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Coronary artery disease and risk of adverse cardiac events and stroke

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ABSTRACT

Background: Patients with acute myocardial infarction are at increased risk of ischemic stroke. Previous myocardial infarction is an important part of risk assessment for ischemic stroke. However, there is a lack of information regarding the association between the severity and extent of coronary artery disease and long-term risk of ischemic stroke.

Materials and methods: A cohort study of coronary angiographies performed in Western Denmark from January 1, 2003 to December 31, 2012. Patients were stratified according to the number of vessels affected by obstructive coronary artery disease (lumen narrowing ≥50%) at the time of angiography: 0-, 1-, 2- or 3-vessel disease and diffuse vessel disease. We followed patients for a maximum of 7 years. Endpoints were all-cause death, cardiac death, myocardial infarction, and ischemic stroke. Cumulative risks and crude and adjusted rate ratios were estimated.

Results: The study population included 78,195 patients. Of these, 32,061 (41.0%) had 0 vessel disease, 6,205 (7.9%) had diffuse vessel disease, 20,202 (25.8%) had 1 vessel disease, 10,675 (13.7%) had 2 vessel disease, and 9,038 (11.6%) had 3 vessel disease. Median follow up was 3.6 years (inter quartile range 1.7-6.0 years). Increasing severity of obstructive coronary artery disease was associated with an increasing risk of all-cause death, cardiac death, MI, and ischemic stroke during follow-up.
Conclusions: The presence and extent of coronary artery disease was associated with an incremental risk of not only death, cardiac death, myocardial infarction, but also ischemic stroke over a 7-year period.

Keywords: coronary artery disease, coronary angiography, ischemic stroke, acute myocardial infarction.

INTRODUCTION

Patients with acute myocardial infarction (MI) are at increased risk of ischemic stroke during their initial hospitalization (11.1 per 1000 MI) and this risk remains relatively high within the first year after MI (21.4 per 1000 MI).[1] Hence, history of MI is an integral part of current risk assessment for ischemic stroke.[2] However, information is lacking on the association between the severity of CAD and long-term risk of future ischemic stroke among patients without prior MI.

The Western Denmark Heart Registry (WDHR) is a clinical database that has collected information on >120,000 coronary angiography procedures (CAGs) since 1999, including a detailed description of the severity of CAD.[3]

We investigated long-term clinical outcomes among patients with varying severity and extent of CAD. Linkage of CAG results obtained from the WDHR with outcomes registered in clinical databases, such as the Danish National Patient Registry (DNPR) and the Danish Register of Causes of Death, allowed us to examine the association between severity of CAD and clinical outcomes.
MATERIALS AND METHODS

Databases: Danish registries are based on the Civil Registration System,[4] which assigns a unique 10-digit personal identifier to each Danish resident at birth or upon immigration. This identifier is used by every health registry in Denmark. The WDHR collects data on CAG procedures performed in Western Denmark (population = 3.3 million people). The DNPR registers each patient encounter with the Danish health care system and includes hospital discharge diagnoses.[5] The Danish National Cause of Death Registry records the causes of every death in Denmark.[6] Linkage of these health registries using the personal identifier ensures highly accurate follow-up information and minimizes risk of loss to follow up.

Patient selection: Our initial cohort was defined as every patient registered in the WDHR who underwent invasive CAG during January 1, 2003 to December 31, 2012. For patients who underwent multiple examinations during the inclusion period, the first CAG served as the index examination. A small number of patients were excluded due to invalid personal identifiers or emigration before their procedure (n=85). Patients with missing information on extent of coronary artery disease were also excluded (n=735), as were patients with prior MI, percutaneous coronary intervention, and/or coronary artery bypass grafting registered in either the WDHR or the DNPR (n=30,767). Patients were stratified according to extent of CAD, i.e., the number of pericardial coronary arteries with obstructive CAD (defined as ≥50% stenosis) at the time of first CAG: 0-vessel disease (0-VD), 1-VD, 2-VD, 3-VD, and diffuse VD, defined as non-obstructive CAD (i.e., <50% lumen narrowing).

Comorbidity: Comorbidities were ascertained through the DNPR based on International Classification of Diseases, Tenth Revision (ICD-10) codes, using a 5-year look-back period from the time of the index CAG. A Charlson Comorbidity Index (CCI) score was estimated for each patient at the time of their index CAG.[7]
**All-cause death:** The Civil Registration System provided data on all-cause death, *i.e.*, the patients’ vital status (dead, alive, or emigrated). In case of emigration, patient data were censored.

