Title page:

The impact of ischemic stroke on atrial fibrillation-related healthcare cost: a systematic review

Xue Li[1], Vicki C Tse[1], Au-Doung Lung Wai[1], Esther W Chan[1], Ian CK Wong[2, 1]

[1]Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, 2/F Laboratory Block, Faculty of Medicine Building, 21 Sassoon Road, Hong Kong SAR, China.

[2]Research Department of Practice and Policy, School of Pharmacy, University College London, 29-39 Brunswick Square, London WC1N 1AX, United Kingdom.

Corresponding Author: Prof. Ian CK WONG, Research Department of Practice and Policy, School of Pharmacy, University College London, 29-39 Brunswick Square, London WC1N 1AX, United Kingdom. Tel: +44 207 753 5966; Email: i.wong@ucl.ac.uk

Abstract

Aim: To summarize healthcare costs incurred by patients with atrial fibrillation (AF) who developed ischemic stroke, explore factors associated with increased cost and highlight the importance of anticoagulation therapy for stroke prophylaxis.

Methods: A systematic literature search of PubMed, EMBASE, Web of Science and the health economic evaluation database was conducted up to December 2015. Studies focused on the cost and/or resource utilization of ischemic stroke in patients with AF were included. Reported costs were converted to international dollars (I$) and adjusted to 2015 values. Alongside the narrative review of included studies, Spearman's correlation, independent-samples t-test and one-way ANOVA were used to explore factors associated with cost differences between studies.

Results: Sixteen studies published from nine countries were identified. Based on currency conversion rates in 2015, ischemic stroke related healthcare costs were estimated to be I$41,420, I$12,895 and I$8,184 for high-income, upper middle-income and lower middle-income economies respectively. Local GDP per capita accounted for approximately 50% of the healthcare cost variation among countries. Major component of overall cost was from hospitalization. Ischemic stroke incurring in patients with AF ≥75 years were 2.3 times that of their younger peers (p=0.049).

Conclusions: The economic burden from ischemic stroke in patients with AF is considerable with positive association to country income. Clinicians and stakeholders should be aware of the importance of anticoagulation therapies in stroke prophylaxis, the occurrence of stroke and the downstream economic burden on an increasingly aging population.

Keywords: stroke prophylaxis; atrial fibrillation; anticoagulation therapy; healthcare cost

Condensed abstract

This systematic review estimated stroke-related healthcare cost across nine countries, with a positive correlation to country income. The cost for elderly patients' ≥75 years was doubled against their younger peers. Adequate anticoagulation therapy for stroke prophylaxis and the downstream clinical and economic benefits in increasingly aging population are highlighted.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia in 1-4% of adults worldwide, with prevalence increasing with age, affecting ≥13% of adults' ≥80 years[1]. Importantly, AF is associated with an approximate five-fold increased risk of stroke and thromboembolism[2]. Age independently increases the risk of ischemic stroke with an adjusted hazard ratio per decade increase of 1.45 times (95%CI: 1.26-1.66) in patients with non-valvular AF (NVAF)[3]. For patients ≤40 years old, only 1.9% suffered from ischemic stroke but this increased to 39-46% in elderly patients ≥80 years[4]. The global aging population[5], prevalence of AF and associated embolism stroke are expected to cause considerable disease and economic burden in forthcoming decades.

Patients with NVAF with CHA2DS2-VASc (Congestive heart failure/left ventricular dysfunction, hypertension, age ≥75 [doubled], diabetes mellitus, stroke [doubled]-vascular disease, age 65-74, and females) score ≥1 are recommended oral anticoagulants (OACs) for stroke prophylaxis[2]. Effective treatment options include warfarin (INR 2.0-3.0)[6], dabigatran[7], rivaroxaban[8], apixaban[9] or edoxaban[10]. The choice of anticoagulation therapy depends on the individual risk of stroke and bleeding as well as patients' values and preferences[2]. Despite published guidelines, a substantial percentage of eligible patients are under-treated. A systematic review on the underuse of OACs revealed over two thirds of published studies reported relatively lower anticoagulation treatment levels (≤ 60%) among high-risk patients with NVAF[11]. In addition, there appears to be a tendency that the prescription rate among elderly patients is less likely to be adequate[12]. Thus improving the prescription rate of anticoagulation therapies is warranted, particularly with the aging population.

The cost of AF has been reported in a published review of economic evaluations[13]. However, the impact of ischemic stroke on AF related healthcare costs had not been researched at the time the study was conducted. Studies have been published in individual countries with diverse healthcare systems. Given the differences in reported currencies and cost components, all these heterogeneities limit the comparability between studies. In the present systematic review, we summarized ischemic

stroke related healthcare costs in patients with AF globally, explored the factors associated with increased cost, and highlighted the importance of stroke prophylaxis in the current situation of anticoagulation underuse and assessed the length of stay (LOS) in hospital to provide an indication of resource utilization.

Methods

Searching strategy

The systematic literature search was conducted in January 2015 and updated in December 2015 using four databases: PubMed, EMBASE, Web of Science and the Health Economic Evaluation Database (HEED). The search focused on original studies published in English from 1995 to 2015 with available full-text. The keywords included the combination of the following terms and their medical subject headings including 'cost,' 'atrial fibrillation' and 'stroke'. References cited in retrieved papers were also examined to identify any pertinent studies. Authors were contacted for further information if clarification was required after full-text digestion. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines[14] were used as the basis for the literature search.

Inclusion and exclusion criteria

Studies were eligible if they focused on patients with AF and reported direct and/or indirect cost and/or hospital length of stay (LOS) in relation to ischemic stroke in those patients. Modeling cost or cost-effective analyses and studies that focused only on the healthcare cost of bleeding events were excluded. However, studies that explicitly mentioned ischemic stroke accounting for at least 70% of all stroke types (includes ischemic stroke, hemorrhagic stroke, unspecified stroke and transient ischemic attack) were included.

Data extraction

Costs were converted into purchasing power parity (PPP) 2015 international dollars (I$) to increase comparability across countries, using the 'CCEMG – EPPI-Centre Cost[15]. This adjusts estimates of cost expressed in one currency and price year to a specific target currency and price year. We chose the International Monetary Fund (IMF) dataset as the source for PPP values as opposed to Organization for Economic Co-operation and Development (OECD), as IMF covers more countries and currencies than OECD (183 vs. 30 countries)[16, 17].

Results were presented according to 2015 World Bank classification of economy income groups, based on gross national income (GNI) per capita in 2014[18]. High-income economies (HIEs) are defined with a GNI per capita of $12,736 or more, middle-income economies (MIEs) are those with a GNI per capita of more than $1,045 but less than $12,736, low-income economies (LIEs) are those with a GNI per capita of $1,045 or less. Lower-middle-income economics (LMIEs) and upper-middle-income economies (UMIEs) are separated at a GNI per capita of $4,125.

Cost was also presented by different healthcare systems mainly according to the deductive classification by Katharina et al[19]. The classification focused on the OECD countries and resulted in five types of healthcare systems based on different provision sectors for regulation, financing, and service in the health system. Healthcare systems for non-OECD members such as China, India and Taiwan (referenced from other publications[20-22]) were classified by the same criteria as per OECD countries. Types of healthcare systems, provision sectors, and country/region examples are presented in ***Table 1***.

Quality assessment methods

Quality appraisal for the included cost analyses was based on a validated quality-scoring instrument of Quality Assessment for Health Economic Studies (QHES, ***Supplementary Table 1***). The checklist of QHES contains 16 criteria with weighted scores from 0-9, emphasizing appropriate methods, valid and transparent results and comprehensive reporting of results for types of health

economic studies (score range=0-100; high quality≥75)[23]. As the present systematic review focused on real-world cost analysis rather than modeling cost-effective and health outcome research, two criteria (no. 11 and 12) relating to the health outcome measurement and modeling methods were not applicable in the quality assessment. With the omission of these two criteria, the quality scores ranged from 0 to 85, however, for the purposes of quality assessment, we maintained the 'high quality' score at ≥75. Two authors (XL and ADLW) screened the search results, crosschecked the retrieved data and assessed paper quality, with disagreements resolved through discussion.

