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THOUGH RESULTS OF NON-STROKES ARE COMMON, SCORE OF STROKE RISK CAN BE USED FOR PREDICTION IN PATIENTS WITH ATRIAL FIBRILLATION

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Abstract:

In this analysis it is investigated whether cardiovascular result configurations diverge across atrial fibrillation (AF) subgroups expressed by valvular status, age, freshly identified vs. predominant cases, or anticoagulation status, and whether risk of stroke models can accurately predict non-stroke results.

It executed a retrospective associated analysis of all 147,952 adults between January 2008 and March 2014: 23,095 (15.6%) had at least 1 thromboembolic incident (stroke, TIA, or systemic embolism) and 52,618 (35.6%) had a non-stroke major adverse cardiovascular incidents (NS-MACE = new heart failure, all-cause mortality, new acute coronary syndrome) during continuation. NS-MACE was 2–3 times additionally numerous than stroke in all subgroups. Freshly identified patients had elevated degrees of all results in the first year than those with predominant AF (and those with valvular AF had the highest degrees): incident vs. predominant NS-MACE degrees per 100 patient years were 53.1 vs. 23.2 for anti-coagulated valvular patients, 32.8 vs. 11.0 for non-anti-coagulated NVAF patients, and 29.6 vs. 14.6 for anti-coagulated NVAF patients.

According to reports the non-anti-coagulated NVAF patients, the risk of stroke models demonstrated comparable accuracy for prediction of NS-MACE as they did for stroke prediction: C-statistics 0.66 [0.66–0.66] vs 0.67 [0.66–0.68] for ATRIA-STROKE, 0.66 [0.66–0.67] vs. 0.62 [0.61–0.62] for CHADS2, and 0.62 [0.61–0.62] vs. 0.52 [0.51–0.52] for CHA2DS2-VASc.

Non-stroke cardiovascular results are additionally communal than stroke in all subgroups but current risk of stroke scores exhibit comparable (modest) ability to predict risk for AF NS-MACE as for stroke, allowing identification of high-risk individuals for intervention.

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INTRODUCTION:

Although studies, guidelines, and decision analyses have focused on the risk of stroke in making treatment decisions for patients with atrial fibrillation (AF), AF patients also exhibit an increased risk for other cardiovascular incidents. In fact, the absolute risk increases are elevated for heart failure (11.1 excess incidents per 1000 patient years) and chronic kidney disease (6.6 incidents per 1000 patient years) than stroke (3.6 incidents per 1000 patient years) after development of AF (Asinger, Shroff and Herzog, 2016).

Stroke degrees have been dropping in recent decades (due not only to increasing use of anticoagulants in patients with AF, but also better control of blood pressure and other non-AF risk of stroke factors), meaning that the importance of non-stroke results in AF patients will increase over time. As some therapies (such as rennin-angiotensin inhibitors or intensive risk factor management) can reduce the risk of developing conditions such as heart failure (HF) or chronic kidney disease (CKD), but are associated with cost and potential adverse effects, being able to identify which patients are at elevated risk for such results would be important (Asinger, Shroff and Herzog, 2016).

The CHADS2, CHA2DS2-VASc, and ATRIA-STROKE scores are clinical prediction models endorsed by major medical societies to assess thromboembolic risk (stroke, transient ischemic attack (TIA), and/or systemic thromboembolism) in patients with non-valvular. AF (NVAF). Whether the CHADS2, CHA2DS2-VASc, or ATRIA scores can predict the risk of major cardiovascular results other than stroke in patients with NVAF is unclear. Thus, we designed this analysis to explore that. Moreover, as reports of outcome degrees in patients with valvular AF are largely based on old studies (prior to aggressive management of hypertension and widespread use of anticoagulation) with small and often highly selected and younger patient populations, we evaluated the frequency of non-stroke major adverse cardiovascular incidents (NS-MACE) in patients with valvular versus NVAF. Finally, as most pharmacoepidemiologic studies in AF are limited to older patients (most drug coverage plans are limited to elderly individuals), we examined whether outcome patterns differed for AF patients older vs. younger than 65 years (Asinger, Shroff and Herzog, 2016).

