PUBLICATIONS OF
THE UNIVERSITY OF EASTERN FINLAND

Dissertations in Health Sciences

MAI VU

CARDIOVASCULAR DRUG UTILIZATION AND POSTOPERATIVE OUTCOMES OF CORONARY ARTERY REVASCULARIZATION PROCEDURES IN PEOPLE WITH ALZHEIMER'S DISEASE

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To be presented by permission of the Faculty of Health Sciences,
University of Eastern Finland, for public examination in
MD100 Auditorium, Kuopio
on April 12th, 2024, at 12 o'clock noon

Publications of the University of Eastern Finland
Dissertations in Health Sciences
No 812

School of Pharmacy
University of Eastern Finland, Kuopio
2024

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PunaMusta Oy
Joensuu, 2024
Distributor: University of Eastern Finland
Kuopio Campus Library

ISBN: 978-952-61-5148-9 (Print)
ISBN: 978-952-61-5149-6 (PDF)
ISSNL: 1798-5706
ISSN: 1798-5706
ISSN: 1798-5714 (PDF)

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Cardiovascular drug utilization and postoperative outcomes of coronary artery revascularization procedures in people with Alzheimer's disease
Kuopio: University of Eastern Finland
Publications of the University of Eastern Finland
Dissertations in Health Sciences 812. 2024, 157 p.
ISBN: 978-952-61-5148-9 (print)
ISSNL: 1798-5706
ISSN: 1798-5706
ISBN: 978-952-61-5149-6 (PDF)
ISSN: 1798-5706 (PDF)

ABSTRACT

Alzheimer's disease (AD), the most common cause of dementia, is a progressive neurodegenerative disorder with increasing global prevalence. Cardiovascular diseases are common among people with AD as cardiovascular diseases and AD share common risk factors. However, more information on the treatment of cardiovascular diseases in this population is needed.

This dissertation investigated the change in the prevalence of cardiovascular drug use before and after AD diagnosis and compared the prevalence to people without AD (Study I), assessed the time and factors associated with statin discontinuation in persons with and without AD (Study II) and studied the incidence of coronary artery revascularizations after AD diagnosis and post-procedural outcomes including mortality and readmissions between persons with and without AD (Study III).

All studies were conducted on the nationwide register-based Medication use in the Alzheimer's Disease (MEDALZ) cohort. This cohort includes 70,718 community dwellers clinically diagnosed with AD in Finland from 2005–2011. Each person in the AD cohort was matched with up to four persons without AD by age, sex, and region of residence. The information

on AD diagnosis was extracted from the Special Reimbursement Register and other information from the Prescription Register, the Care Register for Health Care, and the Causes of Death Register including data on drug use, comorbidities, and outcomes. Drug use periods were modelled by the PRE2DUP method in Study I and the AdhereR package in Study II. The association between AD, age, sex, and cardiovascular drug use was examined by generalized estimating equations logistic regression (Study I). Cox regression modes were applied to assess the factors associated with statin discontinuation (Study II) and outcomes including 30-day and 90-day hospital readmission and 1-year and 3-year mortality after revascularization (Study III).

At the time of AD diagnosis, the prevalence of cardiovascular drug use was comparable between the two cohorts (75.8% and 73.4% in people with and without AD, respectively). However, the prevalence of cardiovascular drug use started to decrease among people with AD, while it plateaued among people without AD.

Statin discontinuation rates were 4.35 and 3.28 per 10,000 person-years among people with and without AD, respectively. Among statin discontinuers, the median time from AD diagnosis to discontinuation was 1.46 years for people with AD and 1.36 years for those without AD. The likelihood of statin discontinuation among people with AD was higher than those without AD (adjusted hazard ratio (aHR) 1.20, 95% CI 1.18–1.24). Higher age and female gender were associated with an increased risk of discontinuation, whereas using other cardiovascular drugs and long duration of statin use before cohort entry were associated with lower risk in both cohorts. Persons with AD were less likely to be revascularized than those without AD, and emergency procedures were more common among them than among persons without AD. There were no differences in the 30-day readmission risk or one-year mortality, but persons with AD had a lower risk of readmission within 90 days (aHR 0.85, 0.74–0.98). The 3-year mortality risk was higher in people with AD, but this observation was due to higher mortality associated with emergency procedures (aHR 1.71, 1.27–2.31), while no difference was observed for elective procedures (aHR 0.96, 0.63–1.46).

The decreased prevalence of cardiovascular drug use could be due to changes related to AD progression, such as weight loss, frailty, declining blood pressure, and serum lipid level. Consequently, it is essential to routinely evaluate medication use, including the possibility of deprescribing, in people with dementia. While the relative risk of statin discontinuation was slightly elevated in those with AD, the absolute difference was small. Thus, cognitive disorder seemed to have only a modest effect on statin discontinuation. The increased mortality rate after emergency but not after elective procedures could be due to the high threshold for elective procedures in persons with AD. It would be important to confirm whether this is the case and evaluate if this results in an increased number of emergency procedures, which have worse prognoses.

Keywords: *Alzheimer's Disease, Cardiovascular Drug, Revascularization, Coronary Artery Disease, Statin Discontinuation, Prevalence, Mortality, Readmission, Cohort Study, Registries, Pharmacoepidemiology*

Vu, Mai
Alzheimerin tautia sairastavien sydän- ja verisuonisairauksien lääkkeiden käyttö sekä sepelvaltimotoimenpiteiden jälkeinen sairaalahoito ja kuolleisuus
Kuopio: Itä-Suomen yliopisto
Publications of the University of Eastern Finland
Dissertations in Health Sciences 812. 2024, 157 s.
ISBN: 978-952-61-5148-9 (nid.)
ISSNL: 1798-5706
ISSN: 1798-5706
ISBN: 978-952-61-5149-6 (PDF)
ISSN: 1798-5706 (PDF)

TIIVISTELMÄ

Alzheimerin tauti on etenevä muistisairaus, joka on yleistynyt maailmanlaajuisesti. Sydän- ja verisuonisairaudet ovat yleisiä Alzheimerin tautia sairastavilla, sillä sairauksilla on paljon yhteisiä riskitekijöitä. Sydän- ja verisuonisairauksien hoidosta muistisairailla tarvitaankin lisätietoa.

Tämän väitöskirjan ensimmäisessä osatyössä tarkasteltiin sydän- ja verisuonisairauksien lääkehoidon muutoksia ennen ja jälkeen Alzheimerin taudin diagnoosin, sekä verrattiin näiden lääkkeiden käytön esiintyvyyttä vertailuväestöön, jolla ei ollut Alzheimer-diagnoosia. Toisessa osatyössä tutkittiin statiinien käytön lopetusta, ja siihen liittyviä tekijöitä Alzheimerin tautia sairastavilla sekä vertailuväestössä. Kolmas osatyö selvitti sepelvaltimotaudin revaskularisaatiohoidon yleisyyttä, ja toimenpiteen jälkeisen kuolleisuuden (1 ja 3 vuotta) ja uudelleen sairaalahoitoon joutumisen (30 ja 90 päivää) riskiä samoissa ryhmissä.

Osatyöt toteutettiin kansallisiin terveydenhuollon rekistereihin perustuvassa Medication use in Alzheimer's Disease (MEDALZ) -tutkimuksessa. Aineistoon kuuluu 70 718 kliinisesti varmennetun Alzheimer-diagnoosin vuosina 2005–2011 saanutta henkilöä, jotka eivät diagnoosihetkellä olleet laitoshoidossa. Jokaiselle henkilölle tunnistettiin 1–

4 iän, sukupuolen ja sairaanhoitopiirin perusteella kaltaistettua vertailuhenkilöä. Alzheimerin tautia sairastavat tunnistettiin lääkkeiden erityiskorvausoikeusrekisterin avulla. Lisäksi työssä hyödynnettiin hoitoilmoitusrekisterin, reseptitiedoston ja kuolemansyyrekisterin sisältämiä tietoja. Osatyössä I lääkehoidon kesto mallinnettiin PRE2DUP-menetelmällä ja osatyössä II käytettiin AdhereR-ohjelmistoa. Sydän- ja verisuonitautien lääkehoidon esiintyvyyttä tutkittiin yleistettyjen estimointiyhtälöiden avulla. Statiinien käytön lopettamiseen liittyviä tekijöitä ja revaskularisaatiohoidon yleisyyttä sekä päätetapahtumia tutkittiin Coxin regressiolla.

Kun Alzheimerin tauti diagnosoitiin sydän- ja verisuonisairauksien lääkkeiden käyttö oli yhtä yleistä Alzheimerin tautia sairastavilla (75,8 %) ja vertailuväestöllä (73,4 %). Diagnoosin jälkeisenä aikana näiden lääkkeiden käyttö väheni Alzheimerin tautia sairastavilla, kun taas vertailuryhmässä lääkkeiden käyttö säilyi samalla tasolla.

Statiinien käytön lopetus oli todennäköisempää Alzheimerin tautia sairastavilla kuin vertailuväestöllä (vakioitu hasardisuhde aHR 1,20, 95 % luottamusväli 1,18–1,24), joskin erot ilmaantuvuustiheyksissä olivat pienehköjä (Alzheimerin tautia sairastavista statiinihoidon lopetti 4,35 ja vertailuryhmästä 3,28 henkilöä 10 000 henkilövuotta kohden). Statiinihoidon mediaanikesto Alzheimer-diagnoosista oli 1,46 vuotta, ja vertailuhenkilöillä kaltaistuspäivästä 1,36 vuotta. Statiinien käytön lopettaminen oli yleisempää naisilla ja kaikkein iäkkäimmillä henkilöillä. Sen sijaan ne, jotka olivat käyttäneet statiineja pidempään ennen seurannan alkua, tai joilla oli käytössä muita sydän- ja verisuonisairauksien lääkkeitä, lopettivat statiinihoidon harvemmin. Samat tekijät olivat yhteydessä statiinien lopettamiseen molemmissa ryhmissä. Alzheimerin tautia sairastaville tehtiin vähemmän revaskularisaatiotoimenpiteitä, mutta heillä nämä toimenpiteet olivat useammin päivystyksellisiä. Toimenpiteen jälkeisessä uudelleen sairaalahoitoon joutumisessa ei havaittu eroja 30 päivän kuluessa, mutta 90 päivän sisällä uudelleen sairaalahoitoon joutuminen oli harvinaisempaa Alzheimerin tautia sairastavilla (aHR 0,85, 0,74–0,98). Alzheimerin tautia sairastavilla oli korkeampi kuolleisuus kolmen vuoden seurannan aikana, mutta tämä havaittiin vain

päivystystoimenpiteiden jälkeen (aHR 1,71, 1,27–2,31). Sen sijaan elektiivisten toimenpiteiden jälkeen kuolleisuudessa ei havaittu eroja (aHR 0,96, 0,63–1,46).

Sydän- ja verisuonilääkkeiden käytön väheneminen Alzheimer-diagnoosin jälkeen voi selittyä taudin etenemiseen liittyvillä kehon muutoksilla, kuten painon laskun tai gerastenian aiheuttamalla verenpaineen ja kolesterolipitoisuuksien laskulla. Tämän vuoksi on tärkeää säännöllisesti arvioida lääkehoidon tarvetta ja tarkoituksenmukaisuutta muistisairailla henkilöillä. Vaikkakin statiinien käytön lopettamisen suhteellinen riski oli suurempi Alzheimerin tautia sairastavilla, absoluuttiset erot olivat varsin pieniä. Tulosten perusteella muistisairaus ei näyttäisi vaikuttavan merkittävästi statiinihoidon lopettamiseen. Väitöskirjatyössä tehty havainto Alzheimerin tautia sairastavien korkeammasta 3-vuotiskuolleisuudesta päivystyksellisen, muttei suunnitellun revaskularisaatiotoimenpiteen jälkeen voi johtua korkeammasta kynnyksestä elektiiviselle toimenpiteelle muistisairaalla. Olisikin tärkeä selvittää, selittyvätkö löydökset korkeammalla kynnyksellä elektiivisiin toimenpiteisiin, ja johtaako tämä päivystyksellisten toimenpiteiden suurempaan määrään.

Avainsanat: *Alzheimerin tauti, sydän- ja verisuonitaudit, lääkehoito, pallolaajennus, sepelvaltimoiden ohitusleikkaus, sepelvaltimotauti, statiinit, esiintyvyys, kuolleisuus, sairaalahoito, kohorttitutkimukset, rekisterit, lääke-epidemiologia.*

ACKNOWLEDGEMENTS

This thesis was conducted in the School of Pharmacy, University of Eastern Finland, in Kuopio campus, during the years 2018-2024. I am grateful for the financial support that I received for my PhD journey from the Schlumberger Foundation Faculty for the Future and the Doctoral Programme in Drug Research of the University of Eastern Finland. Besides, I would like to acknowledge travel grants that I received from the International Society for Pharmacoepidemiology (ISPE), the Nordic Pharmacoepidemiological Network (Norpen), and the Faculty of Health Sciences of the University of Eastern Finland which supported me to attend international courses and conferences during my PhD studies.

Now it is time to express my gratitude to my peer networks who have supported me all the time. First and foremost, I owe the utmost gratitude to my supervisors Professor Anna-Maija Tolppanen, Professor Emerita Sirpa Hartikainen, Associate Professor Heidi Taipale, and Docent Marjaana Koponen (Ph.D.) for their expertise, guidance, and unlimited patience. Thank you for your mentorships, continuous encouragements, support, and contributions that made this PhD work come to fruition. I extend my deepest gratitude to Anna Maija who gave me the chance to begin and follow my dream – working in Pharmacoepidemiology field. Your determination, conscientiousness, and research talent have made you a role model for me. My gratitude also goes to Sirpa for her knowledge in geriatric pharmacotherapy and discussions related to clinical practice. Your expertise embraces not only scientific knowledge but also insights into social and cultural aspects. I am profoundly grateful to Heidi for her unwavering mentorship, for being a beacon of light throughout this journey, and for patiently replying to my (silly) questions. And to Marjaana, I feel incredibly lucky to have you as my supervisor. Thank you for your calm demeanour, diligence, and especially your meticulousness.

I am grateful to the reviewers of this thesis, Professor Kristina Johnell and Associate Professor Pavla Cermakova for their time and valuable comments. I also wish to express my gratitude to Professor Jenni Kulmala

for accepting the invitation to be my opponent. I am looking forward to our discussion.

I am indebted to the assistance of many people. Those listed here are the people I vividly recall while composing this acknowledgement. First, I want to extend my heartfelt thanks to all the members of the MEDALZ group. It has been an immensely enjoyable and rewarding experience working with you. Your collaboration and camaraderie have added a wonderful dimension to my academic journey. I would like to thank the University of Eastern Finland particularly the Social Pharmacy department for providing me with a conducive research environment and valuable networking opportunities. Additionally, I extend my gratitude to the Riikka Laitinen, Rami Ojarinta, and Anne Paakinaho for engaging conversations and discussions about 'very Finnish things.'

I would like to take a moment to express my deepest gratitude to my mentors, my gurus for peaceful moments, insights, and invaluable advice. I especially want to thank Mae Huong Nguyen for her guidance and inspiration. Many thanks to my friends and ‘sensai’ Roshan Mahabir for accompanying me on this journey. I remain grateful to my precious and loving family for their continuous love, support, and encouragement throughout my studies. Special thanks to my Mom for all the sacrifices she has made for me.

Kuopio, Feb 26th 2024.
Mai Vu

LIST OF ORIGINAL PUBLICATIONS

This dissertation is based on the following original publications:

I Vu M, Koponen M, Taipale H, Tanskanen A, Tiihonen J, Kettunen R, Hartikainen S, Tolppanen AM. Prevalence of cardiovascular drug use before and after diagnosis of Alzheimer's disease. Int J Cardiol 300: 221–225, 2020.

II Vu, M., Kettunen, R., Tolppanen, AM., Hartikainen S., Taipale H. Statin discontinuation in persons with and without Alzheimer's disease. Eur J Clin Pharmacol 78: 1145–1153, 2022.

III Vu M, Koponen M, Taipale H, Kettunen R, Hartikainen S, Tolppanen AM. Coronary revascularization and postoperative outcomes in people with and without Alzheimer's disease. J Gerontol A Biol Sci Med Sci 76: 1524–1530, 2021.

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ABBREVIATIONS

ACEi	Angiotensin converting enzyme inhibitors
ACS	Acute coronary syndrome
AD	Alzheimer's disease
AHA	American Heart Association
ALLHAT	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
AMI	Acute Myocardial Infarction
ARB	Angiotensin II receptor blockers
APOE	Apolipoprotein E
ATC	Anatomical Therapeutic Chemical
BB	Beta-blocker
CABG	Coronary Artery Bypass Grafting
CAD	Coronary Artery Disease
CCB	Calcium channel blockers
CI	Confidence Interval
DDD	Defined Daily Dose
ENLIGHTEN	Exercise and Nutritional Interventions for Cognitive and Cardiovascular Health Enhancement
ECG	Electrocardiogram
ESC	European Society of Cardiology
FINGER	Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability
GEE	Generalized estimating equations

eGFR	Estimated glomerular filtration rate
HDL	High-density lipoprotein
HF	Heart failure
ICD	International Classification of Disease
IQR	Interquartile range
JUPITER	The Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin
LDL	Low-density lipoprotein
MAPT	French Multidomain Alzheimer Prevention Trial
MCI	Mild Cognitive Impairment
MEDALZ	Medication Use in Alzheimer's Disease
MIND	Mediterranean Dietary Approaches to Stop Hypertension
MMSE	Mini-Mental State Examination
MRI	Magnetic resonance imaging
NINCDS–ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
NOMESCO	Nordic Medico-Statistical Committee
NSTEMI	Non-ST-segment elevation myocardial infarction
NYHA	New York Heart Association
PCI	Percutaneous Coronary Intervention

PET	Positron Emission Tomography
PreDIVA	Dutch Prevention of Dementia by Intensive Vascular Care
PRE2DUP	From prescription drug purchases to drug use periods
PROSPER	Prospective Study of Pravastatin in the Elderly at Risk
SD	Standard Deviation
START	Screening Tool to Alert doctors to the Right Treatment
STEMI	ST-segment elevation myocardial infarction
STOPP	Screening Tool for Older Person's Prescriptions
WHO	World Health Organization

1 INTRODUCTION

According to the United Nations report, the number of people over 65 years old has been increasing and was forecasted to be up to 2.1 billion in 2050 (1). Therefore, it is essential to assess the treatment of chronic diseases in this population, particularly among vulnerable groups such as those with cognitive decline. Alzheimer's disease (AD), the most common neurodegenerative disease leading to dementia, is considered one of the leading causes of human, economic, and social burdens in the older population. The number of incident cases of AD and other dementias have been increasing dramatically by 148% during the 30 years from 1990 to 2019 (2). According to the Global Burden of Disease, Injuries and Risk Factors Report 2016, AD and other dementias were ranked as one of the most common reasons leading to neurological disability-adjusted life-years lost and neurological burden in 21 global burden disease world regions (3). AD is also one of the common reasons leading to mortality, as it is the fifth leading cause of death in Americans over 65 years old (4). In Finland, mortality due to dementia has been increasing and was at the top of European countries relative to the population in 2013 (5).

Cardiovascular diseases and AD share the same risk factors such as high age, smoking, diabetes, and high blood pressure; thus cardiovascular diseases are common among persons with AD (4). There are several different cardiovascular drug classes, such as diuretics, beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, statins, and nitrates, which are also frequently prescribed for people with dementia (6). However, little is known about changes in the prevalence of cardiovascular drug use before and after AD diagnosis and whether it differs from persons without AD.

Statins are one of the most commonly used cardiovascular drugs (7–9). Statins are prescribed to prevent coronary artery disease (10). However, the efficacy of statins in the older population has been questioned, especially in primary prevention (11,12). It is unknown when statins are

discontinued in people with AD and whether the discontinuation is affected by primary/secondary prevention indications.

Coronary artery disease is one of the most prevalent cardiovascular diseases (13), especially in people with dementia (14). Coronary artery disease can be treated with medications and revascularization procedures, which are also applied to people with dementia. However, one concern associated with coronary revascularization procedures in people with dementia is the potential for postoperative cognitive decline (15). There is a lack of data on the frequency of coronary revascularization procedures and postoperative outcomes in persons with AD.

People with dementia are often excluded from randomized clinical trials and controlled trials due to their cognitive decline, psychotropic medications, and comorbidities (16). Therefore, real-world evidence utilizing register-based data could provide more representative insights into the treatment and medication usage in clinical practice. This thesis is based on the Medication Use and Alzheimer's Disease (MEDALZ) cohort, which includes 70,718 community dwellers with clinically verified AD diagnoses in Finland from 2005–2011 and followed up until 2015. The cohort provided a unique opportunity to investigate the utilization of cardiovascular drug use and postoperative outcomes of coronary artery revascularization procedures in people with AD.

2 REVIEW OF THE LITERATURE

2.1 ALZHEIMER'S DISEASE

2.1.1 Prevalence and incidence of dementia

According to the World Alzheimer Report 2021, the global prevalence of dementia in 2020 was over 55 million, and it has been forecasted to increase to 78 million by 2030 and nearly triple to 139 million by 2050 (17). However, the actual number of people with dementia is likely to be even higher because dementia in low and middle-income countries is still underdiagnosed (17–20). The reasons for this are likely multifactorial, including cultural attitudes to dementia and low levels of socioeconomic status, education, and living in rural areas (19). A study conducted in the Southeast Asian region estimated that there were approximately 6.66 million people with dementia in 2020, and the number will increase to 9.6 million in 2030 (20).

The incidence of dementia increases with age, from approximately 4/1000 person-years in 60–64-year-olds up to 50–136/1000 person-years in persons older than 95 years. The incidence varies between Europe, North America, and Asia (21). In recent reports, the age-specific incidence has started to decline in high-income countries, which may be due to increasing education levels, improvement in cardiovascular health, and programs to improve brain health and prevent dementia (22–24).

In Finland, the estimated number of people with at least mild cognitive decline is nearly 200,000 persons, and 93,000 people have moderate or severe cognitive disorder (25). The annual incidence of cognitive disorder cases is approximately 14,500 people (25).

2.1.2 Clinical picture of Alzheimer's disease

Alzheimer's disease (AD) is a neurodegenerative disease causing a decline in cognitive functioning and activities of daily living. It is the most common cause of dementia, accounting for 60–80% of cases (26,27). AD can be

divided into late and early onset forms, with the late-onset accounting for the majority of cases and the early-onset form that occurs in people <65 years of age accounting for 5% of AD cases (28).

Alzheimer's disease is distinguished from other neurodegenerative diseases by the clinical picture and process of disease as well by specific changes in the brain and accumulation of proteins outside neurons (fragments of beta-amyloid, called beta-amyloid plaques) and inside neurons (twisted tau protein, called TAU tangles) (29). It has been suggested that an accumulation of beta-amyloid and TAU tangles may block the transport of nutrients and other molecules essential for the normal functioning of neurons (30), which then results in neuronal damage and death of neurons (31).

People can also have mixed dementia, with clinical signs and brain changes from more than one disease-causing dementia (32). These mixed pathologies can account for even up to 50% of dementia cases (27,32). Their likelihood increases with age and is highest in people aged 85 years and older (33,34). Other common forms of dementia include vascular dementia, causing 5% to 10% of cases (35), and dementia with Lewy bodies, affecting 5–26% of all dementia cases (36,37).

Stages of Alzheimer's disease

The progress of AD takes years or even decades before the disease is diagnosed, and the symptoms of AD develop gradually and worsen over time. The progression of AD includes three broad states: preclinical AD, mild cognitive impairment (MCI) due to AD, and dementia due to AD (38,39) (Figure 1). In the preclinical AD stage, brain changes and alterations in biomarkers can be observed, but the symptoms of the disease are absent. People in this stage still express normal activities (25,38).

The mild cognitive impairment (MCI) stage is a symptomatic stage with minor effects of the disease manifested as decreasing cognitive capacity that starts to affect memory and thinking (40). Persons at the MCI stage commonly demonstrate preservation of independence in functional abilities but have mild difficulties when performing complex functional tasks (40,41). In mild AD, persons confront memory problems in

remembering new information, finding the right words, planning, organizing daily activities, and performing complex tasks (25). The moderate stage usually is the longest phase after diagnosis, and the symptoms become more noticeable. Persons have decreased independence in instrumental activities of daily living, increasing difficulties with memory and orientation, and dysphasia (25).

People in the severe stage of AD have severe cognitive decline and apraxia and are unable to communicate due to dysphasia. Therefore, they need around-the-clock assistance in all personal care (25).

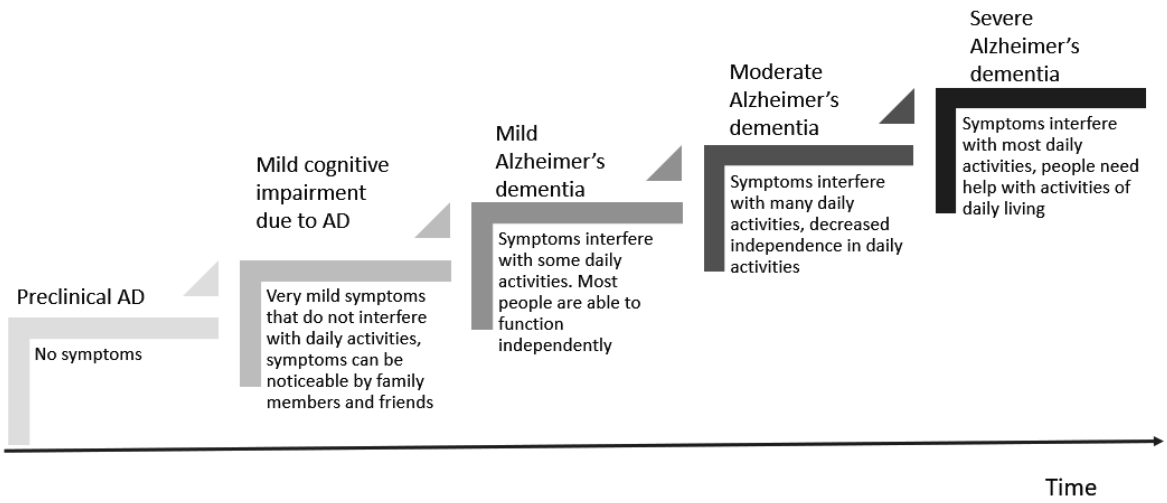


Figure 1. Stages of Alzheimer's Disease.

This figure is adapted from *2021 Alzheimer's Disease Facts and Figures: Race, Ethnicity and Alzheimer's in America* and *Finnish Current Care Guidelines: Memory disorders* (4,25)

2.1.3 Diagnosis

The first version of diagnosis criteria for AD of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorder Association (NINCDS-ADRDA) was published in 1984 (42). The latest version, published in 2011, includes two major updates: (1) the role of the bio-marker regarding pathophysiologic changes

in diagnosis and (2) expanding AD into three phases: (a) probable AD dementia, (b) possible AD dementia, and (c) possible AD dementia with evidence of the AD pathophysiological process (39). This current NINCDS-ADRDA version is incorporated into the Diagnostic and Statistical Manual of Mental Disorders 4th edition criteria (DSM-IV) for a diagnosis of AD, which distinguishes the stages of AD, including pre-clinical AD, MCI due to AD, and AD dementia. A summary of diagnoses at different stages of AD is shown in Table 1.

The fifth edition of DSM criteria has been revised and published in 2013 (43). In the 5th edition, there are some changes in the terms, such as the name 'dementia' has been replaced by the term 'major neurocognitive disorder' and MCI by 'mild neurocognitive disorder'. The purpose of the additional criteria for mild neurocognitive disorder was to promote the early detection and treatment of cognitive decline (43).

Table 1. Diagnosis at different stages of Alzheimer's disease (AD).

(Modified from Alzheimer's Association 2021 and Finnish Current Care Guidelines: Memory disorders (4,25))

Stage	**Diagnostic practice through changes in the brain**
Preclinical AD	No symptoms yet. Some brain changes are seen like abnormal beta-amyloid in positron emission tomography (PET).
Mild cognitive impairment due to Alzheimer's disease	Biomarkers such as abnormal beta-amyloid in PET scans and analysis of cerebrospinal fluid are detected. Some subtle problems with memory and thinking.
Dementia due to AD	Biomarkers are detected. Symptoms develop slowly and get worse over time.