Statistical analysis

The relationship between ischemic stroke related healthcare cost (presented as I$ 2015) and country GDP per capita in the same year was assessed by using Spearman's correlation coefficient. To compare the costs of different age groups, two-tailed independent samples t-test was performed for age groups ≥75 and <75 years old. One-way ANOVA was conducted to explore variations of cost among different healthcare systems. Descriptive statistics was also performed for the summary of LOS. Mean [standard deviation (SD)] or median [interquartile range (IQR)] estimates were presented wherever appropriate. Sensitivity analysis was performed on the correlation analysis by removing data from developing countries. The statistical significance was set at $p<0.05$. All statistical analyses were conducted by IBM SPSS version 22.0.

Results

Paper Selection

The literature search identified 1,530 records and two papers from the bibliographies of relevant review articles were added as pertinent studies. After removing duplicates, titles and abstracts from 954 papers were screened and 78 papers were eligible for full-text review (***Figure 1***). Sixteen studies met the inclusion criteria for this systematic review (n=15 for cost analysis and n=10 for hospital LOS analysis). Of the 62 excluded papers, 15 papers explored all complications related to

costs although not all were specific to ischemic stroke and three papers presented only the cost or LOS differences.

Study Characteristics

Study characteristics of included studies indexed by alphabetical order of first author are summarized in ***Table 2***.

Publication year and regional distribution

Studies were published between 2002 and 2015, with the majority between 2013 and 2014. Search results included studies from nine countries, with the majority of studies (n=7) conducted in Europe, followed by North America (n=5) and Asia (n=4). Regarding country income, 87.5% (n=14) of the studies were conducted in HIEs but only one study from LMIEs and UMIEs respectively. None of the studies were conducted in LIEs.

Study design and data source

Of the 16 included studies, there were seven prospective studies, eight retrospective studies and one cross-sectional study. Data sources were relatively balanced between hospital based (n=7) or registry (i.e. insurance or disease) based (n=9) studies.

Perspective, time horizon and discounting rate

In addition to different study objectives and data sources, the included studies also utilized different study perspectives (***Figure 2-A***). Six studies adopted a payer or insurance perspective that was mainly conducted in the USA. Government/institutional perspectives and societal perspectives were adopted in four and five of the included studies, respectively. As reflected by the follow-up period in these studies, analytical time horizon ranged from one to five years (***Table 2***).

Costing approaches

The variation of costing approaches are illustrated in ***Figure 2-B***. The most common method for cost estimation was a bottom-up approach (n=7) that summed-all unit costs accrued during management, treatment, hospitalization and follow-up of ischemic stroke. Insurance claim data were also used widely (n=4), although mainly in the USA. Top-down method was used only in two of the included studies in which disease-attributable costs were considered using a national reference of disease related group or hospital chart review. Two studies used a mixture of different costing approaches.

Quality Assessment

The overall quality score of the 15 cost analyses was modest to high ranging from 49 to 85 (mean ± SD: 68.7±9.9). The quality of individual papers is shown in ***Table 2*** and the assessment details are provided in ***Supplementary Table 1***. Cost data were all collected from a sample of patients with the sample size ranging from 23 to 23,807 (***Table 2***). As shown in ***Supplementary Table 1***, all the studies provided clear information on the best available data source and methodology for data extraction. Of the included studies, fourteen studies (93%) stated well-justified limitations and conclusions and thirteen (86%) studies specified measurable objectives and utilized statistical model to address random effects. However, six studies (40%) stated the justifications for the chosen study perspective and only two studies (13.3%) justified discounting rate (3-5%) when time horizon was beyond one year. Incremental analysis for resources and costs were performed in nine (60%) of the included papers.

Healthcare Cost

Ischemic stroke related costs in patients with AF are summarized in ***Table 3*** by country income groups. Original and converted cost details from individual studies are provided in ***Supplementary Table 2***. As shown in Table 3, direct costs were reported across all of the 15 studies. Only three studies considered indirect costs although these accounted for only a small proportion of the total costs. Total costs were 3-5 times higher in HIEs than other economies (HIEs: I$41,420,

UMIE: I$12,895 and LMIE I$8,184). Mean total healthcare cost was estimated to be I$37,302 (SD: 21,078) per patient based on PPP values of 2015 across all income groups.

Costing components

Seven studies reported cost components for the direct cost estimation (***Figure 3***). Different cost components, including costs related to hospitalization, readmission, rehabilitation, emergency care, outpatient care, nursing care, healthcare visits, home/community healthcare and prescribed medications were considered in these studies. Inpatient costs accounted for the greatest proportion of total direct cost, ranging from 42.8% to 75.5%.

Correlation of total direct cost and GDP per capita

Direct costs incurred by ischemic stroke was positively correlated with GDP per capita in the same year among all countries (***Figure 4-A***, Spearman's correlation coefficient=0.64, p=0.01). At the upper and lower limits of the reported costs, the cost per patient was 8.8 times greater in the USA (I$72,341) than in India (I$8,184). Overall, current local GDP per capita in 2015 can account for about 50% of the variation in direct cost estimates between countries (r^2=0.338 in ***Figure 4-B***). The sensitivity analysis showed similar results but had marginally failed to reach statistical significance (***Figure 4-B,*** Spearman's correlation coefficient=0.54, p=0.057).

Cost differences between age groups

Fourteen included studies reported patients' age at the time of recruitment (***Table 2***). The mean age of patients was 74.1±8.0 years and 60% of the studies focused on elderly patients aged 75 years or above. Ischemic stroke related costs were compared between age groups with an age cut-off of 75 years old. Among AF patients with a history of ischemic stroke, healthcare costs for elderly ≥75 years was 2.3 times that of the younger age group below 75 years (I$45,622 vs I$20,015, p=0.049).

Cost differences among healthcare systems

No statistically significant cost difference was found among different healthcare systems (p=0.079) using ANOVA, possibly due to the limited sample size in each group (***Figure 5***). Regarding countries with existing healthcare systems (n=14, except for China and India where the healthcare systems are developing), the lowest direct cost estimates were the National Health Service in UK and Finland (I$27,451) and the highest was from the Private Health System in the USA (I$56,039). The trend suggests that the more private sectors are involved in the healthcare system, the higher the cost estimate.

Impact of ischemic stroke on healthcare cost of AF

Four studies reported on the cost differences between patients with AF only compared to those with AF and history of ischemic stroke (***Table 4***). As reported from these studies, the total healthcare cost of patients with AF increased by 31-187% on occurrence of ischemic stroke.

Hospital Lengths of Stay

Ten studies reported the median and/or mean LOS in hospital for the treatment of ischemic stroke (***Supplementary Table 2***). The median LOS estimate reported from these studies was 15.5 days per episode. The longest median LOS of 21 days (IQR: 60 days) was in Ireland[24], while an average LOS of 5.2 days for non-repeated stroke admissions and 6.8 days for repeated stroke admission in the USA were reported as the shortest[25] among the included studies.

Discussion

This systematic review captured 16 studies of ischemic stroke relevant costs and resource utilization in patients with AF from nine countries. The costs varied substantially with respect to differences in costing approaches, country income levels and healthcare systems. By converting reported costs into 2015 international dollars, an average treatment cost for ischemic stroke was estimated to be I$37,302 per patient globally and a positive correlation was found between the cost

and local GDP per capita. Interestingly, the sensitivity analysis showed that the correlation result was affected by China and India. As developing countries, the average GDP of China and India are much lower than other countries included in this review. Consequently, direct costs incurred by ischemic stroke per patient are also much lower than other included countries. There is urgent need for developing countries such as China and India to develop more integrated and efficient healthcare systems, which will minimize risk factors for stroke, such as effective use of anticoagulation therapies[26-27] and smoking cessation strategies[28].