2.0 METHODS:

2.1 Data sources

We conducted a retrospective associated analysis using de-identified but linked (using unique health number identifiers) Alberta Health administrative databases cross-linked with laboratory and pharmacy data for all adult residents of Alberta (population 4.4million people). We received approval from Alberta Health and the Health Research Ethics Boards at for performing analyses on these anonymized datasets without individual signed patient consent (Asinger, Shroff and Herzog, 2016)

2.2 Study sample

The cohort consisted of all adult Albertans (aged 18 years or older)with a diagnosis of AF or atrial flutter (International Classification of Diseases-9 CM 427.3 and ICD-10 CA I48) between January 1, 2014 and March 31, 2016 in any fields of either the discharge abstract database (DAD; which captures all acute care hospitalizations with most responsible diagnosis and up to 24 secondary diagnoses), the national ambulatory care reporting system (NACRS; which captures all visits to emergency rooms or hospital-based specialist clinics in Alberta), or the physician billing claims databases (as mentioned in Table 1 for case definitions for AF and valvular AF (Atterman et al., 2018)

These AF case definitions have been evaluated in multiple studies and in those that used both inpatient and outpatient data sensitivity approached 95% and specificity 99%. Of note, we expressed any patients with mitral stenosis or a valve procedure as having “valvular AF” and all others as having “NVAF”. We included all patients with AF but expressed freshly identified (incident) cases as those without any of the relevant AF diagnostic codes prior to January 2014 patients could only remain in the “freshly identified” subtype for the first year after diagnosis but they continued in the cohort after that year and contributed to the numerators/denominators for predominant cases after that time. For all AF case definitions, the index date was expressed as the date of the first AF code in the DAD, NACRS, or physician billing claims databases (Atterman et al., 2018).

2.3 Classification of anticoagulant exposure

All patients are treated anticoagulant exposure as a time-varying covariate and used the Pharmacy Information Network data (available in participants of all ages since January 2014) and classified participants as being “anticoagulated” for a quarter (3 months) if they had an active prescription for an anticoagulant (warfarin, dabigatran, rivaroxaban, or apixaban for at least 15 days of that quarter. The collated continuation time and incidents per quarter and included time-varying covariates (Atterman et al., 2018).

2.4 Covariates

According to previous studies it was identified co-

morbidities, and other than fixed covariates (such as sex) we treated all others as time-varying covariates quarterly, using the ICD-9-CM or ICD-10-CA codes validated in administrative databases with look-back beginning in April 2014.

Generally, it was projected that GFR glomerular filtration rate (GFR; calculated using the CKD-EPI equation) to categorize patients by kidney function. The scores for CHADS2, CHA2DS2-VASc, and ATRIA Stroke were calculated at baseline for each patient and were also updated quarterly. Although these risk scores are not normally used for patients with valvular AF we examined them for the purposes of this analysis As we employed administrative data-based case definitions to define comorbidities and anticoagulant exposure there were no missing values in these fields. The only covariates with any missing values were rural residence and GFR and in those cases we used the last value carried forward for subsequent quarters or if a patient never had those covariates established we assumed they were not rural and had normal GFR (Coşansu et al., 2017).

2.5 Outcomes

In this study it is examined thromboembolic incidents (stroke, TIA, or systemic arterial embolism), NS-MACE (all-cause death, new heart failure, or new acute coronary syndrome), each of the non-stroke cardiovascular incidents individually, and new chronic kidney disease (see Table 1 in the Online Appendix for details of ICD-9-CMand ICD-10 CA coding algorithms).

Furthermore, it is included all-cause death in the NS-MACE as we did not have access to death certificate data and recent studies have found that only 8% to 9% of deaths in patients with AF are stroke-related. New heart failure was expressed as a first hospitalization or emergency room visit with a most responsible diagnosis of HF (see Table 1 for ICD-10 CA case definition) as this maximizes specificity of the case definition (including outpatient visits with a diagnosis of HF risks inclusion of some false positives where the physician billed the visit as "rule out HF") (Coşansu et al., 2017).

3.0 RESULT:

For this specific research we followed 147,952 AF patients (77,951 [52.7%] were freshly identified, 9544 [6.5%] had valvular AF, and 52,811 [35.7%] were younger than 65 - Table 1) for a median of 46 months (IQR 19 to 75) as mentioned in Fig. 1. During that time, 23,095 (15.6%) had at least 1 thromboembolic incident (stroke, TIA, or systemic embolism), 52,618 (35.6%) had a NS-MACE (death, HF, or ACS), 39,782 (26.9%) died, 37,896 (25.6%) had a non-fatal major cardiovascular incident (first thromboembolic incident, HF, or ACS), 17,264 (11.7%) had new onset heart failure, 16,087 (10.9%) developed CKD, and 4073 (2.8%) had an acute coronary syndrome (Coşansu et al., 2017).

