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Comparison of Frequency of Ischemic Stroke in Patients With versus Without Coronary Heart Disease and Without Atrial Fibrillation

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ABSTRACT

Recent trials of antithrombotic therapy in patients with CAD have demonstrated substantial reductions in ischemic stroke. Our aim was to examine ischemic stroke risk in patients with CAD and to identify those at highest risk. We examined ischemic stroke risk in patients without AF undergoing coronary angiography (CAG) between 2004 and 2012. Patients were stratified according to presence or absence of CAD and further stratified by extent of CAD (0 VD, 1 VD, 2 VD, 3 VD, and diffuse VD). Endpoints were composites of ischemic stroke, transient ischemic attack (TIA), and systemic embolism, as well as major adverse cardiovascular and cerebrovascular events (MACCE) defined as cardiac death, myocardial infarction, plus ischemic stroke/TIA/systemic embolism. Adjusted incidence rate ratios (IRR) were estimated. A total of 68,829 patients were included, 25,032 had 0 VD, 4,736 had diffuse VD, 18,471 had 1 VD, 10,588 had 2 VD, and 10,002 had 3 VD. Median follow-up was 4.0 years. CAD extent was associated with an increased risk of stroke/TIA/systemic embolism (1VD: adjusted IRR 1.02, 95% CI 0.90-1.16; diffuse VD: adjusted IRR 1.22, 95% CI 1.02-1.47; 2 VD: adjusted IRR 1.28, 95% CI 1.12-1.45; 3 VD: adjusted IRR 1.37, 95% CI: 1.20-1.55) compared to patients with 0 VD. Presence and extent of CAD were also associated with MACCE. In conclusion, CAD is associated with an increased risk of stroke/TIA/systemic embolism and MACCE in patients without AF, and patients with coronary MVD are at highest risk and may be candidates for treatment strategies aiming at reducing ischemic stroke incidence.

Key words: coronary artery disease, coronary angiography, ischemic stroke, transient ischemic attack.

Cerebral ischemia and coronary artery disease (CAD) share a common pathophysiology.[1] Recent randomized cardiovascular outcome trials have used CAD or obstructive multi-vessel disease (MVD) as risk factors and inclusion criteria in order to obtain relative, and relevant, high-risk populations.[2, 3] Some of these studies have shown a benefit that primarily was related to a reduction in ischemic stroke.[2, 4] However, the association between extent of CAD and risk of ischemic stroke is not well described. Given ageing populations combined with the medical consequences and economic burden created by ischemic stroke, further understanding of risk identification and possible prevention of ischemic stroke in patients with CAD is of major relevance. The Western Denmark Heart Registry contains information on >240,000 coronary angiographies (CAG) registered since 1999.[5] The current study examined the risk of ischemic stroke, transient ischemic attack (TIA), and systemic embolism, as well as major adverse cardiovascular and cerebrovascular events (MACCE), according to presence and extent of CAD on CAG in patients without atrial fibrillation (AF).

METHODS

The Western Denmark Heart Registry is a regional database that collects information from every invasive cardiac procedure including CAG in Western Denmark.[6] Patients are identified through a unique 10-digit number, which is used in every Danish national and regional registry. The personal identifier can be used to cross-link patient information with other registries. The Civil Registration System registers, among other things, vital status on every Danish resident.[7] The Danish National Patient Registry contains discharge diagnoses from each contact a Danish resident has with the universally covering, taxpayer funded Danish health care system, including visits to outpatient clinics and hospitalizations.[8] The Danish National Database of Reimbursed Prescriptions provides information on all redeemed prescription medicine since 2004.[9] Finally, the Danish

Register of Causes of Death records underlying and contributing causes of death stated in death certificates.[10]