Diagnostic procedure in Finland

The Finnish National Current Care Guideline for Memory Disorders is used for the clinical diagnosis of AD. The guideline was first published in 2006 and updated in 2010, 2017, and 2020. A further update is scheduled for 2023. This guideline is evidence-based and independent of the clinical

practice guideline based on NINCDS-ADRDA criteria. The diagnosis should be done at specialized units such as regional memory clinics. The diagnosis is based on anamnestic information about symptoms from the patients and their family members, assessment of functional abilities comprehensive somatic and neurological examination, and assessment of cognitive function (CERAD: Consortium to Establish a Registry for Alzheimer's Disease, which also includes the Mini-Mental Status Examination (MMSE)). In addition, brain scanning (Magnetic Resonance Imaging (MRI) or Computerized Tomography (CT)) is taken, and to exclude other possible diseases, laboratory tests are taken (25).

2.1.4 Risk and protective factors for AD

Alzheimer's disease is a consequence of exposure to multiple risk factors rather than a single one (44–46). Those risk factors can be grouped into modifiable and non-modifiable risk factors. The modifiable risk factors can be altered by lifestyle modification and/or medications, whilst the non-modifiable factors such as age, sex, and family history cannot be targeted. The risk factors can interact with each other, and the contribution of factors may differ between individuals.

- ***Non-modifiable factors***

Age is the most consistent risk factor for AD in many studies (44,45,47). The incidence of AD in people over 85 is 14 times higher than those between 65 and 69 (4,48). In a register-based study from Finland, the average age at AD diagnosis was 80 (49).

Sex: AD is more common in women than men (50), and approximately two-thirds of people with AD are women (51). The lifetime risk of AD is higher in women than in men after 80 (52). In addition to sex itself being a risk factor, many alternative explanations for the higher prevalence of AD in women compared to men have been proposed. These include the longer life expectancy in women and differences in the prevalence or effect of risk factors between sexes (53). For example, the association of the

apolipoprotein E (*APOE4)* genotype is stronger in women (54). In addition, the prevalence of lifestyle-related risk factors varies between sexes, and historically men have had better access to education and jobs considered to be cognitively demanding, leading to increased cognitive reserve (55).

Family history: Those who have parents or a sibling with AD are more likely to develop AD than those whose family do not have AD (56,57), suggesting the involvement of genetic risk factors.

Genetics: Over 50 different loci have been associated with late-onset AD (58,59). The strongest genetic risk factor is the ε4 apolipoprotein E type (*APOE*) (60,60–62). However, having the APOE ε4 form is not deterministic (63). More than half of those with AD do not have the ε4 allele, and not all individuals who are homozygous for the ε4 allele develop AD (58,64).

- ***Modifiable factors***

Evidence on risk factors that can be targeted to delay or possibly prevent major cognitive disorders, including AD, has accumulated from observational studies and multidomain lifestyle intervention studies.

Some factors include those affecting cognitive reserve (education, social and cognitive activities) and lifestyle-related factors such as (diet, physical activity and avoiding smoking) that can impact the risk via different pathways, including cardiovascular diseases.

Cardiovascular risk factors: Many cardiovascular disease risk factors, including smoking, low physical activity, unhealthy dietary choices, and high body mass index, are associated with a higher risk of dementia (65,66). In addition, high blood pressure, high low-density lipoprotein (LDL) cholesterol, low high-density lipoprotein (HDL) cholesterol, and diabetes are associated with a higher risk of AD (67). The associations between cardiovascular risk factors and the risk of dementia are complex and dependent on the age when the risk factors appear. Mid-life cardiovascular risk factors such as obesity, high total cholesterol, and high systolic blood

pressure have been consistently linked to an increased risk of AD in later life (66,68,69).

Higher body mass index (BMI>30 kg/m^2) in midlife has been associated with a higher risk of dementia in late life, while the association is partially mediated by blood pressure and cholesterol (69). The association was supported by a meta-analysis that showed an association between higher BMI in midlife and the risk of dementia in late life when weight was measured at least 20 years before the dementia diagnosis (70).

The association between higher midlife blood pressure and the risk of dementia or AD has been confirmed in several studies. For example, a study using the Framingham Offspring database showed that persistent high blood pressure in midlife (40–64 years) is associated with an increased risk of AD in later life (71). Consistent with these findings, a systematic review concluded that people with midlife systolic hypertension (defined as >140 mmHg) were strongly associated with AD (72).

Besides, a population-based study showed that high total cholesterol (defined as > 6.5mmol/l) in midlife relates to a higher risk of AD in later life (68). The link between high total cholesterol in midlife and the risk of late-life AD was also supported by a systematic review and meta-analysis (73,74) as well as by a recent study from the UK (75).

The findings from previous observational studies showed that the risk of AD was higher when diabetes was diagnosed in mid-life than in later life (76,77). The association between diabetes mellitus in midlife and the risk of Alzheimer's disease was shown in systematic reviews (78,79). One hypothesis to explain this finding states that insulin resistance in midlife can lead to amyloid accumulation in the brain (80), which is known to occur in AD (81).

Lifestyle factors: Due to the strong link between cardiovascular health and brain health, factors that reduce cardiovascular diseases could also positively impact the risk of developing AD. A 44-year longitudinal study demonstrated that physical activity reduces the risk of AD by almost 60% (82). This risk reduction was also seen in previous studies (83–85). Healthy diets—such as Mediterranean Dietary Approaches to Stop Hypertension

(MIND), which includes low amounts of saturated fatty acids but a lot of vegetables, nuts, berries, beans, whole grains, fish, poultry, and olive oil—could decrease the incidence of AD (86,87). In addition, findings from the Finnish geriatric intervention study showed that dietary intervention based on the Finnish nutrition recommendations—including a high intake of fruits and berries and vegetables, whole grain cereals, low-fat and low-sugar food, fish, and substituting butter and butter-oil mixtures with margarine and rapeseed oil—resulted in beneficial changes in executive function (88).

Cognitive reserve: According to the reserve theory, the brain can cope with neural damage by enlisting compensatory processes (such as the differential recruitment of brain networks) to optimize cognitive performance (89). The reserve hypothesis consists of passive reserve (brain size) and cognitive reserve, which can be improved through positive experiences in a lifetime, such as educational and occupational attainment as well as cognitively stimulating leisure activities throughout life (90,91). The hypothesis was formulated to explain individual differences in cognitive performance after brain damage but later extended to normal ageing (92). The role of cognitive reserve in AD has been demonstrated in studies showing that people with more education had a lower risk of AD than those with less education (93–95). In addition, more socially active people were less likely to develop cognitive decline in old age, and the result was not driven by those with the lowest level of cognition or social activity at baseline (96).

- ***Multidomain lifestyle-based intervention trials***

The effect of different multidomain interventions on cognitive decline has been studied in randomized controlled trials. The Dutch Prevention of Dementia by Intensive Vascular Care (PreDIVA) study, conducted between 2006 and 2015 (97), investigated the effect of a multidomain vascular care program, with both lifestyle and medical intervention based on Dutch GP guidelines. The French Multidomain Alzheimer Prevention Trial (MAPT) (2008–2011) (98) evaluated the effect of a multidomain lifestyle consisting

of physical activity, cognitive training, and nutritional advice with or without omega-3 on cognitive decline. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) (99) assessed whether multimodal intervention combining diet, exercise, cognitive training, and intensive management of vascular risk factors could prevent cognitive decline in people at high risk. The Exercise and Nutritional Interventions for Cognitive and Cardiovascular Health Enhancement (ENLIGHTEN), conducted in the US from 2011 to 2016, evaluated the effect of aerobic exercise and the Dietary Approaches to Stop Hypertension (DASH) diet in at-risk persons with cardiovascular disease risk factors and cognitive impairment with no dementia (100). In PreDIVA and MAPT, the intervention had no effect on cognitive outcomes (97,98), but the FINGER study showed that multidomain lifestyle intervention could improve or maintain cognitive functioning in at-risk people (99). In the ENLIGHTEN study, dietary intervention (DASH diet) or exercise intervention alone or in combination promoted better executive function in people with cardiovascular disease risk factors who did not have dementia at the time of enrolment (100).

2.2 PREVALENCE AND TREATMENT OF CARDIOVASCULAR DISEASES

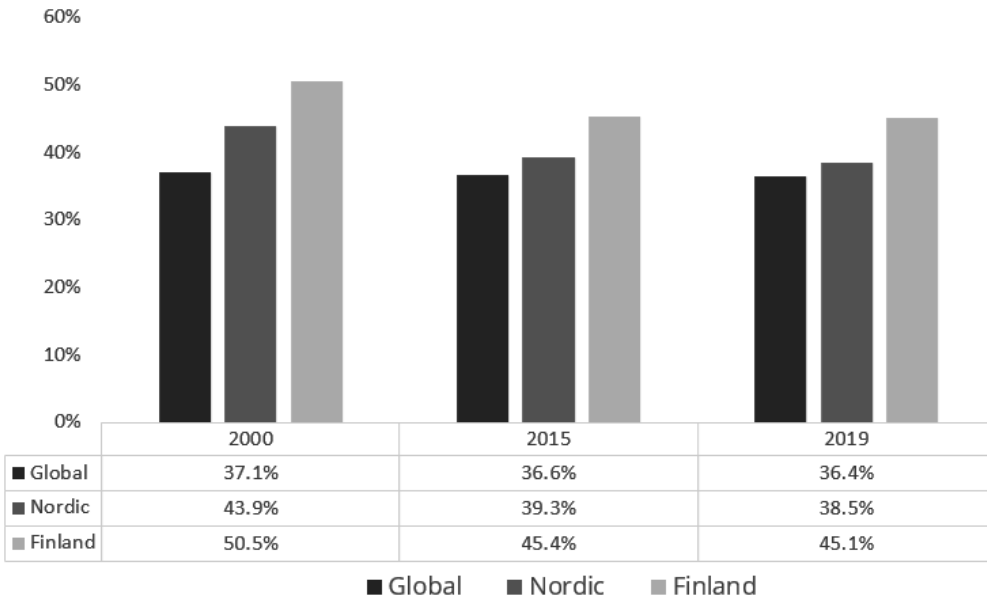
2.2.1 Prevalence of cardiovascular diseases

According to the update from the Global Burden of Cardiovascular Diseases Report in 2020, the global prevalence of cardiovascular diseases, which was defined based on the International Classification of Disease (ICD) 9 and 10, has increased from 271 million cases in 1990 to 523 million cases in 2019 (13). During the same period, the number of deaths due to cardiovascular disease increased globally from 12.1 million in 1990 to 18.6 million in 2019 (13). Although the number of deaths has increased, there has been a slight decrease in the proportion of deaths due to cardiovascular disease—from 37.1% in 2000 to 36.4% in 2019 (Figure 2). In this thesis, the term "cardiovascular diseases" is used to refer to a group of diseases that includes hypertension, coronary artery disease, valve disorders, conduction disorders (e.g., atrioventricular block), arrhythmia, carditis (pericardium and myocardium), heart failure, pulmonary heart disease, and disease of pulmonary circulation, as well as diseases of arteries and veins (101).

In Europe, it is estimated that 60 million potential years of life are lost due to cardiovascular disease annually, with a higher impact on men than on women (34.5 million for men and 25.7 million for women) (102). Cardiovascular disease is also still a major health concern in Finland. Deaths due to the circulatory system comprised a third (34%) of all deaths in 2019 (103). The proportion of deaths due to cardiovascular diseases has decreased in the Nordic countries and Finland (Figure 2). However, the proportion of these deaths in Finland is still higher than that observed globally and the average of all Nordic countries.

Coronary artery disease (CAD) is one of the most common cardiovascular diseases (13,104), and a significant cause of death in both developed and developing countries (13). Deaths due to CAD accounted for nearly 20% of all deaths globally (Figure 3). The global total number of

disability-adjusted life years due to CAD was 182 million in 2019, and the number of deaths due to CAD in 2019 was 91.4 million (13). In Europe, CAD was one of the most common causes of death in both men and women, causing 47% and 40%, respectively, of all cardiovascular deaths (102). Although the number of deaths due to CAD has decreased in Finland since 1971 (103)—a trend similar to other Nordic countries (Figure 3)—CAD is still one of the most common causes of death. It accounted for approximately a quarter of all deaths in 2019.



	2000	2015	2019
Global	37.1%	36.6%	36.4%
Nordic	43.9%	39.3%	38.5%
Finland	50.5%	45.4%	45.1%

Figure 2. Proportion of deaths due to cardiovascular disease globally, in Nordic countries, and in Finland (Reference: (105)).

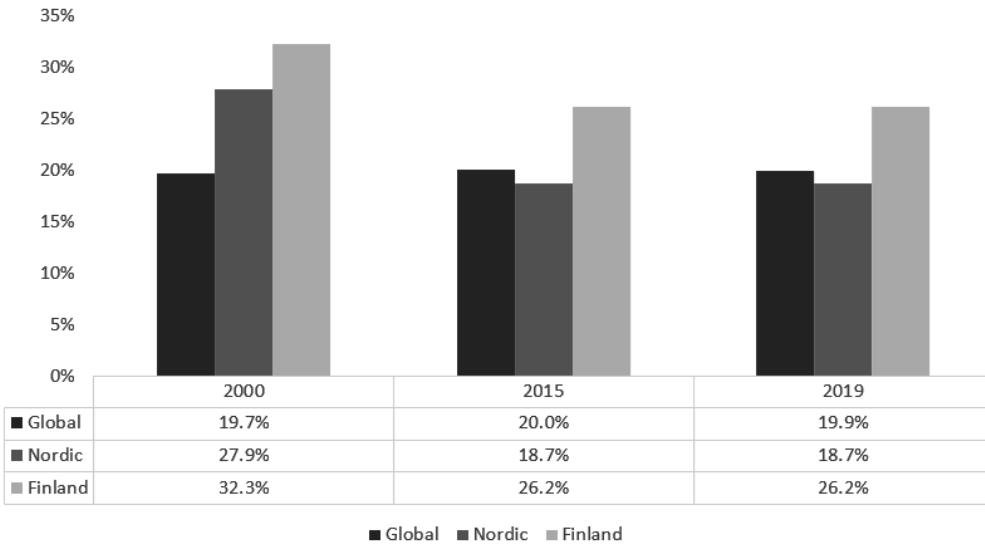


Figure *3.* Proportion of deaths due to coronary artery disease globally, in Nordic countries, and in Finland (Reference: (105)).

2.2.2 Coronary artery disease

In coronary artery disease (CAD), atherosclerosis due to plaque buildup in the arterial walls causes narrowing and stiffening of coronary arteries responsible for supplying oxygen and nutrients to the myocardium (104,106). The size of atherosclerosis plaques compressing deposits of cholesterol and other fats, calcium, and fibrin will increase over time, leading to impeded blood flow and ischaemia in the myocardium (107). Angina pectoris is the most common symptom of coronary artery disease, caused by an imbalance between myocardial oxygen supply and demand (108). In stable CAD (stable angina), angina symptoms are similar each time and occur in the same kind of circumstances (e.g., exercise) (109).

The rupture of atherosclerosis plaques causes platelet adherence, activation, aggregation, and the activation of a clotting cascade, resulting in acute coronary syndromes (109). If the plaque of the clotting cascade obstructs the coronary artery only partly or quickly dissolves naturally or due to therapeutic thrombolysis, it is called unstable angina pectoris (110).

A sudden narrowing or blockage of coronary arteries results in myocardial infarction.

The risk factors for CAD include both modifiable and nonmodifiable factors, and they partially overlap with those of AD. Well-known risk factors for CAD include high blood pressure, hypercholesterolemia, smoking and diabetes, early menopause in women, inflammation, rheumatoid arthritis, and infections like parodontitis (10,111,112). The modifiable risk factors capture 20–37% of the overall prognostic performance of cardiovascular risk models, and the nonmodifiable risk factors (including age, sex, family history, and ethnicity)_capture 63–80% (113).

The principles of CAD treatment are to reduce risk factors by improving the lifestyle (like increasing physical activity), lowering LDL, relieving ischemic symptoms by decreasing myocardial oxygen demand, and increasing myocardial oxygen supply (10,110). Pharmacotherapy for CAD includes different types of cardiovascular drugs. In addition, coronary revascularizations can be performed if pharmacotherapy is not enough to relieve symptoms or if there is a high risk of myocardial infarction (114).

2.2.3 Cardiovascular drugs and pharmacotherapy for coronary artery disease

Cardiovascular drugs are the most commonly used drugs in older adults. According to a home medication survey of the National Social Life, Health & Aging Project in the United States, 15 of the 20 most commonly used drugs were cardiovascular drugs (9). Their use is also common in Finland. In 2020, half of the people over 65 (50%) used agents acting on the renin-angiotensin system, 43% used statins, and 39% used beta-blockers (115,116).

Cardiovascular drugs are a diverse group of drugs used in the treatment of various cardiovascular conditions such as hypertension, heart failure, coronary artery disease, and dyslipidaemias. Table 2 describes the main indications, pharmacological mechanisms, and adverse effects of cardiovascular drug groups.

Table 2. Summary of main cardiovascular drug classes by main indication, mechanism, and adverse effects (adapted from (109,117)).

Drug class	Main indications	Pharmacological mechanism	Examples of common and significant adverse effects
Beta-blocking agents	Hypertension Coronary artery disease Arrhythmias Secondary prevention following myocardial infarction Heart failure	Blockade of β1-adrenoreceptors reduces blood pressure and in the heart reduces cardiac output by decreasing heart rate and contractility.	Bradycardia, depression, fatigue, vivid dreams, bronchospasm
Calcium channel blockers (CCBs)			
Dihydropyridines	Hypertension Chronic stable angina pectoris Prinzmetal's angina	Blockade of calcium channels in the smooth muscle, relaxation of vascular smooth muscle leads to dilation of arteries and reduction of peripheral resistance	Dizziness, flush, ankle swelling, headache, tachycardia, constipation
Non-dihydropyridines *Verapamil* *Diltiazem*	Rate control of atrial flutter/fibrillation Hypertension	Block calcium channels in the myocardium can reduce the heart rate and cardiac output Verapamil is highly selective for the	Atrioventricular block, bradycardia, constipation, dizziness, ankle swelling, headache, and heart failure.

Drug class	Main indications	Pharmacological mechanism	Examples of common and significant adverse effects
	Stable and unstable coronary artery disease (verapamil) Angina (diltiazem)	myocardium Diltiazem has intermediate selectivity, with both vasodilator and cardiac depressant actions	
Angiotensin-converting enzyme inhibitors (ACEi)	Hypertension Heart failure Recent acute myocardial infarction Stable coronary artery disease Secondary prevention following myocardial infarction	Inhibits the conversion of angiotensinogen to angiotensin I by inhibiting the angiotensin-converting enzyme, which leads to dilation of arteries including coronary and renal arteries	Cough, hyperkalemia, rash, angioedema
Angiotensin receptor blockers (ARBs)	Hypertension Heart failure Secondary prevention following myocardial infarction	Block angiotensin AT_1 receptor, decreasing the activation caused by angiotensin, which leads to the dilation of arteries, including coronary and renal arteries.	Hyperkalemia

Drug class	Main indications	Pharmacological mechanism	Examples of common and significant adverse effects
Diuretics			
Loop diuretics	Heart failure	Inhibit the Na-K+-2Cl symporter in the loop of Henle. A profound increase in sodium and water excretion leads to decreased blood volume and a reduction in blood pressure.	Orthostatic hypotension, hypokalaemia, hyperuricemia, hypocalcemia
Thiazide diuretics	Heart failure Hypertension	Inhibit the Na-Cl symporter in the distal tubule. Leads to a moderate increase in sodium and water excretion, a decrease in blood volume, and a reduction in blood pressure. Long-term effects on blood pressure are mainly caused by decreased sodium content of arterial smooth muscle cells, decreasing muscle contraction and thereby decreasing peripheral vascular resistance.	Hypokalemia, hyperuricemia, hyperglycemia
Potassium-sparing diuretics	Chronic heart failure Hypertension (used in combination with thiazide or loop diuretic to avoid potassium depletion)	Inhibits epithelial sodium transport at the late distal and collecting ducts. As a result, reduces potassium loss in the urine.	Hyperkalemia

Drug class	Main indications	Pharmacological mechanism	Examples of common and significant adverse effects
Statins	Hypercholesterolemia Primary and secondary prevention of coronary artery disease	Reduces total cholesterol, mainly in LDL levels through inhibition of hepatocyte HMG-CoA reductase, which leads to a reduction in the formation of plaques.	Muscle pain, myositis, rhabdomyolysis, elevation of liver enzymes, hepatitis
Nitrates	Coronary artery disease Angina pectoris	Metabolized in vascular smooth muscle to release nitric oxide. Leads to dilation of arteries and veins and a reduction in cardiac work and oxygen demand.	Headache, flushing, hypotension, and orthostatic hypotension
Alpha-adrenoceptor blocker	Hypertension	Blocks α-adrenoreceptors on vascular smooth muscle, leading to vasodilation and decreased vascular resistance.	Dizziness, first-dose syncope, orthostatic hypotension

LDL: low density lipoprotein; HMG-CoA: the 3-hydroxy-3-methylglutaryl coenzyme A

- ***Pharmacotherapy for coronary artery disease***

The main goal of pharmacotherapy for coronary artery disease is to relieve the symptoms and improve disease prognosis by preventing myocardial infarctions and cardiac deaths. As the symptoms are controlled and relieved, patients can improve their quality of life through better physical, psychological, and social functioning or well-being (118,119). Numerous cardiovascular drugs are approved for the treatment of coronary artery disease, and also antithrombotic drugs have a major role in the treatment (119,120).

According to the Finnish Current Care Guideline on chronic coronary artery syndrome, each patient with coronary artery disease should be treated with pharmacotherapies improving the prognosis, and with one or more symptomatic pharmacotherapies (10).

Pharmacotherapies improving the prognosis

Statins inhibit 3-hydroxy-3-methyglutaryl-coenzyme A (HMG-CoA) reductase thus increasing the number of LDL receptors and reducing hepatic cholesterol biosynthesis (109). Statins slow the progress of atherosclerosis by stabilizing or even decreasing the size of plaques, improving vascular endothelial function, and reducing inflammation. A more detailed description of statins is provided in section 2.2.6. Statins improve the prognosis of coronary artery disease and are thus recommended to be used for all persons with CAD regardless of their LDL cholesterol levels (10,119).

Angiotensin-converting enzyme inhibitors (ACEi) improve the prognosis in persons with stable coronary artery disease, as they decrease mainly arterial but also venous pressure by vasodilation and reduce myocardial oxygen demand and coronary vasoconstriction (10,109). ACE inhibitors should be initiated in people at high risk of cardiac events (10). Angiotensin receptor blockers (ARBs) dilate arteries and are recommended in cases of intolerance to ACEi in people with renal failure and in older persons with age-related renal impairment (121,122).

Besides cardiovascular drugs, acetylsalicylic acid is the cornerstone of prognostic treatment and should be initiated for all persons with coronary artery disease (10). Acetylsalicylic acid is used to prevent blood coagulation and if people are allergic to it, clopidogrel can be used instead.

Symptomatic pharmacotherapies

Beta-blockers can reduce myocardial oxygen demand by reducing the heart rate, cardiac contractility, and intraventricular pressure, and improving the distribution of coronary flow (109). They are used as a first-choice anti-ischemic drug (10,123)

Of the calcium channel blockers (CCBs), dihydropyridines are recommended to improve the balance between myocardial oxygen supply and demand by vasodilation and reduction of peripheral vascular resistance. CCBs decrease myocardial oxygen demand by decreasing peripheral resistance and increasing oxygen supply by improving coronary flow (109,119). The dihydropyridine subgroup can be used in the treatment of hypertension in people with coronary artery disease or as an anti-ischemic drug, especially in combination with beta-blockers (10,124).

Nitrates are recommended for people with acute coronary syndrome (125) and stable coronary artery disease (126) due to symptom relief caused by vasodilation of peripheral and coronary arteries but mostly peripheral veins (119,123). The vein-dilating effect of nitrates leads to decreased blood return to the heart, decreasing ventricular volume, pressure, and wall tension, thus reducing cardiac work and oxygen demand. Short-acting nitrates are recommended as a first-line symptom-relieving treatment and taken as needed for acute chest pain according to the guidelines of the European Society of Cardiology (122). There is no evidence of improvement in prognosis regarding the use of long-acting nitrates, but they are used to prevent angina symptoms, especially for strain (10). However, long-term use of long-acting nitrates should be cautioned against to avoid nitrate tolerance.

2.2.4 Age-related changes in pharmacokinetics and pharmacodynamics of cardiovascular drugs

Physiological alterations related to age can be characterized as a decrease in the functioning of organs, such as slowed gastric emptying and reduced renal and hepatic functions (126–128) (Table 3). In addition, the progressive loss of organ system functional reserve and impaired adaptive and homeostatic mechanisms can lead to altered pharmacokinetics and pharmacodynamics of drugs in older people (129,130).

- ***Pharmacokinetics***

Pharmacokinetics, including the absorption, distribution, metabolism, and excretion phases, describes the movement of a drug substance in the human body. Age-related reduction in liver mass and blood flow leads to a decrease in first-pass metabolism (131). Then the bioavailability of drugs with high first-pass metabolism is increased, which causes a prolonged elimination half-life of these drugs. Besides, changes in body composition, such as an increase in relative body fat mass and a reduction of lean body mass (132), also impact drug distribution. Thus the distribution volume of lipophilic drugs will increase, leading to an increased half-life of these drugs (131,133,134). In addition, ageing causes lower relative content of intracellular water, leading to a reduced distribution of water-soluble drugs (134).

Age-related blood-brain barrier changes in older people lead to increased permeability of drugs into the central nervous system (135). This is according to new findings on brain barriers due to their essential role in neuroimmune communication, and these changes happen in healthy ageing (136). One example could be the decrease of P-glycoprotein activity, which is an efflux transporter of various drugs in the function of the blood-brain barrier (137). Consequently, changes in the blood-brain barrier could lead to higher drug levels in the brain in older people (135,137). Blood-brain barrier impairments are more severe in people with cognitive impairment (136,138,139), which could increase the risk of CNS adverse drug effects in those people (131).

The most significant and predictable age-related change is a decrease in the renal elimination of drugs. Drugs that are eliminated by the kidneys have a decreased renal clearance due to a decline in the renal blood flow, decreased glomerular filtration rate, and decreased active renal tubular secretory processes (140). This leads to a prolonged half-life of drugs, an increase in serum drug levels, and the potential for adverse drug reactions and effects of drugs eliminated by the kidneys. This is especially important for drugs with a narrow therapeutic index (e.g. digoxin) (141). In clinical practice, renal function is measured by the estimated glomerular filtration rate (eGFR), which is based on creatinine and patient characteristics. The eGFR is applied for adjusting the drug dose or calculating the dosing interval (142,143). For instance, the dosage of ACEi use in older people with moderate renal insufficiency needs to be adjusted (144).

Table 3. Ageing-associated physiological changes and their impact on pharmacokinetics (modified from (126,128,129,131,145–148)).

Phases	**Physiological change in older people in general**	**Impact on drug pharmacokinetics**
Absorption	Slowed emptying of the stomach, especially slowed in bedridden persons. Decrease in intestinal blood flow and gut motility. Hypochlorhydria (reduced gastric acidity).	Impaired drug dissolution Reduced absorption of some drugs and nutrients (calcium, vitamin B12)
Distribution	Alteration in body composition, including reduction of body water and muscle mass and an increase in total fat. Reduction of serum albumin levels in persons with protein malnutrition.	Hydrophilic drugs have decreased distribution volume, and lipophilic drugs have increased distribution volume.
Metabolism	Reduced liver mass, blood flow, and hepatic metabolic capacity. Decreased cytochrome P450 enzyme activity.	May increase bioavailability and decrease the clearance rate of drugs that have high first-pass metabolism (e.g. diltiazem, verapamil, nifedipine, labetalol), leading to increased drug accumulation and prolonged drug effects.
Excretion	The structure of kidneys changes with reduced glomerular filtration. Decreased renal tubular function and blood flow.	Slower clearance of hydrophilic drugs or active metabolites that are eliminated through kidneys.