Another interesting point is the time horizon effect of the medical costs. Mercaldi et al (2012)[55] was the only study which provided the details of costing components of ischemic stroke in the first three years. Their results showed that the costs of ischemic stroke in patients with AF were the highest in first year. The authors referred to the recurrence rate of ischemic stroke as a possible reason for the differences in the costs in different years. In addition, Mercaldi et al (2013)[54] provided an estimation of the costs of ischemic stroke in patients with AF in Quarters 1 to 4. They found that the costs decreased by nearly half from Quarter 1 ($23,334) to Quarter 2 ($12,761) and then stabilized in Quarters 3 ($7,074) and 4 ($6,750). However, the authors did not address either the reason behind it or the details of costing components.

Elderly patients above 75 years of age cost more than twice as much as their younger peers below 75 years, possibly due to increased risk of complications[29] resulting in prolonged LOS in hospital[30]. To our knowledge, this is the only study that has comprehensively quantified the economic impact of ischemic stroke in patients with AF across different countries. The main implication of this study is to highlight the importance of minimizing stroke risk using anticoagulation therapies in patients with AF.

Gaps in standards of care for the diagnosis and management of AF are widely reported in both clinical trial[31] and real-life settings[32-34]. It is estimated that 10-30% of AF are not diagnosed[32, 35] and more than 40% of patients at high risk of stroke fail to receive guideline-recommended oral anticoagulant treatment[11, 35]. The level of treatment varied among regions and study settings, ranging

from 19% in a prospective survey in a teaching hospital in Italy[36] to 81% in an analysis of a national survey database in the USA[37]. Further, ensuring patients at high risk receive the most effective anticoagulation treatment remains a challenge. Although novel anticoagulants have been available since 2009, warfarin is still widely used, especially in the elderly and high-risk patients[33, 38] with inadequate quality control[39] and increased risk of stroke[40, 41]. All these gaps highlight unmet needs for stroke prevention in undiagnosed and undertreated AF, which will shed light on the strategies needed to eliminate disparities in treatment.

Consistent with previous published cost of illness of atrial fibrillation[13], hospitalization cost for the treatment of stroke was the major driver of overall cost in this review. Our study found that the median LOS in hospitals for stroke patients with AF was estimated to be 15.5 days. From a healthcare resource utilization perspective, this economic burden and resource consumption may be reduced or avoided if sufficient anticoagulation care is provided to prevent stroke. Hence, it is important for clinicians and stakeholders to focus efforts to improve stroke prevention in patients with AF.

It is not unexpected that costs are significantly higher for elderly patients compared with younger patients and this is expected to increase markedly over future decades due to the ageing population globally[42]. Another interesting finding of this study is the trend of increased costs associated with more private sector involvement in the healthcare system. It is beyond the scope of our current study to explore the underlying reasons for this phenomenon. Faced with the increased healthcare burden and costs arising from the ageing population, countries around the globe need an integrated and efficient healthcare system to better meet the needs of these challenges. Healthcare system reform and redesign cannot be avoided, perhaps more so for those with private sector involvement.

There are several limitations in this systematic review. First, only studies published in English were included which would introduce language and publication bias. Notably, a considerable proportion of the included studies were hospital-based using questionnaire interviews for costing[43-45], which relied on self-reported data that may lead to selection and recall bias. Second, the quality of

published studies was variable. Only two of the 15 studies discounted the cost at certain rates, therefore the reported cost may not be an accurate reflection of actual cost. Indirect costs were only reported in a small proportion of studies[24, 44, 45], which would hinder the overall cost estimation required for an assessment from the societal perspective. For labor market outcomes, the lack of research on the relevant costs of productivity loss[44, 45] is also apparent. Ischemic stroke related healthcare costs are less clear from LIEs compared with HIEs. However, LIEs specifically involve countries with increasing AF prevalence and rapidly ageing populations where healthcare costs are particularly likely to escalate. Third, is the issue of time horizon, which may have an impact on medical costs. Of the 16 included studies, 15 reported on medical costs. Only 2 of these studies had specified the costs at various different time horizons but insufficient information was provided for further analysis. Due to the limited information provided in the reviewed studies, it is difficult to further explore the relationship between medical costs and time horizon. Lastly, compared with other costs of illness systematic reviews for AF[13] and other diseases[46, 47], this review included a smaller number of studies. However the sample size of the included studies was considered adequate. In general, current research on the economic burden of patients with AF with a history of ischemic stroke is inadequate in both quality and quantity. A standardized approach is imperative to enable fair comparisons across different countries. Despite the limitations, this review provided an overview of stroke related cost in patients with AF and estimated the cost ranges across countries of different incomes with greater certainty than individual studies.

In summary, a considerable economic burden caused by ischemic stroke in patients with AF is consistently reported, especially in the elderly population. Increased costs are positively associated with the income level of the individual country. Stakeholders should recognize the importance of anticoagulation therapies in stroke prophylaxis and allocate sufficient resources to improve the prognosis of AF and thereby reduce the associated downstream economic burden. In addition, high quality studies are required to form the basis for long-term economic evaluation, particularly for less developed countries.

Ethics

This study complies with the Declaration of Helsinki. No informed consent was obtained as no patient contact was required for this systematic review. No conflict of interest needs to be declared by any of the authors.

Funding

No funding support needs to be declared for this study.

Acknowledgements

We thank our colleagues at the Department of Pharmacology and Pharmacy of the University of Hong Kong – Dr. Martijn Schuemie and Mr. Kenneth K.C. Man for statistical advice and Ms. Lisa Wong for proofreading the manuscript.

Table 1. Healthcare systems and relevant countries/regions

Healthcare systems	Regulation	Finance	Service	Countries/regions
National health service	State*	State*	State*	UK, Finland
National health insurance	State*	State*	Private***	Ireland, Taiwan
Etatist social health insurance	State*	Societal**	Private***	France
Social health insurance	Societal**	Societal**	Private***	Germany
Private health system	Private***	Private***	Private***	USA
Healthcare system under developing	NA	NA	NA	China, India

* State sector: government; ** Societal sectors: private non-profit providers including but not limited to social security funds; *** Private sectors: private for-profit providers including but not limited to private insurances, tax financing and out-of-pocket expenditure.

Table 2. Study characteristics

Study no.	Reference	Country and income groups	Healthcare system	Study design	Sample size and patient age (years)	Data source	Perspective	Time horizon	Discounting rate	Costing approach	QHES score
1	Ali N 2015[48]	UK, High-income economy	National Health Service[19]	Prospective cohort	n=73; 80.1±10.1	Hospital based	Institutional (unspecified)	1 year	Unspecified	Bottom-up approach*	59
2	Brüggenjürgen 2007[44]	Germany, High-income economy	Social Health Insurance[19]	Prospective cohort	n=71; 73.7±9.4	Hospital based	Societal (unspecified)	1 year	Unspecified	Bottom-up approach*	68
3	Chang 2002[49]	Taiwan, High-income economy	National Health Insurance [20]	Single-arm prospective	n=23; 64.3±12.5	Hospital based	NA	NA	NA	NA	NA
4	Cotte 2014[50]	France, High-income economy	Etatist Social Health Insurance[19]	Retrospective cohort	n=1,257; 78.8±9.8	Registry based	Insurance	2 years	Unspecified	Top-down approach**	59
5	Fitch 2014[51]	USA, High-	Private	Retrospective	n=261;	Registry	Payer	1 year	Unspecified	Insurance	72

Study no.	Reference	Country and income groups	Healthcare system	Study design	Sample size and patient age (years)	Data source	Perspective	Time horizon	Discounting rate	Costing approach	QHES score
		income economy	Health System [19]	cohort	83.5±8	based	(Medicare) (unspecified)			claim data	
6	Hannon 2014[24]	Ireland, High-income economy	National Health Insurance [19]	Single-arm prospective	n=177; 76.5 ± 10.5	Registry based	Societal	2 years	Unspecified	Mixed approach***	72
7	Hu 2013[45]	China, Upper-middle income economy	NA	Single-arm retrospective	n=73; 69.9±10.3	Hospital based	Societal	1 year	Undiscounted	Bottom-up approach*	66
8	Huang 2013[52]	Taiwan, High-income economy	National Health Insurance [20]	Cross-sectional	n=1,021; 68.1±10.8	Hospital based	Government (unspecified)	Unspecified	Unspecified	Bottom-up approach*	49
9	Luengo-	UK,	National	Single-arm	n=153;	Registry	Institutional	5 years	Unspecified	Bottom-up	55

