



Systematic review of societal costs associated with stroke, bleeding and monitoring in atrial fibrillation

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Aim: Economic consequences associated with the rise in nonvitamin K antagonist oral anticoagulant use on a societal level remain unclear. **Materials & methods:** Evidence from the past decade on the societal economic burden associated with stroke, bleeding and international normalized ratio monitoring in atrial fibrillation was collected and summarized through a systematic literature review. **Results:** There were 14 studies identified that reported indirect costs, which were highest among patients with hemorrhagic stroke and intracranial hemorrhage. The contribution of indirect costs to the total was marginal during acute treatment but substantially increased (30–50%) 2 years after stroke and bleeding events. **Conclusion:** Limited data were available on societal costs in atrial fibrillation and further research is warranted.

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Keywords: atrial fibrillation • costs • indirect costs • INR monitoring • major bleeding • stroke • systematic review

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is associated with a four- to five-fold increase in the risk of stroke [1–3]. The increasing prevalence of AF is attributed to the aging population [4,5]. This has resulted in the growing awareness of the disease burden and, consequently, the adoption of interventions to diagnose and prevent the devastating consequences of stroke. The development of novel oral anticoagulants (NOAC), including nonvitamin K antagonists (VKA), to prevent stroke among patients with nonvalvular AF (NVAf) represents one of the major breakthroughs in medicine over the last decade [6]. NOACs have demonstrated similar or superior efficacy paired with a lower risk of major bleeding as compared with VKA [7–11]; they do not necessitate the frequent monitoring and dose titration required by patients treated with VKA to ensure that the international normalized ratio (INR) is within therapeutic range (INR 2.0–3.0). Patients outside this range are at an increased risk of stroke and bleeding [11], leading to a greater number and longer durations of hospitalizations as well as increased disability and mortality [12]. These complications are associated with a high economic burden to societies and healthcare systems [13].

Since the introduction of NOACs, a proliferation of research on their efficacy and safety [7–10], effectiveness [14], affordability [15,16] and cost-effectiveness [17] has been conducted. Much of the economic evaluations and Health Technology Assessments (HTA) of NOACs has focused on direct medical costs [17,18], with limited consideration of indirect costs, raising questions on whether NOACs are being undervalued [16]. The debate on which perspective to consider to ensure optimal resource allocation is not new, and the societal perspective appears to be gaining momentum. The second panel on cost-effectiveness in health and medicine recommended that all studies should adopt a two reference-case analyses – a healthcare sector perspective and a societal perspective [19]. Methodological guidelines published by the European Network for HTA (EunetHTA) advocate for similar considerations [20].

Previous systematic literature reviews (SLR) have evaluated the costs of AF [21], cost-effectiveness of oral anticoagulation for AF [22,23], and stroke-specific costs of AF [24–26]. No recent study to our knowledge has

systematically assessed the societal costs associated with AF treatment and its complications. The objective of this study was to conduct an SLR to determine the societal costs associated with stroke, major bleeding and INR monitoring in patients with AF. Specifically, our study aimed to understand the indirect costs associated with stroke, major bleeding and INR monitoring and their contribution to total costs.

Materials & methods

Study selection

The SLR was conducted according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [27] and the Cochrane Handbook for Systematic Review of Interventions [28]. Details on data sources and study selection criteria are provided below.

Data sources

Systematic searches were conducted in the MEDLINE (via PubMed) and Embase electronic databases to identify articles published in English between 1 January 2008 and 9 March 2018. The search algorithms used a combination of indexing terms (medical subject heading [MeSH] terms in MEDLINE and Emtree terms in Embase) and free-text keywords for NVAf, as well as terms for the broader AF indication. The indication string was paired with terms for economic burden and for stroke, bleeding and INR monitoring ([Supplementary Table 1](#)). Articles indexed as case reports, editorials, comments/commentary, guidelines, news or narrative reviews were excluded from the searches. A manual check of references from recent SLRs and meta-analyses identified through Cochrane Database of Systematic Reviews was also conducted to ensure optimal and complete literature retrieval.

Abstracts and poster presentations from the 2016 to 2017 International Society of Pharmacoeconomic and Outcomes Research scientific meetings were also reviewed. Any abstracts of studies identified through the conference searches reporting economic models and cost and resource use outcomes were included in the review as grey literature.

Search & screening methods & inclusion/exclusion criteria

Once the literature searches were conducted and duplicates were removed across databases, the titles and abstracts were manually reviewed by two independent investigators against the predefined inclusion and exclusion criteria described in [Table 1](#). Studies that were included at the title/abstract level were screened by two independent investigators against the same inclusion/exclusion criteria at the full-text level. Any discrepancies were resolved by a third investigator. Included studies evaluated patients with NVAf or patients with AF whose absence of valvular disease was not specified (unspecified AF); studies on AF that allowed inclusion of patients with atrial flutter were also eligible. Studies on patients with valvular disease were excluded. Study designs of interest were limited to observational evidence, such as prospective and retrospective cohort studies, cross-sectional studies, and model-based studies (economic evaluations, retrospective cost-of-illness studies with cost estimations). For model-based studies, indirect costs of interest were the costs used for model inputs. Clinical trials were not eligible for inclusion in this SLR because, by design, clinical trials are typically conducted in closed, research environments on highly selective populations and may not be generalizable to the wider AF population [29,30]. A broader perspective was adopted, evaluating direct costs, indirect costs and resource use. This work, however, focused on the indirect costs associated with stroke, major bleeding and INR monitoring.

Data extraction & quality assessment

Study, patient and outcomes data were extracted by a single investigator with confirmation of each data point back to the source article performed by second, senior investigator. As part of the extraction, each study underwent a quality assessment using either the Drummond tool (economic evaluations [32] [[Supplementary Table 2](#)]) or the Good Research for Comparative Effectiveness (GRACE checklist [33] [[Supplementary Table 3](#)]; observational studies). The study quality rating was also conducted by one investigator and confirmed by a second, senior investigator.

Data synthesis

Due to the heterogenous nature of the data, a qualitative synthesis was performed to summarize the SLR results and no statistical analyses were conducted. As part of this synthesis, study and population characteristics, as well as the manner of reporting indirect costs were assessed both individually and across studies, to compare results.

Table 1. PICOS-T criteria for study inclusion and exclusion.