Not surprisingly, freshly identified AF patients were younger and had fewer cardiovascular risk factors, less heart failure, and fewer stroke/TIA at baseline (and thus lower scores on the CHADS2, CHA2DS2-VASc, or ATRIA-STROKE models) than predominant AF cases (Table 1). AF patients younger than 65 demonstrated comparable baseline patterns as freshly identified AF patients, with less comorbidity and risk factors as well as a elevated frequency of alcohol use disorder and liver disease. Of note, 44.8% of AF patients younger than 65 had CHADS2 scores of 0, 24.0% had CHA2DS2-VASc scores of 0, 60.2% had CHA2DS2-VASc scores of 0 or 1, and 90.0% had an ATRIA-STROKE score of ≤ 5. Patients with NVAF were younger and had less cardiopulmonary comorbidities than patients with valvular AF (Table 1).

3.1 Frequency of incidents in AF subgroups

Patients with freshly identified AF had elevated degrees for all results in the first year after diagnosis than those with predominant AF (Fig. 1 and Table 2), and even though they were almost all anticoagulated, patients with valvular AF (Fig. 1 and Table 3) had elevated degrees than those with NVAF, even those not on anticoagulation. For example, NSMACE degrees per 100 patient years in freshly identified vs. predominant cases were 53.1 vs. 23.2 for anticoagulated valvular AF patients, 32.8 vs. 11.0 for non-anticoagulated NVAF patients, and 29.6 vs. 14.6 for anticoagulated NVAF patients. NS-MACE was additionally common than new stroke/TIA and new HF or new onset CKD were also generally additionally usual than stroke/TIA in NVAF patients whether they were anticoagulated or not as mentioned in Table 2 (Haft and Teichholz, 2017).

The frequency of NS-MACE (HF, ACS, or death), HF hospitalizations, or new onset CKD were also two to threefold elevated than the frequency of new stroke/TIA in patients with valvular AF. Given the survivorship bias inherent in this cohort (i.e. patients who survive experience additional non-fatal incidents), we developed probability trees to describe the prognosis for NVAF patients who were anticoagulated (Fig. 2a) or not anticoagulated (Figure 2b) and patients with valvular AF who were anticoagulated (Figure 2c) rather than generating adjusted hazard ratios associated with anticoagulant use in each subgroup.

dult Albertans with atrial fibrillation.