Study no.	Reference	Country and income groups	Healthcare system	Study design	Sample size and patient age (years)	Data source	Perspective	Time horizon	Discounting rate	Costing approach	QHES score
	Fernandez 2013[53]	High-income economy	Health Service[19]	prospective	80±10	based	(unspecified)			approach*	
10	Marfatia 2014[43]	India, Lower-middle income economy	NA	Single-arm prospective	n=400; 61.4±9.4	Hospital based	Societal	1 year	Unspecified	Bottom-up approach*	74
11	Mercaldi 2011[54]	USA, High-income economy	Private Health System [19]	Retrospective cohort	n=119,764; 79.3±8.6	Registry based	Payer (Medicare) (unspecified)	1 year	Unspecified	Insurance claim data	81
12	Mercaldi 2012[55]	USA, High-income economy	Private Health System [19]	Retrospective cohort (matched)	n=7,799; 81.1±7.6	Population based	Payer (Medicare)	3 years	Unspecified	Insurance claim data	78
13	Meretoja 2011[56]	Finland, High-income	National Health	Retrospective cohort	n=1,306; Age	Registry based	Societal	5 years	5% per year	Mixed approach***	85

Study no.	Reference	Country and income groups	Healthcare system	Study design	Sample size and patient age (years)	Data source	Perspective	Time horizon	Discounting rate	Costing approach	QHES score
		economy	Service [19]		unspecified						
14	Sussman 2013[57]	USA, High-income economy	Private Health System [19]	Retrospective cohort	N=23,807; 77±11.6	Registry based	Payer	1 year	Unspecified	Top-down approach**	71
15	Wang 2015[25]	USA, High-income economy	Private Health System [19]	Retrospective cohort	n=2,407; 57.4	Registry based	Insurance (unspecified)	3 years	Unspecified	Insurance claim data (unspecified)	67
16	Yiin 2014[58]	UK, High-income economy	National Health Service [19]	Single-arm prospective	n=383; 80.0 ±9.7	Registry based	Institutional (unspecified)	5 years	3.5% per year	Bottom-up approach*	74

* Bottom-up approach based on national reference, medical chart review and/or physician and patients' questionnaire interview for unit cost estimation as reported; ** Top-down approach based on Diagnosis Related Groups (DRGs) or International Classification of Diseases (ICD) for overall cost estimation as reported; *** Mixed approach used two or three combinations of bottom-up approach, top-down approach and insurance claim data as reported.

Table 3. Ischemic stroke related cost by country income groups*[*]

Income group	Direct costs (n=15)	Indirect costs (n=3)	Total costs (n=15)
HIE (n=13)	40,730±19,623	4,487±5,275	41,420±19,485
UMIE (n=1)	8,302	4,593	12,895
LMIE (n=1)	8,184	-	8,184
Overall (n=15)	36,398±21,464	4,522±3,730	37,302±21,078

[*]Cost data were presented as I$ per patient based on IMF PPP values of 2015;

HIE: high-income economies; UMIE: upper-middle income economies; LMIE: lower-middle income economies.

Table 4. Cost differences of patients with/without ischemic stroke

Study no.	Country (reported year)	Per patient cost of AF only (mean±SD)	Per patient cost of AF with ischemic stroke	Cost increase (%)*
5	USA (2007)	$35,474±41,875	$63,781±48,422	80%
9	UK (2009)	£2,566±6,586	£3,370±7,156	31%
11	USA (2006)	$15,718±36,842	$43,937±49,568	180%
12	USA (2011)	$17,980	$51,605	187%

* Cost increase (%) = $\frac{per\ patient\ cost\ of\ AF\ with\ ischaemic\ stroke - per\ patient\ cost\ of\ AF\ only}{per\ patient\ cost\ of\ AF\ only} \times 100\%$

AF: atrial fibrillation

Figure 1. PRISMA flowchart

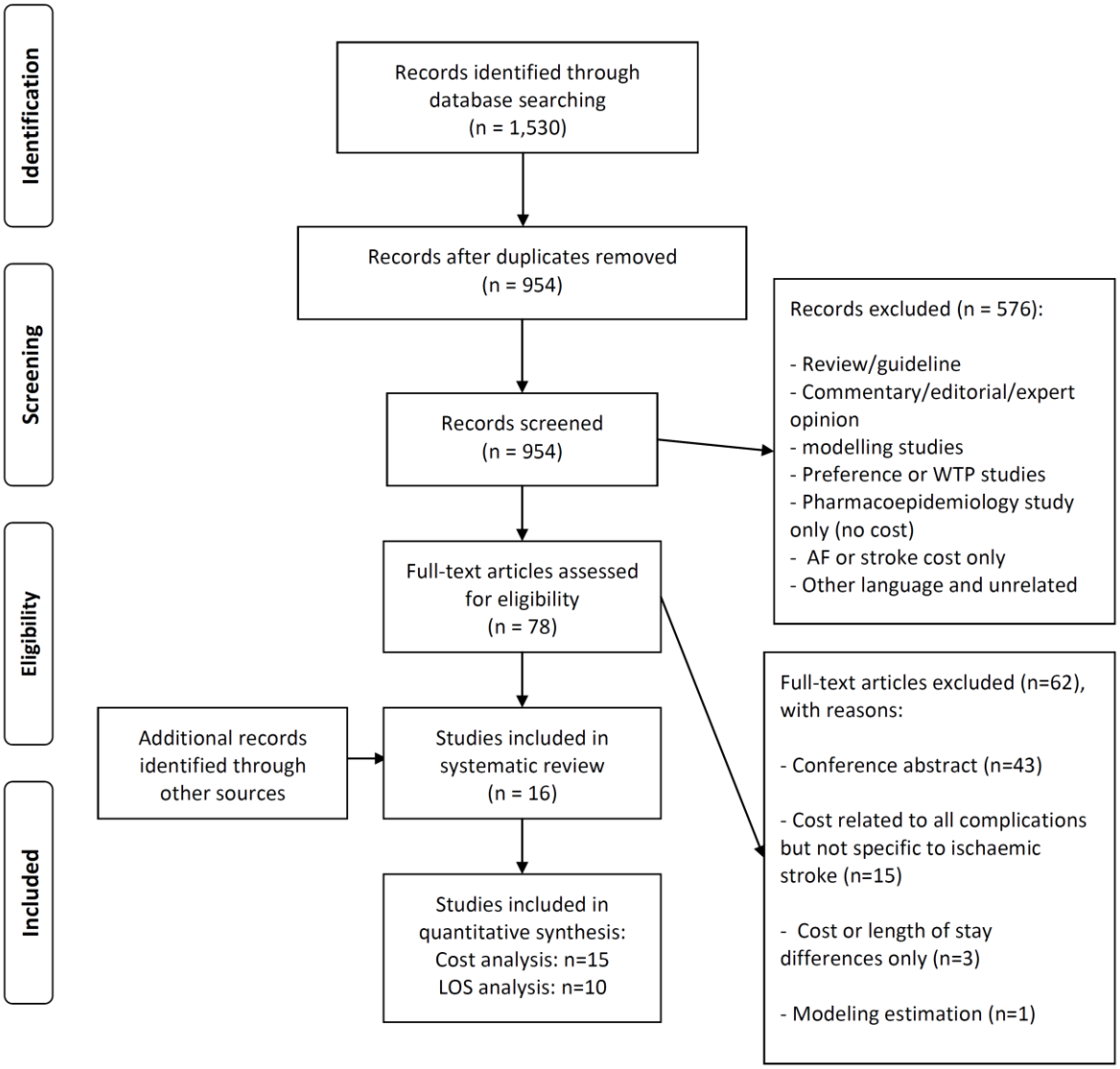
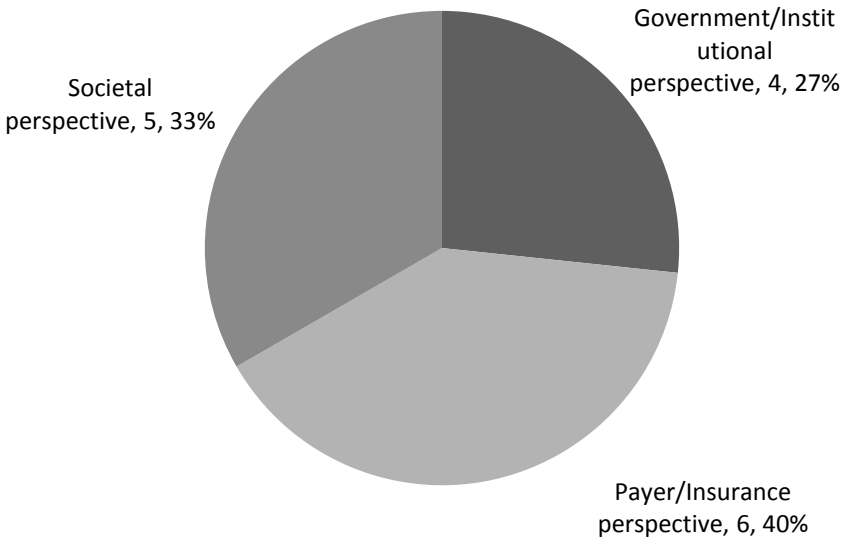


