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Systematic Literature Review

The Cost of Atrial Fibrillation: A Systematic Review

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ABSTRACT

Objectives: Atrial fibrillation (AF) is the most common cardiac arrhythmia, with an increasing incidence and prevalence because of progressively aging populations. Costs related to AF are both direct and indirect. This systematic review aims to identify the main cost drivers of the illness, assess the potential economic impact resulting from changes in care strategies, and propose interventions where they are most needed.

Methods: A systematic literature search of the PubMed and Scopus databases was performed to identify analytical observational studies defining the cost of illness in cases of AF. The search strategy was based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 recommendations.

Results: Of the 944 articles retrieved, 24 met the inclusion criteria. These studies were conducted in several countries. All studies calculated the direct medical costs, whereas 8 of 24 studies assessed indirect costs. The median annual direct medical cost per patient, considering all studies, was €9409 (13 333 US dollars in purchasing power parities), with a very large variability due to the heterogeneity of different analyses. Hospitalization costs are generally the main cost drivers. Comorbidities and complications, such as stroke, considerably increase the average annual direct medical cost of AF.

Conclusions: In most of the analyzed studies, inpatient care cost represents the main component of the mean direct medical cost per patient. Stroke and heart failure are responsible for a large share of the total costs; therefore, implementing guidelines to manage comorbidities in AF is a necessary step to improve health and mitigate healthcare costs.

Keywords: atrial fibrillation, comorbidities, cost of illness, direct costs, indirect costs.

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Introduction

Atrial fibrillation (AF) represents the most common cardiac arrhythmia and is associated with an increasing incidence and prevalence with advancing age.[1] Large cohorts from different European countries have shown that the cumulative incidence of AF increases markedly after the age of 50 years in men and 60 years in women.[2] This is relevant, given that the average population age is increasing and the proportion of those aged over 65 years is constantly growing.[3,4]

It has been projected that by 2060, in Europe, around 18 million people will be living with AF, and 12 million people in the United States will do so by 2030.[5,6] It is therefore an emerging health issue that potentially represents a major (and increasing) public health burden globally.

AF is frequently asymptomatic, especially at early stages, and it is then diagnosed incidentally or when a major AF-related complication occurs.[7] Although there is increasing evidence that wearable and handheld devices may be useful diagnostic tools for AF detection,[8] it is often difficult to systematically diagnose AF, leading to a higher risk of mortality and morbidity from AF-related complications, including stroke, heart failure, and dementia, as well as hospitalizations and impaired quality of life.[9–13] This is despite the potential cost savings of screening for AF and avoiding complications such as stroke.[14] The residual risks of major adverse clinical outcomes despite oral anticoagulation have led to guidelines advocating a more holistic or integrated care approach to the characterization and management of AF patients.[15,16]

According to the cost-of-illness (COI) approach, the economic costs related to AF can be categorized into 2 main components. Direct costs are related to therapies, medical visits, hospitalization, laboratory and instrumental tests, and treatments needed by patients with AF and associated comorbidities and complications. In contrast, indirect costs are related to the loss of productivity that can result from illness, premature death, side-effects of illness or treatment, and the time spent receiving treatment, including the opportunity cost of informal caregivers.[17] The cost burden of AF is expected to increase because of progressively aging populations and the global spread of lifestyles characterized by the presence of risk factors for the development of this condition. Understanding

the economic impact of AF is therefore an important first step in evaluating possible interventions to mitigate the future increase in healthcare expenditure.[3,4,18]

Prior systematic reviews have been conducted on the cost of illness of AF[19-22]; however, in the last 10 years, many other real-world data studies on the burden of this condition have been published that have shown a wide difference in the evaluation of the average annual cost per patient, widely ranging from €3170 in Casajuana et al (2018)[23] and doubling to €7688 in Reinhold et al (2011).[24]

This systematic review aims to analyze the updated available COI studies of AF and to identify the main cost drivers associated with AF care.

Methods

Search Strategy

For this study, a comprehensive and systematic literature search was performed between April and May 2022 of the PubMed and Scopus databases to identify studies investigating the cost of AF. The search strategy and the following review are both based on PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 recommendations.[25] No prespecified protocol was followed for the systematic review.

The search process involved the use of a search string obtained by combining the terms "atrial fibrillation" with the terms "cost*," "health expenditures," "spending," "cost of illness," "cost analysis," and "economic burden" and excluding terms such as "cost effectiveness," "cost utility," and "cost benefit" using Boolean operators. The search strings are reported in Appendix A in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.12.015. We included studies covering all ages and all grades of condition severity and considering patients with AF as a single disease, as well as patients with comorbidities.

Eligibility Criteria

To meet the inclusion criteria, the studies included in the review had to fit the following:

- evaluate the cost of AF, and at least all the direct medical costs and the indirect costs, when available
- be published from 2010 until May 20, 2022 (another systematic review on the cost of illness of AF was published, which included studies published up to 2009[20])
- be written in English

The studies excluded from the review were as follows:

- with cost analyses focused on a particular medical treatment (eg, a drug or surgical technique)
- evaluating cost-effectiveness, cost-utility, and cost-benefits
- evaluating only a single item of direct costs related to AF (eg, only hospitalization)
- reporting only theoretical and methodological analyses of cost measurement

If the studies provided data on both the total annual cost for the entire population with AF in a given country and the yearly cost per patient (or the monthly cost per patient), only the latter was reported in the evidence table.

Data Extraction and Analysis

The records retrieved from the databases were imported into Endnote X9, and duplicates were removed. After removing duplicate citations, the principal reviewer checked the search hits by reading the article titles and abstracts. After the initial screening, the principal reviewer evaluated the abstracts of the remaining publications and applied the eligibility criteria with another research team member. Four research team members performed full-text screening on the publications that met the eligibility criteria. The authors also checked the reference lists of the articles included in the review for any articles not previously considered.

The following data were extracted from each study: the first author's name, year of publication, year of valuation, journal, country of study, study design, perspective (societal, public, or private third-party payer), currency, epidemiological approach, sampling method, case definition of AF, sample size, characteristics of the study sample (eg, age range and sex), percentage of patients with comorbidities, cost indicators, limitations of the study, reported sensitivity analysis, subgroup analysis, and author's conclusions.

Regarding cost indicators, the following data were collected: direct medical costs, direct non-medical costs (eg, social services, transportation associated with healthcare, and accommodation), and indirect costs (productivity losses, such as income forgone by individuals and businesses, and opportunity costs of informal caregiving).

The direct medical costs were, in turn, specified in terms of inpatient costs (related to hospitalization, including interventions), outpatient costs (related to emergency department visits, consultations, lab tests, other diagnostic and follow-up procedures, primary care, nursing, home care, and rehabilitation), and pharmaceutical costs.

The costs identified in the various studies were adjusted for the inflation rate. The values obtained were then converted into euros using the exchange rate on 28 December 2022. We also express the costs in terms of US dollars in current purchasing power parities (US$ PPPs) according to the 2022 Organization for Economic Co-operation and Development conversion rates. These values were calculated only in the case of studies that specified the year in which the costs were obtained.

Summary results were independently presented to the other members of the research team to address any disagreement through discussion or consultation.