Category	Inclusion criteria	Exclusion criteria
Populations	- Adult (≥ 18 years of age) - Patients with NVAFA[†] or with unspecified AF	- Pediatric patients (< 18 years of age) - Patients without AF - Patients with valvular AF - Patients only with atrial flutter and not AF
Interventions/comparators	Any treatment licensed for use in AF patients including NOACs, warfarin, and/or surgical procedures such as cardioversion, radiofrequency or catheter ablation, maze or pacemaker	Treatments not indicated for the management of AF
Outcomes	Cost estimates and/or resource use associated with the following event types: - Stroke (composite and stroke types) - Major bleeding - INR monitoring Cost estimates including but not limited to: <u>Direct costs</u>[‡] - Total costs and itemized cost as reported including: - Pharmacy-related costs - Hospital costs - Healthcare professional costs - Posthospital/community costs - Transportation costs - Long-term care - Legal costs - Administrative costs - Social welfare benefits <u>Indirect costs</u> - Productivity losses - Caregiver work loss - Lost leisure time Resource use including but not limited to:[‡] - Mean number of hospitalizations per patient - Length of stay - ER visits - Cardiologist visits - Anticoagulation clinic visits - ICU admissions - Physician/GP visits - Monitoring visits - Surgical management - Readmissions - INR tests	Noneconomic outcomes such as clinical, epidemiology or health-related quality of life end points Studies in which the only resource use-related outcome is proportion of patients with a hospitalized event (i.e., incidence rate of stroke requiring hospitalization)
Study design	- Observational studies including prospective and retrospective cohort studies and cross-sectional designs evaluating at least 10 NVAFA patients - Economic analyses/economic evaluations	- Clinical trials including randomized controlled trials - Systematic literature reviews - Case studies and studies evaluating fewer than 10 patients <i>In vitro</i> studies - Letters, narrative reviews, expert opinions and commentary
Time period	1 January 2008–9 March 2018 for published literature 2016 and 2017 for gray literature	Studies published prior to 1 January 2008 or after 9 March 2018
Other criteria	Published in English language	Studies published in languages other than English

[†]NVAFA is characterized by an irregular heart rhythm in the upper chambers of the heart in the absence of rheumatic valvular disease (predominantly mitral valve stenosis) or artificial heart valves [31].

[‡]The SLR included outcomes related to direct costs, indirect costs and resource use, but the present study is only evaluating indirect-cost outcomes.

AF: Atrial fibrillation; ER: Emergency room; GP: General practitioner; ICU: Intensive care unit; INR: International normalization ratio; NOAC: Non-VKA oral anticoagulant; NVAFA: Nonvalvular atrial fibrillation; PICOS-T: Participant, intervention, comparison, outcome, study design and time period; VKA: Vitamin K antagonist.

All indirect costs were captured as reported and broken out into monetary costs and nonmonetary costs. The nonmonetary costs were categorized as productivity loss, time loss or caregiver-related.

The proportion of total costs attributable to indirect costs was calculated, when applicable, by dividing the total indirect costs by the total costs. In cases where total costs were not available, individual cost components were added to construct a total indirect cost or total overall cost.

Results

Search results

The SLR identified 2862 unique records through electronic database searches. Of those, 184 were included in the review. One meeting abstract was identified from International Society of Pharmacoeconomic and Outcomes

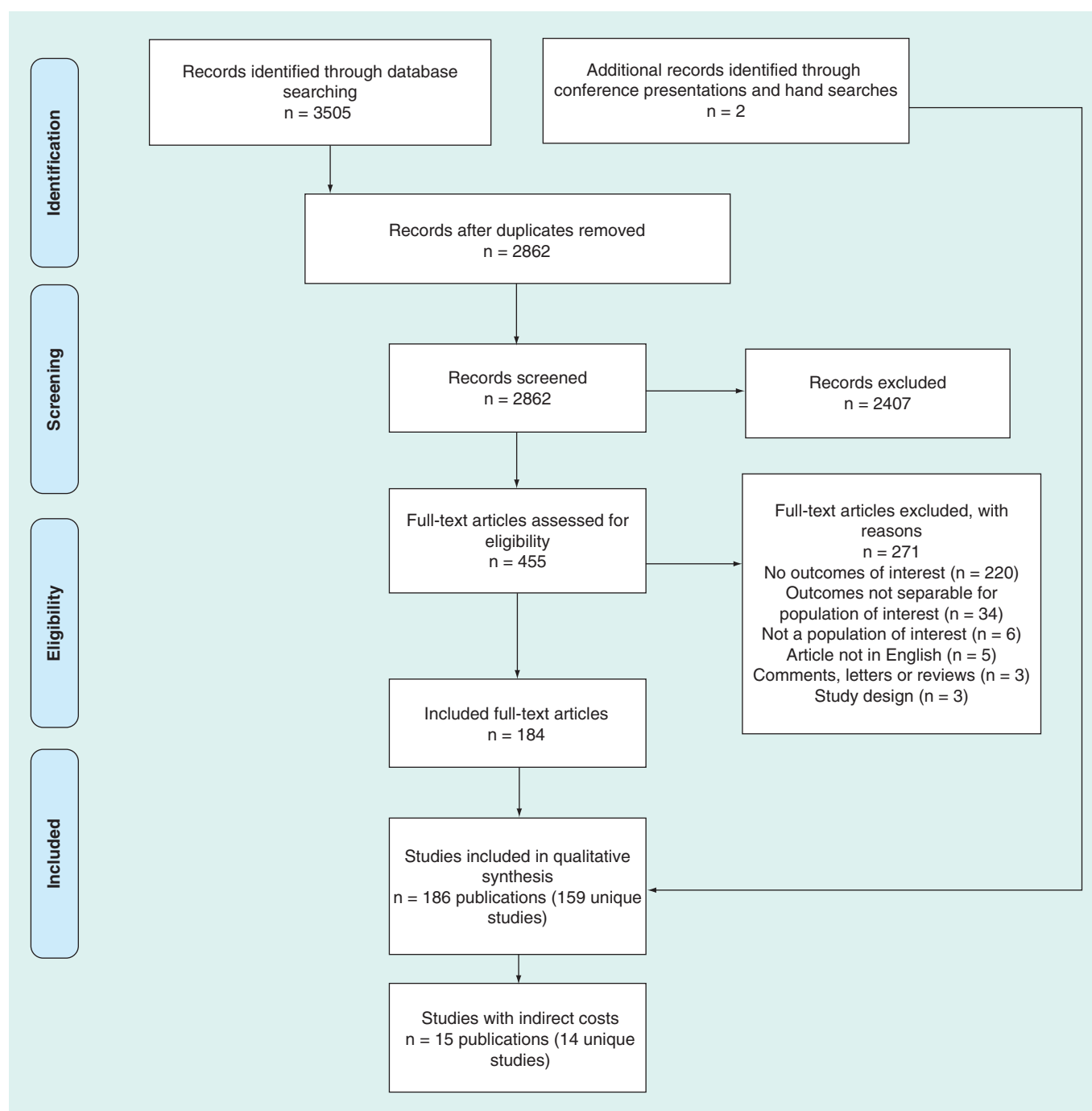


Figure 1. PRISMA diagram of study attrition.

Research and one study from manual searches met the inclusion/exclusion criteria, resulting in 186 total publications (159 unique studies) with direct costs, resource use and/or indirect costs. Among the 186 publications, 15 reported indirect costs (14 unique studies and one related publication reporting on the same study population) [34–47]. Study attrition through the abstract and full-text screening levels are detailed in the PRISMA diagram in Figure 1.

