Economic Burden of Undiagnosed Nonvalvular Atrial Fibrillation in the United States

Mintu P. Turakhia, MD, MAS[a,*], Jason Shafrin, PhD[b], Katalin Bognar, PhD[b], Dana P. Goldman, PhD[c], Philip M. Mendys, Pharm D[d], Younos Abdulsattar, PharmD, BCPS[e], Daniel Wiederkehr, BS[f], and Jeffrey Trocio, MPH[g]

Atrial fibrillation (AF) may be clinically silent and therefore undiagnosed. To date, no estimates of the direct medical cost of undiagnosed AF exist. We estimated the United States (US) incremental cost burden of undiagnosed nonvalvular AF nationally using administrative claims data. To calculate the incremental costs of undiagnosed AF, we compared annual medical costs (in 2014 US Dollars) for patients with AF compared to propensity-matched controls and multiplied this by estimates of undiagnosed AF prevalence derived from the same data sources. The study population included US residents aged ≥18 years with 24 months of continuous enrollment drawn from 2 large administrative claims databases. Mean per capita medical spending for patients with AF aged from 18 to 64 year was $38,861 (95% confidence interval [CI] $35,781 to $41,950) compared to $28,506 (95% CI $28,409 to $28,603) for similar patients without AF (incremental cost difference $10,355, p <0.001); total spending for patients aged ≥65 years with AF was $25,322 (95% CI $25,049 to $25,595) compared to $21,706 (95% CI $21,563 to $21,849) for similar patients without AF (incremental cost difference $3,616, p <0.001). Using estimates of the US prevalence of undiagnosed AF (596,000) drawn from the same data, we estimated that the US incremental cost burden of undiagnosed nonvalvular AF is $3.1 billion (95% CI $2.7 to $3.7 billion). In conclusion, the direct medical costs for patients with undiagnosed AF are greater than patients with similar observable characteristics without AF and strategies to identify and treat patients with undiagnosed AF could lead to sizable reductions in stroke sequelae and associated costs. **(Am J Cardiol 2015;116:733−739)**

The prevalence of diagnosed atrial fibrillation (AF) in the United States (US) was 5.2 million in 2010 and is projected to grow to 12.1 million by 2030.[1,2] AF accounts for 15% of the 700,000 US strokes per year,[3] and AF-associated strokes are associated with greater disability and morbidity than strokes of other origins.[4] Incremental annual medical cost per patient with AF estimates range from $1,300 in a study of adults insured through large employers[5] to over $20,000 in a study in the Medicare population (in 2014 US Dollars [USD]).[6] At the US population level, the incremental annual AF medical cost ranges from $6 to $26 billion,[7,8] in large part because of the short- and long-term costs of care after stroke.[9] However, because AF may be asymptomatic, paroxysmal, or otherwise clinically silent, from 10% to 27% of all patients with AF remain undiagnosed.[10−13] In the United States, the prevalence of undiagnosed AF is about 1% to 2% in the general population.[12,13] Clinical sequelae of AF such as stroke and heart failure may occur even in undiagnosed patients.[14,15] As a result, the true cost burden of AF could be substantially underestimated. To the best of our knowledge, the economic burden of undiagnosed AF has not been previously evaluated. We therefore performed a retrospective, claims-based cohort study to measure the incremental cost undiagnosed AF in the United States.

Methods

To estimate the per capita incremental cost burden of AF in 2009, we use propensity matching.[5−7,9] As patients with undiagnosed AF are not observed in the data, however, we modified the standard propensity matching approach to measure the per capita incremental cost burden for all patients with AF, including both patients who are diagnosed and undiagnosed. A detailed description of this process is mentioned in the following.

To study the cost burden in patients aged 18 to 64 years, we used 2004 to 2010 Touchstone claims data (Optum, Eden Prairie, Minnesota). These commercially available data contain de-identified administrative, claims, and benefit information for employees and dependents insured through 33 Fortune 500 employers. The data contain patient demographics, health status, health service utilization, and

[a]Division of Cardiovascular Medicine, Stanford University Hospital, Stanford University School of Medicine, Palo Alto, California; [b]Precision Health Economics, Los Angeles, California; [c]Leonard D. Schaeffer Center for Health Policy and Economics, University of Southern California, California; [d]Pfizer, Inc., New York, New York; [e]Department of Medical Affairs, Pfizer, Inc., New York, New York; [f]Department of Global Health & Value, Outcomes & Evidence, Pfizer, Inc., New York, New York; and [g]Department of Policy, Pfizer, Inc., New York, New York. Manuscript received February 20, 2015; revised manuscript received and accepted May 20, 2015.