- ***Pharmacodynamics***

Ageing can also lead to changes in the pharmacodynamics of drugs. Pharmacodynamics refers to interactions of the drug with the receptor, including the number and affinity of receptors and the response of cells to the receptor in the target organ. These changes have implications for the quantified drug effect, drug dose, and safety aspects (126,130,131,149). Different from age-related changes in pharmacokinetics, measurement and generalization of the effect of age on the pharmacodynamics of drugs is more challenging. In addition, there are few studies regarding pharmacodynamic changes in older people (150). Alterations in homeostatic mechanisms in receptors at the organ systems can lead to decreased responsiveness to specific drugs in older individuals (149). For example, the sensitivity of cardiac beta-1 and beta-2 adrenergic receptors was shown to decrease during ageing, which can lead to a decreased response to beta-blockers in vascular, cardiac, and pulmonary tissues (150,151). Ageing is associated with decreased cardiovagal baroreflex sensitivity, which increases the risk of orthostatic hypotension (152). Drugs that reduce the heart rate or cause vasodilation like calcium channel blockers and nitrates can have exaggerated effects leading to orthostatic hypotension, especially when two or more drugs with this property are used concomitantly (130,153).

- ***Appropriateness of drugs for older people***

In addition to age-related changes in pharmacokinetics and pharmacodynamics, the treatment of cardiovascular diseases in older people is complicated by comorbidities, concomitant use of multiple drugs, frailty, and cognitive impairment (154). Due to the high number of comorbid conditions, the concomitant use of multiple drugs is common in older people (155). The concomitant use of multiple drugs can increase the risk of adverse drug reactions (156) and the potential for drug-drug interactions (157). All these factors pose a challenge for the prescribers in optimizing the treatment by maximizing the possible benefits and minimizing the risks. Deprescribing—defined in this thesis as the process

of tapering and/or withdrawal of medication without current indication or due to adverse effects or events by medical doctors is an essential part of optimizing treatment (158,159).

In 1991, a group of experts suggested a list of inappropriate medication use in the nursing home—called the Beers criteria (160). The Beers criteria are updated by the American Geriatrics Society every 3 years (161). In the Beers list, some cardiovascular drugs were recommended to avoid or adjust doses such as spironolactone and amiloride due to an increased risk of hyperkalaemia (161). In Europe, the Screening Tool for Older Person's Prescriptions (STOPP)/Screening Tool to Alert Doctors to Right Treatment (START) criteria (Europe) was established to provide an explicit, evidence-based list of commonly encountered potentially inappropriate prescribing and prescribing omissions (162,163). The STOPP & START criteria reflect the consensus opinion of a panel of experts in geriatric pharmacotherapy, which was last updated in 2015 with a 31% increase in criteria over the first version (164). As an example of recommendations on cardiovascular drugs, the STOPP & START criteria recommends that verapamil or diltiazem should not be used for people with New York Heart Association (NYHA) III and IV heart failure because it may worsen the heart failure (164).

Appropriateness of prescribing, defined as *'a range of values and behaviours to express the quality of prescribing'*, may vary between countries because of the difference in treatment guidelines and the availability of drugs on the market (165,166). In Finland, the Meds75+ database listing the suitability of drugs for older people was established and is maintained by the Finnish Medicines Agency (Fimea). The Meds75+ database provides information on medication use for older persons to support clinical decision-making on pharmacotherapy for persons over 75 years old (167). The database was built by a group of experts in geriatrics, clinical pharmacology, and clinical pharmacy. Drug substances or their combination are categorized into 4 subgroups: A (suitable for use in older people), B (not enough evidence of use in older people), C (specific cautions such as dose adjustment due to age-related renal insufficiency or significant risk of interaction, adverse effects), and D (Risk of adverse effects typically exceeds the benefits, and can be used only in exceptional

cases), indicating how suitable the drug is for people aged over 75. The need for changes and cautions in use increases from group A to D. As drugs are assessed on the drug substance level, cardiovascular drugs that belong to the same drug class can be included in different groups in Meds75+. For example, of the CCBs, verapamil and diltiazem belong to group D, whereas the dihydropyridines belong to group A. Drugs in group D can potentially cause more harm than benefits.

2.2.5 Prevalence of cardiovascular drug use in older persons with dementia

Few studies have assessed cardiovascular drug use in persons with dementia (6,168–171). Most studies were carried out on community-dwelling people. The prevalence of cardiovascular drug use in community dwellers with dementia is high, varying from 70% to 80%, depending on the study population, region, study period, data source, definition, and methods used to assess cardiovascular drugs (6,168,169) (Table 4). In studies conducted in nursing homes, the prevalence of cardiovascular drug use in people with cognitive impairment was highest in people without cognitive impairment (90.3% in an Australian study (170) and 77.1% in a Swedish study (171)), whereas in people with cognitive impairment, the prevalence decreased by the stage of cognitive impairment. The prevalence was higher among those with mild cognitive impairment (81% and 72% in Australian and Swedish studies, respectively) than among those with severe cognitive impairment (62% and 42% in Australian and Swedish studies, respectively) (170,171) (Table 4).

Most studies have reported the use specifically in people with AD, and the prevalence of cardiovascular drug use ranged from 59% (168) to 83% (6). However, the time interval in measuring prevalence varied between studies, and some studies did not specify the applied time window. In addition, most studies assessed the prevalence of cardiovascular drug use only after the dementia diagnosis.

The definition of cardiovascular drugs in earlier studies varies in each study. For example, the study based on the Swedish Dementia Registry

defined cardiovascular drugs as including antihypertensives, anticoagulants, lipid-lowering drugs, antidiabetics, and anti-angina medication (168), while other studies included the entire C group of the ATC classification, including C04 (peripheral vasodilators) and C05 (vasoprotectives) but excluding anticoagulants that belong to ATC category B and antidiabetics from ATC class A (6,169).

None of the earlier studies examined the prevalence of cardiovascular drug use before dementia diagnosis nor changes in the prevalence before and after diagnosis.

Table 4. Prevalence of cardiovascular drug use in previous studies.

Author(s), country	Setting – Data source	Study population	Type of study	Years of data collection	Definition of cardiovascular drugs	Prevalence assessment of cardiovascular drug use	Prevalence of cardiovascular drug use
Community-dwelling with incident dementia							
Àvila-Castells et al., 2012 Spain (169)	Registry of Dementia of the Girona Study Group (ReDeGi), Catalonia/Spain	1,894 people newly diagnosed with dementia, 1,092 had AD	Cross-sectional study	Dementia diagnoses registered from 2007–2009	ATC Group C	Data were collected during the year participants were enrolled in the registry	79.4% in people with any dementia; 76.5% in people with AD
Cermakova et al. Sweden (168)	Swedish Dementia Register (SveDem)	19,743 people newly diagnosed with dementia, 8,139 had AD	Cross-sectional study	2007–2012	included antihypertensives, anticoagulants, lipid-lowering drugs, antidiabetics, and anti-angina medication	Point prevalence at the beginning of the diagnosis	70% in people with any dementia; 59% in people with AD

Author(s), country	Setting – Data source	Study population	Type of study	Years of data collection	Definition of cardiovascular drugs	Prevalence assessment of cardiovascular drug use	Prevalence of cardiovascular drug use
Jacob et al. Germany (6)	General practices The Disease Analyser database (MIS HEALTH)	9,225 people with dementia	Cross-sectional study	Jan–Dec 2015	ATC Group C	The type of prevalence was not described, but the prevalence was accessed after the dementia diagnosis	86.3% in people with any dementia; 83.1% in people with AD
Nursing home							
Liu et al. Australia (170)	17 nursing homes in 4 Australian states, Pharmaceutical Benefits Scheme (PBS) database	541 residents	Cross-sectional study	01/2015-02/2016	ATC Group C	Data were collected within 12 months near to enrolment period and after dementia diagnosis	81% in people with mild cognitive impairment; 73.2% in people with moderate cognitive impairment;, 62.0% in people with severe cognitive impairment

Author(s), country	Setting – Data source	Study population	Type of study	Years of data collection	Definition of cardiovascular drugs	Prevalence assessment of cardiovascular drug use	Prevalence of cardiovascular drug use
Svahn et al. Sweden (171)	Nursing homes in Västerbotten county in northern Sweden	2007: 2,494 people	Survey study	2007 and 2013	ATC Group C	Data were collected through questionnaires	67.3% in people with mild, 62.3% in people with moderate cognitive impairment;, 41.8% in people with severe cognitive impairment
		2013: 1654 people					72.4% in people with mild cognitive impairment; 54.4% in people with moderate cognitive impairment; 41.6% in people with severe cognitive impairment

Abbreviations: AD = Alzheimer's Disease, ATC= Anatomical Therapeutic Chemical

2.2.6 Statin use for primary and secondary prevention

- ***Statin use in primary prevention***

Several randomized controlled trials in persons with no clinically evident atherosclerotic cardiovascular disease or no history of myocardial infarction have also demonstrated the impact of statins in primary prevention of acute major coronary events (172–174). The efficacy of statins in primary prevention was consolidated through the Cochrane systematic review that summarized 18 clinical trials (174). The mean age of trial participants was approximately 57 years (ranging from 28–97 years), and a reduction in all-cause mortality, major vascular events, and revascularizations was observed in the statin-treated group compared to the placebo or usual care group. In addition, the meta-analysis did not observe differences in adverse events between statin users and the control group in general (risk ratio (RR) 1.00 (0.97–1.03) or specifically for myalgia and rhabdomyolysis (RR 1.03 (0.97-1.09)) (174).

However, the absolute risk reduction in statin use likely depends on individual characteristics such as age, sex, smoking status, cholesterol levels, blood pressure, and consequent risk of developing cardiovascular disease (175,176). Thus, the use of statins for primary prevention in older people has been controversial (175,177,178) due to the lack of evidence on benefits and whether the benefits of statins outweigh the harms in the aged population (176).

Various clinical trials have been carried out to assess the efficacy of statins in primary prevention in older adults. The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) (12), conducted in people with from 70–82 years without a history of vascular disease showed no difference in mortality due to coronary artery disease between pravastatin and placebo groups. A secondary analysis of the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) (age range 50–97) (11) conducted on people over 70 years old found no difference in all-cause mortality in people using rosuvastatin and those using a placebo. Similarly, the Lipid-Lowering Trial in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack

Trial (ALLHAT-LLT) (179) showed no significant reduction in all-cause mortality or coronary heart disease events in the population aged 65 years and older. Recently, a systematic review concluded that the efficacy of statins in primary prevention in people over 80 years old is uncertain (180).

On the other hand, another systematic review of 28 randomized controlled trials in people over 75 showed that statin therapy reduces the risk of major vascular events irrespective of age (178). However, the effect was smaller in persons older than 75, and due to the small number of studies on primary prevention in this age group, there is less direct evidence among older persons without coronary artery disease (178).

- ***Statin use in secondary prevention***

Many large randomized controlled studies have shown the efficacy of statins in the primary and secondary prevention of coronary heart disease. The Scandinavian Survival Study was the first study to demonstrate the effect of statins on reducing mortality in people with coronary heart disease (181). After that, the effect of statins on secondary prevention was proved in various clinical trials (182–184) and observational studies (185,186). Those studies assessed the effect on the reduction of mortality and morbidity in statin users with cardiovascular diseases such as coronary disease, occlusive arterial disease, and hypertension (182,183). A meta-analysis of 14 randomized trials conducted in adult persons with a wide age range (from 21 to 80) and different baseline risks (such as pre-existing coronary artery diseases, a history of diabetes, and a history of hypertension) showed the efficacy of statins in reducing the overall risk of major vascular events (187).

2.2.7 Prevalence of statin use in Finland

Statin use in Finland has increased over the years (7,8,188). In the report on Medicine Consumption in the Nordic Countries 1999–2003 and 2004–2008, statins were one of the most commonly used drugs in Finland (7,8). During 1995–2005, the prevalence of statin use increased from 7.8 to 88.9 per 1,000 inhabitants, and the incidence increased from 355 to 1772 per

100,000 people, with the largest increase among people aged 65–74 (188). However, from 2011 to 2015, the proportion of statin users in the whole population was around 11–12% (189). The proportion of statin users among people over 65 from 2008–2015 showed an increase from 37% in 2008 to over 40% in 2010 and then slightly decreased to around 38.5% in 2015 (190). In 2020, according to the Social Insurance Institution, 42.8% of people over 65 used statins (ATC code C10AA) (115).

2.2.8 Safety and adverse effects of statin use

Most of the RCTs reported no significant difference in adverse effects in statin users compared to a placebo (187,191,192). For example, in a meta-analysis of 14 clinical trials, a rhabdomyolysis event was reported among 0.023% of statin users and 0.015% of the control group, and the absolute 5-year excess risk in statin users was 0.01% (187). No difference in the absolute risk of myalgia in statin users compared to a placebo (risk difference/1000 patients = 2.7, 95% CI -3.2–8.7) was observed in another systematic review of 35 clinical trials (191). Meta-analysis of clinical trials to assess muscle-related adverse events in people over 65 did not show an increased risk of myopathy (OR 1.03 CI 0.91–1.18) or rhabdomyolysis (OR 2.93 CI 0.30–28.18) (193). However, the incidence of myalgia symptoms in clinical trials has been relatively low, which could be due to the exclusion of participants who had experienced previous muscle complaints or adverse effects due to statins (194).

Unlike the clinical trials summarized above, observational studies have reported a high risk of muscle symptoms (195–198). A cross-sectional study of people without arthritis described a higher prevalence of musculoskeletal pain, defined as pain in the neck, upper back, upper extremities, lower back, or lower extremities among statin users than among non-users (adjusted prevalence ratio of 1.33 (1.06–1.67)) (196), although causality cannot be inferred due to the cross-sectional design. A retrospective cohort study using the Military Health System Management Analysis and Reporting Tool showed a higher risk for all musculoskeletal diseases (OR 1.19 CI 1.08–1.30) and drug-associated musculoskeletal pain

(OR 1.09 Cl 1.02–1.18) in statin users during a 2-year follow-up (199). A self-controlled case series conducted on a large population of primary care patients examining the unintended risks and benefits of new statin use over a six-year period revealed a dose-dependent association between statin use and myopathy (199). The highest risk increase was observed during the first year after treatment initiation (HR in women 4.30 (2.98–6.21); men 9.96 (7.66–12.96)) (198). However, these observational studies may be limited by misclassification bias of outcomes, as diagnoses of muscle pain induced by statins were not validated (198,199).

2.2.9 Statin discontinuation in older people with and without dementia

Several studies have investigated statin discontinuation in people with and without dementia (Table 5). Note that in some studies (200–202) that assessed the rate of discontinuation among the general population, the proportion of discontinuers with dementia was extracted from the subgroup information (Table 5). The proportion and risk of statin discontinuation in people with dementia differ between studies. This variation stems from study settings (e.g. nursing home, community-dwelling), study population, time to assess discontinuation, definition of statin discontinuation, state of dementia, and duration of statin use. Major differences relate to study designs (prevalent versus new users) and duration of follow-up (less than 1 year vs more than 4 years). Studies conducted in a community-dwelling setting considered statin discontinuation as no statin refill in 90 or 180 days after the end of the drug supply (200,201,203,204). However, in an institutional setting, statin discontinuation was defined as no refill within 30 days after the estimated last dose of the statin prescription (205,206). The proportion of statin discontinuation was higher in studies restricted to new users (200,203,204) than in studies of prevalent users (202).

The risk of discontinuation differed in the duration of statin use. Among community-dwelling new users of statins, people with dementia were less likely to discontinue therapy than people without dementia during the one-

year follow-up in a study from the UK and during 4 years in a Danish study (200,201). In contrast, among community-dwelling long-term statin users (e.g. over 1 year in the UK population (200), over 3 years in an Australian study (203), and over 5 years in a Danish study (202)), people with dementia were more likely to discontinue statins than those without dementia.

There are only a few studies that have assessed whether statin discontinuation is different among those with primary vs secondary prevention indications among people with dementia (200). In the UK study, the proportion of new statin users with dementia who discontinued therapy was slightly higher in primary prevention (39.2%) than in secondary prevention (37.4%) (200).

Due to the small number of studies focusing on individuals diagnosed with dementia and the lack of studies that have assessed the discontinuation by different types of dementia, the risk of discontinuation in people with AD and whether the risk differed in primary and secondary prevention are still unknown.

Table 5. Statin discontinuation among persons with dementia in previous studies.

Author(s)/ Data source/ Country/ setting/ Year of data collection/ Age	**Study population (N)**	**Definition of statin discontinuation and follow-up period**	**Proportion/rate of discontinuation**	**Adjusted relative risk of discontinuation in persons with dementia [a]**
Population–based studies: new statin users in community				
Vinogradova et al. 2016 (200), Clinical Practice Research Datalink (CPRD), UK From Jan 2002 – Sep 2013 Range age: 25-84	**Primary prevention** General population 431,023 People with dementia 1629	***Statin discontinuation:*** No refill during the duration of the previous prescription plus 90 days ***Follow up time***: Median time for primary prevention was 137 weeks and secondary prevention was 182 weeks	**Primary prevention** General population 47.5% People with dementia 39.2%	Short-term use: HR 0.63 (0.56-0.71) Long-term use (> 1 year): HR 1.14 (1.03-1.26)
	Secondary prevention General population 139,314 People with dementia 116		**Secondary prevention** General population 41.4% People with dementia 37.4%	Short-term use: HR 0.71 (0.61-0.82) Long-term use: HR 1.22 (1.08-1.39)

Author(s)/ Data source/ Country/ setting/ Year of data collection/ Age	Study population (N)	Definition of statin discontinuation and follow-up period	Proportion/rate of discontinuation	Adjusted relative risk of discontinuation in persons with dementia [a]
Ofori-Asenso et al. 2018 (203), Pharmaceutical Benefits Scheme (PBS) which covers 10% random sample of the Australian population From Jan 2007 – June 2016 in people over 65	People with dementia 589 Did not include people without dementia	***Statin discontinuation:*** No refill during the duration of the previous prescription plus 90 days ***Follow up time***: 3 years	People with dementia 58.7%, rate 38.1/100 person-years	Not applicable
Ofori-Asenso et al. 2019, (204) PBS 10% random sample of Australians aged ≥ 65 years From Jan 2014 – Dec 2015 Mean age: 73.1 (SD 6.8)	General population 22 340 People with dementia 159	***Statin discontinuation:*** No statin coverage for 90 days or more ***Follow up time***: One year	General population * Concessional beneficiaries: 43.1% * General beneficiaries: 50.4% Population with dementia * Concessional beneficiaries: 42.8% * General beneficiaries: 53.9%	Not applicable

Author(s)/ Data source/ Country/ setting/ Year of data collection/ Age	**Study population (N)**	**Definition of statin discontinuation and follow-up period**	**Proportion/rate of discontinuation**	**Adjusted relative risk of discontinuation in persons with dementia [a]**
Thompson et al. 2019 (201) Danish registries /all Danish people aged ≥ 70 years From 2008 – 2012	General population * Early (<1 year): 83788 * 1-2 years: 70727 * 2-4 years: 56234 People with dementia * Early (<1 year): 1815 * 1-2 years: 1464 * 2-4 years: 965	***Statin discontinuation:*** No refill during the duration of the previous prescription plus 180 days ***Follow up time***: 4 years	General population * Early (<1 year): 13.1% * 1-2 years: 11.9% * 2-4 years: 13.3% Population with dementia * Early (<1 year): 9.6% * 1-2 years: 8.9% * 2-4 years: 12.2%	* Early (<1 year): OR 0.67 (0.54-0.82) * 1-2 years: OR 0.61 (0.48-0.77) * 2-4 years: OR 0.70 (0.54-0.90)
Long-term statin users in community				
Thompson et al. 2021, (202) Danish registries /all Danish people aged ≥ 70 years from 2011 – 2016	General population: 169038 statin users for 5 years or more People with dementia: 5161 statin users for 5 years or more	***Statin discontinuation:*** No refill during the duration of the previous prescription plus 180 days ***Follow up time***: 2014 – 2016	General population 19% Population with dementia 33.1%	OR 1.56 (1.42-1.71)

Author(s)/ Data source/ Country/ setting/ Year of data collection/ Age	Study population (N)	Definition of statin discontinuation and follow-up period	Proportion/rate of discontinuation	Adjusted relative risk of discontinuation in persons with dementia [a]
Nursing-home – prevalent statin users				
Mack et al 2020, (207) MDS 3.0 of nursing home assessment database, US, from 2015 – 2016. Residents aged ≥ 65 years and newly admitted to nursing homes for a non-skilled stay	General population 73247 People with dementia 18458	***Statin discontinuation:*** No refill within 30 days after nursing home admission ***Follow up time***: 30 days	General population 19.9% Population with dementia 18%	RR 0.98 (0.92-1.03)
Tjia et al 2014, (206) MDS 2.0 nursing home assessment database, US, from Jan 2007 – Dec 2008 Average age 83.1±7	People with dementia: 10212 with advanced dementia and 1,699 statin users Did not include people without dementia	***Statin discontinuation:*** No refill within 30 days after nursing home admission At least 90 days, mean follow-up time was 185 days, median follow-up time 163 days	Population with dementia 37.2%	Not applicable

[a]Reference: persons without dementia. Abbreviations: MDS Minimum Data Set, OR odds ratio, RR risk ratio, SD standard deviation

2.3 CORONARY ARTERY REVASCULARIZATION

According to the guidelines of the European Society of Cardiology (ESC) on myocardial revascularization (121) and the American Heart Association (AHA) on Coronary Artery Revascularization (208), invasive procedures can be considered if there is a high risk of myocardial infarction or if symptoms in persons with CAD cannot be controlled by medications. A person with stable CAD may also need revascularization due to the severity of symptoms, a prior history of heart failure, and the prevalence of left ventricular dysfunction (208). In addition, other comorbidities or considerations (including frailty, cognitive status, estimated life expectancy, and the severity of CAD) affect the treatment decision (121). The Finnish Guideline in Management of Acute Coronary Artery Disease (110) is in line with the current guidelines from ESC and AHA.

Obstruction of coronary arteries is assessed in angiography by catheterizing coronary arteries and injecting contrast dye (209). Revascularization can be performed as percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). PCI is preferred in persons with single or two-vessel disease, and CABG is mainly indicated for persons with more severe CAD (three-vessel disease, including left main and/or proximal left anterior descending coronary artery stenosis). In addition to the severity of coronary artery disease, the choice of revascularization type is based on coronary artery anatomy, technical aspects related to the procedure and comorbidities, bleeding risk associated with antithrombotic drugs required after PCI, compliance with treatment, and the patient's preference for treatment (110). The decision of elective coronary revascularization is based on the risk stratification and individual characteristics of the patient (122).

Early elective revascularization is recommended for people with unstable coronary artery disease who have signs of ischemia (208). The goal of revascularization treatment is to improve the patient's prognosis, prevent myocardial infarctions and relieve CAD symptoms, and improve functioning. A systematic review and meta-analysis of randomized clinical trials comparing any type of revascularization procedure to optimal

medical therapy in people with non-acute coronary artery disease showed lower mortality rate in revascularized persons during a median of 3-year follow-up (OR 0.74 95% CI 0.63-0.88) (210). However, the included participants in these clinical trials may have had more strict selection criteria than in normal clinical practice.

2.3.1 Percutaneous coronary intervention (PCI)

PCI was introduced by Gruentzig in 1977 and has become increasingly common in recent decades (211–213). A study of the trends of coronary revascularization types in Finland from 1994 to 2013 showed that the rates of PCIs have significantly increased, quadrupling between 1994 and 2013 (212) and nearly tripling from 2000 to 2015 (214) (Figure 4). Nowadays, people are usually discharged on the same day the procedure is performed.

The procedure opens the obstructed coronary arteries after the blockage has been localized with angiography. PCI can be performed in different ways, including balloon angioplasty, angioplasty with stent, rotational atherectomy, and impella-supported PCI (215). PCI is less invasive and has fewer contraindications than CABG, so it is preferred for frail people and if there is a higher risk of periprocedural events (208). On the other hand, re-revascularizations are also more likely after PCI than after CABG (216,217).

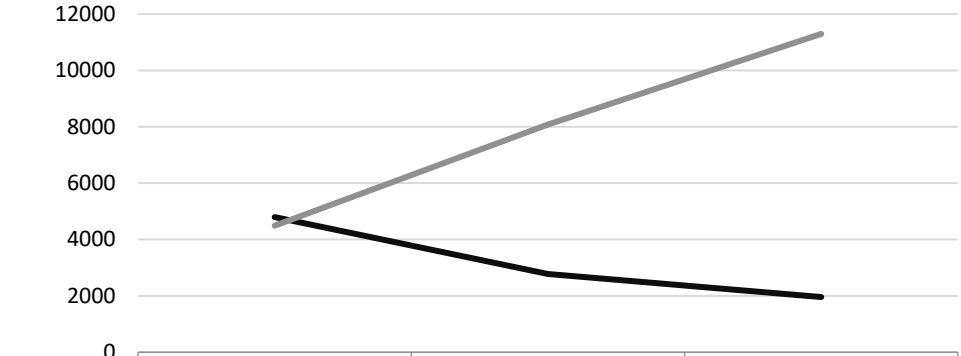
Based on a systematic review of outcomes of revascularization procedures in people over 80, those treated with PCI had shorter hospital stays and lower in-hospital and 30-day mortality, while the overall survival rate, defined as survival during the follow-up, was higher in those treated with CABG (218).

2.3.2 Coronary artery bypass grafting (CABG)

Coronary artery bypass grafting (CABG), an open chest surgery, was introduced earlier than PCI in 1968 and became the standard of care for symptomatic patients with coronary artery disease at that time. In CABG, autologous arteries or veins are used as grafts to bypass the obstructed

coronary arteries (219). Advanced age, frailty, obesity, poorly controlled diabetes or hypertension, and advanced kidney, pulmonary, and cerebral vascular disease are associated with risks and should be taken into account when making the treatment decision (220). Delirium and postoperative cognitive decline are concerns after CABG in older people, particularly in people with dementia. According to a meta-analysis, the risk of postoperative delirium is four times higher in persons with cognitive impairment (221). Therefore, CABG should be considered carefully in old people with dementia (15,222). However, there is a lack of studies on the long-term cognitive outcomes of revascularization procedures based on a systematic review (223).

In Finland, the number of CABG procedures has declined by more than 50% from 2000 to 2015 (214). People who have undergone CABG have to stay in hospital for a few days for follow-up and recovery. The length of postoperative hospital stay is usually 7–10 days. If necessary, rehabilitation is organized in a hospital closer to the patient's home 4 to 5 days after surgery (224).



	2000	2010	2015
CABG	4795	2775	1958
PCI	4490	8082	11297

CABG= Coronary Artery Bypass Grafting; PCI= Percutaneous Coronary Intervention

Figure 4. The number of coronary artery procedures in Finland in 2000, 2010, and 2015 (Source: Statistical Yearbook on Social Welfare and Health Care 2018 (214)).

2.3.3 Revascularization in persons with dementia/AD

Few studies have investigated the revascularization rates in persons with cognitive impairment, and most of these studies were restricted to persons who were hospitalized due to acute myocardial infarction (225–229).

Lower revascularization rates among persons with cognitive disorders were consistently shown in all previous studies (225–230) (Table 6). In a Finnish study of persons with clinically confirmed AD diagnoses and a matched comparison cohort, the rates of revascularization in people with AD and without AD were 4/10,000 and 32/10,000 person-years, respectively (230). This was the only study that was not restricted to an acute setting (as the study population was community-dwelling at the beginning of the follow-up) and people with coronary artery disease (230). On the other hand, in the previous studies restricted to an acute care setting, there was variation in the proportions of revascularized persons with dementia. The proportion of patients with AMI and dementia treated with PCI ranged between 4.1% in the US study (226) and 21.4% in the Taiwanese study (228). There was less variation in the proportion of patients with AMI and dementia treated with CABG (ranging from 0.5% (229) to 1.6% (226)).

Two studies investigated the outcomes after coronary procedures, including in-hospital mortality in people with dementia with acute myocardial infarction (225,227). Both studies observed lower in-hospital or short-term mortality rates in persons who underwent invasive procedures than in those who did not undergo the procedures (225,227). However, the follow-up in those studies was relatively short, not longer than 1 year. In a study based on the SveDem registry, 89% of people with dementia who underwent coronary angiography or PCI survived longer than 1 year, whereas only half (54%) of the people with dementia without procedures survived (HR 0.35 95% Cl 0.21–0.59) (227). In a US study, people with dementia and AMI who underwent PCI (OR 0.57 95% CI 0.47–0.70) or CABG (OR 0.22 95% CI 0.08–0.56) had a significantly lower risk of in-hospital mortality than those without PCI or CABG, respectively (225). To our

knowledge, there are no studies assessing the outcomes of elective revascularization or rates of elective revascularization in persons with AD.

