ORIGINAL RESEARCH

Identifying Predictors of Cumulative Healthcare Costs in Incident Atrial Fibrillation: A Population-Based Study

Maria C. Bennell, MSc, MPH; Feng Qiu, MSc; Andrew Micieli, MMI; Dennis T. Ko, MD, MSc; Paul Dorian, MD, MSc; Clare L. Atzema, MD, MSc; Sheldon M. Singh, MD; Harindra C. Wijeysundera, MD, PhD

***Background*—**Atrial fibrillation (AF) has substantial impacts on healthcare resource utilization. Our objective was to understand the pattern and predictors of cumulative healthcare costs in AF patients after incident diagnosis in an emergency department (ED).

***Methods and Results*—**Patients discharged after a first presentation of AF to an ED in Ontario, Canada, were identified from April 1, 2005, through March 31, 2010. Per-patient cumulative healthcare costs were determined until death or March 31, 2012. Joinpoint analyses identified clinically relevant cost phases. Hierarchical generalized linear models with a logarithmic link and gamma distribution determined predictors of cost per phase. Our cohort was 17 980 patients. During a mean follow-up of 3.9 years, 17.1% of patients died. Three distinct cost phases were identified: 2-month post–index ED visit phase, 12-month predeath phase, and a stable/chronic phase. The mean cost per patient in the first month post–index ED visit was $1876 (95% CI $1822 to $1931), $8050 (95% CI $7666 to $8434) in the month before death, and $640 (95% CI $624 to $655) per month for the stable/chronic phase. The main cost component in the post-index phase was physician services (32% of all costs) and hospitalizations for the predeath phase (72% of all costs). The CHA_2DS_2-VASc clinical risk score was a strong predictor of costs (rate ratio 1.91 and 5.08 for score of 7 versus score of 0 in predeath phase and postindex phase, respectively).

***Conclusions*—**There are distinct phases of resource utilization in AF, with highest costs in the predeath phase. **(*J Am Heart Assoc*. 2015;4:e001684 doi: 10.1161/JAHA.114.001684)**

Key Words: arrhythmia • atrial flutter • cost-benefit analysis • fibrillation

Atrial fibrillation (AF) is the most common cardiac arrhythmia,[1] affecting about 46.1 million people globally,[2] including 350 000 Canadians.[3] AF is associated with significant morbidity, including a 3 to 5 times increase in risk of stroke and a 3 times increase in risk of congestive heart failure.[3–5] It is also associated with a 2-fold increase in comorbidity-adjusted mortality.[6] The prevalence of AF doubles with each decade of life beyond age 50, affecting almost 10% of the population by age 80.[7] Alarmingly, the overall burden, incidence, prevalence, and mortality of AF are increasing,[2] rendering this disease a public health crisis.

AF is associated with substantial healthcare costs, estimated at $6.65 billion (USD) annually in the United States.[8] Limitations of the current literature include the heterogeneity between studies in their use of economic models, surveys, administrative data, and patient-reported data, which has produced inconsistencies in cost estimates.[9] Moreover, most of the literature has focused on hospitalization costs,[8,10] despite most of the treatment for AF actually occurring in the outpatient setting. For example, outpatient and medication costs are estimated to be $1.77 billion (USD) in the United States.[8] Other healthcare sectors such as home care and long-term care may be important components of cumulative cost, given the advanced age of onset of AF and its associated comorbidities. Few studies have examined overall healthcare costs longitudinally from initial AF diagnosis, and these studies have had limited follow-up, from 0.5 to 3 years.[11–14] These studies have simply explored annual costs or short-term costs,

From the Division of Cardiology, Schulich Heart Centre and Department of Medicine, Sunnybrook Health Sciences Centre (M.C.B., D.T.K., S.M.S., H.C.W.), Division of Cardiology and Department of Medicine, St Michael's Hospital (P.D.), Trauma, Emergency and Critical Care Research Program, Sunnybrook Research Institute (C.L.A.), and Institute of Health Policy, Management and Evaluation (C.L.A., H.C.W.), University of Toronto, Ontario, Canada; Institute for Clinical Evaluative Sciences (ICES), Toronto, Ontario, Canada (F.Q., D.T.K., H.C.W.); Faculty of Medicine, University of Ottawa, Ontario, Canada (A.M.); Li Ka Shing Knowledge Institute of St Michael's Hospital, Toronto, Ontario, Canada (D.T.K., P.D., H.C.W.).

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Correspondence to: Harindra C. Wijeysundera, MD, PhD, 2075 Bayview Ave, Suite A202, Toronto, Ontario M4N 3M5, Canada. E-mail: harindra.wijeysundera@sunnybrook.ca

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which does not take into consideration the natural history of AF. Studies in cancer and heart failure suggest that there are distinct phases of cumulative cost accumulation that parallel the natural history of the disease, such as that immediately after diagnosis and that before death.[15,16] It is important to study these phases, because each may have different patient- or system-level predictors of costs. Such information is valuable for decision makers when targeting how to improve the efficiency of care delivery for those with a particular health condition. There have been no studies to date examining these issues in AF.

Accordingly, we sought to address this gap in knowledge by estimating per patient longitudinal cumulative costs over time from initial emergency department (ED) diagnosis to death across all healthcare sectors. Ontario is Canada's largest province, with a population of 13 million, all of whom have universal healthcare coverage provided by a single third-party payer, the Ontario Ministry of Health and Long Term Care (MOHLTC). Our objectives were to determine if there are clinically relevant phases of cumulative cost accumulation after an index diagnosis of AF and to determine the predictors of healthcare cost in these phases.