	Newly diagnosed	Prevalent	NVAF	Valvular AF	≥65 y
cipants	77,951 (52.7)	70,001 (47.3)	138,408 (93.6)	9544 (6.5)	95,141 (64.3)
R) y	70.0 (58.0,80.0)	74.0 (60.0,82.0)	72.0 (58.0,82.0)	74.0 (62.0,82.0)	78.0 (72.0,84.0)
	30,295 (38.9)	22,516 (32.2)	49,891 (36.0)	2920 (30.6)	0 (0.0)
	16,970 (21.8)	15,308 (21.9)	29,897 (21.6)	2381 (24.9)	32,278 (33.9)
	19,264 (24.7)	20,653 (29.5)	37,028 (26.8)	2889 (30.3)	39,917 (42.0)
	11,422 (14.7)	11,524 (16.5)	21,592 (15.6)	1354 (14.2)	22,946 (24.1)
	36,144 (46.4)	32,870 (47.0)	64,574 (46.7)	4440 (46.5)	47,728 (50.2)
	9511 (12.2)	10,062 (14.4)	18,373 (13.3)	1200 (12.6)	13,088 (13.8)
rder	4529 (5.8)	3375 (4.8)	7459 (5.4)	445 (4.7)	3922 (4.1)
	8091 (10.4)	5635 (8.0)	12,944 (9.4)	782 (8.2)	11,474 (12.1)
ilure	21,410 (27.5)	24,125 (34.5)	39,706 (28.7)	5829 (61.1)	37,215 (39.1)
ary disease	21,589 (27.7)	19,832 (28.3)	38,139 (27.6)	3282 (34.4)	33,124 (34.8)
	619 (0.8)	325 (0.5)	879 (0.6)	65 (0.7)	461 (0.5)
	7532 (9.7)	7054 (10.1)	13,696 (9.9)	890 (9.3)	14,099 (14.8)
s	19,251 (24.7)	16,573 (23.7)	33,215 (24.0)	2609 (27.3)	27,029 (28.4)
	2264 (2.9)	1748 (2.5)	3660 (2.6)	352 (3.7)	2272 (2.4)
	53,384 (68.5)	50,938 (72.8)	96,536 (69.7)	7786 (81.6)	80,345 (84.4)
ction	7540 (9.7)	7024 (10.0)	13354 (9.6)	1210 (12.7)	11,103 (11.7)
ase	731 (0.9)	530 (0.8)	1130 (0.8)	131 (1.4)	977 (1.0)
ular disease	3734 (4.8)	3020 (4.3)	6177 (4.5)	577 (6.0)	5736 (6.0)
	15,993 (20.5)	15,807 (22.6)	29,084 (21.0)	2716 (28.5)	26,528 (27.9)
	3801 (4.9)	5351 (7.6)	8358 (6.0)	794 (8.3)	7246 (7.6)
.73 m^2					
	66,921 (85.9)	60,440 (86.3)	119,730 (86.5)	7631 (80.0)	76,534 (80.4)
	5742 (7.4)	4758 (6.8)	9557 (6.9)	943 (9.9)	9373 (9.9)
	3367 (4.3)	3261 (4.7)	5986 (4.3)	642 (6.7)	6195 (6.5)
	1921 (2.5)	1542 (2.2)	3135 (2.3)	328 (3.4)	3039 (3.2)
	16,123 (20.7)	11,898 (17.0)	27,404 (19.8)	617 (6.5)	4388 (4.6)
	16,648 (21.4)	13,751 (19.6)	28,826 (20.8)	1573 (16.5)	15,300 (16.1)
	45,180 (58.0)	44,352 (63.4)	82,178 (59.4)	7354 (77.1)	75,453 (79.3)
	7298 (9.4)	5398 (7.7)	12,436 (9.0)	260 (2.7)	0 (0.0)
	12,366 (15.9)	9143 (13.1)	20,744 (15.0)	765 (8.0)	2383 (2.5)
	58,287 (74.8)	55,460 (79.2)	105,228 (76.0)	8519 (89.3)	92,758 (97.5)
	38,110 (48.9)	30,244 (43.2)	64,953 (46.9)	3401 (35.6)	20,832 (21.9)
	5922 (7.6)	5566 (8.0)	10,724 (7.7)	764 (8.0)	11,471 (12.1)
	33,919 (43.5)	34,191 (48.8)	62,731 (45.3)	5379 (56.4)	62,838 (66.0)

as frequency counts (percentage), or median (inter-quartile range).
; ATRIA anticoagulation and risk factors in atrial fibrillation; $CHADS_2$ congestive heart failure, hypertension, age, diabetes, stroke/transient ischemic atta
lure, hypertension, age ≥ 75 y, diabetes, stroke/transient Ischemic attack, vascular disease, age 65–74 y, (female) sex; eGFR estimated glomerular filtrati
lation; TIA transient ischemic attack.

Source: (Haft and Teichholz, 2017)

3.3 Performance of existing risk of stroke scores for other results

The risk of stroke scores executed accordingly in patients with predominant AF as those with freshly identified AF (as mentioned in Table 2) but demonstrated better discrimination in patients who were not anticoagulated compared to those who were (Table 2). C-statistics were also elevated in patients younger than 65 years compared to older patients, although the accuracy was substantially lower for predicting stroke in non-anticoagulated NVAF patients older than 65 (C-statistics 0.67 [0.67–0.68] for ATRIASTROKE, 0.61 [0.62–0.61] for CHADS2, and 0.52 [0.51–0.52] for CHA2DS2-VASc) this is an important group to highlight since two thirds of AF patients were in this age group and this is the most communal clinical scenario where these risk scores are used.

Table 2
C-statistics for each outcome after one-year of follow-up by risk scores.