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*Corresponding author: Tel: (650) 858-3932; fax: (650) 852-3473.

E-mail address: mintu@stanford.edu (M.P. Turakhia).

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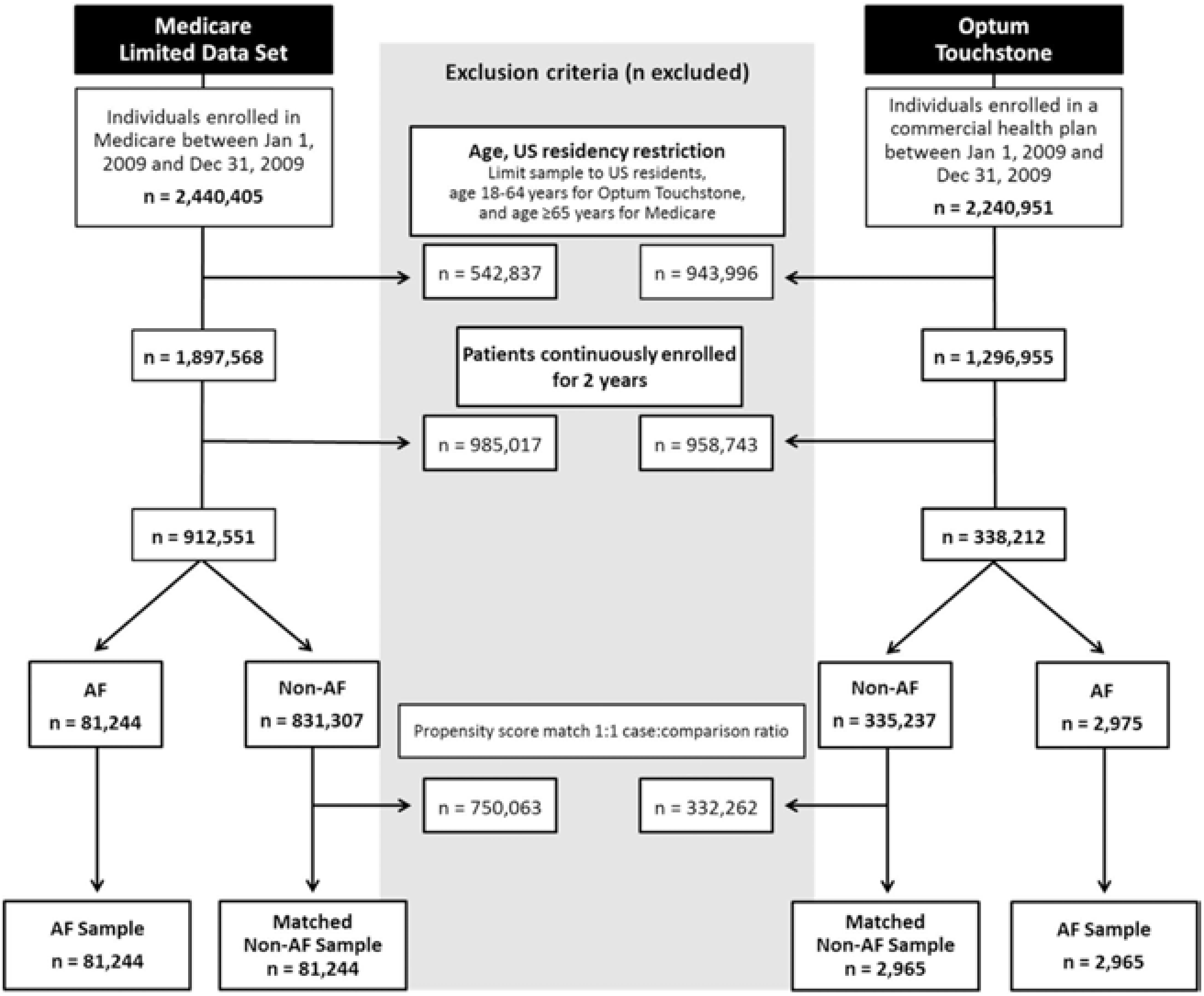

