark; [4]Department of Clinical Medicin, Copenhagen University, Copenhagen, Denmark; [5]Thrombosis Research Group, Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, MA, USA; and [6]Department of Medicine, Harvard Medical School, Boston, MA, USA

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Aims Abdominal aortic aneurysmal disease is associated with increased risk of cardiovascular morbidity and death, which potentially can be reduced with cardioprotective medical therapy. The aim of this study was to observe temporal trends in prevalence and incidence of cardiovascular comorbidity as well as use of medical cardioprotective treatment in patients diagnosed with abdominal aortic aneurysmal disease.

Methods and results This was a population-based cohort study based on data from national health registries, including all patients diagnosed with abdominal aortic aneurysms between 1998 and 2018. Data were stratified into four time periods (1999–2003, 2004–2008, 2009–2013, and 2014–2018) to illustrate trends over time. Outcome measures were (i) cardiovascular comorbidity and medical cardioprotective therapy at time of diagnosis, (ii) new admissions for atherosclerotic cardiovascular disease, and (iii) all-cause mortality after 2-year follow-up. The study cohort included 33 296 individuals. Mean age was 74 years. Prevalence of atherosclerotic cardiovascular comorbidity at diagnosis decreased from 41.5 to 32.6%. Use of statins increased from 17.9 to 66.9%, antiplatelets from 45.6 to 63.3%, and combined therapy with both antiplatelets and statins from 11.3 to 44.8%, and from 12.1 to 50.7% when anticoagulant therapy was included. Developments in medication use plateaued after 2013. Prevalence and incidence of atherosclerotic cardiovascular disease decreased through all four time periods. The same applied to all-cause mortality, which decreased from 24.3 to 12.4 deaths (per 100 person-years).

Conclusion In patients diagnosed with abdominal aortic aneurysm, cardiovascular comorbidity at diagnosis, risk of future cardiovascular events, and all-cause mortality is decreasing. Nevertheless, cardiovascular burden and mortality rates remain substantial, and medical cardioprotective therapy can be further improved.

Keywords Abdominal aortic aneurysm • Medical cardioprotective treatment • Stroke • myocardial infarction • Cardiovascular disease

* Corresponding author. Email: c.nicolajsen@rn.dk

† The results of this study were presented as a Short Oral Presentations at the annual meeting of the European Society of Vascular Surgery 2020 (ESVS Month 2020) September–October 2020.

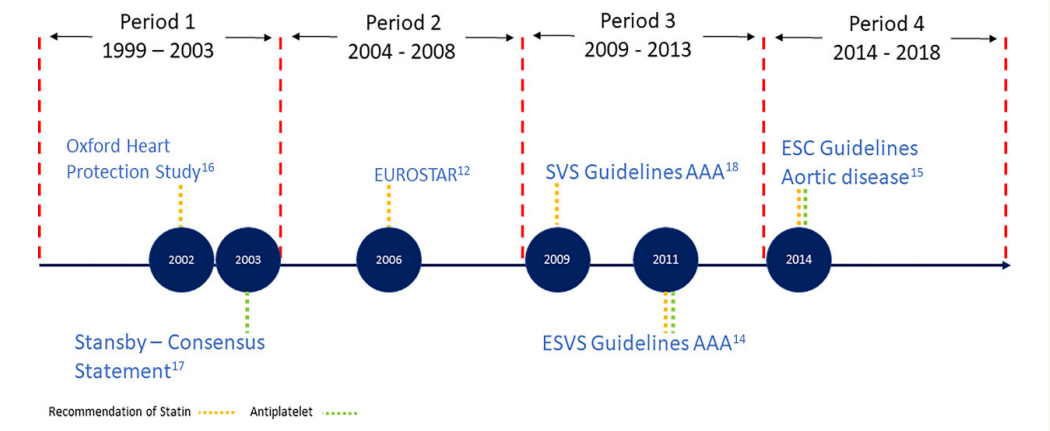

Figure 1 Timeline for pivotal studies and guidelines on medical cardioprotective therapy in the study periods. Oxford Heart Protection Study,[16] Stansby—Consensus Statement,[17] Eurostar 2006,[12] SVS (Society of Vascular Surgery) guidelines 2009,[18] ESVS (European Society of Vascular Surgery) guidelines 2011,[14] ESC (European Society of Cardiology) guidelines 2014.[15] AAA, abdominal aortic aneurysm.

Introduction

Abdominal aortic aneurysmal (AAA) disease is the cause of 1% of all deaths among individuals aged 65 years and older.[1,2] The estimated annual risk of cardiovascular death among patients with AAA is 3% compared with 0.8% in the general population.[3] Paradoxically, morbidity, and mortality remains high, despite improvements in repair techniques and aneurysm-related survival.[4–7] The increased mortality is mediated principally through factors other than the aneurysmal disease itself,[8–10] primarily driven by ischaemic heart disease (IHD), cerebrovascular disease (CeVD), and peripheral arterial disease (PAD).[3,9]

Atherosclerotic vascular events and pre-mature death can be reduced with preventive medical therapy.[9,11] Therefore, a major goal in AAA management is risk factor modification and lifestyle changes. Cardioprotective medications, such as statins, aspirin, and antihypertensive agents, have been associated with a 20–35% lower risk of all-cause mortality among patients with AAA, irrespective of AAA repair.[9,12,13] Thus, a growing international consensus recommends blood pressure control and medical therapy with statins, antiplatelet, and antihypertensive agents at the time of AAA diagnosis (*Figure 1*).[4,14–17]

The aim of this study was to provide updated nationwide data on temporal changes in cardiovascular comorbidity, use of medical cardioprotective treatment at AAA diagnosis, and cardiovascular outcomes in patients diagnosed with AAA.

Methods

This population-based historical cohort study reports consecutive data on patients with AAA from registries covering the entire Danish population. All hospitals in Denmark have a compulsory registry policy, leading to virtually complete enrolment of the Danish population due to the unique personal registration number given to all citizens at birth or immigration.[19]

Data sources

Using the Danish National Patient Registry (DNPR), we identified all patients with a first diagnosis of AAA between 1999 and 2018, covering both in- and outpatient registrations. The DNPR has stored information on hospitalizations since 1977, and outpatient and emergency department visits at all hospitals in Denmark since 1995.[20] Data include Civil Personal Registry numbers, dates of admission and discharge, and up to 20 diagnoses coded by the International Classification of Diseases (ICD-10). Data on medication claims were retrieved from the Danish National Prescription Registry,[21] which has detailed information on the purchase date, Anatomical Therapeutic Chemical classification code, package size, and dose for every prescription claim since 1994. Data on patient characteristics such as age, sex, and vital status were extracted from the Civil Registration Registry.[20] Because of the non-anonymized nature of the data collected for this study, requests to access the data set from third parties are not allowed according to Danish data safety regulations.

Ethics

In Denmark, approval from an ethics committee is not required for registry-based studies in which specific individuals cannot be identified. The study was performed in compliance with the General Data Protection Regulation and the North Denmark Region's record of processing activities (project no. 2017-40). Data were provided by the Danish Health Data Authority.

Study population

The first diagnosis of AAA was identified either by a primary or secondary discharge diagnosis (in- and outpatient ICD-10 codes: I713, I714), in the DNPR (index date). Previous validation studies have reported a positive predictive value of the AAA diagnosis in the

DNPR of >98%.[22] Patients who had not resided in Denmark within the year before AAA diagnosis were excluded. Patients aged <50 years were excluded to account for patients with potential erroneous diagnosis of AAA and to exclude patients with severe connective tissue disease, which has a different aetiology than degenerative AAA.

Comorbidity and cardioprotective treatment

To assess medical cardioprotective treatment at the time of AAA diagnosis, we included baseline medication on antiplatelets, anticoagulants, statins, and antihypertensives. We also assessed the total use of antithrombotic therapy, defined as either anticoagulation or antiplatelet therapy. Patients on anticoagulant therapy were included to provide the most accurate picture of trends, as a chronic indication for anticoagulants in many cases overrules the indication for antiplatelet therapy in patients with AAA. Patients were defined as receiving recommended treatment if they claimed a prescription of both antiplatelet and statin therapy. Antihypertensive treatment was reported separately, as this is only recommended in AAA patients with hypertension in Denmark.

To examine changes in prevalent comorbidities, we extracted data on comorbid conditions requiring secondary healthcare, recorded within 5 years preceding AAA diagnosis, including atherosclerotic vascular disease (CeVD, IHD, and PAD), hypertension, chronic pulmonary disease, chronic kidney disease, heart failure, atrial fibrillation, venous thromboembolism, heart valve replacement, diabetes mellitus, rheumatic disorders, and malignancy (see Supplementary material online, *Table S1*).

For specification of variables and ICD-10/ATC codes used for analysis, please see Supplementary material online, *Table S1*.

Outcomes

Patients were followed for up to 2 years after the index date or until administrative censoring, 31 December 2018, for the occurrence of adverse cardiovascular outcomes (new admissions for CeVD, IHD, and PAD), and death of all causes. To avoid repeated coding of prevalent conditions, cardiovascular outcomes were based on diagnosis in the primary position for hospitalized patients recorded in the DNPR.

Statistical analysis

To illustrate changes over time, patient inclusion was stratified into four time periods: 'Period 1' (1999–2003), 'Period 2' (2004–2008), 'Period 3' (2009–2013), and 'Period 4' (2014–2018), and applied as study exposure groups. Age- and sex-standardized incidence rates of AAA were calculated by dividing the total number of incident patients with AAA per year by the mid-year number of residents in Denmark within the same time period. Descriptive statistics were used to summarize changes in demographics and comorbidities. Categorical data were reported as percentages and continuous data as medians with accompanying interquartile ranges. To distinguish between prevalent use and initiation (new use) of cardioprotective medicine after AAA diagnosis, we conducted a stratified analysis according to whether a prescription was filled in the 365 days before diagnosis or exclusively in the 90 days after (i.e. treatment initiation after diagnosis). Further, we conducted a subgroup analysis on medical treatment, stratified according to the presence of atherosclerotic cardiovascular disease (CeVD, IHD, and PAD) at the time of AAA diagnosis.

Time-to-event analyses were applied to calculate incidence rates of new atherosclerotic vascular admissions during follow-up. Kaplan–Meier estimates were used to describe risk of all-cause mortality. Assuming independent censoring, crude Aalen–Johansen estimates were used to depict cumulative incidence curves for each type of atherosclerotic vascular disease assuming death as a competing risk. Outcomes were reported as cumulative incidence proportions and incidence rates (events/100 person-years) at 2-year follow-up. All-cause mortality stratified by diagnosis [ruptured (DI713) or non-ruptured (DI714) AAA] was included as a secondary analysis.

All analyses were performed using SAS (version 9.4) and STATA/MP (version 16).

Results

Between 1999 and 2018, 33 296 individuals were diagnosed with AAA in Denmark, with an estimated population of 5.8 million. The AAA numbers increased from 5912 in Period 1 (1999–2003) to 9998 in Period 4 (2014–2018; *Table 1*). The age- and sex-standardized incidence of AAA (per 100 000 residents) increased from 68.2 in Period 1 to 84.7 in Period 4, with a peak incidence of 93.6 in Period 3 (2009–2013). The median age at diagnosis was 73 years in Period 1 and 74 years in Period 4; approximately 25% were females in all four periods. The proportion of patients first diagnosed with ruptured AAA decreased from 19.9% in Period 1 to 8.3% in Period 4 (*Table 1*).

Trends in comorbidity

The proportion of AAA patients with at least one comorbid condition ranged between 63.0 and 65.6% throughout the study period. The proportion of patients with any atherosclerotic cardiovascular disease (CeVD, IHD, and PAD) decreased from 41.5% in Period 1 to 32.6% in Period 4 (*Table 1*), primarily caused by decreases in prevalence of IHD (24.3–19.2%) and PAD (17.2–11.0%). Increases were observed in the prevalence of hypertension (17.9–30.8%), diabetes (5.2–8.7%), atrial fibrillation (9.6–12.5%), and cancer (8.8–13.9%), while the prevalence of other comorbid conditions, including CeVD, remained unchanged.

Trends in medical treatment

The use of medical cardioprotective therapy at the time of AAA diagnosis increased from 1999 to 2018, both overall and for new users commencing treatment within 90 days after AAA diagnosis (*Table 2*). The use of antihypertensives increased from 71.3% in Period 1 to 78.5% in Period 4. Most patients were prevalent users, while treatment initiation after AAA diagnosis ranged between 5.0% and 7.7%. Statin use increased from 17.9% in Period 1 to 66.9% in Period 4, while treatment initiation after AAA diagnosis remained

Table 1 Demographics and comorbidity of study cohort stratified by time period

	Period 1 1999–2003	Period 2 2004–2008	Period 3 2009–2013	Period 4 2014–2018
Demographics, % (N)				
N	6009	7784	9602	9998
Age, median (IQR)	73 (67–79)	73 (68–79)	74 (68–79)	74 (69–80)
Female	24.7 (1458)	25.1 (1950)	23.8 (2281)	23.5 (2351)
Ruptured AAA	19.9 (1175)	15.2 (1180)	10.2 (978)	8.3 (828)
Any atherosclerotic cardiovascular disease	41.5 (2456)	40.7 (3169)	36.3 (3487)	32.6 (3264)
Cerebrovascular disease	10.4 (613)	10.7 (832)	9.1 (875)	8.9 (887)
Ischaemic stroke	7.8 (459)	8.0 (620)	6.4 (617)	6.4 (635)
Ischaemic heart disease	24.3 (1439)	24.5 (1910)	21.7 (2080)	19.2 (1916)
Myocardial infarction	7.8 (459)	7.0 (546)	6.0 (575)	5.3 (531)
Peripheral arterial disease	17.2 (1017)	15.0 (1168)	12.9 (1239)	11.0 (1102)
Comorbidity, other				
Hypertension	17.9 (1059)	26.8 (2084)	30.1 (2889)	30.8 (3084)
Diabetes	5.2 (308)	7.3 (571)	8.5 (819)	8.7 (867)
Heart failure	9.9 (585)	9.6 (744)	8.1 (773)	7.9 (774)
Atrial fibrillation	9.6 (559)	11.5 (892)	11.6 (1112)	12.5 (1251)
Chronic pulmonary disease	12.5 (740)	13.2 (1025)	13.4 (1288)	14.4 (1440)
Chronic renal disease	4.9 (290)	5.2 (405)	5.9 (571)	6.2 (617)
Rheumatic disease	2.7 (157)	2.9 (227)	3.2 (308)	3.6 (362)
Cancer	8.8 (522)	10.8 (844)	12.8 (1233)	13.9 (1394)
Venous thromboembolism	2.4 (141)	2.6 (201)	3.0 (285)	3.8 (381)
Mechanical heart valve	0.5 (29)	1.1 (84)	1.4 (132)	1.2 (124)

IQR, interquartile range; *N*, number; AAA, abdominal aortic aneurysm.

modest (2.4–13.5%). The use of antiplatelet therapy increased from 45.6 to 68.7% between Periods 1 and 3, with a small decrease in Period 4 to 63.3%. The proportion of new users continuously increased from 7.7 to 16.2%. When we included OAC, the overall use of antithrombotic therapy (prescription claim of either antiplatelet therapy or OAC) increased from 51.1% in Period 1 to 76.5% in Period 4. Overall, the proportion of patients receiving recommended therapy with both antiplatelets and statins increased from 11.3% in Period 1 to 44.8% in Period 4, with a maximum of 49.0% in Period 3 (50.7% when all antithrombotics were included). Fewer than 10% of treatment-naïve patients started guideline-recommended therapy after AAA diagnosis. For all drug groups, no increases were observed between 2014 and 2018 (Period 4).