Because of the high heterogeneity in terms of interventions and outcome measures among the evaluated studies, a meta-analysis was deemed inappropriate, leading us to proceed with a qualitative analysis.

Methodological Appropriateness of the Included Studies

One author evaluated the methodological appropriateness of the studies included in the review using a 10-item checklist specific to COI studies that was adapted from Molinier et al (2008)[26] and is consistent with the guidelines for cost analysis reported in Drummond et al (2015)[27] (Table B1 in Appendix B in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.12.015). Equal weight was assigned to each item (key methodological question) on the checklist. For each question, the assigned score was 1 if the answer was "yes," 0.5 if the answer was "partial," and 0 if the answer was no." The total score per study was the sum of the scores calculated for the 10 individual items. The studies were classified in terms of methodological appropriateness as being "excellent" if the total score was equal to or higher than 9, "good" if the total score was equal to or higher than 8 and lower than 9, "adequate" if the total score was equal to or higher than 7 and lower than 8, and "limited" if the total score was lower than 7.

Two other authors independently assessed each study. In case of disagreement, the article was discussed with the leader author according to the COI study checklist until an agreement was reached.

Results

The systematic search identified 944 publications. A final sample of 24 studies[23,24,28-49] remained for inclusion in the review, according to the inclusion and exclusion criteria. The article selection process, based on the PRISMA recommendations,[25] is shown in the flow chart in Figure 1.

The review was thus conducted on 24 studies, most of which concerned observational real-world data analyses,[23,24,28,30,33-49] whereas 3 studies were model-based analyses.[29,31,32] These studies can be divided into 3 categories: (1) studies evaluating the total annual cost of AF at the national level, (2) studies assessing the AF average annual cost per patient, and (3) studies evaluating the AF average monthly cost per patient.

As indicated in section 2.4, we assessed the methodological quality of the studies included in the review using a 10-item checklist (Table B1 in Appendix B in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.12.015).

Tables 1[28-31] and 2[23,24,32-49] report the main cost indicators of AF obtained in the analyzed studies. Table 1[28-31] considers the studies evaluating the total annual costs of AF at the national level, whereas Table 2[23,24,32-49] summarizes the main cost data of the studies that calculates a yearly or monthly cost per patient. In Appendix C in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.12.015, Table C1 reports the main

Figure 1. PRISMA flow chart of the study selection process.

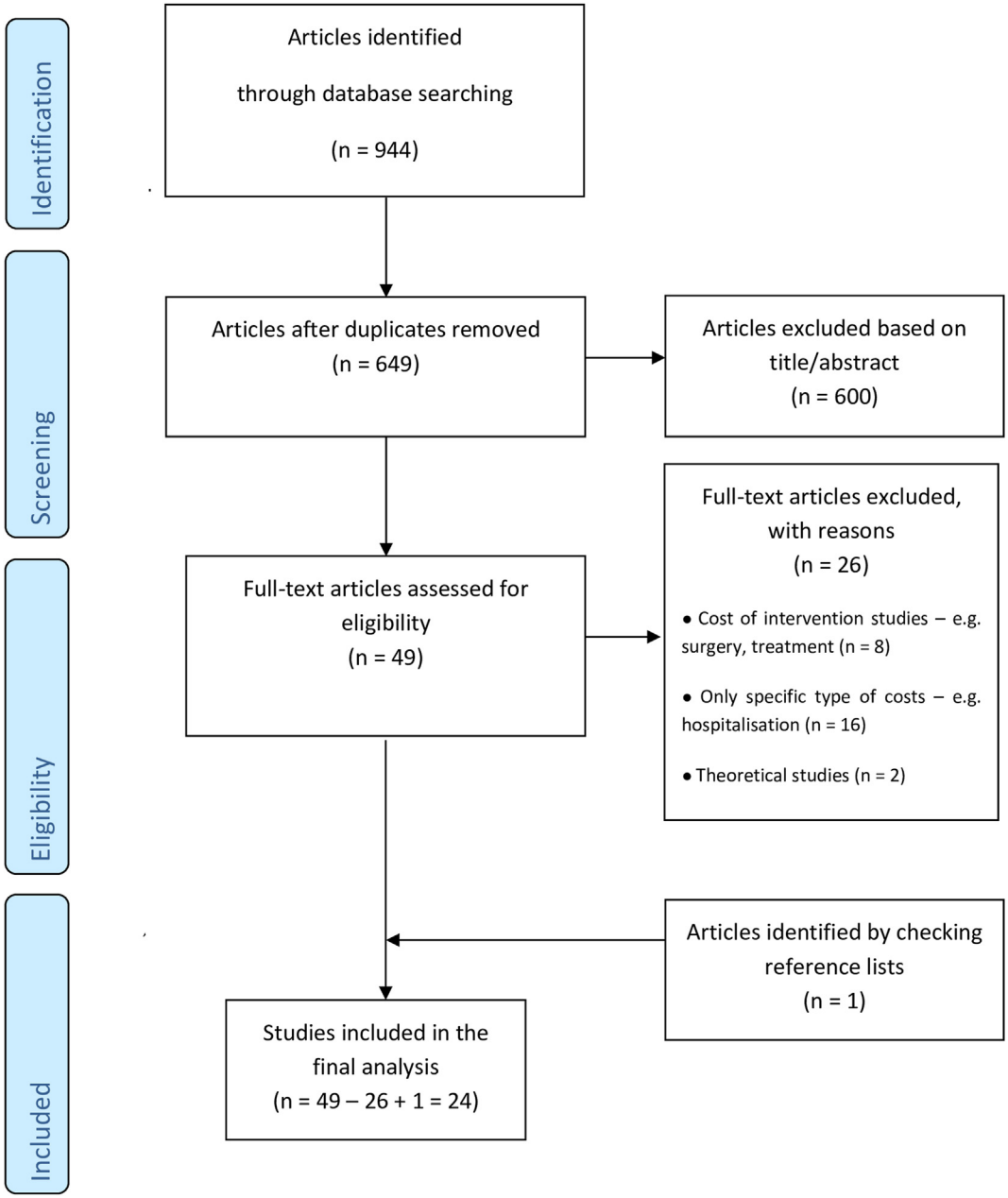

Table 1. Total costs, direct medical costs, direct non-medical costs, and indirect costs of studies evaluating total annual costs of AF at national level.

