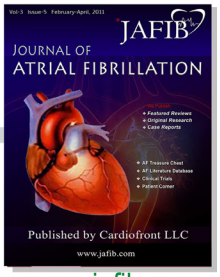
JAFIB
Original Research
Journal of Atrial Fibrillation



www. jafib.com

The Cost of Thromboembolic Events and their Prevention among Patients with Atrial Fibrillation

Thomas Davidson[a], PhD, Magnus Husberg[a], B.Sc, Magnus Janzon[a,b] , MD, Lars-Åke Levin[a], PhD

[a]Center for Medical Technology Assessment, Department of Medical and Health Sciences, Linköping University, Sweden. [b]Division of Cardiovascular Medicine, Department of Medical and Health Sciences, Linköping University, Sweden

Abstract

Aim: Atrial fibrillation (AF) is the most common type of cardiac arrhythmia. People with AF have a significantly increased risk of thromboembolic events, including stroke, and the main treatment is therefore aimed at preventing thromboembolic events via anticoagulation with warfarin or acetylsalicylic acid. However, the development of new anticoagulation treatments has prompted a need to know the current cost of AF-related thromboembolic events, for future cost-effectiveness comparisons with the existing treatments. In this study, we estimated the cost of thromboembolic events and their prevention among Swedish AF patients in 2010.

Methods: The relevant costs were identified, quantified, and valued. The complications included were ischaemic and haemorrhagic stroke, gastrointestinal bleeding, and other types of major bleeding caused by AF. Treatments intended to lower the risk of ischaemic stroke were also included. A societal perspective was used, including productivity loss due to morbidity. Patients with a CHADS2 score of 1 or higher were included.

Results: Among the 9 340 682 inhabitants of Sweden, there are 118 000 patients with AF and at least one more risk factor for stroke, comprising 1.26% of the population. Of these patients, 43.3% are treated with warfarin, 28.3% use acetylsalicylic acid, and 28.3% are assumed to have no anticoagulation treatment. The cost of AF-related complications and its prevention in Sweden was estimated at €437 million for 2010, corresponding to €3 712 per AF patient per year. The highest cost was caused by stroke, and the second highest by the cost of monitoring the warfarin treatment. As the prevalence of AF is expected to increase in the future, AF-related costs are also expected to rise.

Conclusion: Thromboembolic events cause high costs. New, easily-administered treatments that could reduce the risk of stroke have the potential to be cost-effective.

Keywords: cost, thromboembolic events, atrial fibrillation, anticoagulation

Introduction

Atrial fibrillation (AF) is the most common type of cardiac arrhythmia, occurring in over 1 percent of the population .[1] The prevalence increases with age, to about 10 percent in the 80+ age group. [2]As the proportion of elderly people in the population is expected to increase, the number of AF patients

Corresponding Address :Thomas Davidson, Ph.D, Center for Medical Technology Assessment, Department of Medical and Health Sciences, Linköping University, Sweden.

is also expected to increase in the long term.

Patients with AF often suffer a decreased quality of life ,[3-5] and AF also increases the risk of thromboembolic events such as ischaemic stroke. The treatment of AF often varies for different patients and types of AF. Most AF treatments, however are given in combination with anticoagulation treatment to prevent thromboembolic events .[6] The most commonly used anticoagulation treatment today is warfarin (Waran®), which is very effective in preventing stroke. This treatment requires accurate dosing and careful monitoring, to reduce the risk of stroke without greatly increasing the risk of bleeding. Too high a dose carries a risk of serious complications in the form of bleeding, including intracranial haemorrhagic stroke, while too low a dose will fail to protect against thromboembolic events. Hence, the dose is regularly controlled and adjusted, either at a particular anticoagulation clinic or in primary care.