Methods

This study was approved by the Institutional Research Ethics Board at Sunnybrook Health Sciences Centre, University of Toronto. Under Ontario's Personal Health Information Protection Act (PHIPA), the need for patient consent was waived.

Data Sources

We conducted our analyses using population-level administrative databases with information on all Ontario residents. These datasets were linked using unique, encoded identifiers and analyzed at the Institute for Clinical Evaluative Sciences (ICES).

The Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD) was used to identify all acute and chronic care hospitalizations in our cohort. The National Ambulatory Care Reporting System database (NACRS) was used for hospital-based ambulatory care, including ED visits, outpatient surgical procedures, medical day and night care, and high-cost ambulatory clinics data. The Registered Persons Database (RPDB) was used to ascertain death. We obtained postal codes for socioeconomic status and rurality index through Statistics Canada. The Ontario Health Insurance Program (OHIP) fee-for-service claims history was accessed for data on physician services. Comprehensive drug information was obtained from the Ontario Drug Benefit database (ODB) for all patients aged ≥65 years, because the MOHLTC provides full drug coverage only for these patients. The Canadian Institute for Health Information Same Day Surgery (CIHI-SDS) database was used to obtain patient day surgery information. Long-term care data were from the Continuing Care Reporting System (CCRS) database, which contains demographic, clinical, functional, and resource utilization information on patients in long-term care facilities. Home care information was obtained from the Home Care Database (HCD), which contains administrative data regarding care delivery. Data from the National Rehab System (CIHI-NRS) provided information on inpatient rehabilitation programs.

Study Population

Our cohort consisted of newly diagnosed AF patients based on the *International Classification of Diseases Version 10* main diagnosis code I48 in the NACRS database, with their first ED visit between April 1, 2005, and March 31, 2010. We restricted the cohort to patients who were residents of Ontario, who were ≥20 years old, who had valid OHIP identification numbers, who did not have a previous diagnosis of AF within 3 years prior to the index visit, and who survived the index ED visit. We only included patients who were discharged home from the ED after their index presentation, as our algorithm for identification was validated in this population, with a positive predictive value of 93.0% (95% CI 91.6% to 94.2%) and a sensitivity of 96.6% (95% CI 94.1% to 98.2%).[17] For patients with multiple visits during the study timeframe, the first episode was selected as the index event.

Outcomes

The primary outcome was per patient longitudinal cumulative healthcare costs, from the index ED visit to a maximum follow-up until death or March 31, 2012. We included all available cost sectors, from the perspective of the MOHLTC. We used a bottom-up approach, whereby episodes of care for each sector per patient were identified in administrative databases during the follow-up period. Per-episode cost for hospitalizations, ED visits, same-day surgeries, complex continuing care services, home care services, and long-term care were determined by using resource intensity weights (RIWs) and case-mix methodology. We multiplied the RIW associated with the case-mix group for each episode of care by the mean provincial cost per weighted case (CPWC) for that fiscal year.[18] Costs for physician visits and laboratory tests were obtained directly from the OHIP claims history database, while medication costs were obtained directly from the ODB database. We only included medication costs for patients ≥65 years of age, because MOHLTC coverage was limited to this population. Costs per episode were adjusted to 2013 Canadian dollars using the Consumer Price Index, (http://www.bankofcanada.ca/en/cpi.html) and then summed over the entire

follow-period. Cumulative healthcare costs were reported in 30 patient-day intervals.

Phases of Cost

Previous studies by our team and others on heart failure and cancer care have shown that health-related costs are not constant over patient life span but rather have distinct periods of rapid cost accumulation, interspaced by periods of lower cost.[15,16] We hypothesized that there may be a similar pattern over the lifetime of AF patients, with 3 phases of cost: (1) a post–index ED visit phase of high cost, (2) a stable/chronic phase of relatively constant cost, and (3) a predeath phase of increasing cost. We first conducted exploratory analyses in patient subgroups who died 9 to 12 months post-index, 33 to 36 months post-index, or 57 to 60 months post-index and patients who were alive during the entire follow-up period. We examined their cumulative cost profiles to determine if there were clinically relevant phases of cost for post–index ED visit or predeath. If so, join-point analyses (Join-point regression software version 4.1.1, Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute) were conducted on each patient subgroup (death at 9 to 12, 33 to 36, and 57 to 60 months post-index) to determine the inflection points that separated cost phases, by using a Monte Carlo permutation method.[19] Based on the inflections in these subgroups, we approximated the inflections for the overall cohort. This is similar to the methodology used in previous publications in studies on heart failure,[16] prostate cancer,[20] and hepatitis C virus.[21]

After determining the presence and duration of each phase of cost, the total cost for each patient was allocated to each phase in a hierarchical fashion, where predeath phase cost was assigned first, then to the post–index ED visit, and, finally, all remaining cost to the stable phase. Individual patient costs were assigned to each block within each phase hierarchically, first to the predeath phase, then to the post–index ED visit phase, and finally to the stable/chronic phase. For example, for a patient who died 13 months post–index ED visit, the mean cost for the last 12 months was assigned to the 30 patient-day blocks of the predeath phase, and then the mean cost for the first month was assigned to a 30 patient-day block in the post–index ED visit phase. For a patient who died 34 months post–index ED visit, there were 20 months of cost assigned to the stable/chronic phase after assigning the last 12 months' cost to predeath and the first 2 months to the post–index ED visit. Costs for each of the 20 stable/chronic phase months were then averaged to provide a single 30 patient-day block estimate. Importantly, the cost for any particular episode for each individual patient was assigned to only 1 phase. Once assigned, 30 patient-day mean cost was determined for each phase. For the predeath and post-index phases, a separate 30 patient-day mean cost was estimated for each 30-day interval of each phase. For the stable phase, all remaining costs were averaged to produce a single 30-day mean cost estimate.

