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Predicting stroke in patients without atrial fibrillation

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ABSTRACT

Background: Only few studies in selected cohorts have examined whether the CHA_2DS_2-VASc score can predict the risk of atrial fibrillation and thromboembolic events in patients *without* atrial fibrillation.

Materials and methods: Patients with coronary angiography performed between 2004-2012 were grouped according to CHA_2DS_2-VASc score. We excluded patients with atrial fibrillation, anticoagulant therapy, and follow-up <30 days. The endpoints were atrial fibrillation and a composite of ischemic stroke, transient ischemic attack, and systemic embolism. Event rates per 100 person-years were estimated for each CHA_2DS_2-VASc score (0, 1, 2, 3, 4, and >4). Incidence rate ratios were calculated using low-risk patients (CHA_2DS_2-VASc score 0 in males or 1 in females) as reference.

Results: In total, 78,233 patients were included with group sizes varying between 8,299 (CHA_2DS_2-VASc >4) and 19,882 (CHA_2DS_2-VASc 2). An increasing CHA_2DS_2-VASc score was significantly associated with a future diagnosis of atrial fibrillation (p for trend <0.0001) and an incremental risk of ischemic stroke, transient ischemic attack, systemic embolism (p for trend <0.0001), and all-cause death (p for trend <0.0001). Patients with a CHA_2DS_2-VASc score of 3 had a rate of ischemic stroke/transient ischemic attack/systemic embolism of 1.30 per 100 person-years.

Conclusions: Among patients undergoing coronary angiography, the CHA_2DS_2-VASc score predicted a future diagnosis of atrial fibrillation and the composite risk of ischemic stroke, transient ischemic attack, or systemic embolism in patients *without* atrial fibrillation. A CHA_2DS_2-VASc score of 3 was associated with a risk that would justify prophylactic oral anticoagulation treatment in a patient with atrial fibrillation.

Keywords: Prevention, stroke, coronary artery disease, coronary angiography, thromboembolism, CHA_2DS_2-VASc

INTRODUCTION

Atrial fibrillation (AF) is well-recognized as a cause of ischemic stroke due to embolization of thrombus, most often formed in the left atrial appendage.[1] Among AF-patients, the risk of ischemic events can be assessed by the CHA_2DS_2-VASc score (congestive heart failure, hypertension, age, diabetes mellitus, previous stroke/transient ischemic attack (TIA), vascular disease (previous myocardial infarction (MI), or peripheral artery disease (PAD)/aortic plaque), and female sex),[2,3] which is used to guide the initiation of oral anticoagulants (OAC). Currently, a single non-gender stroke risk factor using the CHA_2DS_2-VASc score (CHA_2DS_2-VASc score of 1 in males and 2 in females), corresponding to an annual risk of ischemic stroke/TIA/systemic embolism >1%, is used to indicate OAC therapy according to European guidelines.[2,4–6] Treatment with OAC, i.e. vitamin K antagonists or non-vitamin K antagonist OAC (NOAC), reduces the risk of thromboembolism by two-thirds in AF-patients.[7–9]

However, only 20-30% of patients with thromboembolism are diagnosed with AF prior, or in relation, to their ischemic stroke.[10] Identification of non-AF patients at high risk of developing AF or ischemic stroke/TIA/systemic embolism may enable preventive

strategies. We examined whether the CHA_2DS_2-VASc score can be used to identify non-AF patients at high risk of developing AF or ischemic stroke and thromboembolism.

MATERIALS AND METHODS

We conducted a registry-based cohort study of Danish residents undergoing coronary angiography (CAG) in Western Denmark between 2004-2012. All CAGs are registered in the Western Denmark Heart Registry (WDHR).[11] In case of multiple examinations, the first CAG was used as index CAG.

Setting: Denmark provides a tax-payer funded national health care system, ensuring free access to health care for all Danish residents, who are assigned a unique 10-digit personal identifier upon birth or after immigration. The identifier is used throughout every regional and national registry, ensuring accurate cross-linkage of health care information between registries, which minimizes loss to follow-up.

Databases: WDHR contains information about all cardiac procedures performed in Western Denmark since 1999.[11] The registration is web-based, and contains information concerning, patient characteristics, angiographic findings and procedural indication and priority. Patients are registered by their personal identifier, which is also used in the Danish National Patient Registry (DNPR), that has recorded all hospital-based inpatient and outpatient diagnoses since 1977;[12,13] and the Danish National Database of Reimbursed Prescriptions, which contains data on all reimbursed prescriptions at Danish pharmacies since 2004.[11,14,15]

Patient selection: CAG was performed in 97,321 patients. We excluded patients aged <18 years (n=33), patients with a diagnosis of AF in DNPR within 30 days after the CAG (n=13,226), patients receiving vitamin-K antagonists (n=3,285) or NOACs (n=48) according to the Danish National Database of Reimbursed Prescriptions (ATC-codes:

B01AA03, B01AA04, B01AF02, B01AE07 and B01AF01),[14,15] and patients with follow-up <30 days(n=1,772). Follow-up started day 30 after CAG. We followed the patients using the DNPR to obtain the endpoints ischemic stroke/TIA, systemic embolism, AF, and all-cause death.