**Cardiac death:** Cardiac death was defined as death resulting from ischemic heart disease (ICD-10 codes I-20 to I-25), sudden cardiac death (ICD-10 code I-46), death from ventricular tachycardia (ICD-10 code I-47.2), death due to heart failure (ICD-10 code I-50), or unspecified sudden death (R-96), as recorded on death certificates maintained by the Danish Register of Causes of Death. Because we were unable to access death certificates completed after December 31, 2011, cardiac death could only be documented from January 1, 2003 to December 31, 2011. In case of emigration or non-cardiac death, patient data were censored.

**Myocardial infarction:** MI records were obtained from the DNPR using the ICD-10 code for MI (DI-21), including either a primary (A) or secondary (B) discharge diagnosis from an acute hospital admission.[8] MI follow-up was initiated 30 days after the index CAG since interhospital patient transfers often lead to double registration of an MI within the first 30 days following a CAG procedure. After this period, the sensitivity and specificity of the MI diagnosis have been found to be 94% and 98%, respectively.[8] Data were censored in case of death or emigration.

**Ischemic stroke:** Ischemic stroke diagnoses were ascertained using the DNPR (ICD-10 codes: DI-63, DI-630-635, and DI-638-639) to identify primary (A) discharge diagnoses from an acute hospital admission. In case of emigration or death, patient data were censored.

**Medication:** Records of treatment with statin (Anatomical Therapeutic Chemical (ATC) codes: C10AA01-05, C10AA07), aspirin (ATC codes: B01AC06, N02BA01), adenosine diphosphate receptor inhibitors (ATC-codes: B01AC04, B01AC22, B01AC24),

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beta-blocker (ATC codes: C07AA-AB) angiotensin converting enzyme (ACE)-inhibitor (ATC codes: C09AA01-06, C09AA10), and angiotensin-II receptor blocker (ARB) (ATC codes: C09CA01, C09CA03-04, C09CA06-08) were obtained through the Danish National Database of Reimbursed Prescriptions.[9] Due to lack of database coverage before 2004, prescription reimbursement data could only be obtained in patients examined from 2004-2012.

**Statistical analyses:** Follow-up began on the day of discharge from the hospital stay during which the index CAG was performed (except for MI, for which event registration began 30 days after this discharge date). Follow-up continued until death, emigration, or for 7 years, whichever came first. We counted endpoint events during follow-up for each patient subgroup defined by extent of CAD. Cumulative incidence curves were constructed based on cumulative rates of all-cause death, cardiac death, MI, and ischemic stroke. Cumulative incidences were calculated and unadjusted and adjusted rate ratios (RRs) were estimated during 0-84 months (1-84 months for MI) of follow-up, using patients with 0-VD as reference. RRs were adjusted for age, gender, treatment for hypertension, diabetes mellitus, CCI score, smoking status, procedural priority (urgency of intervention) (Model 1), and further for BMI (Model 2). Modified Poisson regression was used in adjustment analysis.[10] We conducted a stratified analysis dividing patients based on CAG referral diagnosis: MI patients (i.e. ST-segment elevation MI and non ST-segment elevation MI) and non-MI patients (i.e. unstable angina pectoris, stable angina pectoris, etc.). We used SAS software version 9.2 (SAS Institute Inc., Cary, NC, USA) for all analyses.

**Ethical considerations:** This study complies with the Declaration of Helsinki and was approved by the Danish Data Protection Agency (Record no. 2012-41-0914).
RESULTS

A total of 78,195 patients without a history of ischemic heart disease underwent CAG. Among these patients, 32,061 (41.0%) had 0-VD, 6,205 (7.9%) had diffuse VD, 20,202 (25.8%) had 1-VD, 10,675 (13.7%) had 2-VD, and 9,038 (11.6%) had 3-VD (Figure 1). Median follow-up was 3.6 years (IQR 1.7-6.0).

