Anticoagulation reduces population risk of stroke and mortality in incident atrial fibrillation

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Abstract

Background: Atrial fibrillation increases the risk of stroke and mortality. Anticoagulation is an effective therapy for stroke prevention, but remains underutilized in the community. We aim to determine the effectiveness and safety of anticoagulation in an inception cohort with new-onset atrial fibrillation in the province of Alberta, Canada.

Methods: This is a population-wide cohort study of atrial fibrillation using an administrative database from Alberta's publicly funded and universally available health-care system. All new-onset atrial fibrillation patients from January 1 2009 to December 31 2010 were included and followed through December 31 2013. We assessed anticoagulation status as a predictor of stroke and death, using time-to-event analysis and adjusted for sex and CHADS2 score using Cox proportional hazards modeling.

Results: 10745 patients were identified. 7358 (68.5%) received anticoagulation, principally with warfarin (n=6997, 95.1%). Anticoagulation was associated with significantly decreased ischemic stroke (HR 0.69, 95%CI [0.58-0.82]), all stroke (HR 0.77, 95%CI [0.65-0.91]), all stroke and death (HR 0.70, 95%CI [0.62-0.72]), and all-cause mortality (HR 0.67, 95%CI [0.62-0.72]), despite an association with increased hemorrhagic stroke (HR 1.92, 95%CI [1.17-3.16]). There was a neutral association with subdural hemorrhage (HR 1.01, 95%CI [0.53-1.93]) and gastrointestinal hemorrhage (HR 0.96, 95%CI [0.70-1.31]).

Interpretation: In a real-world practice from a complete population with high rates of oral anticoagulation, anticoagulation therapy is effective and safe for stroke prevention and decreases mortality in patients with incident atrial fibrillation.

Introduction

Atrial fibrillation is the most common cardiac arrhythmia, affects 1-2% of the Western world population, and rises in prevalence with advancing age.[1, 2] Compared to those without atrial fibrillation, it is associated with a twofold greater mortality and five-fold greater risk of ischemic stroke.[3, 4] These cardioembolic ischemic strokes are associated with higher rates of disability compared to ischemic stroke from other causes.[5] Warfarin is an inexpensive and effective stroke prevention strategy, but has a narrow therapeutic index requiring close monitoring of the international normalized ratio. The mean time in the therapeutic range lies between 60 to 70% in the setting of clinical trials, but it may be as low as 50% or less in routine clinical practice.[6-8] Anticoagulation for atrial fibrillation does not show a mortality benefit in single clinical trials, but a mortality reduction has been reported with meta-analysis of multiple studies.[9-11] Despite these benefits, oral anticoagulation is underutilized on a population basis.[12-14]

Anticoagulation impairs clotting and therefore, it can uncover or worsen any induced or spontaneous hemorrhage from another cause. Nuisance bleeding such as skin bruising is common. Gastrointestinal hemorrhage is the most common serious form of hemorrhage, but intracranial hemorrhage is the most feared complication by both patients and physicians alike.

To assess the potential population benefit of oral anticoagulation, we used contemporary and complete population data to investigate population rates of stroke, mortality, and the rates of

the most common complications, gastrointestinal hemorrhage and subdural hemorrhage, among patients with a new diagnosis of atrial fibrillation in the province of Alberta, Canada.

Methods

Study design and population

We conducted a population-based retrospective cohort study of incident atrial fibrillation using administrative data from the province of Alberta. All Alberta residents (population 4,025,078 in 2013[15]) are eligible for a publicly funded and universally available health-care system. The Alberta Health Care Insurance Plan (AHCIP) provides medical coverage to most Alberta residents (99%). The only exceptions are members of the Military, federal inmates, individuals who opt out of the AHCIP and the Royal Canadian Mounted Police. Each resident covered by the plan is assigned a personal health number that acts as a unique lifetime identifier. A linked Pharmaceutical Information Network (PIN) records all prescription drug use from outpatient pharmacies. Data were extracted from the Alberta Health hospital inpatient, ambulatory/emergency department, physician claims, and PIN databases. Canadian administrative data have been previously shown to be valid and highly accurate.[16, 17]

