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

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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 5,909 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.

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

Figure 1. Flowchart of cohort definition.
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 mortality and sickness in period of care was studied by logistic regression.

To compare the rehospitalization 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, hypotension 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
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.
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 2. Comparison of Characteristics of Revascularized Persons of AD and Non-AD Cohort |
|---------------------------------------------|---------------|---------------|
|                                | AD (N = 448) | No AD (N = 5909) |
| Age at revascularization (mean, SD)       | 80.0 (6.2)   | 80.4 (6.1)     |
| Average time to revascularization (median, IQR) years | 2.0 (0.8–3.8) | 3.0 (1.4–5.1) |
| Type of revascularization (n, %)           |              |               |
| PCI                                         | 414 (92.4)  | 4599 (77.8)   |
| CABG                                        | 34 (7.6)    | 1310 (22.2)   |
| Electivity (n, %)                           |              |               |
| 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)   |
| Heart failure                               | 89 (19.9)   | 1159 (19.6)   |
| Atrial fibrillation                         | 82 (18.3)   | 1114 (18.9)   |
| Stroke                                      | 62 (13.8)   | 524 (8.9)     |
| Diabetes                                    | 103 (23.0)  | 1097 (18.6)   |
| Asthma/COPD                                 | 68 (15.2)   | 857 (14.5)    |
| Statin use                                  | 230 (51.3)  | 3207 (54.3)   |
| Mortality during period of care (n, %)      |              |               |
| 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       |              |               |
| Length of stay (median, IQR)               | 3 (1–6)     | 4 (1–7)       |
| Required level of care, n (%)               |              |               |
| 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) |     |               |
| Total length of stay (median, IQR)         | 3 (1–6)     | 4 (1–7)       |
| Required level of care, n (%)               |              |               |
| 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.
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.

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Author Contributions
M.V., M.K., T.R., 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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