Atrial fibrillation prevalence and incidence varies by population definition: Association with co-morbidity profiles and multimorbidity in a large United States adult cohort

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Abstract

Background Identification of published data on prevalent/incidence of atrial fibrillation/flutter (AF) often relies on inpatient/outpatient claims, without consideration to other types of healthcare services and pharmacy claims. Purpose To examine AF prevalence/incidence and associated individual comorbidity and multi-morbidity profiles for a large US adult cohort spanning across a wide age range for both males/females based on both medical/pharmacy claims. Methods We studied a population of 8,343,992 persons across many geographical areas in the U.S. continent from 1 January /2016 to 31 October 2019. The prevalence and incidence of AF were comparatively analyzed for different healthcare parameters. Results Based on integrated medical and pharmacy claims, AF prevalence was 12.7% in the elderly population ($>$ 65 years) and 0.9% in the younger population ($<$ 65 years). These prevalence rates are different from estimates provided by the US CDC for those aged $>$ 65 years (9%) and age $<$ 65 years (2%); thus, the prevalence is under-estimated in the elderly population and over-estimated in the younger population. The incidence ratios for elderly females relative to younger females was 15.07 (95%CI 14.47-15.70), a value that is about 50% higher than for elderly males (10.57 (95%CI 10.24-10.92)). Comorbidity risk profile for AF identified on the basis of medical and pharmacy criteria varied by age and sex. The proportion with multimorbidity (defined as [?]2 long term comorbidities) was 10-12%. Conclusion Continued reliance only on outpatient and inpatient claims greatly underestimates AF prevalence and incidence in the general population by over 100%. Multimorbidity is common amongst AF patients, affecting approximately 1 in 10 patients. AF patients with 4 or more co-morbidities captured 20 to 40% of the AF cohorts depending on age groups and prevalent or incident cases. Our proposed methodology can guide future analysis of quality/cost of care for progressive medical conditions at the population level.

Introduction

Atrial fibrillation (AF) is the commonest cardiac rhythm disorder globally, and confers a large healthcare burden from mortality and morbidity from stroke/systemic thromboembolism, heart failure, dementia and hospitalisations(1). Accurate, population-level data that can enable ongoing monitoring of AF epidemiology, quality of care at affordable cost, and complications are needed.

In the US, data on AF prevalence/incidence are typically identified in administrative medical databases using inpatient/outpatient/physician claims with ICD 9/10 codes(2, 3). Nonetheless, identification does not include claims from other healthcare services (e.g., nursing skilled facilities) or procedures peculiar to AF (e.g., catheter ablation). It is also common for fully insured individuals with medical/pharmacy benefits, who are on medications such as anticoagulants and heart rhythm control, not to have medical claims with AF ICD 9/10 codes. Indeed, a Canadian study by Tu et al(4) voiced similar concerns and found that an algorithm relying on a combination of criteria yielded higher prevalence than those simply based on hospital

admissions, emergency room visits or office visits. Collectively, the aforementioned issues may underestimate our knowledge of the true AF prevalence and incidence and the associated co-morbidity profiles.

In a systematic review of validated methods for identifying AF using administrative data, Jensen et al(5) found that 10 of 16 studies used only inpatient data. We hypothesized that prevalent/incidence data would vary by type of population studied, and associated comorbidities would vary accordingly. The aim of this study was to examine AF prevalence/incidence and associated comorbidity profiles for a large US adult cohort spanning across a wide age range (< 65 and> 65 years) for both males/females based on both medical/pharmacy claims. The prevalence and incidence were comparatively analyzed for different healthcare parameters (i.e., emergency room visit, hospital admission, office visit, office observation, cardioversion, catheter observation, all medical claims, anticoagulant medication, heart rhythm control medication, both medical and pharmacy claims). Finally, we assessed co-morbidity profiles, AF + co-morbidity counts, and multi-morbidity in AF cohorts.

Methods

Data sources

Two health benefit plans represented the data sources: Commercial for working population and their families (< 65 years) and Medicare for the elderly (> 65 years). The Commercial plan is rooted in private insurance, while Medicare is a government-sponsored program and managed by healthcare organizations. At the beginning of the study (January 1, 2016 to May 1, 2019), only individuals with both medical/pharmacy benefits were included with at least six months of benefits or more in the prevalence study. To ensure that members in the Commercial plan would not exceed 65 years at the end of the study, only individuals aged 61 years or less participated. The study population included 7,429,464 persons (3,733,874 females and 3,695,590 males) in the Commercial plan, with 914,528 individuals in the Medicare plan (524,573 females and 389,855 males). In total, this investigation spanned over a period of up to 3 years and 10 months (from January 1, 2016 to October 31, 2019).