We defined an inception cohort with new-onset atrial fibrillation from January 1 2009 to December 31 2010 and followed them through December 31 2013. Atrial fibrillation was identified using ICD-9-CM code 427.3x or ICD-10-CA code I48.x in any diagnosis field in any of the Alberta Health hospital inpatient, ambulatory/emergency department encounters, or physician claims databases. Two diagnoses for atrial fibrillation were required at separate

healthcare encounters more than 30 days apart within the first year of diagnosis to meet the case definition in order to minimize misclassification of transient single episodes of atrial fibrillation or flutter. Valvular heart disease was excluded if a patient had the following codes in any of the databases preceding the incidence date: mitral or aortic disease (ICD-9 394-396, 424.0, 424.1 or ICD-10 I05, I06, I34, I35, I08.0, I08.1, I08.2, I08.3) or valve surgery (ICD-9 35.0x, 35.2x, 35.96, 35.97, 35.99 and ICD 10 CCI code 1.HT.89, 1.HV.80, 1.HU.80, 1.HT.80, 1.HS.80, 1.HV.90, 1.HU.90, 1.HT.90, 1.HS.90).[17, 18]

The composite of all stroke (ischemic and hemorrhagic) and all-cause mortality was the primary outcome. Secondary outcomes were individual components of the composite outcome and rates of gastrointestinal and subdural hemorrhages. Stroke was then divided into ischemic and hemorrhagic types. Ischemic stroke was defined as any hospital admission with an ICD9 code of 362.3, 433.x1, 434.x1, 436 or ICD10 code of H34.1, H34.2, I63.x, I64.x. Hemorrhagic stroke was similarly defined using ICD9 code 430.x, 431.x or ICD10 code I60.x, I61.x.[17] We examined subdural hemorrhage (ICD9 code 432.x or ICD10 code I62.x as the primary diagnosis) separately because subdural hemorrhage is not a stroke; it is a specific bleeding complication principally associated with trauma and made more serious with anticoagulation. We also examined rates of gastrointestinal bleeding (ICD10 K25, K26, K27, K28, K29 as the primary diagnosis).[19]

Patients were divided into two categories: primary and secondary prevention cohorts. The primary prevention cohort was composed of patients who met the case definition for non-valvular atrial fibrillation and had no prior occurrence of a cerebrovascular event in Alberta

from the date the patient obtained an AHCIP number or April 1, 1994. In contrast, the secondary prevention cohort was composed of patients with a prior diagnosis of stroke (ischemic or hemorrhage) or transient ischemic attack (TIA). Rarely, patients who migrated to the province with a prior history of TIA or stroke would still be assigned to the primary prevention cohort because prior stroke status could not be determined. Patients were included in the secondary prevention cohort if the diagnosis of atrial fibrillation was made concurrently with the diagnosis of stroke.

The PIN was linked using the unique health care number to assess prescriptions for anticoagulant medications. The PIN contains records for all pharmaceuticals dispensed by community pharmacies in Alberta. Each record contains the unique health care number as well as the drug identification number (DIN) of the pharmaceutical dispensed. Each record, based on the DIN, includes the Anatomical Therapeutic Chemical (ATC) Classification System code that classifies drugs based on organ or body system. We considered oral anticoagulants only, including warfarin and the direct oral anticoagulant medications (ATC codes B01AA, B01AF, B01AX06, and B01AE07). Because acetylsalicylic acid is available over the counter, it could not be reliably assessed. We assigned anticoagulation status according to the date a prescription was filled for the duration of that prescription. The PIN only captures outpatient prescriptions. Therefore, anticoagulants prescribed to patients admitted to an Alberta hospital or long-term care institution may not be captured if the admission length of stay exceeded that of the duration of the last anticoagulant drug prescription. We assessed anticoagulation status as a predictor of stroke and death.

Statistical Methods

Patient characteristics were described using standard descriptive statistics. We used time-to-event analysis to estimate the risk of each outcome. Patients were censored if they moved away from the province prior to the end of the study. We adjusted for sex and CHADS2 score (congestive heart failure, hypertension, age ≥ 75, diabetes mellitus, and prior TIA/stroke), defined by administrative data, using Cox proportional hazards modeling.[16, 20, 21] Patients were considered anticoagulated if they had been prescribed oral anticoagulants within the 6 months prior to an outcome or the last date of follow-up, whichever was first, and if they had at least one renewal of the prescription. We assumed continuous anticoagulation use between the first dispensation date of oral anticoagulant to the day the prescription ends after the last dispensation date. A sensitivity analysis was conducted to risk-adjust for baseline comorbidities by applying the Elixhauser comorbidity index to the subpopulation of patients who were diagnosed with atrial fibrillation while admitted in the hospital.[22]