Figure 2. Study perspectives and costing approaches for 15 included cost analyses

A: Study perspective (numbers, percentage)



B: Costing approach (numbers, percentage)

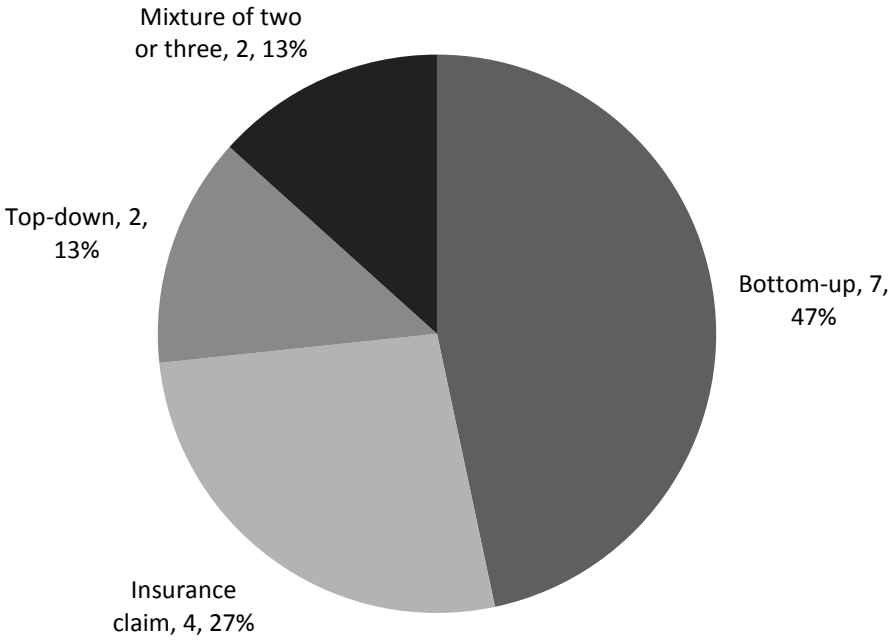


Figure 3. Breakdown of direct cost from seven studies

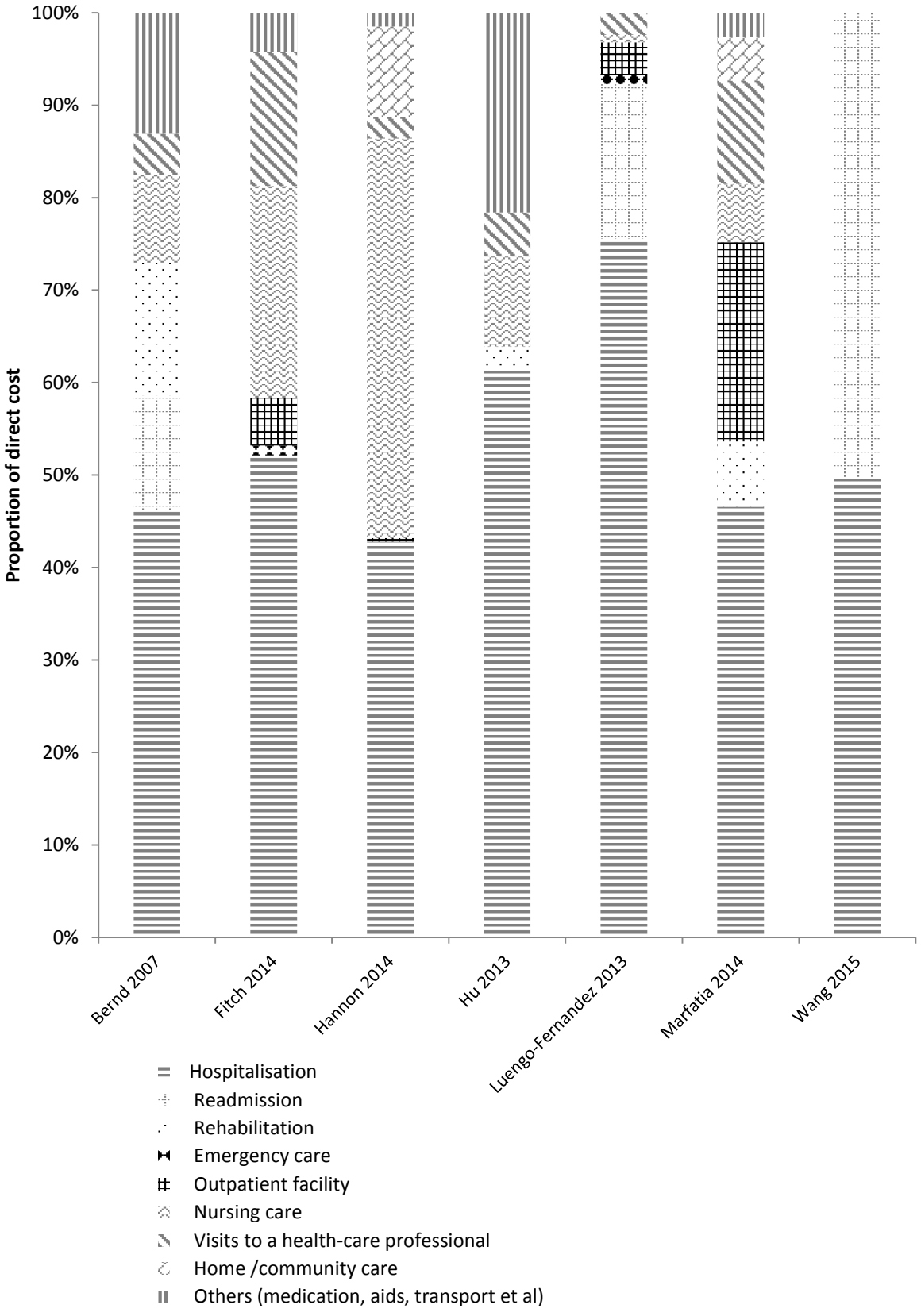
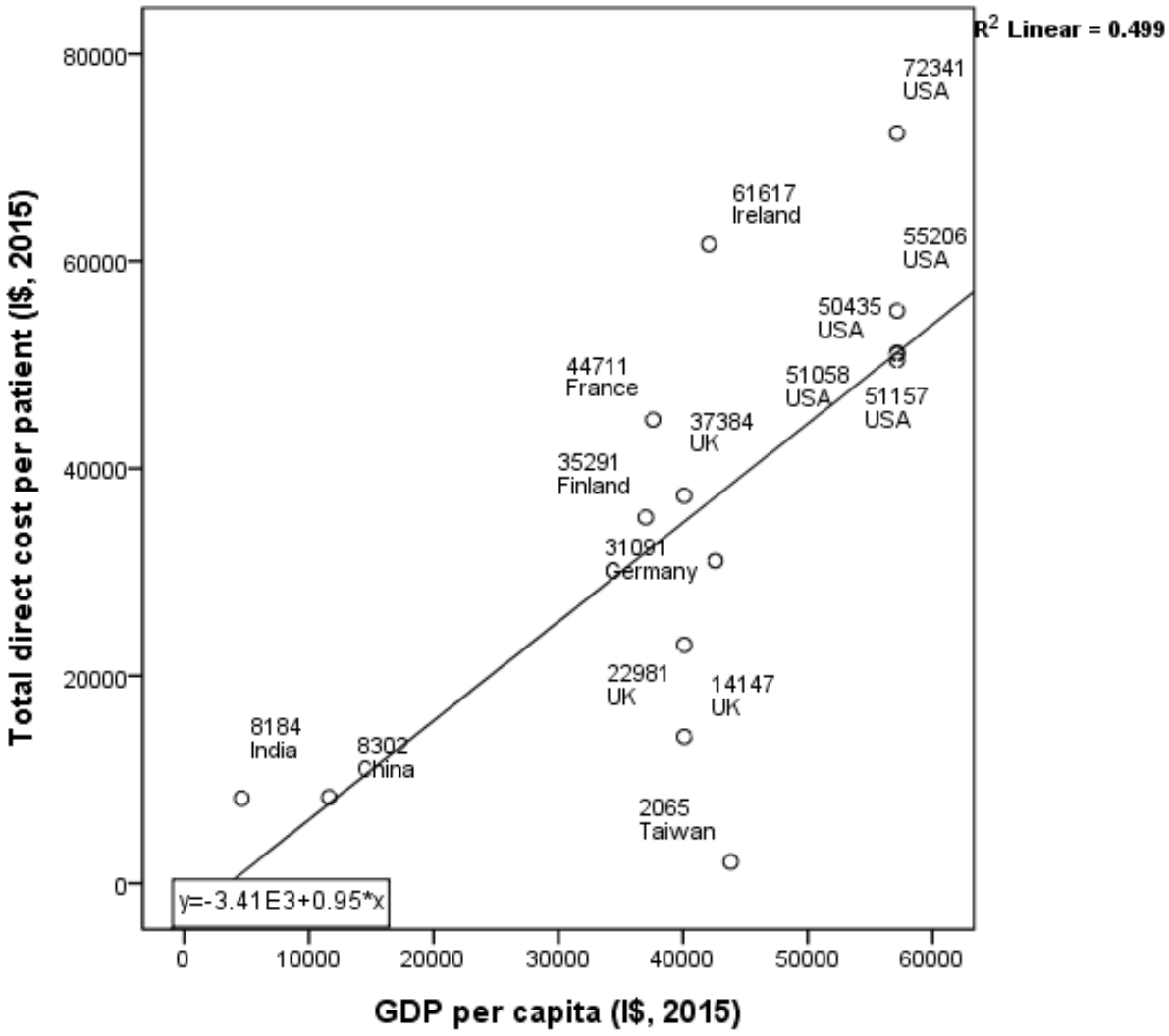