Analysis of medical and pharmacy claims

Identification of the AF population took place in administrative medical and pharmacy databases. The medical claims were characterized for emergency room (ER) visits (using revenue codes and outpatient flag), hospital admissions (using facility type code and inpatient flag), office visits (new and established using CPT or 'Current Procedural Code' codes and outpatient flag), and outpatient observation under physician monitoring (using CPT codes, outpatient flag, with exclusion of ER revenue codes). These healthcare service types are fast becoming the most common criteria in identifying AF cases. The aforementioned claims were additionally identified using ICD 10 primary and secondary diagnosis codes designated for atrial fibrillation and flutter (I480, I481, I482, I483, I484, I4891, I4892). The outpatient procedures were predominantly identified using CPT codes. All claims for AF primary and secondary diagnoses were also analyzed without the specification of type of healthcare service rendered. Patient duplication is eliminated when using the combined medical as well as the integrated medical and pharmacy data.

The pharmacy claims were analyzed for oral anticoagulant medications (warfarin, direct oral anticoagulants (DOACs)) and rhythm control medications (i.e., amiodarone, disopyramide, dofetilide, dronedarone, flecainide, mexiletine, procainamide, propafenone, quinidine gluconate, quinidine sulfate), with exceptions as previously noted in Tu et al(4). The process of preparing and analyzing medical and pharmacy claims are detailed in suppl fig S1. Each medication was analyzed using both NDC (National Drug Code) and GPI (Generic Product Identifier) codes. This is because NDCs can be ambiguous and many can exist for a single product, leading to inaccuracies in the dispensing of drugs. Therefore, GPI was used to ensure consistency, with many (from NDC) to one (to GPI) mapping.

The details of healthcare service and medication types and codes used in this study are provided in suppl table S1. The exceptions for the use of anticoagulants and rhythm control, which are not applicable to atrial fibrillation/flutter, are provided in supplemental table S2.

Analysis of prevalent and incident cases

Prevalent cases utilized members who contributed at least six months of benefits with the health plans to examine existing and new onsets of AF cases(6). The analysis of incident cases utilized members with at least 30 months of benefits with the health plans (suppl fig S1). This period ensured at least six months of benefits similar to members in the prevalence study together with allowing a period of 24 months without filing any medical and pharmacy claims. Piccini et al(2) used a similar methodology for the analysis of incident cases in administrative databases.

For inclusion, prevalent or incident cases had to contribute two or more medical claims and/or two or more medication claims as detailed in suppl fig S1. Prevalence was calculated over the period of the study with the denominator equal to the population count at the beginning of the study and the numerator to the unique persons filing claims during the analysis period as specified previously. An incidence rate was computed for new cases, with the denominator equal to the sum of person-years contributed by those in the incidence study with at least 30 or more months of benefits. The count and rates of prevalent and incident cases were computed for individual medical criteria (ER, hospital admission, office visit, office observation, or outpatient procedure), combined medical (ER, hospital admission, office visit, office observation, or outpatient procedures), all claims with AF ICD 10 codes, pharmacy criteria (anticoagulant or rhythm control medications), and combined medical/pharmacy.

The comorbidity profiles for prevalent and incident AF targets were analyzed for congestive heart failure, hypertension, diabetes mellitus, ischemic stroke, transient ischemic attack, thrombo-embolic events, myocardial infarction, peripheral artery disease, valvular disease, coronary artery disease, obstructive sleep apnea, and chronic kidney disease. The details of diagnosis codes for the comorbidity profiles are given in suppl table S3. We also determined the prevalence and incidence of multimorbidity (defined as [?]2 chronic long-term conditions – but for the purposes of this study, we also looked at AF with [?]2 chronic long term conditions).