Statistical Analysis

We used multivariable hierarchical generalized linear models with a logarithmic link and gamma distribution to determine predictors of cumulative healthcare costs; methods that are consistent with those used in previous studies examining end of life and phases of costs[15,16] to account for the skewed positive nature of the data. We built separate models for the post-index phase and the predeath phase and tested the appropriateness of a log link and gamma distribution for each model by using the Pregibon link test and modified Hosmer–Lemeshow test, respectively. For the post-index phase of cost, the Pregibon link test indicated that the logarithmic link was appropriate for the generalized linear model (P=0.19), and the modified Hosmer–Lemeshow test supported a gamma distribution (P=0.44). For the predeath phase, the Pregibon link test supported the logarithmic link (P=0.394) and the modified Hosmer–Lemeshow test indicated that the gamma distribution was appropriate (P=0.217). The advantage of this type of model is that it accommodates the skewed nature of cost data and produces β-coefficients (rate ratio [RR]) that are interpreted as the relative increase in mean cost for each increment in the covariate. Covariates included in the 2 models were demographics (age, sex) and comorbidities, including hypertension, diabetes, and kidney/liver dysfunction. We then reran the 2 models using only CHA_2DS_2-VASc score as the covariate of interest. The CHA_2DS_2-VASc score consists of congestive heart failure/left ventricular dysfunction, hypertension, age ≥75 years (doubled), diabetes, stroke (doubled)—vascular disease, age 65 to 74 years, and sex category (female). We chose the CHA_2DS_2-VASc score because it is inclusive of common clinically relevant major and nonmajor risk factors for stroke,[22] and it has been validated in multiple cohort studies.[23]

We used SAS version 9.3 (SAS Institute Inc) for statistical analyses and STATA version 13.1 for goodness-of-fit and goodness-of-link tests.

Results

Study Population

There was a total of 61 112 ED visits for AF in Ontario, Canada, between April 1, 2005, and March 31, 2010 (Figure 1). After applying exclusions, our final cohort consisted of 17 980 patients. Baseline characteristics are shown in Table 1. Mean age of the patients was 65.7 years, and

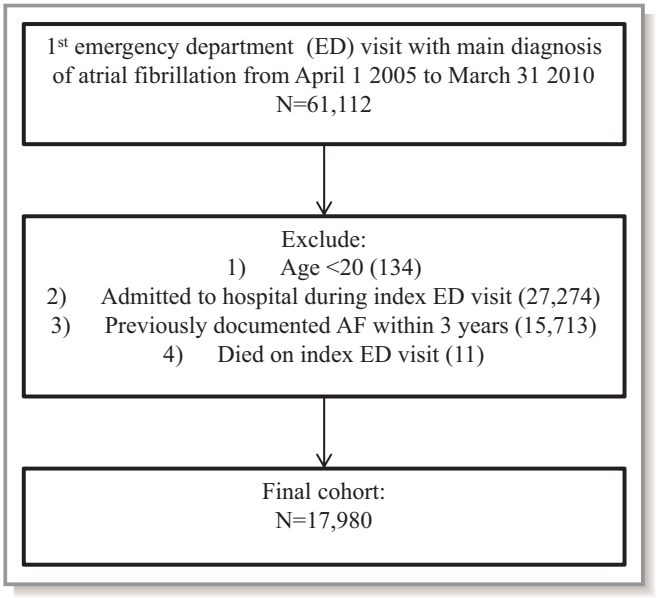

Figure 1. Costing profile for incident emergency department atrial fibrillation. AF indicates atrial fibrillation; ED, emergency department.

45.8% were female. The majority of patients had hypertension (60.7%), while only 18.8% had diabetes mellitus. Approximately 1.2% had a previous stroke. In regard to stroke risk, 35.8% of patients had low CHA_2DS_2-VASc scores (scores 0 to 1), and the majority of patients had scores <5 (90.2%). In our cohort, 17.1% of patients died during the 3.9 years of follow-up. A total of 1055 patients (5.9%) died within 1 year of their index ED presentation.

Table 1. Baseline Characteristics

Covariate	No. of Patients (%) (N=17 980)
Patient characteristics (N=17 980)	
Age, y±SD	65.73±15.68
Sex (female)	8229 (45.8)
Patients ≥65 y old	10 203 (56.7)
Diabetes mellitus	3383 (18.8)
Congestive heart failure	1647 (9.2)
Hypertension	10 916 (60.7)
Stroke	216 (1.2)
Vascular disease	1205 (6.7)
Liver dysfunction	65 (0.4)
Renal disease	237 (1.3)
Bleed	729 (4.1)
Alcohol abuse	77 (0.4)
CHA_2DS_2-VASc score	
0	3058 (17.0)
1	3376 (18.8)
2	3259 (18.1)
3	3338 (18.6)
4	3176 (17.7)
5	1285 (7.1)
6	385 (2.1)
7	92 (0.5)
8	11 (0.1)
9	0 (0.0)

Except for age, all values are n (%).