Figure 1. CONSORT diagram. The selection process applied to enrollees from the Medicare Limited Data Set and the Optum Touchstone database. Inclusion criteria of age and US residency requirements and continuous enrollment for 2 years resulted in matched samples of 81,244 and 2,965 enrollees in Medicare and Optum, respectively.

cost. The Touchstone data have been used previously to study cardiovascular and other conditions.[16–19]

To study the burden of undiagnosed AF in patients aged ≥65 years, we used the 2004 to 2010 Medicare Limited Data Set, which is a 5% national sample of fee-for-service Medicare beneficiaries.[18–21] These data contain information on beneficiary demographics, health status, health service utilization, and cost, but unlike the Touchstone data, the Limited Data Set files do not include prescription drug claims.

To implement a propensity-matching approach, our study identified 2 cohorts of patients: those with a qualifying nonvalvular AF diagnosis and all others. For both groups, we required all patients in our study population to be US residents aged ≥18 years. To identify existing comorbidities and future economic cost, all individuals also were required to be continuously enrolled for ≥12 months before and for ≥12 months Q3 2009.

Patients were identified as having nonvalvular AF if they had a valid AF diagnosis and no indication of valvular or transient AF. Valid diagnoses are ones with an AF diagnosis if an *International Classification of Diseases, Ninth Revision* (ICD-9), code of 427.31 appeared on 1 of their inpatient, outpatient, or physician visits claim.[20] Claims in which the providers were not clinicians or in which the place of service was a laboratory were not considered valid for identifying AF. In those with AF, the sample was limited to patients with nontransient and nonvalvular AF as both transient and valvular AF are associated with different levels of stroke risk, and thus, treatment approaches vary.[21,22] Patients were considered to have valvular AF if they had a diagnosis for a heart valve replacement or mitral valve stenosis (ICD-9-CM codes 42.2, 394.x, 396.1, 396.2, 396.8, or 746.5) or a procedure for a valve replacement (current procedural terminology codes 33405, 33420, 33422, 33425 to 33427, 33430, or 33496; ICD-9 procedure codes 35.0x, 35.1x, or 35.2x). Patients were considered to have transient AF if AF appeared within 12 months after hyperthyroidism (ICD-9-CM code 242.x) or within 30 days after coronary