Co-variate definition: Included parameters were the CHA_2DS_2-VASc score, medical treatment with statin (ATC-code: C10AA), antiplatelets (adenosine diphosphate (ADP)-receptor inhibitors (ATC-codes: B01AC22, B01AC04, and B01AC24) and aspirin (ATC-codes B01AC06 and N02BA01)). Family history of ischemic heart disease (all patients were asked about relatives with ischemic heart disease (≥1 first-generation relative) in relation to the CAG procedure), coronary artery disease (CAD) including previous MI, and PAD/aortic plaque. All co-variates were registered either 6 months before or 30 days after CAG. The parameters were:

Congestive heart failure: Defined as congestive heart failure as registered in DNPR (ICD-codes: I11.0, I13.0, I13.2, I42.0, I50) or a left ventricular ejection fraction ≤40% obtained from WDHR.

Hypertension: Defined as treatment for hypertension according to WDHR or a diagnosis of hypertension from DNPR (ICD-codes: I10, I15.1, I15.8, I15.9).

Age: Defined as age at index CAG.

Diabetes mellitus: Patients were defined as having diabetes mellitus if they 1) were registered receiving insulin treatment and/or oral antidiabetic medication or non-pharmacological dietary treatment as registered in WDHR, 2) redeemed ≥1 prescription for antidiabetic medication (ATC-codes: A10A, A10B) in the Danish National Database of Reimbursed Prescriptions, or 3) had a diabetes diagnosis in DNPR (ICD-codes: E10-14, E36.0, O24.0-24.3, O24.5-24.9).

Stroke/TIA: Defined as a diagnosis of ischemic stroke (ICD-codes I63, I64) or TIA (ICD-code G45) registered in DNPR.

Vascular disease: Defined as a diagnosis of PAD (ICD-code: I70.1-I70.9, I71, I73.9), aortic plaque (ICD-code I70.0), or MI (ICD-code I21) registered in DNPR.

Sex category: Defined by WDHR.

CHA_2DS_2-VASc score: Stroke risk factors assigned 1 point were: congestive heart failure, hypertension, 65 years < age < 75 years, diabetes mellitus, vascular disease, and female sex. Stroke risk factors assigned 2 points were stroke/TIA/systemic embolism and age ≥75 years.[2,3] Patients with only 1 point due to female sex were categorised as CHA_2DS_2-VASc 0.

CAD: Defined as 0 vessel disease (VD), 1 VD, 2 VD, 3 VD or diffuse VD as obtained from index CAG and listed in WDHR.

Endpoints: The composite of ischemic stroke (ICD-codes: I63, I64), TIA (ICD-code: G45) and systemic embolism (ICD-code: I74), ischemic stroke/TIA, systemic embolism, AF (ICD-code: I48) and all-cause death. All endpoints were primary or secondary hospital discharge diagnoses. AF was defined as an elective diagnosis or a primary or secondary hospital discharge diagnosis. All ICD-codes accessed through DNPR.[15] Information regarding death obtained through the Civil Registration System.[16]

Statistical analysis: Follow-up began 30 days after CAG and continued until endpoint event, death, emigration, or end of follow-up, whichever came first. We estimated event rates per 100 person-years for the clinical endpoints according to CHA_2DS_2-VASc score. A sensitivity analysis of the composite endpoint was performed, where we censored patients developing AF. We plotted the cumulative incidence curves for the levels of the CHA_2DS_2-VASc score for the different clinical endpoints, and furthermore, we performed test for trend for all endpoints. Incidence rate ratios (IRR) were estimated for each primary

and secondary endpoint using modified Poisson regression. Patients with a low CHA_2DS_2-VASc score (0 in males and 1 in females) were used as reference group.[17] Data were adjusted for examination year and antiplatelet treatment (defined as having redeemed a prescription of aspirin and/or ADP-inhibitor 6 months before or within 30 days after CAG). Since we are using Poisson regression, adjusting for competing risk is not possible. Finally, a multivariate analysis of all risk factors in the CHA_2DS_2-VASc score were performed in order to obtain information on each risk factor's value in the risk prediction. We used Stata/IC software version 13.1 (StataCorp, College station, Texas, 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

78,233 patients aged ≥18 years, without AF and with no previous OAC treatment, who underwent CAG between July 1, 2004 and December 31, 2012 were included. Among these patients 10,777 (13.8%) were low-risk using the CHA_2DS_2-VASc score (0 in males and 1 in females), 13,024 (16.6%) had CHA_2DS_2-VASc score 1, 19,882 (25.4%) had CHA_2DS_2-VASc score 2, 15,868 (20.3%) had CHA_2DS_2-VASc score 3, 10,373 (13.3%) had CHA_2DS_2-VASc score 4 and 8,299 (10.6%) had CHA_2DS_2-VASc score >4 (Figure 1). Maximum follow-up was 8.4 years, and median follow-up was 3.7 years.

Baseline characteristics: Baseline characteristics are shown in Table 1. The table includes possible risk factors for AF, ischemic stroke and all-cause death. Although higher CHA_2DS_2-VASc scores were associated with increasing extent of CAD, incidence of previous MI, and PAD, it is noteworthy that 36% did not have CAD, 65% had no previous MI, and only 7% had PAD.