Phases of Cost

In our exploratory analyses, we confirmed that cumulative cost curves for AF were defined by discrete cost phases (Figure 2). Inflection points separated the post–index ED visit and stable/chronic phases at 2 months post-index, and the stable/chronic and predeath phases at 12 months predeath. There were two 30 patient-day blocks of consecutive cost for the post-index phase, and 12 blocks for the predeath phase.

Figure 3 shows the mean cost per patient for each 30-day block of each phase, and Table 2 shows the costs divided into components of cost. Of the 3 phases, total cost was highest in the predeath phase. In the predeath phase, total cost increased by 75% across 30 patient-day blocks, from 12 months predeath ($1984, 95% CI $1816 to $2152) to 1 month predeath ($8050, 95% CI $7666 to $8434). For the post-index phase, the mean total cost per patient was highest at 1 month post-index ($1876, 95% CI $1822 to $1931) and decreased substantially by 46% at 2 months post-index ($872, 95% CI $828 to $916). For the stable/chronic phase, mean total cost was the lowest of the 3 phases, at $640 (95% CI $624 to $655) per month. Acute hospitalization cost was the predominant driver of cost in the predeath phase (72% of all costs for 1 month predeath). In the post-index phase, cost was more evenly distributed among physician services, acute hospitalizations, and ED visits (32%, 31%, and 24% of all costs for 1 month post-index, respectively). For the stable/chronic phase, acute hospitalizations were the largest contributor to total costs (29%), but physician services (23% of all costs) and medications (16%) also remained high.

Predictors of Cost

Several patient characteristics were significant predictors of total per patient cost. In the post-index phase, per patient cost was more likely to be higher for patients who were older (RR 1.019, 95% CI 1.018 to 1.020, $P<0.0001$) or who had a history of diabetes mellitus, congestive heart failure,

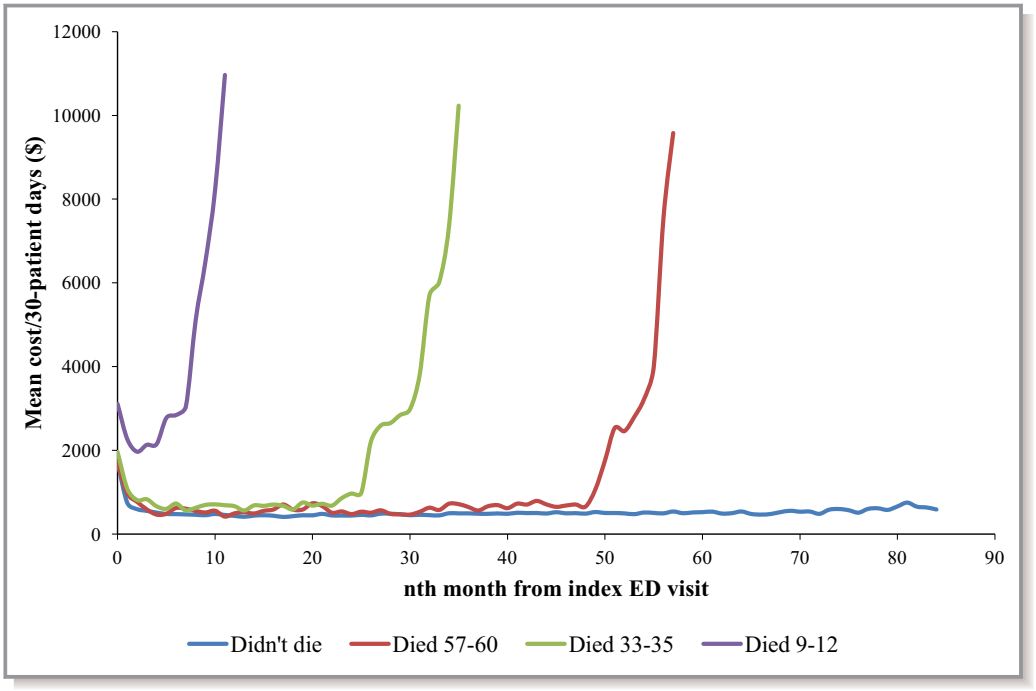

Figure 2. Exploratory analysis of phases of cost associated with atrial fibrillation. ED indicates emergency department.

hypertension, or renal or liver dysfunction (Table 3). In contrast, we found that for the predeath phase, per-patient cost was actually lower for patients who were older (RR 0.996, 95% CI 0.992 to 0.999, *P*=0.0156). However, comorbidities such as a history of diabetes mellitus (RR 1.09, 95% CI 1.01 to 1.19, *P*=0.0323) or renal dysfunction (RR 1.46, 95% CI 1.21 to 1.77, *P*=0.0001; Table 3) were associated with increased costs.