Baseline characteristics: Baseline patient characteristics are displayed in Table 1. Patients with obstructive CAD (1-3 VD) were more commonly male, older, receiving treatment for hypertension and/or hypercholesterolemia, and diabetic. Patients with obstructive CAD had the highest use of aspirin/dual antiplatelet therapy (86.8%-87.3%), follow by patients with diffuse CAD (70.7%) after CAG. Patients with diffuse CAD were most often in statin and antihypertensive treatment prior to examination. After CAG, risk-modifying treatment did increase in all patient groups, however, patients with obstructive CAD were now most often in treatment. Patients with obstructive CAD more often underwent CAG as an acute or subacute procedure due to suspicion of MI. Patients with diffuse VD were more likely to receive treatment for hypercholesterolemia and hypertension at the time of their CAG examination. Patients with 0-VD and diffuse VD were more likely to undergo an elective procedure due to suspicion of stable angina pectoris, cardiomyopathy, or valve disease.

Clinical endpoints: During follow-up, 9,748 patients died, 2,143 died a cardiac death, 2,605 had a MI, and 1,391 had ischemic stroke. Numbers of events stratified by extent of CAD are shown in Supplement eTable 1. We observed an incremental risk of all-cause death, cardiac death, and MI with increasing number of affected coronary vessels (Table 2 and Figure 2). Diffuse VD more than doubled the risk of MI as compared to 0-VD but the risk remained lower than for patients with 1-, 2-, or 3-VD. Patients with 0-VD also had the lowest 7-year cumulated risk of ischemic stroke (2.33%) while patients with diffuse CAD.

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(4.47%) and 3-VD (5.15%) had the highest risks (Table 2). The adjusted analyses confirmed these above-mentioned incremental risks of adverse events (Table 3) and showed that the adjusted RRs for diffuse CAD and 3-VD were identical with regard to the risk of stroke.

In stratified analyses of patients with and without MI at index CAG, we confirmed an increased risk of stroke for both subsets of patients although only reaching statistical significance for patients without MI (eTable S2 and eTable S3).

DISCUSSION

Our results documented that the presence and extent of CAD was associated with an increased risk of all-cause death, cardiac death, MI. The novelty of our findings lies in the demonstration of a similar association with ischemic stroke. Even though the number of vessels with obstructive CAD was associated with a higher risk of events, also patients with diffuse VD had a risk of MI that was higher than for patients with 0-VD but lower than 1-VD. Notably, patients with diffuse VD and 3-VD were at highest risk of future ischemic stroke compared to 0-VD.

Our novel findings are based on a long-term examination of the relationship between documented CAD anatomy, including disease severity and cardiovascular events. The WDHR allowed systematic collection of detailed CAG findings, and linkage to the well-validated Danish registries allowed robust ascertainment of outcome events at follow-up. Our observations, showing that severity of CAD was generally associated with an increasing risk of cardiovascular events (death and MI), are perhaps unsurprising but extended a previously reported relationship between CAD and 1-year risk of recurrent MI and mortality by showing that this association was also present at 7-year follow-up.[11] The most novel observation, however, is that the severity of CAD is also a predictor of ischemic stroke. In this regard, one difference stands out. Patients with diffuse non-obstructive CAD had a risk of MI that was
higher than for patients with 0-VD but lower than for patients with 1-VD. However, they had a risk of ischemic stroke similar to patients with 3-VD. If we accept the premise that the burden of coronary atherosclerosis reflects the peripheral atherosclerotic burden,[12,13] then the atherosclerotic burden in patients with diffuse VD may more comparable to patients with 3-VD leading to the similar risk of stroke. A greater extent of atherosclerosis may also be associated with an increased prothrombotic state and with more abnormalities of coagulation factors and platelets.[14-16] In contrast, patients with 1-VD may only have a focal coronary stenosis with limited atherosclerosis outside the culprit lesion and have a small risk of peripheral artery disease. Moreover, we do not know the mechanism behind the association between the extent of CAD and ischemic stroke. Increasing severity of CAD may be linked to a higher likelihood of atrial fibrillation that subsequently leads to a higher risk of ischemic stroke.