We included patients who underwent CAG registered in the Western Denmark Heart Registry from July 1, 2004 to July 1, 2012. Patients aged <18 years, patients with previous diagnoses of ischemic stroke/TIA or AF in the Danish National Patient Registry, or who had had redeemed ≥1 prescription of oral anti-coagulant treatment including new oral anti-coagulants6 months before CAG. With follow-up starting 30 days after CAG, patients redeeming prescriptions of oral anti-coagulant agents within 30 days after CAG were excluded.[8, 9] Patients who died or emigrated ≤30 days after CAG were also excluded. We stratified patients according to presence or absence of CAD. In subgroup analyses, we further stratified patients according to extent of CAD (0-vessel disease (VD), 1 VD, 2 VD, 3 VD, and diffuse VD). Diffuse VD was defined as non-obstructive CAD (1-49% lumen narrowing) in ≥1 coronary vessel.

Congestive heart failure was defined as an ejection fraction ≤40% registered in the Western Denmark Heart Registry, or diagnoses of congestive heart failure or left ventricular dysfunction before or 1 month after CAG obtained from the Danish National Patient Registry. Hypertension was defined as receiving treatment for hypertension at the time of CAG in the Western Denmark Heart Registry or diagnoses of hypertension registered in the Danish National Patient Registry either before or 1 month after CAG. Diabetes was defined as 1) in treatment with insulin ± oral glucose lowering treatment, oral glucose lowering treatment, or dietary treatment for diabetes mellitus in the Western Denmark Heart Registry, 2) having diabetes diagnoses before or 1 month after CAG in the Danish National Patient Registry, or 3) having redeemed ≥1 prescription of diabetes medication 6 months before or 1 months after CAG from the Danish National Database of Reimbursed Prescriptions. Previous history of peripheral vascular disease was a composite of peripheral arterial disease (PAD) and aortic plaque either before or 1 month after CAG from the

Danish National Patient Registry. Previous diagnosis of renal disease defined by the Charlson Comorbidity Index before or 1 month after CAG from the Danish National Patient Registry.[11] Smoking status was defined as either active smoker or never/former smoker at the time of CAG examination as listed in the Western Denmark Heart Registry.

Treatment with either statin or anti-platelet agents (aspirin and/or adenosine diphosphate receptor (ADP) inhibitors) was defined as redeeming ≥1 prescription 6 months before and 1 month after CAG obtained through the Danish National Database of Reimbursed Prescriptions.

Endpoints included a composite of primary and secondary diagnoses of ischemic stroke, TIA, or systemic embolism during hospitalization obtained from the Danish National Patient Registry. We also examined MACCE, which was a composite of cardiac death from the Danish Register of Causes of Death, primary or secondary diagnosis of myocardial infarction (MI) during and acute hospitalization from the National Patient Registry, and ischemic stroke/TIA/systemic embolism. Follow-up started 1 month after CAG for multiple reasons: 1) to avoid the risk of double registration of the same CAG related MI event, when patients were transferred from PCI center to a regional hospital, 2) to be able to detect changes in patient medication and registration of comorbidity as a results of CAG, 3) to avoid registration of CAG related ischemic stroke incidence. Follow-up continued until endpoint event, death, emigration or end of follow-up (December 31, 2012). We only had access to patients' death records until December 31, 2011, why MACCE was estimated in patients examined from July 1, 2004 – July 1, 2011 with end of follow-up on December 31, 2011. We counted the number of endpoint events during follow-up. Cumulative incidence proportion curves of ischemic stroke/TIA/systemic embolism were constructed. We estimated event rates per 100 person-years for each endpoint. We also calculated unadjusted and adjusted incidence rate ratios (IRRs) using the event as outcome and the natural log of person-years

as the offset in a Poisson regression.[12] Patients with 0 VD were used as reference. We adjusted IRRs for sex, age category (<65, 65-74, and ≥75 years), hypertension, diabetes, previous MI, congestive heart failure, renal disease, PAD/aortic plaque, smoking, statin treatment, and anti-platelet treatment. In sensitivity analysis, we censored follow-up if the patient was diagnosed with AF prior to diagnosis of ischemic stroke, TIA, or systemic embolism. Stata/IC software version 13.1 (StataCorp, College Station, Texas, USA) was used for statistical analyses. The study complied with the Declaration of Helsinki and was approved by the Danish Data Protection Agency (record number 2015-57-0002, identification number AU420).

