Ability of the DANCAMI to predict the risk ischemic stroke and mortality in patients with atrial fibrillation/flutter

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Objectives: Comparison of the danish comorbidity index for acute myocardial infarction (DANCAMI), the charlson comorbidity index (CCI), the elixhauser comorbidity index (ECI), and the CHA_2DS_2-VASc score to predict ischemic stroke, cardiovascular mortality, and all-cause mortality after atrial fibrillation/flutter. *Materials and Methods:* A population-based cohort study of all Danish patients with incident atrial fibrillation/flutter during 2000−2020 (n=361,901). C-Statistics were used to evaluate the discriminatory performance for predicting 1 and 5-year risks of the outcomes for a baseline model (including age and sex) +/- the individual indices. *Results:* For the DANCAMI, the 5-year risk did not increase with comorbidity burden for ischemic stroke (5.9% for low vs. 5.6% for severe) but did increase for cardiovascular mortality (10% for low vs. 16% for severe) and all-cause mortality (33% for low vs. 61% for severe). C-Statistics for predicting 5-year ischemic stroke risk were similar for all models (0.64). C-Statistics for predicting 5-year cardiovascular mortality risk were also similar for the baseline (0.76), the DANCAMI (0.77), the CCI (0.76), the ECI (0.76), and the CHA_2DS_2-VASc (0.76) models. C-Statistics for predicting 5-year all-cause mortality risk were lower for the baseline (0.71) and the CHA_2DS_2-VASc (0.71) models than for the DANCAMI (0.75), the CCI (0.74), and the ECI (0.74) models. The 1-year C-Statistics were comparable. *Conclusion:* The DANCAMI predicted ischemic stroke and cardiovascular mortality risks similar to the CCI, the ECI, and the CHA_2DS_2-VASc. The DANCAMI predicted all-cause mortality risk similar to the CCI and the ECI, but better than the baseline and the CHA_2DS_2-VASc.

Keywords: Atrial fibrillation—Atrial flutter—Comorbidities—Ischemic stroke—Mortality—Prediction

Atrial fibrillation is the most common rhythm disorder in clinical practice and is associated with a 2.5 to 4.5-fold increased risk of ischemic stroke[1] and a 2 to 3-fold increased mortality risk.[2,3] Many patients with atrial fibrillation are burdened with comorbidities that increase mortality (*e.g.*, diabetes and heart failure).[4,5] The CHA_2DS_2-VASc score, a clinical score used to predict ischemic stroke, incorporates diabetes, heart failure, hypertension, vascular disease, and previous thromboembolism.[6] However, it is unclear whether comorbidity indices can be used in population-based research to predict atrial fibrillation prognosis.

Therefore, we examined the ability of the newly-developed Danish Comorbidity Index for Acute Myocardial Infarction (DANCAMI)[7] to predict 1 and 5-year risks of ischemic stroke, cardiovascular mortality, and all-cause mortality after atrial fibrillation/flutter. We compared

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this ability with that of the Charlson Comorbidity Index (CCI), the Elixhauser Comorbidity Index (ECI), and the CHA_2DS_2-VASc score.

Methods

Setting

The Danish National Health Service provides universal tax-financed health care services to all Danish citizens and legal residents.[8] These services include free access to general practitioners and hospitals in Denmark and partial reimbursement for the costs of prescription drugs from Danish community pharmacies.[8] Danish citizens and legal residents receive a unique 10-digit Civil Personal Register number at birth or upon immigration.[9] This number is used as a personal identifier for all health care services in Denmark, thus allowing for linkage on an individual level among all Danish health care registries.[9]

Study design and cohort

We conducted a nationwide, population-based cohort study of all patients aged at least 18 years with an incident primary or secondary, inpatient or outpatient clinic diagnosis for atrial fibrillation/flutter (DI48) between 1 January 2000 and 31 December 2020, based on records in the Danish National Patient Registry (DNPR).[10] The DNPR contains nationwide information on all non-psychiatric inpatient contacts since 1977 and on all non-psychiatric outpatient contacts, psychiatric inpatient and outpatient contacts, and emergency department contacts since 1995.[10] We collapsed atrial fibrillation and flutter into a single condition because atrial fibrillation and flutter share risk factors and pathophysiology and commonly occur simultaneously.[11] Recording of the combined atrial fibrillation/flutter diagnosis has been validated within the DNPR with a positive predictive value of 95%.[12]

When predicting ischemic stroke, we restricted the cohort to patients with atrial fibrillation/flutter who had no previous diagnosis of stroke and followed them from the day after their atrial fibrillation/flutter diagnosis until occurrence of ischemic stroke, death, emigration, end of follow-up, or 31 December 2020, whichever occurred first. We chose to start follow-up the day after the diagnosis of atrial fibrillation/flutter to avoid including cases in which atrial fibrillation/flutter was diagnosed during hospitalization for ischemic stroke. When predicting mortality risk, we followed all patients with atrial fibrillation/flutter from the date of atrial fibrillation/flutter diagnosis until death, emigration, end of follow-up, or 31 December 2020, whichever occurred first. We identified the date of ischemic stroke based on DNPR data. The dates of death and emigration were provided by the Danish Civil Registration System, which has maintained nationwide information on mortality and emigration status since 1968.[9] We obtained information on the cause of death from the Danish Register of Causes of Death, which contains nationwide information on cause of death since 1970.[13]