Summary of study characteristics

Among the 14 indirect cost studies, eight were observational [34–36,39,41,43,44,47] and six were model-based, including economic evaluations or retrospective cost-of-illness studies based on published estimates reporting indirect cost

inputs for their economic models [37,38,40,42,45,46]. Among the observational studies, two each were conducted in Denmark and Ireland and one each in the UK, Russia, Mexico and India. Indirect costs were evaluated for stroke in three studies, major bleeding in one and INR monitoring in four. Four studies specified that the population had NVAf, another four did not specify AF type and one included atrial flutter. Three studies were retrospective cohorts, three were prospective cohorts and two were cost-of-illness studies with real-world estimates. Five (62.5%) were funded by industry. Three studies were of high quality based on the GRACE quality checklist – studies which had a response of yes or not applicable to all or all but one checklist item, were rated as high quality. There were no trends in study quality by funding source. The remaining observational studies were of moderate quality since they lacked clear reporting of treatment, control of covariates and/or measurement of primary outcomes.

Among the model-based studies, two were conducted in Sweden, two were from the USA, and one study each was based in Denmark and Thailand. Three studies evaluated indirect costs of stroke and four addressed INR monitoring. No model-based analyses reported cost inputs for the indirect costs associated with major bleeding. Four studies specified that patients had NVAf, two did not specify type of AF, and one allowed inclusion of atrial flutter. Three studies were cost-effectiveness analyses (CEA), two were cost-of-illness studies with estimated population costs, and one was a budget impact model. Three studies (50%) were industry funded and half were of high quality based on the Drummond assessment, despite their funding source.

Framework for results

The indirect costs results were summarized by event type (stroke, major bleeding and INR monitoring) then by outcome type (indirect costs, indirect cost in relation to total cost) in the following sections.

Stroke

Six studies, three of which were observational in design, reported data on the indirect costs of stroke among patients with AF. Model-based studies included one economic evaluation and two retrospective cost-of-illness analyses informed from published data. Two studies characterized the population to have NVAf, with the remaining four did not specify AF type. Four studies were conducted in Europe (Ireland, $n = 1$; Denmark, $n = 1$; Sweden, $n = 2$) and two studies were conducted in Asia (Thailand, $n = 1$; India, $n = 1$). The mean age of patients ranged from 61.4 to 78 years, where reported. The timeframe for which costs were reported varied (ranging from 1 to 2 years, or unspecified), with observational studies reporting costs as a function of time since onset of stroke. Model-based studies provided limited details on the timeframe. The study quality was rated as high in four studies and moderate in two. Data on monetary indirect costs associated with stroke are summarized in [Table 2](#).

Four studies reported on productivity losses (or sick days) for patients, due to inability to work because of stroke [37–39,41]. Only three studies provided monetary values for productivity losses [37,39,41], with one reporting on the average number of sick days [38]. Nonmonetary costs (hours, days and proportions of patients) are summarized in [Table 3](#). The number of cases and average duration of sick leave was reported by stroke type in one study (ischemic stroke [IS] vs unspecified type). The average duration of sick leave was similar by stroke type (403 vs 353 days, respectively [38]). Of the remaining studies providing monetary values for productivity loss, two observational studies used the human capital approach to estimate these [39,41]. One cost-of-illness analysis, conducted in Denmark, estimated lost earnings among patients aged 18–65 years, assuming that patients older than 65 years were unemployed [41]. This was the only study that presented costs at different timepoints after stroke onset [41]. Productivity loss attributed to stroke alone increased threefold from the year of the incident stroke up to the 1-year follow-up (from \$288 to \$843). A twofold increase was reported from 1 to 2 years following the stroke incident (from \$843 to \$1444) [41]. The remaining observational study, conducted in Ireland, collected data on employment status at the time of stroke onset and length of hospital stay. Productivity losses were estimated using the days spent in hospital and assigning the national median wage to patients who were employed and the minimum wage to stroke patients who were homemakers [39]. The average productivity loss at the end of a 2-year follow-up after stroke period was \$930 [39]. A cost-of-illness analysis conducted in Sweden reported a productivity loss of €15,145 over lifetime post stroke (IS or hemorrhagic stroke); published estimates were used to inform the analysis [37].

Two studies, a retrospective cohort [44] and a CEA [42], considered the costs associated with informal care by unpaid caregivers. The observational study relied on estimates of informal care hours provided by patients, without providing details on assumptions used to convert informal care hours to a monetary value [44]. Caregivers spent an average of 3.2 h per day on informal care, representing an average annual loss of 13,370 [44]. The CEAs, conducted in Thailand, utilized informal care (not defined) costs per month by IS severity to inform their model. The cost

Table 2. Monetary indirect costs of stroke in patients with atrial fibrillation and relation of indirect costs to total costs.

Study (year)	Study design sample size quality rating [†]	Country study setting data source	Definition of stroke	Patient characteristics	Follow-up/time-horizon	Indirect cost definition and methods	Units	Indirect costs	Total costs	Percent of total costs attributed to indirect costs (%)	Ref.
Observational											
Jakobsen et al. (2016) [§]	Registry based cost-of-illness study N = 21,673 High	Country: Denmark Costing year: 2012 Setting: Hospital (societal perspective) Data source: Danish National Patient Registry and National Health Insurance Service Registry (1994–2012)	IS	AF type: Not specified Mean age: 78 years Percentage of males: 46% CHA ₂ D ₂ -VASc score: 3.01	Enrollment: 1994–2012 Follow-up: 2 years	Definition: Productivity losses attributable to stroke Methods: Lost earnings of patients aged 18–65 years estimated using human capital approach	Incident year	US\$288	US\$19,989	1.4	[41]
Hannon et al. (2014)	Prospective cohort N = 177 High	Country: Ireland Costing year: 2007 Setting: Hospital Perspective: Public Data source: North Dublin population Health study patient hospital and community healthcare records (2005–2006)	IS, ICH or subarachnoid hemorrhage	AF type: Not specified Mean age: 76.5 (10.5) years Percentage of males: 45.8% Mean CHA ₂ D ₂ -VASc score: NR	Enrollment: December 2005 to November 2006 Follow-up: NR	Definition: Lost productivity due to morbidity of stroke Methods: Human capital approach; lost earnings of patients in employment at time of stroke onset estimated based on median wage and length of hospital stay; minimum wage assigned to homemakers	Year 1 after stroke	US\$843	US\$7683	11.0	[39]
							Year 2 after stroke	US\$1442	US\$5176	27.9	
							Total (3 years)	US\$2338	US\$30,925	7.6	
Marfatia et al. (2014)	Retrospective cohort NVAF N = 400 Moderate	Country: India Costing year: 2012 Setting: Hospital Perspective: Private Data source: Medical charts, patient billing records and questionnaires	Any stroke	AF type: Nonvalvular Mean age: 61.4 years (9.4) Percentage of males: 62% Mean CHA ₂ D ₂ -VASc score: NR	Enrollment: January 2010 to December 2011 Follow-up: NR	Definition: Informal care from caregivers Methods: Estimates of lost productivity of caregivers provided by patients	First year after stroke	13,370 [¶]	504,973	2.6	[44]

[†] Quality assessment ratings were completed using the Good Research for Comparative Effectiveness (GRACE) checklist for observational studies and the Drummond Checklist of Economic Evaluations for model-based study designs.