An alternative to warfarin is treatment with acetylsalicylic acid (ASA). ASA prolongs bleeding time, and therefore provides some protection against thrombosis, but also slightly increases the risk of bleeding. ASA is, however, not as effective as warfarin in preventing thromboembolic events. [7] The Swedish National Board of Health and Welfare recommends that ASA should not be used unless warfarin is contraindicated. [6] However, less than 50 per cent of all AF patients in Sweden receive warfarin treatment today, [8] and many patients are without any anticoagulation treatment. In the near future, new anticoagulation treatments will challenge the established treatments. There is therefore a need to know the current cost of AF-related complications, so that cost-effectiveness comparisons can be performed when the new treatments are available.

The risk of ischaemic stroke in an AF patient depends on several factors including age, sex, previous complications, hypertension, and diabetes. [7] Patients can therefore be classified according to their risk for stroke. The most commonly used risk classification system is CHADS2, which rates the patient on a scale from 0 to 6, relating to the risk based on predefined risk factors. [9] In CHADS2, incidence of chronic heart failure, hypertension, an age over 75 years, and diabetes each generate 1 point, while previous stroke or transient ischaemic attack generates 2 points.

The aim of this study was to calculate the societal cost of thromboembolic events and their prevention among Swedish AF patients in 2010. The costs and consequences of using self-testing equipment to monitor warfarin were not included, as this is not common in Sweden today. [10]

Material and Methods

This study can be classified as a cost-of-illness study. The cost calculation included hospitalizations, primary health care, anticoagulation treatment including monitoring costs, and costs of complications (direct and indirect). The complications included were ischaemic and haemorrhagic stroke, gastrointestinal (GI) bleeding, other types of severe bleeding, and minor bleeding. The analysis was undertaken from a societal perspective, including productivity loss due to morbidity. The unit costs for AF patients were calculated on the basis of the county of Östergötland (population 420 000 inhabitants) and then aggregated to a national level. The treatment of AF patients in Östergötland was assumed to be representative of the rest of Sweden. Costs that would occur in the future were discounted at 3 percent annually.

Prevalence

At the end of 2009, the population in Sweden was 9 340 682. [11] A recent study using the Swedish national register found that 100 557 individuals were diagnosed with either primary or secondary AF.. [12] However, as some individuals with AF are not diagnosed, this figure is not complete. According to a study of AF in England and Wales, the prevalence was 1.24 per cent of the total population (1.21 for men and 1.27 for women). [1] The same study showed that the incidence of AF increased between 1994 and 1998. Several other studies have shown similar prevalence. [13, 2, 14] Applying the prevalence data from England and Wales to the age and gender structure of the Swedish population, we estimated the number of patients

with AF in Sweden to be 135 278 (see Table 1).

The fact that different patients have different background risks of stroke also had to be taken into account in the calculations. One study has analyzed the distribution of patients with AF in different CHADS2 scores, [15] using a population of 51 807 patients in the UK who were diagnosed by general practitioners. The results are presented in [Table 2], together with estimates of what the corresponding results would be in Sweden. Our calculations included only patients with CHADS2 = 1 or higher, giving an estimate of 117 827 for the prevalence in Sweden. These patients are assumed to be equally distributed between the three CHADS2 -score groups 1, 2 and 3-6.

Anticoagulation Treatment

Patients with AF can be divided into three treatment groups depending on their anticoagulation treatment: warfarin, ASA, or no anticoagulation. In Sweden, 43.3 percent of patients with AF are treated with warfarin, [8] around 28% with ASA, and again around 28% with no anticoagulation treatment. Warfarin treatment can be further divided into three groups: well-controlled (international normalised ratio [INR] within therapeutic range more than 70% of the time), non-controlled (INR within therapeutic range less than 70% of the time), and new (warfarin-naïve) patients.

The percentage of patients monitored at the anticoagulation clinics rather than in primary care varies greatly between different regions in Sweden. In this study, however, it was assumed that the county of Östergötland, with 90 percent of patients monitored at the anticoagulation clinics, represented an acceptable estimate for the rest of Sweden.