Figure 4. Scatterplot of converted direct cost per patient and GDP per capita (I$ 2015)

A: Scatterplot of converted direct cost per patient and GDP per capita (in all countries)



B: Scatterplot of converted direct cost per patient and GDP per capita (Exclusion of India and China)

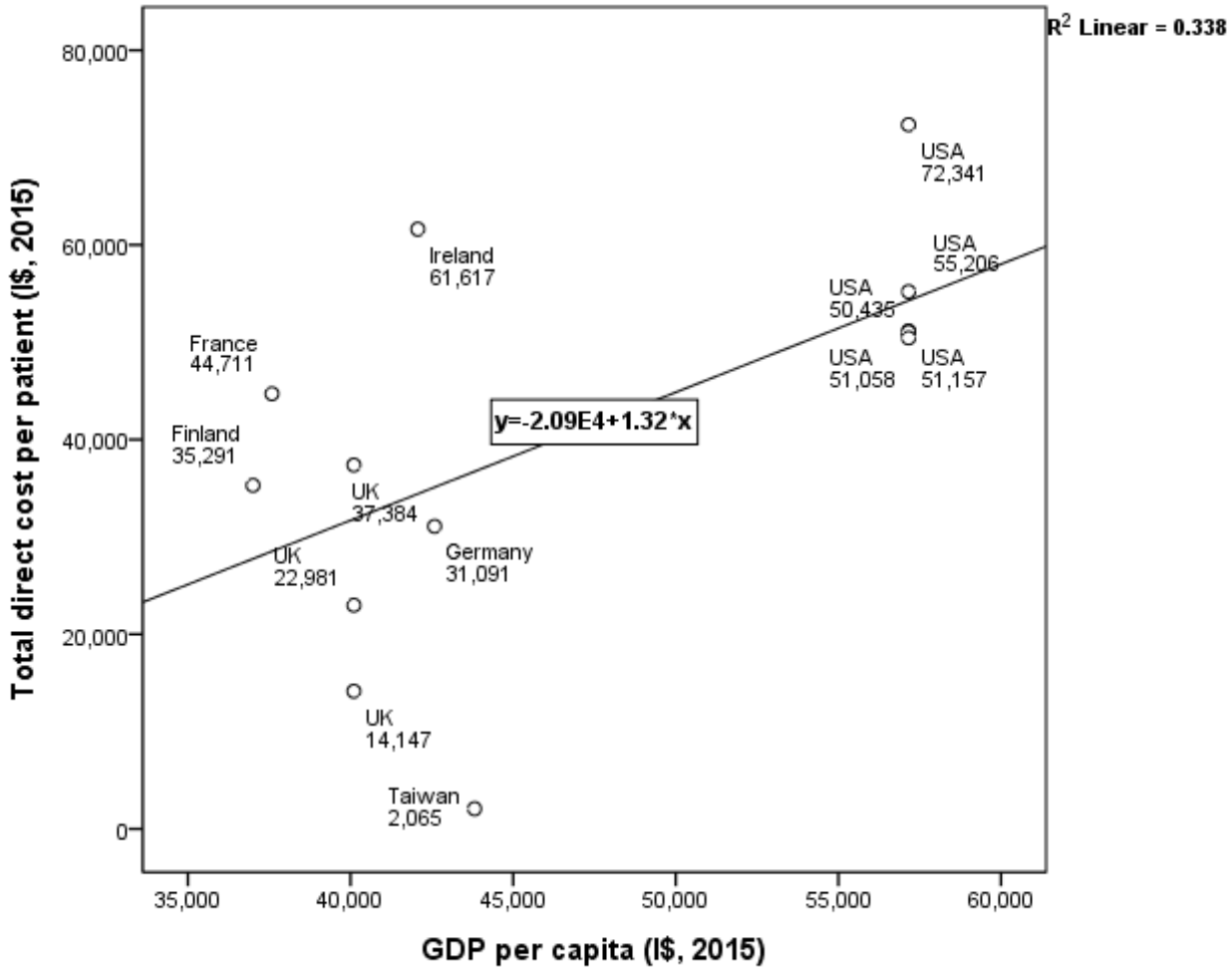
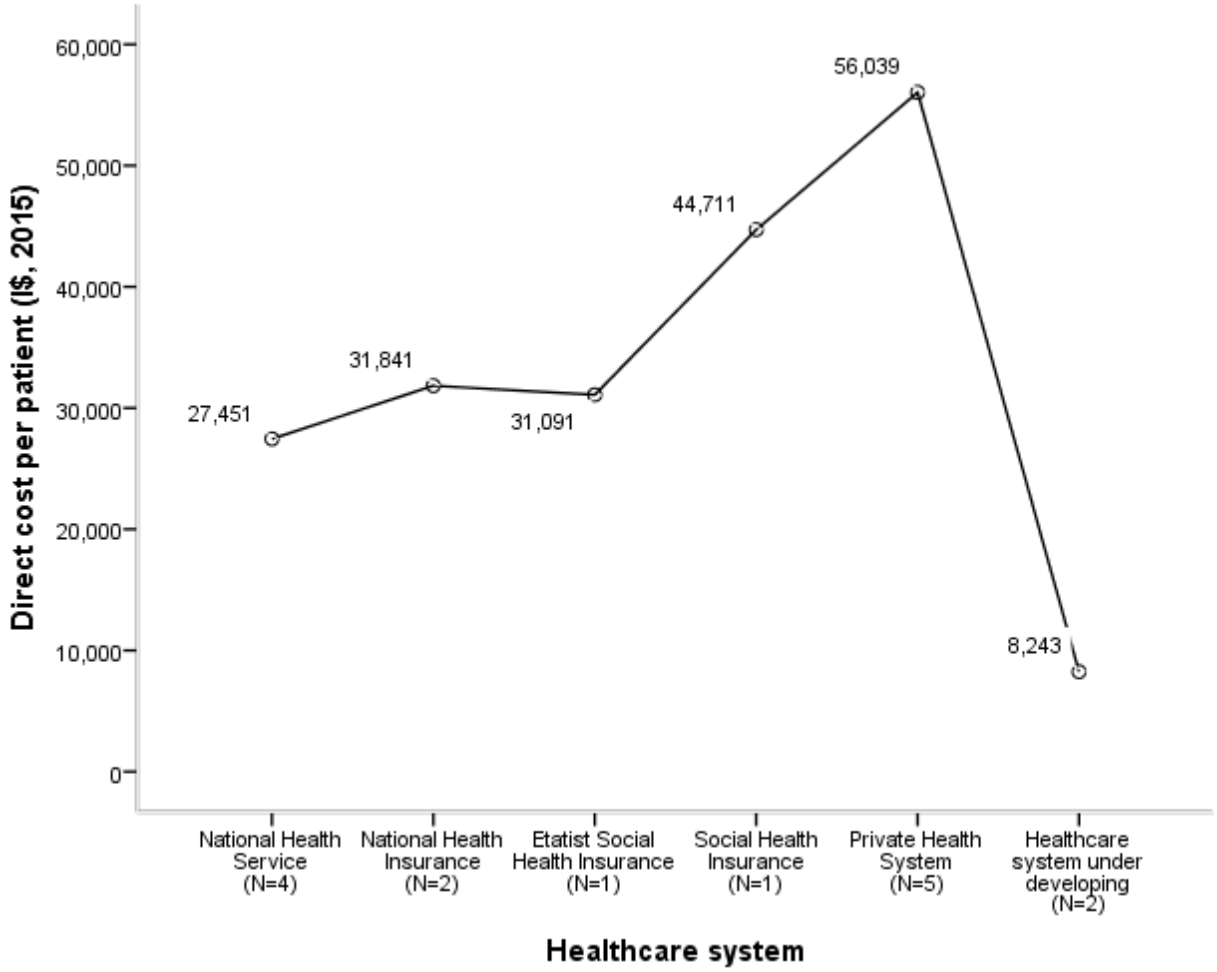