Results

From a population of 4 million Alberta residents, a total of 10745 patients with newly diagnosed atrial fibrillation were identified, of whom 1203 (11.2%) had suffered a prior cerebrovascular event (Table 1). 7358 (68.5%) were prescribed anticoagulation therapy at least once. 6997 (95.1%) received warfarin and 1430 (19.4%) a direct oral anticoagulant; some patients switched from warfarin to a direct oral anticoagulant during the follow-up period and are therefore counted twice. Amongst the 747 patients with a prior ischemic stroke, 214 (28.6%) were

diagnosed with atrial fibrillation on the same hospital admission as the stroke. 172 (1.6%) patients were censored because they moved away from the province prior to the end of the study.

Anticoagulation was consistently associated with decreased risk of stroke and death in all cohorts (Table 2). There was no evidence that CHADS2 score modified the protective effect of anticoagulation status (p for interaction = 0.74). Anticoagulation prescription was also associated with reduction in the secondary outcomes of ischemic stroke, all stroke, and death. Of the 500 acute ischemic stroke events, 25 (5.0%) were residents in long-term care institutions at the time of their event and of the 3097 composite endpoints of all stroke or all-cause mortality, 537 (17.3%) occurred in patients residing in long-term care facilities. In the subgroup of hospitalized atrial fibrillation patients (n=3598), the beneficial association with decreased all stroke and death remained true after adjustment for the Elixhauser index (Table 3).

Anticoagulation was associated with increased intracranial hemorrhage in the total population, but not in the individual primary or secondary prevention cohorts (Table 2). There was a neutral association with the risks of gastrointestinal hemorrhage (n=158) and subdural hemorrhage (n=37) with adjusted HR 0.96, 95%CI [0.70-1.31] and HR 1.01, 95%CI [0.53-1.93], respectively.

Interpretation

In a large population with universal health care coverage and high rates of anticoagulation use for atrial fibrillation, oral anticoagulation is associated with reduced risk for stroke and

mortality. This is true with and without a history of prior strokes.[11, 23] Stratification by CHADS2 scores did not change this result.

The all-cause mortality reduction may be due to the high rates of anticoagulant prescription (68.5%), comparable to randomized controlled trials. In contrast to prior Alberta data from over a decade earlier, the rates of anticoagulation show a substantial 20% absolute increase.[14] While it is not known what an expected ceiling rate of appropriate anticoagulation might be, a recent population study from the United Kingdom showed that, despite a rising trend in anticoagulation rates in the last decade, only 58% of men and 52% of women with atrial fibrillation received oral anticoagulation in 2012.[12]

Stroke was the initial presenting symptom of atrial fibrillation in more than one in four patients with acute ischemic stroke. Similarly, a recent nation-wide Swedish study shows that a third of acute ischemic stroke patients have atrial fibrillation.[24] Because anticoagulation is such an effective therapy, it begs the question whether more aggressive strategies for screening and diagnosis of atrial fibrillation in the community, including prolonged electrocardiography recording or the use of implantable recording devices, would lead to better prevention of stroke and cardiovascular events.[13, 25, 26] Whether or not the temporal relationship between new atrial fibrillation and stroke can be definitively interpreted as a causal relationship remains controversial.[27, 28] In ASSERT, some patients with atrial fibrillation detected by their implanted pacemakers had the arrhythmia recorded after they had suffered a stroke.[25] Nevertheless, extended cardiac monitoring detecting new paroxysmal atrial fibrillation in the

acute period after ischemic stroke is highly predictive of chronic paroxysmal atrial fibrillation.[29] Current guidelines suggest that these patients should receive lifelong anticoagulation.[30]

In our study, anticoagulation was associated with an increased risk of intracranial hemorrhage occurrence, but the effect size was variable, the absolute rate was low, and it did not negate the beneficial association with all strokes (hemorrhagic and ischemic strokes combined) or all stroke and death. Gastrointestinal hemorrhage and subdural hemorrhage were not associated with anticoagulation status but the number of events was very low. This is consistent with the pathophysiological knowledge that anticoagulant medications impair thrombosis, but are not the direct cause of hemorrhage. For instance, spontaneous intracranial hemorrhage, commonly due to chronic hypertension or underlying amyloid angiopathy, is more severe among anticoagulated patients.[31] A recent longitudinal population-based study showed a decreasing trend in incidence and mortality related to warfarin-related intracerebral hemorrhages despite a four-fold increase in warfarin use.[32] The appropriate use of anticoagulation among patients with non-valvular atrial fibrillation may also be a marker of better overall care, including treatment of hypertension. Spontaneous hemorrhagic transformation of ischemic stroke is not distinguished from primary intracerebral hemorrhage using administration data. Hemorrhagic transformation is common after cardioembolic ischemic strokes and may be secondarily reduced due to the expected reduction in ischemic stroke.[33] The perceived risk of serious hemorrhage is a major reason for non-prescription of anticoagulation.[12, 34] Our study supports the use of anticoagulants in this population as the risks of hemorrhage are