Author. No Ref. Journal. Year, Country	Year and currency of costs	Costs within total costs	Cost indicators	Total costs (€ at current prices in brackets)
Stevens et al.[28] *Archivos de Cardiologia de Mexico.* 2018. Mexico	2015 Pesos	Total costs include Health system costs (hospitalization), Productivity losses, Income forgone by individuals, Income forgone by businesses, Opportunity cost of informal care by family/ friends, tax revenue forgone by government.	Total annual costs at national level.	Mex$ 8357 million (€584.75 million)
Gouveia et al.[29] *Revista Portuguesa de Cardiologia.* 2015. Portugal	2013 Euros	Inpatient, outpatient (includes direct medical costs (consultations, emergencies, diagnostic and therapeutic interventions, drugs, physiotherapy sessions, etc.), and direct non-medical costs (urgent and non-urgent patient transportation and institutionalization), productivity loss	Total annual costs at national level.	Attributable to AF: €140.7 (161.2) million
Ericson et al.[30] *European Journal of Health Economics.* 2011. Sweden	2007 Euros	Societal Direct medical (hospitalizations, hospital outpatient care, primary health care, non-pharmacological interventions, pharmaceuticals, and anticoagulation monitoring) and non-medical (transportation associated with health care visits) costs of AF, direct costs of AF complications (stroke and heart failure), and indirect costs (production loss), were included	Total annual costs at national level.	€708 (944.4) million: €293 (391) million of AF and €415 (553.4) million of complications (58.6% of total costs)
Heemstra et al.[31] *Netherlands Heart Journal.* 2011. The Netherlands	2003-2004 Euros	Direct medical costs (diagnostics, interventions, drug therapy, consultations, inpatient care) and indirect costs (work loss)	Total annual cost national level.	€583 093 264 (€843,27 million) based on the mean annual costs of €2328 (€3367) per patient for AF, calculated in: Ringborg A., Nieuwlaat R., Lindgren P., et al. Costs of atrial fibrillation in 5 European countries: results from the Euro Heart Survey on atrial fibrillation. Europace. 2008;10(4):403-11

Note. Currency exchange rates as of 28 December 2022.
AF indicates atrial fibrillation; PPP, purchasing power parity.

characteristics of the studies, Table C2 describes the composition of direct medical costs and of the costs of complications and adverse events calculated in the studies, and Table C3 summarizes the main findings and limitations of the studies.

The studies included in our review were mainly conducted in Europe (12 studies)[23,24,29-33,35,36,38,41,42]—considering 10 countries: Germany,[24,42] The Netherlands,[31,41] United Kingdom,[32,33,38] Italy,[36,41] Denmark,[35] Spain,[23] Sweden,[30] Portugal[29] Greece,[41] and

Table 1. Continued

Direct medical costs at current prices	Direct medical costs at current prices converted into € (US$ PPPs in brackets)	Direct non-medical costs (€ at current prices in brackets)	Indirect costs (€ at current prices in brackets)
Mex$ 11 726 million	567 471 000 (1 127 519 590)	-	Productivity losses 3.0% of total cost; Mex$246 (€17.28) million: a) Income forgone by individuals Mex$143 (€10.05) million, b) Income forgone by businesses Mex$73 (€5.13) million, c) Tax revenue forgone by government Mex$30 (€2.10) million
€132 160 519	132 160 519 (237 698 775)	-	Attributable to AF: €2529 million, 17.9% of total cost (73% attributable to complications caused by stroke)
€795 940 320		€28.01 (36.83) million, 3.9% of total cost	€83.29 (111.63) million, 11.7% of total cost (37% attributable to complications caused by stroke and heart failure)
€701 758 118	701 758 118 (918 531 568)	-	€97,96 (141.5) million 16.8% of total cost

Poland[41]—and in the United States (10 studies),[34,37,39,40,43-47,49] whereas 2 studies were conducted in Mexico[28] and Canada.[48]

The studies adopted different perspectives on cost evaluation. Eight studies adopted a societal point of view, considering also the indirect costs related to AF.[23,28-31,35,42,43] Sixteen studies adopted the payer perspective; of these, 9 studies, related to the United States, considered the private and public third-party payer perspective,[34,37,39,40,44-47,49] 5, conducted in Europe,

Table 2. Total costs, direct medical costs, direct non-medical costs, and indirect costs of studies evaluating the AF average annual costs per patient.

Author. No Ref. Journal. Year, Country	Year and currency of costs	Costs within total costs	Cost indicators	Total costs	Direct medical costs at current prices	Direct medical costs per year at current prices converted into € (US$ PPPs in brackets)	Direct non-medical costs (€ at current prices in brackets)	Indirect costs (€ at current prices in brackets)
Burdett and Lip.[32] *European Heart Journal - Quality of Care & Clinical Outcomes.* 2022. UK	Pounds	GP consultations cost, GP referred OPD visits cost, prescriptions and monitoring visits cost, primary admissions cost, post-discharge OPD visits cost, nursing home care, additional hospital admissions (secondary diagnosis AF), hospital admissions (secondary diagnosis), days of long-term nursing care.	Mean annual cost per patient. Costs from 2020 onward assumed to increase at annual rate of 3%/year; and the UK inflation rate to increase by 2% annually	Average cost per AF patients: 2010: £2832. 2020: £3731. 2030: £4548. 2040: £5544.	£4273	4832 (5622)	-	-
Ciminata et al.[33] *BMJ Open.* 2020. Scotland	2013-2014 Pounds	Inpatient, outpatient, prescribing and care home costs	Mean annual costs per patient	mean annual cost for a patient with AF: £3785 Male: £3669. Female: £3968	£4736	5355 (6232)	-	-
Casajuana et al.[23] *European Journal of Health Economics.* 2018. Catalonia, Spain	2012 Euros	PHC visits, hospital admissions, referrals, diagnostic test, laboratory test, all drugs dispensed, sick leave (indirect costs).	Mean annual cost per patient.	€3170.7	€3521	3521 (5367)	-	Sick leave: €136.9 (161); 4.4% of total cost
Delaney et al.[34] *SAGE Open Medicine.* 2018. US	2009 US Dollars	Costs included all sources of payment from Medicare Parts A and B for expenses incurred in treating participants, including inpatient hospitalizations, physician visits, skilled nursing facility care, and hospice care.	Mean annual cost per patient in follow-up year (estimates of difference in cost between pre-event year and follow-up year per patients diagnosed with atrial fibrillation (AF) compared with matched referents free of AF).	$25 674 (CHS cohort: $18 060. FHS cohort $20 717)	$34 829	32 739 (34 829)	-	-
Johnsen et al.[35] *BMC Health Services Research.* 2017. Denmark	2013 Euros	Primary sector costs, outpatient costs, hospital admission costs, medicine costs, home care costs, productivity loss (total and attributable costs).	Mean annual cost per patient (based on calculation of 3-year cost per patient)	Total: €10 718.7 Attributable: €7626	€9481	9481 (13 840)	-	Productivity loss Total: €2844.3 (3727); 26.5% of total cost. Attributable: €392 (513.7); 5.1% of total cost
Zoni Berisso et al.[36] *European Review for Medical and Pharmacological Sciences.* 2017. Italy	2015 Euros	Hospitalizations for AF, hospitalizations for Ischemic stroke, ECG Holter recordings, exercise stress tests, echocardiograms, cardioversions, electrophysiologic study, pacemaker implants rhythm control, rate control, transcatheter ablation	Mean annual cost per patient (3 different scenarios)	€613, €891, and €1213 for the "Low-cost," "Medium-cost" and "High-Cost Clinical Scenario," respectively	€741.15 €1077.27 €1466.58	741.15 (1090) 1077.27 (1584) 1466.58 (2157) Average: 1.095 (1.610)	-	-
Turakhia et al.[37] *American Journal of Cardiology.* 2015. 2015. US	2014 US Dollars	Direct medical costs included inpatient medical, outpatient medical and pharmacy costs (AF-related, other cardiovascular, and non-cardiovascular costs)	Mean annual cost per patient	<65 years: $38 861. ≥65 years: $25 322	$47 775	44 908 (47 775)	-	-
Kassianos et al.[38] *Drugs Context.* 2014. UK	2011 Pounds	Investigations (ECG, Holter ECG, ECHO, and CXR) blood testing AF-related primary care visits AF-related secondary care visits (outpatient, day case, A&E) AF-related inpatient admissions	Mean 12-weeks cost during initiation phase and mean annual cost during maintenance phase	initiation phase: £941 maintenance phase: £426	Init.: £1240 Maint.: £561	Init.: 1402 (1632) Maint.: 635 (738)	-	-
Reinhold et al.[24] *Europace.* 2011. Germany	2015 Euros	Inpatient, drugs, remedies, adjuvants, sickness benefits, outpatient	Mean annual cost per patient (year after first AF documentation).	€7688	€9337	9337 (12 826)	-	-