	Anticoagulated NVAF patients			Non-anticoagulated NVAF patients		
	$CHADS_2$	CHA_2DS_2-VASc	ATRIA stroke	$CHADS_2$	CHA_2DS_2VASc	ATRIA stroke
Newly diagnosed (incident) patients						
All-cause mortality	0.60 (0.59,0.61)	0.55 (0.55,0.56)	0.63 (0.62,0.65)	0.66 (0.66,0.67)	0.62 (0.62,0.63)	0.67 (0.66,0.67)
First thromboembolic event[a]	0.63 (0.62,0.63)	0.56 (0.56,0.56)	0.71 (0.70,0.72)	0.73 (0.72,0.73)	0.64 (0.64,0.64)	0.78 (0.78,0.79)
New heart failure	0.61 (0.60,0.62)	0.55 (0.55,0.56)	0.57 (0.56,0.58)	0.68 (0.68,0.69)	0.62 (0.62,0.63)	0.63 (0.62,0.63)
New chronic kidney disease	0.56 (0.55,0.57)	0.55 (0.54,0.55)	0.54 (0.52,0.55)	0.57 (0.56,0.58)	0.58 (0.58,0.59)	0.55 (0.54,0.56)
Acute coronary syndrome	0.59 (0.58,0.61)	0.56 (0.55,0.57)	0.57 (0.54,0.59)	0.59 (0.57,0.61)	0.60 (0.58,0.61)	0.57 (0.55,0.59)
Non-stroke MACE[b]	0.61 (0.60,0.62)	0.56 (0.55,0.56)	0.58 (0.57,0.59)	0.67 (0.67,0.68)	0.63 (0.63,0.63)	0.66 (0.65,0.66)
Prevalent patients[c]						
All-cause mortality	0.58 (0.58,0.59)	0.54 (0.54,0.54)	0.62 (0.61,0.63)	0.68 (0.67,0.68)	0.62 (0.61,0.62)	0.71 (0.70,0.71)
First thromboembolic event[a]	0.60 (0.60,0.60)	0.54 (0.54,0.54)	0.68 (0.67,0.68)	0.70 (0.70,0.70)	0.62 (0.62,0.62)	0.76 (0.75,0.76)
New heart failure	0.58 (0.58,0.59)	0.54 (0.53,0.54)	0.56 (0.55,0.57)	0.68 (0.67,0.68)	0.61 (0.61,0.61)	0.65 (0.64,0.66)
New chronic kidney disease	0.53 (0.52,0.53)	0.52 (0.52,0.53)	0.51 (0.50,0.52)	0.57 (0.57,0.58)	0.58 (0.57,0.58)	0.55 (0.54,0.56)
Acute coronary syndrome	0.54 (0.53,0.56)	0.54 (0.53,0.54)	0.54 (0.51,0.56)	0.61 (0.60,0.63)	0.60 (0.60,0.61)	0.60 (0.58,0.62)
Non-stroke MACE[b]	0.58 (0.58,0.58)	0.54 (0.54,0.54)	0.58 (0.57,0.59)	0.67 (0.67,0.68)	0.62 (0.61,0.62)	0.69 (0.68,0.69)

[a] First stroke, transient ischemic attack, or systemic arterial thromboembolism.
[b] Defined as all-cause mortality, new heart failure, and/or new acute coronary syndrome.
[c] Using the first four prevalent anticoagulant or non-anticoagulated quarters.

Source: (Haft and Teichholz, 2017)

4.0 DISCUSSION:

There are several findings worthy of comment from our large, population-based analysis of AF patients. First, although freshly identified AF patients had elevated degrees for all results in the first year than those with predominant AF, the C-statistics for all risks of stroke prediction models were comparable when tested in our incident and predominant AF populations. Thus, the risk of stroke models recommended in current guidelines may be applied for prognostication at any stage in a patient's AF trajectory (Haft and Teichholz, 2017).

Second, prognosis for patients with valvular AF (mitral stenosis or a valve procedure) was poorer than for patients with NVAF, with a slightly elevated rate of stroke/TIA but approximately two to three fold elevated degrees of all non-stroke results we studied compared to patients with NVAF. This updates the existing literature on the risks of valvular AF which is largely based on studies from several decades ago when hypertension management was less aggressive and anticoagulant use less widespread.