RESULTS

In total, 68,829 patients were included. Of these, 25,032 (36%) had no CAD and 43,797 (64%) had CAD. Of the latter, 18,471 (27%) had 1 VD, 10,588 (15%) had 2 VD, 10,002 (15%) had 3 VD, and finally 4,736 (7%) had diffuse VD (*Figure 1*). Median follow-up was 4.0 years (IQR 2.1-6.0).

Patients with CAD were older and more often men and had greater burden of comorbidity, such as hypertension, diabetes mellitus, congestive heart failure, and PAD/aortic plaque (*Table 1*). Anti-platelet and statin treatment was also more prevalent among patients with CAD. During follow-up, 7.8% of patients with CAD and 6.8% of patients without CAD were diagnosed with AF.

The rate of ischemic stroke/TIA/systemic embolism was increased in patients with CAD compared to patients without. The cumulative incidence of ischemic stroke/TIA/systemic embolism is presented in *Figure 2*. In the adjusted analysis, CAD remained associated with an increased risk of ischemic stroke/TIA/systemic embolism (*Table 2*). Furthermore, CAD extent was associated with an incremental risk of ischemic stroke/TIA/systemic embolism. Patients with

obstructive MVD had an increased risk compared to patients with 0 VD. Diffuse VD was also associated with an increased. Similar results were seen when restricting analyses to only ischemic stroke and TIA. When censoring follow-up at time of AF diagnosis, the results did not change compared to the main analysis (data not shown). Presence and extent of CAD was also associated with an increased risk of MACCE.

DISCUSSION

The primary finding of this study was that presence and extent of CAD was associated with an increased risk of ischemic stroke/TIA/systemic embolism in patients without AF. This was primarily driven by an increased risk among patients with obstructive MVD but was also found in patients with diffuse VD. Obstructive CAD in a single vessel was not associated with any increased risk compared to patients with 0 VD. Furthermore, our study confirmed an association between the extent of CAD and an incremental risk of MACCE, thereby validating the use of MVD as an indicator of a high-risk population.

Data examining the association between CAD and ischemic stroke in patients without AF are scarce. Stroke risk in relation to CAG has often focused on catheterization-related stroke, which is a rare complication to CAG.[13-15] However, in a case-control study of patients (n=1,183) without AF after diagnostic CAG[16] patients suffering subsequent hemorrhagic or ischemic stroke after CAG were more likely to have obstructive MVD (defined as ≥70 coronary stenosis in >1 coronary vessel) than patients who did not experience stroke, which corresponds with our results.

Ischemic stroke has been associated with CAD and MI.[17] Several studies have examined incident ischemic stroke and prevalence of CAD, and found that 52% of patients with ischemic stroke had asymptomatic obstructive CAD.[18] Patients with ischemic stroke had a 3% risk

of MI within 1 year after the stroke incident.[18] Cross-sectional coronary computed tomography angiography (CTA) studies have also established ischemic stroke as a "CAD equivalent" as prognosticator of MI and found that CAD was more prevalent in patients with ischemic stroke.[19, 20] Greater plaque burden detected by coronary CTA was much more prevalent among patients with ischemic stroke, which again aligns with our findings.[20]