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Table 2. Continued

Author. No Ref. Journal. Year, Country	Year and currency of costs	Costs within total costs	Cost indicators	Total costs	Direct medical costs at current prices	Direct medical costs per year at current prices converted into € (US$ PPPs in brackets)	Direct non-medical costs (€ at current prices in brackets)	Indirect costs (€ at current prices in brackets)
Amin et al[39] *Advances in Therapy.* 2011. US	2007 to 2008 US Dollars	Overall mean costs over the 12-month post-index period in the AF/AFL patients with ≥1 ARF: inpatient costs; outpatient costs; prescription drug costs	Mean annual cost per patient in the year after index (incremental cost differences between AF/AFL patients with ≥1 ARF versus the non-AF/AFL control patients)	$22 490	$31 568	29 676 (31 568)	-	-
Kim et al.[40] *Circulation: Cardiovascular Quality and Outcomes.* 2011. US	2008 US Dollars	Inpatient (hospitalization including death), outpatient medical (emergency department visits, physician visits, laboratory services, and other outpatient services), outpatient pharmacy	Mean annual costs per patient in the year after index (incremental cost in AF patients)	$20 670 ($8705)	$27 941	26 267 (27 941)	-	-
Holstenson et al.[41] *Europace.* 2011. Greece, Italy, Poland, Spain, The Netherlands	2007 Euros	costs of diagnostics (transthoracic and transesophageal echocardiography, chest X-ray, Holter monitoring, exercise tests, electrophysiology, and event recorders), interventions (CABG, cardiac valve replacement, catheter ablation, pacemaker implantation, implantable cardioverter-defibrillator implantation, surgical therapy, and PCI), drug therapy (vitamin K antagonist treatment, other antithrombotic treatments, and antiarrhythmic/rate control treatments), consultations, and inpatient days incurred during the year of follow-up.	Mean annual cost per patient.	€1401 in Greece, €3083 in Italy, €922 in Poland, €2118 in Spain, and €1977 in The Netherlands.	GR 1872.3 IT 4120.13 PL 1232.16 ES 2830.5 NL 2642.07	GR 1872.3 (3506) IT 4120.13 (6059) PL 1232.16 (1799) ES 2830.5 (4315) NL 2642.07 (3458)	-	-
Jönsson et al.[42] Applied Health Economics and Health Policy. 2010. Sweden, Germany	2005 Euros	Direct medical costs include costs for pharmacological treatment (antiarrhythmic and antithrombotic drugs, and other concomitant medications), outpatient visits and inpatient care. Direct non-medical costs include accommodation, home help, day care, transportation, and home-delivered meals. Indirect costs include costs deriving from early retirement, sick leave, reduced working time, and changes in work tasks	Mean annual cost per patient.	Sweden: €7241. Germany: €5586	SW 3270.89 GE 4589.08	SW 3270.89 (4775) GE 4589.08 (6304)	Sweden: €1646 (2310.7); 22.7% of total cost Germany: €295 (414); 5.3% of total cost	Sweden: €3265 (4583.5); 45.1% of total cost Germany: €2023 (2840); 36.2% of total cost
Rohrbacker et al.[43] *Journal of Occupational and Environmental Medicine.* 2010. US	2008 US Dollars	Adjusted medical costs, drug costs, sick leave costs and days, short-term disability costs, long-term disability costs, workers' compensation costs, objectively measured productivity	Mean annual cost per employee in the year after index (incremental cost in AF patients versus the control group)	$6961 ($3958)	$9049	8507 (9049)	-	Sick leave costs, days of disability and workers' compensation: $920 [€1295]); 13.2%of total cost