Table 6. Summary of previous studies on revascularization procedures in people with dementia.

Authors/ Data source/ setting/ Year of data collection and follow-up period/ Country	**Study population**	**Mean age (SD)**	**Dementia diagnosis**	**Definition of invasive intervention**	**Proportion/rate to get revascularization**	
					Dementia/ AD	**No dementia/ AD**
Cermakova et al. (227), Swedish Dementia Registry (SveDem), from May 2007 – Dec 2012, Sweden.	525 people with dementia who had a record of AMI as main diagnosis and hospitalized due to AMI	82.4 (6.5)	clinical diagnosis of dementia	use of coronary angiography and/or PCI	PCI 16%	Not applicable
Tehrani et al.(225) Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project-National Inpatient Sample, in 2009, US.	631,734 people admission with a primary AMI diagnosis, of which 15,335 people had a secondary dementia diagnosis In-hospital period	People with dementia: 83.5 (7.7) People without dementia: 67.0 (14.4)	secondary diagnosis of dementia by ICD-9 (codes 290.10-290.13)	Cardiac catheterization , PCI, or CABG	PCI 12.7% CABG 1.4%	PCI 43.9%, CABG 9.3%

Authors/ Data source/ setting/ Year of data collection and follow-up period/ Country	Study population	Mean age (SD)	Dementia diagnosis	Definition of invasive intervention	Proportion/rate to get revascularization	
					Dementia/ AD	No dementia/ AD
Sloan et al. (226) The Cooperative cardiovascular project and The American Hospital Association's Annual Survey of Hospitals from Feb 1994 -July 1995, US.	129,092 people with a primary diagnosis of AMI: 5851 people with dementia and 123,241 people without dementia 1-year post-admission	People with dementia: 81.6 (6.9) People without dementia: 75.5 (7.0)	History of dementia was noted on the medical chart	coronary angioplasty, cardiac bypass surgery	Coronary angioplasty: 4.1%, Cardiac bypass surgery:1,6%	Coronary angioplasty: 14.7% Cardiac bypass surgery 8.7%
Tolppanen et al. (230), A register-based matched cohort study of persons with and without AD, alive from 31.12.2005-31.12.2009 (MEDALZ 2005), Finland	28 093 community-dwelling individuals with AD matched with 28 093 comparison persons from 2006-2009	People with dementia: 79.5 (6.9) People without dementia: 79.5 (6.9)	Based on special reimbursement criteria consistent with NINCDS-ADRDA, mild/moderate stage of DSM-IV	Angioplasties and bypass operations	4/10000 person-years	32/10000 person-years

Authors/ Data source/ setting/ Year of data collection and follow-up period/ Country	Study population	Mean age (SD)	Dementia diagnosis	Definition of invasive intervention	Proportion/rate to get revascularization	
					Dementia/ AD	No dementia/ AD
Lin et al. (228) Taiwan National Health Insurance Research Database (NHIRD), from Jan 2006-Dec 2007, Taiwan.	111347 people hospitalized due to ACS, 1835 people with dementia, and 3670 matched people without dementia	People with dementia: 79.1 (8.8) Matched people without dementia: 78.8 (9.3)	Dementia was defined based on ICD 9	PCI, CABG	Any: 22.4% PCI: 21.4% CABG: 1.1%	Any: 36.0% PCI: 33.2% CABG: 3.1%
Li et al. (229) Health Insurance Association in Fukuoka Prefecture, from April 1, 2013–March 31, 2019, Japan.	13593 people with dementia and hospitalized due to AMI, 8308 (61.12%) people with AD	84.9 (10.4)	Dementia was defined based on ICD 10	Use of PCI and CABG during the hospitalization for AMI	14.38% (1954) received invasive procedures, PCI: 14.03% (1907) CABG: 0.5% (68)	Not applicable

aHR = adjusted hazard ratio; ACS = acute coronary syndrome; AD=Alzheimer's disease; AMI = acute myocardial infarction; aOR = adjusted odds ratio; CABG = coronary artery bypass graft; PCI = Percutaneous Coronary Intervention; RR = risk ratio; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment-elevation myocardial infarction

3 AIMS OF THE STUDY

The purpose of this thesis was to investigate the use of cardiovascular drugs and postoperative outcomes of coronary artery revascularization procedures in persons with Alzheimer's disease. The specific aims of three sub-studies were to investigate:

– The change in the prevalence of cardiovascular drug use in persons with AD and without AD in relation to the AD diagnosis (Study I).
– Time to statin discontinuation and factors associated with statin discontinuation in persons with and without AD (Study II).
– The incidence of revascularization after AD diagnosis and post-procedural outcomes, including mortality and readmissions between persons with and without AD (Study III).

4 PARTICIPANTS AND METHODS

4.1 STUDY COHORT AND DATA SOURCES

4.1.1 Medication use and Alzheimer's disease (MEDALZ) study

All three studies in this thesis were conducted on the nationwide register-based Medication Use and Alzheimer's Disease (MEDALZ) study.
The MEDALZ study includes 70,718 community-dwelling residents of Finland who were diagnosed with AD in 2005–2011 (49) and matched comparison persons by age, sex, and hospital district. The age of people included in MEDALZ varies from 35 to 105, with a mean age of 80.1 years. The majority of study participants were women (65%).

Identification of persons with AD
People with AD were identified through the Special Reimbursement Register maintained by the Social Insurance Institution of Finland (SII). This register contains information on reimbursement for drugs for specific chronic diseases such as diabetes, several cardiovascular diseases, and Alzheimer's disease (231). The reimbursement for antidementia drugs (acetylcholinesterase inhibitors or memantine) was considered as a clinically confirmed AD diagnosis. People with dementia due to Parkinson's disease (ICD code G20 as the accompanying diagnosis code for reimbursement) were not included in the MEDALZ study.

To be eligible for reimbursement for acetylcholinesterase inhibitors or memantine for AD, people had to fulfil specific diagnostic criteria based on the NINCDS–ADRDA (National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association) and the fourth edition of DSM-IV criteria for AD (39,42). The SII criterion for reimbursement included a nontransient decrease in social capacity over a period of at least 3 months, symptoms consistent with AD, CT, or MRI, and exclusion of possible alternative diagnoses. The diagnosis had to be confirmed by a geriatrician or neurologist, and a medical

certificate including supporting evidence confirming the diagnosis was submitted to the SII where the applications were systematically reviewed by medical experts in cognitive disorders.

Identification of comparison cohort

Up to four matched comparison persons for each individual with AD were identified from the SII registers. The comparison persons had to fulfil these criteria: (1) alive and community-dwelling during the last day of the month when the case was diagnosed with AD (index date); (2) no special reimbursement for AD medication or acetylcholinesterase inhibitor or memantine purchases (ATC code N06D) before the index date and within the following 12 months. Matching criteria were age (+/- one year), sex, and hospital district at the date of AD diagnosis. In case the comparison persons got an AD diagnosis later, they were censored from the cohort at the date of AD diagnosis.

In the sub-studies of this thesis, each person in the AD cohort was matched with one comparison person (studies I and II) or up to four persons (Study III) without AD; the matching date is the index date.

Register linkage in the MEDALZ study

The MEDALZ study combines data from the Prescription Register, the Special Reimbursement Register, the Care Register for Health Care, and Statistics Finland. The register maintainers used a unique personal identity number (PIN) to link and retrieve the data, but all data were pseudonymized before submission to the research team. PINs have enabled linkage since 1972 (232).

The Special Reimbursement Register is maintained by SII, and data have been available since 1972. The register contains data on entitlement to special reimbursement due to chronic diseases. People diagnosed with AD between 2005 and 2011 were identified from this register. In addition, it was used to extract information on comorbid conditions from 1972 to 2015. Due to strict criteria to get special reimbursement, diagnoses of those diseases are based on explicit, predefined criteria.

The Prescription Register, maintained by SII, contains information on all Reimbursed drugs purchased since 1995 (233), including patient information (e.g. the patient's PIN), information on prescriber, data on the drug product, such as date of dispensing, Nordic article number (Vnr), the Anatomical Therapeutic Chemical (ATC) classification code, number of packages, strength, number of tablets, drug form, defined daily dose (DDD) dispensed, and costs. All medication dispensations reimbursed to community-dwelling residents of Finland are recorded, whilst non-reimbursable medication like over-the-counter medications and medication used in hospitals or public nursing homes are not included in this register. Data on cardiovascular drug use in studies I and II and statin use in Study III were extracted from this register data from 1995 to 2015.

The Care Register for Health Care is administrated by the Finnish National Institute for Health and Welfare THL (Finnish: Terveyden ja hyvinvoinnin laitos). The register contains information on hospital discharge (since 1969), specialized outpatient care (since 1998), and primary healthcare (since 2011). In the MEDALZ study, the hospital discharge and specialized healthcare outpatient visit data were used. This thesis used information on admission and discharge dates, diagnosis codes, procedure dates, and procedure codes, level of assistance required at discharge, place of discharge, and classification of the hospital (university/central/other, based on the service provider code). In addition, procedure-related data (procedure date, code, and electivity) were also obtained from the extra sheet of patients with advanced cardiac conditions. Procedures are coded according to the International Classification by Nordic Medico-Statistical Committee Classification (NOMESCO), defined by Nordic collaboration and used in Nordic countries since 1996/1997 (234). In addition, the extra sheet has its own classification system.

Statistics Finland is a public authority maintaining registers on causes of death and socioeconomic information collected from population censuses. Mortality and cause of death date in this thesis were updated until 31 Dec 2015. In addition, occupational social class was used as an indicator of socioeconomic position. The highest occupational social class was

categorized as ‘managerial/professional’, ‘office worker’, ‘farming/forestry’, ‘sales, industrial, cleaning’, and ‘unknown’. The summary of data sources, years of data extraction, and information is shown in Table 7.

Table 7. Summary of data sources used in studies.

National registers	**Register maintainer**	**Years of data**	**Information available**
Prescription Register	SII	1995–2015	Purchased reimbursed prescription drugs
Special Reimbursement Register	SII	1972–2015	Entitlement to special reimbursement due to chronic diseases such as Alzheimer’s disease, diabetes, and heart failure
Care Register for Health Care – data on discharge from care	THL	1972–2015	Data on hospital admissions, length of hospital stay, dates of care, and discharge diagnoses
Care Register for Health Care, including the extra sheet for patients with advanced cardiac condition	THL	1996–2015	Procedures in hospitals such as percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG), level of assistance required, place of discharge, and discharge diagnoses
Statistics Finland	Statistics Finland	2005–2015 1972–2012	Causes of death Data on occupational social class

4.2 STUDY DESIGNS

4.2.1 Study I – Prevalence of cardiovascular drug use

Population

In this study, the 70,718 persons with AD were matched with the 70,718 persons without AD by age (+/-1), sex, and hospital district. The prevalence of cardiovascular drug use was assessed in both cohorts during 10 years of follow-up – from five years before to five years after AD diagnosis.

Cardiovascular drugs

Cardiovascular drugs were identified from the Prescription Register with ATC codes C*, excluding C04 (peripheral vasodilators) and C05 (vasoprotectives). The categorization of drugs based on ATC codes is described in detail in Table 8. In drug class-specific analyses, the combination products that contain two or more active ingredients were counted as a use of each drug substance. For example, the combination product containing an ACE inhibitor and a diuretic (for example C09BA) was considered as a use of both an ACE inhibitor and a diuretic.

Table 8. Definitions for cardiovascular medication use in Study I.

Drug groups	**Anatomical Therapeutic Chemical (ATC) code**
Antiarrhythmic drugs	C01A (Cardiac glycosides) C01B (Antiarrhythmics)
Adrenergic and dopaminergic agents	C01CA (Adrenergic and dopaminergic agents)
Organic nitrates and combination products	C01DA (Organic nitrates)
Loop diuretics and combination products	C03CA (Sufonamides) C03EB (Low-ceiling diuretics and potassium-sparing agents)
Other diuretics and combination products	C02L (Antihypertensives and diuretics in combination) C03A (Low-ceiling diuretics, thiazides) C03B (Low-ceiling diuretics, excl. thiazides) C03D (Potassium-sparing agents) C03E (Diuretics and potassium-sparing agents in combination) C07BB (Beta blocking agents, selective, and thiazides) C09BA (ACE inhibitors and diuretics) C09DA (Angiotensin II receptor blockers (ARBs) and diuretics) C09DX (Angiotensin II receptor blockers (ARBs) and other combinations
Beta-blockers and combination products	C07 (Beta blocking agents)
Calcium channel blockers and combination products	C08 (Calcium channel blockers) C07FB (Calcium channel blockers and beta blocking agents) C09BB (Calcium channel blockers and ACE inhibitors) C09DB (Calcium channel blockers and angiotensin II receptor blockers) C09DX (Calcium channel blockers, angiotensin II receptor blockers, and diuretics)
ACE inhibitors and combination products	C09A (ACE inhibitors) C09B (Combination of ACE inhibitors) C09X (Other agents acting on the renin-angiotensin system)

Drug groups	Anatomical Therapeutic Chemical (ATC) code
ARBs and combination products	C09C (Angiotensin II receptor blockers) C09D (Combination of Angiotensin II receptor blockers)
Other antihypertensives	C02 (Antihypertensives)
Statins and combinations of statins and various lipid modifying agents	C10AA (HMG CoA reductase inhibitors) C10BA (Combinations of various lipid modifying agents)
Other lipid-lowering drugs	C10AB (Fibrates) C10AX (Other lipid modifying agents) C10BA (Combinations of various lipid modifying agents)
Any cardiovascular drug	ATC-code C* excluding C04, C05

Abbreviations: ACE=Angiotensin converting enzyme; ARB= Angiotensin II receptor blockers;

Modelling of duration of drug use

Information on drug use periods, i.e. when continuous drug use started and ended, is not recorded in the Prescription Register. Thus, cardiovascular drug use periods were constructed by utilizing the validated mathematical modelling method PRE2DUP for each specific drug for each person (235–237). The method is based on the modelling of each ATC code for each person by considering the purchased amount by the defined daily doses (DDDs), individual purchasing behaviour, stockpiling of drugs, and periods in hospital/institutional care when drugs are provided by the caring unit. The PRE2DUP model utilizes purchase data, hospital care periods, and expert-defined parameters controlling the joining of drug purchases. The parameters include the upper and lower limit for a daily dose, the longest allowed refill time length, the maximum duration of a single purchase, and the longest duration of continuous hospital stay. In a previous validation study, the method was accurate for cardiovascular drugs with nearly 90% agreement (235).

Outcome and study design

The prevalence of cardiovascular drug use was assessed in two-week assessment windows every six months and from five years before to five years after the date of AD diagnosis. People were censored at a specific time point if they were hospitalized for 10 days or more within that window. The follow-up ended on the date of death, five years after the index date, or the end of data linkage (December 31, 2015), whichever occurred first. In addition, persons in the non-AD group were censored at their AD diagnosis date if they received the diagnosis during the follow-up. The study design is shown in Figure 5.

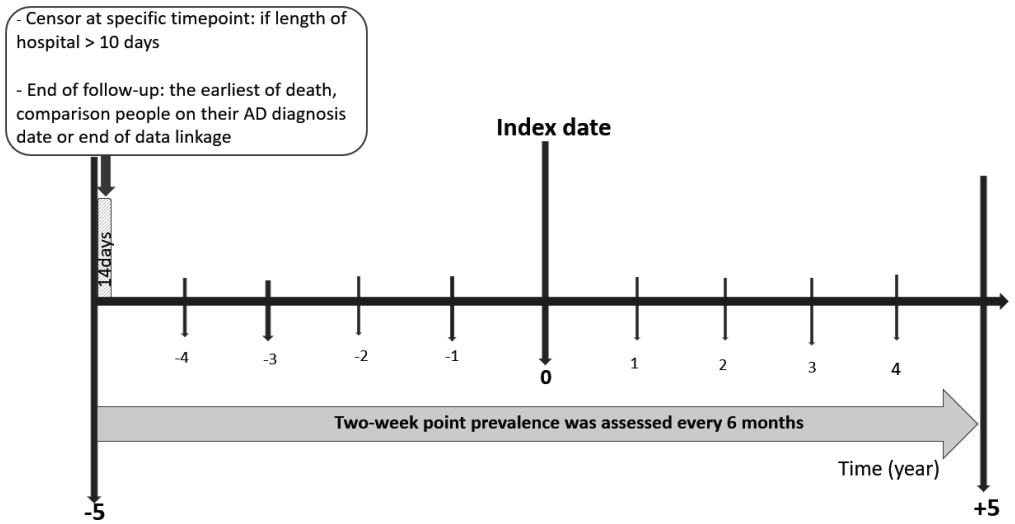


Figure 5. Study design for Study I.

4.2.2 Study II – Discontinuation of statin use

Study population

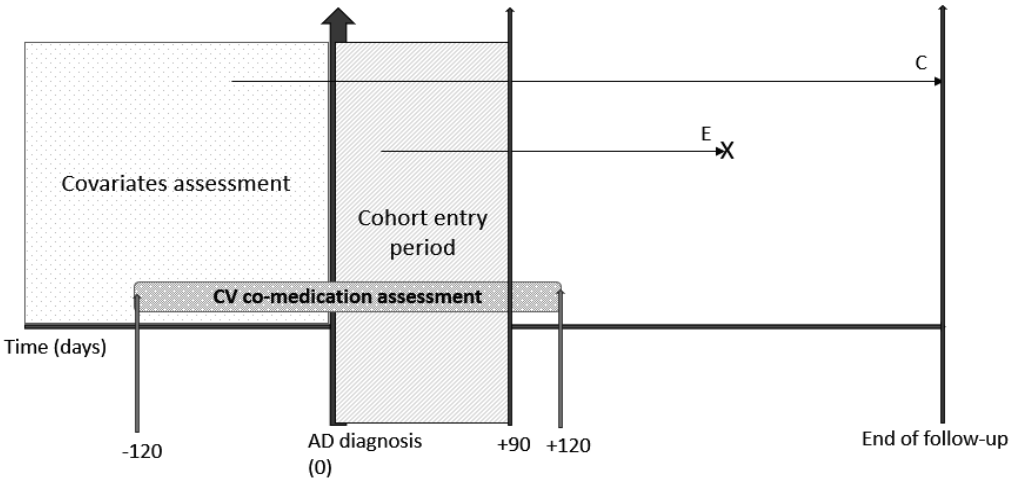
This study was restricted to the people who used statins on the index date (date of AD diagnosis) or initiated use within 90 days. Altogether, 25,137 statin users with AD (35.5% of the MEDALZ cohort) and 22,692 statin users without AD (32.1% of the MEDALZ comparison cohort) were included in the study.

Statin users

Statin users were identified from the Prescription Register with ATC code C10AA. We assumed that statins are used with one tablet per day. This was validated in a previous study that showed that the assumption of one tablet per day held for 97% of the population (238). In this study, the AdhereR package for R (239) was used to estimate the episodes of statin treatment. The AdhereR package calculates the duration of a treatment episode based on purchase dates, assumed or prescribed number of tablets per day, and an allowed gap (grace period) defined by the researcher. A grace period was used to deal with situations of non-perfect adherence, short-term hospitalization (when outpatient care drugs are not used, but drugs are provided by the caring unit), and other reasons causing a small variation in refill lengths. We applied a 120-day grace period in this study because in Finland the maximum length of dispensing is 90–100 days (240).

Outcomes and study design

Statin discontinuation was defined as not filling a statin prescription during the day's supply of the previous dispensing plus the grace period. The study design is shown in Figure 6. The statin users with and without AD were followed up from the cohort entry date to a maximum of 4 years to ensure that all people in the cohort had the same possible observation period. The cohort entry date was the date of the AD diagnosis or the statin initiation date for those who initiated within 90 days after the AD diagnosis. People were followed up until discontinuation of statin use, censored to death, over 60 straight days of hospitalization, end of follow-up (4 years or December 31, 2015), or the date when persons without AD were diagnosed with AD, whichever came first. Sensitivity analyses with a 90-day grace period, and censoring to 30-day hospitalization were conducted to evaluate whether the choices for length of grace period or hospital stay affect the discontinuation rates.



E: Event (statin discontinuation)
C: Censored at earliest of death, hospitalization, date when persons without AD were diagnosed with Alzheimer's disease, or end of data linkage/4 years
CV: Cardiovascular

Figure 6. Study design for Study II.

4.2.3 Study III – Coronary artery revascularizations and postoperative outcomes

Study population

The original MEDALZ study included 70,718 people with AD and 212,880 unique comparison persons without AD. This study evaluated incident coronary artery revascularization, and therefore, 4,538 people with AD and 18,640 people without AD who had been revascularized before the index date were excluded. In addition, those comparison people without AD (n=12,179) and people with AD (n=1894) who no longer had a matched pair were excluded. The postoperative outcomes were studied among 448 people with AD and 5,909 people without AD who underwent the revascularization procedure.

Identification of coronary revascularization procedures

The data on CABG and PCI procedures were extracted from the Care Register for Health Care (1996–2015), based on NOMESCO codes (234) of procedures and the extra sheet of cardiac patients. The information on

electivity was obtained from the extra sheet of cardiac patients, where it was recorded as 'emergency', 'elective, scheduled within one week', and 'elective, scheduled over one week ago'. People with missing data on electivity (23.2% and 18.4% of people with and without AD, respectively) were put into their own categories in the analyses.

The coding of those procedures follows the NOMESCO system: coronary artery bypass grafting (CABG) was identified as FNA, FNC, or FNE, and code AA in the extra sheet of the cardiac patient; percutaneous coronary intervention (PCI) cases were identified as NOMESCO codes FNG00, FNG10, FN1AT, FN1BT, FN1YT, FN2, or FN_2, and codes AN2, AN3, or AN4 in the extra sheet of the cardiac patient. In addition to these codes, ICD 10 codes Z95.1 and Z95.5 were used to identify persons who had been revascularized before the cohort entry (241).

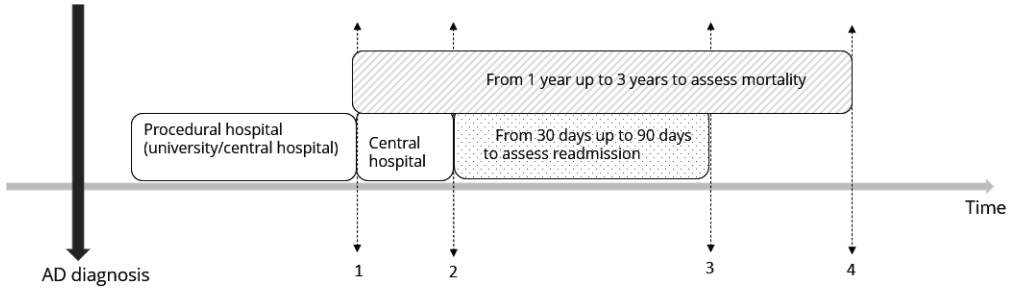
Postoperative outcomes and study design

The information on all-cause mortality during the one- and three-year follow-up was obtained from Statistics Finland. The 30- and 90-day readmissions to a central or university hospital were identified from the Care Register for Health Care. Both all-cause and coronary artery disease-related (ICD 10 codes I20–I25 and Z95.1 and Z95.5) readmissions were studied. In addition, the information on stays in a municipal hospital and social institution was extracted from the Care Register for Health Care and the Care Register for Social Welfare, respectively.

Typically, after the revascularization procedure, the patients stay in the procedural hospital (university/central hospital) for some days and are then moved to a central hospital to continue their recovery. Figure 7 shows the study design for postoperative outcomes. The follow-up for mortality began at discharge from the procedural unit and ended at death, end of follow-up (one or three years after discharge), or end of data linkage (December 31, 2015), whichever came first. In addition, persons in the non-AD group were censored at their AD diagnosis date if they received the diagnosis during the follow-up.

Similarly, to evaluate readmission risks, those people were followed after discharge from the period of care (discharge from central or university

hospital) until readmission, end of follow-up (30 or 90 days), death, end of data linkage (December 31, 2015), or AD diagnosis date for comparison people, whichever came first.



1: Date of discharge from university/central hospital

2: Date of discharge from central hospital (period of care)

3: Follow-up of readmission after discharge from central hospital within 30-and 90-day

4: Follow-up of mortality after discharge from procedural hospital with 1 and 3 years

Figure 7. Study design for Study III.

4.3 COVARIATES

Data on comorbidities were extracted from the Finnish registries including the Special Reimbursement Register, the Care Register of Health Care, and the Prescription Register. Data sources, time periods, and codes for comorbidities used in Studies I, II, and III are shown in Table 9.

In Studies I and II, the number of cardiovascular drug substances used was extracted from the Prescription Register data with ATC code C* (except C01C, C04, C05, and C10AA in Study II) and calculated by taking into account the actual number of drug substances from combination products.

In addition, in Study II, secondary prevention was defined by using ICD-10 codes for cardiovascular diseases, including coronary artery disease, coronary procedures (CABG or PCI), atherosclerosis of all arteries of the neck and brain including ischemic strokes. Primary prevention was defined as having no conditions defined as secondary prevention.

Table 9. Definitions of exposure/outcomes/comorbidities as covariates.

Comorbidities	Data source and codes used in data extraction	Time	Applied in study
Atrial fibrillation	Care Register for Health Care ICD-9: 4273A	1987-1995	I
	ICD-10: I48	1996-until AD diagnosis	I, II, III
Hypertension	Care Register for Health Care ICD-9: 401-405	1987-1995	I
	ICD-10: I10-I15	1996-2015	I, III
	Special Reimbursement Register code 205	1972-2015	I, III
Heart failure	Care Register for Health Care ICD-9: 4029B, 425, 428,	1987-1995	I
	ICD-10: I42, I43, I50, I110	1996- until AD diagnosis	I, II, III
	Special Reimbursement Register code 201	1972- until AD diagnosis	I, II, III
Stroke	Care Register for Health Care ICD-9 430-434, 438	1987-1995	I
	ICD-10 I60-I64, I69	1996- until AD diagnosis	I, II, III
Coronary artery disease	Care Register for Health Care ICD-9 410-414	1987-1995	I
	ICD-10 I20-I25	1996- until AD diagnosis	I, II, III
	Procedure codes from the Care Register for Health Care Sairaalaliitto 5311-5315, NOMESCO FNA, FNC, FNE, FNG00, FNG10, FN1AT, FN1BT, FN1YT)	1987-1995	I
	Special Reimbursement Register codes 206, 213, 280	1972- until AD diagnosis	I, II, III

Comorbidities	Data source and codes used in data extraction	Time	Applied in study
Diabetes	Special Reimbursement Register code 103	1972 – until AD diagnosis	I, II, III
	Prescription register ATC code A10, excluding guar gum (A10BX01)	1995 – until AD diagnosis	I, II, III

AD= Alzheimer's Disease; ATC= Anatomical Therapeutic Chemical; ICD: International Classification of Disease, NOMESCO=Nordic Medico-Statistical Committee

4.4 STATISTICAL ANALYSIS

Descriptive statistics were carried out in all studies using the mean, median, interquartile range (IQR), standard deviation (SD), and percentages. To compare characteristics between groups, we applied an independent samples T test for continuous variables with normal distribution, the Mann-Whitney U test or Kruskal-Wallis test for continuous variables with skewed distribution, and the chi-square test for categorical variables. The results were presented with 95% confidence intervals.

4.4.1 Study I: Prevalence of cardiovascular drug use

The prevalence of specific cardiovascular drug classes over time was evaluated only for those classes with a prevalence ≥10% on the index date. The generalized estimating equations (GEE) logistic regression model was applied to assess the longitudinal association between AD and the use of cardiovascular drugs. The GEE model is used in unbalanced panel data by fitting the population-averaged panel data model with the use of the unstructured correlation option (242,243). In this study, the imbalance was caused by the varying number of persons included at each time point due to exclusion/censoring criteria. The models also accounted for age, sex, time point, calendar year of AD diagnosis/matching date, and occupational social class.