outweighed by the benefit of decreased ischemic stroke and mortality. Moreover, the risks may be further attenuated by the direct oral anticoagulants (dabigatran, apixaban, rivaroxaban, and edoxaban), which are potentially safer and easier to use than warfarin.[7, 35-37]

Limitations

Our paper contains limitations, including those inherent to studies using administrative data. The rate of stroke outcomes in our study is similar to the rate observed in the Stroke Prevention in Atrial Fibrillation Trials.[4] However, we adjusted outcomes with CHADS2 instead of CHA2DS2-VASc (vascular disease, age 65-74 years, sex category), which may be superior in predicting patients at high risk.[38] Vascular disease, which includes peripheral arterial disease, complex aortic plaque, and prior myocardial infarction, is not well validated in administrative data sets. The possibility of misclassification of anticoagulation could not be completely ruled out because the Alberta PIN data does not include all patients admitted to an inpatient hospital unit or a long-term care facility; however, the occurrence of events in a long-term care institution was relatively low meaning that misclassification would have only a marginal effect on the point estimates. Moreover, the PIN does not allow us to ascertain that patients are continuously anticoagulated between the drug dispensation dates, but this bias is unlikely to be systematically unidirectional. Most anticoagulated patients included in our study were receiving warfarin. The effect of the direct oral anticoagulants may be more significant in terms of stroke prevention, mortality reduction, and reduced bleeding risk on a population level, particularly given the findings from recent clinical trials.[6, 7, 36, 37] Finally, the Elixhauser comorbidity index has only been validated for inpatients and therefore could not be applied to the entire

population which primarily includes outpatients.[22] In the subgroup of inpatient atrial fibrillation patients, likely the sickest patients, adjustment for the 30 comorbidities of the Elixhauser index, which includes various conditions such as organ failure, Acquired Immunodeficiency Syndrome/Human Immunodeficiency Virus, malignancy, and psychiatric disorders did not significantly change the direction of effect for our primary outcome. Nevertheless, there still remains a possibility that there is confounding by indication: patients with less comorbid illness may be judged to have the highest likelihood of benefit from anticoagulation and are therefore treated. Patients who have multiple comorbid illnesses are at higher risk of stroke, but may also be the most likely to suffer harm, and therefore are not anticoagulated. We addressed this issue by defining anticoagulation status in a conservative manner by including all patients who received an oral anticoagulant within six months of their outcome event.

Conclusion

In summary, analysis of large population data sets are adjuncts to randomized controlled trials where follow-up may not have been long enough or the sample size large enough to detect longer term treatment effects including the mortality benefit. On a population basis, anticoagulation is an effective and safe stroke prevention strategy, associated with decreased mortality among patients with incident atrial fibrillation in real-world practice. Stroke is the presenting symptom of atrial fibrillation in 28.6% of acute ischemic stroke patients. Evaluation of community screening for atrial fibrillation as a strategy for population-wide stroke prevention is needed.

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Table 1 Baseline characteristics