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Table 2. Continued

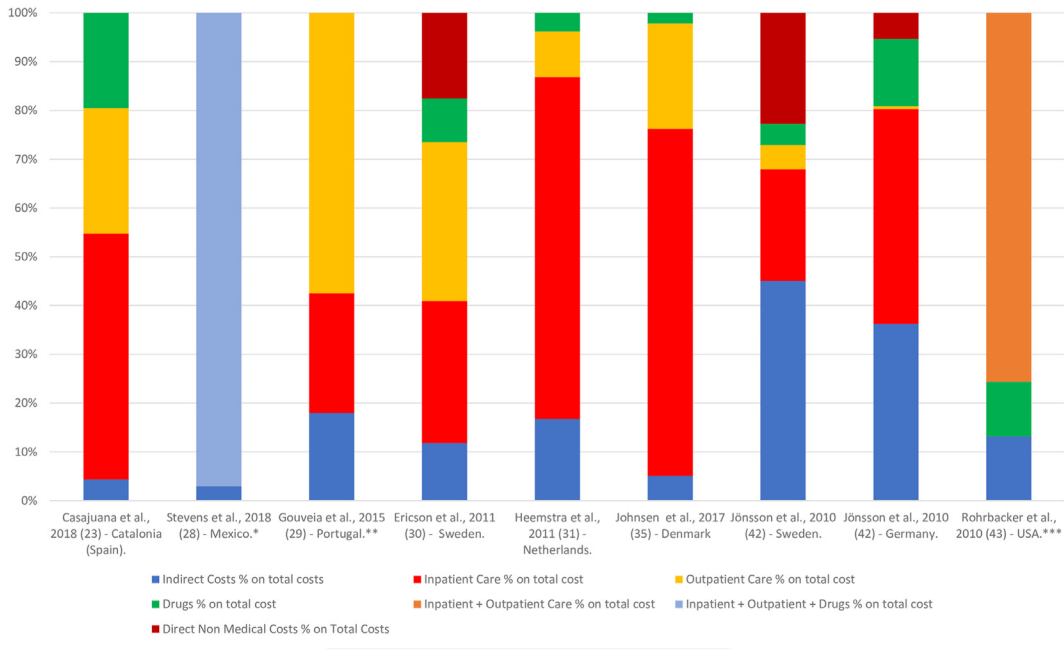
Author. No Ref. Journal. Year, Country	Year and currency of costs	Costs within total costs	Cost indicators	Total costs	Direct medical costs at current prices	Direct medical costs per year at current prices converted into € (US$ PPPs in brackets)	Direct non-medical costs (€ at current prices in brackets)	Indirect costs (€ at current prices in brackets)
Amin et al.[44] *Journal of Managed Care & Specialty Pharmacy.* 2020. US	2014 US Dollars	All-cause medical costs represent the sum of reimbursed costs for inpatient, outpatient (office, ER, and other outpatient costs), and other costs (durable medical equipment, skilled nursing facility, home health agency, and hospice costs); total healthcare costs represent the sum of All-cause medical and pharmacy costs.	Mean monthly cost per patient.	Total health care costs: Apixaban vs Warfarin: $3183 vs $3577. Apixaban vs Dabigatran: $3060 vs $3217. Apixaban vs Rivaroxaban: $3180 vs $3878.	$3913 vs 4397 $3762 vs 3955 $3909 vs 4768	Average annual cost: 46 446 (49 451)		
Chowdhury et al.[45] *Journal of Medical Economics* 2019. US	2017 US Dollars	Hospitalizations, outpatient visits, ER, pharmacy visits	Mean monthly cost per patient.	Dabigatran vs Warfarin: $3309 vs $3362. Dabigatran vs Rivaroxaban: $3285 vs $3474. Dabigatran vs Apixaban: $3192 vs $2986	$3929 vs 3992 $3900 vs 4125 $3790 vs 3545	Average annual cost: 43 774 (46 606)	-	-
Gilligan, et al.[46] *Current Medical Research and Opinion.* 2018. US	2015 US Dollars	Total healthcare costs, Inpatient, Outpatient, Emergency dept, Office visits, Other services, Pharmacy costs are specified.	Mean monthly cost per patient.	Dabigatran vs Warfarin: $4199 vs $4872. Dabigatran vs Rivaroxaban: $4093 vs $4636.	$5156 vs 5982 $5026 vs 5693	Average annual cost: 61 644 (65 632)	-	-
Jain et al.[47] *Journal of Managed Care & Specialty Pharmacy.* 2018 US	2012 US Dollars	All-cause medical costs (hospitalization, ER visits, physician office visits, outpatient visits), all-cause pharmacy costs, all-cause total costs. Stroke-related, myocardial infarction-related, bleed-related are specified.	Mean monthly cost per patient.	Dabigatran: $3151. Warfarin: $3221.	$3994 vs 4083	Average annual cost: 45 558 (48 505)	-	-
Bennell et al.[48] *Journal of American Heart Association.* 2015. Canada.	2013 Canadian Dollars	Three distinct cost phases were identified: 2-month post-index ED visit phase, 12-month predeath phase, and a stable/chronic phase. Per-episode cost for hospitalization, same-day surgery, emergency department, physician fees, medications, home care, long-term care.	Mean monthly cost per patient.	first month post-index $1876, month before death $8050, stable/chronic phase $640 per month.	(stable phase) $803.9	Average annual cost - stable phase: 6709 (11 866)	-	-
Ladapo et al.[49] *Journal of Cardiovascular Electrophysiology.* 2012. US.	2009 US Dollars	Medication expenditures, ambulatory care (office visits and hospital outpatient appointments), inpatient or emergency care (hospitalizations and emergency department)	Mean 6-months costs per patient (before and after ablation).	Before ablation: $11 861. After ablation: $9600.	$16 090 (b.a.) $13 023 (a.a.)	Average annual cost: 27 367 (29 137)	-	-

Note. Currency exchange rates as of 28 December 2022. AF indicates atrial fibrillation; ARF, additional risk factors; CABG, coronary artery bypass graft surgery; CHS, cardiovascular health study; CXR, chest x-ray; ECG, electrocardiogram; ECHO, echocardiography; ED, emergency department; ER, emergency room; FHS, Framingham Heart Study; GP, general practitioner; OPD, outpatient department; PCI, percutaneous coronary intervention; PPPs, purchasing power parities.

considered the perspective of public healthcare systems,[32,33,36,38,41] 1 considered the perspective of a German statutory health insurance plan,[24] and 1 considered the perspective of the province of Ontario in Canada.[48] As for the epidemiological approach, 11 studies[23,24,33-35,43-48] used incident cases, and 13 calculated the costs based on prevalent cases.[28-32,36-42,49] The data on the costs faced in relation to the treatment of AF were derived in different ways in the included studies; 4 studies calculated only the annual cost at the national level,[28-31] 14 the mean annual cost per patient,[23,24,32-43] 5 the mean monthly cost per patient,[44-48] and 1 the mean 6-month cost per patient.[49]

Several studies included comorbidity analyses, but only a few cost estimates incorporated detailed measurements of

Figure 2. Percentage distribution of annual costs of atrial fibrillation in the studies adopting a societal perspective.



Notes:
* The study by Stevens et al. (28) does not specify the single components of direct costs.
** The study by Gouveia et al. (29) does not specify the costs of medication within the direct medical costs.
*** The study by Rohrbacker et al. (43) quantifies a weight of health care services on total costs of 75.6% without differentiating between inpatient and outpatient care.

comorbidities and their effects on costs.[33,39,41,42,48] Some studies enrolled a hospital-based sample,[29,30,33,48,49] whereas several enrolled patients at the primary care level. Three studies only enrolled patients undergoing specific drug treatments[44,46,47] to compare the costs of illness according to specific pharmaceutical therapies.

Among the 24 studies included,[7,23,24,36-38,41,42] considered only costs exclusively related to AF, whereas 14 studies[28-34,43-49] considered all healthcare costs for an AF patient. Three studies,[35,39,40] in addition to all healthcare costs for an AF patient, calculated also the "attributable" costs of AF, that is the increase in costs that is attributable solely to the presence of the disease, using a matched control/regression approach typically considered in COI studies.

Indirect Costs

All 8 studies adopting a societal perspective[23,28-31,35,42,43] measured the indirect costs related to AF using a human capital approach. In these studies, the percentage weight of direct medical costs on the total cost ranged from a minimum of 32.2%[42] to the highest values of 95.7% and 97%.[23,28] Jönsson et al (2010)[42] included in the indirect costs those derived not only from productivity losses due to reduced working time but also from early retirement and changes in work tasks and found that a large amount of the costs related to AF derived from indirect costs (45.1% in Sweden and 36.2% in Germany). In contrast, the other studies[23,28] considered only productivity loss and sick leave from work as indirect costs, with the result being that only a very small percentage of the total cost (3% and 4.4%, respectively) depended on indirect costs, whereas almost the entire cost was from direct medical costs. Indirect costs represented a minor (although variable) proportion of the total annual costs, ranging from 5.1% to 17.9% in the other 5 studies[29-31,35,43] that evaluated mainly sick leave, production and work loss as the indirect burden due to AF. It is worth highlighting that none of the studies considered informal caregiving within indirect costs and that, in these studies (except for the study by Rohrbacker et al,[43] which concerned an employed population), indirect costs were averaged over all patients, employed or not, whereas these costs are only incurred by the employed population; therefore, the average indirect costs per employed person would be even higher.