Table 1
Patient demographics and comorbidities before and after matching

Variable	18-64 years of age (Source: Touchstone Claims Data)					≥65 years of age (Source: Medicare Claims Data)				
	AF	Non-AF (Unmatched)	Standardized Difference (%)	Non-AF (Matched)	Standardized Difference (%)	NVAF	Non-AF (Unmatched)	Standardized Difference (%)	Non-AF (Matched)	Standardized Difference (%)
Age, years, mean (SD)	56 (6.6)	48 (10.7)	-90.9	56 (6.5)	2.0	79 (7.0)	76 (7.1)	-44.9	79 (6.9)	1.1
Female	983 (33.0%)	188,498 (56.2%)	48.0	972 (32.7%)	0.8	43,030 (53.0%)	507,370 (61.0%)	16.4	43,044 (53.0%)	0.0
Comorbidities										
Cancer, metastatic	24 (0.8%)	1,076 (0.3%)	-6.5	18 (0.6%)	2.4	1,461 (1.8%)	10,664 (1.3%)	-4.2	1,298 (1.6%)	1.5
Cancer, solid tumor	191 (6.4%)	11,698 (3.5%)	-13.5	176 (5.9%)	2.1	13,327 (16.4%)	113,811 (13.7%)	-7.6	13,255 (16.3%)	0.2
Cardiomyopathies	395 (13.3%)	2,088 (0.6%)	-51.4	376 (12.6%)	1.9	11,226 (13.8%)	25,056 (3.0%)	-39.7	11,077 (13.6%)	0.5
Chronic pulmonary disease	511 (17.2%)	28,607 (8.5%)	-26.0	501 (16.8%)	0.9	28,743 (35.4%)	177,335 (21.3%)	-31.5	27,380 (33.7%)	3.5
Congenital heart disease	66 (2.2%)	1,569 (0.5%)	-15.2	53 (1.8%)	3.2	807 (1.0%)	4,210 (0.5%)	-5.6	638 (0.8%)	2.2
Congestive heart failure	650 (21.8%)	4,121 (1.2%)	-68.2	641 (21.5%)	0.8	35,768 (44.0%)	95,169 (11.4%)	-78.1	35,465 (43.7%)	0.8
Coronary atherosclerosis	938 (31.5%)	16,494 (4.9%)	-73.4	957 (32.2%)	-1.4	45,388 (55.9%)	227,979 (27.4%)	-60.3	45,708 (56.3%)	-0.8
Diabetes, complicated	230 (7.7%)	7,581 (2.3%)	-25.3	398 (13.4%)	-18.4	11,407 (14.0%)	80,222 (9.7%)	-13.6	11,573 (14.2%)	-0.6
Dyslipidemia	1,830 (61.5%)	124,888 (37.3%)	-50.0	1,905 (64.0%)	-5.2	60,877 (74.9%)	577,109 (69.4%)	-12.3	61,343 (75.5%)	-1.3
Hypertension	1,917 (64.4%)	103,006 (30.7%)	-71.7	1,929 (64.8%)	-0.8	71,640 (88.2%)	622,917 (74.9%)	-34.7	71,732 (88.3%)	-0.4
Ischemic heart disease	87 (2.9%)	1,072 (0.3%)	-20.7	85 (2.8%)	0.5	3,863 (4.8%)	13,375 (1.6%)	-18.0	3,777 (4.6%)	0.5
Myocarditis	387 (13.0%)	4,351 (1.3%)	-46.7	370 (12.4%)	1.7	20,822 (25.6%)	72,063 (8.7%)	-46.2	20,753 (25.5%)	0.2
Obesity	234 (7.9%)	12,170 (3.6%)	-18.3	204 (6.9%)	3.8	5,719 (7.0%)	40,487 (4.9%)	-9.2	5,424 (6.7%)	1.4
Pericarditis	6 (0.2%)	98 (0.0%)	-5.1	2 (0.1%)	3.4	235 (0.3%)	669 (0.1%)	-4.9	148 (0.2%)	2.2
Peripheral vascular disorders	264 (8.9%)	5,851 (1.7%)	-32.2	238 (8.0%)	3.1	24,877 (30.6%)	147,709 (17.8%)	-30.4	24,481 (30.1%)	1.1
Renal failure	175 (5.9%)	3,968 (1.2%)	-25.7	183 (6.2%)	-1.1	14,860 (18.3%)	75,256 (9.1%)	-27.1	14,637 (18.0%)	0.7
Sleep apnea	407 (13.7%)	12,128 (3.6%)	-36.4	404 (13.6%)	0.3	6,899 (8.5%)	33,550 (4.0%)	-18.5	6,817 (8.4%)	0.4
N	2,975	335,237	-	2,975	-	81,244	831,307	-	81,244	-

NOTE: Comorbidities were identified if the patient had a claim which contained one of the following ICD-9 diagnosis codes: Cancer, metastatic (196.x-199.x); Cancer, solid tumor (140.x-172.x, 174.x, 175.x, 179.x-195.x); Cardiomyopathies (425.0-425.9, 425.11, 425.18); Chronic pulmonary disease (490.x-496.x); Congenital heart disease (717.2, 745.0, 745.1x, 745.2, 745.3 , 746.1, 746.3, 747.1, 747.11, 746.7, 747.3x, 747.41,); Congestive heart failure (428.x); Coronary atherosclerosis (411.x-414.x); Diabetes, complicated (250.4x-250.9x); Dyslipidemia (272.x); Hypertension (401.x-405.x); Ischemic heart disease (410.x); Myocarditis (422.x, 429.x, 442.9); Obesity (278.00, 278.01); Pericarditis (420.0, 420.90, 420.91, 420.99); Peripheral vascular disorders (443.x); Renal failure (585.x); Sleep apnea (327.2, 327.21, 327.23, 327.27, 327.29, 780.51, 780.53, 780.57, 786.03, 786.04).