4.4.2 Study II: Time to discontinuation and risk factors associated with statin discontinuation

The Cox regression was used to compare the risk of statin discontinuation and to assess factors related to statin discontinuation in persons with and without AD. The results were adjusted for age at cohort entry, sex, statin use before cohort entry, indication (primary/secondary prevention), sum of cardiovascular drug substances other than statin, diabetes, atrial fibrillation, heart failure, calendar year, and hospital district. The proportionality assumption was confirmed by Kaplan-Meier curves.

To assess factors associated with statin discontinuation, the same analyses were performed among persons with and without AD and stratified based on AD status, primary/secondary prevention, age at cohort entry, sex, comorbidities, number of cardiovascular drug substances, years of statin use before cohort entry, and calendar years.

Sensitivity analyses were performed to evaluate whether the length of the grace period and hospital stay would affect the main results. Thus, different lengths of the grace period (90 days) and hospital stay (30 days) were performed.

4.4.3 Study III: Incidence of revascularization and post-procedural outcomes

The Cox regression was applied to analyse the incident revascularization risk between people with and without AD after the date of AD diagnosis and adjusted for sociodemographic characteristics, comorbidities, and statin use.

Similarly, hazard ratios with 95% confidence intervals were used to compare the difference in postoperative outcomes, including mortality and readmission. The results were adjusted for sociodemographic characteristics, comorbidities, statin use, type of revascularization, length of stay in procedural unit or period of care, and level of assistance required at discharge. The models were performed in general for both types of revascularizations (PCI and CABG). Logistic regression was used to assess

whether electivity was associated with in-hospital mortality during the period of care.

To assess whether the risk of outcomes was different according to procedure type or electivity, the interaction between AD and procedure type or electivity was assessed, and stratified analyses by procedure type and electivity were performed. To check whether stays in municipal hospitals or nursing homes affected the readmission risk, interaction analyses were used between the stay in a municipal hospital or nursing home and AD.

All statistical analyses were performed using STATA 14 (Stata Corporation, College Station, TX, USA) software for all studies and the R 4.0 program (244) for Study II.

4.5 ETHICAL CONSIDERATIONS

All data were pseudonymized by the register maintainer before being sent to the research group, and the study participants were not contacted. Therefore, according to Finnish legislation, no ethics committee approval was required because only de-identified register-based data were used, and the study participants were not contacted. The study protocol for MEDALZ was approved by the register holders (SII, THL, and Statistics of Finland).

All the data related to the studies of this thesis were saved and handled in the local drive of the University of Eastern Finland (UEF). The MEDALZ study has its own disk space, which can be accessed only through the internal network of UEF. Researchers who have signed the non-disclosure agreement and have explicit permission from the principal investigator and register maintainers may access the data. Accessing the data can only be done with UEF credentials. Each login to the disk spaces where the data is stored is recorded in a separate log file.

All personal data were reported in aggregated form, and therefore individual study participants were not able to be identified.

5 RESULTS

5.1 STUDY I

5.1.1 General characteristics of the study population on the index date

Both cohorts included old people with an average age of approximately 80, and the majority were women (Table 10). On the date of AD diagnosis (index date), 49,574 (75.8%) people with AD and 50,878 (73.4%) people without AD used at least one cardiovascular drug. The majority of people in both cohorts had a hypertension diagnosis, and coronary artery disease was the second most common comorbidity (Table 10). As shown in Figure 8, there were no major differences in the prevalence of different cardiovascular drugs between people with and without AD on the index date. Beta-blockers were the most commonly used category in both AD and non-AD cohorts, followed by the renin-angiotensin system, diuretic groups, statins, calcium channel blockers, and nitrates. Antiarrhythmics were the least commonly used category in both cohorts.

Table 10. General characteristics of the study cohorts on the index date.

	Persons with AD (n = 65,423)	**Persons without AD** (n = 69,318)	**P-value**
Cohort characteristics			
Age (y), mean ±SD	79.92 ± 7.08	79.95 ± 7.08	0.44
Sex female % (n)	65.0 (42,497)	65.1 (45,128)	0.57
Socioeconomics – highest occupational social class, % (n)			
Managerial/Professional	21.1 (13,770)	21.6 (14,970)	<0.0001
Office worker	8.4 (5488)	8.4 (5833)	
Farming, forestry	19.2 (12,563)	19.5 (13,483)	
Sales, industrial, cleaning	42.4 (27,747)	38.9 (26,972)	

Unknown	8.9 (5855)	11.6 (8060)	
Number of concomitant cardiovascular drug substances, % (n)			
1	16.8 (11,008)	14.8 (10,257)	<0.0001
2	18.0 (11,761)	17.0 (11,803)	
3	17.3 (11,295)	17.0 (11,784)	
4	12.5 (8168)	12.6 (8707)	
5 or more	11.2 (7342)	12.0 (8327)	
Comorbidities, % (n)			
Hypertension	41.5 (27,159)	40.4 (28,033)	<0.0001
Coronary artery disease	29.0 (18,997)	26.4 (18,311)	<0.0001
Diabetes	18.1 (11,807)	15.1 (10,482)	<0.0001
Atrial fibrillation	15.4 (10,061)	12.9 (8921)	<0.0001
Chronic heart failure	13.3 (8698)	11.8 (8185)	<0.0001
Stroke	9.8 (6389)	8.0 (5567)	<0.0001

Abbreviations: AD=Alzheimer's disease; SD= Standard Deviation

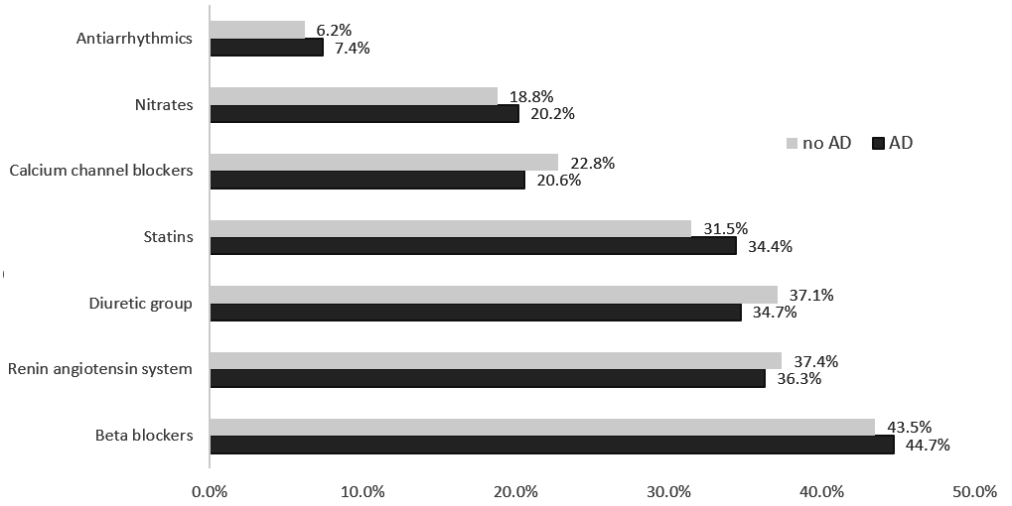


Figure 8. Prevalence of use of specific cardiovascular drug classes on the index date among persons with and without Alzheimer's disease (AD).

5.1.2 Prevalence of cardiovascular drug use before and after AD diagnosis

The change in the prevalence of any cardiovascular drug use during a 10-year follow-up is shown in Figure 9. In people with AD, the prevalence of cardiovascular drug use increased until six months after the index date and started to decline after that. In contrast, among persons without AD, the prevalence of cardiovascular drug use remained at the same level throughout the follow-up time. A similar trend was seen also in statin use, which started to decline after 1.5 years in people with AD (Figure 9-a). The prevalence of beta-blockers declined immediately after AD diagnosis, while a similar decrease was not observed for calcium channel blockers (Figure 9-b).

In the renin-angiotensin group, a similar trend was seen in the angiotensin-converting enzyme inhibitors (ACEi) sub-group and angiotensin II receptor blockers (ARBs), although the decline in the prevalence of ARBs was slower and occurred later than the decline in ACEi use (Figure 10-a). In the diuretics group, there was a distinctive increase in the prevalence of loop diuretics use during the follow-up time, while the prevalence trend in the group of other diuretics was similar to the general trend (Figure 10-b). The prevalence of nitrate use followed the general trend, with an increase before AD diagnosis and a decline immediately after the disease diagnosis among people with AD (Figure 10-c).

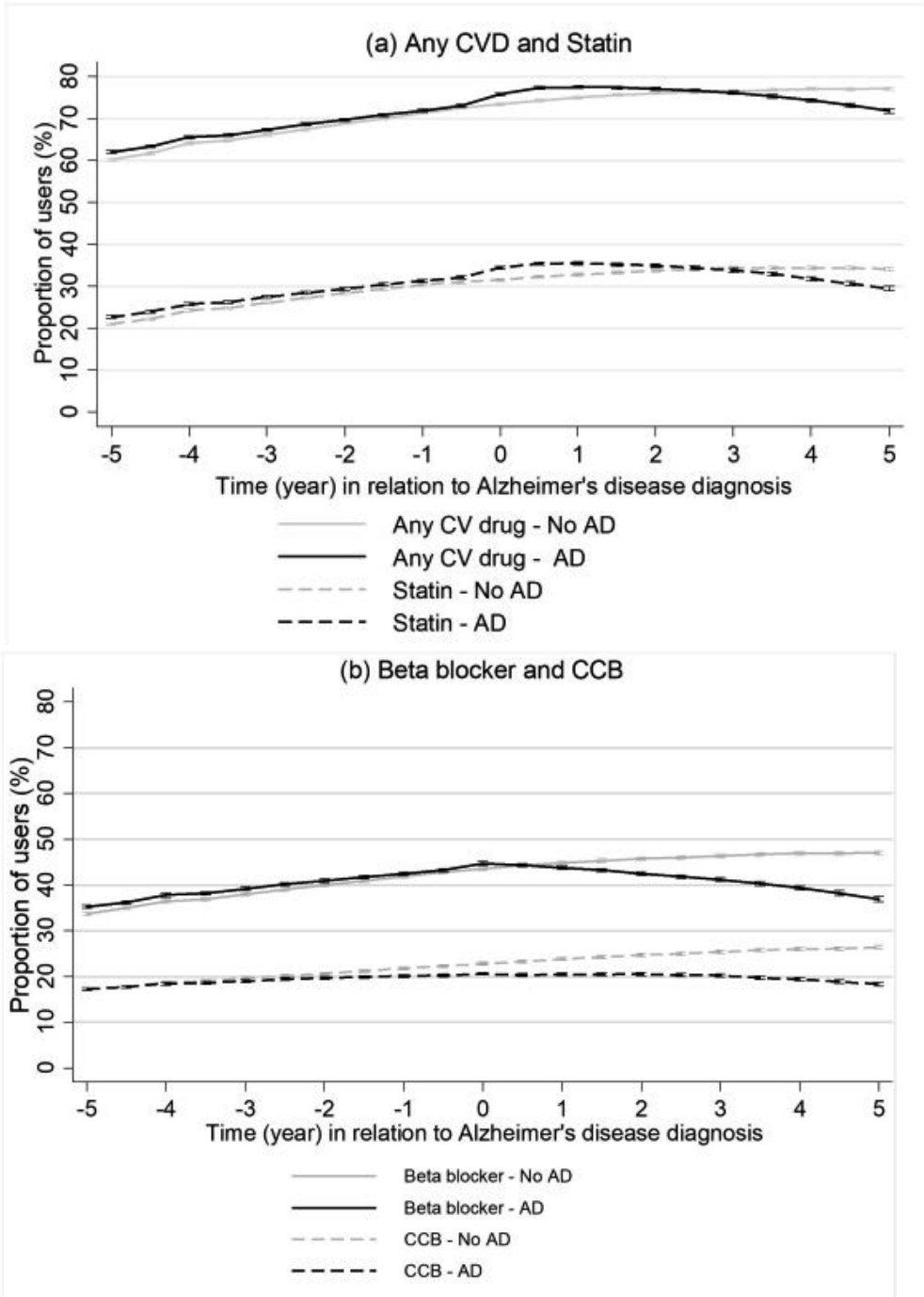


Figure 9. Prevalence of (a) any cardiovascular drug use and statin and (b) beta-blocker and calcium channel blocker in persons with and without Alzheimer's disease (AD) before and after AD diagnosis.

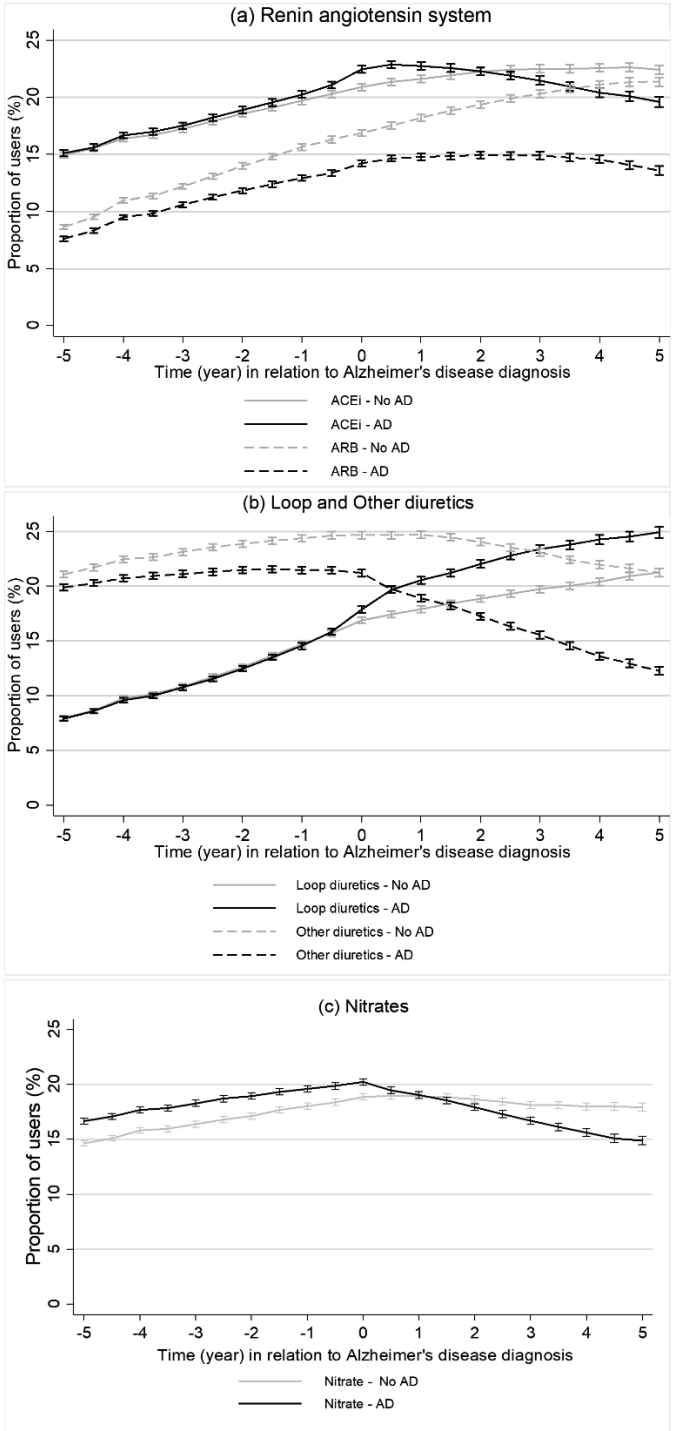


Figure 10. Prevalence of (a) renin-angiotensin system drugs, (b) diuretics, (c) nitrate use in persons with and without Alzheimer's disease (AD) before and after AD diagnosis.

5.2 STUDY II

5.2.1 General characteristics of the study cohort

Study II included 25,137 statin users with AD and 22,692 statin users without AD. Table 11 shows the characteristics of the study population, in which the mean age on cohort entry was approximately 79 years for both cohorts. The prevalence of comorbidities such as diabetes, atrial fibrillation, and chronic heart failure was higher in people with AD than in those without AD. During the 4-year follow-up, 9,931 (39.5%) people with AD and 7,880 (34.7%) of those without AD discontinued statin use. The median time to statin discontinuation was 1.46 and 1.36 years in persons with and without AD, respectively. Statin use for secondary prevention was more common in both persons with and without AD (54.7% vs 55.0% in persons with and without AD, respectively) than statin use for primary prevention. Most statin users in both cohorts had used statins before the cohort entry.

Table 11. General characteristics of the study cohorts on the cohort entry date.

	AD (N= 25137) (% (n))	**No AD (N= 22692) (% (n))**	**p-value**
Age in years at cohort entry (mean, SD)	79.1 (6.3)	79.3 (6.1)	<0.0001
<70	6.8 (1700)	6.1 (1386)	<0.0001
70–74	14.2 (3582)	13.4 (3053)	
75–79	27.9 (7011)	27.6 (6268)	
80–84	31.9 (8028)	33.5 (7596)	
≥85	19.1 (4816)	19.3 (4389)	
Sex (women) (%, (n))	63.7 (16,003)	63.8 (14,478)	0.752
Highest occupational social class before AD			<0.0001
Managerial/ Professional	21.6 (5424)	22.8 (5169)	
Office	8.5 (2146)	8.7 (1984)	

Farming/forestry	19.1 (4794)	19.8 (4502)	
Sales/industry/ cleaning	43.6 (10956)	41.2 (9353)	
Unknown	7.2 (1817)	7.5 (1684)	
Median (IQR) follow-up time (years)	2.72 (1.1–4.0)	4.0 (1.6–4.0)	
Reason for end of follow-up			<0.0001
Statin discontinuation	39.5 (9931)	34.7 (7880)	
End of follow-up	34.8 (8749)	51.4 (11663)	
Over 60 days of hospitalization	16.0 (4026)	4.3 (985)	
Death	9.7 (2431)	7.6 (1713)	
Persons without AD who received an AD diagnosis	0	2.0 (451)	
Median (IQR) time to discontinuation (years)	1.46 (0.5- 2.5)	1.36 (0.5-2.6)	0.009
Number of other cardiovascular drug substances than statin			<0.0001
0	15.5 (3888)	12.2 (2765)	
1–2	42.7 (10,734)	39.5 (8974)	
3–4	32.9 (8266)	36.9 (8365)	
5 or more	8.9 (2249)	11.4 (2588)	
Comorbidities			
Diabetes	27.4 (6892)	24.2 (5489)	<0.0001
Atrial fibrillation	19.2 (4831)	17.5 (3964)	<0.0001
Chronic heart failure	16.5 (4141)	15.5 (3510)	0.003
Primary/Secondary prevention			<0.56
Primary prevention	45.2 (11,369)	45.0 (10,203)	
Secondary prevention	54.7 (13,768)	55.0 (12,489)	
Ischemic coronary artery diseases and PCI/CABG	47.8 (12,006)	49.1 (11,135)	
Ischemic strokes, atherosclerosis of neck, and brain arteries	14.5 (3648)	12.5 (2839)	
Duration of statin use before cohort entry (years)			<0.0001
0	7.9 (1977)	5.0 (1131)	
1–3	38.4 (9653)	33.8 (7677)	

4–6	20.3 (5095)	23.5 (5338)	
7–10	20.0 (5038)	23.1 (5233)	
>10	13.4 (3374)	14.6 (3313)	

Abbreviations: AD=Alzheimer's disease; CABG= Coronary Artery Bypass Grafting; IQR= Interquartile range; PCI= Percutaneous Coronary Intervention; SD= Standard Deviation

5.2.2 Rates of statin discontinuation in persons with and without AD

The relative risk of discontinuation was 20% higher in people with AD than in people without AD for the entire study population (adjusted hazard ratio (aHR) 1.20, 95% CI 1.18–1.24). The higher discontinuation rate among people with AD was also observed among those with primary prevention (aHR 1.11, 1.06–1.16) or secondary prevention (aHR 1.30, 1.25–1.35). Similar results were observed with sensitivity analyses that censored at 30-day hospitalization or used a 90-day grace period (Figure 11).

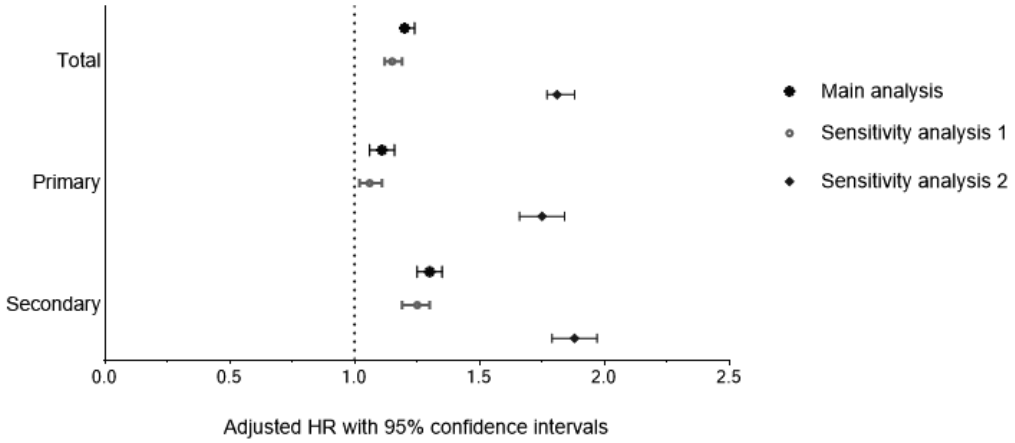


Figure 11: Relative risk of statin discontinuation in people with AD. Results are presented with main analysis (120-day grace period and censoring to >60 days of hospital care), sensitivity analysis 1 (120-day grace period and censoring to >30 days hospital care), and sensitivity analysis 2 (90-day grace period and censoring to >60 days of hospital care). HR: hazard ratio.

The same factors were associated with statin discontinuation in persons with and without AD. Discontinuation was more common among women

and those with more advanced age. People who used more other cardiovascular drugs or had a longer duration of statin use before the cohort entry were less likely to discontinue the statin therapy (Figure 12).

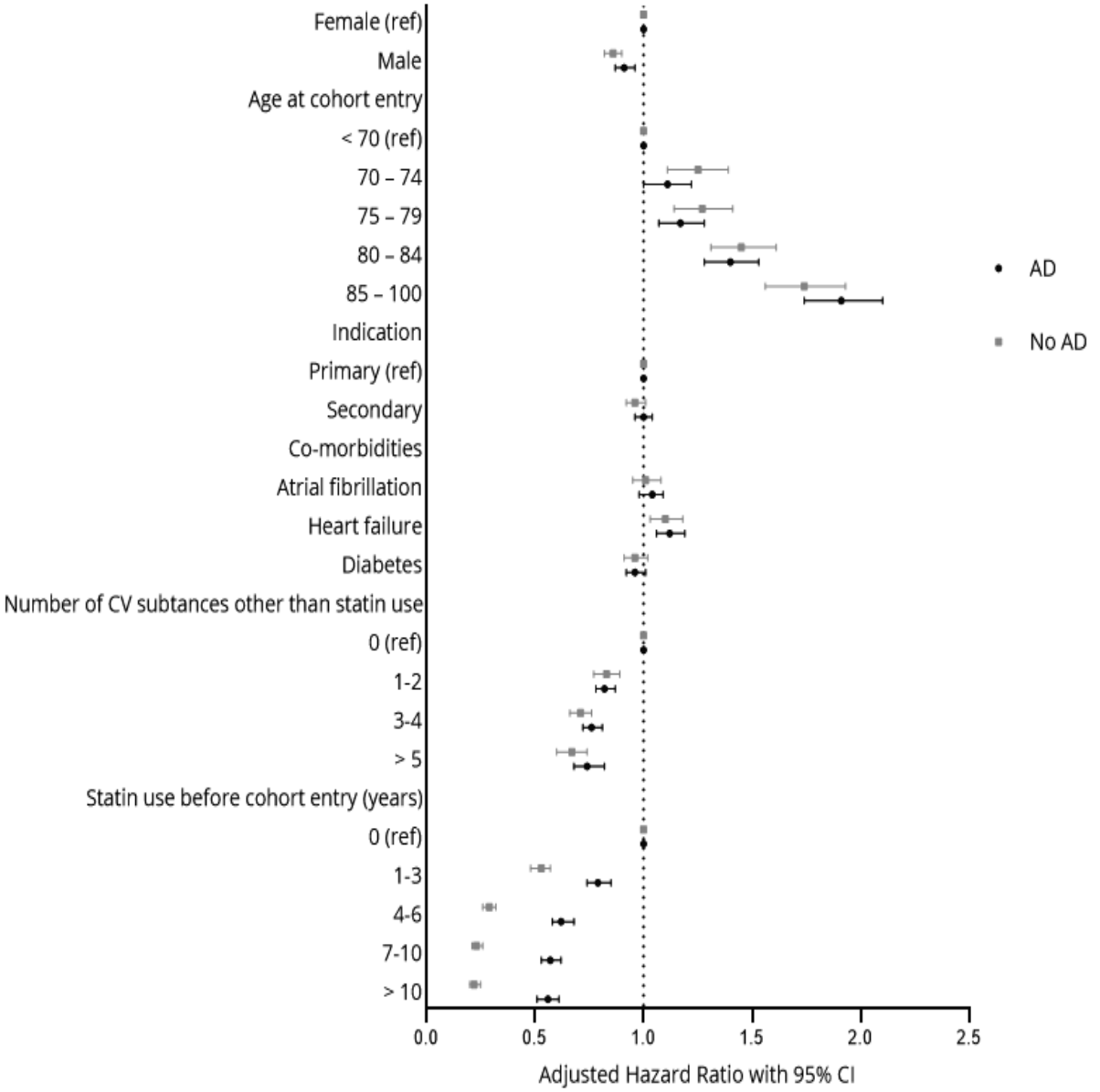


Figure 12. Adjusted hazard ratios of factors associated with statin discontinuation among persons with and without Alzheimer's disease (AD). CI: confidence interval

5.3 STUDY III

5.3.1 General characteristics of the study cohort

The characteristics of people with and without AD according to revascularization status are shown in Table 12. Altogether, 448 persons with AD and 5,909 without AD had incident revascularization after the index date. In both people with AD and without AD, those who got revascularization were younger and more likely to be men than those who were not treated with revascularization. Hypertension was the most common comorbidity in both revascularized and non-revascularized persons.

Table 12. General characteristics of people with and without AD in Study III according to revascularization status.

	AD (n=64,286)			No AD (n=182,061)		
	Revascularization			Revascularization		
	Yes (n= 448)	No (n= 63,838)	P value	Yes (n= 5909)	No (n= 176,152)	P value
Age at AD diagnosis (mean, SD)	77.5 (6.1)	80.0 (7.2)	<0.0001	77.0 (6.1)	79.2 (7.7)	<0.0001
Sex, women (%, (n))	44.6 (200)	66.9 (42,753)	<0.0001	48.0 (2836)	67.6 (119,098)	<0.0001
Age at revascularization (mean, SD)	80.0 (6.2)	NA		80.4 (6.1)	NA	
Average time to revascularization (median, IQR) years	2.0 (0.8 – 3.8)	NA		3.0 (1.4–5.1)	NA	
Highest occupational social class before AD (%, (n))						
Managerial/Professional	23.2 (104)	20.6 (13,288)	<0.0001	24.5 (1445)	22.5 (39,543)	<0.0001
Office	5.4 (24)	8.7 (5531)		7.2 (427)	8.8 (15,558)	
Farming/forestry	16.9 (76)	18.7 (11,911)		21.3 (1256)	18.5 (32,611)	
Sales/industry/cleaning	50.4 (226)	42.5 (27,115)		42.4 (2505)	38.6 (68,048)	
Unknown	4.11 (18)	9.5 (5993)		4.7 (276)	11.6 (20,392)	
Comorbidities (%, (n))						
Hypertension	44.6 (200)	42.5 (27,159)	0.371	43.9 (2594)	40.6 (71,440)	<0.0001
Atrial fibrillation	13.2 (59)	16.5 (10,529)	0.059	10.1 (598)	13.4 (23,538)	<0.0001
Heart failure	12.0 (54)	13.7 (8778)	0.299	8.5 (505)	12.0 (21,076)	<0.0001
Stroke	10.7 (48)	10.2 (6518)	0.726	5.5 (327)	7.8 (13,768)	<0.0001
Diabetes	21.4 (96)	12.4 (7916)	<0.0001	14.4 (848)	10.5 (18,563)	<0.0001
Statin use[a]	48.6 (218)	34.2 (21,820)	<0.0001	41.8 (2468)	31.4 (55,228)	<0.0001
Anticholinesterase use[a]	81.0 (363)	77.4 (49,394)	0.065	NA	NA	

[a]One year before the index date. Abbreviations: AD=Alzheimer's disease; SD = standard deviation, IQR = interquartile range

5.3.2 Incidence of revascularization

The revascularization rate was lower in people with AD (14.1/10,000 person-years) than those without AD (58.9/10,000 person-years). People with AD were 76% less likely to be revascularized than people without AD after adjusting for sociodemographic characteristics, comorbidities, and statin use (aHR 0.24, 95% CI 0.22–0.27).