Guidelines recommend long term aspirin, ACE inhibition, and statins, as well as blood pressure lowering where appropriate for patients with obstructive CAD,[21] as well as for those with non-cardioembolic ischemic stroke or TIA.[22] The Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial was a large, double-blinded, randomized study examining the effect of anti-platelet and anti-coagulant therapy in patients with stable CAD and PAD.[2] 27,395 patients were assigned to rivaroxaban 5-mg BID monotherapy, aspirin monotherapy, or combined rivaroxaban 2.5-mg BID and aspirin. Even though the COMPASS trial was not specifically designed to prevent stroke, the combination of rivaroxaban 2.5-mg BID and aspirin treatment substantially reduced risk of both ischemic stroke (HR 0.51, 95% CI 0.38–0.68) and MACCE (HR 0.76, 95% CI 0.66-0.86) compared to patients in aspirin monotherapy. Rivaroxaban 5-mg BID alone, i.e. without aspirin, did not produce a net benefit but nevertheless reduced ischemic stroke risk (HR 0.69, 95% CI 0.53–0.90) compared to aspirin. The PEGASUS (Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis In Myocardial Infarction 54) trial was a 3-arm randomized clinical trial where patients with previous MI within 1-3 years were assigned to; 60-mg ticagrelor twice daily, 90-mg ticagrelor twice daily, or placebo, with simultaneous aspirin treatment. The 60-mg dose numerically reduced the risk of stroke (1-year HR 0.73, 95% CI: 0.73-1.13) and reduced MACCE significantly (1-year HR 0.82, 95% CI 0.67-0.99) compared to placebo.[23] In both the COMPASS trial and PEGASUS trial obstructive MVD was part of the inclusion criteria to

identify high-risk patients who would potentially benefit from more intensive antithrombotic treatment. Our real-world data confirm that MVD is associated with an increased risk of ischemic stroke/TIA/systemic embolism. These patients may benefit from adjuvant therapy on top of aspirin with either rivaroxaban or ticagrelor, which both have been shown to reduce cardiovascular and cerebrovascular events.[2, 23] However, these treatment regiments have, so far, not been included in international guidelines and further investigation is required. Furthermore, there is a delicate balance between ischemic risk reduction and increased bleeding risk to consider when initiating anti-coagulant or escalating anti-platelet therapy. Aspirin combined with rivaroxaban in COMPASS (HR 1.70, 95% CI 1.40–2.05) or ticagrelor in PEGASUS (HR 3.22, 95% CI 1.86-5.57) increased major bleeding risk compared to aspirin monotherapy, a risk that needs to be taken into account.[2] Thus, it is imperative to properly identify CAD patients with a high risk of ischemic stroke, which offsets any potential bleeding risk, before recommending newer treatment strategies.

Endpoint events were identified based on hospital discharge diagnoses from national databases instead of individual review of patient records or imaging. However, the stroke diagnoses in the Danish National Patient Registry has been found to have a high positive predictive value (93%).[24] The medical doctor who issues the death certificate is responsible for classification of cause of death.[10] Thus, coding of causes of death relies on the individual physician, without any central validation. This may affect the validity of information retrieved from the Danish Register of Causes of Death. Information regarding the primary exposure (presence and extent of CAD) relied on the visual assessment of the CAG by experienced cardiologists but might depend on the acting physician. We cannot account for any potential misclassification concerning CAD status at a patient level. However, in this large real-world cohort of >68,000 patients undergoing CAG, we found incremental ischemic stroke risk with increasing CAD extent and any misclassification would draw results towards no difference between groups.

CAD is associated with an increased risk of ischemic stroke/TIA/systemic embolism and MACCE in patients without AF, driven by an increased risk among patients with MVD. These patients may be candidates for treatment strategies aiming at reducing ischemic stroke incidence.