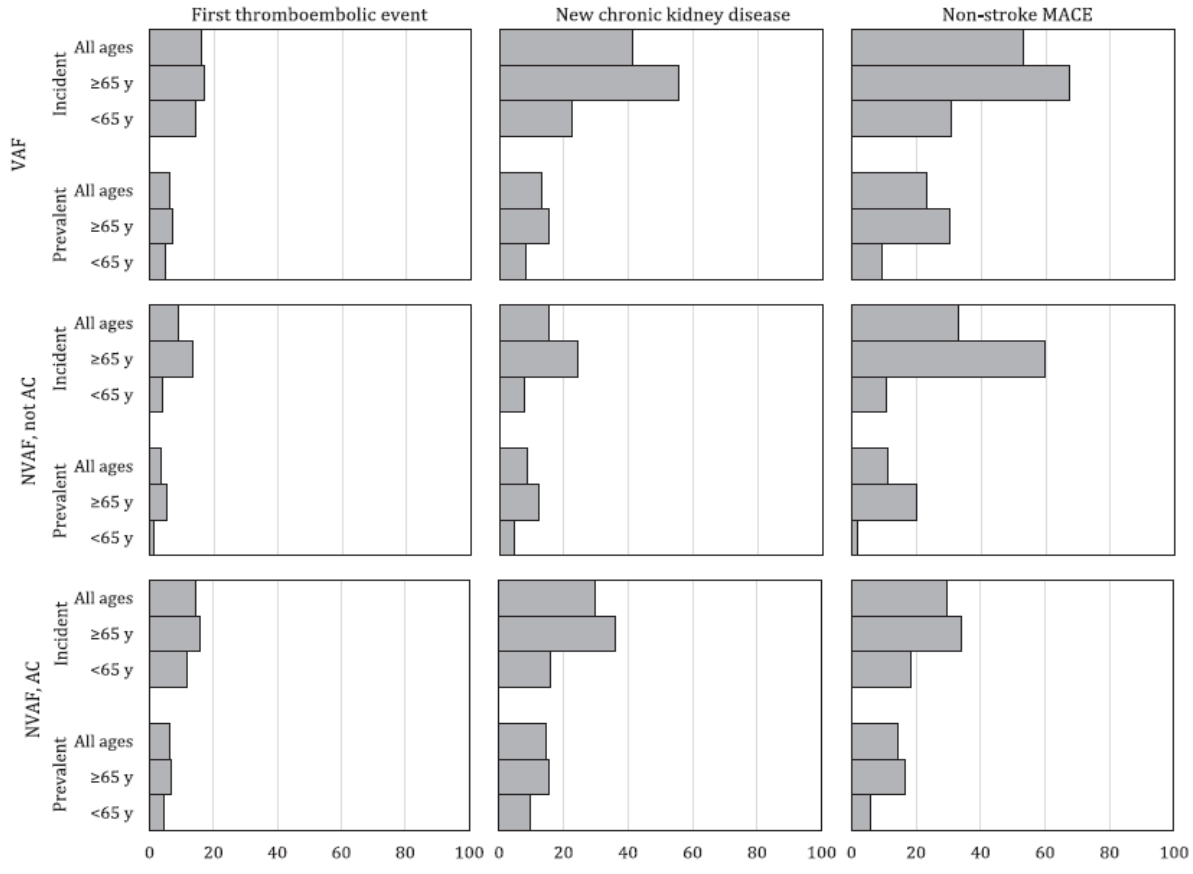

Fig. 1. Outcome rates per 100 participant-years in adult Albertans with valvular (VAF) or non-valvular (NVAF) atrial fibrillation.

Source: (Harrison and Marshall, 2017)

Third, in patients with NVAF, non-stroke major cardiovascular incidents (HF, ACS, or death) were additionally communal than stroke/TIA and new onset HF or CKD was also additionally communal than stroke/TIA whether they were anticoagulated or not. While earlier studies have demonstrated this in older patient populations, our data illustrated degrees that this excess risk is also seen in NVAF patients younger than 65 years and those who are freshly identified with NVAF. Fourth, the proportion of NVAF patients younger than 65 meeting thresholds for anticoagulation differ markedly depending on which risk model is chosen: 55% had CHADS2 scores ≥1, 40% had CHA2DS2- VASc scores ≥2, and 10% had an ATRIA-STROKE score of ≥6 (Harrison and Marshall, 2017).

There are many reasons for suboptimal anticoagulation practices in patients with NVAF, and the confusion generated by conflicting estimates of patient risk undoubtedly plays a role.