Clinical endpoints: The endpoints are shown in Table 2. The composite endpoint ischemic stroke/TIA/systemic embolism occurred incrementally as the CHA_2DS_2-VASc score increased (Figure 2, p for trend <0.0001). The rate of ischemic stroke/TIA/embolism increased from 0.46 [0.41-0.53] for low-risk patients (CHA_2DS_2-VASc score 0 in males and 1 in females), to 3.45 [3.22-3.69] per 100 person-years for patients with CHA_2DS_2-VASc >4 (p for trend <0.0001). A CHA_2DS_2-VASc score of 3 corresponded to an event rate of 1.30 per 100 person-years. When censoring patients developing AF, the event rate slightly decreased to 1.24 per 100 person-years.

When the IRR were calculated in reference to the low-risk patients (CHA_2DS_2-VASc score 0 in males and 1 in females), a CHA_2DS_2-VASc score >4 corresponded to an IRR of 7.41[6.37-8.63] without significant change when adjusting for antiplatelet treatment and examination year (Table 2).

Similar incremental risks were observed when studying development of AF (Figure 2). Patients with low CHA_2DS_2-VASc scores (0 in male and 1 in female) had an event rate of 0.87 [0.79-0.96] while patients with a CHA_2DS_2-VASc score >4 had an event rate of 4.08 [3.84-4.34] per 100 person-years (p for trend <0.0001). The rate of all-cause death increased from 0.77 [0.70-0.86] among low-risk patients (CHA_2DS_2-VASc 0 in males and 1 in females) while patients with CHA_2DS_2-VASc >4 had a rate of all-cause death of 9.12 [8.77-9.49] per 100 person-years (p for trend <0.0001). Systemic embolism accounted only few events.

Multivariate analysis: In the multivariate analysis of all risk factors in the CHA_2DS_2-VASc score, age ≥75 years constituted the greatest risk (IRR 2.38 [2.18-2.59]) of the composite endpoint. When separating the vascular component into PAD/aortic plaque and MI, it revealed the first mentioned having an IRR of 1.52 [1.37-1.69], while previous MI had

a non-significant IRR of 1.07 [0.99-1.14]. Female sex had an IRR of 0.87 [0.81-0.93]. IRRs for all risk factors are shown in Table 3.

DISCUSSION

The main findings in this analysis of 78,233 non-AF patients who had undergone CAG were that the CHA_2DS_2-VASc score predicted a future diagnosis of AF and an incremental risk of ischemic stroke/TIA/systemic embolism. A CHA_2DS_2-VASc score of 3 was associated with a rate of ischemic events of 1.3 per 100 person-years, which is identical to the stroke risk that, according to European guidelines, warrants OAC treatment among AF-patients.[2,5] The current data may therefore provide a background for future stroke prevention trials in non-AF patients, including the potential to guide future follow-up for AF detection in non-AF patients with high CHA_2DS_2-VASc scores.

Risk stratification of thromboembolism

Only 20-30% of patients suffering thromboembolism are diagnosed with AF prior, or in relation, to their ischemic stroke.[10] In contrast to AF-patients, where the CHA_2DS_2-VASc score is used to guide initiation of prophylactic therapy, there is a knowledge gap on how to risk-stratify non-AF patients.

The current study showed that the CHA_2DS_2-VASc score predicted the risk of ischemic stroke/TIA/systemic embolism among non-AF patients, which to some extent might be due to a higher risk of a future AF diagnosis. The incremental risk of the composite thromboembolic endpoint remained significant, however, after censoring patients who developed AF. Other studies have already pointed at the possibility that $CHADS_2$ and CHA_2DS_2-VASc can be used in stroke risk stratification among non-AF patients,[18–20] and an association with incident AF has also been reported.[20] Moreover, higher CHA_2DS_2-VASc

scores have also been associated with an increased risk of AF among post-STEMI patients and postoperative patients after cardiac surgery.[21,22] The largest of the studies evaluating CHA_2DS_2-VASc and the risk of stroke among non-AF patients included 20,970 patients with acute coronary syndromes, and the authors reported that both $CHADS_2$ and CHA_2DS_2-VASc were predictors of ischemic stroke/TIA.[20] Our study was approximately 4 times larger (78,233 patients), and included patients with stable CAD. Our study thus extends the previous findings to a larger and more generalizable population although still with the caveat that even our data are limited to patients with indication for CAG. However, it still suggests that the predictive value of the CHA_2DS_2-VASc score can be applied to much broader populations than previously assessed.

Accessing the weight of the individual risk factors in the CHA_2DS_2-VASc score, when applied on non-AF patients, revealed a strong association between advanced age and stroke risk. The second strongest predictor of ischemic stroke was previous ischemic stroke/TIA. Furthermore, dividing the vascular component into PAD/aortic plaque and MI, revealed that PAD/aortic plaque accounted for a greater risk of stroke than previous MI.