[‡] Data source for model-based studies reflects source used to inform indirect costs.

[§] All costs were inflated by the study to 2012 prices and converted to USD based on an average exchange rate in 2012 (\$100 = 579.72 Danish krona [DKK]).

[¶] Based on 3.2 informal care hours per day.

^{*} Percent of total costs attributed to indirect costs not estimated as total costs and indirect costs were not reported in the same units.

AF: Atrial fibrillation; HS: Hemorrhagic stroke; ICH: Intracerebral hemorrhage; IS: Ischemic stroke; NR: Not reported; NVAF: Nonvalvular atrial fibrillation.

Table 2. Monetary indirect costs of stroke in patients with atrial fibrillation and relation of indirect costs to total costs (cont.).

Study (year)	Study design sample size quality rating [†]	Country study setting data source	Definition of stroke	Patient characteristics	Follow-up/time-horizon	Indirect cost definition and methods	Units	Indirect costs	Total costs	Percent of total costs attributed to indirect costs (%)	Ref.
Model-based											
Jarungsuwattana et al. (2014) (2123)	Cost-effectiveness analysis High	Country: Thailand Costing year: 2013 Perspective: Societal Data source: Riewpaiboon et al. 2009 [48]	IS	AF type: Nonvalvular Mean age: ≥65 Percentage of males: NR Mean CHAD _s score: ≥2	Lifetime	Definition: Informal care Methods: Not reported	Per month, severe disabling stroke	฿ 12,261	NR	Not estimable [#]	[42]
Davidson et al. (2011) (2203)	Cost-of-illness study AF-type not specified Moderate	Country: Sweden Costing year: 2010 Perspective: Societal Data source: Ghatnekar, 2004 [49]	IS or HS	AF type: Not specified Mean age: NR Percentage of males: NR Mean CHAD _s score: NR	1 year	Definition: Productivity losses Methods: NR	NR (incidence-based approach cited)	€15,145	€77,342	19.6	[37]

[†] Quality assessment ratings were completed using the Good Research for Comparative Effectiveness (GRACE) checklist for observational studies and the Drummond Checklist of Economic Evaluations for model-based study designs.

[‡] Data source for model-based studies reflects source used to inform indirect costs.

[§] All costs were inflated by the study to 2012 prices and converted to USD based on an average exchange rate in 2012 (\$100 = 579.72 Danish krona [DKK]).

[¶] Based on 3.2 informal care hours per day.

[#] Percent of total costs attributed to indirect costs not estimated as total costs and indirect costs were not reported in the same units.

AF: Atrial fibrillation; HS: Hemorrhagic stroke; IS: Ischemic stroke; NR: Not reported; NVAF: Nonvalvular atrial fibrillation.

Table 3. Nonmonetary indirect costs of stroke, bleeding and international normalized ratio monitoring in patients with atrial fibrillation[†].

Study (year)	Study design AF type sample size quality rating [‡]	Country study setting data source	Mean age percentage of males CHADS ₂ score, mean (SD)	Follow-up/endpoint/costing year/time horizon	Productivity loss	Travel time/costs	Patient's/caregiver's time loss	Other indirect costs	Ref.
Stroke									
Marfatia et al. (2014)	Retrospective cohort N = 400 Moderate	Country: India Setting: Hospital Payer: Private Data source: Medical charts, patient billing records and questionnaires	61.4 years 62% NR	Enrollment: January 2010 to December 2011 Follow-up: NR Duration: NR Costing year: 2012	NR	NR	Informal care, hours per day, Mean (SD): 3.2 (1.3)	NR	[44]
Ericson et al. (2011) (2570)	Cost-of-illness study AF-type not specified (includes flutter) High	Country: Sweden Costing year: 2007 Perspective: NR Data source Swedish Social Insurance Agency and Swedish National Board of Health and Welfare	AF type: Nonvalvular Mean age: 74.9 years Percentage of males: 56% Mean CHADS ₂ score: NR	1 year	Average sick days per stroke, mean IS: 403 days; Mean unspecified stroke: 353 days	NR	NR	NR	[38]
Major bleeding									
No studies identified									
INR monitoring									
Briere et al. (2017A)	Prospective cohort study N = 400 Moderate	Country: Mexico Setting: Hospital Payer: Public Data source: cardiologists: Online record form for patient data Patients: questionnaire	65.6 years 52.8% 2.8 (1.7)	Received treatment for minimum of 12–24 months Costing year: 2016	Proportion of unemployed/retired patients with VKA-related work-loss hours: 1%	NR	Time spent at appointment: 59.8 min (SD: 35) Patient travel time: 80.3 min (54.1) Hours off work (employed patients): 5.6 (SD: 7.5) worktime loss for caregivers: 2.6 h (6.3)	Proportion of patients accompanied by caregivers to usual hospital appointments: 70.8% [35]	[35]
Briere et al. (2017B)	Prospective cohort study N = 351 High	Country: Russia Setting: Hospital Payer: Public Data source cardiologists: Online record form for patient data Patients: Questionnaire	63.2 years 47% 2.9 (1.7)	Received treatment for minimum of 12–24 months Costing year: 2016	NR	NR	Time spent at appointment: 62.1 min (SD: 42.8) Patient travel time: 63 min (49.3) Hours off work (employed patients): 4.9 (SD: 3.2) Worktime loss for caregivers (past month): 5.7 h (SD: 3.5)	Proportion of patients accompanied by caregivers to usual hospital appointments: 17.9%	[36] [50]
Ref. ID 548, Walsh et al. (2014)	Retrospective cohort AF type not specified N = 158 Moderate	Country: Ireland Setting: Hospital Payer: Private Data source: Mercy University Hospital, Cork, Ireland	70 years NR NR	Enrollment: NR Follow-up: NR Duration: NR Costing year: 2011	NR	NR	Time spent at clinic, hours: 2.13	NR	[47]

[†]All studies reporting nonmonetary values were observational studies.[‡]Quality assessment ratings were completed using the Good Research for Comparative Effectiveness (GRACE) checklist for observational studies and the Drummond Checklist of economic evaluations for model-based study designs.

AF: Atrial fibrillation; HS: Hemorrhagic stroke; ICH: Intracerebral hemorrhage; IS: Ischemic stroke; NR: Not reported; NVAF: Nonvalvular atrial fibrillation; SD: Standard deviation; VKA: Vitamin K antagonist.

inputs were obtained from published estimates and were higher for severe IS as compared with mild-to-moderate IS (£12,260.59 vs £5023.93, respectively [42]).

Indirect costs in relation to total costs

The contribution of indirect costs to total cost was marginal in the two studies, with short-term follow-up data reported (1.1–1.4% [39,44]). In the study with 3-year data, indirect costs appeared marginal in relation to total costs in the year of the incident stroke event (1.4% [41]). However, the relative contribution of indirect costs increased to 11% of total costs in the first year of follow-up, and rose to 27.9% in the second year following the index event. In the cost-of-illness analyses that utilized lifetime costs, indirect costs made up almost a fifth of total costs (19.6% [37]).