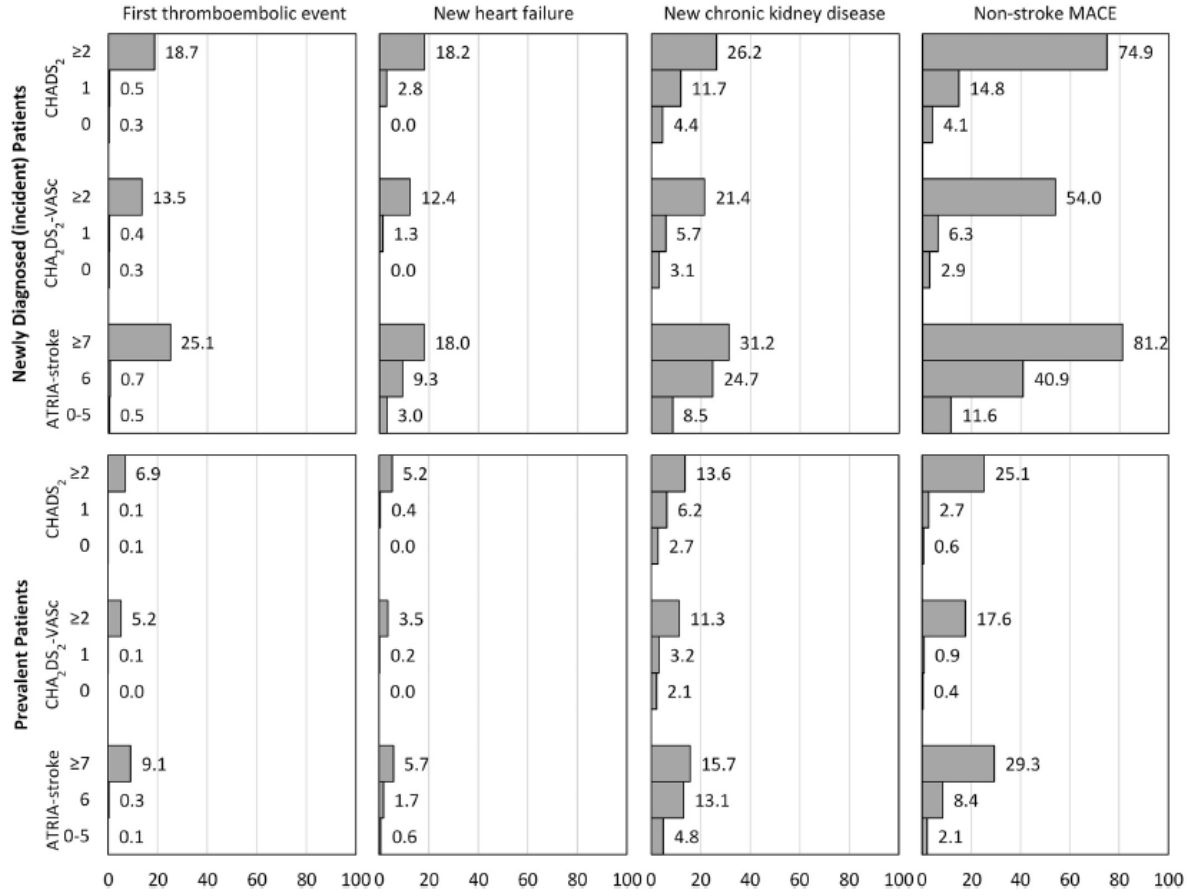

Fig. 2. Outcome rates per 100 participant-years in adult Albertans with non-valvular atrial fibrillation not anticoagulated.

Source: (Harrison and Marshall, 2017)

We did not have access to any biomarker data and future research should examine whether incorporating biomarker values into existing risk prediction models improves their accuracy for either stroke or NS-MACE prediction. Indeed, given the greater frequency of non-stroke results further research should focus on developing and validating risk prediction models for each of these results individually (Lip et al., 2017).

5.0 CONCLUSION:

In conclusion, we have demonstrated that non-stroke cardiovascular results are communal in all AF subtypes and regardless of whether patients are anticoagulated or not. Current risk of stroke scores exhibit comparable accuracy for freshly identified or predominant cases of NVAF, but are additionally accurate in predicting stroke in younger patients than those 65 years or older. Importantly, the CHADS2, CHA2DS2-VASc, and ATRIA-Risk of stroke models endorsed in current AF guidelines for prediction of risk of stroke in older individuals with AF exhibit a comparable ability to discriminate risk for non-stroke cardiovascular results. Thus, they may be used to identify patients at elevated risk for non-stroke cardiovascular results who would benefit from closer continuation and initiation of preventive therapies.

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