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Figure 1

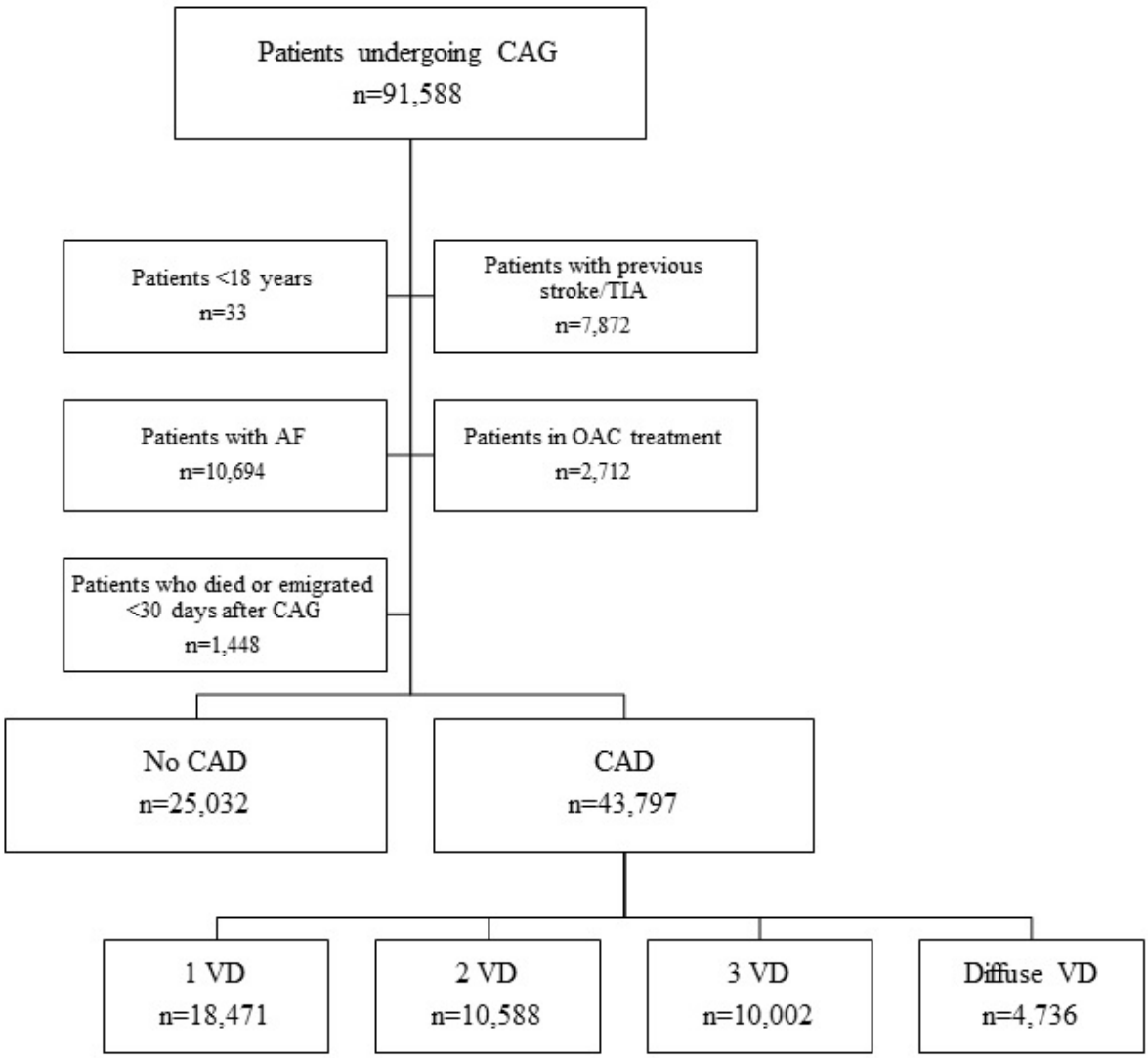

Figure 1. Patient selection.