When our models were repeated with only the CHA_2DS_2-VASc score, we found that the score was a strong predictor of per-patient cost for both post-index and predeath analyses. There was a general gradient of cost with increasing

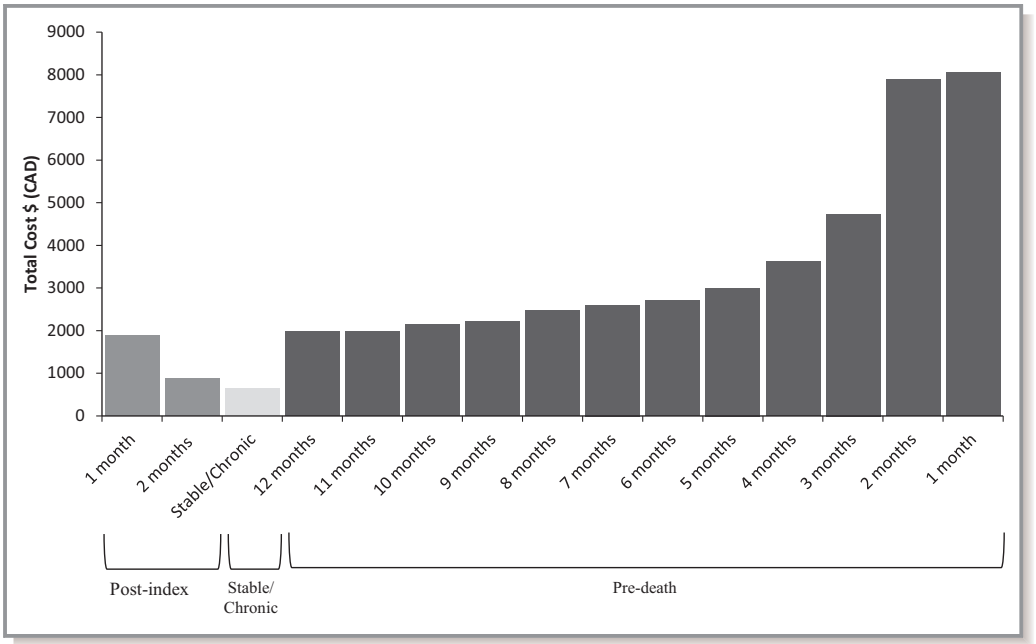

Figure 3. Mean cost per patient for each 30-day block of each phase of cost.

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Table 2. Costs per Phase

	Costs (Range)							
	Total	Hospitalization	Same-Day Surgery	Emergency Department	Physician Fees	Medications (Patients ≥65 y Old)	Home Care	Long-Term Care
Postindex*								
Month								
1 (n=16 925)	1876 (1822 to 1931)	574 (532 to 617)	38 (32 to 44)	452 (447 to 456)	604 (595 to 613)	105 (101 to 108)	53 (49 to 58)	31 (26 to 35)
2 (n=16 872)	872 (828 to 916)	307 (273 to 341)	39 (34 to 44)	46 (44 to 49)	290 (282 to 298)	95 (91 to 98)	41 (38 to 45)	31 (27 to 36)
Stable/chronic								
Month								
1 (n=16 821)	640 (624 to 655)	186 (177 to 195)	22 (21 to 23)	28 (27 to 29)	149 (146 to 151)	104 (102 to 107)	50 (47 to 53)	78 (72 to 84)
Pre-death†								
Month								
1 (n=3074)	8050 (7666 to 8434)	5776 (5425 to 6128)	17 (10 to 24)	342 (326 to 358)	869 (823 to 915)	125 (116 to 133)	369 (335 to 403)	329 (302 to 357)
2 (n=2875)	7893 (7454 to 8331)	5140 (4736 to 5544)	22 (14 to 29)	292 (276 to 309)	847 (801 to 893)	256 (242 to 270)	535 (491 to 580)	644 (597 to 691)
3 (n=2742)	4736 (4412 to 5059)	2534 (2250 to 2817)	34 (14 to 55)	158 (146 to 171)	550 (511 to 589)	270 (249 to 290)	456 (415 to 496)	630 (582 to 678)
4 (n=2653)	3620 (3358 to 3882)	1747 (1516 to 1978)	26 (18 to 34)	127 (115 to 138)	446 (415 to 477)	251 (237 to 265)	364 (331 to 398)	603 (555 to 651)
5 (n=2569)	2999 (2764 to 3234)	1211 (1020 to 1401)	33 (21 to 45)	103 (93 to 114)	388 (356 to 419)	250 (235 to 265)	332 (300 to 363)	587 (538 to 635)
6 (n=2470)	2706 (2519 to 2894)	1036 (882 to 1190)	25 (16 to 33)	95 (85 to 105)	349 (324 to 374)	258 (241 to 276)	307 (279 to 336)	577 (528 to 626)
7 (n=2389)	2602 (2402 to 2802)	982 (819 to 1144)	29 (20 to 39)	100 (89 to 111)	333 (310 to 356)	244 (229 to 259)	288 (258 to 318)	566 (517 to 616)
8 (n=2308)	2477 (2277 to 2678)	889 (730 to 1049)	49 (30 to 68)	79 (70 to 88)	328 (302 to 355)	243 (227 to 259)	265 (237 to 293)	559 (510 to 609)
9 (n=2237)	2217 (2039 to 2395)	762 (613 to 910)	24 (15 to 33)	71 (62 to 80)	298 (277 to 318)	247 (231 to 263)	241 (214 to 267)	540 (491 to 589)
10 (n=2190)	2152 (1968 to 2336)	736 (585 to 886)	30 (20 to 40)	72 (63 to 82)	301 (275 to 327)	229 (214 to 244)	227 (203 to 252)	515 (466 to 563)
11 (n=2146)	1983 (1830 to 2136)	597 (477 to 717)	23 (16 to 30)	70 (60 to 79)	283 (260 to 305)	243 (224 to 262)	228 (204 to 252)	502 (454 to 549)
12 (n=2089)	1984 (1816 to 2152)	615 (482 to 748)	49 (23 to 76)	68 (59 to 78)	287 (260 to 314)	230 (216 to 244)	222 (198 to 245)	478 (430 to 525)

ED indicates emergency department.
*Per month after discharge alive from the ED.
†Per month prior to death.