Major bleeding

The SLR identified only one study [43], conducted in Denmark, which reported indirect costs of bleeding among patients with AF. Data were used from a large Danish registry ($n = 21,046$) of patients with unspecified AF type or atrial flutter who were hospitalized from 1994 to 2012 to estimate indirect costs attributable to intracerebral hemorrhage (ICH), gastrointestinal (GI) bleeding, and other major bleeding events (not specified). Costs were estimated during the year of the bleeding event and over two additional years of follow-up. The average 3-year cost of productivity loss due to ICH events was estimated to be higher than that of GI and other major bleeding events. Total costs per patient were €2042 for patients with ICH compared with €317 and €1218 for GI and other major bleeding, respectively (Table 4). The productivity loss associated with ICH events amounted to a cost of €194 per patient in the incident year and increased sixfold to €1438 per patient during the 2 years after the event. By contrast, only a small increase was observed between the incident year and the 1-year follow-up among patients with GI bleeding. This cost decreased by 43% from the incident year to 3-year postevent. For other major bleeding events, an increase of about €200 per year per patient (50%) was observed. The study was rated of moderate quality due to the lack of reporting on treatment and analyses to test key assumptions that could impact results. Table 3 summarizes the characteristics of this study and the indirect costs per patient.

Indirect costs in relation to total costs

The Danish study reported both total direct and indirect costs. For ICH and other major bleeding events, the contribution of indirect costs to total costs was marginal in the incident year of the bleeding event as direct costs, due to hospitalization, were the initial cost driver. Indirect costs driven by productivity loss accounted for as much as 33% of total costs 2 years after an ICH event, and 48% of total costs for other major bleeding events (Table 4) [43].

INR monitoring

The SLR identified eight studies (nine publications) [34–37,40,45–47,50], four of which were observational [34–36,47,50], reporting indirect costs associated with INR monitoring among patients with AF. The other four studies included two CEAs [40,45], a cost-of-illness study [37], and a budget impact model [46]. Two studies were conducted in the USA, and one each in the UK [51], Mexico [52], Ireland [46], Russia [36,50], Denmark [46] and Sweden [37]. AF type was specified to be nonvalvular in the majority of studies [34–36,40,45,46,50]. The mean age of patients ranged from 63.2 to 72.3 where reported. Costs were most commonly reported annually per patient or per test [34–37,40,47,50]. Three out of eight studies were rated of high quality and the remaining five were judged to be of moderate quality.

Indirect costs included productivity losses (worktime loss) and opportunity losses (lost leisure time) for patients and caregivers due to INR monitoring. Only three studies, two by the same first author [35,36,50] provided sufficient details on how indirect costs were defined and valued. The two observational studies by the same author, one based in Mexico and the other in Russia, reported costs in US dollars (USD) and were similar in both design and costs reported [36,52]. Both studies were conducted in the hospital setting, used a costing year of 2016, and reported data for patients with a mean age of approximately 65 years. Worktime loss was valued separately for patients who were employed, patients unemployed due to VKA use, and patients unemployed not due to VKA use. The median wage was used to determine productivity losses for employed patients and those without employment due to VKA; while the minimum wage was used to value the opportunity cost of lost leisure time for patients whose unemployment was unrelated to VKA. The cost of worktime loss for employed patients was similar in the two countries (Russia: \$186.90 vs Mexico: \$164.10) but the cost of opportunity loss for unemployed or retired patients was much higher in Russia compared with Mexico (\$4458.30 vs \$1337.20, respectively). The time spent at appointments and the

Table 4. Monetary indirect costs of major bleeding in patients with atrial fibrillation and relation of indirect costs to total costs.

Study (year)	Study design sample size quality rating [†]	Country study setting data Source	Type of bleeding	Patient characteristics	Follow-up/time- horizon	Indirect-cost definition and methods	Units	Indirect costs	Total costs	Percent of total costs attributed to indirect costs (%)	Ref.
Observational											
Jakobsen et al. (2017)	Cost-of-illness study N = 21,046	Country: Denmark Costing year: 2015 Setting: Hospital (Societal Perspective) Payer: Public Data source: Danish National Patient Registry and the National Health Insurance Service Registry (1994–2012)	ICH	AF type: Not specified (includes flutter) Mean age: 77 years Percentage of males: 55% Mean CHADs ₂ : NR	Enrollment: 1994–2012 Follow-up: 2002–2012 (bleeding follow-up) and 2 years of bleeding follow-up for costs	Definition: Productivity losses Methods: Human capital approach; value of lost earnings estimated using data from Statistics Denmark on income; lost earnings estimated for patients aged 18–65	Incident year	€194	€18,049	1.1	[43]
							Year 1 after bleeding event	€624	€6922	9.0	
							Year 2 after bleeding event	€1438	€4356	33.0	
							Total (3 years)	€2042	€27,627	7.4	
			GI bleeding	AF type: Not specified (includes flutter) Mean age: 76 years Percentage of males: 51% Mean CHADs ₂ : NR			Incident year	€115	€13,702	0.83	
							Year 1 after bleeding event	€160	€3093	5.2	
							Year 2 after bleeding event	€66	€2063	3.2	
							Total (3 years)	€317	€17,868	1.8	
			Other major bleeding	AF type: Not specified (includes flutter) Mean age: 78 years Percentage of males: 71% Mean CHADs ₂ : NR			Incident year	€281	€9526	2.9	
							Year 1 after bleeding event	€419	€2244	18.7	
							Year 2 after bleeding event	€631	€1294	48.7	
							Total (3 years)	€1,218	€12,384	9.8	
Model-based											
No studies identified											

[†]Quality Assessment ratings were completed using the Good Research for Comparative Effectiveness (GRACE) checklist for observational studies and the Drummond Checklist of Economic Evaluations for model-based study designs.
AF: Atrial fibrillation; GI: Gastrointestinal; HS: Hemorrhagic stroke; ICH: Intracerebral hemorrhage; IS: Ischemic stroke; NR: Not reported; NVAF: Nonvalvular atrial fibrillation; SD: Standard deviation; VKA: Vitamin K antagonist.

hours taken off from work (among employed patients) was similar across both studies (Table 3). A retrospective study conducted in Ireland adopted a similar approach valuing lost time separately for employed and unemployed patients [47]. The average worktime lost/opportunity cost per patient per visit was €20.4, based on an average of 2.13 h spent at the clinic. The final observational study reported the mean cost of time off work for patients and caregivers of £1.2 and the mean travel costs of £33.9; however, there were limited details on whether the time off work was only composed of productivity losses and how those losses were valued [34].

Although all model-based evaluations reported indirect costs based on lost time due to INR monitoring, the cost components and how they were valued were less clear. The two CEAs used model inputs representing economic value of patient time for INR tests, at an average of about \$1751 yearly or \$153 per test [40,45]. The cost-of-illness analyses reported that the productivity loss per patient was €2.9 [37]; however, no further details were provided on the estimates. Finally, the budget impact analysis reported that the total societal cost associated with INR monitoring was \$1212 [46].