Figure 5. Direct cost per patient in different healthcare systems



References

[1] Rahman F, Kwan GF, Benjamin EJ. Global epidemiology of atrial fibrillation. *Nat Rev Cardiol* 2014; **11**: 639-654.

[2] Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J* 2012; **33**: 2719-2747.

[3] van Walraven C, Hart RG, Connolly S, Austin PC, Mant J, Hobbs FD, et al. Effect of age on stroke prevention therapy in patients with atrial fibrillation: the atrial fibrillation investigators. *Stroke* 2009; **40**: 1410-1416.

[4] McGrath ER, Kapral MK, Fang JM, Eikelboom JW, O'Conghaile A, Canavan M, et al. Association of atrial fibrillation with mortality and disability after ischemic stroke. *Neurology* 2013; **81**: 825-832.

[5] Suzman R, Beard J. Global health and ageing. *WHO report* 2011.

[6] Connolly S, Pogue J, Hart R, Pfeffer M, Hohnloser S, Chrolavicius S, et al. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet* 2006; **367**: 1903-1912.

[7] Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009; **361**: 1139-1151.

[8] Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011; **365**: 883-891.

[9] Granger CB, Alexander JH, McMurray JJV, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus Warfarin in Patients with Atrial Fibrillation. *N Engl J Med* 2011; **365**: 981-992.

[10] Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013; **369**: 2093-2104.

[11] Ogilvie IM, Newton N, Welner SA, Cowell W, Lip GY. Underuse of oral anticoagulants in atrial fibrillation: a systematic review. *Am J Med* 2010; **123**: 638-645.e634.

[12] Lip GY, Laroche C, Dan GA, Santini M, Kalarus Z, Rasmussen LH, et al. 'Real-world' antithrombotic treatment in atrial fibrillation: The EORP-AF pilot survey. *Am J Med* 2014; **127**: 519-529.e511.

[13] Wolowacz SE, Samuel M, Brennan VK, Jasso-Mosqueda JG, Van Gelder IC. The cost of illness of atrial fibrillation: a systematic review of the recent literature. *Europace* 2011; **13**: 1375-1385.

[14] Moher D, Liberati A, Tetzlaff J, Altman DG, The PG. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med* 2009; **6**: e1000097.

[15] CCEMG - EPPI-Centre Cost Converter (v.1.4 last update: 27 January 2014). http://eppi.ioe.ac.uk/costconversion/default.aspx (June 29th 2015 date last accessed).

[16] Internal Monetary Fund. World Economic Outlook Database. http://www.imf.org/external/pubs/ft/weo/2013/02/weodata/index.aspx (Dec 10th 2015 date last accessed).

[17] OECD. Members and parters. http://www.oecd.org/about/membersandpartners/ (Dec 10th 2015 date last accessed).

[18] Country and Lending Groups. http://data.worldbank.org/about/country-and-lending-groups (June 29th 2015 date last accessed).

[19] Bohm K, Schmid A, Gotze R, Landwehr C, Rothgang H. Five types of OECD healthcare systems: empirical results of a deductive classification. *Health Policy* 2013; **113**: 258-269.

[20] Lee SY, Chun CB, Lee YG, Seo NK. The National Health Insurance system as one type of new typology: The case of South Korea and Taiwan. *Health Policy* 2008; **85**: 105-113.

[21] Blumenthal D, Hsiao W. Lessons from the East — China's Rapidly Evolving Health Care System. *N Engl J Med* 2015; **372**: 1281-1285.

[22] India's Healthcare System – Overview and Quality Improvements. http://www.tillvaxtanalys.se/download/18.5f097bc113eacc3d6d5140/1369033657507/direct_response_2013_04.pdf (June 25th 2015 date last accessed).

[23] Ofman JJ, Sullivan SD, Neumann PJ, Chiou CF, Henning JM, Wade SW, et al. Examining the value and quality of health economic analyses: implications of utilizing the QHES. *J Manag Care Pharm* 2003; **9**: 53-61.

[24] Hannon N, Daly L, Murphy S, Smith S, Hayden D, Chroinin DN, et al. Acute Hospital, Community, and Indirect Costs of Stroke Associated With Atrial Fibrillation Population-Based Study. *Stroke* 2014; **45**: 3670-3674.

[25] Wang G, Joo H, Tong X, George MG. Hospital costs associated with atrial fibrillation for patients with ischemic stroke aged 18-64 years in the United States. *Stroke* 2015; **46**: 1314-1320.

[26] Wen-Hang QI. Retrospective investigation of hospitalised patients with atrial fibrillation in mainland China. *Int J Cardiol* 2005; **105**: 283-287.

[27] Guo GB, Chang HW, Chen MC, Yang CH. Underutilization of anticoagulation therapy in chronic atrial fibrillation. *Jpn Heart J* 2001; **42**: 55-65.