Table 3. Predictors of Cumulative Cost for the 2 Months Post–Index ED Visit and the 12 Months Before Death

	Postindex		Predeath	
Covariate	Rate Ratio* (95% CI)	*P* Value	Rate Ratio* (95% CI)	*P* Value
Patient characteristics				
Age, y	1.019 (1.018 to 1.020)	<0.0001	0.996 (0.992 to 0.999)	0.0156
Sex, male	1.01 (0.98 to 1.04)	0.5348	0.94 (0.87 to 1.01)	0.0885
Congestive heart failure	1.38 (1.31 to 1.46)	<0.0001	1.07 (0.97 to 1.17)	0.1631
Stroke	1.01 (0.92 to 1.12)	0.8008	0.96 (0.82 to 1.13)	0.6244
Vascular disease	1.14 (1.03 to 1.26)	0.0129	1.14 (0.95 to 1.35)	0.1569
Diabetes mellitus	1.29 (1.24 to 1.34)	<0.0001	1.09 (1.01 to 1.19)	0.0323
Hypertension	1.07 (1.03 to 1.10)	<0.0001	1.05 (0.96 to 1.15)	0.2827
Liver dysfunction	1.63 (1.28 to 2.07)	<0.0001	0.87 (0.57 to 1.32)	0.5025
Renal dysfunction	1.60 (1.41 to 1.82)	<0.0001	1.46 (1.21 to 1.77)	0.0001
Bleed	1.21 (1.09 to 1.34)	0.0005	1.15 (0.95 to 1.39)	0.1427
Alcohol abuse	1.27 (1.02 to 1.58)	0.0323	1.20 (0.79 to 1.81)	0.3881
CHA_2DS_2-VASc score†				
1	1.22 (1.16 to 1.27)	<0.0001	1.43 (1.08 to 1.89)	0.0127
2	1.62 (1.55 to 1.70)	<0.0001	1.48 (1.14 to 1.93)	0.0038
3	1.98 (1.89 to 2.07)	<0.0001	1.34 (1.04 to 1.73)	0.0231
4	2.38 (2.27 to 2.50)	<0.0001	1.34 (1.04 to 1.72)	0.0236
5	2.79 (2.62 to 2.97)	<0.0001	1.44 (1.11 to 1.86)	0.0059
6	3.28 (2.95 to 3.64)	<0.0001	1.59 (1.20 to 2.12)	0.0014
7	5.08 (4.10 to 6.29)	<0.0001	1.91 (1.29 to 2.82)	0.0012
8	2.72 (1.52 to 4.85)	0.0007	1.55 (0.72 to 3.33)	0.2648

ED indicates emergency department.
*Rate ratio=the % increase in mean cost for each unit increase in the covariate.
†Separate models with only CHA_2DS_2-VASc score.

comorbidity, as reflected by a higher CHA_2DS_2-VASc score (RR 5.08 and 1.91 for a score of 7 compared with a score of 0, respectively).

Discussion

The authors examined per-patient longitudinal cumulative cost from initial ED visit diagnosis across all healthcare sectors, by determining clinically relevant phases of total cost and the predictors of cost in these phases. We found that cost was highest in the predeath phase, due mainly to acute hospitalization cost, and increased as patients approached death. Cost was next highest in the post-index phase, with physician services, acute hospitalizations, and ED visits as the highest costs, and cost was greater during the first month post-index. Cost was lowest in the stable/chronic phase and was mainly attributable to acute hospitalizations, physician services, and medications. Comorbidities contributed to higher healthcare cost, and CHA_2DS_2-VASc score was a particularly strong predictor.

Previous studies have determined that AF-related medical costs are high. A recent systematic review estimated a mean overall annual per-patient cost of AF at $2000 to $14 200 USD in the United States, using both prevalent and incident AF cohorts.[24] Our study provides a more complete picture of individual patient cumulative costs, as we examined longitudinal cost from index AF diagnosis to death and incorporated the impact of the natural history of AF by examining phases of cost. Of the studies in the literature that examined longitudinal costs from AF diagnosis,[11–14] we are only aware of studies where follow-up was short term (0.5 to 3 years), which prevents direct comparisons to our results. Our study highlights that simply examining annual costs is potentially misleading, as costs are highly dependent on the phase of the disease, with a 10-fold difference in monthly costs between the stable phase and predeath phase.

In terms of contributors of cost in AF, systematic reviews have determined that hospitalization is the largest cost,[9,24] accounting for 50% to 70% of mean total cost.[24] Our phase-based AF costing method provides additional insights, as we

found that contributors of cost were also highly dependent on the disease phase. While hospitalization was a large contributor of cost in all phases in our study, it was only within the same range of total cost of previous studies during the predeath phase, where hospitalizations contributed to 51% of total cost. Other cost components were also predominant contributors of cost during the stable/chronic and post-index phases.