Comorbidities

We identified all comorbidities using all inpatient and outpatient information from the DNPR for the 10 years before diagnosis of atrial fibrillation/flutter. Recording of all cardiovascular[12] and CCI comorbidities[14] in the DNPR have been validated. We used the 10-year look-back window to ensure that the comorbidities were present at the time of the atrial fibrillation/flutter diagnosis and to limit the varying influences that short-term *vs.* long-term comorbidities may have on atrial fibrillation/flutter prognosis. We also used information on redeemed prescriptions of relevant drugs from the Danish National Prescription Registry[15] to identify affective disorders, schizophrenia, uncomplicated diabetes, chronic pulmonary disease, and hypertension. This registry contains nationwide information on all prescriptions redeemed in Danish community pharmacies since 1995, but no information on over-the-counter sales or in-hospital drug use.[15] Supplementary Table 1 lists all *International Classification of Diseases* and *Anatomical Therapeutic Chemical Classification* codes used in the study.

To calculate comorbidity scores, we used the original weights for the DANCAMI and the DANCAMI restricted to non-cardiovascular diseases (rDANCAMI)[7], the Quan-modified weights for the CCI,[16] and the Van Walraven-modified weights for the ECI.[17] To calculate the CHA_2DS_2-VASc score, we chose codes based on previous validation studies. Supplementary Table 2 lists the comorbidities included in the comorbidity indices, the CHA_2DS_2-VASc score components, and their respective weights. The comorbidity indices are described in detail elsewhere.[7,16,17]

Outcome

The outcomes were 1 and 5-year risks of ischemic stroke, cardiovascular mortality, and all-cause mortality after incident atrial fibrillation/flutter. Cardiovascular mortality was defined as a main underlying cause of death from venous thromboembolism, myocardial infarction, heart failure, ischemic stroke, hemorrhagic stroke, aortic disease, or valvular heart disease. We identified the cause of death from the Danish Register of Causes of Death, which contains information on the main underlying and potential contributory cause(s) of death since 1970.[13]

Statistical analyses

We described the baseline characteristics of patients with atrial fibrillation/flutter using counts with percentages for categorical variables and using medians with interquartile ranges for continuous variables. We calculated the discriminatory performance measures for a

baseline model, including age (restricted cubic splines with 5 knots)[18,19] and sex, and for models including the individual indices plus age and sex. We focused on the discriminatory performance measure Harrell's C-Statistic (and not a calibration measure) as the indices are intended for comorbidity adjustment in research rather than prediction of absolute risk in clinical use. The Harrell's C-Statistic reflects the probability that for a pair of random individuals, the model will assign a greater predicted risk to the individual experiencing the outcome first.[20] A C-Statistic of 0.5 indicates chance prediction and 1 indicates perfect prediction.[20] We calculated 95% confidence intervals (CIs) for the C-Statistic using bootstrapping (100 replicates). We used a Fine and Gray estimator to calculate and illustrate the risk of ischemic stroke (considering death a competing event), cardiovascular mortality (considering death due to non-cardiovascular causes a competing event), and all-cause mortality.[21] We tested the proportional-hazards assumption graphically using log-log plots and found no violations.

We tested whether the categorized comorbidity burden performed similarly to the continuous comorbidity score by categorizing the total score for each index as no, low, moderate, or severe based on the categorization in the original DANCAMI study.[7] The categorization of the CHA_2DS_2-VASc score as 0, 1, and ≥2 was based on common clinical risk categorization.[22] We also tested whether the model performance differed according to age (aged 18−64, 65−74, 75−84, or ≥85 years), sex, valvular *vs.* non-valvular atrial fibrillation/flutter, CHA_2DS_2-VASc score, atrial fibrillation/flutter separately, and whether patients had received their atrial fibrillation/flutter diagnosis before or after March 15, 2020 (the day of the first COVID-19 lockdown in Denmark). All statistical analyses were computed using STATA Version 16.1 (StataCorp, College Station, Texas 77845 USA). The study was approved by the Danish Data Protection Agency (record number: 2015-57-0002) via Aarhus University (record number: 2016-051-000001).

Informed consent and patient details

Registry-based research does not require informed consent from study subjects according to Danish law.[9] The study was approved by the authors' institution.

Results

Study cohort characteristics

We identified 361,901 patients diagnosed with incident atrial fibrillation/flutter from 2000 through 2020 in Denmark. The median age was 75 years (interquartile range: 66−83), 165,636 (46%) were female, 7,906 (2.2%) had valvular atrial fibrillation/flutter, and 275,004 (76%) had a CHA_2DS_2-VASc score of ≥2 (Table 1). The most frequent comorbidities were hypertension (38%), chronic pulmonary disease (17%), uncomplicated diabetes (11%), and affective disorders (11%) (Supplementary Table 3).