AF = atrial fibrillation; SD = standard deviation.

Table 2
Per patient incremental cost burden

Cost Breakdown	Individuals <65 years of age			Individuals ≥65 years of age		
	AF Cost (n=2975)	Non-AF Matched Cost (n=2975)	Incremental Burden	AF Cost (n=81,244)	Non-AF Matched Cost (n=81,244)	Incremental Burden
All	$38,861	$28,506	$10,355*	$25,322	$21,706	$3,616*
Males	$35,015	$26,982	$8,033*	$24,100	$20,628	$3,472*
Females	$46,654	$31,594	$15,060*	$26,407	$22,663	$3,744*
All	$38,861	$28,506	$10,355*	$25,322	$21,706	$3,616*
AF	$3,649	$85	$3,563*	$1,263	$148	$1,115*
Other CV	$6,778	$4,649	$2,129*	$4,786	$3,908	$877*
Non-CV	$28,434	$23,771	$4,662*	$19,273	$17,649	$1,624*
Inpatient Medical	$16,531	$8,881	$7,650*	$9,139	$7,323	$1,816*
AF	$1,830	$55	$1,775*	$423	$70	$353*
Other CV	$44,180	$2,728	$1,453*	$2,239	$1,813	$426*
Non-CV	$10,521	$6,098	$4,422*	$6,478	$5,441	$1,037*
Outpatient Medical	$15,668	$12,922	$2,746*	$16,183	$14,383	$1,800*
AF	$1,789	$29	$1,760*	$840	$79	$762*
Other CV	$2,458	$1,815	$642*	$2,547	$2,096	$451*
Non-CV	$11,422	$11,078	$344†	$12,795	$12,208	$587*
Pharmacy	$5,163	$5,438	-$275†	-	-	-
AF	$524	$72	$452*	-	-	-
Other CV	$1,535	$1,398	$136†	-	-	-
Non-CV	$3,104	$3,967	-$863*	-	-	-

All costs are in 2014 USD.
AF = atrial fibrillation; CV = cardiovascular.
* : p<0.01; †: p>0.05.

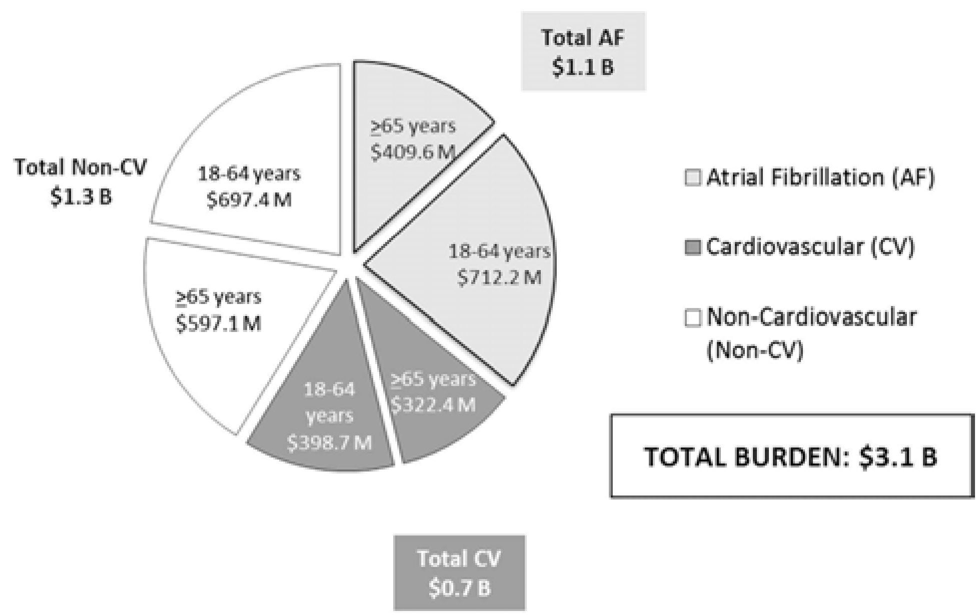

Figure 2. Incremental cost burden of undiagnosed AF in the United States. Total burden exacted by undiagnosed AF is shown across 3 treatment cost areas (AF, CV, non-CV) and stratified by subjects aged 18 to 64 years and aged ≥65 years. The largest burden is experienced in the non-CV treatment group ($1.3 billion), followed by AF ($1.1 billion) and CV ($0.7 billion). In each treatment area, subjects aged 18 to 64 years experienced greater costs compared to subjects aged ≥65 years. CV = cardiovascular.