Use of cardioprotective therapy increased over time in all subgroups yet remained lower among patients with no prior atherosclerotic vascular disease compared with those with concomitant atherosclerosis (*Figure 2A and B*). Among patients with no history of atherosclerotic disease, use of antiplatelet therapy increased from 31.9% in Period 1 to 53.9% in Period 4, with a peak of 58.2% in Period 3, and 19.9% with treatment initiation after AAA diagnosis in Period 4 (*Figure 2A*). When OAC was included, antithrombotic therapy increased continuously from 36.3 to 66.0% (*Figure 2B*). In patients with concomitant atherosclerotic vascular disease, the use of antiplatelets increased from 64.8% in Period 1 to 82.8% in Period 4, with a peak of 86.8% in Period 3, and a maximum of 9% new users. Antithrombotic use increased continuously from 71.9 to 98.0% between Periods 1 and 4. Statin use increased from 8.9 to 60.3% in patients with no previous record of atherosclerotic vascular disease (14.3% new users in Period 4) and from 30.6 to 82.2% in patients with atherosclerotic vascular disease (4.9% new users in Period 4). Among those with no history of atherosclerotic vascular disease, prevalence of patients receiving recommended therapy with both statins and antiplatelets never exceeded 40%. In contrast, cardioprotective treatment was more frequently used among patients with concomitant atherosclerosis. In this subgroup, 74.1% received both antiplatelets and statin in Period 4 (*Figure 2A*).

Trends in incidence of atherosclerotic vascular admissions and all-cause mortality

Incidence rates of new hospitalizations for atherosclerotic cardiovascular disease after AAA diagnosis were lower in each successive time period (*Figure 3A*). The largest difference over time was observed for IHD and PAD. For IHD, the incidence rate of new admissions was 6.2 (per 100 person-years) in Period 1 and 2.8 in Period 4, and for PAD, the incidence rates were 3.8 in Period 1 and 1.7 in Period 4 (*Table 3*). Similarly, the cumulative all-cause mortality at 2-year follow-up was lower in each successive time period (*Figure 3B*), with a change in rate from 24.3 in Period 1 to 12.4 in Period 4 (*Table 3*), despite higher patient age at diagnosis. The cumulative mortality differed according to presentation at diagnosis (ruptured, non-ruptured; *Figure 3B*).

Table 2 Proportion of study cohort receiving medical therapy, stratified by time periods

Treatment, % (*N*)	Period 1 1999–2003 (*n* = 5912)	Period 2 2004–2008 (*n* = 7784)	Period 3 2009–2013 (*n* = 9602)	Period 4 2014–2018 (*n* = 9998)
Any antiplatelet	45.6 (2692)	59.5 (4633)	68.7 (6592)	63.3 (6333)
Prevalent use	37.9 (2238)	47.9 (3731)	53.3 (5116)	47.1 (4714)
New use	7.7 (454)	11.6 (902)	15.4 (1476)	16.2 (1619)
Any antithrombotic[a]	51.1 (3022)	66.2 (4757)	76.2 (7314)	76.5 (7648)
Prevalent use	41.7 (2468)	53.0 (4128)	59.1 (5672)	57.6 (5754)
New use	9.4 (554)	13.2 (1026)	17.1 (1642)	18.9 (1894)
Statin	17.9 (1058)	50.8 (3954)	68.2 (6550)	66.9 (6691)
Prevalent use	15.5 (915)	39.4 (3069)	54.7 (5252)	55.7 (5568)
New use	2.4 (143)	11.4 (885)	13.5 (1298)	11.2 (1123)
Any antihypertensive	71.3 (4218)	77.7 (4393)	79.1 (7589)	78.5 (7839)
Prevalent use	63.6 (3761)	69.6 (5419)	73.7 (7074)	73.5 (7344)
New use	7.7 (457)	8.1 (632)	5.4 (515)	5.0 (495)
Recommended therapy[b]	11.3 (671)	34.7 (2704)	49.0 (4703)	44.8 (4477)
Prevalent use	10.5 (621)	29.0 (2258)	40.7 (3907)	37.2 (3717)
New use	0.8 (50)	5.7 (446)	8.3 (796)	7.6 (760)
Recommended therapy (including OAC)[c]	12.1 (716)	36.8 (2861)	51.9 (4983)	50.7 (5068)
Prevalent use	11.2 (661)	30.9 (2402)	43.4 (4169)	42.9 (4289)
New use	0.9 (55)	5.9 (459)	8.5 (814)	7.8 (779)

AAA, abdominal aortic aneurysm; new use, patients with a first drug redemption within 90 days after diagnosis of AAA.
[a]Antithrombotic treatment with either antiplatelet therapy or anticoagulant therapy.
[b]Guideline-recommended therapy with antiplatelet and statin therapy.
[c]Antiplatelet or oral anticoagulant therapy and statin.

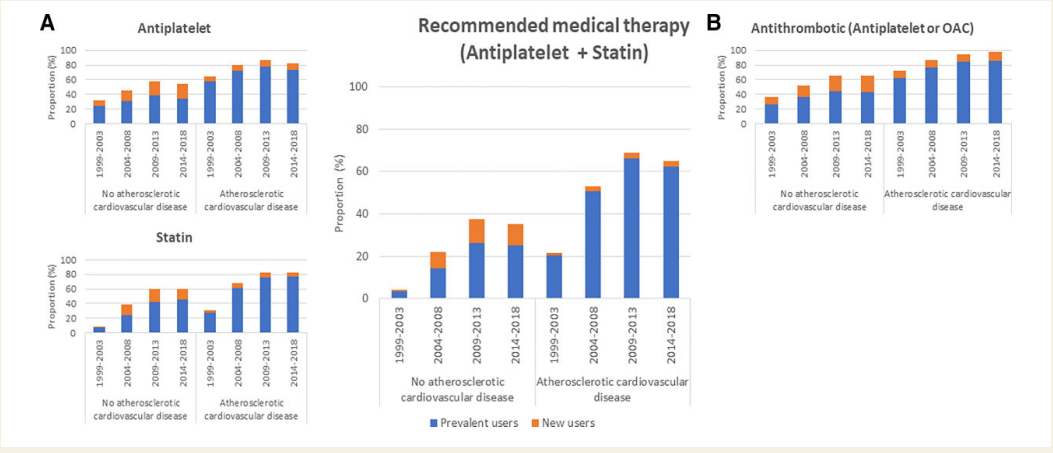

Figure 2 Temporal changes in use of cardiopreventive therapy among patients with incident abdominal aortic aneurysm according to the history of atherosclerotic cardiovascular disease. (*A*) Trends in use of antiplatelet, statin, and recommended combined therapy with both drugs. (*B*) Trends in antithrombotic therapy with either antiplatelets or oral anticoagulation. AAA, abdominal aortic aneurysm; OAC, oral anticoagulation.

Discussion

In our 20-year study, the overall incidence of AAA increased, with a peak in 2009–2013, while the proportion of patients presenting with a primary diagnosis of ruptured AAA plummeted by >50%. The prevalence of concomitant atherosclerotic cardiovascular disease decreased over time. The rate of adverse atherosclerotic cardiovascular events leading to hospitalization and death of all causes also

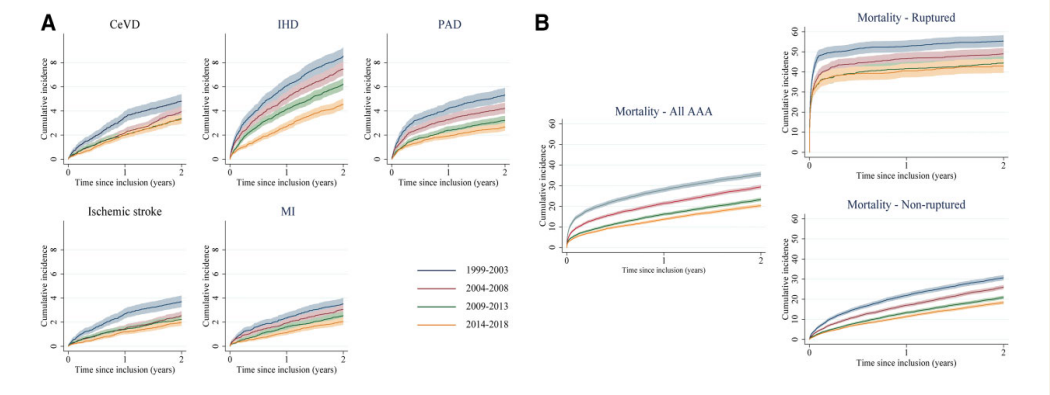

Figure 3 (*A*) (Cumulative incidence (with 95% confidence intervals) of new atherosclerotic vascular admissions after abdominal aortic aneurysm diagnosis according to time periods. (*B*) Cumulative mortality (with 95% confidence intervals) according to time periods, overall, and stratified on type of diagnosis (non-ruptured vs. ruptured). AAA, abdominal aortic aneurysm; CeVD, cerebrovascular disease; IHD, ischaemic heart disease; PAD, peripheral arterial disease; MI, myocardial infarction.

Table 3 Incidence rates of all outcomes (incident cardiovascular admissions and all-cause mortality) at 2-year follow-up

Outcome	Period 1 1999–2003	Period 2 2004–2008	Period 3 2009–2013	Period 4 2014–2018
Cerebrovascular disease	3.4 (285)	2.5 (370)	2.0 (324)	2.0 (279)
Ischaemic stroke	2.6 (219)	1.6 (197)	1.3 (214)	1.2 (166)
Ischaemic heart disease	6.2 (505)	4.9 (582)	3.8 (597)	2.8 (388)
Myocardial infarction	2.5 (208)	2.0 (238)	1.5 (244)	1.2 (174)
Peripheral arterial disease	3.8 (315)	2.7 (327)	1.9 (309)	1.7 (240)
All-cause death	24.3 (2100)	18.5 (2289)	13.7 (2231)	12.4 (1784)

Expressed as event rate per 100 person-years (no of events).

declined. Mortality, however, remained substantial. One in five patients diagnosed with AAA between 2014 and 2018 died within 2 years of diagnosis. This finding persisted even when excluding patients with ruptured AAA. Despite a consensus endorsing intensified medical therapy for these patients,[14,18] no further increase in the utilization of medical cardioprotective therapy was observed after 2013. Half of the AAA patients still did not receive concomitant medical therapy with statin and antiplatelet (or any antithrombotic) therapy in Period 4.

We found a decreasing and consistently lower prevalence of comorbid atherosclerotic vascular disease at the time of AAA diagnosis than previously described.[3,9] The rate of new atherosclerotic events requiring hospitalization was 2.0 (per 100 person-years) for CeVD, 2.8 for IHD, and 1.7 for PAD in Period 4. In comparison, the Danish Heart Association found hospitalization rates of 0.8 for CeVD, 1.0 for IHD, and 0.5 for PAD in 2018 in the general population of comparable age and sex (males, age group 65–74 years).[23] Thus, atherosclerotic cardiovascular disease continues to be a major cause of long-term morbidity in patients with AAA, highlighting the importance of addressing cardiovascular risk management and prevention at time of AAA diagnosis.

Our findings of an increasing percentage of AAA patients receiving medical cardioprotective treatment at diagnosis from 1999 to 2013 support the trend described by Bahia *et al.*[9] who examined general practice records of AAA patients in the UK. For most AAA patients, the benefits of secondary cardioprotective treatment outweigh the costs and risk of side-effects associated with antiplatelet and statin treatment, regardless of comorbid atherosclerotic status and age.[9,11,13] Nevertheless, we discovered a plateau in the use of cardioprotective drugs in Period 4 (2014–2018). These findings were consistent in patients with and without comorbid atherosclerotic vascular disease. Similar observations were made in the USA and in several European countries in other patient groups with cardiovascular disease, suggesting a more general trend in cardiovascular preventive medicine.[24–27]

Study strengths and limitations

Our 20-year observation period may have included potential confounding factors, such as changes in availability of diagnostics, leading to increased opportunistic screening for AAA. This may partially

explain the observed changes in incidence of AAA and a lower proportion presenting with ruptured AAA. Records in the Danish health registries are generally considered an accurate depiction of clinical diagnosis.[21,28] Still, there is a risk of misclassification and a risk of changes in coding behaviour over time, e.g. caused by more aggressive monitoring and stricter limits for blood pressure and lipid levels. This may explain the large increases in diagnosis of prevalent hypertension observed over time. Additionally, we used prescription data to estimate trends in medical cardioprotective therapy. As aspirin is also dispensed over the counter in Denmark, this may potentially have introduced underestimation of antiplatelet use. However, most low-dose aspirin (75–150 mg) are dispensed by prescription (>90% in 2012[29]), and thus, retail aspirin use is considered to have only limited influence on observed trends. Further, causes of death could not be ascertained separately, leading to a potential underestimation of the true incidence of cardiovascular hospitalizations during follow-up. Another limitation of our study is the lack of data on smoking status, exercise, and body mass index; factors which may have influenced morbidity and all-cause mortality.[30]

This study provided nationwide, detailed, and unselected coverage of data, reflecting real-life clinical practice from health registries of high validity. Updated information was provided on comorbidity and medical treatment with no bias from loss to follow-up. We included all AAAs, independent of size and presentation (ruptured, non-ruptured AAA), thus providing a comprehensive picture of trends in morbidity and cardioprotective medical treatment at the time of AAA diagnosis.

Conclusions

The prevalence of concomitant atherosclerotic cardiovascular disease and the incidence of new atherosclerotic admissions after AAA diagnosis decreased over the 20-year study period. However, the burden of prevalent and incident IHD and PAD remained high compared with the general population. Efforts to intensify implementation of medical cardioprotective therapy have the potential to further reduce morbidity and enhance survival in patients with AAA.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

Author contributions

C.W.N., M.S., N.E., T.B.L., and S.Z.G. contributed to the conception or design of the work. C.W.N., M.S., M.J., and P.B.N. contributed to the acquisition, analysis, or interpretation of data for the work. C.W.N. drafted the manuscript. C.W.N., M.S., N.E., T.B.L., S.Z.G., and P.B.N. critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Conflict of interest: M.S. has received consulting fees from Bayer. N.E. has served as an investigator for Bayer, and has received fees for speaking engagement from Bayer, Amgen, and AstraZeneca. T.B.L. has served as an investigator for Janssen Scientific Affairs, LLC and Boehringer Ingelheim. T.B.L. has also participated in speaker panels for Bayer, Bristol-Myers Squibb, Pfizer, Roche Diagnostics, and Boehringer Ingelheim. T.B.L. has also received honoraria for consulting activities from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, and Pfizer. T.B.L.'s institution has received unrestricted funds for investigator-initiated research activities from Bayer, Pfizer, and Daiichi Sankyo. P.B.N. has received fees for speaking engagements from Boehringer Ingelheim and BMS/Pfizer; fees for consulting from Bayer and Daiichi Sankyo; and grant support from BMS/Pfizer and Daiichi-Sankyo Europe. All other authors declare no conflicts of interest.

Data availability

The data underlying this article were provided by the Danish Health Data Authority. Because of the non-anonymized nature of the data collected for this study, requests to access the dataset from third parties are not allowed according to Danish data safety regulations.

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Supplemental Material

Title: Temporal trends in abdominal aortic aneurysmal disease: A nationwide cohort study on cardiovascular morbidity and medical cardioprotective therapy

Authors: Chalotte W. Nicolajsen MD[a, b], Mette Søgaard PhD[a, b], Nikolaj Eldrup MD PhD[c], Martin Jensen[a], Torben B. Larsen MD PhD[a, b], Samuel Z. Goldhaber MD[e,f], Peter B. Nielsen PhD[a, b]

Affiliations: [a]Aalborg Thrombosis Research Unit, Department of Clinical Medicine,
Faculty of Health, Aalborg University, Aalborg, Denmark, [b]Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark, [c]Department of Vascular Surgery, Rigshospitalet, Copenhagen, Denmark, [d]Copenhagen University, Copenhagen, Denmark, [e]Thrombosis Research Group, Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, Massachusetts, [f]Harvard Medical School, Boston, Massachusetts.