Table 1. *Characteristics of patients with incident atrial fibrillation/flutter in Denmark, 2000−2020.*

Characteristic	Number (%)
Total	361,901
Female sex	165,636 (46)
Age, years	
18−64	83,380 (23)
65−74	98,754 (27)
75−84	113,588 (31)
≥85	66,179 (18)
Year of atrial fibrillation/flutter	
2000−2004	73,318 (20)
2005−2009	77,205 (21)
2010−2014	91,978 (25)
2015−2020	119,400 (33)
Type of atrial fibrillation/flutter	
Valvular	7,906 (2.2)
Non-valvular	353,995 (98)
CHA_2DS_2-VASc score	
0	34,674 (9.6)
1	52,223 (14)
≥2	275,004 (76)
DANCAMI category	
No (score: 0)	108,707 (30)
Low (score: 1−3)	122,925 (34)
Moderate (score: 4−5)	44,994 (12)
Severe (score: ≥6)	85,275 (24)
rDANCAMI category	
No (score: 0)	189,484 (52)
Low (score: 1−3)	95,821 (26)
Moderate (score: 4−5)	27,218 (7.5)
Severe (score: ≥6)	49,378 (14)
Charlson Comorbidity Index category	
No (score: 0)	216,454 (60)
Low (score: 1)	51,602 (14)
Moderate (score: 2)	55,106 (15)
Severe (score: ≥3)	38,739 (11)
Elixhauser Comorbidity Index category	
No (score: 0)	214,832 (59)
Low (score: 1−5)	78,416 (22)
Moderate (score: 6−13)	54,741 (15)
Severe (score: ≥14)	13,912 (3.8)

Abbreviations: DANCAMI, Danish Comorbidity Index for Acute Myocardial Infarction; rDANCAMI, Danish Comorbidity Index for Acute Myocardial Infarction restricted to non-cardiovascular diseases.

Model performance

Ischemic stroke

The 1 and 5-year risks of ischemic stroke did not differ noteworthy according to the comorbidity indices but did differ according to the CHA_2DS_2-VASc score (Fig. 1). The 5-year risk of ischemic stroke was 2.5% for a