Prevention of ischemic stroke/TIA/systemic embolism in patients without AF

Among AF-patients, the tipping point of when stroke risk outweighs risk of bleeding, i.e. when anticoagulant treatment is recommended, is an annual risk of ≈1%.[2,3,23] The rate of ischemic stroke/TIA/systemic embolism in patients with a CHA_2DS_2-VASc score of 3 were 1.30 per 100 person-years and the rate was even higher with increasing scores. In patients with CHA_2DS_2-VASc scores ≥3, it is likely that prophylactic antithrombotic treatment may outweigh the risk of bleeding.

Recently, secondary cardiovascular prevention among patients with stable atherosclerotic vascular disease (CAD and/or PAD) was examined in the COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial, where patients were randomised to receive rivaroxaban alone, combined with aspirin, or aspirin alone.[24] The primary endpoint was a composite of cardiovascular death, stroke, and MI. The study was terminated early due to a difference in the primary efficacy outcome in favour of treatment with low-dose rivaroxaban combined with aspirin, but this was at cost of a higher risk of major bleeding. In relation to the current study, it is worth noting that the combination therapy with rivaroxaban and aspirin did not reduce MI (1.9% vs 2.2%) while the main benefit was caused by a 42% relative reduction of ischemic stroke (0.9% vs 1.6%). A non-significant intermediate reduction of stroke was seen in the rivaroxaban arm alone (1.3%). This suggests that combination therapies with platelet inhibitor and low-dose NOAC may have the potential to reduce the stroke risk among non-AF patients. In this regard, it is important that we, when balancing the benefit of reducing thromboembolism against harm from bleeding, can identify patients at high risk of thromboembolism.[25] Our study may provide the missing link by showing that it is possible, in a very large cohort of routine clinical care patients, to identify high-risk non-AF patients by use of a well-known clinical scoring system. Still, further investigations are needed to define the score where the benefit of reducing ischemic stroke and mortality exceeds the risk of major bleeding.

Pathogenesis of thromboembolism in patients without AF

The pathogenesis of ischemic stroke in non-AF patients may differ from AF-patients. Ischemic stroke and thromboembolism among AF-patients is thought to be caused primarily by embolization of thrombus formed in the left atrial appendage. Still, even in AF-patients the cause of stroke is not limited to thrombus embolization from the left atrium.[2,19]

Non-AF patients may have, or develop, unrecognized paroxysmal AF as cause of ischemic stroke. Indeed, we observed that incremental CHA_2DS_2-VASc scores was significantly associated with a future AF diagnosis, and it seems very likely that unrecognized AF play an important role for the higher risk of thromboembolic events observed in our cohort study. This association was also found in another study, which reported that subclinical episodes of AF occurred frequently in diabetic patients, and that the absolute burden of subclinical AF was significantly associated with both size and number of silent cerebral infarcts.[26] Such episodes of subclinical AF was also seen in older patients with cardiovascular risk factors,[27] and AF is often found in cryptogenic stroke patients with prolonged monitoring.[28–30] These observations only make it more important to identify patients at high risk of future AF and stroke, and to evaluate strategies for identification and risk reduction. Another important cause of ischemic stroke are embolisms from carotid artery plaques, which may well be the leading cause of ischemic stroke in non-AF patients. This differentiation is not trivial since it remains unknown whether OAC, a superior strategy for AF-patients, may be a good prophylactic strategy in non-AF patients.

Limitations

This is a registry-based evaluation and our results must primarily be considered hypothesis-generating. Moreover, all patients in our study had undergone CAG, which affects the external validity, and we can primarily conclude that it is possible to identify a group of non-AF patients at high risk of first-time AF, ischemic stroke, and mortality within this CAG cohort.

Conclusions

Among patients *without* AF, undergoing CAG, the CHA_2DS_2-VASc score predicted a future diagnosis of AF and the composite risk of ischemic stroke, TIA, or systemic embolism. A CHA_2DS_2-VASc score of 3 was associated with a risk that would justify prophylactic oral anticoagulation treatment in a patient with atrial fibrillation.

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AUTHOR CONTRIBUTIONS:

KS, KKWO, TT, JCN, MoMa, GYHL and MM designed the study. TT, SEJ, LOJ, SDK and MM collected the data. KKWO and MoMa performed the statistical analysis. KS, KKWO, TT, SDK, GYHL and MM analysed and interpreted the data. KS, KKWO and MM drafted the manuscript, which subsequently was revised and finally approved by all authors.

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FIGURE LEGENDS

Figure 1. Patient flow chart. The flow chart illustrates the inclusion of 78,233 patients without atrial fibrillation, registered in the Western Denmark Heart Registry, and examined by coronary angiography between July 1, 2004 - December 31, 2012.

Figure 2. Cumulated incidence of clinical endpoints in patients without atrial fibrillation. Cumulated incidence of A: the composite endpoint ischemic stroke/TIA/embolism; B: ischemic stroke/TIA/embolism when censored for development of atrial fibrillation; C: ischemic stroke/TIA; D: systemic embolism; E: atrial fibrillation; and F: all-cause death.

Table 1. Baseline characteristics of 78,233 patients without atrial fibrillation, registered in the Western Denmark Heart Registry, and examined by coronary angiography between July 1, 2004 – December 31, 2012.