Supplemental Table I. List of variables

Disease	Code prefix	ICD-10 codes	ATC-code
Study Population			
Abdominal aortic aneurysm	aaa_spec	I713, I714	
Characteristics			
Sex			
Ruptured Abdominal Aortic Aneurysm	aaa_acute	I713	
Outcome			
Hypertension	hyplpr	I10 I11 I12 I13 I15	
Hypercholesterolemia	hypliplpr	E780-E782 E784 E785	
Chronic pulmonary disorder	cpd	J40-J47, J60-J67, J684 J701 J703 J841 J920 J921 J982 J983	
Chronic kidney disease	crenal	E102 E112 E142 I120 I131 I132 I150 I151 N03 N05 N06 N07 N08 N110 N14 N15 N16 N18 N19 N26 N27 N280 N391 Q61	
Ischemic heart disease	ihd	I20 I21 I23 I24 I25	
Myocardial Infarction	mi	I21	
Congestive Heart failure	Hf2	I110 I130 I132 I42 I50	
Atrial Fibrillation	afli	I48	
Stroke			
Transient	TIA	G45	
Ischemic	Istroke	I63	
Haemorrhagic	Ibleed	I60 I61 I62	
Unspecified	ustroke	I64	
Peripheral arterial disease	Pad4	I70 I71 I72 I73 I74 I77	
Diabetes	diab3lpr	E10 E11 E14	

Cancer	Cancer1	C1 C2 C3 C40 C41 C42 C43 C45 C46 C47 C48 C49 C5 C6 C7 C8 C9	
Rheumatic disease	rheuma	M01-06, M08, M09, M30-36, D86	
Deep Vein Thrombosis	dvt	I801 I802 I803 I808 I809 I819 I636 I676 I822 I823 I828 I829	
Pulmonary Embolism	pe	I26	
Venous Thromboembolism	Vte	I26 I801 I802 I803 I808 I809 I828 I829 I81 I822 I823 I636 I676	
Mechanical Heart Valve	Valve	Z952, Z953, Z954	
Medication			
Statins	statins		C10
Platelet-inhibitor			
Aspirin	aspirin		B01AC06
Clopidogrel	clopi		B01AC04
Thienopyridines (tricagrelor, prasugrel)	Thien		B01AC24 B01AC22
Anticoagulant			
Coumarin	coumarin		B01AA
Warfarin	warfarin		B01AA03
Phenprocoumon	Phen		B01AA04
DOAC (Rivaroxoban, Apixaban, Dabigatran, Fondaparinux	noac		B01AE07, B01AF01, B01AF02, B01AX05
Low Molecular Weight Heparin	heparins		B01AB
Anti-hypertensive	HypATC1		(C02, C07, C08, C09,
Anti-hypertensive + diuretic	Hypatc2		C02, C03, C07, C08, C09
ACE inhibitor	ACEinhib		C09
Anti-diabetic	DiabATC		A10

DOAC – Direct oral anticoagulant therapy, ACE – Angiotensin converting enzyme

Stroke and Myocardial Infarction in Patients with Abdominal Aortic Aneurysm and New-Onset Atrial Fibrillation

Chalotte W. Nicolajsen[1,2,3] Peter B. Nielsen[1,2] Martin Jensen[1] Nikolaj Eldrup[4,5] Torben B. Larsen[1,2] Gregory Y. H. Lip[1,6] Samuel Z. Goldhaber[7,8] Mette Søgaard[1,2]

[1] Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Faculty of Health, Aalborg University, Aalborg, Denmark
[2] Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark
[3] Department of Vascular Surgery, Viborg Regional Hospital, Viborg, Denmark,
[4] Department of Vascular Surgery, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark
[5] Copenhagen University, Copenhagen, Denmark
[6] Liverpool Centre for Cardiovascular Science, University of Liverpool, Liverpool John Moores University and Liverpool Heart and Chest Hospital, Liverpool, United Kingdom
[7] Division of Cardiovascular Medicine, Thrombosis Research Group, Brigham and Women's Hospital, Boston, Massachusetts, United States
[8] Department of Medicine, Harvard Medical School, Boston, Massachusetts, United States

Address for correspondence Chalotte W. Nicolajsen, MD, Aalborg Thrombosis Research Unit, Department of Cardiology, Aalborg University Hospital, Sdr. Skovvej 15, 9000 Aalborg, Denmark (e-mail: c.nicolajsen@rn.dk).

Thromb Haemost

Abstract

Objective We investigated the association between new-onset atrial fibrillation (AF) and risk of stroke and myocardial infarction (MI) in patients with abdominal aortic aneurysmal (AAA) disease.

Methods Observational crossover study using Danish nationwide data, including patients with AAA and incident AF between 1997 and 2018. We estimated the 1-year risk of stroke and MI and the within-individual odds ratios (ORs) of ischemic events before and after an AF diagnosis, stratified by year of AF diagnosis (1997–2010 and 2011–2018), and supplemented with analyses on changes in use of antithrombotic therapy.

Results A total of 3,035 AAA patients were included: 1,040 diagnosed during 1997 to 2010, and 1,995 during 2011 to 2018 (22.2% females, median age 78 years; median CHA_2DS_2-VASc score 4; interquartile range: 3–5). One-year risk of ischemic events after AF was 5.9% (confidence interval [CI] 95%: 4.6–7.5%) and 4.5% (CI 95%: 3.7–5.5%) for stroke and 5.4% (CI 95%: 4.2–6.9%) and 4.0% (CI 95%: 3.2–4.9%) for MI during 1997 to 2010 and 2011 to 2018, respectively. The OR of ischemic stroke before and after incident AF was 2.8 (CI 95%: 1.6–5.2) during 1997 to 2010; and 2.4 (CI 95%: 1.5 to 3.9) during 2011 to 2018, and 3.5 (CI 95%: 1.7–7.5) and 1.5 (CI 95%: 0.9–2.4) for MI. One-

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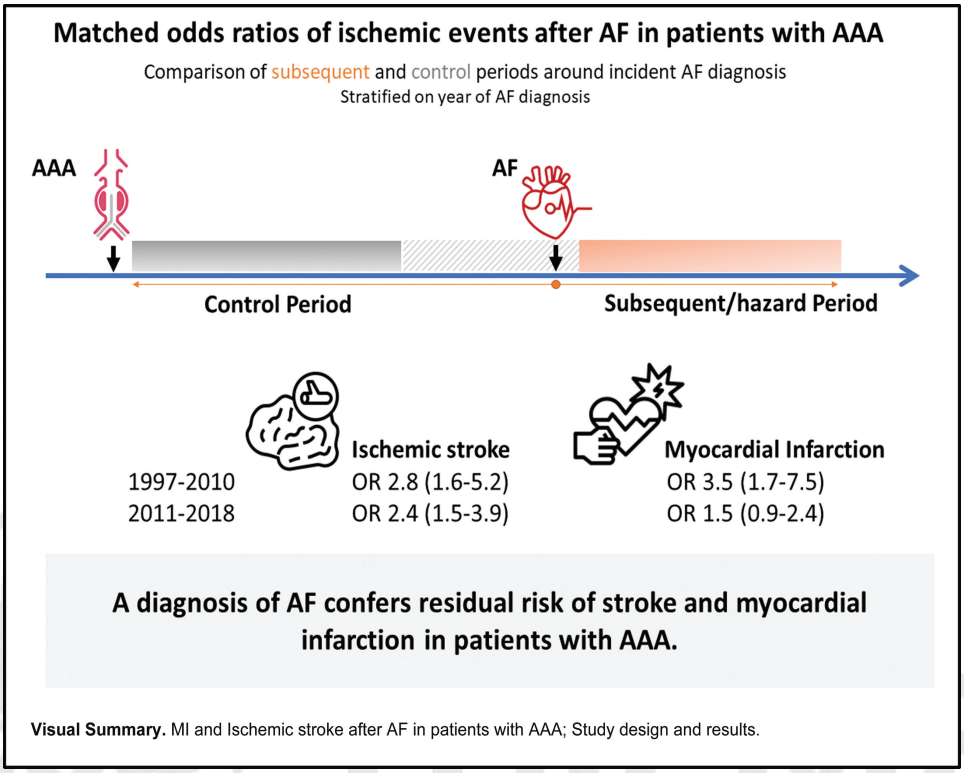

Visual Summary. MI and Ischemic stroke after AF in patients with AAA; Study design and results.

year proportion of prescription claims for oral anticoagulants after AF changed from 66.1% in 1997 to 2010 to 82.6% in 2011 to 2018, while antiplatelet prescription claims changed from 80.8 to 60.9%.

Conclusion Cardiovascular prognosis has improved in patients with prevalent AAA disease and new-onset AF in concordance with optimization of antithrombotic therapy over time. A diagnosis of AF conferred residual risk of stroke and MI.

Introduction

Abdominal aortic aneurysmal (AAA) disease is associated with a twofold higher risk of stroke and myocardial infarction (MI).[1,2] Factors affecting ischemic risk include underlying comorbidities, but mechanisms are not well understood. Atrial fibrillation (AF) is independently associated with a four- to fivefold increased risk of debilitating stroke and cardiovascular morbidity, such as MI and death.[3–5] This risk is further increased in patients with AF and concomitant cardiovascular atherosclerotic disease.[6–8] AAA and AF share several clinical risk factors, including similar age at diagnosis, smoking habits, and hypertension.[9,10] Taken together with the increasing prevalence of AF in AAA populations,[4,11] AF is an important contributing factor for adverse cardiovascular outcomes in AAA disease.

Appropriate antithrombotic therapy is central to management, and medical thromboprophylaxis is associated with a reduced risk of cardiovascular events.[12,13] Prophylaxis with antiplatelets as monotherapy is therefore recommended at the time of AAA diagnosis,[14] while a subsequent diagnosis of AF warrants a change to oral anticoagulant (OAC) from antiplatelet therapy.[4] Implementation of recommendations on thromboprophylaxis for both diseases has increased over the last decade.[11,15] However, the extent of implementation of OAC therapy in patients with AAA in the presence of concomitant new-onset AF remains uncertain.

To investigate the association between incident AF diagnosis and the risk of ischemic events among patients with prevalent AAA disease, we conducted an observational study based on data from the Danish national health registries.

Methods

Observational cohort study using data from the Danish nationwide cohort. With an exposure-crossover design, we ascertained the risk of ischemic events and examined the antithrombotic treatment changes before and after incident AF among patients with prevalent AAA.

Data Sources

The Danish national health registries contain comprehensive individual-level health information on all Danish citizens from birth or immigration. From the Danish National Patient Registry (DNPR) we retrieved information on in- and outpatient discharge diagnoses classified by the International Classification of Diseases, 10th Revision (ICD-10) as well as data on dates of admission and discharge.[16] From the Danish National Prescription Registry, we retrieved information on dispensed prescriptions identified by the Anatomic Therapeutic Chemical (ATC) classification code and dates of purchase.[17] From the Danish Civil Registration System, we retrieved information on sex, date of birth/immigration, emigration, and vital status.[18] The permanent and unique registration number given to all Danish residents enabled crosslinking of databases and establishment of the study population.

Study Population

All patients with a hospital diagnosis of AAA in the DNPR between January 1, 1997 and December 31, 2018 were identified, including both in- and outpatient registrations as well as asymptomatic and symptomatic AAA. Of these, patients with a subsequent new-onset diagnosis of AF were considered for inclusion in the study cohort. Previous validation studies have reported positive predictive values of > 98% for the AAA diagnosis and 92.6% for the AF diagnosis in the DNPR.[19,20] We excluded individuals immigrating to Denmark within the year prior to inclusion, patients with ischemic events or death occurring on the date of AF diagnosis, and patients diagnosed with AAA before 50 years of age (to exclude patients with severe connective tissue disease, which has a different etiology than degenerative AAA). To enable comparison of risks before and after AF diagnosis in the exposure-crossover analysis, we excluded patients with time intervals between AAA and AF diagnosis of less than 1 year (53 weeks).

Detailed specification of definitions of exposure, outcome, comorbidities, and comedications is provided in ►**Supplementary Table S1** (available in the online version).

Study Design

Patients with AAA and AF may differ from AAA patients without AF with respect to clinical characteristics, demographic factors, and lifestyle behavior, which are not readily available from registry data. Consequently, observational studies analyzing ischemic risk associated with the AF diagnosis can be susceptible to confounding by factors potentially related to the outcome of interest. For these reasons, we applied a self-matched study design: an exposure crossover analysis that minimizes measured and unmeasured time-invariant confounding such as genetics, education level, and lifestyle.[21] The self-matching consisted of a within-patient comparison of ischemic outcome events occurring in a predefined period after AF diagnosis (the "subsequent interval") compared with outcome events occurring in a matched period before AF (the "baseline interval") (►**Fig. 1**).[22] This design allowed for

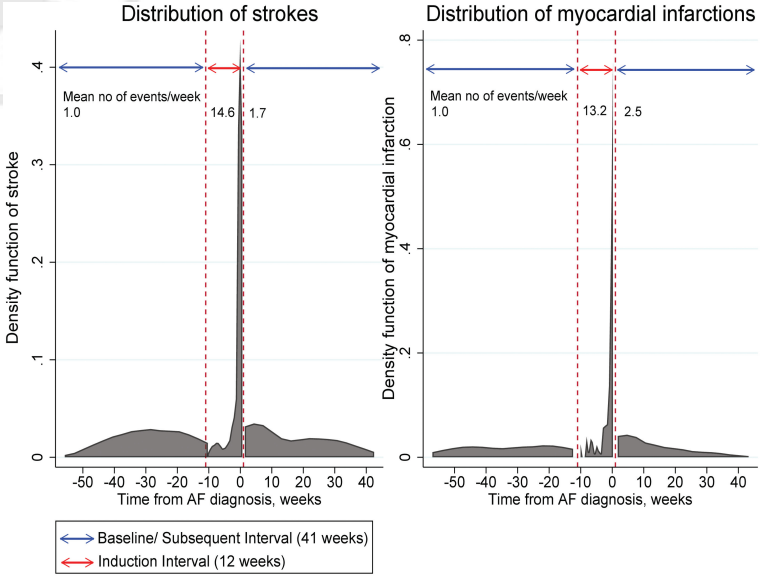

Fig. 1 Exposure crossover analyses: Distribution and length of study intervals (blue) and number of events (stroke and myocardial infarction) per segment (weeks).

analysis of changes in risk of ischemic events associated specifically to the AF diagnosis.[21]

The date of exposure was defined as the time of new-onset AF diagnosis (index date). To ascertain the time-invariance of covariates and minimize effects of increasing age, aneurysm size, and incident comorbidity during the study period, the baseline and subsequent interval was defined within the 1-year period before and after AF diagnosis, respectively. For this analysis, the observation periods were organized in segments of 7 days. To encompass potential unknown AF status and to ensure reproducible event-counts within the time intervals of interest, we applied an induction interval from 11 weeks before to 1 week after the AF diagnosis to the analyses. Consequently, a total induction interval of 12 weeks and baseline and subsequent intervals of 41 weeks each were applied (►**Fig. 1**).

Comorbidity and Comedications

Concomitant comorbidity (history of stroke, MI, congestive heart failure, peripheral arterial disease, diabetes, chronic pulmonary disease, renal insufficiency, and venous thromboembolism), cardiovascular risk factors (hypertension, hyperlipidemia), CHA_2DS_2-VASc score (cardiac failure or dysfunction, hypertension, age > 75 years [doubled], diabetes, stroke [doubled]-vascular disease [atherosclerotic, excluding aneurysmatic disease], age 65 to 74 years, and sex category [female]),[23] and comedication use of anticoagulants, antiplatelets, statins, antihypertensives, and antiarrhythmics were assessed at baseline. Comorbidities were defined as any primary or secondary inpatient or outpatient discharge diagnosis. Concomitant baseline pharmacotherapy was defined as a prescription claim within 1 year prior to the AF diagnosis. Specifications of variables and ICD-10/ATC codes used for analyses are provided in ►**Supplementary Table S1** (available in the online version).

Outcome Measures

Patients were followed from index date until occurrence of study endpoints, emigration, end of study (1-year follow-up or December 31, 2018), or death, whichever came first. The primary outcomes were ischemic stroke and MI. To illustrate the use of OAC and antiplatelet therapy before and after incident AF, and to support the interpretation of outcomes of the main analyses, a secondary endpoint was the filling of at least one prescription for antiplatelets or OAC. In the absence of AF, combination therapy with OAC and antiplatelets is not recommended in patients with stable vascular disease.[4,24] Antiplatelet therapy was defined as at least one prescription claim of aspirin, clopidogrel, ticagrelor, or prasugrel, and OAC therapy included warfarin, dabigatran, rivaroxaban, apixaban, and edoxaban (►**Supplementary Table S1**, available in the online version).