Only three studies reported on the indirect costs associated with lost time of caregivers [34], with one providing limited details on valuation [34–36,50]. The remaining two observational studies used the national median wage [35,36,50] to assign value to caregiver time to attend INR visits. No distinction was reported for employed versus unemployed caregivers. The indirect cost for caregivers was different across the two studies. In the study conducted in Mexico, 70.8% of patients were accompanied by caregivers to their usual hospital appointments in contrast to 17.9% in the Russian study. The cost of worktime/opportunity loss for nonprofessional caregivers in Mexico was double that of Russia (\$66.3 vs \$34.7, respectively), but the worktime/productivity loss in hours per caregiver was lower in Mexico than in Russia (2.6 vs 5.7 h). All indirect costs of INR monitoring by study are summarized in Table 5.

Indirect costs in relation to total costs

Based on the available data, the contribution of indirect costs to total costs was calculated for each study and varied greatly, ranging from 1 to 73%. Indirect costs contributed to only 1% of total costs in a UK retrospective study, which appeared to only consider productivity losses [34]. Higher estimates were observed among studies considering the economic value of, or opportunity cost of, lost leisure time of patients [36,45].

Discussion

The SLR identified a limited body of evidence assessing the indirect costs associated with complications and management of AF. Fourteen unique studies reported on the indirect costs of stroke, major bleeding and INR monitoring – this was considerably less than the number that reported on direct medical costs or resource use ($n = 159$). Indirect costs were mostly composed of productivity losses incurred by patients or caregivers and, to a lesser extent, the cost of lost leisure time for unemployed patients and caregivers.

The majority of studies reported a population older than 65 (mean range of 61.4–78), consistent with epidemiological estimates [56]. The elderly demographic of AF may contribute to the scarce data on indirect costs, since a large proportion of these patients would likely be retired. Nonetheless, a proportion of the cohorts examined were employed [39,41,43] and potentially accrued productivity losses as a consequence of complications associated with NVAf.

The review and synthesis of the results were hindered by a wide range of indirect cost definitions, assessment timeframes, units and currencies, and the approaches used to quantify this data. This limited the ability to determine cost drivers based on study and patient characteristics.

Based on the limited number of studies reporting both direct and indirect costs, inconsistent findings arose regarding the importance of indirect costs. Direct costs accounted for most costs related to the morbidity of stroke and bleeding events when evaluating costs in the incident year of the event (97.4–98.9% [41,43,44]). This is consistent with findings from an earlier systematic review which assessed the costs of IS among patients with AF and reported a majority of them to be related to hospitalization [26], which may, in part, explain the paucity of studies assessing indirect costs.

However, two studies conducted in Denmark highlighted that the influence of indirect costs is magnified beyond the acute care period, with these having a meaningful impact on the costs of managing stroke, ICH and other bleeding in the first and second years after the event [41,43]. Productivity losses accounted for 28, 33 and 49% of the total costs of stroke, ICH and other major bleeding in the second year after each of the events, respectively [41,43]. Therefore, the importance of indirect costs may depend on follow-up duration. This is corroborated by evidence

Table 5. Monetary indirect costs of international normalized ratio monitoring in patients with atrial fibrillation and relation of indirect costs to total costs.

Study (year)	Study design Sample size	Country study setting data source	Patient characteristics	Follow-up/time- horizon	Indirect-cost definition and methods	Units	Indirect costs	Total costs	Percent of total costs attributed to indirect costs (%)	Ref.
Observational studies										
Ali et al. (2012)	Retrospective cohort study N = 402	Country: UK Costing year: 2011 Setting: Clinic Data source: Patients: Survey Payer: Public Costs: Financial Development Branch, NHS Executive (UK) (1999–2000)	AF type: Nonvalvular Mean age: 72.3 years Percentage of males: 56% Mean CHAD ₂ : 2.1 (1.1)	Enrollment: November 1999 to July 2001 Follow-up: mean (SD): 19 (8.1) months, range: 1–31 months	Definition: Mean cost of time-off work for patient and carer Methods: NR	Per patient per year	£1.2	£117.6	1.0	[34]
Briere et al. (2017A)	Prospective cohort study N = 400	Country: Mexico Costing year: 2016 Setting: Hospital Payer: Public Data source cardiologists: Online record form for patient data Patients: Questionnaire	AF type: Nonvalvular Mean age: 65.6 years Percentage of males: 52.8% Mean CHA ₂ D ₂ S ₂ VASc: 2.8 (1.7)	Enrollment: NR Follow-up: NR Duration: Received treatment for minimum of 12–24 months	Definition: Total indirect costs including worktime and opportunity loss for patients and caregivers, when applicable. Methods: see below	Per patient per year	US\$132.1 [†]	US\$1035.50	12.8	[35]
					Definition: Mean cost of travel time Methods: NR		£33.9	£117.6	28.8	
					Definition: Productivity loss as for employed patients. Methods: Lost worktime as reported by employed patients per month multiplied by median hourly wage		US\$164.1	NA	NA	
					Definition: Worktime loss for unemployed patients, with unemployment attributed to VKA Methods: Applicable to patients unemployed due to VKA for a period greater than 12 months (as reported by patients) valued using median annual wage		US\$1337.2 [‡]	NA	NA	
All costs were inflated by the study to 2012 prices and converted to USD based on an average exchange rate in 2012 (\$100 = 579.72 Danish krona [DKK]).										
[†] Converted from Mexican peso using an exchange rate of 1 peso = 0.061 USD.										
[‡] Applicable for just one patient, so SD could not be calculated.										
[§] Indirect cost of INR testing would increase to \$620.3 if physicians/patients adhered to one appointment per month as per guideline recommendations.										
[¶] Converted from Russian rubles using 1 ruble = 0.015 USD.										
[#] Estimated based on reported annual cost of warfarin \$164.25, INR testing (monthly) \$83.8 (multiplied by 12), minimal established visits (monthly) \$408.00 (multiplied by 12) and annual economic value of patient time for INR test \$1750.92.										
^{††} Estimated based on total societal costs \$1212 minus healthcare costs \$898.										
AF: Atrial fibrillation; CEA: Cost-effectiveness analyses; HITAP: Health Intervention and Technology Assessment; HTA: Health Technology Assessment; INR: International normalized ratio; IS: Ischemic stroke; NR: Not reported.										

Table 5. Monetary indirect costs of international normalized ratio monitoring in patients with atrial fibrillation and relation of indirect costs to total costs (cont.).