We discovered major differences in post-exam treatment between patient groups. Patients with diffuse CAD were less likely to be in risk-modifying treatment such as aspirin, ADP-inhibitors, statins, and antihypertensive agents compared to patients with obstructive CAD. Aspirin is currently recommended for patients with high risk of cardiovascular disease, including ischemic stroke.[17] Statins have similarly proved to reduce stroke incidence in patients with high risk of atherosclerosis, and is recommended in stroke prevention in patients with high risk of cardiovascular events.[17-19] Antihypertensive agents such as beta-blockers, ACE-inhibitors, and ARBs have also been found to be beneficial in primary prevention of stroke.[20,21] Management of patients with diffuse CAD, for whom there are less clear guidelines, seems insufficient. Lower rates of statins, anti-thrombotic therapy and anti-hypertensive agents in patients with diffuse CAD compared to obstructive CAD may have contributed to the increased risk of ischemic stroke. Hence, our
results may reflect the importance of more intensive preventative treatment of patients with diffuse CAD.

CAD and ischemic stroke share many risk factors, as reflected by the CHA2DS2-VASc score, which is used to assess stroke risk in patients with atrial fibrillation.[2,22] One component of the CHA2DS2-VASc score is vascular disease, which covered peripheral artery disease, aortic plaque, and MI in its initial description.[2,22] Although our study was not limited to patients with atrial fibrillation, our results demonstrate that the ischemic stroke risk correlated with the severity of CAD, even among patients without a prior MI. Our results may thus suggest that presence and severity of CAD, including diffuse CAD, should be included as part of the vascular disease component of the CHA2DS2-VASc score, i.e. our study underscores the importance of considering not only history of MI, but also extent of CAD, when assessing the risk of ischemic stroke.

CAD and ischemic stroke share other common features and are caused in part by the common pathology of atherosclerosis.[1,2,22] Congestive heart failure can be caused by CAD and is a risk factor for ischemic stroke.[1] Hypertension, older age, and diabetes are risk factors for both CAD, atrial fibrillation, and ischemic stroke.[1,17] Moreover, recent studies suggest that CAD and ischemic stroke even share a similar genetic pathogenesis.[23-25] As such, the observed association between severity of CAD and risk of ischemic stroke appears intuitive. Currently, the severity of CAD as a risk factor for stroke has not been validated as part of risk scores for ischemic stroke in patients with or without atrial fibrillation. Our data provide a novel background for this approach in future studies.

Even though patients with diffuse VD lack significant coronary obstruction, they still were found to have a more than doubled risk of MI compared to patients with 0-VD. The relation of MI to severity of coronary lesions per se is controversial.[11] The question
remains whether disease severity depends on the severity of focal stenosis or the extent of
diffuse CAD. MI events can occur in association with non-obstructive moderate lesions,
while more severe calcified lesions may persist as stable lesions, with low propensity for
plaque rupture leading to a MI event.[11,26,27] The Providing Regional Observations Study
Predictors of Events in the Coronary Tree (PROSPECT) study demonstrated that while
plaque area stenosis did not always cause significant coronary stenosis, it was associated with
future cardiovascular events.[28] This is in overall accordance with the present study.

Our study is limited by its registry design and its dependency on coding
accuracy. However, the Danish registries are well validated and the diagnoses of MI,
ischemic stroke, and other endpoints have been validated.[8] Left ventricular function is an
important factor to consider when assessing ischemic stroke risk. However, due to a high rate
of missing values of left ventricular ejection fraction, we omitted these data in the study. The
coding of CAD severity is limited to the available scoring system in WHDR. E.g., a patient
with 1-VD may also have diffuse VD but will only be allocated to the 1-VD group.
Moreover, the distinction between 0-VD and diffuse VD is not clearly defined and is
operator-dependent. Nevertheless, our data clearly showed that the PCI operators on a group
level could distinguish between 0-VD and diffuse VD. Other methods to assess CAD, such as
coronary computed tomography, may provide a more accurate tool for description of CAD
severity. Associated cardiovascular prevention strategies and drug therapies, such as blood
pressure lowering, smoking cessation, statin use, and post-intervention antiplatelet treatment,
which are also confounders, should principally tend to limit differences. Finally, the current
data are limited to maximum 7-year follow-up and the interpretation of our data cannot be
extended beyond this period.
In conclusion, the increasing severity of CAD was associated with increasing risk of not only cardiac events (death, cardiac death, and MI) but also ischemic stroke. Diffuse VD and 3-VD was associated with the highest risk of future ischemic stroke.