Statistical Analysis

Baseline demographics and comorbidities are presented descriptively. Summarized categorical data are reported as percentages and continuous data as medians with accompanying interquartile ranges (IQRs). To investigate possible changes in risk of ischemic events and antithrombotic treatment, according to temporal changes in implementation of preventive antithrombotic therapy through the last decade, all analyses were stratified in two time periods (1997–2010 and 2011–2018).

To estimate the association between incident AF and the risk of ischemic events in AAA disease, we performed two separate analyses. First, we applied time-to-event analyses of all outcomes to calculate the cumulative incidence of outcomes after AF diagnosis. The absolute risk of events was derived using crude Aalen–Johansen estimates with death as competing risk at 1-year follow-up. Second, we applied the exposure-crossover analyses to estimate the relative odds of primary outcomes in the subsequent interval after AF diagnosis compared with the baseline interval before AF. Distribution plots of events were visualized using Gaussian kernel density functions,[25] and matched odds ratios (ORs) were calculated using McNemar's test for matched pair's data. Outcome measures were reported with 95% confidence intervals (CIs). SAS (version 9.4) and STATA/MP (version 16) were used for statistical analyses.

Preplanned sensitivity analyses included assessing the length of the induction interval by extending and reducing the interval before AF diagnosis to 4, 8, 16, and 24 weeks, respectively, and by changing the induction interval after AF diagnosis to 0 and 2 weeks. Based on a potential risk of immortal time bias (i.e., patients must survive until AF diagnosis to be included in the analyses), a sensitivity analysis was performed in which we restricted the cohort to patients surviving until the end of the observation period.

Ethics

In Denmark, approval from an ethics committee is not required for registry-based studies in which specific individuals cannot be identified. The study was performed in compliance with the General Data Protection Regulation and the North Denmark Region's record of processing activities (project no. 2017–40). Data were provided by the Danish Health Data Authority.

Results

Of 35,624 patients diagnosed with AAA between 1997 and 2018, 3,035 patients met the inclusion criteria (►**Supplementary Fig. S1**, available in the online version). ►**Table 1** summarizes baseline characteristics at the time of incident AF diagnosis. In the overall study cohort, 22.2% were females, and the median age was 78 (IQR 73–83) years, with the proportion aged > 80 years highest in the later period: 34.9% in 1997 to 2010 and 43.6% in 2011 to 2018. Concomitant cardiovascular comorbidity included previous stroke (18.0%), previous MI (23.9%), peripheral occlusive arterial disease (38.5%), and heart failure (28.4%). The median CHA_2DS_2-VASc score was 4 (IQR: 3–5) at time of incident AF diagnosis. Baseline statin use increased from 47.5% in 1997 to 2010 to 71.2% in 2011 to 2018.

Risk of Ischemic Events Associated with AF Diagnosis

In patients with AAA and incident AF, the cumulative incidence of stroke after AF diagnosis was 5.9% (95% CI:

Table 1 Demographics and patient characteristics of the study population with AAA and incident AF

	AF diagnosed 1997–2010 % (*n*)	AF diagnosed 2011–2018 % (*n*)	AF total % (*n*)
N	1,040	1,995	3,035
Demographics			
Sex, female	21.5 (224)	22.6 (451)	22.2 (675)
Age, median (IQR)	77.0 (72.0–81.0)	78.0 (73.0–83.0)	78.0 (73.0–83.0)
Age group, y			
50–59	1.1 (11)	0.7 (14)	0.8 (25)
60–69	16.3 (170)	11.7 (233)	13.3 (403)
70–79	47.7 (496)	44.1 (879)	45.3 (1,375)
80+	34.9 (363)	43.6 (869)	40.6 (1,232)
Median time since AAA diagnosis, y	3.9 (2.3–6.2)	5.2 (2.8–8.7)	4.6 (2.6–7.8)
Average follow-up, median (IQR)	2.5 (0.4–6.3)	1.6 (0.5–3.4)	1.8 (0.5–4.0)
Comorbidity			
Stroke	18.0 (187)	17.9 (358)	18.0 (545)
Myocardial infarction	21.3 (222)	25.2 (502)	23.9 (724)
Congestive heart Failure	31.4 (327)	26.8 (534)	28.4 (861)
Peripheral atherosclerotic disease	38.4 (399)	38.5 (769)	38.5 (1,168)
Diabetes	13.6 (141)	17.7 (354)	16.3 (495)
Hyperlipidemia	19.1 (199)	34.4 (686)	29.2 (885)
Hypertension	48.1 (500)	64.2 (1,280)	58.6 (1,780)
Chronic pulmonary disease	31.0 (322)	31.3 (625)	31.2 (947)
Renal impairment	14.7 (153)	18.7 (374)	17.4 (527)
Venous thromboembolism	8.6 (89)	10.7 (214)	10.0 (303)
CHA_2DS_2-VASc score ≤ 2 in men or ≤ 3 in women	6.6 (68)	4.8 (94)	5.4 (162)
CHA_2DS_2-VASc score > 2 in men or > 3 in women	93.5 (972)	95.3 (1,901)	94.7 (2,873)
CHA_2DS_2-VASc score, median (IQR)	4.0 (3.0–5.0)	4.0 (3.0–5.0)	4.0 (3.0–5.0)
HASBLED score, median (IQR)	3.0 (2.0–4.0)	3.0 (2.0–4.0)	3.0 (2.0–4.0)
Medication			
Antithrombotics			
Platelet inhibitor	64.5 (671)	69.9 (1,394)	68.0 (2,065)
Aspirin	62.6 (651)	59.9 (1,195)	60.8 (1,846)
Other	6.9 (72)	19.4 (387)	15.1 (459)
OAC	18.1 (188)	27.6 (550)	24.3 (738)
Warfarin	17.0 (177)	15.6 (311)	16.1 (488)
DOAC	–	12.6 (252)	8.3 (252)
OAC + platelet inhibitor	10.0 (104)	14.9 (298)	13.2 (402)
No antithrombotic treatment	27.4 (285)	17.5 (349)	20.9 (634)
Other			
Statin	47.5 (496)	71.2 (1,420)	63.1 (1,914)
Antihypertensive	74.3 (773)	82.7 (1,649)	79.8 (2,422)
Antiarrhythmics	2.9 (30)	1.9 (38)	2.2 (68)

Abbreviations: AAA, abdominal aortic aneurysm; AF, Atrial fibrillation; CHA_2DS_2-VASc, cardiac failure or dysfunction, hypertension, age > 75 years (doubled), diabetes, stroke (doubled)-vascular disease, age 65 to 74 years, and sex category (female); DOAC, direct oral anticoagulant therapy; HAS-BLED, hypertension, abnormal renal and/or liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly (> 65 years), drugs (antiplatelet drugs or nonsteroidal anti-inflammatory drugs)/alcohol excess concomitantly; IQR, interquartile range; OAC, oral anticoagulant therapy.

Table 2 Cumulative 1-year incidences of primary (stroke and myocardial infarctions) and secondary (prescription claims of platelet inhibitors and anticoagulants) outcomes

	1997–2010 *N* 1,040		2011–2018 *N* 1,995	
	Total events (*N*)	Cumulative proportion % (95% CI)[a]	Total events (*N*)	Cumulative proportion % (95% CI)[a]
Stroke	62	5.9 (4.6–7.5)	87	4.5 (3.7–5.5)
Myocardial infarction	56	5.4 (4.2–6.9)	77	4.0 (3.2–4.9)
Use of platelet inhibitor	834	80.8 (78.2–83.1)	1,173	60.9 (58.6–63.0)
Use of oral anticoagulation	682	66.1 (63.1–68.9)	1,588	82.6 (80.8–84.2)

Abbreviation: CI, confidence interval.
[a]With death as competing risk.

4.6–7.5%) at 1-year follow-up in patients diagnosed with AF between 1997 and 2010, and 4.5% (95% CI; 3.7–5.5%) among patients diagnosed in 2011 to 2018. The cumulative incidence of MI was 5.4% (95% CI: 4.2–6.9%) in 1997 to 2010 and 4.0% (95% CI: 3.2 to 4.9%) in 2010 to 2018 (►**Table 2**, ►**Fig. 2**).

In crossover analyses, a total of 330 strokes occurred during the baseline, induction, and subsequent interval (total duration of observation time per patient was 94 weeks). The mean number of strokes per week was 1.0 in the baseline interval, 13.2 in the induction interval, and 2.5 per week in the subsequent interval (►**Fig. 1**). Stratified by time of diagnosis, 20 strokes occurred in the baseline interval compared with 53 events in the subsequent interval in 1997 to 2010, corresponding to a matched OR of ischemic stroke of 2.8 (95% CI: 1.6–5.2) after AF diagnosis. During 2011 to 2018, there were 26 strokes in the baseline interval compared with 62 in the subsequent interval, matched OR 2.4 (95% CI: 1.5–3.9) (►**Fig. 3**).

Overall, 319 MIs were observed during the baseline, induction, and subsequent intervals. The mean number of events per week was 1.0 in the baseline interval, 14.6 in the induction interval, and 1.7 in the subsequent interval (►**Fig. 1**). In 1997 to 2010, 13 events occurred in the baseline interval compared with 40 events in the subsequent interval, corresponding to a matched OR of MI after AF diagnosis of 3.5 (95% CI; 1.7–7.5), see ►**Fig. 3**. From 2011 to 2018, 33 MIs occurred in the baseline interval compared with 47 in the subsequent interval, matched OR 1.5 (95% CI: 0.9–2.4) (►**Fig. 3**).

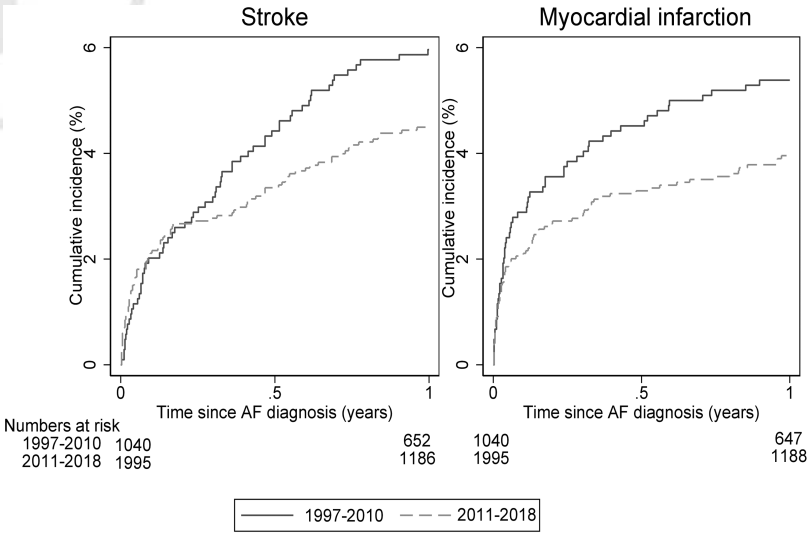

Fig. 2 Cumulative incidence of stroke and myocardial infarction after atrial fibrillation (AF) diagnosis at 1-year follow-up according to year of AF diagnosis.

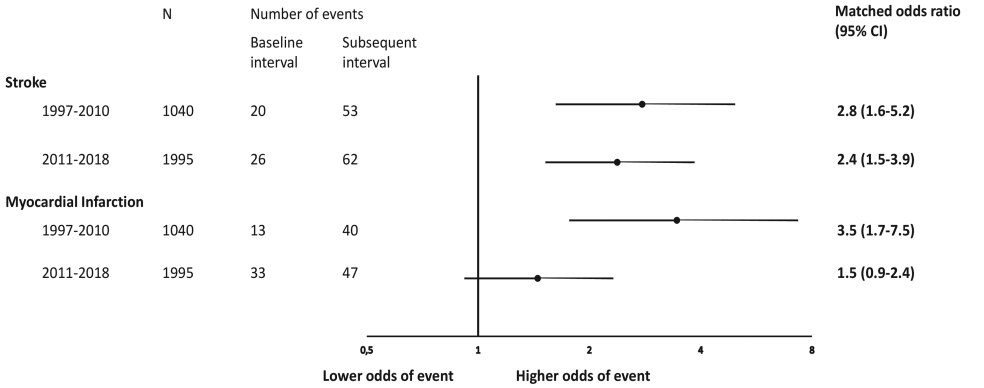

Fig. 3 Odds ratio of stroke and myocardial infarction after atrial fibrillation (AF) diagnosis in patients with abdominal aortic aneurysmal (AAA), according to year of AF diagnosis.

Medical Antithrombotic Treatment Associated with AF Diagnosis

Among AAA patients diagnosed with AF in 1997 to 2010, 66.1% filled a prescription for OAC in the year after AF diagnosis, increasing to 82.6% during 2011 to 2018 (►**Table 2**, ►**Fig. 4**). The cumulative proportion of antiplatelet claims showed an opposite trend, with 80.8% filling a prescription claim for antiplatelets in 1997 to 2010, compared with 60.9% in 2011 to 2018. A total of 92.1% claimed a prescription of OAC and/or antiplatelets in the follow-up period after AF diagnosis during 1997 to 2010, and similarly in 2011 to 2018, 96.3%.

The crossover analysis showed that incident AF was associated with a change in prescription pattern toward more prescription claims for OAC. The OR was 14.7, (95% CI: 9.1–25.1) for initiating OAC after AF in 1997 to 2010, while during 2011 to 2018, the OR was 24.6 (95% CI: 17.3–36.2). For antiplatelets the OR was 4.0 (95% CI: 3.2–5.1) for initiating therapy after AF diagnosis during 1997 to 2010 and OR 1.2 (95% CI: 1.0–1.4) during 2011 to 2018. Forest plots of change in prescription claims are available in ►**Supplementary Fig. S2** (available in the online version).

Sensitivity Analyses

Changing the duration of the induction interval affected the number of observed primary outcome events but had little impact on the estimated matched ORs (►**Supplementary Fig. S3**, available in the online version). The same applied to sensitivity analyses restricted to patients who survived until the end of observation period.

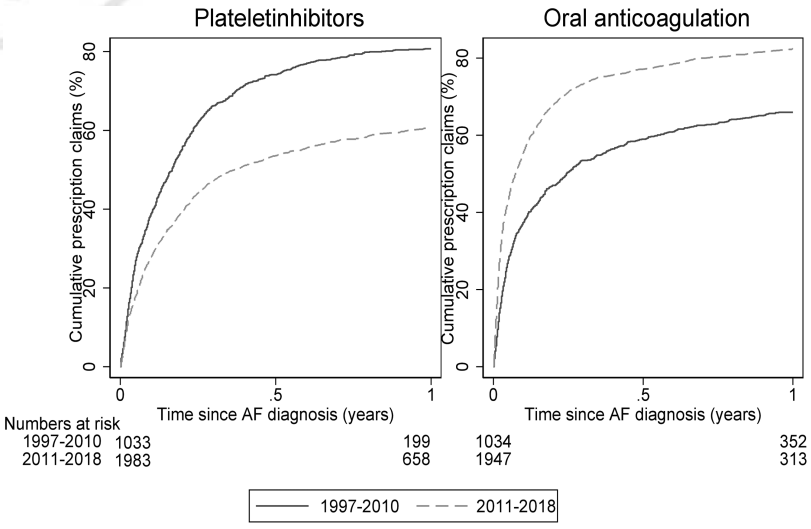

Fig. 4 Cumulative proportion of prescription claims of antithrombotic drugs within the first year after atrial fibrillation (AF) diagnosis in patients with abdominal aortic aneurysmal (AAA).

Discussion

In this cohort of more than 3,000 patients with prevalent AAA, we observed a high risk of both ischemic stroke and MI after incident AF. The risk was lower during recent years (2010–2018), in concordance with a higher implementation of OAC therapy. Regardless of improvements in antithrombotic treatment, the AF diagnosis was associated with a more than twofold higher odds of stroke, while the associated higher odds of MI after AF were strongest among patients diagnosed with AF before 2010.