	CHA_2DS_2-VASc score						
	0 (male) or 1 (female)	**1 (nonfemale)**	**2**	**3**	**4**	**>4**	**Total**
	(n = 10,777))	**(n = 13,024)**	**(n = 19,882)**	**(n = 15,868)**	**(n = 10,373)**	**(n = 8,299)**	**(n = 78,233)**
	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*
Median follow-up (IQR*) (years)							
	4.2 (2.2-6.2)	4.1 (2.1-6.1)	3.9 (1.9-6.0)	3.6 (1.7-5.7)	3.2 (1.5-5.3)	2.8 (1.2-5.0)	3.7 (1.8-5.8)
CHA_2DS_2-VASc parameters							
CHF†	0 (0.0)	663 (5.1)	1,926 (9.7)	2,418 (15.2)	2,428 (23.4)	3,440 (41.5)	10,875 (13.9)
Hypertension	0 (0.0)	4,997 (38.4)	11,722 (59.0)	11,456 (72.2)	8,441 (81.4)	7,474 (90.1)	44,090 (56.4)
Diabetes mellitus	0 (0.0)	418 (3.2)	2,364 (11.9)	3,346 (21.1)	2,718 (26.2)	3,273 (39.4)	12,119 (15.5)
Stroke/TIA‡	0 (0.0)	0 (0.0)	212 (1.1)	754 (4.8)	1,336 (12.9)	3,540 (42.7)	5,842 (7.5)
Vascular disease§	0 (0.0)	4,829 (37.1)	7,209 (36.3)	7,022 (44.3)	5,677 (54.7)	6,106 (73.6)	30,843 (39.4)
Age category							
<65 years	10,777 (100.0)	10,907 (83.7)	11,952 (60.1)	4,669 (29.4)	1,464 (14.1)	479 (5.8)	40,248 (51.5)
65-74 years	0 (0.0)	2,117 (16.3)	7,030 (35.4)	7,731 (48.7)	3,870 (37.3)	2,287 (27.6)	23,035 (29.4)
≥75 years	0 (0.0)	0 (0.0)	900 (4.5)	3,468 (21.9)	5,039 (48.6)	5,533 (66.7)	14,940 (19.1)

Gender							
Male	6,599 (61.2)	13,024 (100.0)	12,593 (63.3)	8,681 (54.7)	4,765 (45.9)	3,231 (38.9)	48,893 (62.5)
Female	4,178 (38.8)	0 (0.0)	7,289 (36.7)	7,187 (45.3)	5,608 (54.1)	5,068 (61.1)	29,330 (37.5)
Other characteristics							
Family history‖	5,060(47.0)	5,636 (43.3)	8,731 (43.9)	6,129 (38.6)	3,634 (35.0)	2,660 (32.1)	31,850 (40.7)
Previous MI#	0 (0.0)	4,670 (35.9)	6,592 (33.2)	6,172 (38.9)	4,733 (45.6)	5,074 (61.1)	27,241 (34.8)
PAD**/aortic plaque	0 (0.0)	256 (2.0)	886 (4.5)	1,287 (8.1)	1,455 (14.0)	1,882 (22.7)	5,766 (7.4)
Vessel disease							
0 VD††	7,354 (68.2)	4,196 (32.2)	7,432 (37.4)	4,878 (30.7)	2,602 (25.1)	1,367 (16.5)	27,829 (35.6)
1 VD	1,686 (15.6)	4,397 (33.8)	5,558 (28.0)	4,356 (27.5)	2,790 (26.9)	2,056 (24.8)	20,843 (26.6)
2 VD	642 (6.0)	2,068 (15.9)	2,978 (15.0)	2,730 (17.2)	1,884 (18.2)	1,742 (21.0)	12,044 (15.4)
3 VD	446 (4.1)	1,474 (11.3)	2,453 (12.3)	2,654 (16.7)	2,247 (21.7)	2,483 (29.9)	11,757 (15.0)
Diffuse VD	649 (6.0)	889 (6.8)	1,461 (7.3)	1,250 (7.9)	850 (8.2)	651 (7.8)	5,750 (7.4)
Smoking							
Active	3,353 (31.1)	4,879 (37.5)	6,256 (31.5)	4,167 (26.3)	2,339 (22.5)	1,606 (19.4)	22,600 (28.9)
Never	3,428 (31.8)	2,967 (22.8)	5,216 (26.2)	4,389 (27.7)	2,970 (28.6)	2,363 (28.5)	21,333 (27.3)
Former	2,998 (27.8)	3,996 (30.7)	6,656 (33.5)	5,796 (36.5)	4,053 (39.1)	3,351 (40.4)	26.850 (34.3)
Medication							
Statin	5,211 (48.4)	9,783 (75.1)	14,948 (75.2)	12,702 (48.4)	8,332 (48.4)	6,884 (48.4)	57,860 (48.4)
DAPT‡‡	844 (7.8)	3,226 (24.8)	4,717 (23.7)	4,238 (26.7)	3,047 (29.4)	3,003 (36.2)	19,075 (24.4)

Any antiplatelets[§§]	5,386 (50.0)	9,783 (75.1)	15,353 (77.2)	13,409 (84.5)	9,074 (87.5)	7,611 (91.7)	60,616 (77.5)
Aspirin	5,089 (47.2)	8,972 (68.9)	14,490 (72.9)	12,842 (80.9)	8,669 (83.6)	7,199 (86.7)	57.261 (73.2)
ADP[‖‖]-inhibitors	1,141 (10.6)	4,037 (31.0)	5,580 (28.1)	4,805 (30.3)	3,452 (33.3)	3,415 (41.1)	22,430 (28.7)

[*] IQR: Interquartile range

[†] CHF: Congestive heart failure

[‡] TIA: Transient ischemic attack

[§] Vascular disease: Defined as previous myocardial infarction and/or PAD/aortic plaque

[‖] Family history of ischemic heart disease (at least one 1st generation relative). Patients were asked in relation to CAG-procedure.