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FIGURE LEGENDS

**Figure 1.** Flow chart illustrating patient recruitment.

**Figure 2.** Cumulated 7-year incidence of all-cause death (A), cardiac death (B), myocardial infarction (C) and ischemic stroke (D).
Table 1. Baseline characteristics at the time of coronary angiography.

| Characteristic                                      | 0 VD (n=32,061) | diffuse VD (n=6,205) | 1 VD (n=20,202) | 2 VD (n=10,675) | 3 VD (n=9,038) |
|----------------------------------------------------|------------------|----------------------|-----------------|-----------------|----------------|
| Median follow up (IQR)                             | 3.9 (1.9-6.1)    | 2.3 (0.9-4.0)        | 3.7 (1.7-6.1)   | 3.8 (1.6-6.2)   | 3.7 (1.4-6.2)  |
| Male                                               | 48.9%            | 57.8%                | 67.5%           | 73.2%           | 75.1%          |
| Age (IQR)                                          | 61 (52-69)       | 67 (59-74)           | 64 (56-73)      | 67 (60-75)      | 70 (62-77)     |
| Family history of coronary artery disease          | 39.1%            | 42.0%                | 40.0%           | 38.1%           | 38.2%          |
| Hypertension                                       | 44.8%            | 60.5%                | 44.6%           | 50.0%           | 55.6%          |
| Hypercholesterolemia                               | 37.8%            | 53.3%                | 38.3%           | 44.6%           | 48.8%          |
| Diabetes                                           | 9.6%             | 16.4%                | 10.9%           | 13.4%           | 17.3%          |
| Active smoker                                      | 23.3%            | 27.0%                | 36.3%           | 33.0%           | 28.8%          |
| Former smoker                                      | 32.2%            | 39.2%                | 32.9%           | 34.7%           | 37.4%          |
| Aspirin, only                                      |                  |                      |                 |                 |                |
| Before                                             | 42.4%            | 51.1%                | 35.2%           | 42.3%           | 49.3%          |
| After                                              | 39.5%            | 62.4%                | 18.6%           | 21.6            | 37.6%          |
| Dual anti platelet therapy                         |                  |                      |                 |                 |                |
| Before                                             | 0.6%             | 0.7%                 | 0.5%            | 0.4%            | 0.9%           |
| After                                              | 3.8%             | 8.3%                 | 68.3%           | 65.7%           | 49.2%          |
| Statin                                             |                  |                      |                 |                 |                |
| Before                                             | 37.3%            | 52.0%                | 34.2%           | 40.4%           | 45.5%          |
| After                                              | 44.1%            | 75.3%                | 89.6%           | 91.2%           | 89.3%          |
| Beta-blocker                                       |                  |                      |                 |                 |                |
| Before                                             | 40.5%            | 42.8%                | 31.4%           | 35.8%           | 40.7%          |
| After                                              | 46.2%            | 57.4%                | 76.6%           | 79.4%           | 82.1%          |
| Angiotensin converting enzyme                      |                  |                      |                 |                 |                |
| Before                                             | 20.9%            | 25.2%                | 16.9%           | 19.6%           | 23.1%          |
| After                                              | 26.5%            | 31.0%                | 37.4%           | 40.0%           | 43.7%          |
| Angiotensin-II receptor blocker                    |                  |                      |                 |                 |                |
| Before                                             | 8.7%             | 11.8%                | 8.2%            | 9.1%            | 9.8%           |
| After                                              | 10.7%            | 13.6%                | 11.5%           | 11.9%           | 12.1%          |
| Charlson Comorbidity Index score (%)               |                  |                      |                 |                 |                |
| 0                                                  | 58.1             | 48.2                 | 61.5            | 57.7            | 52.3           |
| 1                                                  | 21.7             | 22.9                 | 18.6            | 19.9            | 21.3           |
| 2                                                  | 11.8             | 15.1                 | 11.4            | 12.2            | 13.8           |
| ≥3                                                 | 8.5              | 13.8                 | 8.5             | 10.1            | 12.6           |
| BMI†                                               |                  |                      |                 |                 |                |
| Median BMI (IQR)                                   | 26.4 (23.6-29.8) | 26.8 (24.0-30.1)     | 26.5 (24.1-29.4)| 26.5 (24.2-29.4)| 26.5 (24.2-29.4)|
| <18.5                                              | 1.6%             | 1.7%                 | 1.2%            | 1.1%            | 0.9%           |
| 18.5-25                                            | 30.7%            | 29.7%                | 27.6%           | 27.3%           | 27.0%          |
| 25-30                                              | 32.5%            | 36.6%                | 36.7%           | 36.3%           | 37.0%          |
| >30                                                | 20.8%            | 23.5%                | 17.3%           | 18.4%           | 17.2%          |
| Procedural priority (%)                            |                  |                      |                 |                 |                |
| Acute                                              | 7.4              | 6.0                  | 34.3            | 29.5            | 25.1           |
| Subacute                                           | 21.5             | 21.4                 | 24.7            | 26.5            | 28.6           |
| Elective                                           | 71.0             | 72.6                 | 41.0            | 44.0            | 46.3           |
| Procedural indication (%)                          |                  |                      |                 |                 |                |
| STEMI ‡                                            | 4.3              | 3.8                  | 32.4            | 27.8            | 22.0           |
| NSTEMI ‡                                           | 8.1              | 9.7                  | 18.4            | 20.1            | 22.4           |
| Unstable AP                                        | 2.2              | 3.2                  | 1.9             | 1.8             | 1.6            |
| Stable AP                                          | 46.0             | 50.5                 | 32.9            | 36.0            | 38.5           |
| Arrhythmia                                         | 3.6              | 3.3                  | 1.2             | 1.1             | 1.6            |
| Valvopathy or aortic disease                       | 11.7             | 9.1                  | 5.2             | 5.8             | 4.9            |
| Cardio-                                            | 8.4              | 6.7                  | 2.5             | 2.8             | 3.6            |
Table 2. Cumulated 7-year risk of all-cause death, cardiac death, myocardial infarction, and ischemic stroke.