Patients with AAA suffer a high risk of ischemic events compared with the general population, with previous studies reporting 2-year incidences of 2 to 4% in the total AAA population.[1,11,26] In the present study, we observed an even higher incidence of both stroke and MI (4–6%), in patients suffering subsequent AF after just 1 year of follow-up. Furthermore, we demonstrated higher odds of both stroke and MI associated with the incident AF diagnosis itself in the self-matched comparison. Our results indicate that patients with AAA and AF represent a vulnerable subgroup at high risk of subsequent ischemic outcomes, comparable to patients with AF and concomitant atherosclerotic vascular diseases.[6,7,27] Hence, awareness of concomitant AF in the management and risk assessment of patient with AAA is essential, even in the absence of symptomatic atherosclerosis. Coexistence of AF and AAA identifies a more vulnerable subgroup of patients, at high risk of more severe cardiovascular disease and poorer prognosis; hence, this necessitates a more holistic or integrated care plan[28] to improve outcomes.[29,30]

The increasing proportion of patients initiating OAC after AF diagnosis over time reflects changes in recommendations and temporal trends in OAC and antiplatelet therapy, as observed in other studies on use of OAC in patients with AF.[31,32] More than 80% of patients claimed a prescription of OAC after incident AF during 2011 to 2018. Apart from the generally lower incidence of ischemic events observed in that time period, the increased use of OAC over time was also accompanied by lower odds of MI after incident AF. OAC has been demonstrated to reduce the risk of MI and cardiovascular mortality in AF patients more than antiplatelet agents.[33] Further, increasing emphasis on reduction of atherosclerotic risk factors over time, such as public bans on smoking, lower target levels of low-density lipoprotein cholesterol and blood pressure, combined with increasing use of cardioprotective medications, such as statins and antihypertensives, as observed in the present study, likely play a beneficial role.[12,34,35] Unlike MI, the increasing implementation of OAC after 2010 was accompanied by only modest reduction in the odds of stroke after incident AF. The preventive effect conferred by appropriate OAC therapy on stroke risk in general is evident, and was reflected in the lower cumulative incidence of all ischemic events observed after 2010.[36] Thus, the limited changes over time in odds of stroke after developing AF may reflect the higher residual risk of stroke found in older, multimorbid patients, such as the AAA population, despite optimal anticoagulation.[37,38] Further, age itself contributes to risk of stroke in AF, a factor with potential high impact on results in this study population of high median age.[39] Meanwhile, the consistent higher odds of both stroke and MI following incident AF, also after high implementation of OAC, underline the need to focus on AF as an important marker of high cardiovascular risk. AF can be a silent comorbidity, contributing to a poor cardiovascular prognosis also in asymptomatic subjects.[40,41] Yet at present, there is no recommendation on screening for AF in patients with AAA, as opposed to recommendations in patients with symptomatic atherosclerotic peripheral arterial disease.[4] Given the high and increasing prevalence of AF in the general population (2–5%)[4,42] as well as among patients with AAA (up to 12.5%),[11,43] it might be prudent to incorporate AF screening in the management of patients with AAA.

Strengths and Limitations

Strengths of this study include the use of nationwide health registries of high validity with virtually no loss to follow-up.[16] The large size of the cohort enabled the exposure-crossover design, accounting for both measured and potential unmeasured confounding factors, permitting estimation of risks directly associated with the diagnosis of incident AF. The induction interval, applied in the exposure-crossover analyses, ensured that short-term changes in risk of ischemic events, for instance caused by isolated peri- and postoperative cardiac arrhythmia, should not affect outcomes. The use of administrative health registries in this study carries a risk of misclassification bias. Improvements in diagnostics and hospital referral patterns, and changes in coding protocols due to the introduction of diagnosis-related groups were introduced in 2000.[16] These changes may, in part, explain the increasing number of patients with AAA and AF and prevalence of comorbidity over time. The exposure-crossover design also has inherent limitations. The need for an induction interval to ensure the validity of AF status in the time intervals compared, and the need to exclude patients with insufficient time between AAA and AF diagnosis, limited the number of patients and events included.

Conclusion

Cardiovascular prognosis has improved over time in patients with AAA and new-onset AF in concordance with increasing implementation of anticoagulant therapy. Yet, a diagnosis of AF still confers an additional high risk of stroke and MI. These findings suggest a compelling need to focus on identifying coexistent AF in the management and medical optimization of high-risk patients with AAA.

What is known about this topic?

- Atrial fibrillation is a contributing factor for adverse cardiovascular event in patients with atherosclerotic disease.
- The association has not been previously examined in patients with abdominal aortic aneurysmal disease.

What does this paper add?

- This study demonstrates the high risk of ischemic stroke and myocardial infarction conferred by atrial fibrillation in patients with abdominal aortic aneurysmal disease.
- Atrial fibrillation was associated with more than two-fold higher odds of stroke, regardless of improvements in antithrombotic treatment over time.
- The higher odds of stroke and myocardial infarction underscore a need to focus on coexisting atrial fibrillation as a marker of high-risk patients with aortic aneurysmal disease.

Data Availability Statement

Because of the nonanonymized nature of the data collected for this study, requests to access the data set from third parties are not allowed according to Danish data safety regulations.

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Conflict of Interest

M.S. has received consulting fees from Bayer. N.E. has served as an investigator for Bayer, and has received fees for speaking engagement from Bayer, Amgen, and AstraZeneca. T.B.L. has served as an investigator for Janssen Scientific Affairs, LLC, he has also participated in speaker panels for Bayer, Bristol-Myers Squibb/Pfizer and Roche Diagnostics and has also received honoraria for consulting activities from Bayer AG, Bristol-Myers Squibb, and Pfizer. T.B.L.'s institution has received unrestricted funds for investigator-initiated research activities from Bayer, Pfizer, and Daiichi Sankyo. P.B.N. has received fees for speaking engagements from Boehringer Ingelheim and BMS/Pfizer; fees for consulting from Bayer and Daiichi-Sankyo; and grant support from BMS/Pfizer and Daiichi-Sankyo Europe. All other authors declare no conflicts of interest.

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Supplemental Files

Stroke and myocardial infarction in patients with abdominal aortic aneurysms and new-onset atrial fibrillation: An observational crossover study

Authors:
Chalotte W. Nicolajsen[a, b, c], Peter B. Nielsen[a, b], Martin Jensen[a], Nikolaj Eldrup[d,e], Torben B. Larsen[a, b], Gregory Y. H. Lip[a,f], Samuel Z. Goldhaber[g,h], Mette Søgaard[a,b]

Affiliations:
[a]Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Faculty of Health, Aalborg University, Aalborg, Denmark, [b]Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark, [C]Department of Surgery, Unit of vascular Surgery, Viborg Regional Hospital, [d]Department of Vascular Surgery, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark, [e]Copenhagen University, Copenhagen, Denmark, [f]Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, United Kingdom, [g]Thrombosis Research Group, Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, Massachusetts, [h]Harvard Medical School, Boston, Massachusetts.

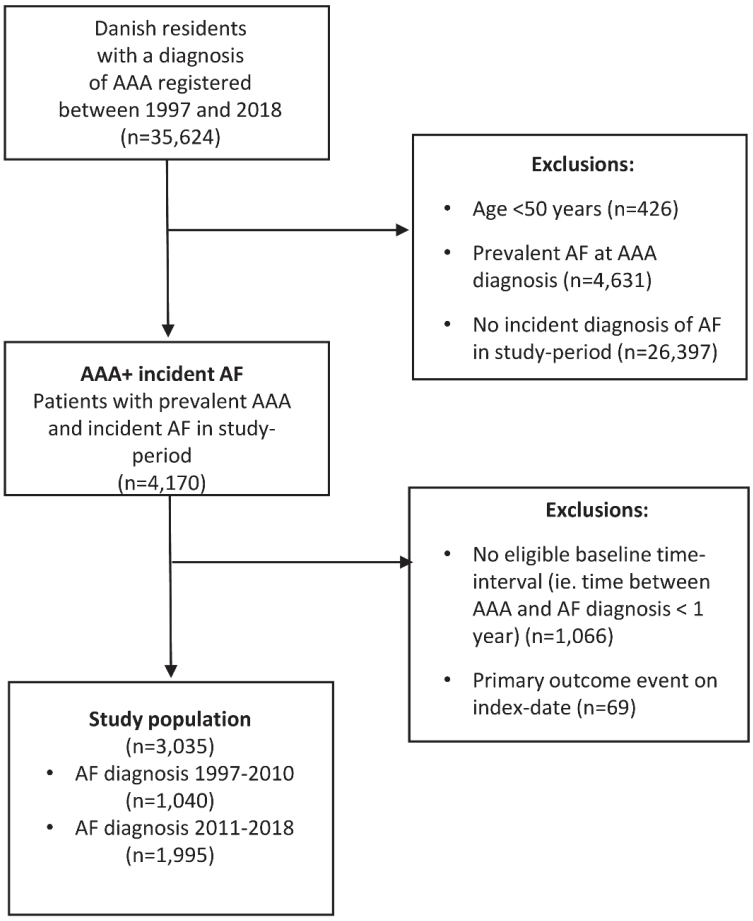
Supplemental Table 1. List of variables

Disease	Code prefix	ICD-10 codes	ATC-codes
Study population			
Abdominal aortic aneurysm	aaa	I713 I714	
Exposure group			
Atrial fibrillation	afli	I48	
Outcome			
Stroke			
Ischemic stroke	istroke	I63	
Unspecified stroke	ustroke	I64	
Myocardial infarction	mi	I21	
Comorbidity			
Cardiac Heart Failure (CHA_2DS_2-VASc)	Hf2lpr	I110 I130 I132 I50	
Peripheral arterial disease (CHA_2DS_2-VASc)	pad4	I70 I72 I73 I74 I77	
Diabetes (CHA_2DS_2-VASc)	diab3lpr	E10 E11 E14	
Hyperlipidemia	hyplip	E78-E782 E784 E785	
Hypertension (CHA_2DS_2-VASc)	hyp	I10-15	
Renal impairment	renal	I12 I13 N00 N01 N02 N03 N04 N05 N07 N11 N14 N17 N18 N19 Q61	
Chronic pulmonary disease	cpd	J40-J47 J60-J67, J684 J701	
Venous Thromboembolism	Vte	I26 I801 I802 I803 I808 I809 I828 I829 I81 I822 I823 I636 I676	
Medication			
Antithrombotic			
Aspirin	aspirin		B01AC06
Clopidogrel	clopi		B01AC04
Other thienopyridines (tricagrelor, prasugrel)	thien		B01AC24 B01AC22
Warfarin	warfarin		B01AA03
Phenprocoumon	phen		B01AA04
DOAC (Dabigatran Rivaroxoban Apixaban Edoxaban)	noac		B01AE07 B01AF01 B01AF02 B01AF03

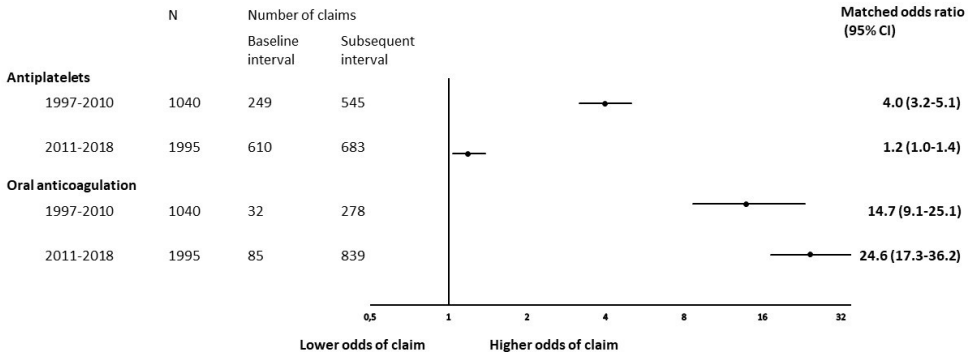
			B01AX05
Other			
Antihypertensives	Hypatc1		C02 C07 C08 C09
Statins	statins		C10
Anti-arrhythmic agents	arythmics		C01B

CHA_2DS_2-VASc); congestive heart failure, hypertension, age ≥75 years (doubled), diabetes, stroke (doubled), vascular disease, age 65-74 and sex (female), DOAC; direct oral anticoagulant therapy.

Supplemental Figure 1. Flowchart of inclusions

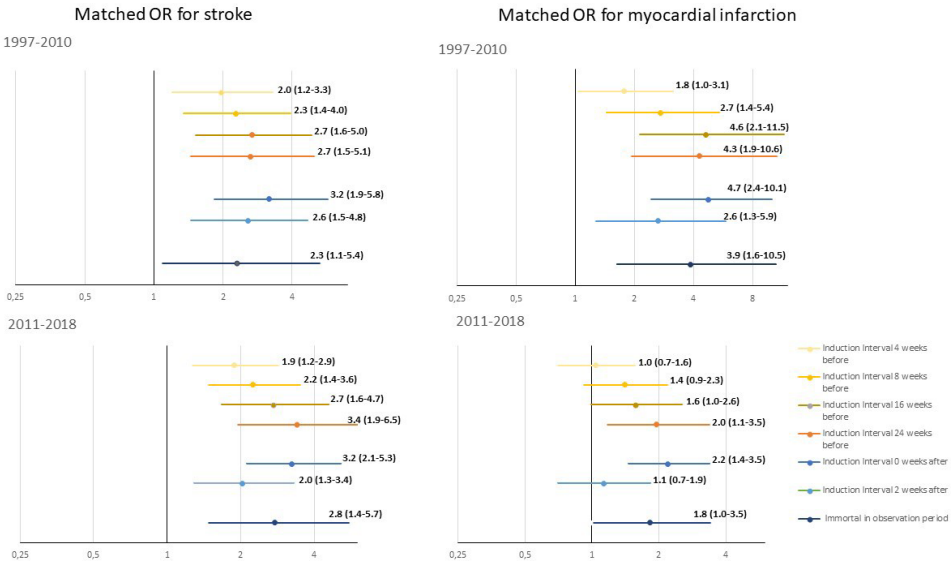


Supplemental Figure 2. Odds ratio of prescription claims for antiplatelet and OAC after AF diagnosis according to year of AF diagnosis



OAC; oral anticoagulant therapy, AF; atrial fibrillation

Supplemental Figure 3. Forest plots of ischemic events, comparing number of events before and after AF diagnosis



AF; atrial fibrillation, OR; odds ratio

Title

Antiplatelet therapy in patients with abdominal aortic aneurysm without symptomatic atherosclerotic disease: A target trial emulation of national observational data

Chalotte W. Nicolajsen MD[a,b,c], Mette Søgaard PhD[a,b], Martin Jensen[a], Nikolaj Eldrup MD, PhD[d,e], Torben B. Larsen MD, PhD[a,b], Samuel Z. Goldhaber MD[f,g], Christian-Alexander Behrendt MD[h,i], Peter B. Nielsen PhD[a,b]

Affiliations

[a] Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark, [b] Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Faculty of Health, Aalborg University, Aalborg, Denmark , [c] Department of Vascular Surgery, Viborg Regional Hospital, Viborg, Denmark, [d] Department of Vascular Surgery, Rigshospitalet, Copenhagen, Denmark, [e] Institute of clinical medicine, Copenhagen University, Copenhagen, Denmark, [f] Thrombosis Research Group, Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, Massachusetts, [g] Harvard Medical School, Boston, Massachusetts, [h] Department of Vascular and Endovascular surgery, Asklepios Medical School, Asklepios Clinic Wandsbek,

Hamburg, Germany, [i] Brandenburg Medical School Theodor Fontane, Neuruppin, Germany

Short Title

Antiplatelet therapy in patients with AAA without symptomatic atherosclerosis

Corresponding author

Chalotte W Nicolajsen MD, Department of Vascular Surgery, Viborg Regional Hospital, Heibergs Alle 5A, 8800 Viborg, Denmark

c.nicolajsen@rn.dk / chalotte.winther@rm.dk/ +45 6130 2095

Word count: 3005 (full, excluding references), 349 (abstract)

Abstract

Objective Patients with abdominal aortic aneurysm suffer a high risk of ischemic events associated with concomitant atherosclerotic cardiovascular disease, and current clinical practice guidelines recommend antiplatelet therapies to mitigate this risk. However, in patients with aneurysms and no symptomatic atherosclerosis, the benefit of antiplatelet is sparsely investigated. Our aim was to assess the effect of antiplatelets on the risk of ischemic events and bleeding in individuals with abdominal aneurysms with no concomitant atherosclerotic vascular disease.