[28] Lipska K, Sylaja PN, Sarma PS, Thankappan KR, Kutty VR, Vasan RS, et al. Risk factors for acute ischaemic stroke in young adults in South India. *J Neurol Neurosurg Psychiatry* 2007; **78**: 959-963.

[29] Modrego PJ, Pina MA, Lerín FJ. The impact of ageing on stroke subtypes, length of stay and mortality: study in the province of Teruel, Spain. *Acta Neurologica Scandinavica* 2003; **108**: 435-442.

[30] Naccarelli GV, Johnston SS, Dalal M, Lin J, Patel PP. Rates and implications for hospitalization of patients >/=65 years of age with atrial fibrillation/flutter. *Am J Cardiol* 2012; **109**: 543-549.

[31] Lowres N, Neubeck L, Redfern J, Freedman SB. Screening to identify unknown atrial fibrillation. A systematic review. *Thromb Haemost* 2013; **110**: 213-222.

[32] Clua-Espuny JL, Lechuga-Duran I, Bosch-Princep R, Roso-Llorach A, Panisello-Tafalla A, Lucas-Noll J, et al. Prevalence of Undiagnosed Atrial Fibrillation and of That Not Being Treated With Anticoagulant Drugs: the AFABE Study. *Revista Española de Cardiología (English Version)* 2013; **66**: 545-552.

[33] Patel AD, Tan MK, Angaran P, Bell AD, Berall M, Bucci C, et al. Risk stratification and stroke prevention therapy care gaps in Canadian atrial fibrillation patients (from the Co-ordinated National Network to Engage Physicians in the Care and Treatment of Patients With Atrial Fibrillation chart audit). *Am J Cardiol* 2015; **115**: 641-646.

[34] Clua-Espuny JL, Bosch-Princep R, Roso-Llorach A, López-Pablo C, Giménez-Garcia E, González-Rojas N, et al. Diagnosed, undiagnosed and overall atrial fibrillation research on population over 60 year-old. AFABE study. *Cardiovascular System* 2014; **2**.

[35] Department of Health AG. Review of Anticoagulation Therapies in Atrial Fibrillation 2012.

[36] Ageno W, Ambrosini F, Nardo B, Imperiale D, Dentali F, Mera V, et al. Atrial fibrillation and antithrombotic treatment in Italian hospitalized patients: a prospective, observational study. *J Thromb Thrombolysis* 2001; **12**: 225-230.

[37] Rowan SB, Bailey DN, Bublitz CE, Anderson RJ. Trends in anticoagulation for atrial fibrillation in the U.S.: an analysis of the national ambulatory medical care survey database. *J Am Coll Cardiol* 2007; **49**: 1561-1565.

[38] Halperin JL, Huisman M, Diener H-C, Dubner S, Ma C, Rothman K, et al. ANTITHROMBOTIC TREATMENT IN RELATION TO AGE IN PATIENTS WITH NEWLY DIAGNOSED ATRIAL FIBRILLATION IN NORTH AMERICA (GLORIA-AF PHASE II). *J Am Coll Cardiol* 2015; **65 (10_S**).

[39] Molteni M, Cimminiello C. Warfarin and atrial fibrillation: from ideal to real the warfarin affaire. *Thromb J* 2014; **12**: 5.

[40] Albertsen IE, Rasmussen LH, Overvad TF, Graungaard T, Larsen TB, Lip GY. Risk of stroke or systemic embolism in atrial fibrillation patients treated with warfarin: a systematic review and meta-analysis. *Stroke* 2013; **44**: 1329-1336.

[41] Ho CW, Ho MH, Chan PH, Hai JJ, Cheung E, Yeung CY, et al. Ischemic stroke and intracranial hemorrhage with aspirin, dabigatran, and warfarin: impact of quality of anticoagulation control. *Stroke* 2015; **46**: 23-30.

[42] WHO. World report on ageing and health 2015. http://www.who.int/ageing/events/world-report-2015-launch/en/ (Oct 29th 2015 latest accessed).

[43] Marfatia S, Monz B, Suvarna V, Bhure S, Sangole N. Treatment costs of stroke related to nonvalvular atrial fibrillation patients in India-a multicenter observational study. *Value in Health Regional Issues* 2014; **3**: 205-210.

[44] Brüggenjürgen B, Rossnagel K, Roll S, Andersson FL, Selim D, Müller-Nordhorn J, et al. The Impact of Atrial Fibrillation on the Cost of Stroke: The Berlin Acute Stroke Study. *Value in Health* 2007; **10**: 137-143.

[45] Hu S, Zhan L, Liu B, Gao Y, Li Y, Tong R, et al. Economic burden of individual suffering from atrial fibrillation-related stroke in China. *Value in Health Regional Issues* 2013; **2**: 135-140.

[46] Seuring T, Archangelidi O, Suhrcke M. The Economic Costs of Type 2 Diabetes: A Global Systematic Review. *Pharmacoeconomics* 2015; **33**: 811-831.

[47] Laurence YV, Griffiths UK, Vassall A. Costs to Health Services and the Patient of Treating Tuberculosis: A Systematic Literature Review. *Pharmacoeconomics* 2015; **33**: 939-955.

[48] Ali AN, Howe J, Abdel-Hafiz A. Cost of acute stroke care for patients with atrial fibrillation compared with those in sinus rhythm. *Pharmacoeconomics* 2015; **33**: 511-520.

[49] Chang KC, Tseng MC, Weng HH, Lin YH, Liou CW, Tan TY. Prediction of length of stay of first-ever ischemic stroke. *Stroke* 2002; **33**: 2670-2674.

[50] Cotte FE, Chaize G, Kachaner I, Gaudin AF, Vainchtock A, Durand-Zaleski I. Incidence and cost of stroke and hemorrhage in patients diagnosed with atrial fibrillation in France. *J Stroke Cerebrovasc Dis* 2014; **23**: e73-83.

[51] Fitch K, Broulette J, Kwong WJ. The economic burden of ischemic stroke and major hemorrhage in medicare beneficiaries with nonvalvular atrial fibrillation: A retrospective claims analysis. *Am Health Drug Benefits* 2014; **7**: 200-9.

[52] Huang YC, Hu CJ, Lee TH, Yang JT, Weng HH, Lin LC, et al. The Impact Factors on the Cost and Length of Stay among Acute Ischemic Stroke. *Journal of Stroke & Cerebrovascular Diseases* 2013; **22**: E152-E158.

[53] Luengo-Fernandez R, Yiin GS, Gray AM, Rothwell PM. Population-based study of acute- and long-term care costs after stroke in patients with AF. *Int J Stroke* 2013; **8**: 308-314.

[54] Mercaldi CJ, Ciarametaro M, Hahn B, Chalissery G, Reynolds MW, Sander SD, et al. Cost efficiency of anticoagulation with warfarin to prevent stroke in medicare beneficiaries with nonvalvular atrial fibrillation. *Stroke* 2011; **42**: 112-118.

[55] Mercaldi CJ, Siu K, Sander SD, Walker DR, Wu Y, Li Q, et al. Long-Term Costs of Ischemic Stroke and Major Bleeding Events among Medicare Patients with Nonvalvular Atrial Fibrillation. *Cardiol Res Pract* 2012; **2012**: 645469.

[56] Meretoja A, Kaste M, Roine RO, Juntunen M, Linna M, Hillbom M, et al. Direct costs of patients with stroke can be continuously monitored on a national level: performance, effectiveness, and Costs of Treatment episodes in Stroke (PERFECT Stroke) Database in Finland. *Stroke* 2011; **42**: 2007-2012.

[57] Sussman M, Menzin J, Lin I, Kwong WJ, Munsell M, Friedman M, et al. Impact of atrial fibrillation on stroke-related healthcare costs. *J Am Heart Assoc* 2013; **2**: e000479.

[58] Yiin GS, Howard DP, Paul NL, Li L, Luengo-Fernandez R, Bull LM, et al. Age-specific incidence, outcome, cost, and projected future burden of atrial fibrillation-related embolic vascular events: a population-based study. *Circulation* 2014; **130**: 1236-1244.