Study (year)	Study design Sample size	Country study setting data source	Patient characteristics	Follow-up/time- horizon	Indirect-cost definition and methods	Units	Indirect costs	Total costs	Percent of total costs attributed to indirect costs (%)	Ref.
					Definition: Opportunity cost of lost time for unemployed patients (with unemployment not attributed to VKA) Methods: Applicable to patients unemployed due to VKA for a period greater than 12 months (as reported by patients) valued using median annual wage		US\$8.4	NA	NA	
					Definition: Worktime/opportunity loss for nonprofessional caregivers Methods: Patient reported loss of time for attending appointment valued using minimum wage		US\$66.3	NA	NA	
					Definition: Mean indirect costs per INR test Methods: Calculated as the annual cost by the number of INR tests	Per INR test	US\$51.7 [§]	US\$242.1	21.3	
Briere <i>et al.</i> (2017B)	Prospective cohort study Patients: N = 351 Cardiologists: N = 50	Country: Russia Costing year: 2016 Setting: Hospital Payer: Public Data source cardiologists: Online record form for patient data Patients: Questionnaire	AF type: Nonvalvular Mean age: 63.2 years Percentage of males: 47% Mean CHA₂DS₂ VASc: 2.9 (1.7)	Enrollment: NR Follow-up: NR Duration: Received treatment for minimum of 12–24 months	Definition: Total indirect costs including worktime and opportunity loss for patients and caregivers, when applicable. Methods: See below	Per patient per year	US\$275.6 [¶]	US\$449.6	61.3	[36] [50]
					Definition: Productivity loss as for employed patients. Methods: Lost worktime as reported by employed patients per month multiplied by median hourly wage		US\$186.9	NA	NA	

All costs were inflated by the study to 2012 prices and converted to USD based on an average exchange rate in 2012 (\$100 = 579.72 Danish krona [DKK]).

† Converted from Mexican peso using an exchange rate of 1 peso = 0.061 USD.

‡ Applicable for just one patient, so SD could not be calculated.

§ Indirect cost of INR testing would increase to \$620.3 if physicians/patients adhered to one appointment per month as per guideline recommendations.

¶ Converted from Russian rubles using 1 ruble = 0.015 USD.

Estimated based on reported annual cost of warfarin \$164.25; INR testing (monthly) \$83.8 (multiplied by 12); minimal established visits (monthly) \$408.00 (multiplied by 12) and annual economic value of patient time for INR test \$1750.92.

†† Estimated based on total societal costs \$1212 minus healthcare costs \$898.

AF: Atrial fibrillation; CEA: Cost-effectiveness analyses; HITAP: Health Intervention and Technology Assessment; HTA: Health Technology Assessment; INR: International normalized ratio; IS: Ischemic stroke; NR: Not reported.

Table 5. Monetary indirect costs of international normalized ratio monitoring in patients with atrial fibrillation and relation of indirect costs to total costs (cont.).

Study (year)	Study design Sample size	Country study setting data source	Patient characteristics	Follow-up/time- horizon	Indirect-cost definition and methods	Units	Indirect costs	Total costs	Percent of total costs attributed to indirect costs (%)	Ref.
					Definition: Worktime loss for unemployed patients, with unemployment attributed to VKA Methods: Applicable to patients unemployed due to VKA for a period greater than 12 months (as reported by patients) valued using median annual wage		US\$4458.3	NA	NA	
					Definition: Opportunity cost of lost time for unemployed patients (with unemployment not attributed to VKA) Methods: Applicable to patients unemployed due to VKA for a period greater than 12 months (as reported by patients) valued using median annual wage		US\$16.1	NA	NA	
					Definition: Worktime/opportunity loss for nonprofessional caregivers Methods: Patient reported loss of time for attending appointment valued using minimum wage		US\$34.7	NA	NA	
					Definition: Mean indirect costs per INR test Methods: Calculated as the annual cost by the number of INR tests	Per INR test	US\$35.88	US\$58.14	61.7	
Walsh et al. (2014)	Retrospective cohort N = 158	Country: Ireland Costing year: 2011 Setting: Hospital Payer: Private Data source: Mercy University Hospital, Cork, Ireland	AF type: Not specified Mean age: 70 years Percentage of males: NR Mean CHAD₂: NR	Enrollment: NR Follow-up: NR Duration: NR	Definition: Total indirect cost includes worktime or opportunity loss per visit Methods: Worktime/opportunity loss was calculated based on average clinic attendance time elicited from semistructured interviews. For patients in employment the national average wage was used, while opportunity loss for unemployed patients using national minimum wage	Per patient per visit	€20.4	€70.07	29.1	[47]

All costs were inflated by the study to 2012 prices and converted to USD based on an average exchange rate in 2012 (\$100 = 579.72 Danish krona [DKK]).

† Converted from Mexican peso using an exchange rate of 1 peso = 0.061 USD.

‡ Applicable for just one patient, so SD could not be calculated.

§ Indirect cost of INR testing would increase to \$620.3 if physicians/patients adhered to one appointment per month as per guideline recommendations.

¶ Converted from Russian rubles using 1 ruble = 0.015 USD.

Estimated based on reported annual cost of warfarin \$164.25; INR testing (monthly) \$83.8 (multiplied by 12); minimal established visits (monthly) \$408.00 (multiplied by 12) and annual economic value of patient time for INR test \$1750.92.

†† Estimated based on total societal costs \$1212 minus healthcare costs \$898.

AF: Atrial fibrillation; CEA: Cost-effectiveness analyses; HITAP: Health Intervention and Technology Assessment; HTA: Health Technology Assessment; INR: International normalized ratio; IS: Ischemic stroke; NR: Not reported.

Table 5. Monetary indirect costs of international normalized ratio monitoring in patients with atrial fibrillation and relation of indirect costs to total costs (cont.).

Study (year)	Study design Sample size	Country study setting data source	Patient characteristics	Follow-up/time- horizon	Indirect-cost definition and methods	Units	Indirect costs	Total costs	Percent of total costs attributed to indirect costs (%)	Ref.
Model-based studies										
Harrington et al. (2013) (2177)	CEA NVAF	Country: US Costing year: 2012 Data source: Jonas et al. 2010 [53]	AF type: nonvalvular Mean age: 70 Percentage of males: NR Mean CHADS ₂ : NR	Lifetime	Definition: Economic value of patient time for INR test, warfarin Methods: Patient-time requirements for an INR test were used to estimate economic cost of patient time.	Mean annual cost per patient	US\$1750.92	US\$7816.2 [#]	22.4	[40]
Nguyen et al. (2016) (2151)	CEA NVAF	Country: USA Costing year: 2014 Data source: Harrington et al. 2013 (2177)	AF type: Nonvalvular Mean age: 70 Percentage of males: NR Mean CHADS ₂ score: NR	Lifetime	Definition: Economic value of patient time for INR test, warfarin Methods: NR	Per patient per month	US\$153.15	US\$210	73	[45]
Davidson et al. (2011) (2203)	Cost-of-illness study AF-type not specified	Country: Sweden Costing year: 2009 Data source: Svensson, 2004 [54]	AF type: Not specified Mean age: NR Percentage of males: NR Mean CHADS ₂ score: NR	NR	Definition: Productivity loss Methods: NR	Per patient per visit	€2.9	NR	NR	[37]
Poulsen et al. (2017) (HS-1001)	Budget Impact Model NVAF	Country: Denmark Costing year: 2015 Data source: Danish health authorities [55]	AF type: Nonvalvular Mean age: NR Percentage of males: NR Mean CHADS ₂ score: NR	1 year	Definition: Time used visiting the clinic for INR-monitoring Methods: NR	NR	US\$312 ^{††}	US\$1212	25.9	[46]

All costs were inflated by the study to 2012 prices and converted to USD based on an average exchange rate in 2012 (\$100 = 579.72 Danish krona [DKK]).