Design A target trial emulation of a pre-defined target trial utilizing longitudinal health registry data. Trials were emulated as sequential trials, contingent on patient eligibility at time of inclusion. The emulated trials were pooled by means of pooled logistic regression models, to estimate the intention-to-treat and on-treatment effects, expressed as hazard ratio and event-free survival.

Setting Population-based, using observational data from the Danish national health registries containing comprehensive, individual-level information on all Danish citizens.

Participants Antiplatelet-naïve patients diagnosed with abdominal aortic aneurysms with no history of atherosclerotic vascular disease from January 2010 through August 2021.

Exposure/Intervention Prescription claim of aspirin or clopidogrel

Main outcomes Risk of ischemic events (myocardial infarction and/or ischemic stroke) and risk of major bleeding

Results A total of 6,344 patients provided 131,047 trial participants; 3,363 of these were initiators of antiplatelet therapy, 127,684 were non-initiators. Among initiators and non-initiators 182 and 354 ischemic events occurred, respectively, corresponding to an intention-to-treat HR of 0.91 (CI 95% 0.73 to 1.17) and an estimated absolute event-free survival difference of -0.6%. After censoring non-adherent person-time, the on-treatment HR was 0.90 (CI 95% 0.68 to 1.20), with similar risk difference. For bleeding, the intention-to-treat HR was 1.26 (CI 95% 0.97 to 1.58) and the event-free survival difference was 1.0%. The on-treatment HR was 1.21 (CI 95% 0.82 to 1.72), and event-free survival difference 0.8%.

Conclusion In this target trial emulation on patients with abdominal aortic aneurysms and no symptomatic atherosclerosis, we found no evidence of effectiveness of antiplatelets to lower the risk of ischemic events and a trend

toward higher bleeding risk. The observed differences between the treatment groups were minimal, suggesting limited clinical relevance of treatment.

Background

Abdominal aortic aneurysm (AAA) has been associated with a two-fold increase in risk of cardiovascular ischemic events compared with individuals without AAA.[1] Co-existing cardiovascular disease is one of the key determinants of prognosis during surveillance and post-AAA repair.[2,3] Observational studies suggested higher survival among patients with AAA on antiplatelet therapy.[4,5] Accordingly, clinical guidelines recommend antiplatelet therapy for patients presenting with AAA, particularly in the presence of symptomatic atherosclerotic disease.[6,7] However, the proportion of AAA patients with a record of symptomatic atherosclerosis is declining[8], and the benefits and risk of antiplatelet prophylaxis in those without atherosclerotic disease are still not clear.

To date, there are no randomized clinical trials (RCTs) assessing efficacy and safety of antiplatelet therapy versus placebo in patients with AAA, and current recommendations are accordingly based on level B/C-evidence.[6] At the same time, pharmacological prophylaxis with antiplatelets in patients with AAA who do not exhibit symptoms of atherosclerosis is controversial, considering the associated risk of bleeding and a potential limited clinical benefit of antiplatelets in asymptomatic atherosclerotic individuals.[7,9–11]

To bridge this knowledge gap, we designed a target trial[12] with the purpose of estimating the effect of antiplatelet therapy vs. no antiplatelets on the risk of ischemic events (myocardial infarction (MI) and ischemic stroke) and bleeding in a cohort of patients with AAA without concomitant symptoms of atherosclerotic vascular disease. We emulated the trial using observational healthcare data with complete national coverage.[13,14]

Methods

We designed and specified a target trial, and emulated the trial, utilizing observational data from Danish national health registries containing comprehensive longitudinal, individual-level information on all Danish citizens, which are linked using the unique identity-number assigned to all residents at birth or immigration. The results were reported in accordance with RECORD standards.[15,16]

Target trial and target trial emulation

We developed a protocol for a hypothetical target trial, that could have answered the causal question of interest, to investigate the average treatment effect of antiplatelet therapy versus no treatment on the incidence of ischemic events and bleeding in antiplatelet-naïve patients with AAA disease without other diagnosed atherosclerotic cardiovascular diseases. Specifications of trial components are listed in Supplement A and Table S1 in the Supplementary Appendix. Briefly, trial eligibility criteria included a diagnosis of AAA, age between 50 and 90 years, no previous antiplatelet treatment, no other indication for antiplatelet therapy (any history of atherosclerosis; peripheral arterial occlusive disease, ischemic heart disease, ischemic stroke, or transient ischemic attack), and no contraindications

for antiplatelet therapy. Eligible patients were followed for up to a maximum of five years.

We emulated the target trial using data from the Danish national health registries and mirrored the target trial components, with modifications required to accommodate the use of observational data. We retrieved information on diagnoses, hospitalizations, and outpatient visits from the Danish National Patient Registry (DNPR). The DNPR hold information on hospitalizations since 1977, and outpatient visits at all hospitals in Denmark since 1995. Data include Civil Personal Registry numbers, dates of admission and discharge, primary and up to 20 secondary diagnoses coded by the International Classification of Diseases (ICD-10).[17]Diagnoses used for definition of eligibility has been previously validated with high positive predictive values (above 90%).[18] Data on prescriptions claims were retrieved form the Danish National Prescription Registry, which holds detailed information on the purchase date, Anatomical Therapeutic Chemical (ATC) classification code, package size, and dose for every prescription claim since 1994.[19] Data on patient characteristics such as age, sex, and vital status were extracted from the Civil Registration System.[20]

Study population and exposure

We applied trial eligibility criteria to individuals registered in the DNPR between 1 January 2010 and 21 August 2021. Individuals could potentially meet the eligibility criteria multiple times during the study period. To enable inclusion of patients eligible more than once, and to include non-initiators who later initiated antiplatelet therapy, we emulated the target trial as a sequence of trials, with a new trial starting at each month, similar to previous study designs in other disease areas.[21] This allowed individuals to contribute information to multiple trials, depending on eligibility status.[12,13] Based on the number of months from January 2010 through August 2021 (end of data), 140 trials was constructed. Screening for inclusion was assessed in the first (baseline) month of each of the sequential trials, and eligible patients were assigned to a treatment group and followed up in the registries. Individuals with an outcome in first trial month were excluded. An illustration of target trial emulation and data flow are provided in Figure 1, while details on flowchart of inclusions are provided in Figure S1 and specifications on ICD-10 and ATC codes in Table S2 in the Supplementary Appendix.

Among antiplatelet-naïve AAA patients, we compared two treatment strategies of i) initiation of antiplatelet therapy (aspirin or clopidogrel), or ii) no initiation of antiplatelet therapy. Individuals were classified as 'initiators' or 'non-initiators' according to the treatment strategy, compatible with the data at baseline (i.e.,

prescription claim of antiplatelet therapy within baseline trial month). To emulate randomization, exchangeability between groups was assumed conditional on the propensity for receiving the observed treatment.

Outcome measures

The primary outcome was risk of ischemic events, defined as a composite outcome of a diagnosis of MI and/or ischemic stroke. Secondary outcomes were risk of MI and ischemic stroke separately, and a safety outcome of major bleeding (defined as bleeding events leading to hospital contact); see Supplemental Table S2. Follow-up started at the end of the baseline month of every sequential new trial, and ended at the first outcome event, death, loss to follow-up, five years after baseline, or administrative end of data.

Statistical analysis

Baseline demographics and comorbidities are presented descriptively for the trial populations. Summarized categorical data are reported as percentages and continuous data as medians with interquartile ranges (IQR). Outcomes under exposure were contrasted by pooling the emulated trials and by fitting a pooled logistic regression model of each effect estimate (Intention-to-treat; ITT and On-

treatment; OT). Analyses were performed using SAS (version 9.4), R (version 4.2.2), and STATA/MP (version 17).

Estimation of the observational analogue to Intention to treat (ITT)

In the target trial emulation, the indicator for treatment was defined as initiation of antiplatelet therapy within the baseline month. Confounding control was handled by means of propensity scores that were derived to calculate stabilized inverse probability of treatment weights (IPTW).[22] Calculation of the propensity score included age (continuous and squared terms), sex, relevant comorbidity (hypertension, diabetes, atrial fibrillation, renal insufficiency, and heart failure), medical treatment with other cardioprotective agents (statins and antihypertensive therapy), and a proxy for smoking status (diagnosis of smoking-related COPD, tobacco abuse/registered smoking status, smoking cessation advice, or prescription claim of medicine for smoking cessation). Supplemental Figure 2 provides a directed acyclic graph depicting the underlying causal assumptions of the exposure-outcome association. Because of the incremental covariate time related to the multiple trial eligibilities for the same individual, we post hoc decided to include time since first AAA diagnosis (restricted cubic spline) in the final model.

We estimated the average treatment effect as the difference in 5-year risk of outcomes, expressed as hazard ratios (HR) and depicted by event-free survival-curves.[23] We used nonparametric bootstrapping with 500 samples to calculate 95% confidence intervals (CI) for the main analyses.

Estimation of the observational analogue to on treatment (OT)

The OT analyses investigated the observed effect under continuous adherence to the treatment assigned in the baseline trial month. Briefly, individuals in the treatment-arm were censored if they discontinued antiplatelet therapy, whereas individuals in the non-treatment arm were censored, if they initiated antiplatelet therapy. Discontinuation was defined as the end of the data for last available tablet, based on a daily dose (DD) calculation with a maximum gap between DDs of 60 days (grace period). The OT analytic approach was performed with adjustments for the same baseline covariates as applied in the ITT analyses, and post-baseline (time-varying) covariates including hypertension, diabetes, atrial fibrillation, renal insufficiency, heart failure, medical treatment with other cardioprotective agents (statins and antihypertensive therapy), and smoking.

Subgroup and sensitivity analyses

A priori, we selected clinically relevant subgroups, for whom treatment effect could potentially be different, and performed analyses stratified by i) with or without concomitant statin therapy; ii) restricting the analyses to include only aspirin as exposure (opposed to the main analysis including aspirin or clopidogrel); iii) patients aged ≥80 years; and iv) excluding patients with a cancer diagnosis within the last five years. We also conducted sensitivity analyses by prolonging the discontinuation gap between DDs of prescriptions claims to 90 days (only for the OT analyses). Last, we conducted analyses in a cohort restricted to patients with a maximum of six months between AAA diagnosis and study inclusion. For all subgroup and sensitivity outcomes, we used robust variance estimates when calculating the 95% CI's, which may yield more conservative estimates.

Ethics

This study was conducted in accordance with the General Data Protection Regulation and the North Denmark Region's record of processing activities (project no. 2017-40). Data were provided by the Danish Health Data Authority.

Results

A total of 25,326 individuals were registered with a diagnosis of AAA between January 2010 and August 2021. Of these, 6,344 individuals (25.1%) met eligibility

criteria at least once during the study period. As individuals could be eligible for multiple sequential trials, the patients contributed a total of 131,047 individual trial cases, of which 3,363 initiated antiplatelet therapy, and 127,684 did not receive antiplatelets. Figure 1 demonstrates the data flow according to study design, while the flowchart in Figure S2 summarizes inclusions and exclusions of trial population.

Among initiators of antiplatelets, 3,166 participants (94.1%) claimed a prescription of aspirin, while 197 (5.9%) initiated clopidogrel. In the IPTW weighted population, the median age was 72 years (IQR 64.0 to 78.0), 34% were females, 19% were registered smokers, 7.5% had a history of diabetes, 34% received concomitant statin, and 50% antihypertensive therapy (Table 1). After the IPTW was applied, the standardized mean differences in baseline characteristics were below 0.1 (Figure S3). Table S3 summarizes baseline characteristics for the unweighted cohort.

Effect estimates for ischemia

During a total of 5,011,227 person-months of follow-up, 182 ischemic events were observed among antiplatelet initiators, while 354 ischemic events were observed among those who did not initiate antiplatelet therapy. Median follow-up duration

was 24 months (IQR 11 to 40 months) for initiators and 23 months (IQR 11 to 38) for non-initiators. Table 2 displays the risks of ischemic events between antiplatelet therapy initiators and non-initiators at five years follow-up. In the ITT analyses, the HR for ischemic events was 0.91 (CI 95% 0.73 to 1.17), with an event-free survival-difference of -0.6% (CI 95% -1.7 to 0.5) between the two groups (Figure 2). For the separate outcomes of MI and ischemic stroke, the ITT HR was 0.81 (CI 95% 0.57 to 1.23) and 0.95 (CI 95% 0.73 to 1.17) while the event-free survival difference was -0.7% (CI 95% -1.6 to 0.6) and -0.3% (CI 95% -1.2 to 0.7), respectively (Table 2). Following censoring for non-adherent trial participation, 114 ischemic events was observed among antiplatelet initiators and 218 ischemic events among non-initiators, during a median follow-up of 18 months (IQR 8 to 34 months) for initiators and 20 months (IQR 9 to 35 months) for non-initiators. The OT HR was 0.90 (CI 95% 0.68 to 1.20) (Table 2), and the five-year survival difference was -0.6% (CI 95% -2.2 to 1.1) (Figure 1).

Safety estimates for bleeding events

For the safety outcome of bleeding, 129 events occurred among initiators and 238 events among non-initiators during follow-up. The ITT HR for major bleeding event was 1.26 (CI 95% 0.97 to 1.58) (Table 2). The event free survival-difference

between initiators and non-initiators was 1.0% (CI 95% -0.1% to 2.3%) at five years follow-up (Figure 3). The OT analytic approach, with censoring of non-adherent person-time, yielded similar effect estimates, OT HR of 1.21 (CI 95% 0.82 to 1.72), with an event-free survival difference of 0.8% (CI 95% -0.8 to 2.5) (Table 2)).

Subgroup and sensitivity analyses

Subgroup analyses showed results generally comparable to those found in the main analyses with minimal risk differences (Supplemental Table S4). For patients using concomitant statin therapy, we observed no difference with a HR of 1.02 (CI 95% 0.77 to 1.35) for ischemic events and a HR of 1.11 (CI 95% 0.78 to 1.58) for bleeding events, whereas for those not using statin therapy, the difference was more pronounced, yet risk differences were less than 1%. For patients aged ≥80 years, only 568 initiators and 31,655 non-initiators were available for analyses and showed a higher risk of ischemic events (ITT HR 1.11 (CI 95% 0.75 to 1.63)) and a higher risk of bleeding (ITT HR 1.12 (CI 95% 0.69 to 1.82); however, the difference in event-free survival was marginal.

Sensitivity analyses revealed similar results with marginal differences between groups (Supplemental Table S5). Restricted to patients with a maximum of six

month between AAA diagnosis and inclusion the ITT OR was 0.84 (CI 95% 0.69 to 1.01) for ischemia, and ITT HR 1.10 (CI 95% 0.88 to 1.38) for major bleeding.

Discussion

In this target trial emulation including patients with AAA without a history of symptomatic atherosclerosis, we observed a trend toward lower risk of ischemic events among those on antiplatelets but higher risk of major bleeding. However, the risk difference was minimal; -0.6% for ischemic events and 1.0% for major bleeding over five years follow-up, indicating no clinically relevant difference.