artery bypass surgery (ICD-9 procedure codes 36.10 or 36.19), pericardial surgery (37.10 to 37.12, 37.24, 37.25, 37.31 to 33, 37.35, or 37.40), or structural cardiac repair surgery (35.31 to 35.39, 35.41 to 35.42, 35.50 to 35.54, 35.60 to 35.63, or 35.70 to 36.73).[23]

The primary outcome of interest was direct medical costs (in 2014 USD).[24] Direct medical costs included payments by insurers and patients (e.g., co-insurance, co-payments, deductibles) and were measured over a 12-month period. We divided costs into AF-related, other cardiovascular, and

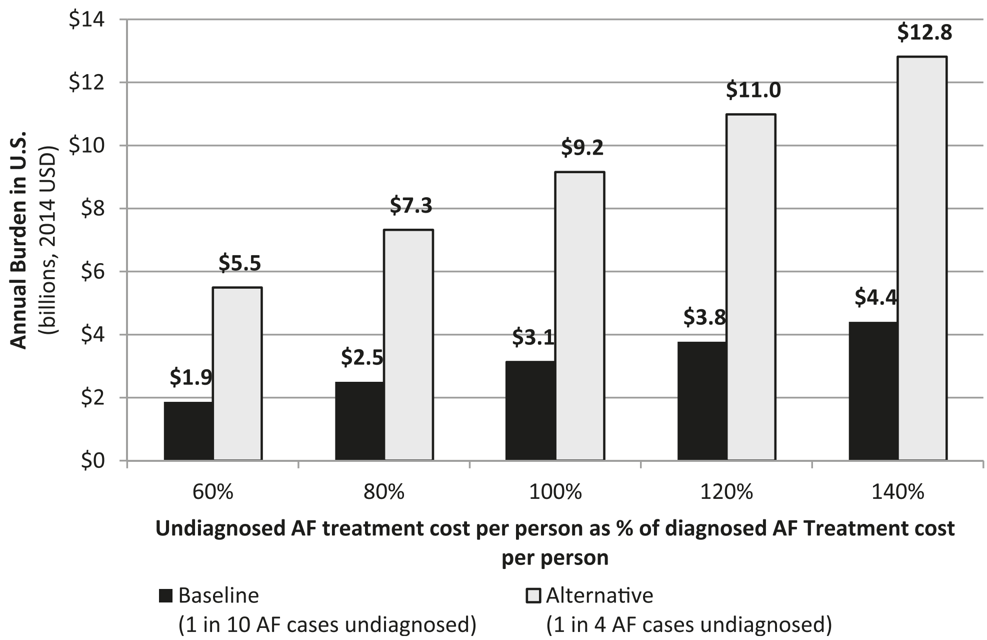

Figure 3. Incremental cost burden of undiagnosed AF by prevalence of undiagnosed AF. Two estimates of the incremental cost burden based on 2 scenarios of the prevalence of undiagnosed AF, 1 in 10 and 1 in 4. Examining undiagnosed AF treatment cost as a percentage of diagnosed AF treatment cost, the annual burden of undiagnosed AF ranges from $1.9 billion to $12.8 billon.

noncardiovascular costs.[7] We defined costs associated with claims with a primary diagnosis code of 427.31 as AF-related cost. Costs appearing on claims with primary diagnosis codes for cardiovascular disease other than AF[9,22,23] were defined as other cardiovascular costs, whereas cost for claims with neither AF nor other cardiovascular diagnosis code at the primary position were placed in the noncardiovascular cost category. For the Touchstone data, we considered drug costs associated with anticoagulant prescriptions as AF-related costs, and costs for prescriptions included in RedBook Therapeutic Group 7 (cardiovascular system) as other cardiovascular costs. All other prescription drug costs were included in the noncardiovascular category.