Statistical analysis

Detailed age treatment effect was conducted for several groups, namely, < 45, 45-54, 55-64, 65-74, 75-84 and > 85 years. AF prevalence rates (%) and incidence rates (per 1000 person-years) were computed for individual and combined medical and pharmacy service criteria. Duplication was eliminated whenever 2 or more criteria are integrated. This was performed via use of unique, non-duplicative identifiers for patients in the claim system. Comparative analyses were performed relative to the youngest age group (< 45 years). In these instances, prevalence and incidence rate ratios were calculated together with 95% confidence intervals. Analysis of individual comorbidity profiles was performed for each comorbid condition as a binary outcome with gender and age as input variables in logistic regression models. Computations were made for prevalent and incident cases (% of total prevalent or incident cases) as a function of AF + multi-comorbidity count. Cumulative prevalence and incidence were additionally performed. Multi-morbidity were defined in the conventional way as AF + 1 or more-comorbidity (i.e.,$>$ 2 chronic conditions) as well as AF + 2 or more comorbidities. All descriptive and inferential statistical analyses were conducted using the Statistical Analysis Software(7).

Results

Overall prevalence based on integrated medical and pharmacy claims was 12.7% in the elderly and 0.94% in those age < 65 (table 1a), with males having higher prevalence (14.8% for Medicare and 1.2% for commercial) than females (11.2% for Medicare and 0.64% for Commercial). Anticoagulants, office visits, and combined medical*underestimated* AF prevalence in the younger and elderly populations by up to 50% (table 1a). The degree of prevalence underestimation was much higher in the younger cohort relative to the elderly population. The overall prevalence of AF was 2.2%, with males having higher prevalence (2.5%) than females (1.9%). One should note that the prevalence ratios for elderly females relative to younger females was 17.29 (95%CI 17.29-17.81), a value that is higher than for elderly males (11.91 (95%CI 11.73-12.09)). Collectively, older females were at 50% higher risk for prevalent AF than the older males.

When individual medical and pharmacy services were assessed using combined medical and pharmacy criteria, office visits captured the highest scores (61%) for Medicare followed by anticoagulants (51.2%) (Table 1b). For commercial, the trend was opposite with anticoagulant scoring 53.5% followed by 44.6% for office visits. ER and hospital admission scores were lower than office visits and anticoagulants (23.3% and 6.8%, respectively for the Medicare population; and much lower for the commercial cohort, 1.3% and 0.5%, respectively). Procedures yielded higher prevalence targets in the younger population than the elderly (7-8% for commercial relative to 2% to 5% for Medicare). Office observation was higher in Medicare (8.6%) than Commercial (5.3%). Rhythm control resulted in higher values for Commercial (15.2%) than Medicare (11.6%). Combined medical criteria yielded slightly higher values than office visits.

Prevalence and incidence in relation to increasing age strata

Figure 1 shows the effect of age on AF prevalence in an AF cohort. In general, prevalence increased in a non-linear fashion from age <45 years to [?] 85 years (table 2). There was a departure from linear effects of age to non-linearity for age groups> 55 years relative to those < 55 years. On average, the obtained *prevalence ratios* for different age groups relative to the age <45 year group were as follows: (a) 45-54 years:4.59 (95%CI 4.50-4.69); (b) 55-64 years: 9.22 (95%CI 9.04-9.40); (c) 65-75 years: 31.85 (95%CI 31.28-32.47); (d) 75-84 years: 49.46 (95%CI 48.55-50.38); and (e) > 85 years: 60.64 (95%CI 59.43-61.88).

The incidence rate for older females was much higher than older males. For age < 65 years, the incidence rate for females was less than males (Table 1). The incidence ratios for elderly females relative to younger females was 15.07 (95%CI 14.47-15.70), a value that is about 50% than for elderly males (10.57 (95%CI 10.24-10.92)). Incidence rates increased steadily with age, with the exception of the 65-74 and 75-84 having similar rates (Figure 2).

A detailed treatment of prevalence and incidence measures in terms of frequency estimates and 95% CI is provided suppl table S4 age group (ages < 45, 45-54, 55-64, 65-74, 75-84, >85 years) and gender.

Individual co-morbidity profiles, AF + co-morbid count, and multi-morbidity in AF cohorts

The individual comorbidity profiles for AF prevalence and incidence are shown in Table 2. With the exception of sleep apnea, the prevalence of comorbidities was higher for the elderly than the younger populations (<0.0001). The prevalence ratios of the older (> 65 years) to the younger (< 65 years) were: 2.42 (95%CI 2.379-2.420) for congestive heart failure; 1.37 (95%CI 1.366-1.375) for hypertension; 1.91 (95%CI 1.868-1.906) for diabetes mellitus; 2.03 (95%CI 1.976-2.027) for history of stroke and thromboembolic events; 2.42 (95%CI 2.375-2.423) for vascular disease; 1.51 (95%CI 1.493-1.514) for valvular disease; 2.29 (95%CI 2.257-2.294) for coronary artery disease; and 3.49 (95%CI 3.545-3.639) for chronic kidney disease. For sleep apnea, the elderly had about 50% lower prevalence and incidence compared to those age < 65, with a prevalence ratio of 0.49 (95%CI 0.474-0.491).