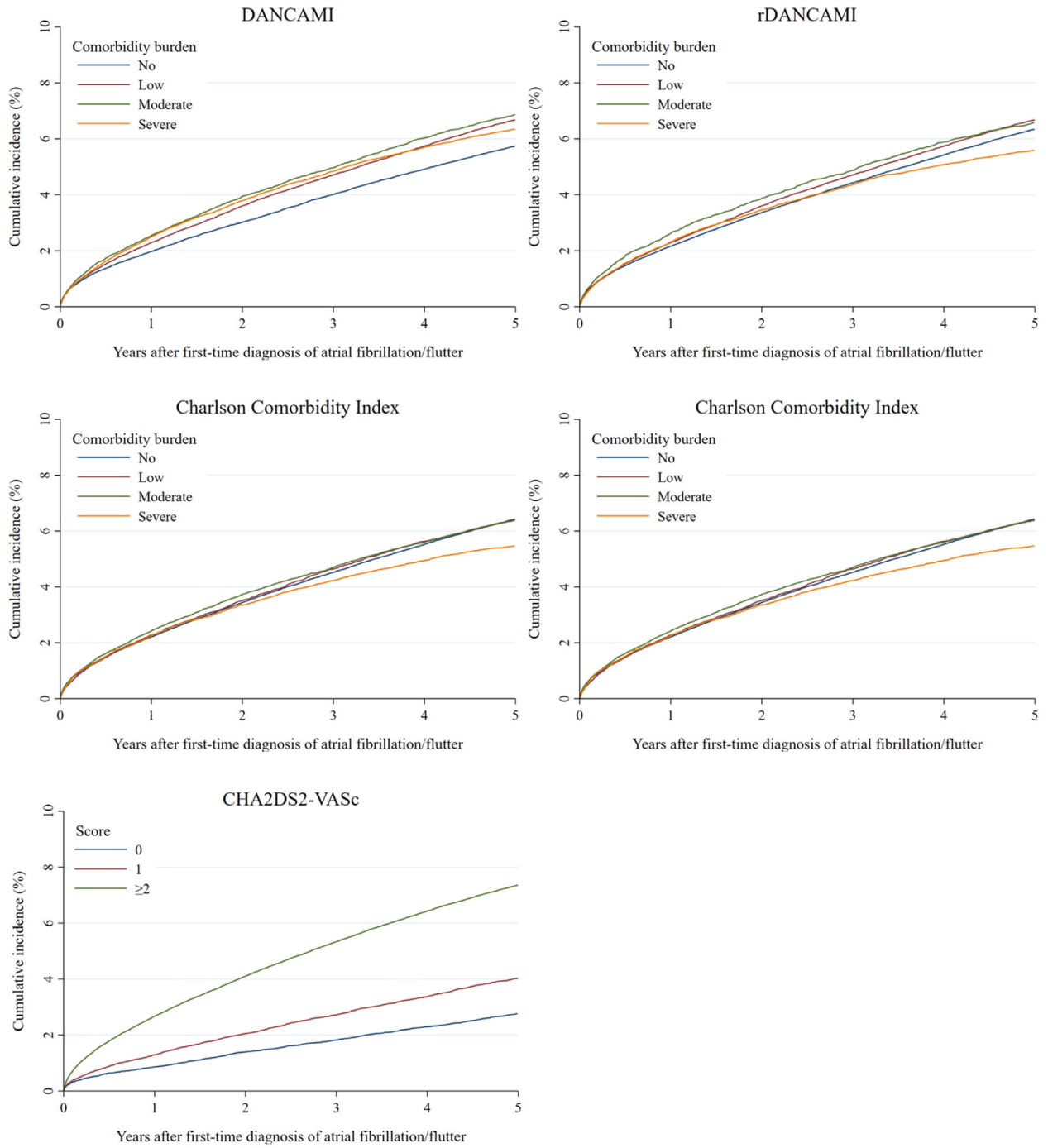

Fig. 1. *Five-year cumulative incidence of ischemic stroke according to the comorbidity and the CHA_2DS_2-VASc categories in patients with atrial fibrillation/flutter.*

Abbreviations: DANCAMI, Danish Comorbidity Index for Acute Myocardial Infarction; rDANCAMI, Danish Comorbidity Index for Acute Myocardial Infarction restricted to non-cardiovascular diseases.

CHA_2DS_2-VASc score of 0, 3.6% for a CHA_2DS_2-VASc score of 1, and 6.1% for a CHA_2DS_2-VASc score of ≥2 (Supplementary Table 4). The C-Statistics were comparable for all indices both for predicting 1 and 5-year risks of ischemic stroke (Table 2). The C-Statistic for predicting 5-year risk of ischemic stroke was 0.64 for all indices (Table 2).

Cardiovascular mortality

The 1 and 5-year cardiovascular mortality risks differed for the various DANCAMI and ECI categories, but not consistently for the rDANCAMI, the CCI, or the CHA_2DS_2-VASc score categories (Fig. 2 and

Table 2. *Predictive performance of indices in patients with incident atrial fibrillation/flutter.*

	Ischemic stroke		Cardiovascular mortality*		All-cause mortality	
Performance measure	1-year	5-year	1-year	5-year	1-year	5-year
Harrell's C-Statistic[†]						
Baseline[‡]	0.63 (0.63−0.64)	0.64 (0.64−0.64)	0.75 (0.75−0.76)	0.76 (0.75−0.76)	0.70 (0.70−0.70)	0.71 (0.71−0.71)
DANCAMI[§]	0.63 (0.63−0.64)	0.64 (0.64−0.65)	0.77 (0.77−0.77)	0.77 (0.77−0.77)	0.76 (0.76−0.76)	0.75 (0.75−0.75)
rDANCAMI[§]	0.63 (0.63−0.64)	0.64 (0.64−0.64)	0.76 (0.76−0.76)	0.76 (0.76−0.76)	0.76 (0.75−0.76)	0.75 (0.75−0.75)
Charlson Comorbidity Index[§]	0.63 (0.63−0.64)	0.64 (0.64−0.64)	0.76 (0.76−0.76)	0.76 (0.76−0.77)	0.75 (0.74−0.75)	0.74 (0.74−0.74)
Elixhauser Comorbidity Index[§]	0.63 (0.63−0.64)	0.64 (0.64−0.64)	0.76 (0.76−0.77)	0.76 (0.76−0.77)	0.74 (0.74−0.74)	0.74 (0.74−0.74)
CHA_2DS_2-VASc score[§]	0.63 (0.63−0.64)	0.64 (0.64−0.65)	0.76 (0.75−0.76)	0.76 (0.76−0.76)	0.70 (0.70−0.70)	0.71 (0.71−0.71)

Note: The results are presented as C-Statistic (95% confidence interval).

Abbreviations: DANCAMI, Danish Comorbidity Index for Acute Myocardial Infarction; rDANCAMI, Danish Comorbidity Index for Acute Myocardial Infarction restricted to non-cardiovascular diseases.

*Death due to venous thromboembolism, myocardial infarction, heart failure, ischemic and hemorrhagic stroke, aortic disease, and valvular heart disease.

[†]Harrell's C-Statistic is the probability that for a pair of random individuals the model will assign a greater predicted risk to the individual experiencing the outcome first. C-Statistic of 0.5 indicates chance prediction and 1 indicates perfect prediction.

[‡]A Cox model including age and sex.

[§]The baseline model plus the individual index score.

Supplementary Table 4). According to the DANCAMI, the 5-year cardiovascular mortality risk was 7.7% for no, 10% for a low, 14% for a moderate, and 16% for a severe comorbidity burden (Supplementary Table 4). Compared with the baseline model, the C-Statistic was similar for the DANCAMI both in terms of predicting 1-year (0.77 vs. 0.75) and 5-year cardiovascular mortality risks (0.77 vs. 0.76; Table 2). Compared with the DANCAMI, the C-Statistics for the rDANCAMI, the CCI, the ECI, and the CHA_2DS_2-VASc score were comparable both in terms of predicting 1 and 5-year cardiovascular mortality risks (Table 2). For predicting 5-year cardiovascular mortality risk, the C-Statistic was 0.76 for the rDANCAMI, the CCI, the ECI, and the CHA_2DS_2-VASc score (Table 2).