This is the largest-scale study to formally investigate the effectiveness of antiplatelet therapy versus no treatment on the risk of ischemic events and bleeding in an AAA population with no history of atherosclerosis. Our findings are consistent with the outcomes from the most recent RCTs investigating the efficacy of aspirin in the general population without atherosclerotic manifestations. The ARRIVE trial, a multinational RCT including 12,546 patients with an estimated moderate to high 10-year risk (10-20%) of future ischemic events, found a hazard ratio of 0.96 (CI 95% 0.81–1.13) for ischemic events and 2.11 (CI 95% 1.36–3.28) for major bleeding.[10] The ASCEND trial, including 15,480 participants with

diabetes and no cardiovascular atherosclerosis, found a HR of 0.98 (CI 95% 0.80 to 1.19) for MI, 0.88 (CI 95% 0.73 to 1.06) for ischemic stroke, and 1.29 (CI 95% 1.09–1.52) for major bleeding.[11]

Based on results from the above-mentioned trials, suggesting no or moderate ischemic risk reduction at the expense of an increased risk of bleeding, recommendations have changed in patients without manifest atherosclerosis.[10,11,24,25] Antiplatelets are no longer recommended routinely but are considered beneficial only in specific patients at very high cardiovascular risk and with minimal risk of bleeding.[26–28] These revisions provoke critical inquiries: In light of the current AAA guidelines,[6,7] should the concept of very high cardiovascular ischemic risk for all patients with AAA be taken into account for the possible advantage of antiplatelet therapy? Alternatively, is it more prudent to heed the contemporary guidelines on primary cardiovascular disease prevention for patients without atherosclerotic manifestations and restrict the recommendation of antiplatelet therapy to AAA patients with symptomatic atherosclerotic cardiovascular disease?[26,28] The current study adds to the understanding of benefit and risk associated with use of antiplatelet therapy and allows us to estimate differences in risk of outcomes under treatment vs no treatment.

The current recommendations on antiplatelet therapy in AAA management are based on evidence extrapolated from trials investigating secondary prevention in atherosclerotic cardiovascular disease and from retrospective studies., They suggest a lower all-cause mortality among patients with AAA on antiplatelet therapy.[7,29] In 2022, a meta-analysis found no survival difference associated with antiplatelet therapy in patients with small AAA's (defined by an aneurysm-diameter between 3 and 5.5 cm); HR 0.91 (CI 95% 0.75-1.11), while antiplatelet therapy was associated with lower all-cause mortality in a patients undergoing AAA repair (HR 0.84, CI 95% 0.76-0.92).[30] Given the limited evidence for a beneficial effect of antiplatelets, including our findings, a dedicated trial investigating the effect of antiplatelet therapy in patients with AAA with and without symptomatic atherosclerotic is warranted.

Strength and weaknesses

The main strengths of this study were the large sample size, the broad variety of available variables, the long follow-up period, and the high validity of inclusion and outcome diagnoses retrieved from the DNPR.[18,31] The completeness of data available from the Danish health registries allowed us to quantify the association between antiplatelet therapy and clinical outcomes, with adjustments for a wide range of confounding factors. Further, it allowed for analyses of rare, and

potentially late outcomes, such as major bleeding, and effect-measures based on adherence to treatment. Our study design of emulating a hypothetical trial is a useful framework for comparative effectiveness research using observational data to mitigate confounding, immortal time bias, and selection bias between exposure groups.[32]

A key challenge in analyses using data from routine clinical practice is that treatment is not randomly assigned, possibly resulting in biased effect estimates from unmeasured confounding factors. In clinical practice, physicians may tend to initiate treatment in patients with expected high ischemic risk, but at the same time with a low risk of bleeding. Therefore, particularly the OT estimates may be subject to selection bias, while a study without selection bias might find higher risk of bleeding. Indeed, successful emulation of randomization depends on adjustments for baseline confounders and the untestable assumption of no residual confounding. Our estimates are limited to covariates available from the Danish health registries. Differences in unmeasured characteristics, potentially confounding our results, cannot be excluded.

Conclusion

In patients with AAA without concomitant symptomatic atherosclerotic vascular disease, we found an associated lower risk of MI and ischemic stroke but also a trend toward higher risk of major bleeding under treatment with antiplatelet therapy. Notably, the absolute differences in risk between initiators and non-initiators of antiplatelet therapy were negligible, indicating no clinically meaningful difference. Overall, these findings do not support recommendations of prophylactic antiplatelet therapy in this target population. Along with the absence of high-level evidence on antithrombotic strategies, this study highlights the necessity for a RCT. In the meantime, careful consideration in prescribing prophylactic antiplatelets should be given to all patients with AAA.

Transparency Declaration

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Disclosures

M. Søgaard has received consulting fees from Bayer. N. Eldrup has served as an investigator for Bayer, and has received fees for speaking engagement from Bayer, Amgen, and AstraZeneca. T.B. Larsen has been a speaker for Bayer, Bristol Meyers Squibb, Pfizer, Janssen Pharmaceuticals, and Roche Diagnostics, and on an advisory board for Bayer, Bristol Meyers Squibb, Pfizer and Roche Diagnostics. P. B. Nielsen has received fees for speaking engagements from Daiichi-Sankyo and BMS/Pfizer; fees for consulting from Bayer and Daiichi-Sankyo; and grant support

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Figure Legends

Figure 1. Illustration depicting the study design and data processing in relation to target trial specifications and trial emulation.

Figure 2. Graph of ischemia-free survival estimates for Intention-to-treat (ITT) and on-treatment (OT) analyses

HR – Hazard ratio, CI- Confidence Interval (nonparametric bootstrapping with 500 samples)

Figure 3. Graph of Bleeding-free survival estimates for Intention-to-treat (ITT) and On treatment (OT) analyses

HR – hazard ratio, Risk.diff. – event-free survival difference

Table 1. Baseline characteristics of the trial population after IPTW

	Non-initiators % (N)	Initiators % (N)	Std Diff
N	127,684	3,363	
Sex, female	34.6 (44215)	34.7 (1188)	0.003
Age, median (IQR) years	72.0 (64.0-78.0)	72.0 (66.0-77.0)	0.072
Smoking*	18.6 (23701)	19.0 (648)	0.010
Comorbidity			
Hypertension	24.1 (30739)	24.9(851)	0.019
Diabetes mellitus	7.3 (9385)	7.4 (252)	<0.001
COPD	15.5 (19760)	15.0 (513)	0.013
Chronic renal disease**	0.7 (867)	0.7 (24)	0.002
Heart failure	1.5 (1882)	1.5 (51)	0.002
Atrial fibrillation	1.8 (2250)	1.9 (65)	0.011
Venous thromboembolism	3.4 (4287)	2.7 (94)	0.036
Major Bleeding***	5.4 (6896)	4.2 (144)	0.056
Obesity****	3.7 (4741)	3.6 (122)	0.007
Medical treatment			
Aspirin (in baseline month)		3166	-
Clopidogrel (in baseline month)		197	-
Statins*****	34.2 (43720)	34.6 (1181)	0.007
Antihypertensives*****	49.7 (63428)	51.1 (1748)	0.030
Antidiabetics*****	6.4 (8209)	6.2 (213)	0.008

*Registered smokers, previous/current**Disease registered > 5 years prior to inclusion, ***Gastrointestinal, Intracranial and other major bleeding registered > 6 months prior to inclusion, ****Registered Body Mass Index >25, ***** Prescription claim within 1 year prior to inclusion. Abbreviations: IPTW; Inverse probability of treatment weights, IQR; interquartile range, Std Diff; standardized difference,

Table 2. Intention-to-treat and on-treatment hazard ratios of ischemic events and major bleeding outcomes.

Target trial emulation; No treatment vs. antiplatelet therapy												
	Intention-to-treat effect						On-treatment effect					
	Initiator N 3,363		Non-initiator N 127,684		Effect estimate		Initiator N 3,363		Non-initiator N 127,684		Effect estimate	
ıtcome	No of events	Event-free survival	No of events	Event-free survival	HR	CI 95%	No of events	Event-free survival	No of events	Event-free survival	HR	CI 95%
:hemic ents	182	0.937	354	0.931	0.91	0.73 to 1.17	114	0.943	218	0.937	0.90	0.68 to 1.20
Myocardia nfarction	66	0.977	136	0.972	0.81	0.57 to 1.23	40	0.979	89	0.972	0.76	0.50 to 1.24
schemic troke	118	0.959	228	0.957	0.95	0.73 to 1.17	74	0.965	131	0.964	0.96	0.73 to 1.20
ajor eeding	129	0.947	238	0.958	1.26	0.97 to 1.58	86	0.951	130	0.961	1.21	0.82 to 1.72

HR – Hazard ratio, CI- Confidence Interval (nonparametric bootstrapping with 500 samples)

Figure 1. Illustration depicting the study design and data processing in relation to target trial specifications and trial emulation.

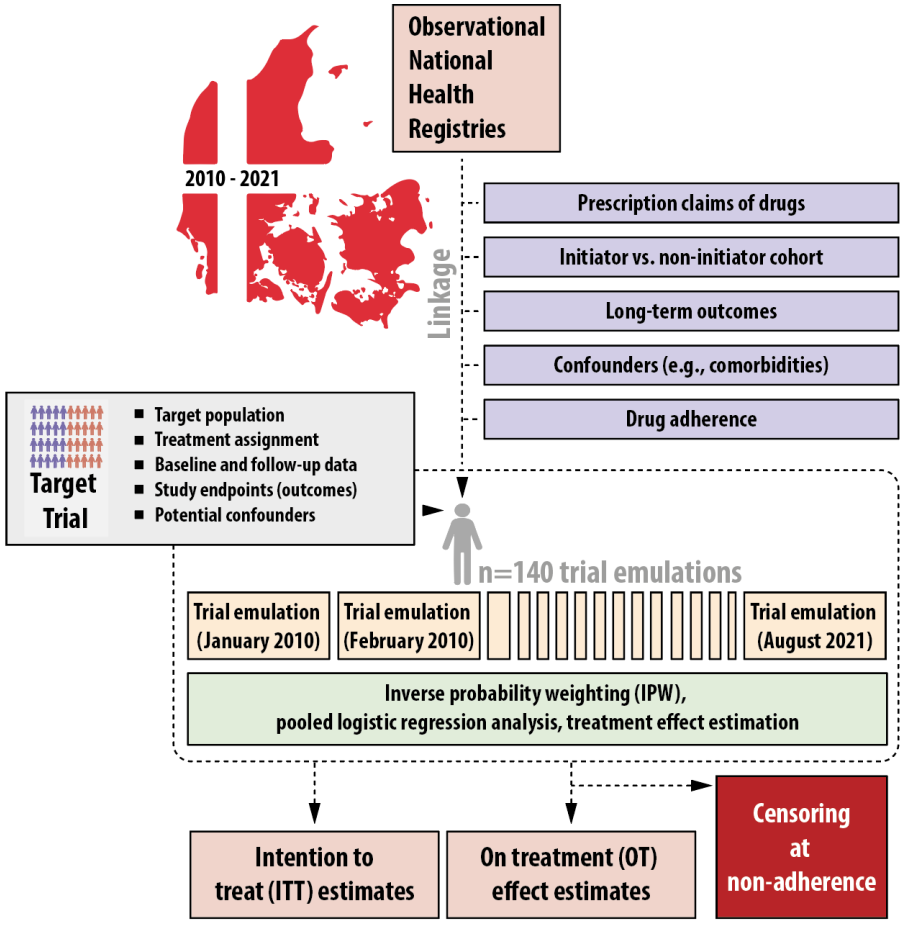
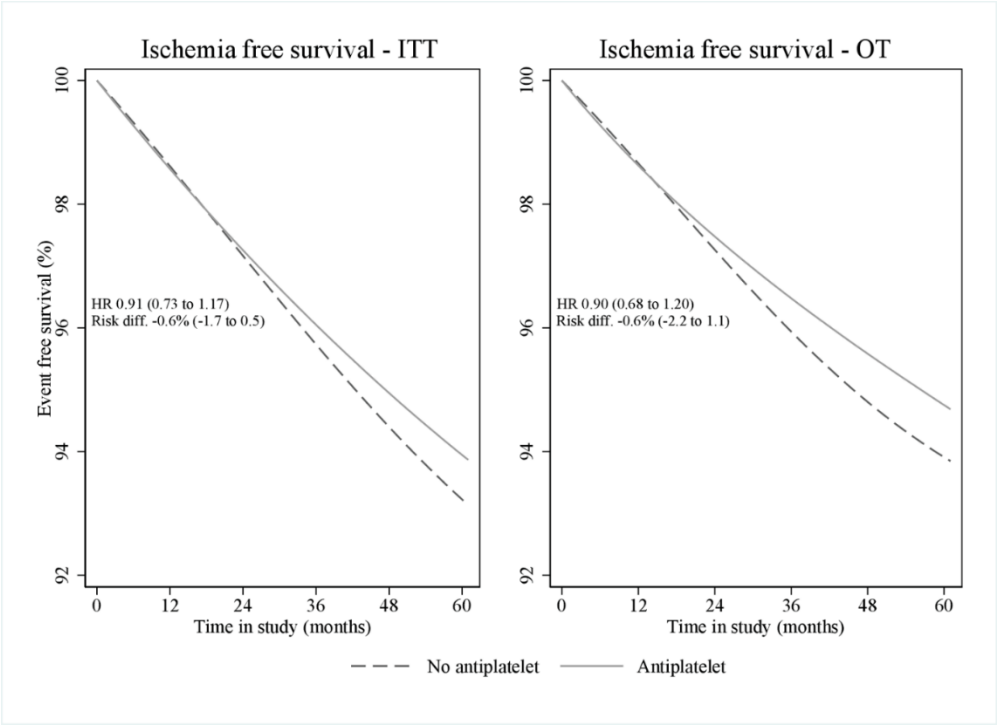
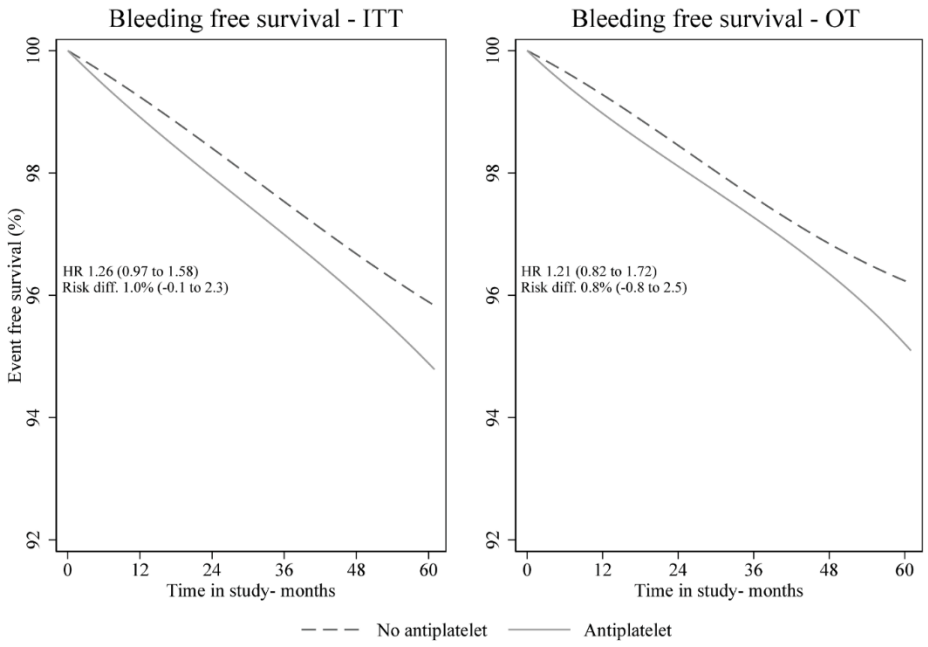


Figure 2. Graph of ischemia-free survival estimates for Intention-to-treat (ITT) and on-treatment (OT) analyses



HR – Hazard ratio, CI- Confidence Interval (nonparametric bootstrapping with 500 samples)

Figure 3. Graph of Bleeding-free survival estimates for Intention-to-treat (ITT) and On treatment (OT) analyses



HR – hazard ratio, Risk.diff. – event-free survival difference

Supplementary appendix for

Antiplatelet therapy in patients with abdominal aortic aneurysm without symptomatic atherosclerotic vascular disease: A target trial emulation using national observational data

List of supplementals

A. Specifications of target trial protocol

A target trial was specified with the following components (resumé in Table S1)

Eligibility criteria. Enrollment of patients with a diagnosis of AAA, aged ≥50 and ≤ 90 years between January 2010 and August 2021, who had no manifestations of symptomatic peripheral arterial disease (PAD); intermittent claudication, rest pain, ischemic ulcers and gangrene, ischemic heart disease (IHD); angina, previous myocardial infarction (MI), manifestations of chronic myocardial ischemia, or ischemic stroke. Participants must not have any contraindications for antiplatelet therapy (major liver- or kidney impairment within the last 5 years of inclusion, recent major bleeding, or prevalent anticoagulant (OAC) treatment (within 6 months of inclusion), and no history of cancer (except non-melanoma skin-cancer)

within 5 years from inclusion. Participants must not have used antiplatelet therapy (including ticagrelor and prasugrel) within the last 12 months prior to inclusion.