[#] MI: Myocardial infarction

[**] PAD: Peripheral artery disease

[††] VD: Vessel disease

[‡‡] DAPT: Dual antiplatelet treatment with Aspirin and ADP-inhibitor 6 months before or 30 days after coronary angiography

[§§] Antiplatelet treatment with Aspirin and/or ADP-inhibitor 6 months before or 30 days after coronary angiography

[‖‖] ADP: Adenosine diphosphate receptor

Table 2. Clinical endpoints for 78,233 coronary angiography patients with no history of atrial fibrillation. Patients were grouped according to their CHA_2DS_2-VASc score. The endpoints were ischemic stroke/TIA[*]/systemic embolism, ischemic stroke/TIA/embolism when censured for development of atrial fibrillation, ischemic stroke/TIA, systemic embolism, atrial fibrillation, and all-cause death.

Ischemic stroke/TIA/systemic embolism

CHA_2DS_2-VASc score	Patients	Events	Rate per 100 person-years	Unadjusted IRR[†] (95% CI[‡])	Adjusted[§] IRR (95% CI)
0 (male) or 1 (female)	10,777	208	0.46 [0.41-0.53]	1 [reference]	1 [reference]
1 (nonfemale)	13,024	359	0.68 [0.62-0.76]	1.47 [1.24-1.74]	1.50 [1.27-1.79]
2	19,882	663	0.86 [0.80-0.93]	1.85 [1.58-2.16]	1.89 [1.62-2.21]
3	15,868	752	1.30 [1.21-1.40]	2.80 [2.40-3.26]	2.88 [2.46-3.37]
4	10,373	680	1.97 [1.83-2.13]	4.24 [3.63-4.95]	4.37 [3.72-5.12]
>4	8,299	852	3.45 [3.22-3.69]	7.41 [6.37-8.63]	7.65 [6.54-8.96]

Ischemic stroke/TIA/systemic embolism. Censored for development of atrial fibrillation

0 (male) or 1 (female)	10,777	200	0.46 [0.40-0.53]	1 [reference]	1 [reference]
1 (nonfemale)	13,024	328	0.65 [0.58-0.72]	1.41 [1.19-1.69]	1.46 [1.22-1.74]
2	19,882	609	0.82 [0.76-0.89]	1.80 [1.53-2.11]	1.85 [1.57-2.17]
3	15,868	678	1.24 [1.15-1.33]	2.70 [2.31-3.16]	2.80 [2.38-3.29]
4	10,373	614	1.90 [1.75-2.05]	4.15 [3.36-4.86]	4.30 [3.65-5.07]
>4	8,299	783	3.40 [3.17-3.65]	7.43 [6.36-8.68]	7.74 [6.58-9.10]

Ischemic stroke/TIA

0 (male) or 1 (female)	10,777	199	0.44 [0.39-0.51]	1 [reference]	1 [reference]
1 (nonfemale)	13,024	343	0.65 [0.59-0.73]	1.47 [1.23-1.75]	1.50 [1.26-1.79]
2	19,882	637	0.82 [0.76-0.89]	1.85 [1.58-2.17]	1.90 [1.62-2.23]
3	15,868	725	1.25 [1.16-1.35]	2.82 [2.41-3.30]	2.91 [2.48-3.41]
4	10,373	647	1.87 [1.73-2.02]	4.21 [3.59-4.94]	4.35 [3.69-5.11]
>4	8,299	829	3.35 [3.13-3.58]	7.53 [6.45-8.80]	7.79 [6.64-9.15]

Systemic embolism

0 (male) or 1 (female)	10,777	9	0.02 [0.01-0.04]	1 [reference]	1 [reference]
1 (nonfemale)	13,024	18	0.03 [0.02-0.05]	1.70 [0.76-3.78]	1.63 [0.74-3.61]
2	19,882	32	0.04 [0.03-0.06]	2.05 [0.98-4.28]	1.95 [0.94-4.04]
3	15,868	32	0.05 [0.04-0.08]	2.70 [1.29-5.67]	2.54 [1.22-5.31]
4	10,373	38	0.11 [0.08-0.15]	5.32 [2.57-10.99]	4.98 [2.44-10.16]
>4	8,299	27	0.10 [0.07-0.15]	5.14 [2.42-10.94]	4.80 [2.29-10.08]