All-cause mortality

The 1 and 5-year all-cause mortality risks increased consistently with increasing comorbidity burden in all indices (Fig. 3). According to the DANCAMI, the 5-year all-cause mortality risk was 21% for no, 33% for a low, 45% for a moderate, and 61% for a severe comorbidity burden (Supplementary Table 4). Compared with the baseline model, the C-Statistic was higher for the DANCAMI both in terms of predicting 1-year (0.76 vs. 0.70) and 5-year all-cause mortality risks (0.75 vs. 0.71; Table 2). The C-Statistics for the rDANCAMI, the CCI, and the ECI were comparable to that of the DANCAMI, but lower for the CHA_2DS_2-VASc score, in terms of predicting 1 and 5-year all-cause mortality risks (Table 2). The C-Statistic for predicting 5-year all-cause mortality risk was 0.75 for the rDANCAMI, 0.74 for the CCI and the ECI, and 0.71 for the CHA_2DS_2-VASc score (Table 2).

Subgroup analyses

The categorical comorbidity burden and the categorical CHA_2DS_2-VASc score predicted all outcomes comparable to the continuous comorbidity score and the continuous CHA_2DS_2-VASc score (Supplementary Table 5).

When predicting ischemic stroke, the DANCAMI and the CHA_2DS_2-VASc score showed higher C-Statistics in younger than in older patients (Supplementary Table 6). The C-Statistic for predicting 5-year ischemic stroke risk was 0.59 in patients aged 18−64 years and 0.54 in patients aged ≥85 years for the DANCAMI and 0.59 in patients aged 18−64 years and 0.53 in patients aged ≥85 years for the CHA_2DS_2-VASc score (Supplementary Table 6). As regards the rDANCAMI, the CCI, and the ECI, the ability to predict ischemic stroke risk was comparable in younger and older patients (Supplementary Table 6). All indices predicted cardiovascular and all-cause mortality risk better in younger than in older patients (Supplementary Table 6). The C-Statistic for the DANCAMI was 0.73 in patients aged 18−64 years and 0.55 in patients aged ≥85 years when predicting cardiovascular mortality risk and 0.77 in patients aged 18−64 years and 0.57 in patients aged ≥85 years when predicting 5-year all-cause mortality risk (Supplementary Table 6).

All indices predicted ischemic stroke and cardiovascular mortality risks comparable in males and females, but all-cause mortality risk better in males than in females