Control variables for the propensity score matching included patient demographics (i.e., age, gender), and comorbidities (acute myocardial infarction, cancer, cardiomyopathies, chronic pulmonary disease, congenital heart disease, congestive heart failure, diabetes, dyslipidemia, hypertension, ischemic heart disease, obesity, pericarditis, peripheral vascular disorders, renal failure, and sleep apnea). We also measured the annual number of evaluation and management physician visits to predict the likelihood an AF diagnosis was reported in the claims data.

To determine the per capita incremental burden of undiagnosed AF using propensity matching, we estimated the propensity of undiagnosed AF for all patients, matched patients with undiagnosed AF to patients with no AF, and calculated the difference in average costs. As patients with undiagnosed AF are not observed in the data, we implemented a modified propensity-matching approach to measure the per capita incremental cost burden for both patients with diagnosed and undiagnosed AF. First, we calculated the probability of having diagnosed or undiagnosed AF using a constrained maximum likelihood estimator. We used patient demographics and co-morbidities to predict the probability of having AF (diagnosed or undiagnosed) and then used the number of physician visits to model the likelihood a patient is diagnosed. Then, we matched patients with diagnosed AF to those without an AF diagnosis using a 1:1 "nearest neighbor" matching technique.[25] Finally, we reweighted the sample to account for that the propensity score of having AF is applied only to a subset of the full AF population (i.e., those observed to be diagnosed with AF in the data). After the mean per capita incremental cost of AF was estimated, we used estimates of the prevalence of undiagnosed AF estimates from our previous work—based on the same Medicare and commercial data set—to calculate the total US incremental cost burden of undiagnosed AF.[13] See Supplementary data for a more complete description of this approach.

We conducted two sensitivity analyses to test how our conclusions would change various assumption. First, undiagnosed AF may be less costly to treat if undiagnosed patients have less-severe symptoms than those with diagnosed AF; alternatively, the incremental cost burden for these patients may be greater if undiagnosed patients are less likely to receive cost-effective treatments. To address this issue, we tested how the national cost burden of undiagnosed AF would change if the incremental cost burden of undiagnosed AF ranged from 40% less to 40% greater than the measured incremental cost burden for diagnosed AF. Second, we assumed that approximately 10% of US adults with AF are undiagnosed, but some research indicated that rates of undiagnosed AF may fall from 18% to 27% of all patients with AF. We recalculated the US burden of undiagnosed AF using these alternative undiagnosed AF prevalence rates.

Results

Of the initial sample of 2.4 million Medicare beneficiaries and 2.2 million commercially insured people in the

Touchstone database in 2009, we identified approximately 913,000 Medicare and 338,000 privately insured beneficiaries who met the age (≥18-year-old), US residency, and continuous enrollment requirements (Figure 1). In the Medicare cohort, we found 81,244 patients with diagnosed AF and in the privately insured cohort, 2,975 patients were found with diagnosed AF. The AF and matched non-AF cohorts were well balanced with regard to gender, age, and co-morbidity covariates after matching (i.e., standardized difference <5%) with the exception of diabetes and dyslipidemia characteristics in the population aged 18 to 64 years (Table 1).

Incremental per capita cost burden was greater for patients aged 18 to 64 years compared to patients aged ≥65 years. For patients aged ≥65 years, mean annual direct costs per patient were $25,322 (95% confidence interval [CI] $25,049 to $25,595) for patients with AF compared to $21,706 (95% CI $21,563 to $21,849) for the matched beneficiaries without AF; an incremental cost difference of $3,616 (95% CI $3,308 to $3,924, p <0.001). For patients aged 18 to 64 years, the per capita annual costs were $38,861 (95% CI $35,781 to $41,950) for patients with AF compared to $28,506 (95% CI $28,409 to $28,603) for matched patients without AF, an incremental cost difference of $10,355 (95% CI $7,050 to $13,659, p <0.001). The incremental AF burden per capita was greater for women compared to men, and inpatient cost was the key driver of additional AF-related cost (Table 2).