Our phase-based costing approach is the first of its kind for AF costing, and to our knowledge this method has only been previously applied to cancer and heart failure.[15,16] Cost per phase and the contributors of cost differ depending on the diseases studied thus far. A previous study by our research team found that mean total cost per phase was highest in the predeath phase for heart failure clinic patients[16]; this is similar with our results in AF. In contrast to our AF study, hospitalization was overwhelmingly the largest contributor of cost for heart failure clinic patients, representing >80% of total healthcare costs for patients in the predeath and post–hospital discharge phases and 50% of total costs in the stable/chronic phase.[16] A study by Brown and colleagues found that for colorectal cancer, overall total cost was highest for the predeath phase, as is consistent with these 2 studies, although monthly mean cost was highest for the post-index phase,[15] rather than for predeath as in the current study. Unfortunately, cost was not broken down into its components, so no comparison could be made to AF costing components.

It is important to note that our costing approach is not specific to the cost of treating AF but is instead closely tied with other comorbidities, and so it can be thought of as the cost of patients with AF. It is well known that comorbidities are commonly associated with AF, especially cardiovascular conditions such as ischemic heart disease, heart failure, and hypertension.[25,26] A recent retrospective observational study reported that 98% of the AF population had at least 1 other comorbidity, and 63% had ≥4 comorbidities, 45% and 21% had a moderate or high comorbidity burden, and 45% had a moderate risk for stroke ($CHADS_2$ scores of ≥2).[25] The large influence of comorbidities is reflected in our AF costing results, as we found that comorbidities were the largest predictors of AF-related cost. The CHA_2DS_2-VASc score was a particularly important predictor, a result that is consistent with another study that examined predictors of AF cost.[27]

Limitations

Our study has several potential limitations that merit discussion. First, we did not take on a societal perspective but rather that of the third-party payer for the province. As such, there were costs that we excluded. For example, we could not include medication costs for patients <65 years old, as Ontario only provides comprehensive coverage for patients ≥65 years old. Moreover, we did not include patient out-of-pocket costs or loss of productivity related to missed work. Inclusion of these components would have driven AF costs higher. However, given the elderly age of most AF patients, we do not believe this would have made a large difference in our conclusions. Second, we limited our analyses to 3 phases and did not look at other potentially important clinical events such as the occurrence of a major stroke or major bleed. These are important foci for further research. Third, we did not include location of death (ie, hospital, home) in our analyses. Patients who die in hospital would incur higher immediate predeath costs than those who die at home. If characteristics of patients who die at home differ from those of other patients in the cohort, then location of death can be an important predictor of healthcare costs. Unfortunately, our available databases do not provide the location of death, so we could not include this covariate. Fourth, there are limitations to existing methods for estimating healthcare costs and implications for the choice of method of analysis. We used generalized linear models, which are generally an improvement to the transformed linear models that were previously commonly used.[28] A criticism of generalized linear models is that they can be imprecise and lack robustness, consistency, and efficient methods.[28] Therefore, applying the appropriate link function and distribution to the model is important. However, there are issues with the diagnostic tests used to determine the optimal model. The modified Hosmer–Lemeshow test is prone to influential outliers,[28] the value of the statistic depends on the choice of cutpoint that defines the groups, and the test can have low power for detecting lack-of-fit.[29] The Pregibon test and other link tests are more parsimonious tests, but mildly influential observations can result in false-positive and -negative results.[28] New alternative methods for estimating costing have been developed, but further research is needed to improve these methods.[28] Finally, endogeneity in costs is a well-recognized phenomenon, in particular for costs at the end of life, where costs are likely to be impacted by unmeasured confounders and other selection biases. As such, in light of these features of cost data, compounded by the observational nature of our study, we cannot assume causality between predictors of cost and cost; therefore, our findings should be considered hypothesis generating rather than conclusive.

Conclusion

In our phase-based longitudinal costing approach to AF-related costs in patients from AF diagnosis to death, we have identified 3 distinct phases of costs and found that costs were highest in the predeath phase, where hospitalization cost was a far greater contributor to total cost than in other phases.

Further research is needed on methods to incorporate these phase based costs into cost-effectiveness analyses for AF therapies.

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Disclosures

None.