[†] Converted from Mexican peso using an exchange rate of 1 peso = 0.061 USD.

[‡] Applicable for just one patient, so SD could not be calculated.

[§] Indirect cost of INR testing would increase to \$620.3 if physicians/patients adhered to one appointment per month as per guideline recommendations.

[¶] Converted from Russian rubles using 1 ruble = 0.015 USD.

[#] Estimated based on reported annual cost of warfarin \$164.25, INR testing (monthly) \$83.8 (multiplied by 12); minimal established visits (monthly) \$408.00 (multiplied by 12) and annual economic value of patient time for INR test \$1750.92.

^{††} Estimated based on total societal costs \$1212 minus healthcare costs \$898.

AF: Atrial fibrillation; CEA: Cost-effectiveness analyses; HITAP: Health Intervention and Technology Assessment; INR: International normalized ratio; IS: Ischemic stroke; NR: Not reported.

from model-based studies which utilized indirect cost inputs over longer time horizons to inform their analyses. A Swedish cost-of-illness analysis suggested that approximately 20% of total lifetime costs per incident stroke case can be attributed to indirect costs [37]. Finally, the Thai economic evaluation assumed that only informal care costs would apply beyond the acute period of stroke [42], implying that indirect costs were the major driver in the long term. Findings from these studies implied that NOACs may be associated with considerable offsets in indirect costs following the incident years of stroke and major bleeding.

The same conclusions cannot be drawn for INR monitoring; due to the nature of the outcome, indirect costs or time lost from work would be accrued consistently with direct costs at each visit. The SLR identified eight studies reporting on indirect costs associated with INR monitoring, more than the studies identified for stroke or major bleeding. Two studies indicated a negligible contribution of indirect costs to total costs of INR monitoring, while the remainder indicated a more pronounced contribution accounting for 13–78% of total monitoring costs. These differences can primarily be attributed to how indirect costs were defined in the studies. Studies reporting a higher contribution of indirect costs to total costs monetized loss of leisure time for attending appointments for INR monitoring. Although findings from these studies may suggest lost leisure time should factor into cost considerations, there is no consensus on whether resources such as informal care or patient time costs, for which no market exists, should be valued.

Previous reviews assessed the costs associated with managing IS [26,57], or focused on the direct costs of complications and AF management [58]. To our knowledge, this is the first SLR to focus on the indirect costs associated with AF complications and management. The paucity in indirect cost data limited the ability to conduct economic evaluations using a broader perspective as recommended by EunetHTA [59] and the second panel on cost-effectiveness in health and medicine [19]. This hindered the ability to understand the potential influence of NOACs on a societal level. Based on the limited data identified, the indirect costs associated with stroke, major bleeding and VKA monitoring appear to be far from insignificant. Therefore, to determine the influence of NOACs on costs borne by nonhealthcare sectors, further evidence generation and research is required, ideally over longer follow-up durations, beyond the acute period of complications.

Future perspective

Further research is needed, ideally conducted over longer periods following incident stroke or bleeding events among patients with AF, to enhance current understanding of the influence of NOACs on costs generated outside of the healthcare sector.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/cer-2019-0089

Author contributions

AL Martin, SE Berger, K Snook, M Nejati, T Lanitis, AG Reeves, GD Wygant, M Di Fusco and M Savone all contributed to the concept and design of the study. AL Martin, SE Berger, K Snook, M Nejati and T Lanitis participated in the acquisition and interpretation of data for the work. AL Martin, SB, K Snook, M Nejati, T Lanitis, AG Reeves, GD Wygant, M Di Fusco and M Savone were responsible for drafting the work or revising it critically for important intellectual content. AL Martin, SE Berger, K Snook, M Nejati, T Lanitis, AG Reeves, GD Wygant, M Di Fusco and M Savone all provided final approval of the version to be published.

Financial & competing interests disclosure

Bristol-Myers Squibb and Pfizer provided funding for this study. AL Martin, SE Berger, K Snook, M Nejati and T Lanitis are employees of Evidera, which provides consulting and other research services to pharmaceutical, medical device and related organizations. In their salaried positions, they work with a variety of companies and organizations, and are precluded from receiving payments or honoraria directly from these organizations for services provided. A Garcia Reeves and GD Wygant are employees of, and own stock in Bristol-Myers Squibb. M Di Fusco and M Savone are employees of, and own stock in Pfizer. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Executive summary

Background

- Atrial fibrillation (AF) is the most common cardiac arrhythmia and is associated with a four- to five-fold increase in the risk of stroke.
- The rising use of novel oral anticoagulant (NOACs) among patients with AF has contributed to a decline in stroke-related morbidity, with additional treatment cost.
- We conducted a systematic literature review to determine the societal costs associated with stroke, major bleeding and international normalized ratio (INR) monitoring in patients with AF.

Methods

- MEDLINE and Embase were searched for observational and model-based studies evaluating the economic burden of stroke, major bleeding and INR monitoring in patients with AF.

Results

- The systematic literature review identified 14 studies reporting indirect costs, which was considerably less than the number of studies that reported direct medical costs and/or resource use ($n = 159$).
- Among the included studies, eight were observational and six were model-based in design. The studies were conducted in Denmark ($n = 3$), Ireland ($n = 2$), Sweden ($n = 2$), USA ($n = 2$) and one each in the UK, Russia, Mexico, Thailand and India.
- Indirect costs were mostly composed of productivity losses incurred by patients or caregivers and, to a lesser extent, the cost of lost leisure time for unemployed patients and caregivers. Indirect costs were reported as monetary cost of lost work/leisure time and as nonmonetary cost as lost hours, number of sick days and time spent off from work and/or at appointments.
- Among limited evidence reporting both direct and indirect costs, direct costs accounted for most costs related to stroke and bleeding events in the incident year of the event (97–99%). However, two studies in Denmark highlighted that the influence of indirect costs is magnified beyond the acute care period. Productivity losses accounted for 28, 33 and 49% of the total costs of stroke, intracerebral hemorrhage and other major bleeding in the second year after each of the events, respectively.
- In contrast, among the eight studies reporting indirect costs of INR monitoring, two studies indicated a negligible contribution of indirect costs to total costs of INR monitoring, while the remainder indicated a more pronounced contribution accounting for 13–78% of total monitoring costs. Studies reporting a higher contribution of indirect costs to total costs monetized loss of leisure time for attending appointments for INR monitoring.

Discussion

- Based on the limited data identified, the indirect costs associated with stroke, major bleeding and nonvitamin K antagonists monitoring appear to be far from insignificant.

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