Our previous research indicated that the prevalence of nonvalvular AF was 9.9% (8.8% diagnosed, 1.1% undiagnosed) for patients aged ≥65 years and 0.90% (0.83% diagnosed, and 0.07% undiagnosed) for patients aged 18 to 64 years. Extrapolating age or gender prevalence rates from US Census population estimates resulted in a population with undiagnosed nonvalvular AF of 460,000 subjects aged ≥65 years and 136,000 subjects aged 18 to 64 years. Combining the incremental per capita cost burden and US prevalence estimates, the incremental cost burden of undiagnosed nonvalvular AF in the United States is $3.1 billion (95% CI $2.7 to $3.7 billion). The cost burden was $1.8 billion for subjects aged ≥65 years and $1.3 billion for patients aged 18 to 64 years, with costs split fairly evenly between AF-related cost, cardiovascular costs, and noncardiovascular cost (Figure 2).

We tested how our baseline $3.1 billion estimate of US annual incremental cost burden changed when we altered some key assumptions. If per capita incremental cost of undiagnosed AF was 40% less than the cost for patients with diagnosed AF, the estimated national burden of undiagnosed AF would have been $1.9 billion; if per capita incremental cost of undiagnosed AF was 40% more than the cost burden of the diagnosed AF, the estimated national burden of undiagnosed AF would have been $4.4 billion (Figure 3). When we assumed that 1 in 5 patients with AF rather than 1 in 10 were undiagnosed, our estimates of the burden of undiagnosed AF increased to $9.2 billion, with a range between $5.5 and $12.8 billion depending on whether undiagnosed patients were more or less costly to treat than diagnosed patients.

Discussion

Our principal finding was that the estimated annual incremental cost burden of AF in patients with an undiagnosed form of the disease was $3.1 billion (95% CI 2.7 to 3.7 billion). Incremental cost was greater for patients aged 18 to 64 years compared to those aged ≥65 years, which is not unexpected, as physicians may be more willing to treat AF aggressively for younger patients.

This is the first study to measure the incremental cost burden of undiagnosed AF using large, nationally representative claims data. Previous estimates of the incremental burden of diagnosed AF range from $5,400 to $22,000, depending on whether the study was conducted in privately insured,[5,26] Medicare,[6] or adults ≥20[9] populations. Thus, our incremental cost figures ($3,616 for Medicare beneficiaries and $10,355 for commercially insured) are conservative relative to the existing reports.

Our results shed light on the considerable cost burden undiagnosed AF imposes on our society. Moreover, as the prevalence of AF is expected to continue to grow,[1,23,27] the number of undiagnosed AF cases is also likely to grow. Because stroke represents a major cost driver in long-term costs of AF, strategies to identify and treat patients (usually with anticoagulation) with silent or undiagnosed AF could lead to sizable reductions in stroke sequelae and associated costs in the United States. Small studies of ambulatory screening have demonstrated yields of 4% of AF in patients at moderate to high risk of stroke in whom anticoagulation is indicated.[13] The STROKE-STOP study, currently ongoing in Sweden, will evaluate whether intermittent ambulatory electrocardiographic screening for AF in adults aged ≥75 years can reduce stroke and improve survival.[28]

Our study has a number of limitations. First, accuracy of an AF diagnosis depends on how well providers document diagnoses on their claims data. To address the issue of false-positive diagnoses, we required confirmatory diagnoses when the diagnosis was made in a non-inpatient claim, and we excluded diagnoses where providers were not clinicians or when the place of service was a laboratory (to exclude rule-out diagnoses). Second, the propensity matching relies on observable patient characteristics to match comparable patients; thus, unobservable differences between patients with and without AF may still remain. Third, although this study relied on two large national databases, the study's per capita cost burden estimates may not be nationally representative. For instance, the cost burden for subjects aged ≥65 years included only Medicare fee-for-service beneficiaries. Similarly, the Touchstone data excluded patients who are not covered by commercial insurance (e.g., Medicaid, Veterans Affairs). Fourth, we did not have Medicare Part D (prescription drug) data and therefore may have underestimated health care costs for patients aged ≥65 years. Finally, our costs estimates do not include nonmedical AF costs such as increased worker absences or lost productivity.

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Disclosures

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Supplementary Data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.amjcard.2015.05.045.

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