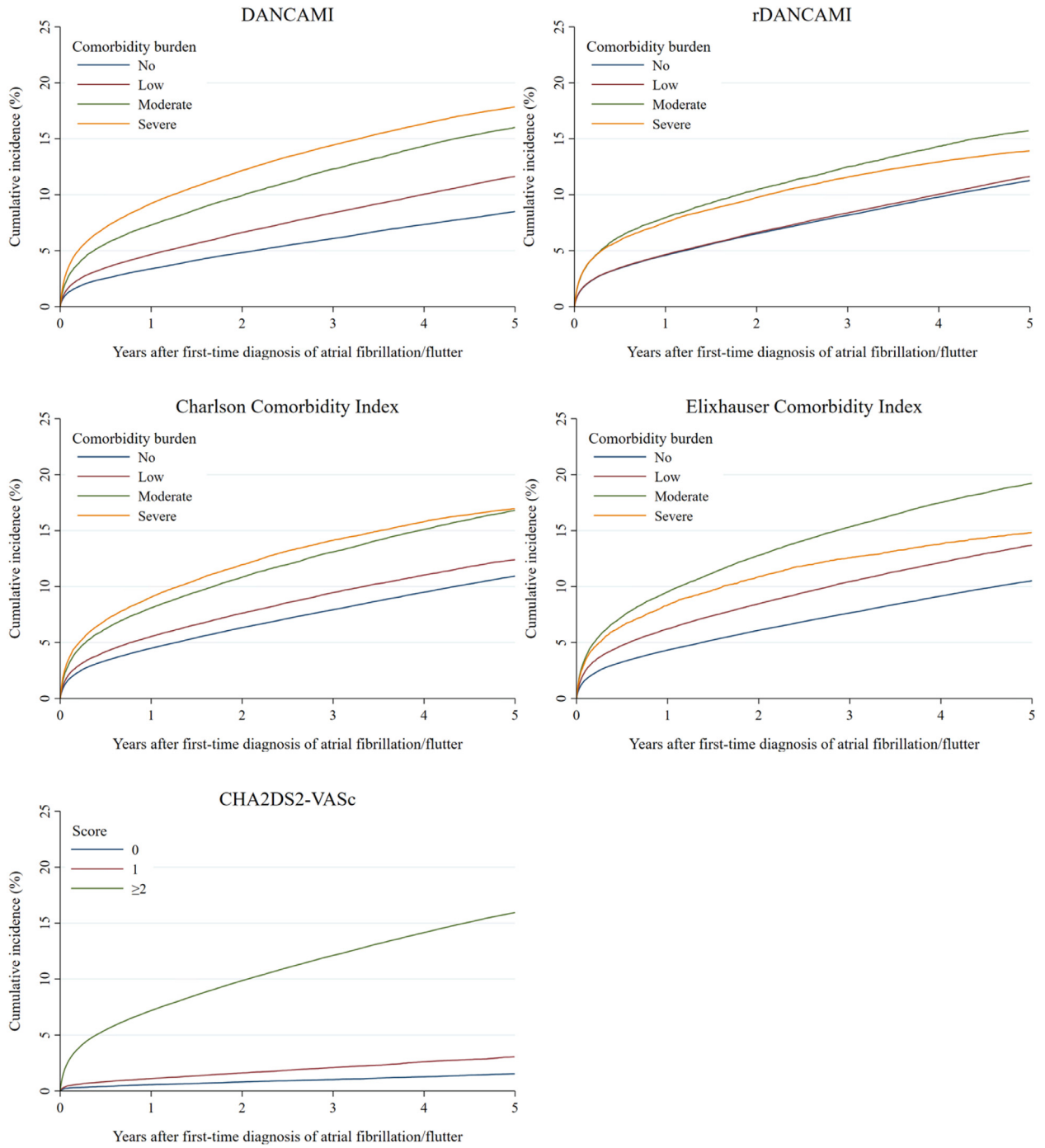

Fig. 2. *Five-year cumulative incidence of cardiovascular mortality according to the comorbidity and the CHA_2DS_2-VASc categories in patients with atrial fibrillation/flutter.*

Abbreviations: DANCAMI, Danish Comorbidity Index for Acute Myocardial Infarction; rDANCAMI, Danish Comorbidity Index for Acute Myocardial Infarction restricted to non-cardiovascular diseases.

(Supplementary Table 7). The C-Statistic for the DANCAMI in terms of predicting 5-year all-cause mortality risk was 0.76 in males and 0.74 in females (Supplementary Table 7).

For all outcomes, all indices showed higher C-Statistics in patients with non-valvular than valvular atrial fibrillation/flutter (Supplementary Table 8). In terms of predicting 5-year cardiovascular mortality risk, the C-Statistic for the DANCAMI was 0.65 for valvular and 0.77 for non-valvular atrial fibrillation/flutter (Supplementary Table 8). In terms of predicting 5-year all-cause mortality risk, the C-Statistic for the DANCAMI was 0.66 for valvular and 0.75 for non-valvular atrial fibrillation/flutter (Supplementary Table 8).