Baseline was defined as the first month of randomization when all eligibility criteria were met.

Treatment strategies. 1. Usual medical care or 2. Initiation of antiplatelet therapy (aspirin or clopidogrel, type of antiplatelet at the discretion of the physician). When clinically warranted during the follow-up, patients and their physicians will decide whether to start, stop or switch therapy.

Treatment assignment. Each eligible participant will be randomly assigned to a strategy with initiation of treatment within 1 month from randomization. Patients with events of interest within this period will be excluded. Patients will be aware of the strategy to which they are assigned.

Outcomes. Outcomes of interest is a composite of MI and ischemic stroke. Secondary outcome is MI and ischemic stroke as separate outcomes as well as major bleeding, defined as any bleeding requiring hospital contact.

Follow-up. All participants will be followed from baseline and until first ischemic stroke, MI, death, loss to follow-up, or administrative end of follow-up (five years or august 2021), whichever happens first.

Causal contrasts. The intention-to-treat (ITT) effect of being assigned to antiplatelet therapy versus no initiation of antiplatelet therapy at baseline and the On-treatment (OT) effect of antiplatelet initiation and continuation over follow-up.

Statistical analysis. In both ITT and PP analyses, we will use pooled logistic regression analysis to estimate the effect of antiplatelet therapy via comparison of 5-year risk of outcome expressed as hazard ratios and standardized survival curves.[1] For ITT analyses we fitted a pooled logistic regression with an indicator for of assigned strategy and a flexible function of months since randomization. For OT analyses we fitted a model after censoring participants if and when they deviate from assigned treatment. Time-varying stabilized inverse-probability

weights will be used to adjust for time-varying confounding associated with adherence and outcome of interest.

To identify potential subgroups for whom treatment may potentially be more beneficial, stratified analyses will be conducted based on baseline information on age (>= 80 years), with and without concomitant statin therapy and according to type of antiplatelet (aspirin/ clopidogrel).

B. Table S1. Protocol Components of target trial and trial emulation

Component	Target trial specification	Target trial emulation
Eligibility criteria	Diagnosis of AAA, age ≥ 50 years and ≤ 90 years, no previous symptomatic PAD, IHD, CVD, no use of antiplatelet therapy*, no contraindications for antiplatelet therapy**, no prevalent cancer*** Baseline defined as day of randomization.	Same as target trial Baseline defined as the first of every trial month where all eligibility criteria were met, yielding potentially 140 sequential trial months for each participant.
Treatment strategies	i) Initiation of antiplatelet therapy (aspirin, clopidogrel) ii) No initiation of antiplatelet Within 30 days from randomization	Same as target trial. Study participants were classified according to treatment strategy at baseline, assuming exchangeability. Initiation of treatment defined as +/- prescription claim of antiplatelet (aspirin or clopidogrel) within 30 days from baseline (first trial month)
Treatment assignment	Non-blinded random assignment	Assignment according to treatment vs. no treatment in first trial month Randomization was emulated by adjusting for baseline confounders
Outcomes	1. Composite of MI and ischemic stroke 2. Major bleeding	Same as target trial
Follow-up	Starts at randomization, ends at first outcome diagnosis, death, loss to follow-up or	Same as target trial

	administrative censoring (emigration, end of study) Patients were followed for up to five years	
Causal contrasts	Intention-to-treat (ITT) effect On-treatment (OT) effect	Observational analogue
Statistical analyses	ITT + OT analyses	Pooled logistic regression analyses ITT: Adjustment for baseline prognostic factors associated with the probability of initiating antiplatelet therapy to emulate randomization OT: Censuring at deviation from assigned treatment Adjustments for baseline and time-varying prognostic factors associated with treatment adherence

AAA; abdominal aortic aneurysmal disease, PAD; peripheral arterial disease (intermittent claudication, ischemic rest pain, ischemic ulceration, or gangrene), IHD; ischemic heart disease (angina, myocardial infarction), CVD; cerebrovascular disease (ischemic stroke or transient ischemic attack), OAC; oral anticoagulation therapy, MI; myocardial infarction, DD; daily dose. *Use of aspirin, clopidogrel, ticagrelor, or prasugrel within 12 months prior to randomization, ** Contraindications (major liver- and/or kidney deficiency or haemodialysis < five years before randomization, major bleeding < six months before and/or OAC therapy < 12 months prior to randomization), *** All cancer (except non-melanoma skin cancer) diagnosed within five years before randomization,

C. Table S2. Definition of variables

Diagnosis / treatment	**ICD**	**ATC**
Inclusion		
Abdominal aortic aneurysm	I713, I714	
Exclusion		
Ischemic heart disease	I20, I21	
Angina	I20	
Myocardial infarction	I21	
Ischemic cerebrovascular disease		
Ischemic stroke	I63	
Transient ischemic attack	G45	
Peripheral atherosclerotic arterial disease	I702, I739A, I739C	
Claudication	I739A	
Restpain, gangrene	I739C, I702	
Major liver impairment	B150, B160, B162, B190, K704, K72, K766, I85	B150 B160 B162 B190 K704 K72 K766 I85
Major renal impairment (stage 5)	N185	
Major acute renal impairment	N17	
Major bleeding		

Intracranial	I60, I61, I62	
Gastrointestinal	I850I 864A K226 K228F K250 K252 K254 K256 K260 K262 K264 K266 K270 K272 K274 K276 K280 K282 K284 K286 K290 K298A K625 K638B K638C K661 K838F K868G K920 K921 K922	
Other (minus nosebleed and traumatic bleeding)	E078B E274B G951A I230 I312 I319A J942 M250	
Outcome		
Ischemic stroke	I63	
Myocardial infarction	I21	
Other comorbidity		
Diabetes	E10-14, H360, O240-43	A10A, A10B ≥ 1 category
Hypertension	I10-13, I15	
Chronic obstructive pulmonary disease	J40-J47, J60-J67, J684 J701 J703 J841 J920 J921 J982 J983	
Chronic obstructive pulmonary disease, smoking-related	J42, J44, J684, J841	

Tobacco abuse	F17, T652, Z716, Z720A, Z720E	
Treatment (drugs)		
Antiplatelet		B01AC04, B01AC06
Aspirin		B01AC06
Clopidogrel		B01AC04
Oral anticoagulant		
Coumarin		B01AA01-04
Direct oral anticoagulant		B01AE07, B01AF01, B01AF02, B01AX05
Other		
Statin		C10
Antihypertensive		C02, C03D, C07, C08, C09
Smoking cessation		N06AX12, N07BA01, N07BA03,
Procedures		
Hemodialysis		BJFD2
Smoking cessation interviews		BQFT01, BQFS01 ZZP01A1A, ZZP0020

D. Table S3. Baseline characteristics of the study population before IPTW

	Non-initiators % (N)	Initiators % (N)	Std Diff
N	127,684	3,363	-
Sex, female	34.9 (44599)	23.2 (780)	0.26
Age, Median (IQR)	72.0 (64.0-78.0)	72.0 (66.0-77.0)	0.05
Registered smokers, previous/current	18.6 (23797)	15.7 (528)	0.08
Comorbidity			
Hypertension	24.2 (30867)	20.2 (681)	0.10
Diabetes mellitus	7.4 (5720)	6.8 229)	0.02
COPD	15.5 (19837)	12.5 (420)	0.09
COPD, smoking-related	12.4 (15871)	10.8 (362)	0.05
Chronic renal disease*	0.7 (867)	0.7 (23)	< 0.01
Heart failure	1.5 (1880)	1.5 (52)	0.01
Atrial fibrillation	1.8 (2256)	1.6 (53)	0.02
Venous thromboembolism	3.4 (4288)	2.6 (88)	0.04
Major Bleeding**	5.4 (6904)	4.0 (134)	0.07
Obesity***	3.7 (4761)	2.9 (96)	0.05
Medical treatment			
Statins****	34.2 (43684)	34.2 (1150)	< 0.01
Antihypertensives****	49.7 (63405)	50.2 (1687)	0.01
Antidiabetics****	6.4 (8222)	5.9 (198)	0.02

*Disease registered > 5 years prior to inclusion, **Gastrointestinal, intracranial and other major bleeding registered > 6 months prior to inclusion, ***Registered BMI>25, **** Prescription claim within 1 year

prior to inclusion. Abbreviations: Std Diff; standardized difference, IPTW; Inverse probability of treatment weights

E. Table S4. Intention-to-treat estimates of outcomes (ischemic and bleeding events) in subgroups

Subgroup	Treatment group	N	Ischemic events			Bleeding		
			Event-free survival	ITT HR (CI 95%)	Event-free survival difference, %	Event-free survival	ITT HR (CI 95%)	Event-free survival difference, %
Aspirin-only	Initiators	3652	0.936	0.87 (0.73 to 1.03)	-1.0	0.944	1.20 (0.97 to 1.49)	0.9
	Non-initiators	151231	0.927			0.953		
Statin	Initiators	1137	0.935	1.02 (0.77 to 1.35)	0.1	0.943	1.11 (0.78 to 1.58)	0.5
	Non-initiators	51672	0.936			0.948		
No Statin	Initiators	2548	0.929	0.90 (0.73 to 1.11)	-0.8	0.947	1.21 (0.69 to 1.56)	0.8
	Non-initiators	99326	0.922			0.956		
Age ≥ 80 years	Initiators	568	0.887	1.11 (0.75 to 1.63)	1.0	0.913	1.12 (0.69 to 1.82)	0.8
	Non-initiators	31655	0.897			0.922		
No cancer last 5 years	Initiators	3363	0.937	0.91 (0.76 to 1.09)	-0.6	0.947	1.26 (0.99 to 1.60)	1.0
	Non-initiators	127684	0.931			0.958		

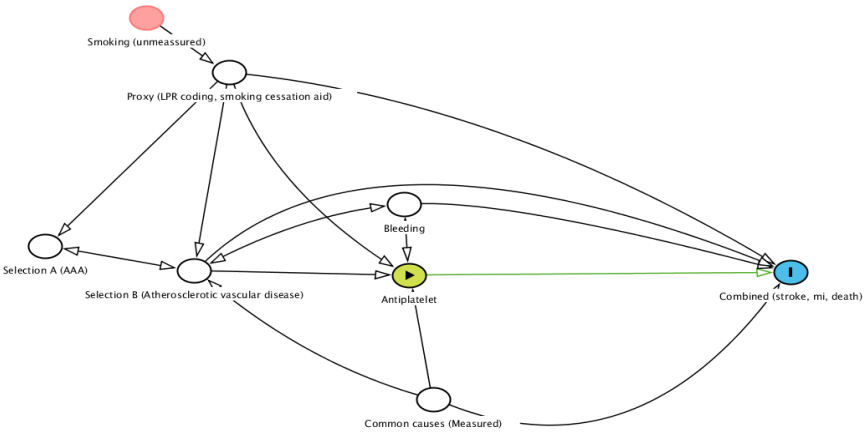
CI- Confidence Interval (robust variance estimates)

F. Table S4. Sensitivity analyses with estimates of outcomes (ischemic and bleeding events)

Analysis	Treatment group	N	Ischemic events			Bleeding		
			Event-free survival	Hazard ratio (CI 95%)	Survival difference (%)	Event-free survival	Hazard ratio (CI 95%)	Survival difference (%)
90 days gap in DDD*	Initiators	3363	0.937	0.94 (0.74-1.19)	-0.4	0.949	1.22 (0.92-1.62)	0.9
	Non-initiators	127684	0.934			0.958		
AAA <= 6 months from inclusion**	Initiators	2443	0.928	0.84 (0.69-1.01)	-1.4	0.947	1.10 (0.88-1.38)	0.5
	Non-initiators	20624	0.915			0.952		

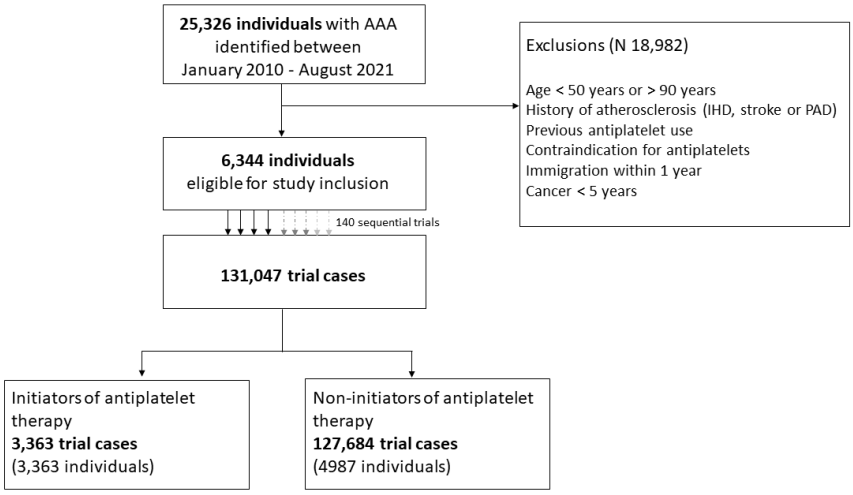
CI- Confidence Interval, DD-Daily Dose, *Intention-to-treat analyses, **On-Treatment analyses

G. Figure S1. Directed Acyclic Graph of potential confounding factors

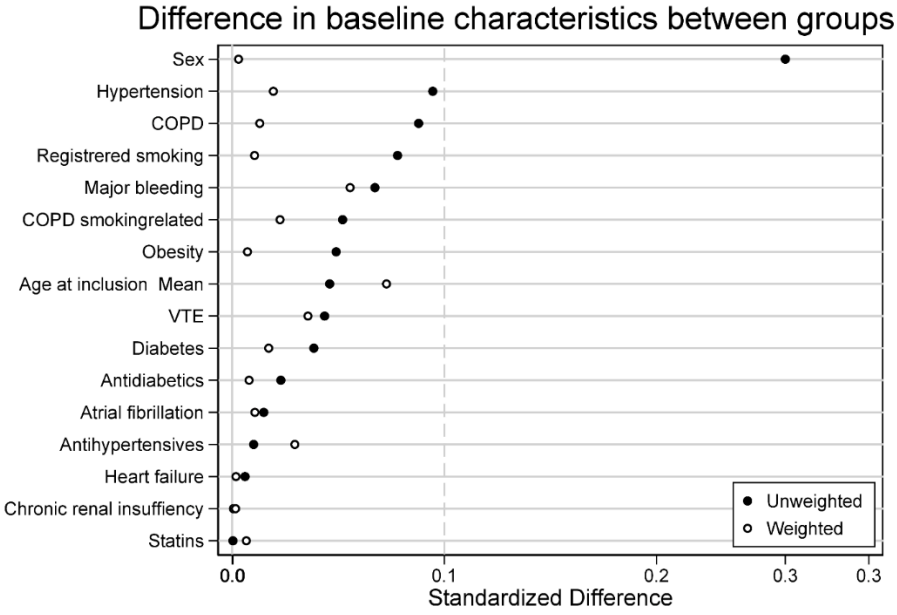


Common causes with association to exposure and outcome: sex, age, calendar year of inclusion, time since abdominal aortic aneurysm diagnosis, relevant comorbidity (diabetes, hypertension, atrial fibrillation, heart failure) use of other cardioprotective medication (statin, antihypertensives)

H. Figure S2. Flowchart of inclusion



I. Figure S3. Plot of maximum standardized difference of baseline covariates of study-population before and after applying IPTW.



Abbreviations: IPTW - inverse probability weights of propensity scores, COPD – chronic obstructive pulmonary disease, VTE – venous thromboembolism.

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