	All patients (n=10745)		Primary prevention (n=9568)		Secondary prevention (n=1177)	
	A/C	No A/C	A/C	No A/C	A/C	No A/C
Number (n, %)	**7358 (68.5)**	**3387 (31.5)**	**6497 (67.9)**	**3071 (32.1)**	**861 (73.2)**	**316 (26.8)**
Median Age (IQR)	74 (17)	70 (27)	74 (18)	68 (27)	78 (14)	83 (15)
Male (n, %)	4149 (56.4)	1785 (52.7)	3710 (57.1)	1638 (53.3)	439 (51.0)	147 (46.5)
Hypertension (n, %)	3461 (47.0)	1333 (39.4)	2991 (46.0)	1168 (38.0)	470 (54.6)	165 (52.2)
Diabetes (n, %)	1833 (24.9)	645 (19.0)	1585 (24.4)	546 (17.8)	248 (28.8)	99 (31.3)
Ischemic stroke and/or TIA (n, %)	843 (11.5)	301 (8.9)	0	0	843 (97.9)	301 (95.3)
Ischemic stroke (n, %)	561 (7.6)	186 (5.5)	0	0	561 (65.2)	186 (58.9)
Hemorrhagic stroke (n, %)	34 (0.5)	25 (0.7)	0	0	34 (3.9)	25 (7.9)
CHADS 2 (n, %)						
0	1553 (21.1)	1140 (33.7)	1551 (23.9)	1138 (37.1)	2 (0.2)	2 (0.6)
1	2550 (34.7)	1089 (32.2)	2544 (39.2)	1082 (35.2)	6 (0.7)	7 (2.2)
2	2029 (27.6)	709 (20.9)	1935 (29.8)	672 (21.9)	94 (10.9)	37 (11.7)
3	795 (10.8)	266 (7.9)	445 (6.8)	168 (5.5)	350 (40.7)	98 (31.0)
4	354 (4.8)	153 (4.5)	22 (0.3)	11 (0.4)	332 (38.6)	142 (44.9)
5	76 (1.0)	27 (0.8)	0	0	76 (8.8)	27 (8.5)
6	1 (0)	3 (0)	0	0	1 (0)	3 (0.9)

Table 2 Outcomes according to anticoagulation status

	Anticoagulated		Not Anticoagulated		Hazard ratio [95% CI][b]
	Events N	Event rate [95%CI][a]	Events N	Event rate [95%CI][a]	
All patients (n=10745)					
All stroke and death	1492	73.7 [70.0-77.7]	1605	112.6 [107.0-118.3]	**0.70 [0.62-0.72]**
Ischemic stroke	237	11.8 [10.3-13.5]	263	18.0 [15.8-20.4]	**0.69 [0.58-0.82]**
Hemorrhagic stroke	56	2.8 [2.1-3.7]	22	1.5 [1.0-2.4]	**1.92 [1.17-3.16]**
All stroke	279	14.0 [12.3-15.8]	276	19.0 [16.8-21.5]	**0.77 [0.65-0.91]**
Mortality	1338	63.8 [60.4-67.4]	1478	102.0 [96.8-107.4]	**0.67 [0.62-0.72]**
Primary prevention cohort (n=9568)					
All stroke and death	1265	70.6 [66.7-74.7]	1361	103.7 [98.2-109.5]	**0.70 [0.65-0.76]**
Ischemic stroke	171	9.7 [8.3-11.4]	216	15.9 [13.8-18.3]	**0.62 [0.51-0.76]**
Hemorrhagic stroke	41	2.3 [1.7-3.3]	19	1.4 [0.9-2.3]	1.71 [0.98-2.96]
All stroke	203	11.7 [10.1-13.5]	227	16.9 [14.7-19.3]	**0.71 [0.58-0.85]**
Mortality	1149	61.9 [58.3-65.7]	1248	94.2 [89.0-99.7]	**0.68 [0.63-0.74]**
Secondary prevention (n=1177)					
All stroke and death	227	103.9 [90.7-120.1]	244	190.7 [167.2-217.8]	**0.55 [0.46-0.66]**
Ischemic stroke	66	31.0 [23.9-41.5]	47	37.1 [27.0-50.9]	0.89 [0.61-1.30]
Hemorrhagic stroke	15	6.4 [3.6-13.2]	3	2.2 [0.42-8.9]	2.96 [0.86-10.25]
All stroke	76	35.5 [27.9-46.4]	49	38.6 [28.4-52.7]	0.97 [0.67-1.39]
Mortality	189	81.5 [70.3-95.7]	230	168.2 [146.9-192.8]	**0.49 [0.40-0.59]**

[a]Adjusted event rate per 1,000 person years

[b]Adjusted for Sex and CHADS2 score

Table 3 Inpatient cohort (n=3598) with Elixhauser Comorbidity Index adjustment using anticoagulation as a time dependent covariate

	Hazard ratio [95% CI][b]
All stroke and death	**0.61 [0.55-0.67]**
Ischemic stroke	0.84 [0.64-1.11]
Hemorrhagic stroke	2.18 [0.97-4.89]
All stroke	0.95 [0.73-1.23]
Mortality	0.57 [0.52-0.64]

[b]Adjusted for Sex and CHADS2 score

Figure 1 Cox survival curve for all stroke and death with anticoagulation as a static covariate