AF = atrial fibrillation

CAD = coronary artery disease

CAG = coronary angiography

OAC = oral anti-coagulant

VD = vessel disease

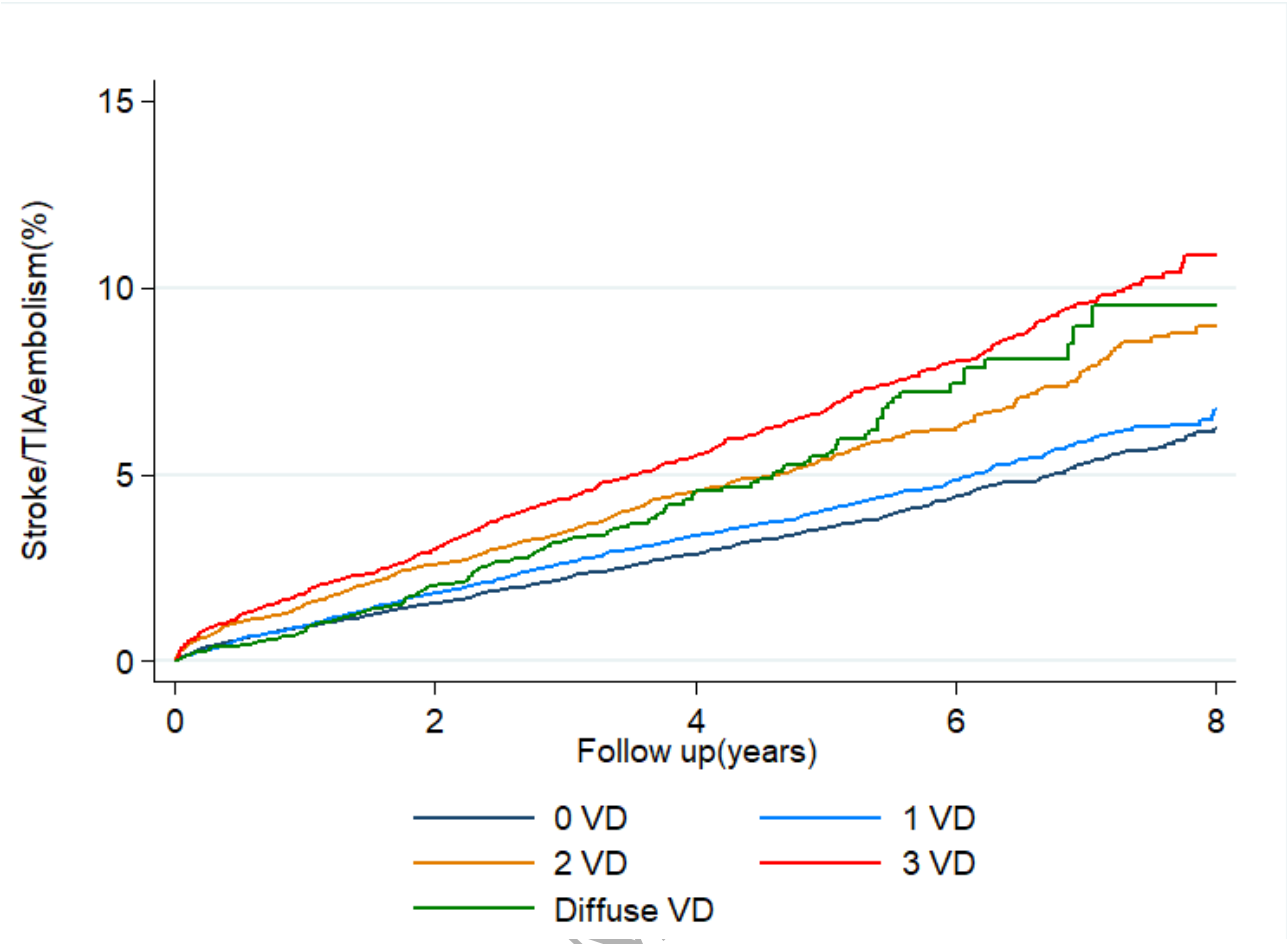

Figure 2. Cumulative incidence of ischemic stroke, TIA, and systemic embolism according to extent of coronary artery disease with throughout follow-up.

TIA = transient ischemic attack

VD = vessel disease

Table 1. Characteristics of patients without atrial fibrillation according to presence of coronary artery disease.