PCI was more common than CABG in both groups (92.4% vs 7.6% in people with AD; 77.8% vs 22.2% in people without AD) (Table 13). The median length of stay in the procedural unit and period of care was shorter in people with and without AD. People with AD needed more assistance after discharge from the procedural unit as well as hospital than people without AD.

People with AD were more likely to have emergency procedures than those without AD (Figure 13).

Table 13. Comparison of characteristics of revascularized persons in AD and non-AD cohorts.

	AD (N = 448)	**No AD (N = 5909)**	**P value**
Type of revascularization (%,n)			<0.0001
PCI	92.4 (414)	77.8 (4599)	
CABG	7.6 (34)	22.2 (1310)	
At the discharge from the procedural unit			
	AD (N = 415)	No AD (N = 5 644)	
Length of stay (median, IQR)	3 (1–6)	4 (1–7)	0.03
Level of assistance required, % (n)			<0.0001
Independent/nearly independent	27.7 (114)	41.1 (2315)	
Intermittent need	28.9 (120)	21.9 (1232)	
Recurrent need	19.4 (79)	15.6 (882)	
Nearly continuous	5.8 (24)	4.0 (223)	

Continuous	7.2 (30)	4.7 (264)	
Data missing	11.6 (48)	12.9 (728)	
At discharge from period of care (university/central hospital)			
	AD (N = 415)	No AD (N = 5630)	
Total length of stay (median, IQR)	3 (1–6)	4 (1–7)	0.006
Level of assistance required, % (n)			<0.0001
Independent/nearly independent	27.0 (112)	42.7 (2402)	
Intermittent need	29.4 (122)	22.0 (1237)	
Recurrent need	19.3 (80)	15.1 (851)	
Nearly continuous	24 (5.8)	3.7 (206)	
Continuous	7.2 (30)	4.3 (244)	
Data missing	11.3 (47)	12.3 (690)	

Abbreviations: AD=Alzheimer's disease; IQR = interquartile range

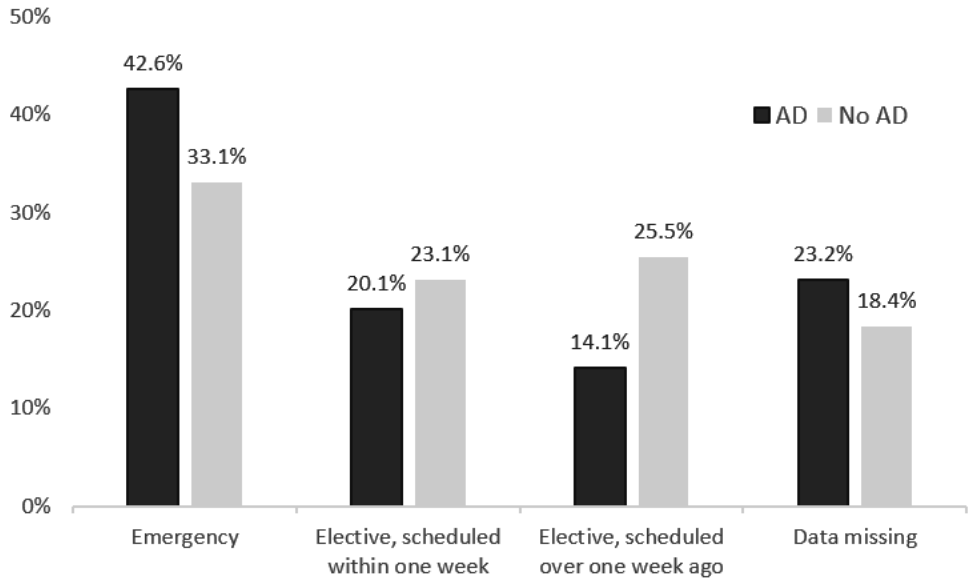


Figure 13: Proportion of elective and emergency revascularizations in total of all procedures in people with and without Alzheimer's disease (AD).

5.3.3 Postoperative outcomes

Inpatient, 1-year and 3-year mortality

People with AD had higher mortality during the period of care that includes the procedural unit and the continuing hospital care than those without AD (7.4% vs 4.5% in people with and without AD, respectively) (Figure 14).

There was no difference in one-year mortality in people with AD compared to those without AD (aHR 1.04, 95% CI 0.75–1.42) when all revascularizations were considered (elective or emergency) (Figure 15), but higher three-year mortality (aHR 1.42, 95% CI 1.15–1.74) was observed in people with AD. Similarly, for emergency procedures and those with missing data on electivity, an increased risk of three-year mortality was observed among people with AD. There was no difference in three-year mortality after an elective procedure.

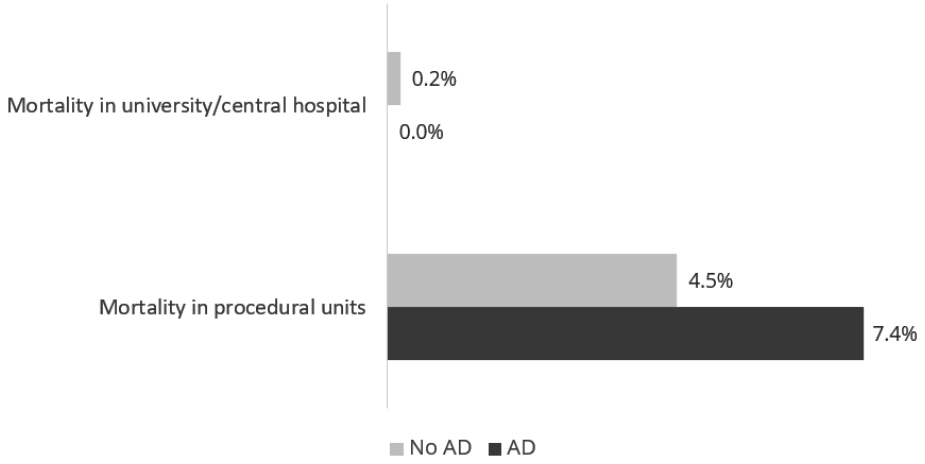


Figure 14: Proportion of mortality in the period of care in people with and without Alzheimer's disease (AD).

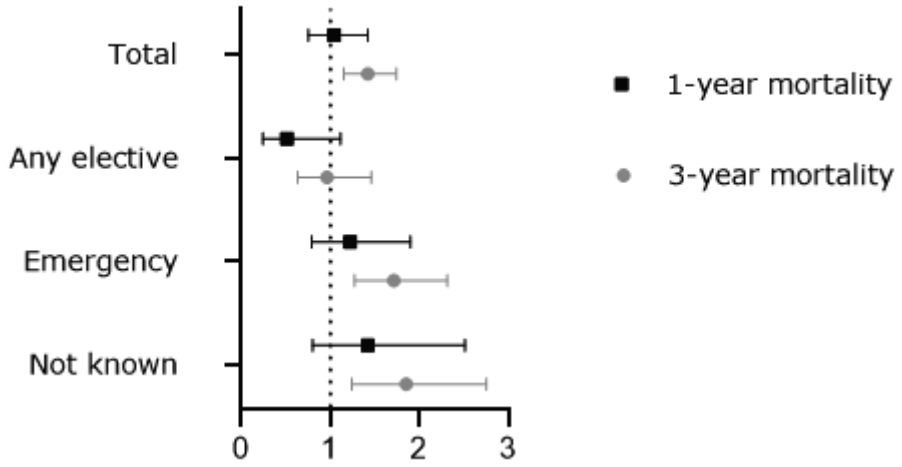


Figure 15. Association of Alzheimer's disease with 1-year and 3-year mortality stratified by electivity status of the operation.

30- and 90-day hospital readmission

There was no difference in all-cause 30-day readmission risk (aHR=0.97 95% CI 0.80–1.16) or coronary artery disease-related 30-day readmissions (aHR=0.74, 95% CI 0.50–1.08) between persons with and without AD. However, people with AD had lower risk all-cause 90-day readmission than people without AD (aH=0.85, 95% CI 0.74–0.98) and 90-day readmissions due to coronary artery disease (aHR=0.58, 95% CI 0.44–0.78) (Figure 16).

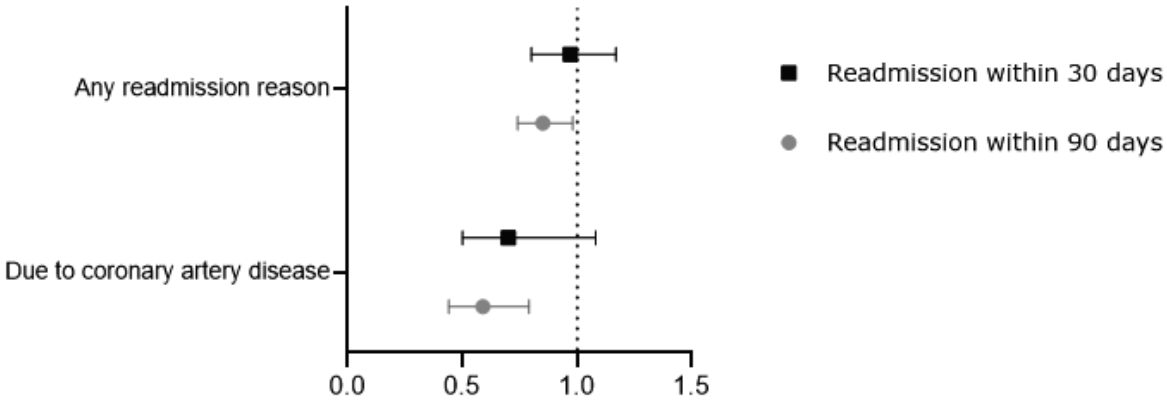


Figure 16. Risk of readmission within 30 days and 90 days among persons with Alzheimer's disease (AD) compared to persons without AD.

6 DISCUSSION

In summary, the prevalence of cardiovascular drug use in people with AD was higher than among people without AD before the diagnosis. However, after an AD diagnosis, the prevalence of cardiovascular drug use began to decrease among people with AD, and statin discontinuation was more common in people with AD than those without AD regardless of the indication of statin use. Revascularization procedures were less common in people with AD than in those without AD. There was no evidence for a higher rate of readmission or mortality outcomes after elective procedures in persons with AD, although higher three-year mortality was observed after nonelective procedures.

6.1 PREVALENCE OF CARDIOVASCULAR DRUG USE

Approximately three-quarters of the AD and non-AD cohorts used cardiovascular drugs at the time of AD diagnosis. The result is in line with the Spanish study (76.5%) but higher than in the Swedish study (59%) and lower than in the German (83.1%) study (6,168,169). The similarity in the prevalence of cardiovascular drug use among persons with AD in Study I (MEDALZ cohort) and the Spanish study (ReDeGi cohort) may be explained by the similar distribution of the AD stage at the time of disease diagnosis, as the majority of both study populations were in the mild or moderate stage (169). In addition, the age at AD diagnosis was comparable in both cohorts (average age was 79.8 in the Spanish study and 79.9 in Study I), while the age at AD diagnosis was slightly lower in the SveDem study (77.7) (168). There were, however, some differences between Study I and the others, for example, in the definition of cardiovascular drugs. The German, Swedish (SveDem cohort), and Spanish studies (6,168,169) also included peripheral vasodilators (C04) and vasoprotectives (C05) that were excluded from Study I, which may explain the lower prevalence in Study I than in the German study (6). Furthermore, the time point when the prevalence of

cardiovascular drug use was assessed was unclear in the German study, while the prevalence in Study I was assessed at the time of AD diagnosis. Moreover, the difference in the categorization of AD between MEDALZ and previous studies could also potentially explain the difference from the AD group in SveDem (245). That study had separated persons with AD into two groups (AD and mixed AD), whereas no such categorization was applied for MEDALZ, which includes persons with AD as the main reason for cognitive disorder. But they can also have symptoms or findings of another cognitive disorder (Lewy-body dementia, vascular dementia), as in most older adults, cognitive disorder includes symptoms or findings of several neurodegenerative disorders (25). The prevalence of cardiovascular drug use in the mixed dementia group in SveDem was 76.9%, which is close to that observed in Study I.

Study I and the Swedish study (168) also used a different information source to assess cardiovascular drug use. The cardiovascular drug use in the Swedish study appears to be based on a self-report, and approximately 8% of the study population was excluded due to missing information on cardiovascular drug use. Consequently, there was a possibility of recall and selection biases. Therefore, although the Swedish study had a broader definition of cardiovascular drugs (e.g. including also anticoagulants and antidiabetics), the lower prevalence of cardiovascular drugs compared to Study I could be due to the stricter definition of AD, a somewhat younger population at AD diagnosis (77.7 vs 79.8 years in Study I), and the possibility of missing data in the SveDem.

Study I provided new insights into the changes in cardiovascular drug use before and after AD diagnosis, whereas previous studies reported only one cross-sectional prevalence. The increasing prevalence of cardiovascular drug use in people with and without AD before the index date (AD diagnosis) could reflect the accumulation of cardiovascular diseases by ageing (246). However, after AD diagnosis, there was a notable decline in the prevalence of cardiovascular drug use among people with AD, whereas a slightly continued increase was observed among those without AD. It is possible that the decline in the prevalence of cardiovascular drug use among people with AD could be due to changes

related to the progression of AD, such as weight loss, malnutrition, and frailty (247–249). As a consequence, those changes could lead to a lowering of blood pressure (250–252), which may explain the declining prevalence of drugs used to treat high blood pressure, such as CCBs, ACE inhibitors, ARBs, and diuretics. In a recent study among older persons aged 80–89 years or with severe frailty antihypertensives were associated with increased risk of increased risk of hospitalization or death from falls compared to nonuse of antihypertensives (249). The authors concluded that among older people and those with moderate or severe frailty, the absolute risk of harm was close to the likelihood of benefiting from antihypertensive treatment. Therefore, it is possible that concerns about adverse effects led to deprescribing antihypertensive drugs in people with AD.

In addition, the initiation of treatment with acetylcholinesterase inhibitors (AChEIs) after the AD diagnosis could lead to a lowering of the dose or discontinuation of beta-blockers, as concomitant use of beta-blockers with AChEIs could lead to bradycardia (253). In Finland, a clinical examination and electrocardiogram (ECG) are conducted to identify possible bradycardia before starting AChEIs and after a short period of use. In the case of sick sinus syndrome, a pacemaker has to be installed before AChEI therapy can be started.

While the prevalence of most cardiovascular drug classes declined, the use of loop diuretics increased in both people with and without AD during the study period and even after AD diagnosis. This could be explained by the age-related decrease in renal function and the increase in the prevalence of heart failure with age in older people (254).

A noteworthy decrease in the prevalence of cardiovascular drug use after AD diagnosis could be due to the progress of AD to the severe stage during the study period. As a consequence, clinicians could deprescribe cardiovascular drugs due to shifting the focus to palliative care and emphasizing the quality of life (255,256). The treatment must always be personalized to the needs and preferences of each individual (255,257).

The inverse association between the stage of cognitive impairment and cardiovascular drug use was also reported in people living in nursing

homes (9, 174). In an Australian study, the prevalence of cardiovascular drug use in persons with the mild stage of dementia was 81%, and it decreased to 62% in the severe stage (170). In a Swedish study, the prevalence of cardiovascular drug use was 72.4% in mild dementia and 41.6% in severe dementia (171).

6.2 STATIN DISCONTINUATION IN PEOPLE WITH AND WITHOUT AD

Nearly two-fifths of people with AD discontinued statin therapy, whereas the proportion of discontinuation was over one-third among people without AD during the four-year study period. The proportion of statin discontinuation in previous studies varied widely and depended on study design. The proportions were higher in new-user studies where discontinuation ranged from 23% to 59% (200,201,203,204) than among prevalent users with dementia (33%) (202). Study II included both prevalent users, who comprised the majority of the study population, and incident users who started statin within 90 days after AD diagnosis. Thus, comparing the proportion of statin discontinuation in Study II with other studies is not feasible. In addition, it should be noted that most of the previous studies (200–202,204) focused on statin discontinuation in the general older population, the subgroups of people with dementia were relatively small, and the definition of cognitive disorder varied between studies.

In Study II, the likelihood of statin discontinuation began to increase in people 75 and was highest in people over 85 compared to people under 70 in both cohorts. This finding is in line with other studies (201,202,204). Statin discontinuation occurs commonly in the oldest people, regardless of their dementia status. The higher discontinuation rates are likely a result of various factors, including deprescribing and discontinuation for other reasons. Deprescribing may happen due to shifting the treatment to palliative care in patients with advanced-stage dementia (206,258). In addition, older people could be more sensitive to statin-associated muscle symptoms (259–261). A survey among current and former statin users in

the US among the adult population (mean age 61 years) showed that muscle-related adverse effects contributed up to 62% of the reason for discontinuation (262). Concerns or experienced adverse effects were the main reasons for statin discontinuation also in a Finnish study, with a higher rate of adverse effects reported by former users than current users (77% and 28%, respectively) (263).

The higher relative risk of discontinuation in people with AD than in people without AD in Study II was comparable to previous studies among long-term users (200,202). However, the absolute difference in Study II was small. A systematic review of statin discontinuation indicated an 18% higher relative risk of discontinuation in people with dementia than those without dementia (264). In a previous study, deprescribing was more likely to happen in people with frailty, and it increased with the severity level of frailty (265,266). So the higher discontinuation rate may be due to frailty in persons with dementia, as the prevalence of frailty was approximately 32% in persons with AD in a recent systematic review (267). Another reason suggested in the literature is nonadherence in people with dementia (268–270). In Finland, however, family caregivers or home care services often take care of medications for older people with dementia rather than the persons themselves. However, the patient might not be able to take medicines correctly, leading to deprescribing.

In Study II, the risk of statin discontinuation among primary prevention users did not differ from secondary prevention users, either in people with AD or without AD. The findings of a Danish study conducted on people over 70 who had used statin for more than 5 years were similar (202). On the other hand, in some studies, discontinuation was less common in secondary prevention than in primary prevention (201,264,271). One possible reason could be the clinician's scepticism and a lack of data regarding the effectiveness of statin treatment in primary prevention in older adults over 75(272).

Several guidelines address statin therapy regarding primary/secondary prevention in older people over 75 (273–275). The Guideline of the American College of Cardiology/American Heart Association on the Management of Blood Cholesterol suggested discontinuing statin for

primary prevention when physical or cognitive decline, multimorbidity, frailty, or reduced life-expectancy limits the potential benefits of statin therapy, whilst advocating for continuing statin use for secondary prevention among people aged over 75 years (275). Before deciding whether to continue or deprescribe statin therapy, the clinician should assess the clinical status and the risk of cardiovascular disease and discuss the risks with the patient (273,275). Similar to these guidelines, the Finnish Guideline on the Management of Dyslipidaemias (274) emphasized secondary prevention, there is no age limit for initiating statins, and statin use should not be discontinued based on chronological age. More importantly, biological age, comorbidities, and life expectancy must be taken into account, and the guideline recommends considering discontinuation of statins at the end of life on an individual basis.

Moreover, the findings of Study II showed that the factors associated with increased risk of discontinuation were higher age and female gender, while concomitant cardiovascular drug use and the duration of previous statin use were associated with decreased risk. The likelihood of statin discontinuation in Study II was lower in those who used multiple cardiovascular drug substances, suggesting that active deprescribing or patients stopping the use was less common among persons with severe or multiple cardiovascular diseases.

6.3 POSTOPERATIVE OUTCOMES AFTER CORONARY REVASCULARIZATION IN PEOPLE WITH AD

People with AD were 76% less likely to be revascularized than people without AD, which is in line with previous studies (225–229). PCI was the more common procedure type for both cohorts with and without AD. CABG procedures were performed more often to people without AD (7.6% and 22.2% for people with and without AD got CABG procedures, respectively). The proportion of emergency procedures was higher in people with AD than those without AD (42.6% and 33.1%, respectively). As the previous studies were restricted to emergency settings, Study III

provided new information on elective procedure outcomes in people with AD.

One-year mortality after revascularization did not differ between people with and without AD in Study III. However, people with AD had higher 3-year mortality than those without AD, which could reflect the increased risk of mortality associated with AD (276,277). There was evidence for a different association with AD for each electivity status; in stratified analyses, the increased mortality in people with AD was observed only for emergency procedures and not for elective procedures. One reason could be that the criteria for the elective procedures were stricter with people with AD. In an emergency, the preparation of the patient before a procedure could be shorter or lacking, which might partly explain the difference in mortality (278). The time for the health assessment is short in an acute situation. And if there is a lack of information about a comprehensive assessment and patient prognosis, that might have affected the decision-making for the procedure. All persons with home care or with chronic diseases needing regular check-ups by health professionals should have a care plan that describes the clinical condition and aims of the care. In case a care plan is missing, the decision-making for a procedure is done on insufficient information and might partly explain the findings.

There was no difference in 30-day readmission risk between persons with and without AD, but the 90-day readmission risk was lower among people with AD. The lack of earlier studies on readmission rates after revascularization in persons with AD prevents a comparison to previous studies. Although people with dementia are generally considered to have a higher risk of readmission than people without dementia (279), the lower risk of 90-day readmission in people with AD in this study could reflect the post-procedural care pathway for persons with AD so that they were discharged to municipal hospitals for rehabilitation instead of to home. In these hospitals, several CAD-related problems and delirium can be treated without referral to procedural hospitals.

The benefits of both procedures for older people were stated in the recent guideline of the American Heart Association in 2021 (208).

Compared to pharmacotherapy alone, both coronary artery revascularization procedures more effectively relieve angina and improve exercise capacity among older people (121,280). In previous studies conducted in emergency settings, people with dementia who were treated with revascularization procedures had a better survival rate than those without the procedure (225,227,229). However, this could reflect the impact of selection criteria for the procedure, as the revascularized persons had a higher MMSE score and were younger than those who did not receive the procedure (227). On the other hand, the goals of revascularization vary between populations, and the results can also reflect personal preferences. Improved quality of life and functional ability may be prioritized in older people, whereas increased life expectancy may be more valued by younger people (281). Additionally, the guideline by the Association of Anaesthetists in 2019 recommended that access to healthcare should be equal between people with and without cognitive impairment (282). The decision-making should be based on the consideration of the benefits and risks of these procedures in people with cognitive disorders such as frailty, cognitive status, estimated life expectancy, and the patient's preferences (121,208).

6.4 METHODOLOGICAL CONSIDERATIONS

The strengths of the three sub-studies were that they used multiple nationwide registers with a long follow-up (data linkage was a maximum of 9 years and a minimum of 4 years). An advantage of using register-based data is that recall bias is eliminated. The study population represents a wider patient population (namely community-dwelling persons with AD) than in RCT studies that just include a specific population. The information on community dwellers with AD was extracted from the Special Reimbursement Register, which was shown in a previous study to have 63.5% sensitivity and a positive predictive value up to 97.1% (283). The Finnish Hospital Discharge Register of the Care Register for Health Care covers more than 95% of discharges and provides information on a wide

range of covariates with an accuracy rate of 75–99%, particularly for vascular diseases (accuracy ranged from 78–98%), and the positive predictive value was 87–94% (284). The Hospital Discharge Register and the Causes of Death Register for coronary heart disease were validated in a previous study with 85% overall sensitivity and 83% positive predictive value (285). In addition, data on comorbidities in the sub-studies were obtained by extracting information from multiple registers including the Care Register for Health Care, the Prescription Register, and the Special Reimbursement Register.

The Prescription Register includes dispensed prescribed drugs that are reimbursed by the Social Insurance Institution. Thus, it captures all reimbursed medications and reflects drug use more accurately than written prescriptions (286). However, the Prescription Register does not capture all relevant information about a patient's drug use, such as the indication, dosage, frequency, or duration of use. Hence, to overcome those limitations, drug use modelling was applied to estimate the duration of use. The PRE2DUP method used in Study I has shown very good validity (82%–93%) for cardiovascular drug use among older persons (235). The modelling is based on individual purchase behaviour and expert-defined parameters for each drug package. Therefore, the results represent an accurate estimation of the drug use periods (235,237). In Study II, statin use periods were computed with the AdhereR package (239). In this algorithm, the assumption of one tablet per day was applied to statins. This assumption was validated in a previous Finnish study that found that up to 95.8% of statin prescriptions were prescribed for one tablet per day dose (238). In addition, the Prescription Register does not include information on drug use during hospital or institutional care. This was taken into account in the analyses by censoring to long hospital/ institutional stays. Therefore, the results may not be applied to people living in institutionalized settings. In Study II, to handle imperfect adherence, short-term hospitalizations, and variations in purchasing behaviour, a grace period was applied. In addition, different lengths of grace periods were also used in the sensitivity analyses, and the results remained the same.

Furthermore, in Study III, coronary artery revascularization procedures were extracted from the Care Register for Health Care. As there were missing values in electivity status in both AD and no AD cohorts (23.2% and 18.4%, respectively), people with missing data were analysed in their own category. The results of this group were similar to those from the emergency group, which suggests that the missing values likely represent emergency cases. We only had information on the procedures that were actually conducted and not just planned. Therefore, it is possible that some of the emergency procedures were performed on persons who were scheduled for elective surgery but then needed to undergo an emergency procedure due to an acute worsening of the coronary artery disease.

A dearth of clinical information, an indication of drug use, and changes in the progress of comorbidities in Study I limited the investigation and understanding of the reasons for changes in the prevalence of cardiovascular drug use. In Study II, primary prevention could have been misclassified, as people with mild coronary artery symptoms may not have been recorded in the Care Register for Health Care or the Special Reimbursement Register, as they were treated in primary care not covered by these registers. Hence, the primary prevention group may include people who should have been in the secondary prevention group.

In addition, other information such as the severity of cardiovascular disease or AD and the frailty index, which could impact the discontinuation of statins, was not recorded in the registers. The number of cardiovascular drug substances was used as a proxy for the severity of cardiovascular diseases in Study II. Besides, the reasons for statin discontinuation were not available in the registers. Therefore, it is unclear whether the decision to discontinue statin was made by the prescribers, caregivers, or statin users.

The level of assistance required at discharge from the Care Register for Health Care was used as an indicator of overall health status in post-procedural outcomes. Although this study controlled for multiple confounders, delirium and post-procedural cognitive outcomes associated with readmission and mortality risk (287) could not be assessed due to a lack of information on delirium or cognitive status post-operation.

However, postoperative cognitive decline and delirium are common after CABG (288), but their occurrence after PCI was not high in a previous study (289). Additionally, living alone has been previously associated with an increased risk of mortality and readmission (290). However, there were no data on living status (alone or with another family member) or services provided at home.

7 CONCLUSIONS

The following conclusions can be drawn from the results of Studies I–III:

- The decline in the prevalence of cardiovascular drug use could result from changes related to the progress of AD, including weight loss, frailty, and declining blood pressure and serum lipid levels. Therefore, it is necessary to regularly assess medication and consider tapering doses or deprescribing cardiovascular drugs in people with AD.
- Although the risk of statin discontinuation was slightly higher in people with AD than without AD, the absolute difference was small. The finding suggests that cognitive decline has only a minor impact on statin discontinuation in older adults.
- The higher three-year mortality in persons with AD after emergency revascularizations, together with no difference in mortality after elective procedures, may be due to the high threshold for elective procedures in individuals with AD.
- If revascularization is indicated for a person with AD, it appears to be more feasible to conduct this as an elective instead of postponing it to an emergency setting. However, the patient and caregiver preferences need to be taken into account.

7.1 FUTURE DIRECTIONS

Although the findings of Studies I–III provided new information on specific areas of cardiovascular disease treatment in people with AD, further research is needed to understand:

- How frequently cardiovascular medication assessment is done in real-life clinical practice in people with cognitive disorders.