|                  | All-cause death (95% CI) | Cardiac death (95% CI) | Myocardial infarction (95% CI) | Ischemic stroke (95% CI) |
|------------------|--------------------------|------------------------|-------------------------------|-------------------------|
| Control          | 0.1                      | 0.0                    | 0.0                           | 0.0                     |
| Unspecified AP<sup>b</sup> | 4.5                      | 6.8                    | 1.0                           | 0.7                     |
| Cardiac arrest   | 0.2                      | 0.1                    | 0.1                           | 0.3                     |
| Other            | 8.2                      | 6.3                    | 2.3                           | 1.8                     |
| Missing data     | 2.2                      | 0.5                    | 2.0                           | 1.9                     |

<sup>a</sup>VD = vessel disease  
<sup>b</sup>IQR = interquartile range  
<sup>c</sup>BMI = body mass index at the time of examination (kg/m²)  
<sup>d</sup>STEMI = ST-segment elevation myocardial infarction  
<sup>e</sup>NSTEMI = non-ST segment elevation myocardial infarction  
<sup>f</sup>AP = angina pectoris
Table 3. 7-year rate ratio of all-cause death, cardiac death, myocardial infarction, and ischemic stroke.

|                                | Unadjusted RR<sup>a</sup> (95% CI<sup>b</sup>) | p-value | Adjusted RR<sup>c</sup> (95% CI) | p-value | Adjusted RR<sup>d</sup> (95% CI) | p-value |
|--------------------------------|-----------------------------------------------|---------|----------------------------------|---------|----------------------------------|---------|
| **All-cause death**            |                                               |         |                                  |         |                                  |         |
| 0 VD<sup>e</sup> (reference)  | 1                                             | -       | 1                                | -       | 1                                | -       |
| Diffuse VD                     | 1.56 (1.43-1.71)                               | <0.001  | 0.92 (0.83-1.02)                 | 0.10    | 0.91 (0.82-1.02)                 | 0.10    |
| 1 VD                           | 1.35 (1.28-1.43)                               | <0.001  | 0.90 (0.84-0.96)                 | <0.001  | 0.90 (0.84-0.96)                 | 0.002   |
| 2 VD                           | 1.86 (1.75-1.98)                               | <0.001  | 1.04 (0.97-1.11)                 | 0.28    | 1.05 (0.97-1.13)                 | 0.24    |
| 3 VD                           | 2.73 (2.58-2.90)                               | <0.001  | 1.34 (1.25-1.43)                 | <0.001  | 1.31 (1.21-1.42)                 | <0.001  |
| **Cardiac death**              |                                               |         |                                  |         |                                  |         |
| 0 VD (reference)               | 1                                             | -       | 1                                | -       | 1                                | -       |
| Diffuse VD                     | 1.92 (1.47-2.50)                               | <0.001  | 1.07 (0.79-1.44)                 | 0.67    | 0.98 (0.71-1.35)                 | 0.89    |
| 1 VD                           | 3.01 (2.62-3.47)                               | <0.001  | 1.57 (1.34-1.84)                 | <0.001  | 1.37 (1.14-1.65)                 | <0.001  |
| 2 VD                           | 5.45 (4.73-6.28)                               | <0.001  | 2.30 (1.95-2.72)                 | <0.001  | 2.10 (1.74-2.53)                 | <0.001  |