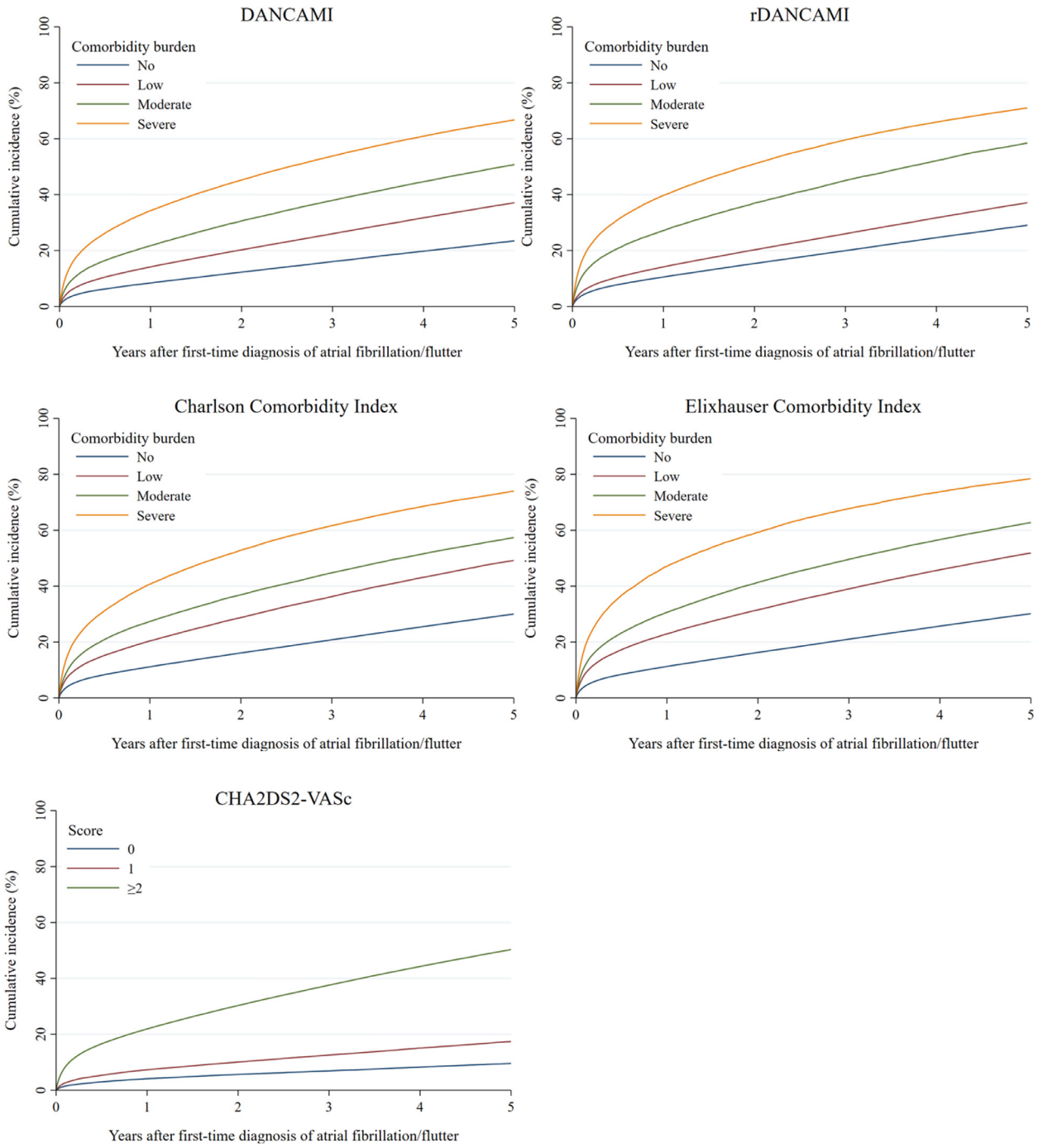

Fig. 3. *Five-year cumulative incidence of all-cause mortality according to the comorbidity and the CHA_2DS_2-VASc categories in patients with atrial fibrillation/flutter.*

Abbreviations: DANCAMI, Danish Comorbidity Index for Acute Myocardial Infarction; rDANCAMI, Danish Comorbidity Index for Acute Myocardial Infarction restricted to non-cardiovascular diseases.

All comorbidity indices predicted ischemic stroke and all-cause mortality risks better in patients with a CHA_2DS_2-VASc score of 0 compared with patients with a CHA_2DS_2-VASc score of ≥2 (Supplementary Table 9). For the DANCAMI, the C-Statistic for predicting 1-year risk of ischemic stroke was 0.64 for a CHA_2DS_2-VASc score of 0 and 0.59 for a CHA_2DS_2-VASc score of ≥2 (Supplementary Table 4). For predicting 1-year all-cause mortality risk, the C-Statistic for the DANCAMI was 0.82 for a CHA_2DS_2-VASc score of 0 and 0.72 for a CHA_2DS_2-VASc score of ≥2 (Supplementary Table 9). In contrast, all indices predicted the cardiovascular mortality risk better in patients with a CHA_2DS_2-VASc score of ≥2 than in patients with a CHA_2DS_2-VASc score of 0

(Supplementary Table 9). For the DANCAMI, the C-Statistic for predicting 1-year cardiovascular mortality risk was 0.64 for a CHA_2DS_2-VASc score of 0 and 0.73 for a CHA_2DS_2-VASc score of ≥2 (Supplementary Table 9).

In patients with a specified diagnosis for atrial fibrillation, the C-Statistics for all indices increased compared with the main analyses for predicting cardiovascular and all-cause mortality risk (Supplementary Table 10). As regards the 5-year risks, the C-Statistic for the DANCAMI was 0.63 for predicting ischemic stroke risk, 0.81 for predicting cardiovascular mortality risk, and 0.78 for predicting all-cause mortality risk (Supplementary Table 10). In patients with a specified atrial flutter diagnosis, the C-Statistics for predicting all outcomes increased compared with the main analysis for all indices. The C-Statistic of the DANCAMI was 0.67 for predicting 5-year ischemic stroke risk, 0.80 for predicting 5-year cardiovascular mortality risk, and 0.78 for predicting 5-year all-cause mortality risk (Supplementary Table 10).

The C-Statistics to predict 1-year outcomes for the DANCAMI were 0.64 (95% CI: 0.64−0.65) for ischemic stroke before the COVID-19 lockdown, 0.64 (95% CI: 0.61−0.67) for ischemic stroke after the lockdown, 0.76 (95% CI: 0.75−0.76) for all-cause mortality before the lockdown, 0.78 (95% CI: 0.77−0.80) for all-cause mortality after the lockdown (Supplementary Table 11). We were unable to compute C-Statistics for 1-year cardiovascular mortality after the lockdown due to few events.

Discussion

Adding the DANCAMI to a baseline model including age and sex increased the ability to predict 1 and 5-year all-cause mortality risks, but not the ability to predict 1 and 5-year risks of ischemic stroke or cardiovascular mortality. No index increased the discriminatory ability beyond that of age and sex when predicting ischemic stroke or cardiovascular mortality risks. When predicting all-cause mortality risk, all comorbidity indices increased the discriminatory ability similarly, and more than that of the CHA_2DS_2-VASc score.