Table 3 provides data for individual comorbidity profiles in relation to prevalent and incident AF. For Medicare patients aged [?]65, the prevalence of stroke, hypertension and valvular disease were significantly higher for females than males. There was no significant difference for congestive heart failure between males and females. Other comorbidities were significantly higher for males. For those age <65 (Commercial), there was no significant difference between males and females for valvular disease. Other comorbidities were significantly higher for males than females, except for history of stroke, which was significantly higher for females than males.

The relationship between the AF + co-morbidity count is displayed in fig 2 (parts a and b) for incident cases, and appears to be an inverted U-shape. Pure incident AF targets are greatly underestimated when one relies only on ICD 10 codes. Therefore, the use of both pharmacy and medical claims is greatest for AF targets in the absence of co-morbid history. In addition, the peak of AF + co-morbidity count is achieved in the range of 2 to 5 depending on the criterion used and case prevalence/incidence. The relationship for prevalent AF targets was slightly different from incident AF targets (fig 2 parts c and d). Relative to incident cases, prevalent cases are greatly underestimated on the basis of ICD 10 claims for pure AF and those with

lower co-morbidity count, then, overestimated in the higher range of co-morbidity count. The cumulative incidence and prevalence were higher the overall population relative to the age > 65 year cohort.

The prevalence of multimorbidity in AF patients aged [?]65 using medical and pharmacy claim databases was 11.73%, when defined as AF with [?]1 other chronic long term condition. This figure was 10.14% if defined as AF plus [?]2 chronic long term conditions (Table 4). Both prevalence figures are higher than if relying on ICD claim codes alone, which would underestimate multimorbidity in this cohort. Similar patterns were seen for incidence of multimorbidity.

Trends with incidence relative to prevalence and other parameters including increasing age

The general trend for AF prevalence was similar for AF incidence with minor changes (Table 1). AF incidence based on procedures is more than double in the younger population than the older population; while incidence based on ER visits and hospital admission is negligible in the younger population compared to older cohorts. Incidence based on office observation was 9.3% in the younger population, relative to 5.3% in prevalent cases which may explain the negligible cases based on ER visits, The comorbidity profile for incident cases was similar to prevalent cases with the exception that the frequency of different comorbidities was generally higher among incident cases particularly for vascular and valvular diseases in Medicare (Table 3).

Incidence cases based on rhythm control were similar to those based on prevalent cases. Anticoagulation rates are similar for both incident and prevalent cases in commercial cohorts and slightly lower for incident cases in elderly population relative to prevalent cases.

Discussion

In this comprehensive analysis of prevalent and incident AF targets obtained from medical and pharmacy claim databases based on a large US adult population, we show that continued reliance only on outpatient and inpatient claims alone greatly underestimates AF prevalence and incidence in the general population by over 100%. Second, we show the comorbidity profile in our AF patients, with the prevalence of multimorbidity being approx. 10-12% in those aged [?]65 years. Again, reliance only on outpatient and inpatient claims alone greatly underestimates multimorbidity in the AF population. Our proposed methodology can guide future analysis of the quality/cost of care for progressive medical conditions at the population level.

Our findings differ from the United States CDC(8) that found approximately 2% of people age < 65 years have AF, while about 9% of people age [?] 65 years have AF. Instead, our results indicate that the working population aged < 65 years has a 0.9% prevalence and the Medicare population aged [?]65 had a 12.7% prevalence. The difference could possibly be attributed to computation methodologies and different time spans used (i.e., 2009-2014 for the CDC estimates and the 2016-2019 period in the current study). Piccini et al(2) reported a 7.3% prevalence in a study conducted on a 5% random sample of the Medicare population in the US, relying on the use of 2 outpatient visits or 1 inpatient visit within a 365 day period. The prevalence reported by Piccini et al(2) for 2007 is st*ill* lower than the overall 12.7% value reported in the present study. There was an increase in prevalence with the analyzed period (3.7%, 5.7%, 6.8%, and 7.3%, respectively for 1993, 1998, 2003 and 2007). In elderly Germans, Ohlmeier et al(9) reported an increased prevalence with the analysis period 7.7%, 9.4%, 9.8%, and 10.3%, respectively for the years of 2004 to 2007.