Atrial fibrillation

0 (male) or 1 (female)	10,777	385	0.87 [0.79-0.96]	1 [reference]	1 [reference]
1 (nonfemale)	13,024	715	1.39 [1.29-1.50]	1.60 [1.41-1.81]	1.72 [1.51-1.95]
2	19,882	1,216	1.61 [1.53-1.71]	1.85 [1.65-2.08]	1.99 [1.77-2.24]
3	15,868	1,352	2.40 [2.28-2.53]	2.75 [2.46-3.09]	3.02 [2.69-3.39]
4	10,373	1,095	3.26 [3.07-3.46]	3.74 [3.33-4.21]	4.11 [3.65-4.64]
>4	8,299	997	4.08 [3.84-4.34]	4.68 [4.16-5.27]	5.19 [4.59-5.86]

All-cause death

0 (male) or 1 (female)	10,777	350	0.77 [0.70-0.86]	1 [reference]	1 [reference]
1 (nonfemale)	13,024	677	1.27 [1.18-1.37]	1.64 [1.44-1.87]	1.73 [1.52-1.97]
2	19,882	1,464	1.86 [1.77-1.96]	2.40 [2.14-2.70]	2.56 [2.28-2.88]
3	15,868	2,015	3.38 [3.24-3.54]	4.38 [3.91-4.90]	4.74 [4.22-5.31]
4	10,373	1,972	5.48 [5.24-5.72]	7.08 [6.32-7.93]	7.72 [6.88-8.67]
>4	8,299	2,412	9.12 [8.77-9.49]	11.80 [10.55-13.20]	12.99 [11.59-14.56]

* TIA: Transient ischemic attack

† IRR: incidence rate ratio

‡ CI: Confidence interval

§ Adjusted for examination year and antiplatelet therapy 6 months before or 30 days after coronary angiography

Table 3. Multivariate adjusted Poisson regression including components in the CHA_2DS_2-VASc score, estimating the relative risk of ischemic stroke, TIA[*], and systemic embolism in a non-AF[†] cohort. The vascular component is both included as a combined variable and divided into PAD[‡]/aortic plaque and myocardial infarction. IRRs[§] are calculated in reference to patients without the condition, IRRs in the age categories are calculated in reference to patients <65 years.

Risk factor	Adjusted[‖] IRR [95%CI[#]]
Female sex	0.87 [0.81-0.93]
Age 65-74 years	1.54 [1.42-1.67]
Age ≥75 years	2.38 [2.18-2.59]
Congestive heart failure	1.30 [1.19-1.42]
Hypertension	1.25 [1.16-1.34]
Diabetes mellitus	1.45 [1.33-1.57]
Stroke/TIA	1.93 [1.85-2.01]
Vascular disease	1.18 [1.10-1.26]
Myocardial infarction[**]	1.07 [0.99-1.14]
PAD/aortic plaque[**]	1.52 [1.37-1.69]