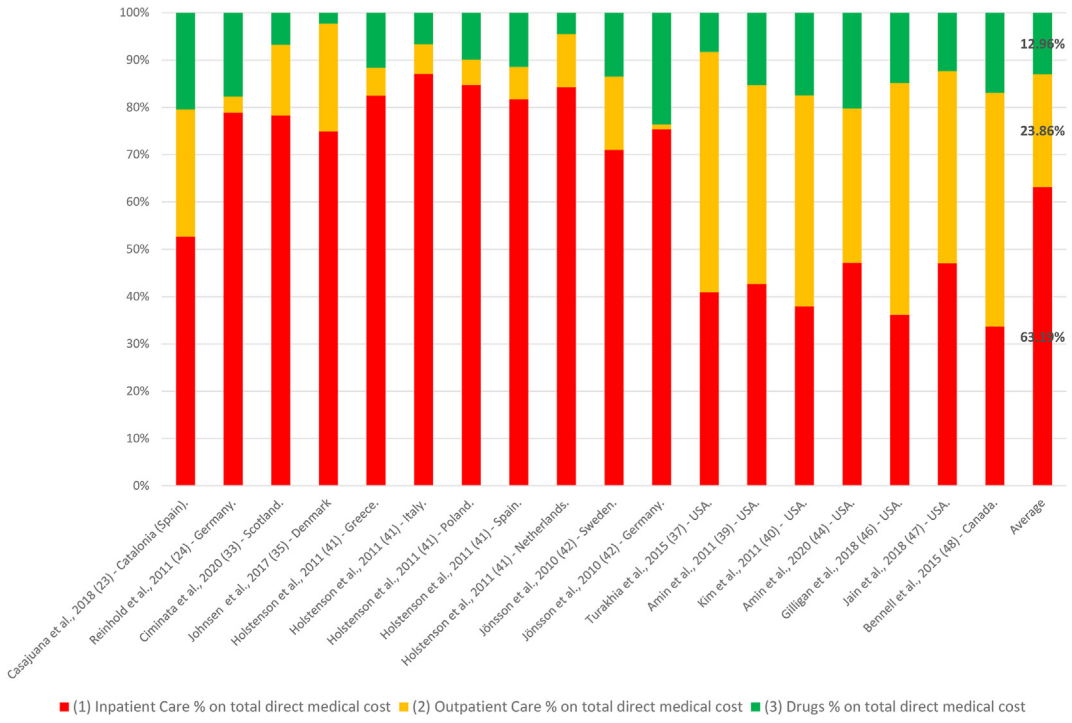
Figure 2 reports the composition of annual costs in the 8 studies adopting a societal perspective and shows that in almost all studies (the analysis on Sweden by Jönsson et al (2010)[42] is the 1 exception) costs were mainly driven by direct medical costs and in most cases by inpatient care. Only 2 studies in Sweden and Germany[30,42] measured direct non-medical costs, such as transportation associated with hospital and primary healthcare center visits, accommodation, home help, daycare, and home-delivered meals.

Direct Medical Costs

Among the analyses that calculated a yearly or monthly cost per patient (Table 2[23,24,32-49]), 13 studies measured all 3 main items of medical direct costs, namely, inpatient care, outpatient care services, and pharmacy costs.[23,24,33,35,37,39-42,44,46-48]

Overall, in 9[23,24,33,35,39,41,42,44,47] out of 13 studies, inpatient care costs (including interventions) had the greatest weight on the mean direct medical cost per patient, whereas in 4 studies conducted in the United States[37,40,46] and Canada (for patients in the stable/chronic phase),[48] the main cost component was given by outpatient costs (Fig. 3). In 1 study[37] only patients aged >65 years reported outpatient care as the larger portion of costs, whereas for patients <65 years, the larger portion of costs was because of inpatient care. The percentage weight of inpatient care on the total direct medical cost ranged from a minimum of 36.1%, for patients aged 65 years or older in the United States,[37] to a maximum of

Figure 3. Proportion of different cost items in the studies with a complete analysis of medical direct costs of atrial fibrillation.



87.1% in Italy.[41] The very high incidence of inpatient care costs in the latter study depended on the overrepresentation of patients enrolled at highly specialized centers that admitted only more severely ill patients, followed up with more sophisticated procedures, with higher costs and a higher hospitalization rate.

The share of outpatient care costs on the total direct medical cost was the lowest (3.5%) in Reinhold et al (2011)[24] because of the design, which consisted of a population-based cohort with a sampling method that included only hospitalized patients. Conversely, Turakhia et al (2015)[37] reported a higher proportion of outpatient care costs (63.9%) on the yearly direct medical cost for patients aged >65 years, using a claims-based sampling method and involving both hospitalized and not hospitalized patients.

The share of costs related to medication ranged from a minimum of 2.2% of the annual average direct medical cost per patient[35] to a maximum of 25.1%,[44] which considered patients treated with apixaban. In this last study, the percentage share of drugs on total direct costs was reduced to 20.5% for patients treated with dabigatran and 10.3% for patients treated with warfarin.

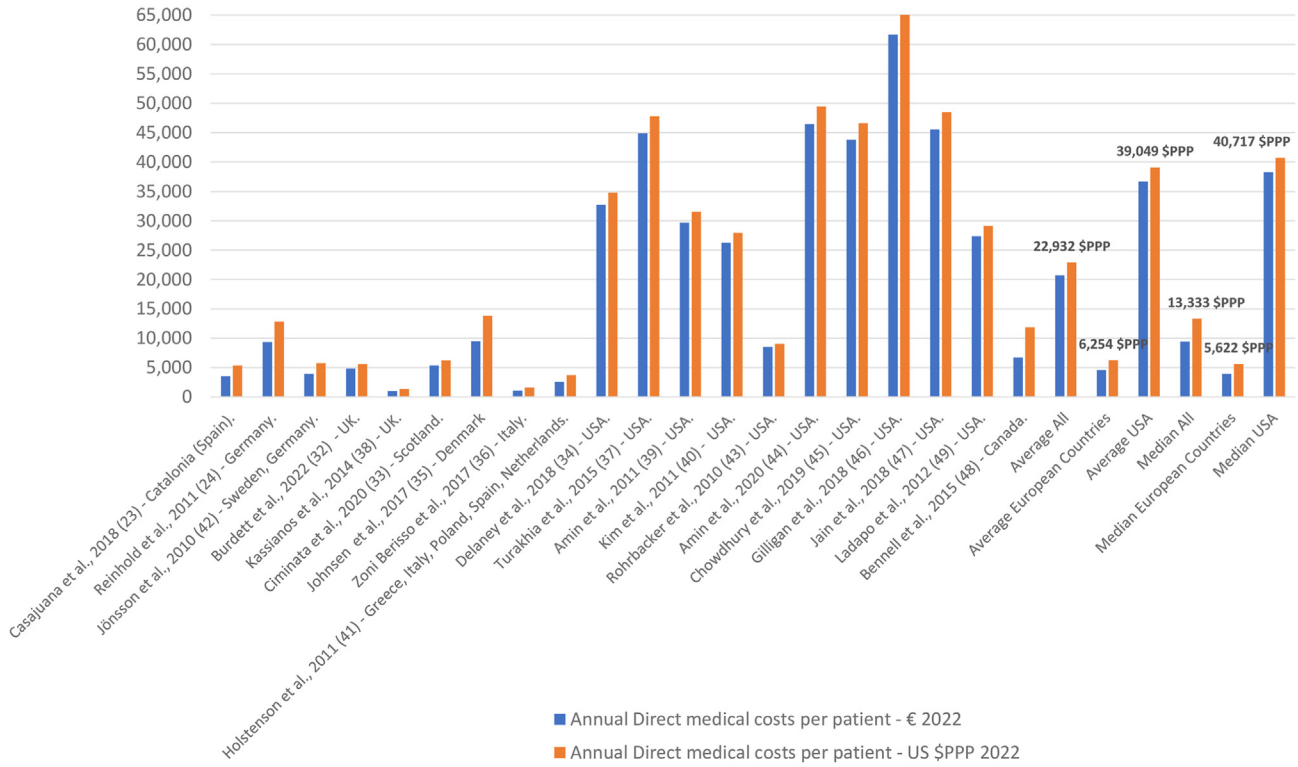
Among the studies considered in this systematic review, 4 analyzed the direct medical costs of AF associated with different pharmacological strategies[44-47] as part of a full range of direct costs of AF (even if they did not measure any indirect cost). From the 4 studies covered by this analysis, warfarin-based drug therapy, in all cases, resulted in higher average individual monthly costs when compared with therapies using novel oral anticoagulants (NOACs). This cost difference was because NOACs do not require frequent laboratory tests to monitor coagulation and consultations for the possible adjustment of doses, which would have been needed for safe warfarin administration.[47] Second, the higher risk of hospitalization because of stroke/systemic embolism and major bleeding-related conditions with warfarin determines the difference in costs.[44] Among the 2 studies evaluating apixaban, this drug was the NOAC with the lowest individual average monthly cost.[44,45]