Our results emphasize the impact of joining pharmacy and medical claims in the calculation of AF prevalence and incidence rates. Using both types of databases, the overall prevalence rate was 2.2%, being 2.5% and 1.9%, respectively for males and females; the overall incidence rate was 3.3 per 1000 person-years (3.6 and 2.9 per 1000 person-years, respectively for males and females). Our overall AF prevalence was close to the 2.4% reported by Tu et al(4) in Canada using a similar approach, and the 2% and 2.13% prevalence reported for Europe(10) and Germany(11), respectively. It should be noted that the methodologies by Tu et al(4) is similar to that used in this study with the exceptions that the claim system in Canada is somewhat different from that used in the US. Indeed, our incidence rates were lower than those obtained in Germany(11) for the general population (males – 4.4 cases/1000 person-years; females – 3.9 cases/1000 person-years).

Although OAC use and office visits captured the highest number of targets in the identified AF population, they cannot be used as a proxy for identifying the prevalence and incidence of AF cases in the general population. OACs accounted for about half of AF prevalent cases, indicating that about 50% of the remaining population are not on anticoagulants, in line with prior studies (4)(12)(13). Office visits explained 55% and 43%, respectively of the AF prevalent and incident cases, with the remainder of AF population not making office visits.

Although males have higher AF prevalence than females, the present study suggest that older (65 years or older) females (normalized relative to younger population aged less than 65 years) have a 50% higher prevalence ratio than older males (normalized to relative to younger population less than 65 years). This is in line with the incidence rates obtained in the Medicare population for males and females (12.3 and 18.2 per 1000 person-years, respectively). Additionally, there is an increase in prevalence with age for the Medicare population from 65-74 to 75-84 to $>$ 85 years.

Hospital admissions accounted for 4% or less of AF prevalent/incident targets. Furthermore, ER visits captured 14% or less of AF prevalent/incident cases. In a systematic review of validated methods for identifying AF using administrative data, Jensen et al(5) found that 10 of 16 studies used only inpatient data. Office observations captured 8.6% of prevalent AF targets in the Medicare population and 5.3% in the working population or Commercial plan. A similar trend was found for incident AF targets (11.3% and 9.4%, respectively in Medicare and Commercial cohorts). Thus, one cannot rely on ER visits, office observation and hospital admissions as the only sources to establish AF prevalence and incidence targets. There was an even smaller percentage of AF cases identified based on rhythm control (14%), in line with Tu et al(4) and LaPointe et al[10]. The latter study found among AF patients younger than 65 years that 16% received rhythm control medication and 84% had rate control drugs.

The practical implications of our analysis are worth highlighting. The number of prevalent/incident AF targets doubles when one integrates the use of medical and pharmacy claim databases in comparison to the utilization of outpatient and inpatient healthcare services from medical claim databases. We also show that the multimorbidity is common amongst AF patients (affecting approximately 1 in 10 patients), which puts such patients at risk of cardiovascular and non-cardiovascular mortality and morbidity (14). In particular, for incident AF cases, about 40% of the older population and 30% of the overall population have 4 or more co-morbidities; for prevalent cases, these proportions are 30% and 20%, respectively (fig 2 e and f). Collectively, these results empathize that AF cohorts are at an increased risk of complications such as stroke and bleeding events; hence, there has been an increasing move towards a more holistic or integrated approach to AF management(15). Indeed, integrated care management of AF patients is associated with improved clinical outcomes(16-18).

Limitations

Our study is limited by its observational design and its dependence on claims datasets, and inaccuracies in coding and claims may be possible. Nonetheless, such claims data are often used to assess AF epidemiology, in relation to risk factors and healthcare costs. As with observational cohorts, the possibility of residual confounding remains.

Conclusion

Continued reliance only on outpatient and inpatient claims greatly underestimates AF prevalence and incidence in the general population by over 100%. Multimorbidity is common amongst AF patients (affecting approximately 1 in 10 patients). AF patients with 4 or more co-morbidities captured 20 to 40% of the AF cohorts depending on age groups and prevalent or incident cases. Our proposed methodology can guide future analysis of the quality/cost of care for progressive medical conditions at the population level.

Data availability

Data are available as presented in the paper. According to US laws and corporate agreements, our own approvals to use the Anthem and IngenioRx data sources for the current study do not allow us to distribute

or make patient data directly available to other parties.

Disclosure s

The authors report no conflicts of interest in this work.

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