- The reasons for discontinuing cardiovascular drugs.

- Whether the apparently high threshold for elective revascularizations in people with AD leads to a higher frequency of emergency procedures with worse outcomes.

- Whether elective revascularizations change to emergency procedures in people with AD due to an unstable health condition related to AD.

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ORIGINAL PUBLICATIONS (I – III)

I

Prevalence of cardiovascular drug use before and after diagnosis of Alzheimer's disease

Vu M, Koponen M, Taipale H, Tanskanen A, Tiihonen J, Kettunen R, Hartikainen S, Tolppanen AM.

International Journal of Cardiology 300: 221–225, 2020

II

Statin discontinuation in persons with and without Alzheimer's disease

Vu, M., Kettunen, R., Tolppanen, AM., Hartikainen S., Taipale H.

European Journal of Clinical Pharmacology 78: 1145–1153, 2022.

European Journal of Clinical Pharmacology (2022) 78:1145–1153
https://doi.org/10.1007/s00228-022-03320-3

PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Statin discontinuation in persons with and without Alzheimer's disease

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Received: 13 January 2022 / Accepted: 12 April 2022 / Published online: 21 April 2022

Abstract

Background Although statin use is reported to decrease after dementia diagnosis, time to statin discontinuation and factors associated with discontinuation have not been studied in persons with Alzheimer's disease (AD). We compared the risk of discontinuation and factors associated with discontinuation, including secondary and primary prevention indication, in statin users with and without AD.

Methods The register-based Medication Use and Alzheimer's Disease (MEDALZ) cohort includes community dwellers with a clinically verified AD diagnosed during 2005–2011 in Finland. On the AD diagnosis date (index date), each person with AD was matched with a comparison person without AD. We included 25,137 people with AD and 22,692 without AD who used statin on the index date or initiated within 90 days after. Cox regression models restricted to 4-year follow-up were conducted.

Result The median time to statin discontinuation was 1.46 years in people with AD and 1.36 years in people without AD. People with AD were more likely to discontinue than people without AD (adjusted HR (aHR) 1.20 (95% CI 1.18–1.24)). This was observed for both primary (aHR 1.11 (1.06–1.16)) and secondary prevention (aHR 1.30 (1.25–1.35)) purpose. Factors associated with discontinuation included higher age and female gender, whereas concomitant cardiovascular drug use and previous statin use were associated with decreased risk.

Conclusion The absolute difference in discontinuation rates was small, and the same factors were associated with statin discontinuation in people with and without AD. The findings suggest that cognitive decline plays a minor role on statin discontinuation.

Keywords Statins · Discontinuation · Alzheimer's disease · Primary prevention · Secondary prevention · Register-based study

Introduction

Statins are used for prevention of atherosclerotic cardiovascular diseases. However, there have been doubts about statin efficacy in older persons, especially when used for primary prevention [1]. Previous studies have showed that the prevalence of statin use declines after dementia/Alzheimer's disease (AD) diagnosis [2, 3]. An Australian study of persons over 65 years with dementia observed that over a half of them (58.7%) discontinued statin use during a 3-year follow-up [4]. In a United Kingdom (UK) cohort study conducted in primary care, long-term statin users with dementia were more likely to discontinue statins than people without dementia, regardless of whether statins were prescribed for primary or secondary prevention [5]. In a Danish study of

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persons over 70 years, 33% long-term users with dementia discontinued statin therapy [6].

Although the more common discontinuation in people with dementia has consistently been reported, it is unknown when statins are discontinued in persons with AD and which characteristics, including primary or secondary prevention, are associated with discontinuation. Hence, the purpose of our study was to investigate the time to statin discontinuation from AD diagnosis and to compare the risk of statin discontinuation and associated factors in persons with and without AD.

Methods and material

The Medication Use and Alzheimer's Disease study

Study was conducted on the MEDALZ (Medication Use and Alzheimer's Disease) study. MEDALZ includes 70,718 community-dwelling people who got a clinically verified AD diagnosis during 2005–2011 [7] and a matched comparison cohort without AD. The Special Reimbursement Register, maintained by the Social Insurance Institution of Finland (SII), was used to identify persons with AD. This register also contains information on reimbursement according to specific chronic diseases such as diabetes, cardiovascular diseases, and Alzheimer's disease. This study utilized data from Prescription Register, the Special Reimbursement Register, the Care Register for Health Care, and Statistics Finland.

The AD diagnosis is consistent with criteria of NINCDS–ADRDA (National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association) and DSM-IV criteria for AD (Diagnostic and Statistical Manual Fourth edition) [8, 9] including computed tomography or magnetic resonance, exclusion of alternative diagnosis, and confirmation of diagnosis by a geriatrician or neurologist. Hence, at the time of AD-diagnosis, the MEDALZ cohort contains persons from mild to moderate stages of AD.

Each person in the AD cohort was matched with one comparison person without AD by age (± 1 year), sex, and region of residence at the date of AD diagnosis. The comparison persons were identified from the Social Insurance Institution of Finland database including all residents. To fulfill the criteria of matching, those persons had to meet criteria including (a) alive and community-dwelling on the last day of the month when case was diagnosed with AD, and (b) no special reimbursement for AD medication or acetylcholinesterase inhibitor or memantine purchase before or within 12 months after matching date. The matching date was assigned as index date for these comparison persons.

Identification of statin users

Statin users were identified from Prescription Register with ATC code C10AA. Statin treatment episodes were constructed by AdhereR package of R [10] which calculates duration of use based on purchase dates, assumed or prescribed daily dose (in tablets per day), and with allowed gap (grace period) defined by the investigator. We assumed that statins were used 1 tablet per day [11]. Because we do not have information of drug use during stay in hospital/nursing home, we censored statin users who had hospital stay longer than 60 days to minimize misclassification and the risk of exposure misclassification. A sensitivity analysis was performed with censoring to < 30-day stays.

This study included people who had a treatment episode ongoing on the date of AD diagnosis or the corresponding (index date for persons without AD) or who initiated statin use day within 90 days after the index date. (Supplementary Fig. 1).

Cohort entry date was defined as the date AD diagnosis or the first date of the first statin purchase that began within 90 days after the index date.

Statin discontinuation

Discontinuation was defined as not filling a statin prescription during the days' supply of the previous dispensing plus grace period. Grace period is an allowed gap which is added to the drug use duration to deal with non-perfect adherence and other variation in purchasing behavior. We used a 120-day grace period to capture true discontinuation. In Finland, medication can be dispensed for 90 days (maximum of 100 days) of treatment at the time and grace period reflects this.

The maximum follow-up time was restricted to 4 years to ensure all people in cohort had the same possible observation period. People were followed up until discontinuation of statin use, and censored to death, over 60 days of hospitalization, end of follow-up (4 years or December 31, 2015) or date when persons without AD were diagnosed with AD, whichever came first.

Covariates

Statin use was categorized as for primary and secondary prevention. Secondary prevention was defined using ICD-10 codes for cardiovascular (CV) diseases including coronary artery disease, coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI), ischemic strokes, and atherosclerosis of any neck or brain

arteries. Primary prevention was defined as having no conditions defined as secondary prevention. Diagnosis codes, data sources, and time periods are defined in Supplementary Table 1.

Data on comorbidities (chronic heart failure, atrial fibrillation, and diabetes) were extracted from the Special Reimbursement and Care Register for Health Care (including hospital discharges and specialized healthcare outpatient visit) based on ICD 10 (Supplementary Table 2).

A number of cardiovascular drug substances other than statins were extracted from the Prescription Register data with ATC code C* excluding C01C, C04, C05, C10AA. The prevalence of cardiovascular drug substances was identified in 120-day period before and after the index date because this time window matched with our grace period definition and should capture all regular users. The number of cardiovascular drugs substances used was calculated by taking into account on the actual number of drug substances from combination products.

Statistical analysis

We performed descriptive statistics as means, standard deviations (SD), median (interquartile range (IQR)), or frequency and percentages where appropriate. We applied *T* test for continuous variables with normal distribution, Mann–Whitney *U* test for continuous variables with skewed distribution, and chi-square test for categorizing variable to compare characteristics between groups. We presented results with 95% confidence intervals.

We used Cox regression models to compare the risk of statin discontinuation between people with and without AD and to assess factors related to statin discontinuation in persons with and without AD. The results were adjusted for age at cohort entry, sex, statin use before cohort entry, indication, sum of cardiovascular drug substances, diabetes, atrial fibrillation, heart failure, calendar year, hospital district. The proportionality assumption was confirmed with Kaplan–Meier curves.

To assess factors associated with statin discontinuation, the same analyses were performed between persons with and without AD and stratified based on primary/secondary prevention and AD status.

To evaluate whether the results were affected by choice of grace period and maximum allowed length of hospital stay, sensitivity analyses were performed with grace period of 90 days and by censoring to 30-day hospital stays.

To illustrate temporal trends in the cohort, the proportions of statin users of each annual cohort (per AD diagnosis year), as well as the cumulative survival (i.e., continuation of statin use), are presented as supplementary analyses.

All statistical analyses were performed using the software R 4.0 program [12] and STATA 14 (Stata Corporation, College Station, TX, USA).

Results

Characteristics of statin users in both cohorts

Altogether, 25,137 persons with AD and 22,692 persons without AD used statin on the index date (date of AD diagnosis) or initiated statin within 90 days after the index date (Table 1). The mean age on cohort entry was approximately 79 years, and majority of persons in both cohorts were women. Statin users with AD had higher prevalence of diabetes, atrial fibrillation, and chronic heart failure than persons without AD.

During the 4-year follow-up, 39.5% of people with AD and 34.7% in of those without AD discontinued statin use (Table 1). The median time from the cohort entry date to the date of discontinuation was similar in both cohorts: 1.46 years in persons with AD and 1.36 years in persons without AD. In both cohorts, over half of persons (55%) had a secondary prevention indication for statin use. Over 90% of people used statins already before cohort entry and over 80% used at least one other cardiovascular drug.

Rates of statin discontinuation

The rate of statin discontinuation was 4.35/10000 person-years in persons with AD and 3.28/10000 person-year in those without AD (Table 2). The relative risk for discontinuation in people with AD was 20% higher than in people without AD (adjusted hazard ratio (aHR) 1.20, 95% CI 1.18–1.24). The relative difference between AD and comparison group was slightly larger in secondary prevention (aHR 1.30, 95% CI 1.25–1.35) than in primary prevention (aHR 1.11, 95% CI 1.06–1.16).

In sensitivity analyses with censoring to 30-day hospitalization, the difference between people with and without AD was similar to that in the main analyses (Table 2). In sensitive analyses with shorter (90 days) grace period, the difference between people with and without AD became larger (80% higher relative risk).

Factors associated with statin discontinuation between people with and without AD

The same characteristics were associated with statin discontinuation in people with and without AD (Table 3). Discontinuation was less common in men than in women and most common in age groups over 75 years or over in people with AD and in age groups 70 years or over in people without

Table 1 Characteristics of statin users with Alzheimer's disease (AD) and non-AD cohorts at the date cohort entry

	AD ($n=25,137$)	No AD ($n=22,692$)	p value
Age in years at cohort entry (mean, SD)	79.1 (6.3)	79.3 (6.1)	< 0.0001
< 70	1700 (6.8)	1386 (6.1)	< 0.0001
70–74	3582 (14.2)	3053 (13.4)	
75–79	7011 (27.9)	6268 (27.6)	
80–84	8028 (31.9)	7596 (33.5)	
≥ 85	4816 (19.1)	4389 (19.3)	
Sex (women) (n,%)	16,003 (63.7)	14,478 (63.8)	0.752
Highest occupational social class before AD			< 0.0001
Managerial/professional	5424 (21.6)	5169 (22.8)	
Office	2146 (8.5)	1984 (8.7)	
Farming/forestry	4794 (19.1)	4502 (19.8)	
Sales/industry/cleaning	10,956 (43.6)	9353 (41.2)	
Unknown	1817 (7.2)	1684 (7.5)	
Median (IQR) follow-up time (years)	2.72 (1.1–4.0)	4.0 (1.6–4.0)	
Reason for end of follow-up			< 0.0001
Statin discontinuation	9931 (39.5)	7880 (34.7)	
End of follow-up	8749 (34.8)	11,663 (51.4)	
Over 60 days hospitalization	4026 (16.0)	985 (4.3)	
Death	2431 (9.7)	1713 (7.6)	
Non AD diagnosed with AD	0	451 (2)	
Median (IQR) time to discontinuation (years)	1.46 (0.5–2.5)	1.36 (0.5–2.6)	
Duration of statin use before cohort entry (years)			< 0.0001
0	1977 (7.9)	1131 (5.0)	
1–3	9653 (38.4)	7677 (33.8)	
4–6	5,095 (20.3)	5,338 (23.5)	
7–10	5,038 (20.0)	5,233 (23.1)	
Over 10	3,374 (13.4)	3,313 (14.6)	
Comorbidities			
Diabetes	6892 (27.4)	5489 (24.2)	< 0.0001
Atrial fibrillation	4831 (19.2)	3964 (17.5)	< 0.0001
Chronic heart failure	4141 (16.5)	3510 (15.5)	0.003
Primary/secondary prevention			< 0.561
Primary prevention	11,369 (45.2)	10,203 (45.0)	
Secondary prevention	13,768 (54.7)	12,489 (55.0)	
Ischemic coronary artery diseases and PCI/CABG	12,006 (47.8)	11,135 (49.1)	
Ischemic strokes, atherosclerosis of neck and brain arteries	3,648 (14.5)	2,839 (12.5)	
Number of other cardiovascur drug substances than statin			< 0.0001
0	3888 (15.5)	2765 (12.2)	
1–2	10,734 (42.7)	8974 (39.5)	
3–4	8266 (32.9)	8365 (36.9)	
5 and more	2249 (8.9)	2588 (11.4)	
Number of statin users in calendar year			0.323
2005	2303 (9.2)	2120 (9.3)	
2006	2555 (10.2)	2434 (10.7)	
2007	3110 (12.4)	2867 (12.6)	
2008	3645 (14.5)	3271 (14.4)	
2009	4128 (16.4)	3700 (16.3)	
2010	4437 (17.6)	3934 (17.3)	
2011	4959 (19.7)	4366 (19.4)	

Table 2 Association of Alzheimer's disease with statin discontinuation

		AD			No AD			HR	
		Number of observation	Number of events	Event/10000 person-years	Number of observation	Number of events	Event/10000 person-years	Unadjusted	Adjusted
Main analysis									
Grace period 120 days and censoring to > 60 days hospital care	Total	25,137	9931	4.35	22,692	7880	3.28	1.31 (1.27–1.35)	1.20 (1.18–1.24)
	Primary	11,065	4633	4.44	9917	3736	3.55	1.25 (1.20–1.31)	1.11 (1.06–1.16)
	Secondary	14,072	5298	4.27	12,775	4144	3.08	1.39 (1.31–1.43)	1.30 (1.25–1.35)
Sensitivity analyses									
Grace period 120 days and censoring to > 30 days hospital care	Total	25,124	9005	4.09	22,692	7568	3.19	1.26 (1.23–1.30)	1.15 (1.12–1.19)
	Primary	11,368	4400	4.26	10,203	3727	3.47	1.21 (1.16–1.26)	1.06 (1.02–1.11)
	Secondary	13,756	4605	3.94	12,489	3841	2.97	1.32 (1.26–1.37)	1.25 (1.19–1.30)
Grace period 90 days and censoring to > 60 days hospital care	Total	26,171	7954	3.03	23,931	4773	1.66	1.85 (1.79–1.93)	1.81 (1.77–1.88)
	Primary	11,921	3777	3.03	10,918	2258	1.67	1.83 (1.73–1.92)	1.75 (1.66–1.84)
	Secondary	14,250	4177	3.04	13,013	2515	1.64	1.89 (1.80–1.98)	1.88 (1.79–1.97)

Adjusted: age at cohort entry, sex, statin use before cohort entry, sum of cardiovascular drug substances, hospital district, diabetes, atrial fibrillation, heart failure, calendar year

Reference group is no AD

AD. The risk of discontinuation was not different between primary and secondary prevention indication users, or those with and without diabetes or atrial fibrillation (Table 3). Heart failure was weakly associated with risk of discontinuation. The risk of discontinuation was lower among users who used higher number of other cardiovascular drugs, or who had used statins before the cohort entry. The association between duration of previous statin use was stronger in people without AD. In both cohorts, statin discontinuation was more common in those with later cohort entry years in comparison to those with index date in 2005 (Table 3, and Supplementary Fig. 2).

Discussion

To our knowledge, this is the first study comparing the statin discontinuation risk and factors associated with discontinuation between people with and without AD. Although people with AD had higher relative risk of statin discontinuation than people without AD during the 4-year follow-up, the absolute difference in discontinuation rates was small. The same factors were associated with discontinuation in people with and without AD, as older people and women were more likely to discontinue whereas users of other cardiovascular drugs and those who had used statins for longer time before the index date were less likely to discontinue in both cohorts. Discontinuation was equally common in primary and secondary indication in both cohorts.

Most of the previous studies on statin discontinuation in people with dementia have applied new user design [4, 5, 13] and only one study included prevalent long-term statin users [6]. The proportion of people with dementia who discontinued in these previous studies has ranged between 33 [6] and 59% [4], with the smallest proportion being observed in the study of long-term statin users. The proportion of people who discontinued in our study is comparable with the earlier Danish study of long-term users [6], although direct comparisons are not meaningful due to differences in study design. Our study included both prevalent users and those who initiated within 90 days of AD diagnosis, with the majority being prevalent users. In the previous studies, discontinuation was more common in people with dementia in the study with long-term statin users [6] while the opposite association was observed in studies conducted among incident short-term users [5, 13].

In our study, statin discontinuation was relatively common in both cohorts and the highest HRs were observed in the oldest age groups. This finding is in line with previous studies [6, 13, 14]. In a Danish study, the difference in the discontinuation between age groups 70–74 years and those aged > 95 years was twofold (aOR = 2.06, 95% CI 1.35–3.16) at 1 year and nearly fourfold at 4 years (aOR3.94, 95% CI 1.83–8.49) of follow-up [13]. A third of participants in our study were aged over 80 years and nearly fifth were at least

Table 3 Factors associated with statin discontinuation stratified by AD status

	AD		No AD	
	Unadjusted HR	**Adjusted HR**	**Unadjusted HR**	**Adjusted HR**
Age at cohort entry				
< 70 years	ref	ref	ref	ref
70–74	1.06 (0.97–1.17)	1.11 (1.00–1.22)	1.13 (1.01–1.27)	1.25 (1.11–1.39)
75–79	1.09 (1.00–1.20)	1.17 (1.07–1.28)	1.10 (0.99–1.22)	1.27 (1.14–1.41)
80–84	1.32 (1.21–1.44)	1.40 (1.28–1.53)	1.25 (1.13–1.38)	1.45 (1.31–1.61)
85–100	1.85 (1.68–2.02)	1.91 (1.74–2.10)	1.55 (1.40–1.73)	1.74 (1.56–1.93)
Sex				
Female	ref	ref	ref	ref
Male	0.88 (0.85–0.93)	0.91 (0.87–0.96)	0.87 (0.83–0.91)	0.86 (0.82–0.90)
Indication				
Primary prevention	ref	ref	ref	ref
Secondary prevention	0.95 (0.92–0.99)	1.00(0.96–1.04)	0.87 (0.83–0.91)	0.96 (0.92–1.01)
Comorbidities				
Diabetes	0.92 (0.88–0.96)	0.96 (0.92–1.01)	0.91 (0.86–0.96)	0.96 (0.91–1.02)
Heart failure	1.11 (1.05–1.17)	1.12 (1.06–1.19)	1.04 (0.98–1.11)	1.10 (1.03–1.18)
Atrial fibrillation	1.05 (1.00–1.11)	1.04 (0.98–1.09)	0.98 (0.93–1.04)	1.01 (0.95–1.08)
Number of cardiovascular drug substance other than statin use				
0	ref	ref	ref	ref
1–2	0.84 (0.80–0.89)	0.82 (0.78–0.87)	0.84 (0.78–0.90)	0.83 (0.77–0.89)
3–4	0.81 (0.76–0.86)	0.76 (0.72–0.81)	0.73 (0.68–0.78)	0.71 (0.66–0.76)
more than 5	0.81 (0.74–0.87)	0.74 (0.68–0.82)	0.70 (0.64–0.77)	0.67 (0.60–0.74)
Statin use before cohort entry (years)				
0	ref	ref	ref	ref
1–3	0.79 (0.74–0.85)	0.79 (0.74–0.85)	0.54 (0.49–0.58)	0.53 (0.48–0.57)
4–6	0.63 (0.58–0.68)	0.62 (0.58–0.68)	0.30 (0.27–0.33)	0.29 (0.26–0.32)
7–10	.058 (0.54–0.63)	0.57 (0.53–0.62)	0.25 (0.23–0.27)	0.23 (0.21–0.26)
Over 10	0.61 (0.56–0.67)	0.56 (0.51–0.61)	0.26 (0.23–0.29)	0.22 (0.20–0.25)
Calendar year				
2005	ref	ref	ref	ref
2006	0.98 (0.89–1.08)	0.98 (0.89–1.09)	0.95 (0.85–1.06)	0.97 (0.88–1.09)
2007	1.04 (0.95–1.15)	1.06 (0.97–1.17)	1.00 (0.91–1.11)	1.05 (0.95–1.16)
2008	1.15 (1.05–1.26)	1.16 (1.06–1.27)	1.18 (1.06–1.30)	1.29 (1.17–1.43)
2009	1.29 (1.18–1.41)	1.31 (1.21–1.43)	1.29 (1.17–1.41)	1.46 (1.33–1.60)
2010	1.48 (1.36–1.61)	1.51 (1.38–1.64)	1.48 (1.35–1.63)	1.71 (1.56–1.88)
2011	1.43 (1.32–1.55)	1.46 (1.35–1.59)	1.44 (1.32–1.58)	1.71 (1.56–1.88)

Adjusted by: age at cohort entry, sex, statin use before cohort entry, indication, sum of cardiovascular drug substances, diabetes, atrial fibrillation, heart failure, calendar year, hospital district

85 years old which may partly explain the same kind of risk of discontinuation in both cohorts. In addition, the oldest persons are at the higher risk of statin-related adverse effects [15], and the health status is more unstable than in younger persons, which may explain the higher discontinuation rates among the older participants in our and earlier studies. The changes in health status may also have led to deprescribing. Other comorbidities or progression of disease which negatively affect life expectancy such as cancer [16] could also affect decision of statin deprescribing [17]. In addition, frailty, which is common among older persons with high age and even more common in persons with AD [18], might increase the decision to deprescribe [19]. Although regular medication reviews are recommended by the Finnish authorities, those recommendations are not always applied in clinical practice; therefore, we do not expect that statin discontinuation rates in our study were significantly affected by regular reviews.

Time period–related trends have been observed in the use of statins among older persons aged over 79 years in USA that the proportion of statin users increased from the year 1999 until 2009 in secondary prevention and until 2007 in

primary prevention, then decreased after that [20]. Similarly, there was an increase in prevalence of statin use between years 2008 and 2010 among people aged 65 years in Finland and prevalence remained at the same level after that to the end of year 2015 [21]. Consistent with this, we observed an increase in the prevalence of statin use per diagnosis year until 2011, while the discontinuation rate was also higher in those who entered the cohort in later years. Public discussion on whether statins should be used for other than secondary prevention indications [22] and relatively high drug prices but low reimbursement together with time trends described may have impacted our study results. Only a small proportion of statin users in Finland reported to have discontinued statin therapy due to worrying or experienced of side effects [23].

Our results showed that discontinuation was not different due to primary versus secondary prevention in both people with and without AD, which is in line with Danish study [6]. It could be due to consideration of clinicians in the period when benefits of statin in primary prevention were still debated [24]. However, the discontinuation risk was lower among users of other cardiovascular drugs. It could be partly because we may not have captured all milder cardiovascular diseases and consequently in the primary prevention group may include persons with mild coronary disease or atherosclerosis of other arteries. Therefore, it is possible that the number of other cardiovascular drugs better describes the presence and severity of cardiovascular diseases than our diagnosis-based measure of secondary versus primary prevention. Besides, using statin in long period increases adherence to statin use which partially explained the necessaries of statin therapy and stronger commit to therapy in these cases [25].

The slightly higher risk of discontinuation in persons with AD in our study, observed in both primary and secondary prevention indication, may also be due to lower adherence in persons with cognitive decline [26–28] that is also reported in Finland [29]. However, for persons with dementia, caregiver or home care services often take care of medications instead of the patient and in this kind of situation, adherence does not describe the behavior of the patient. The relative risk of statin discontinuation in our study is comparable to findings from a systematic review that reported 18% higher risk of statin discontinuation in persons with dementia compared to those without dementia [14].

Strengths and limitations

Use and linkage of different registers from a country with public healthcare system allowed us to perform a nationwide study with low risk of selection bias. We used Prescription Register which captures dispensed medication; thus, the time people redeemed prescription was more precise than prescriptions. Moreover, we use ATC code C10AA which captured statins in general thus accounting for switches into another statin.

However, our study has some limitations. Firstly, this is a register-based study; thus, like other studies, we do not know whether discontinuation decision is made by prescriber (i.e., deprescribing) or by the caregiver or patient and we do not know whether medications were actually taken by patients. We also lack information about changes in severity of comorbidities during the follow-up, which could impact on discontinuation of statin therapy in both cohorts. We also lacked data on patient-related factors such as income that has been previously linked to discontinuation [30]. Due to lacking indication in register data, we may have misclassified some people into primary prevention category. Therefore, further research is needed on the reasons of statin discontinuation, as well as by who and how the decision of statin discontinuation is initiated and made.

Conclusion

Discontinuation was common in both groups and the absolute difference in statin discontinuation rates was small between people with and without AD. These findings suggest that cognitive decline does not have a large impact on discontinuation of statins in older persons.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1007/s00228-022-03320-3.

Author contribution M.V., R.K., S.H., A.M.T., and H.T. planned the study. M.V. and H.T. had full access to all the data in the study. H.T. prepared data. M.V. performed statistical analyses and took responsibility for the integrity of the data and the accuracy of the data analysis. M.V drafted the manuscript. All authors contributed to the interpretation of the data, revised the manuscript, and approved the final manuscript.

Funding Open access funding provided by University of Eastern Finland (UEF) including Kuopio University Hospital. M.V. was funded by the University of Eastern Finland.

Availability of data and material The authors are unable to openly share the data used to conduct this study. The data that support the findings of this study are available from the corresponding author upon reasonable request and with permission of the register maintainers.

Declarations

Ethic approval All data were de-identified before sending to research team, and participants were not contacted; therefore, according to Finnish legislation, ethic committee approval was not required.

Conflict of interest H.T has participated in research projects funded by grants from Janssen-Cilag and Eli Lilly, with grants paid to the employing institution. H.T reports personal fees from Janssen-Cilag and

Otsuka. S.H. has got lecture fee from Astellas Pharma (outside this study). A.M.T acknowledges a research grant from Amgen, paid to the institution where she is employed (outside of the submitted work). M.V. and R.K. have nothing to disclose.

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III

Coronary revascularization and postoperative outcomes in people with and without Alzheimer's disease

Vu M, Koponen M, Taipale H, Kettunen R, Hartikainen S, Tolppanen AM.

The Journals of Gerontology: Series A: 1524–1530, 2021.

THE GERONTOLOGICAL SOCIETY OF AMERICA®

Journals of Gerontology: Medical Sciences
cite as: *J Gerontol A Biol Sci Med Sci*, 2021, Vol. 76, No. 8, 1524–1530
doi:10.1093/gerona/glab006
Advance Access publication January 9, 2021

OXFORD

Research Article

Coronary Revascularization and Postoperative Outcomes in People With and Without Alzheimer's Disease

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Received: October 23, 2020; Editorial Decision Date: December 30, 2020

Decision Editor: Anne B. Newman, MD, MPH, FGSA

Abstract

Background: Little is known on the incidence and postoperative outcomes of revascularizations according to electivity in persons with Alzheimer's disease (AD).