Only a few studies took into account and calculated the cost of home care separately from other cost items.[32-35,48] This particular component of costs ranged from 2.8% of the monthly direct cost per patient[48] (but only in the first month after the initial emergency department diagnosis of AF; in the stable phase, it was 6.4%) to 11.2%.[35]

Five studies[33,39,41,42,48] analyzed particularly noteworthy factors influencing the medical costs of AF, presenting in-depth analyses to estimate the extent to which the comorbidities and the complications related to AF could lead to increased costs. Ciminata et al (2020)[33] considered patients hospitalized with a known diagnosis of AF or atrial flutter in Scotland and found that the average annual cost per patient (in particular the inpatient component) increased considerably with the number of comorbidities ranging (at current prices) from about €3660 (US$ PPPs 4815) (no comorbidities) to €4487 (US$ PPPs 5904) (+23% with 1 comorbidity) and €6136 (US$ PPPs 8074) (+68% with more comorbidities). Similarly, Amin et al (2011)[39] showed that the yearly cost per patient increased with the Charlson Comorbidity Index (CCI) score; as the CCI score increased, from 1-2 to >5, so did the costs: +30% for inpatient care, +28% for outpatient care, and + 70% for prescription drug costs. Bennell et al (2015)[48] found that the monthly per-patient cost was significantly higher for patients who had a history of diabetes mellitus, congestive heart failure (CHF), hypertension, and renal or liver dysfunction; they also showed that the CHA_2DS_2-VASc clinical risk score was a particularly strong predictor of higher healthcare costs.

Jönsson et al (2010)[42] found that the comorbidities with the most significant impact on costs were cerebrovascular disease (increasing total medical costs by 80%), coronary artery disease

Figure 4. Annual direct medical costs per patient with atrial fibrillation (in Euros 2022 and US $PPP 2022).



(+51%), heart failure (+50%), and asthma (+26%). The study by Holstenson et al (2011)[41] primarily aimed to analyze the costs associated with cardiovascular disease among patients with AF in 5 European countries (Greece, Italy, Poland, Spain, and The Netherlands). The comorbidities identified as determinants of higher average annual direct costs were valvular heart disease (VHD) in Greece, Italy, and Spain, angina pectoris (AP) in Italy and Spain, stroke and diabetes in Poland, CHF in Italy, heart attack (MI) in Spain, and other minor heart diseases in Poland and The Netherlands. In the Italian cohort, for example, VHD, CHF, and AP generated an increase in the average annual direct cost per patient (evaluated at current prices) of 1955 (+47%), 2654 (+64%) and 2982 (+72%) Euros (ie, US$ PPPs 2875, 3903, and 4385), respectively. Hence, it became evident that the monitoring and management of comorbidities are issues closely related to the total cost of AF.

Three studies[35,39,40] analyzed the costs "attributable" to AF. Attributable costs are obtained through the propensity score matching technique from the difference between the total cost calculated for a cohort of patients with the disease and the total cost calculated for a control cohort consisting of patients not affected by the disease but sharing the same characteristics (age, gender, comorbidities, etc.) as the affected patients; thus, the costs attributable to AF were derived without risk of bias due to the intrinsic characteristics of the sample (mainly elderly and co-morbid patients). In the 3 studies, the proportion of attributable costs to the total cost ranged from 42.1% to 71.1%. In the study by Johnsen et al (2017),[35] attributable costs accounted for 71.1%; in Amin et al (2011),[39] they accounted for 54.9% in the first post-diagnosis year. In the study by Kim et al (2011),[40] they accounted for 42.1%.

Figure 4 reports the annual direct medical costs per patient in the studies which calculated a yearly or monthly cost per patient. The mean annual direct medical cost per patient adjusted for the inflation rate (ie, at current prices) ranged from the lower levels of €741 (US$ PPPs 1090) in the study by Zoni Berisso et al (2017)[36] for Italy (considering a "low-cost clinical scenario") to a maximum of €61 644 (US$ PPPs 65 632) in the study by Gilligan et al (2018)[46] for the United States. Considering all studies, the median annual direct medical cost per patient was €9409 (US $ PPPs 13 333), whereas the mean was €20 735 (US $ PPPs 22 932), signaling a distribution of reported costs skewed to the right because of the presence of outliers referring to US-based studies.[37,44-47]

Discussion

Main Findings

The present review shows that in the studies adopting a societal perspective (including both direct and indirect costs), the direct medical costs generally far exceeded the indirect costs. Focusing on the direct medical costs, the main cost driver was hospitalization (inpatient care), whereas in almost all studies, the cost of medications was the one with the least impact on overall cost, with variability that mainly depends on the different prices of drugs, which are higher in the United States, whereas in most European countries, the drugs are generally reimbursed after negotiating substantial discounts with the pharmaceutical companies. Drug costs may differ due to different clinical characteristics of patients and different choices in prescribing drugs (eg, the type of comorbidity and its clusters or the type of anticoagulant therapy, oral or otherwise).

The substantial variability in direct medical costs may also be largely related to the different composition of the samples of patients analyzed; samples only of patients who have been

hospitalized differ from population-based samples, resulting in higher inpatient costs in the former case, as well as by a selection of patients more affected by comorbidities and in worse clinical conditions. However, these findings align with those of previous systematic reviews on the cost of illness of AF.[20-22]

The median annual direct medical cost per patient, considering all studies, was €9409 (US $ PPPs 13 333), with significant variability due to the heterogeneity of different analyses (Fig. 4). This observed variability in the annual costs per patient depended not only on the particular characteristics of the design and the population in different studies (eg, population-based sampling only of patients who have been hospitalized versus primary care sampling, implying the enrolment of patients with different levels of illness severity or with a different distribution of comorbidities) but also, and to a very significant extent, on the different country and institutional context in which each study was conducted. Moreover, a marked difference emerged between European countries and the United States: the median annual cost per patient found in the studies considering European countries was substantially lower than that found in the studies related to the United States, namely, €3930 (US $ PPPs 5622) compared with €38 256 (US $ PPPs 40 717).