[*] TIA: Transient ischemic attack

[†] AF: Atrial fibrillation

[‡] PAD: Peripheral artery disease

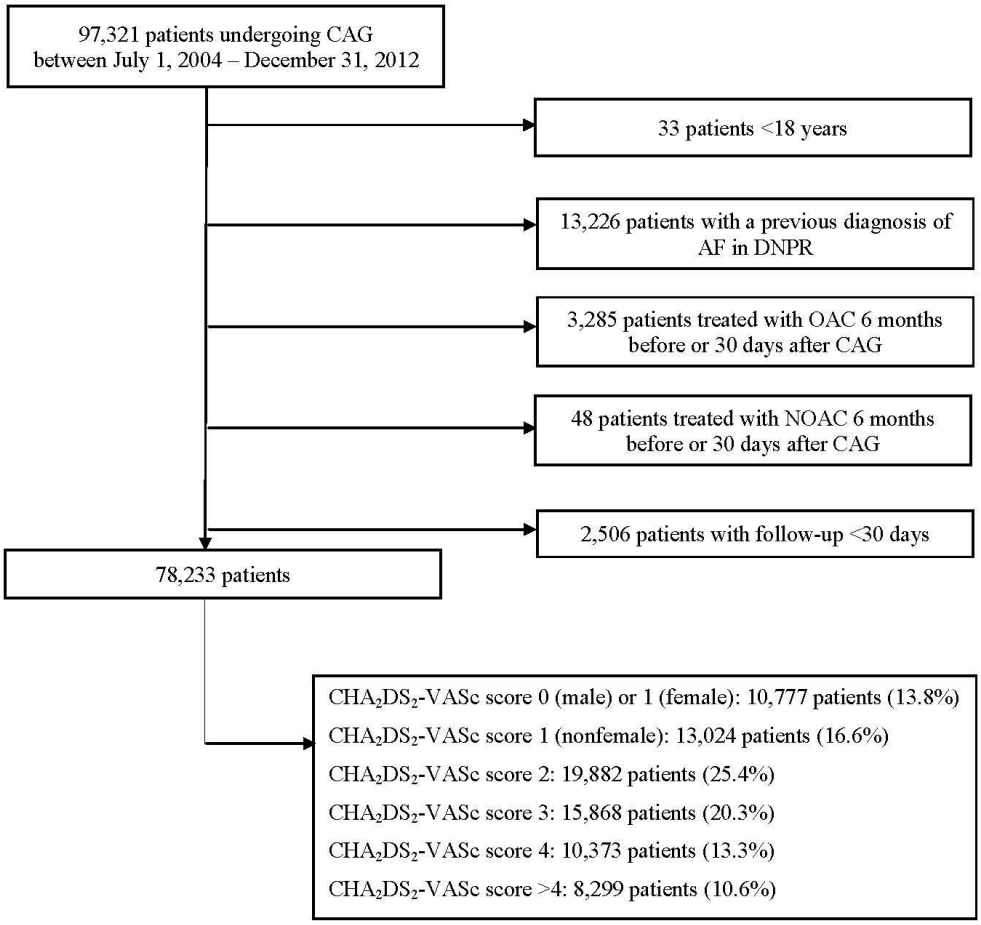
[§] IRR: Incidence rate ratio

[‖] Adjusted for all other risk factors included in the CHA_2DS_2-VASc score

[#] CI: Confidence interval

[**] Multivariate Poisson regression where the vascular component is divided into PAD/aortic plaque and myocardial infarction where both are considered as individual risk factors.

Figure 1. Patient flow chart. The flow chart illustrates the inclusion of 78,233 patients without atrial fibrillation, registered in the Western Denmark Heart Registry, and examined by coronary angiography between July 1, 2004 - December 31, 2012.



AF: Atrial fibrillation

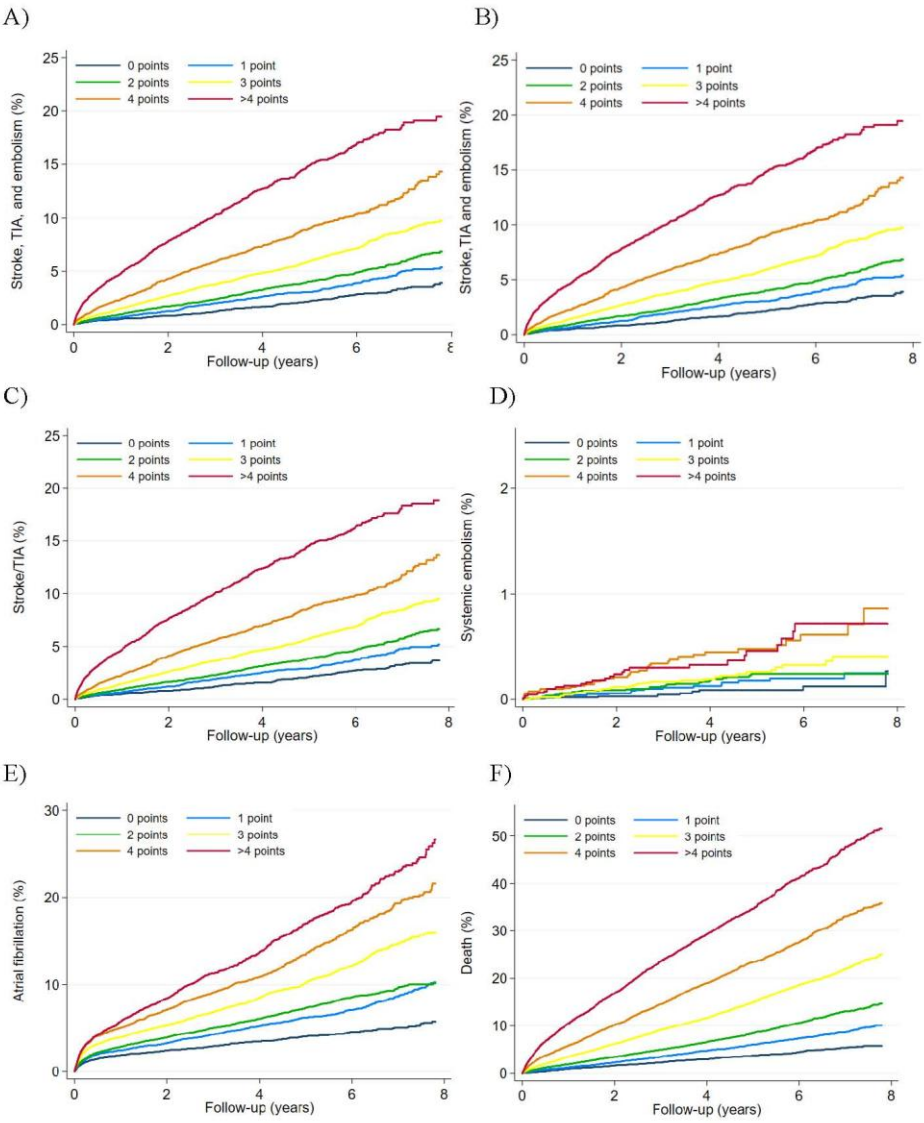
CAG: Coronary angiography

DNPR: Danish National Patient Registry

OAC: Oral anticoagulant agent

NOAC: Non-vitamin K antagonist oral anticoagulants

Figure 2. Cumulated incidence of clinical endpoints in patients without atrial fibrillation. Cumulated incidence of A: the composite endpoint ischemic stroke/TIA/embolism; B: ischemic stroke/TIA/embolism when censored for development of atrial fibrillation; C: ischemic stroke/TIA; D: systemic embolism; E: atrial fibrillation; and F: all-cause death.



TIA: Transient ischemic attack