Methods: The Medication Use and Alzheimer's disease (MEDALZ) cohort includes 70 718 community dwellers diagnosed with incident AD during 2005–2011 in Finland. For each person with AD, 1–4 age-, sex-, and hospital district-matched comparison persons without AD were identified. Altogether 448 persons with AD and 5909 without AD underwent revascularization during the follow-up. The outcomes were 30-day and 90-day re-admission rate after discharge, and all-cause 1-year and 3-year mortality. Risk of outcomes in persons with AD were compared to those without AD using Cox proportional hazard models adjusted with age, sex, comorbidities, statin use, revascularization type, length of stay, and support at discharge.

Result: People with AD had less revascularizations (adjusted hazard ratio 0.24, 95% confidence interval 0.22–0.27). Emergency procedures were more common (42.6% vs 33.1%) than elective procedures (34.2% vs 48.6%) among people with AD. There was no difference in 30-day readmissions (0.97, 0.80–1.17) or 1-year mortality (1.04, 0.75–1.42) and 90 days readmission risk was lower in persons with AD (0.85, 0.74–0.98). People with AD had higher 3-year mortality (1.42, 1.15–1.74), but the risk increase was observed only for emergency (1.71, 1.27–2.31), not for elective procedures (0.96, 0.63–1.46).

Conclusion: People with AD did not have worse readmission and mortality outcomes following elective revascularization. These findings in conjunction with lower revascularization rate especially for elective procedures raise questions on the threshold for elective procedures in people with AD.

Keywords: Alzheimer's disease, Coronary artery disease, Elective, Emergency, Mortality, Readmission, Revascularization

Coronary artery disease and cognitive disorders share common risk factors (1) and approximately one third of people with Alzheimer's disease (AD) have coronary artery disease (2). Coronary artery bypass graft surgery (CABG) and percutaneous coronary interventions (PCI) are recommended by guidelines as a standard of care for coronary artery disease (CAD) (3), particularly in high-risk patients (4).

Revascularizations have been suggested to be more beneficial in comparison to medical treatment, particularly in aged population (5). A previous observational study showed that older people, especially persons aged 80 years, were more likely to benefit from both types of revascularization than medical therapy (6). The observed absolute risk reduction in 4-year mortality in relation to medical therapy was 17% for CABG and 11% for PCI.

Despite these benefits observed in the general aged population, people with cognitive impairment are less likely to undergo invasive coronary procedure than people without cognitive impairment (7–9). In one study, only 12.7% of persons with dementia hospitalized due to acute myocardial infarction were treated by PCI and 1.4% received

CABG in comparison to 43.9% being treated by PCI and 9.3% by CABG among people with acute myocardial infarction without cognitive disorder (7). Similarly, another previous study reported that among people with non-ST segment elevation myocardial infarction (NSTEMI), 59.7% persons without cognitive impairment got PCI and CABG while 30.5% persons with mild cognitive and only 13.5% persons with moderate/severe cognitive impairment received the procedures (8).

However, little is known about the effectiveness and survival rate after coronary artery revascularization procedures in persons with AD. It is also unknown whether there is a difference in frequency of elective and emergency procedures between the people with and without dementia, and whether the outcomes differ by electivity status. Therefore, we compared the incidence of revascularization procedures after AD diagnosis and postprocedural outcomes including mortality and readmissions between persons with and without AD by accounting for electivity.

Methods and Material

Data Source

The MEDALZ cohort includes residents of Finland who received a clinically verified AD diagnosis during 2005–2011. The cohort consists of 70 718 persons with AD, with an age range from 35 to 105 and mean age of 80.1 years; 65% of the study population were women. The study cohort and data sources have been described previously (10).

Briefly, data were extracted from the Finnish nationwide health care registers, including the Prescription Register, the Special Reimbursement Register, Care Register for Health Care, the Statistics Finland (Supplementary Table S1). All data were deidentified before sending to research team, and participants were not contacted; therefore, according to Finnish legislation, ethic committee approval was not required.

Identification of AD and Comparison Cohorts

Persons with incident AD diagnosis were identified from the Special Reimbursement Register which is maintained by the Social Insurance Institution of Finland (SII). The diagnostic criteria of AD were based on NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association) and DSM-IV criteria for AD (Diagnostic and Statistical Manual Fourth edition) (11,12). All cases had to meet clinical diagnosis criteria such as received a computed tomography/magnetic resonance imaging scan, symptoms consistent with AD and exclusion of alternative diagnosis, and confirmation of the diagnosis by a registered neurologist or geriatrician.

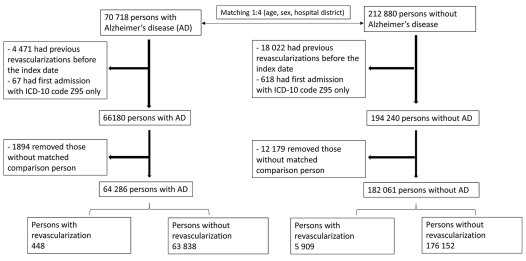

Figure 1. Flowchart of cohort definition.

Each person in the AD cohort was matched with 4 comparison persons without AD by age (± 1 year), sex, and region of residence at the date of AD diagnosis (index date). The matched controls were identified from nationwide registers of the Social Insurance Institution of Finland (SII) including all residents with the following criteria: (i) alive and community dwelling during the last day of the month when case was diagnosed with AD (index date); (ii) no special reimbursement for AD medication or acetylcholinesterase inhibitor or memantine purchases (N06D) before index date and within 12 months after it.

Identification of Revascularization Procedures

The procedures were identified from the Care Register for Health Care (1996–2015), where the operations are recorded with NOMESCO codes (13). In addition, to general procedure code fields, data from the extra sheet of cardiac patients were used. CABG cases were identified with NOMESCO codes FNA, FNC, and FNE, and code AA in the extra sheet of cardiac patient. PCI cases were defined as NOMESCO codes FNG00, FNG10, FN1AT, FN1BT, FN1YT, FN2, FN_2 codes AN2, AN3, and AN4 in the extra sheet of cardiac patient. Data on electivity were obtained from the extra sheet of cardiac patient. Electivity status was recorded as "emergency," "elective, scheduled within one week" and "elective, scheduled over one week ago." People with missing data on electivity were included as their own category in the analyses.

As the focus was on new operations, persons who had been operated before the index date were excluded. We excluded those with an operation between 1996 and the index date. In addition, to procedure codes mentioned above, ICD-10 codes Z95.1 and Z95.5 were used to exclude people operated prior to index date (Supplementary Table S1) (14). Exclusion of persons who had previous revascularization procedures lead to unmatched comparisons in both cohorts. Therefore, we removed persons with AD without any matched comparison persons and vice versa (Figure 1).

Postoperative Readmission and Mortality

The observation periods for readmission and mortality outcomes are illustrated in Supplementary Figure S1. One- and 3-year mortality risks were assessed after discharge from procedural unit. Mortality during period of care includes mortality in procedural unit and mortality in university/central hospital.

After the procedure, people were often moved to other hospital. Therefore, 30- and 90-day readmissions were defined as readmission to central or university hospital after the care period (Supplementary Figure S1). People who were discharged after the procedure-associated care period were included in these analyses.

Readmissions, and main discharge diagnosis for readmissions were identified from the Care Register for Health Care using service provider codes and the main diagnosis codes. Readmission due to coronary artery disease was defined as ICD 10 codes I20 – I25 and Z95.1 and Z95.5. Data on mortality were obtained from the Statistics Finland.

Other Characteristics

Data on comorbidities (hypertension, heart failure, stroke, atrial fibrillation, and diabetes) and statin use were extracted from the Finnish nationwide health care registers (Supplementary Table S1). In addition, socioeconomic position, defined as the highest occupational social class before AD diagnosis, was obtained from the censuses maintained by Statistics Finland. The highest position reported

was taken for each person. An ordinal variable with the following categories was derived "managerial/professional," "office," "farming/forestry," "sales, industry, cleaning," and "unknown." Required level of care after discharge from procedural unit or procedural-associated care period in university/central hospital was categorized as follows: "independent or nearly independent," "intermittent need," "recurrent need," "nearly continuous," "continuous," and "data missing."

To assess whether stays in municipal hospitals or nursing home affected the rehospitalization rate, stays in municipal hospital after discharge were identified from the Care Register for Health Care using service provider codes, and stays in social institutions were identified from the Care Register for Social Welfare.

Statistical Analysis

Descriptive statistics were carried out using means, standard deviations (*SD*), and percentages. The results were presented with 95% confidence intervals (CIs). To compare characteristics between groups, we applied an independent sample *T* test for continuous variables with normal distribution, Mann–Whitney *U* test, or Kruskal–Wallis test for continuous variables with skewed distribution and chi-square test for categorical variables. Association between electivity and mortality in during period of care was studied by logistic regression.

To compare the revascularization risk between people with and without AD after the index date, we applied Cox regression models to estimate the hazard ratios (HRs) with 95% CIs and the results were adjusted for sociodemographic characteristics, comorbidities, and statin use. The proportionality assumption was confirmed with Kaplan–Meier curves.

To compare the difference in postoperative outcomes among people who discharge alive either from procedural unit in mortality analysis or from period of care in readmission analysis, we use the same methods and adjusted the result for sociodemographic characteristics, comorbidities, statin use, type of revascularization, length of stay in procedural unit or period of care, and required assistance level at discharge. The main analyses were performed for PCI and CABG together. To assess whether the risk of outcomes was different according to procedure type, interaction between AD and procedure type was assessed and sensitivity analyses stratified by procedure type were performed. To investigate whether the association between AD and mortality outcomes were modified by electivity, models with AD*electivity interaction term were fitted, and stratified analyses according to electivity were performed.

To assess whether stays in municipal hospitals or nursing home affected the readmission rate to central or university hospitals, interaction analyses were performed between stay in municipal hospital or nursing home and AD.

In mortality analyses, people were followed after discharge from procedural unit until death, end of follow-up (1 or 3 years after the discharge), or end of data linkage (December 31, 2015), whichever came first. In addition, persons in the non-AD group were censored at their AD diagnosis date if they received the diagnosis during the follow-up.

In the readmission analyses, the people were followed after discharge from the period of care until readmission, end of follow-up (30 or 90 days), death, or end of data linkage (December 31, 2015), whichever came first.

All statistical analyses were performed using the software STATA 14 (Stata Corporation, College Station, TX).

Results

Characteristics of Study Population on the Index Date and Revascularization Rate After the Index Date

Altogether 448 persons with AD and 5909 without AD had incident revascularization after the index date (Table 1). In both AD and non-AD cohorts, revascularized persons were younger on the index date (approximately 2 years) and more likely to be men than persons who were not treated with revascularization. In both cohorts, hypertension was the most common comorbidity and statin use was more frequent among revascularized than non-revascularized persons.

The revascularization rate was of 14.1/10 000 person-years among people with AD and 58.9/10 000 person-years among persons without AD. After adjusting for sociodemographic characteristics, comorbidities, and statin use, people with AD were 76% less likely to undergo revascularization (adjusted HR [aHR] 0.24, 95% CI 0.22–0.27).

Characteristics of Revascularized Persons

Majority of all revascularizations were PCIs and PCIs were more common in AD cohort (92.4% of revascularizations) than in non-AD cohort (77.8%) (Table 2). People with AD were less likely to undergo elective procedure (34.2% of procedures were elective) than persons without AD (48.6%) and the difference was mainly due to procedures scheduled more than 1 week ago. Emergency procedures were more common in the AD cohort (42.6%) compared to the non-AD cohort (33.1%). The average age at time of procedure was 80 years in both cohorts and the average time to revascularization from index date was shorter in AD than in non-AD cohort (median 2.0 and 3.0 years, respectively).

The median length of stay in the procedural unit (PCI/CABG) and period of care was on average one day shorter in persons with than without AD (Table 2). People with AD were considered to require more assistance than those without AD after discharge from procedural unit as well as hospital. At discharge from central/university hospital, 27.0% of AD cohort and 42.7% of non-AD cohort were considered to be independent or nearly independent.

Inpatient, 1-and 3-Year Mortality

Higher mortality during period of care (including staying in the operative unit and hospital care continuing directly from that stay) was observed in revascularized people with AD (7.4% died in the operative unit) than without AD (4.5% died in the operative unit and 0.2% during the care period) (Table 2). Mortality during the care period was more common among those with emergency procedure in comparison to elective procedures (Supplementary Table S2). The risk difference between emergency and elective procedures was larger in people with AD than without AD.

There was no difference in 1-year mortality, also after accounting for sociodemographic characteristics, comorbidities, statin use, length of period of care-required assistance level at discharge from university/central hospital, and type of revascularization (aHR 1.04, 95% CI 0.75–1.42), and the risk was similar in different electivity categories (Table 3). People with AD had higher 3-year mortality risk (aHR 1.42, 95% CI 1.15–1.74), but the risk was modified by electivity (p for interaction <.0001). People with AD had higher 3-year mortality risk in emergency procedures (aHR 1.71, 95% CI 1.27–2.31) while no

Table 1. Characteristics of Person With AD and Non-AD Cohorts at the Index Date (date of AD diagnosis)

	AD Cohort (64 286)			No AD Cohort (182 061)		
	Revascularization (*n* = 448)	No Revascularization (*n* = 63 838)	*p* Value	Revascularization (*n* = 5909)	No Revascularization (*n* = 176 152)	*p* Value
Age at AD diagnosis (*SD*)	77.5 (6.1)	80.0 (7.2)	<.0001	77.0 (6.1)	79.2 (7.7)	<.0001
Sex (women) (*n*, %)	200 (44.6)	42 753 (66.9)	<.0001	2836 (48.0)	119 098 (67.6)	<.0001
Comorbidities						
Hypertension	200 (44.6)	27 159 (42.5)	.371	2594 (43.9)	71 440 (40.6)	<.0001
Atrial fibrillation	59 (13.2)	10 529 (16.5)	.059	598 (10.1)	23 538 (13.4)	<.0001
Heart failure	54 (12.0)	8778 (13.7)	.299	505 (8.5)	21 076 (12.0)	<.0001
Stroke	48 (10.7)	6518 (10.2)	.726	327 (5.5)	13 768 (7.8)	<.0001
Diabetes	96 (21.4)	7916 (12.4)	<.0001	848 (14.4)	18 563 (10.5)	<.0001
Statin use (1 y before the index date)	218 (48.6)	21 820 (34.2)	<.0001	2468 (41.8)	55 228 (31.4)	<.0001
Anticholinesterase use (within 1 y after the index date)	363 (81.0)	49 394 (77.4)	.065	NA	NA	
Highest occupational social class before AD						
Managerial/professional	104 (23.2)	13 288 (20.6)	<.0001	1445 (24.5)	39 543 (22.5)	<.0001
Office	24 (5.4)	5531 (8.7)		427 (7.2)	15 558 (8.8)	
Farming/forestry	76 (16.9)	11 911 (18.7)		1256 (21.3)	32 611 (18.5)	
Sales/industry/cleaning	226 (50.4)	27 115 (42.5)		2505 (42.4)	68 048 (38.6)	
Unknown	18 (4.11)	5993 (9.5)		276 (4.7)	20 392 (11.6)	

Note: AD = Alzheimer's disease.

difference was observed with elective procedures (aHR 0.96, 95% CI 0.63–1.46). There was no evidence for different association with mortality outcomes per procedure type (*p* for interaction >.5, Supplementary Tables S3 and S4), but the CIs in the CABG group were wide due to small number of CABGs.

30- and 90-Day Hospital Readmission

The all-cause 30-day readmission risk was comparable between people with and without AD (aHR = 0.97 95% CI 0.80–1.16; Table 4). There were no differences in readmission risk due to CAD between AD and non-AD cohorts after 30 days (aHR = 0.74, 95% CI 0.50–1.08). However, people with AD had lower all-cause 90-day readmission risk (aHR = 0.85, 95% CI 0.74–0.98), and readmission due to CAD (aHR = 0.58, 95% CI 0.44–0.78). This was not explained by stays in municipal hospitals or in nursing homes after the initial discharge (*p* for interaction between stays in municipal hospital and AD = 0.58 and stays in nursing homes and AD = 0.15). There was no evidence for different association with readmission risks per procedure type (*p* for interaction >.7, Supplementary Tables S5 and S6).

Discussion

The findings of this nationwide study show that people with AD were less likely to undergo revascularization and their procedures were often conducted in emergency setting. Revascularized people with AD had higher 3-year mortality and also higher in-hospital mortality, but these were driven by higher mortality in emergency procedures, whereas no difference in 3-year mortality was observed among those who underwent elective procedures.

Our finding on the lower revascularization rate in people with AD cohort compared to non-AD persons is in line with previous studies (7–9). Those previous studies were conducted among inpatients hospitalized due to acute myocardial infarction and thus, our findings complement those finding by studying both elective and nonelective procedures.

The higher overall 3-year mortality among revascularized people with AD may reflect the increased mortality in AD (15,16) as people with AD have substantially shortened life expectancy and the median survival after AD diagnosis ranges between 3 and 10 years (17). Frailty is common in persons with AD (18) and it accelerates mortality (19). The study of National Surgical Quality Improvement Program used modified Canadian study of Health and Aging-frailty index, and each unit increase in frailty index increased the risk of postoperative mortality (odds ratios [OR] 1.33–46.33) (20).

Interestingly, the higher 3-year mortality was observed for emergency procedures but not for elective ones. One possible explanation may be the selection process for elective procedures. It seems that persons with AD have much higher criteria for elective revascularization to ensure they will benefit from the procedure. Furthermore, each person with AD in Finland should have an advance care plan which also states how situations such as the need for invasive or emergency procedures are handled. In case care plan was missing, the threshold for emergency procedure might have been lower due to lack of comprehensive assessment and information about patient prognosis.

In our study, there was no difference in 30-day readmissions and the risk of readmission during 90-day was lower in AD cohort. The finding is opposite to most previous studies where persons with dementia had higher readmission rate (21,22). This might be due to differences in the health care systems. As in Finland, older people and especially older persons with cognitive disorders are often discharged to municipal hospitals for rehabilitation, although in our study stays in municipal hospitals or nursing home did not modify the readmission risk. In these hospitals, several CAD-related problems and delirium can be treated without referral to procedural hospitals.

Coronary artery revascularization relieves angina and improves exercise capacity more effectively medical therapy alone (3,4,6) and these benefits are more pronounced in aged population (5). The benefits were also observed in a systematic review, as both PCI and CABG significantly impacted health-related quality of life physical functioning (23). Although people with cognitive impairment are less likely to receive these treatments (7–9), the aforementioned benefits are unlikely restricted to those with normal cognition. Still,

Table 2. Comparison of Characteristics of Revascularized Persons of AD and Non-AD Cohort

	AD (*N* = 448)	No AD (*N* = 5909)	*p* Value
Age at revascularization (mean, *SD*)	80.0 (6.2)	80.4 (6.1)	.18
Average time to revascularization (median, IQR) years	2.0 (0.8–3.8)	3.0 (1.4–5.1)	<.0001
Type of revascularization (*n*, %)			<.0001
PCI	414 (92.4)	4599 (77.8)	
CABG	34 (7.6)	1310 (22.2)	
Electivity (*n*, %)			<.0001
Emergency	191 (42.6)	1954 (33.1)	
Elective, scheduled within 1 week	90 (20.1)	1362 (23.1)	
Elective, scheduled over 1 week ago	63 (14.1)	1505 (25.5)	
Data missing	104 (23.2)	1088 (18.4)	
Comorbidities (*n*, %)			
Hypertension	237 (52.9)	3284 (55.5)	.27
Heart failure	89 (19.9)	1159 (19.6)	.90
Atrial fibrillation	82 (18.3)	1114 (18.9)	.77
Stroke	62 (13.8)	524 (8.9)	<.001
Diabetes	103 (23.0)	1097 (18.6)	.021
Asthma/COPD	68 (15.2)	857 (14.5)	.70
Statin use	230 (51.3)	3207 (54.3)	.23
Mortality during period of care (*n*, %)			.013
Mortality in procedural units	33 (7.4)	265 (4.5)	
Mortality in university/central hospital	0 (0)	14 (0.2)	
At the discharge from procedural unit			
	AD (*N* = 415)	No AD (*N* = 5644)	
Length of stay (median, IQR)	3 (1–6)	4 (1–7)	.03
Required level of care, *n* (%)			<.0001
Independent/nearly independent	114 (27.7)	2315 (41.1)	
Intermittent need	120 (28.9)	1232 (21.9)	
Recurrent need	79 (19.4)	882 (15.6)	
Nearly continuous	24 (5.8)	223 (4.0)	
Continuous	30 (7.2)	264 (4.7)	
Data missing	48 (11.6)	728 (12.9)	
At discharge from period of care (university/central hospital)			
	AD (*N* = 415)	No AD (*N* = 5630)	
Total length of stay (median, IQR)	3 (1–6)	4 (1–7)	.006
Required level of care, *n* (%)			<.0001
Independent/nearly independent	112 (27.0)	2402 (42.7)	
Intermittent need	122 (29.4)	1237 (22.0)	
Recurrent need	80 (19.3)	851 (15.1)	
Nearly continuous	24 (5.8)	206 (3.7)	
Continuous	30 (7.2)	244 (4.3)	
Data missing	47 (11.3)	690 (12.3)	

Note: AD = Alzheimer's disease; CABG = Coronary artery bypass graft surgery; COPD = chronic obstructive pulmonary disease; IQR = Interquartile range; PCI = Percutaneous coronary intervention.

understanding the risks and benefits of these procedures in procedures in people with cognitive disorders is necessary.

In general, we did not observe any association of AD and worse outcomes except for higher 3-year mortality and mortality during the stay in procedural unit which were driven by emergency procedures. Thus, our findings should not be interpreted as discouraging, especially when there was no difference in the long-term outcomes after elective procedures. However, the latest European guidelines highlight that in addition to clinical presentation, comorbidities and risk stratification including factors like frailty, cognitive status, estimated life expectancy, and the functional and anatomical severity of CAD must take into account in treatment decision (24).

Strengths and Limitations

The strengths of our data include nationwide representative cohort of people with verified AD diagnosis, as well as use of validated registers for outcome assessment. The study was conducted in a country with state-funded health care. This may affect the generalizability of findings to countries with substantially different health care organizations, particularly countries with large socioeconomic or ethnic disparities in access to health care. Further, as this study was based on administrative registers, we were not able to assess preferences or cognitive outcomes, symptom improvement and quality of life. We also lacked data on services provided to home, which could have affected the readmission risk. Similarly, we had no information about living alone which may affect mortality or readmission rate (25).We could not assess postprocedural cognitive outcomes or delirium which are associated with readmission and mortality risk (26). However, although postoperative cognitive decline and delirium are common after CABG, their occurrence after PCI was not high in a previous study (27). Unfortunately, there are no previous studies on the incidence of postprocedural delirium in people with AD, so it is difficult to know how much delirium would

Table 3. Rates and Risks of Mortality After Revascularization Procedures Associated With AD

	AD (N = 415)		No AD (N = 5644)		Hazard Ratio (95% CIs)*	
	Number of Events (n)	Event/10 000 Person-years	Number of Events (n)	Event/10 000 Person-years	Unadjusted	Adjusted[a]
Overall mortality						
1-year	46	4.42	498	2.76	1.25 (0.92–1.69)	1.04 (0.75–1.42)
3-year	109	3.30	888	2.00	1.65 (1.35–2.02)	1.42 (1.15–1.74)
1-year mortality stratified by electivity (p interaction = .023)						
Any elective	9	1.7	184	2	0.89 (0.46–1.75)	0.51 (0.24–1.11)
Emergency	23	4.1	203	3.5	1.18 (0.77–1.82)	1.22 (0.79–1.90)
Not known	14	5	111	3.5	1.40 (0.80–2.44)	1.42 (0.80–2.51)
3-year mortality stratified by electivity (p interaction <.0001)						
Any elective	27	2.1	366	1.6	1.30 (0.88–1.92)	0.96 (0.63–1.46)
Emergency	53	4	330	2.4	1.66 (1.24–2.22)	1.71 (1.27–2.31)
Not known	29	4.4	192	2.5	1.73 (1.17–2.55)	1.85 (1.24–2.75)

Note: AD = Alzheimer's disease; CI = Confidence interval.

[a]Adjusted for age (at revascularization date), sex, hospital district, calendar year of revascularization, comorbidities (heart failure, hypertension, atrial fibrillation, stroke, diabetes, and asthma/COPD), statin use, total days in procedural unit, and required assistance level at discharge from procedural unit, and type of revascularization (CABG/PCI).

*HR calculated using No AD as a reference group.

Table 4. Association of AD With Readmission

	AD (N = 415)		No AD (N = 5630)		Hazard Ratio (95% CIs)*	
	Number of Events (n, %)	Event/10 000 Person-years	Number of Events (n, %)	Event/10 000 Person-years	Unadjusted	Adjusted[a]
Readmission within 30 days						
Any readmission	122 (29.4)	120.7	1779 (31.6)	131.5	0.91 (0.76–1.10)	0.97 (0.80–1.17)
-Due to CAD	28 (6.7)	27.7	500 (8.9)	37.0	0.75 (0.51–1.10)	0.7 (0.50–1.08)
Readmission within 90 days						
Any readmission	205 (49.4)	87.8	3274 (58.2)	108.6	0.82 (0.70–0.93)	0.85 (0.74–0.98)
-Due to CAD	48 (11.6)	20.6	1073 (18.0)	35.6	0.58 (0.44–0.78)	0.59 (0.44–0.79)

Note: AD = Alzheimer's disease; CAD = Coronary artery disease; CI = Confidence interval.

[a]Adjusted for age (at revascularization date), sex, hospital district, calendar year of revascularization, comorbidities (heart failure, hypertension, atrial fibrillation, stroke, diabetes, and asthma/COPD), statin use, total days in period of care, and required assistance level at discharge from period of care, and type of revascularization (CABG/PCI).

*HR calculated using No AD as a reference group.

impact our results. As majority of revascularizations in our study were PCIs, we suppose that delirium, or concerns about delirium following elective PCI can only partly explain the results. Although we lacked data on severity of coronary artery disease, Alzheimer's disease or functional capacity, we used required level of assistance at discharge as an indicator of overall health status. We were also able to assess whether stays in nursing home or municipal hospital affected the readmission rate. However, residual confounding cannot be ruled out.

Conclusion

Persons with and without AD had similar mortality after elective revascularization. However, the association with higher 3-year and inpatient mortality in people with AD was observed with emergency procedures. These findings in conjunction with lower revascularization rate especially for elective procedures raise questions on the threshold for elective procedures in people with AD.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

Acknowledgment

The authors thank Prof. Juha Hartikainen for confirming the changes in electivity coding on the extra sheet of cardiac patient.

Funding

M.V. was funded by the Schlumberger Foundation Faculty for The Future Program. A.M.T. acknowledges funding from Academy of Finland (grants 295334, 307232, 327152).

Author Contributions

M.V., M.K., H.T., R.K., S.H., and A.M.T planned the study. M.V. and A.M.T. had full access to all the data in the study. A.M.T. preprocessed the data. M.V. and A.M.T. performed statistical analyses, takes responsibility for the integrity of the data and the accuracy of the data analysis. M.V. drafted the manuscript. All authors contributed to the interpretation of the data, revised the manuscript, and approved the final manuscript.

Sponsor's Role

Funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

Conflict of Interest

H.T. has participated in research projects funded by grants from Janssen-Cilag and Eli Lilly, with grants paid to the employing institution. H.T. reports personal fees from Janssen-Cilag. M.V., M.K., R.K., S.H., and A.M.T have nothing to disclose.

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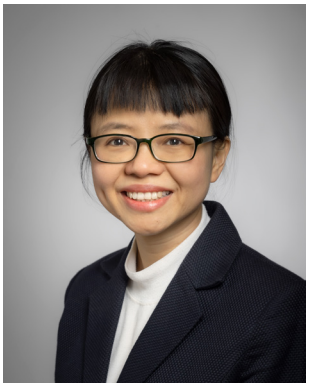

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Cardiovascular diseases are common among people with Alzheimer's disease (AD). However, there is a lack of information on the treatment of cardiovascular diseases in this population. This nationwide register-based study investigated the prevalence of cardiovascular drug use before and after AD diagnosis, and described the time and factors associated with statin discontinuation in persons with AD compared to persons without AD. Furthermore, the incidence of coronary artery revascularizations after AD diagnosis and postoperative outcomes between persons with and without AD were compared.

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**PUBLICATIONS OF
THE UNIVERSITY OF EASTERN FINLAND**
Dissertations in Health Sciences

ISBN 978-952-61-5148-9
ISSN 1798-5706