Previous literature

DANCAMI in patients with other diseases

The DANCAMI has been shown to be able to predict 1-year mortality risk after myocardial infarction (C-Statistic: 0.77)[7] and venous thromboembolism (C-Statistic: 0.76),[23] but not after heart transplantation (C-Statistic: 0.58).[24] Thus, whether specific comorbidity indices need to be developed for each individual disease, or whether existing comorbidity indices can be used, seem to depend on the disease of interest. However, comorbidity indices may be applicable to other cohorts as exemplified by the wide use of the CCI. Thus, despite being developed in a cohort of 559 medical patients admitted to a single hospital in 1984,[25] the CCI has shown high discriminatory performance of several outcomes in several patient cohorts.[26-28]

Prognostic scores in patients with atrial fibrillation

A clinical single-center study performed 6-month follow-up of 128 patients hospitalized for myocardial infarction who had atrial fibrillation.[29] The study found that a 1-point increase in CCI score was associated with a 19% increased rate of hospital readmission and a 32% increased all-cause mortality rate.[29] The C-Statistic was 0.63 for predicting hospital readmission and 0.71 for predicting all-cause mortality risk — slightly lower than our results.[29]

A Danish cohort study examined the ability of the CHA_2DS_2-VASc score to predict 1 and 12-year risks of ischemic stroke after incident atrial fibrillation.[30] Compared with patients with a CHA_2DS_2-VASc score of 0, the hazard ratios of ischemic stroke during 1 year of follow-up was 2.2 when the CHA_2DS_2-VASc score was 1, 4.2 when the CHA_2DS_2-VASc score was 2, 6.5 when the CHA_2DS_2-VASc score was 3, and 9.1 when the CHA_2DS_2-VASc score was 4.[30] However, in a Cox proportional-hazards model including CHA_2DS_2-VASc score, year of inclusion, and use of antiplatelet therapy, the C-Statistic for predicting 1-year risk of ischemic stroke was only 0.64 in patients with a CHA_2DS_2 score of 0 and 0.58 in patients with a CHA_2DS_2 score of 1.[30] These C-Statistics are comparable to our results for both the baseline and the CHA_2DS_2-VASc models. This suggests that the ability of the CHA_2DS_2-VASc score to predict ischemic stroke might be due more to its inclusion of age and sex and less to its inclusion of the comorbidities: congestive heart failure, hypertension, diabetes, vascular disease, and previous thromboembolism. However, dissimilarities between estimating CHA_2DS_2-VASc scores from population-based data and data obtained in a clinical setting likely led to different predictive abilities.

Application of comorbidity indices

Comorbidity scores are commonly used to adjust for confounding in prognosis studies as it increases statistical efficiency in smaller study populations[31] and may reduce confounding to a similar extent as the individual comorbidities used to create the score. However, in several settings, a model including age and sex seems to predict disease outcomes equivalent to a model including age, sex, and a comorbidity score.[31] Consequently, after accounting for age and sex, also accounting for a comorbidity score may not reduce confounding further in such settings. The reason for this little (if any) benefit of adding a comorbidity score when predicting disease outcome, could be the oversimplistic estimation of comorbidity burden when using registry data.[31]

Confounding occurs when a covariate influences the association between the exposure and the outcome under

study. Thus, the ability of a comorbidity score to reduce confounding depends on its association with both the exposure and the outcome. Considering the discriminatory performance of the DANCAMI, it may be beneficial in controlling for confounding when examining all-cause mortality risk after atrial fibrillation/flutter. Importantly, the benefit depends on the study setting and the aim. Although the discriminative performances of the different comorbidity indices were not substantially different, DANCAMI may provide a more contemporary and clinically relevant index than existing indices. Thus, the DANCAMI was developed in a contemporary cohort (2000−2013) of patients with myocardial infarction, incorporates additional comorbidities that predict mortality (e.g., psychiatric diseases), and excludes comorbidities with limited clinical implications in current clinical practice (e.g., AIDS).[7]

Limitations

Comorbidities treated solely by a general practitioner is likely underestimated in the DNPR. We mitigated this limitation by adding information on redemptions of relevant prescription drugs to identify such comorbidities, but some underestimation may persist. Also, obesity is underestimated as its completeness is only 11% in the DNPR.[32] Underestimation of comorbidities would result in lower comorbidity scores, but would not necessarily change the discriminatory performance measures.

Conclusions

The ability of the DANCAMI model to predict 1 and 5-year risks of ischemic stroke and cardiovascular mortality was similar to that of the other models. The ability of the DANCAMI model to predict 1 and 5-year all-cause mortality risk was similar to that of the CCI and the ECI models, but better than that of the baseline and the CHA_2DS_2-VASc models.

Author contributions

K. Bonnesen and M. Schmidt designed the study. K. Bonnesen performed the analyses. K. Bonnesen, U. Heide-Jørgensen, H.T. Sørensen, and M. Schmidt interpreted the results. K. Bonnesen and M. Schmidt drafted the manuscript. U. Heide-Jørgensen and H.T. Sørensen critically revised the drafted work. All authors approved the final version and agreed to be accountable for the full aspects of the work.

Declaration of Competing Interest

None.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2023.107219.

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