References

1. Healey JS, Parkash R, Pollak T, Tsang T, Dorian P; CCS Atrial Fibrillation Guidelines Committee. Canadian Cardiovascular Society atrial fibrillation guidelines 2010: etiology and initial investigations. *Can J Cardiol*. 2011;27:31–37.
2. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, Gillum RF, Kim YH, McAnulty JH Jr, Zheng ZJ, Forouzanfar MH, Naghavi M, Mensah GA, Ezzati M, Murray CJ. Worldwide epidemiology of atrial fibrillation: a global burden of disease 2010 study. *Circulation*. 2014;129:837–847.
3. Heart & Stroke Foundation. Heart disease—atrial fibrillation. 2014. Available at: http://www.heartandstroke.com/site/c.ikIQLcMWJtE/b.5052135/k.2C86/Heart_disease__Atrial_fibrillation.htm. Accessed December 3, 2014.
4. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, Hindricks G, Kirchhof P. 2012 focused update of the ESC guidelines for the management of atrial fibrillation: an update of the 2010 ESC guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J*. 2012;33:2719–2747.
5. Patel PJ, Keating RJ, Gersh BJ, Hodge DO, Hammill SC, Shen WK. Outcome of patients with newly diagnosed atrial fibrillation at the Mayo Clinic and residing in that area. *Am J Cardiol*. 2004;94:1379–1382.
6. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation*. 1998;98:946–952.
7. Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. *Am J Cardiol*. 1998;82:2N–9N.
8. Coyne KS, Paramore C, Grandy S, Mercader M, Reynolds M, Zimetbaum P. Assessing the direct costs of treating nonvalvular atrial fibrillation in the United States. *Value Health*. 2006;9:348–356.
9. Wodchis WP, Bhatia RS, Leblanc K, Meshkat N, Morra D. A review of the cost of atrial fibrillation. *Value Health*. 2012;15:240–248.
10. O'Reilly DJ, Hopkins RB, Healey JS, Dorian P, Sauriol L, Tarride JE, Burke N, Goeree RA. The burden of atrial fibrillation on the hospital sector in Canada. *Can J Cardiol*. 2013;29:229–235.
11. Boccuzzi SJ, Martin J, Stephenson J, Kreilick C, Fernandes J, Beaulieu J, Hauch O, Kim J. Retrospective study of total healthcare costs associated with chronic nonvalvular atrial fibrillation and the occurrence of a first transient ischemic attack, stroke or major bleed. *Curr Med Res Opin*. 2009;25:2853–2864.
12. Kim MH, Lin J, Hussein M, Kreilick C, Battleman D. Cost of atrial fibrillation in United States managed care organizations. *Adv Ther*. 2009;26:847–857.
13. Reinhold T, Lindig C, Willich SN, Bruggenjurgen B. The costs of atrial fibrillation in patients with cardiovascular comorbidities—a longitudinal analysis of German health insurance data. *Europace*. 2011;13:1275–1280.
14. Wolf PA, Mitchell JB, Baker CS, Kannel WB, D'Agostino RB. Impact of atrial fibrillation on mortality, stroke, and medical costs. *Arch Intern Med*. 1998;158:229–234.
15. Brown ML, Riley GF, Potosky AL, Etzioni RD. Obtaining long-term disease specific costs of care: application to Medicare enrollees diagnosed with colorectal cancer. *Med Care*. 1999;37:1249–1259.
16. Wijeysundera HC, MacHado M, Wang X, Van Der Velde G, Sikich N, Witteman W, Tu JV, Lee DS, Goodman SG, Petrella R, O'Flaherty M, Capewell S, Krahn M. Cost-effectiveness of specialized multidisciplinary heart failure clinics in Ontario, Canada. *Value Health*. 2010;13:915–921.
17. Atzema CL, Dorian P, Ivers NM, Chong AS, Austin PC. Evaluating early repeat emergency department use in patients with atrial fibrillation: a population-based analysis. *Am Heart J*. 2013;165:939–948.
18. Jacobs P, Yim R. *Using Canadian Administrative Databases to Derive Economic Data for Health Technology Assessments*. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2009. Available at: http://www.cadth.ca/media/pdf/H0483_Canadian_Admin_Databases_mg_e.pdf. Accessed December 3, 2014.
19. Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. *Stat Med*. 2000;19:335–351.
20. Krahn MD, Zagorski B, Laporte A, Alibhai SM, Bremner KE, Tomlinson G, Warde P, Naglie G. Healthcare costs associated with prostate cancer: estimates from a population-based study. *BJU Int*. 2010;105:338–346.
21. Krajden M, Kuo M, Zagorski B, Alvarez M, Yu A, Krahn M. Health care costs associated with hepatitis C: a longitudinal cohort study. *Can J Gastroenterol*. 2010;24:717–726.
22. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on Atrial Fibrillation. *Chest*. 2010;137:263–272.
23. Lip GY. Stroke in atrial fibrillation: epidemiology and thromboprophylaxis. *J Thromb Haemost*. 2011;9(suppl 1):344–351.
24. Wolowacz SE, Samuel M, Brennan VK, Jasso-Mosqueda JG, Van Gelder IC. The cost of illness of atrial fibrillation: a systematic review of the recent literature. *Europace*. 2011;13:1375–1385.
25. LaMori JC, Mody SH, Gross HJ, daCosta DiBonaventura M, Patel AA, Schein JR, Nelson WW. Burden of comorbidities among patients with atrial fibrillation. *Ther Adv Cardiovasc Dis*. 2013;7:53–62.
26. Carroll K, Majeed A. Comorbidity associated with atrial fibrillation: a general practice-based study. *Br J Gen Pract*. 2001;51:884–886, 889–891.
27. Kotowycz MA, Filion KB, Joza J, Dube D, Reynolds MR, Pilote L, Eisenberg MJ, Essebag V. In-hospital management of atrial fibrillation: the $CHADS_2$ score predicts increased cost. *Can J Cardiol*. 2011;27:506–513.
28. Basu A, Manning WG. Issues for the next generation of health care cost analyses. *Med Care*. 2009;47:S109–S114.
29. Hosmer DW, Hosmer T, Le Cessie S, Lemeshow S. A comparison of goodness-of-fit tests for the logistic regression model. *Stat Med*. 1997;16:965–980.