	Patients without coronary artery disease *(n=25,032)*	**Patients with coronary artery disease** *(n=43,797)*
Follow-up in years (inter-quartile range)	4.0 (2.2-6.0)	3.9 (2.0-5.9)
Median age in years (inter-quartile range)	59.2 (51-68)	65.4 (58-74)
Male	11,797 (47.1)	31,167 (71.2)
Active smoker	5,895 (26.3)	14,202 (35.6)
Hypertension	12,460 (49.8)	25,262 (57.7)
Diabetes mellitus	2,818 (11.3)	7,409 (16.9)
Congestive heart failure	2,807 (11.2)	6,511 (14.9)
Renal disease	640 (2.6)	1,208 (2.8)
Peripheral artery disease/aortic plaque	951 (3.8)	3,627 (8.3)
Myocardial infarction	2,480 (9.9)	21,561 (49.2)
Aspirin treatment	13,669 (54.6)	36,584 (83.5)
Adenosine diphosphate-inhibitor treatment	1,165 (4.7)	17,879 (40.8)
Statin treatment	12,186 (48.7)	38,220 (87.3)

Values are number of patients (%) unless otherwise stated.

Table 2. Number events, event rates and incidence rate ratios of stroke, TIA, and systemic embolism, as well as major adverse cardiovascular and cerebrovascular events.

	Patients (events)	Events per 100 person-years (95% CI)	Unadjusted IRR (95% CI)	Adjusted IRR* (95% CI)
Stroke/TIA/systemic embolism				
No CAD	25,032 (775)	0.77 (0.71-0.82)	1	1
CAD	43,797 (1,890)	1.10 (1.06-1.16)	1.44 (1.33-1.57)	1.20 (1.08-1.33)
1 VD	18,471 (636)	0.86 (0.80-0.93)	1.13 (1.01-1.25)	1.05 (0.93-1.19)
2 VD	10,588 (508)	1.18 (1.08-1.29)	1.54 (1.38-1.73)	1.28 (1.12-1.45)
3 VD	10,002 (585)	1.46 (1.35-1.59)	1.91 (1.72-2.13)	1.37 (1.20-1.55)
Diffuse VD	4,736 (161)	1.13 (0.97-1.32)	1.48 (1.25-1.75)	1.22 (1.02-1.47)
Stroke/TIA				
No CAD	25,032 (750)	0.74 (0.69-0.80)	1	1
CAD	43,797 (1,798)	1.05 (1.00-1.10)	1.42 (1.30-1.54)	1.15 (1.03-1.28)
1 VD	18,471 (607)	0.82 (0.76-0.89)	1.11 (1.00-1.24)	1.02 (0.90-1.16)
2 VD	10,588 (476)	1.10 (1.01-1.21)	1.49 (1.33-1.67)	1.20 (1.04-1.38)
3 VD	10,002 (562)	1.40 (1.29-1.52)	1.89 (1.70-2.11)	1.32 (1.15-1.51)
Diffuse VD	4,736 (153)	1.08 (0.92-1.26)	1.45 (1.22-1.73)	1.19 (0.98-1.43)
MACCE (cardiac death, myocardial infarction, and ischemic stroke/TIA)				
No CAD	22,027 (1,180)	1.20 (1.14-1.28)	1	1
CAD	38,307 (5,334)	3.33 (3.24-3.42)	2.76 (2.60-2.95)	1.95 (1.80-2.12)
1 VD	16,183 (1,706)	2.45 (2.34-2.57)	2.03 (1.89-2.19)	1.63 (1.48-1.78)
2 VD	9,403 (1,403)	3.48 (3.31-3.67)	2.89 (2.67-3.12)	2.04 (1.85-2.25)
3 VD	9,054 (1,921)	5.17 (4.95-5.41)	4.29 (3.99-4.62)	2.63 (2.40-2.88)
Diffuse VD	3,667 (304)	2.33 (2.08-2.61)	1.93 (1.70-2.19)	1.59 (1.38-1.82)

* Adjusted for sex, age, congestive heart failure, hypertension, diabetes, renal disease, peripheral artery disease/aortic plaque, smoking, statin treatment, and anti-platelet treatment.
CI = confidence interval
IRR = incidence rate ratio
MACCE = major adverse cardiovascular and cerebrovascular events

TIA = transient ischemic attack
VD = vessel disease