As shown in the previous section, 5 of the analyzed studies[33,39,41,42,48] highlighted that comorbidities (in particular, stroke, CHF, and diabetes) considerably increase the annual direct medical cost of AF. Multimorbidity is a growing occurrence globally, particularly in high-income countries; in many European countries, the percentage of people aged 50 years or older living with multimorbidity was estimated to be between 40% and 60%[50] and complex multimorbidity (comprising at least 3 chronic conditions affecting at least 3 body systems) is increasing.[51] This phenomenon is caused by population aging and puts a strain on healthcare systems and public finances, especially because the treatment of multimorbidity is more expensive and complex than curing single diseases.[52]

According to a recent systematic review on costs of multimorbidity, the concomitant cardiac/vascular pathologies (including AF and diabetes) are among the most expensive conditions, with an average annual direct medical cost per patient of 37 090 international dollars (2021); that is, a value close to €35 000.[53] Comorbidity is thus a major public health problem that needs to be urgently addressed with regard to the correct quantification of the costs associated with AF. To this end, it might be appropriate to identify clusters of such "clinically complex" patients characterized by different comorbidities and significantly different use of healthcare resources, considering also associated polypharmacy.[54,55] It is also necessary to rethink the models of care and patient management. In that sense, many projects have been developed to promote effective guidelines, paying particular attention to an individualized management plan to improve quality of life by reducing treatment burden, adverse events, and unplanned care and to improve coordination of care across services.[56-59] Guidelines to comprehensively manage comorbidity is a necessary step to reduce costs related to the treatment of AF, given its greater prevalence in old age. A holistic or integrated care approach is likely to be needed for AF patients with multimorbidity, given the improved outcomes by adherence to such a management pathway.[60,61] The Atrial Fibrillation Integrated Approach in Frail, Multimorbid, and Polymedicated Older People (AFFIRMO), is an ongoing European project involving 8 countries, that includes a randomized clinical trial, with its main purpose being to assess the effectiveness of an integrated care model for the treatment and care of older persons with AF and comorbidity.[62,63]

Regarding the costs attributable to complications,[29,30] such costs are responsible for a significant part of the total cost of AF (last column of Table C2 in Appendix C in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.12.015). Gouveia et al (2015)[29] found that of the €140.7 million estimated to be the total annual cost of AF in Portugal, based on prevalent cases in 2011 (€161.2 million at current prices), about 50% were attributable to the management of thromboembolic strokes, the main and most serious complication of AF. Ericson et al (2011)[30] estimated that of the €708 million total cost per year of AF in Sweden (€944.4 million at current prices), based on prevalent cases in 2007, about 58.6% was related to the management of thromboembolic stroke and heart failure. Hence, a large share (more than a half) of the total cost of AF is due to the control of pathologies that originated as complications, in particular thromboembolic stroke, which itself represents a condition with significant costs that often requires long periods of hospitalization and rehabilitation, generating a loss of productivity due to frequent residual disability or early death.[64] Another complication affecting costs is major bleeding (MB) associated with anticoagulant therapy, although only 1[46] of the few studies that have addressed this issue[44-47] has analytically quantified the effect of MB on costs highlighting a limited impact on the total cost of treatment (from 2.3% with dabigatran to 4.4% with warfarin).

Four studies focusing on total AF costs in specific subgroups of patients defined according to the adopted drug therapy[44-47] have shown that NOAC-based therapies (and in particular apixaban) resulted in lower total healthcare costs per patient compared with warfarin-based drug therapy. The results of these analyses must be interpreted with caution because they were studies funded by pharmaceutical companies involved in the provision of NOACs; however, even other studies not funded by pharmaceutical companies confirmed this evidence.[65-67] Moreover, it is essential to recognize that the variation in cost profiles between the 2 treatment options could also be based on a set of covariates that predict the probability of an individual being assigned to a particular treatment, for example, age profiles.[68] Therefore, the age distribution of patients in each treatment group may play a role in determining the observed cost differences. Further research and analysis are needed to fully understand the multiple aspects influencing the cost dynamics between warfarin and NOACs in the management of AF.

To address the economic burden of AF, it is also important to understand which therapeutic procedures may reduce the average annual cost of patients with AF.[69] In this regard, 1 of the studies included in this systematic review, by Ladapo et al (2012),[49] analyzed how the direct costs related to the treatment of AF vary following transcatheter ablation, a minimally invasive procedure. Individual average direct costs were calculated for 6-time intervals of 6 months each, including 1 related to 6 months before ablation and 5 related to 6 to 12, 12 to 18, 18 to 24, 24 to 30, and 30 to 36 months after the intervention. Compared with 6 months before ablation, in the entire sample population, there was a significant reduction in the number of outpatient visits, hospitalization days, and emergency department visits, resulting in decreased total healthcare expenditure in 4 of the 5-time intervals analyzed and annual savings derived from the intervention between 20% and 57% of the total annual cost.

Strengths and Limitations of the Analysis

Our review provides useful and updated information on the economic burden that AF has on society and health systems in a wide variety of countries and identifies the main cost drivers of the disease.

The main limitation of this systematic review was the considerable heterogeneity among the included studies. They varied significantly in perspectives, objectives, analyzed

populations, years of evaluation, and the intrinsic characteristics of the countries concerned (eg, demography, social and health services offered, and types of healthcare system). Not all studies considered the same types of costs. For example, 2 studies did not explicitly calculate inpatient care costs as direct medical costs.[45,49] It is therefore desirable to implement guidelines to standardize methods and study designs for COI studies to facilitate a better comparison of the studies in future revisions and also to address methods for evaluating the costs attributable to AF condition in patients with complex multimorbidity.

Studies may have conscious or unconscious biases related to their funding sources; for instance, a study funded by an AF charity may have an unconscious bias to reinforce a high cost of AF; or a study funded by a pharmaceutical company may wish to maximize the cost of any complications that are prevented by a drug to maximize its benefits.[70] This may be less of an issue for this study because the review omitted pure cost-effectiveness studies, in which there is evidence of potential biases associated with funding sources.

Directions for Future Research

In light of the present literature review, future research in the field of cost assessment of AF has considerable potential to improve the design of analysis methods that consider the implication that the burden of comorbidities has on the costs of patients with AF. Furthermore, to assess the economic burden of AF comprehensively, studies should include population cohorts derived from the recruitment of both hospitalized and non-hospitalized patients with AF. Moreover, by recruiting incident cases, researchers could provide an estimate of the change in the costs of the disease in the years after diagnosis.

Conclusion

Inpatient care (hospitalization) costs are generally the main cost drivers in cases of AF, whereas pharmaceutical costs generally represent a limited proportion of the direct medical costs. The presence of comorbidities and complications, such as stroke, considerably increases the average annual direct medical cost of AF. Stroke and heart failure account for a substantial portion of the total costs; therefore, implementing guidelines to manage comorbidities in AF is a necessary step to improve health and mitigate healthcare costs.

Author Disclosures

Links to the disclosure forms provided by the authors are available here.

Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2023.12.015.

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