| 3 VD                           | 10.47 (9.16-11.95)                             | <0.001  | 3.95 (3.38-4.62)                 | <0.001  | 3.74 (3.14-4.46)                 | <0.001  |
| **Myocardial infarction**      |                                               |         |                                  |         |                                  |         |
| 0 VD (reference)               | 1                                             | -       | 1                                | -       | 1                                | -       |
| Diffuse VD                     | 2.55 (2.07-3.14)                               | <0.001  | 2.09 (1.67-2.61)                 | <0.001  | 2.11 (1.66-2.68)                 | <0.001  |
| 1 VD                           | 4.16 (3.67-4.71)                               | <0.001  | 3.26 (2.84-3.74)                 | <0.001  | 3.22 (2.76-3.75)                 | <0.001  |
| 2 VD                           | 5.26 (4.61-6.01)                               | <0.001  | 3.98 (3.43-4.63)                 | <0.001  | 4.07 (3.45-4.80)                 | <0.001  |
| 3 VD                           | 7.50 (6.59-8.53)                               | <0.001  | 5.47 (4.72-6.34)                 | <0.001  | 5.57 (4.73-6.55)                 | <0.001  |
| **Ischemic stroke**            |                                               |         |                                  |         |                                  |         |
| 0 VD (reference)               | 1                                             | -       | 1                                | -       | 1                                | -       |
| Diffuse VD                     | 1.92 (1.56-2.37)                               | <0.001  | 1.45 (1.16-1.81)                 | 0.0011  | 1.50 (1.18-1.90)                 | <0.001  |
| 1 VD                           | 1.34 (1.17-1.55)                               | <0.001  | 1.04 (0.89-1.23)                 | 0.59    | 1.05 (0.88-1.25)                 | 0.63    |
| 2 VD                           | 1.73 (1.48-2.02)                               | <0.001  | 1.19 (0.99-1.43)                 | 0.058   | 1.25 (1.02-1.53)                 | 0.0301  |
| 3 VD                           | 1.92 (1.56-2.37)                               | <0.001  | 1.45 (1.16-1.81)                 | <0.001  | 1.47 (1.20-1.79)                 | <0.001  |

<sup>a</sup> RR = rate ratio  
<sup>b</sup> CI = confidence interval  
<sup>c</sup> Model 1: RR adjusted for age, gender, Charlson Comorbidity Index score, hypertension, diabetes mellitus, smoking, and procedural priority  
<sup>d</sup> Model 2: RR adjusted for age, gender, Charlson Comorbidity Index score, hypertension, diabetes mellitus smoking, procedural priority, and Body Mass Index  
<sup>e</sup> VD = vessel disease
Figure 1. Flow chart over patient selection.

109,782 patients undergoing first CAG\(^a\)
- 99 patients with procedural emigration
- 109,683 patients
  - 735 patients with missing information on extent of CAD\(^b\)
  - 108,940 patients
    - 30,767 patients with previous MI, PCI, or CABG\(^c\)
    - 78,181 patients included
      - 32,061 patients with 0 VD\(^d\)
      - 6,205 patients with diffuse VD
      - 20,202 patients with 1 VD
      - 10,675 patients with 2 VD
      - 9,038 patients with 3 VD

\(^a\) CAG = coronary angiography
\(^b\) CAD = coronary artery disease
\(^c\) MI = myocardial infarction
\(^d\) PCI = percutaneous coronary intervention
\(^*\) CABG = coronary artery bypass grafting
\(^f\) VD = vessel disease
Figure 2. Cumulated 7-year incidence of all-cause death (A), cardiac death (B), myocardial infarction (C) and ischemic stroke (D).