The percentage of test results lying in the therapeutic range is between 76 and 78 percent in all of the anticoagulation clinics in Östergötland. As both the national average and the average from the Swedish centres in the recent RE-LY trial have 77 percent of tests within therapeutic range, [16,8] the clinics in Östergötland are representative in this matter. The average number of samples per patient per year at Linköping anticoagulation clinic (the largest hospital within Östergötland) is 16.94. New patients have been removed from these statistics, and it is estimated that it takes about five tests to stabilize a new patient; we therefore assumed a figure of 21.94 for the average number of samples during the first year for new patients. In a non-published study, the number of tests in primary care in Östergötland was found to be 13.7 in 2005. No data were given for new patients, but in the present paper, we estimated the number of new samples in primary care to be 18.71

A study has shown that the proportion of INR within therapeutic range is similar between the anticoagulation clinics and primary care in Östergötland .[17] In that study, all INR tests during a specific week in 2004 from both anticoagulation clinics (470 samples) and primary care (517 samples) were analyzed.

Costs

All costs were calculated in Swedish kronor (SEK) and adjusted to the 2009 values by using the consumer price index. The costs are presented in Euros (€), using an exchange rate of €1 = SEK9.50.

The cost of warfarin is generated both by the medication itself and by the monitoring that is needed for it to be effective. The price of warfarin is €11.4 for 100 tablets of 2.5 mg. [18] Given a use of 4 mg daily, the annual cost was estimated at €66. The cost of visiting a doctor once a year was also included; according to the price list in the Southeast regional hospital, this is €188. [19] Warfarin monitoring can take place either at the anticoagulation clinic or in primary care, causing different costs. According to the price list for medical laboratory centres in Östergötland in 2010, the cost per sample in an anticoagulation clinic is €20.6 .[20] This value is in line with the average values estimated in a study of the cost of monitoring the anticoagulation clinics in Sweden .[21] The patients' travel costs to get to the clinic have been estimated at €5 per occasion. [22] The productivity loss (indirect costs) arising from the patient's being unable to work during the monitoring is estimated at €2.9. [22]

The cost per visit for warfarin treatment in primary care is estimated at €61 ,[23]including a higher cost in 10 percent of the cases due to samples taken in the patients' homes. In addition to these costs, we assumed that the patients' travel expenses

and productivity losses are equivalent to those arising from the visit to the anticoagulation clinic.

The cost of ASA treatment in the calculation was set at the price of the medication and one annual medical examination. The pharmaceutical Trombyl® costs €6.4 for 100 tablets of 160 mg each .[18]With an average daily dose of 160 mg, this corresponds to an annual cost of €23. The cost of a medical consultation has been estimated at €188. [19] Ghatnekar et al. ,[24] who studied the cost of stroke in Sweden in 2004, used an incidence based approach in which direct costs amounted to €62 197 and indirect costs to €15 145 in 2009 values. This estimate includes admission costs, re-stroke admission costs, outpatient costs, and costs for social services. These values were used for the cost calculations of both ischaemic and haemorrhagic stroke in this study. A study from the UK found that the average acute care costs one year after stroke come to €7 666, and that the cost of stroke for patients with a history of AF is higher than for patients with no AF history .[25] It is therefore likely that stroke patients with AF are more costly than the average cost of stroke used in the calculation in this study.

Existing data on the cost of bleeding is poor, partly due to the difficulty of defining major and minor bleeding. A study based on registry data estimated the average cost of serious bleeding at €2 773, [26] while a study from Canada estimated the cost of GI bleeding at €3 303 ,[27] based on the cost of hospitalization and outpatient care [28]. On the basis of these costs, for the purposes of our analysis we estimated the cost of minor bleeding at €32.

Risk of Complications

Patients with AF who are not receiving anticoagulation treatment have an annual risk of stroke of about 6 percent. [7] When patients are divided into different risk groups by CHADS2 score, the annual risk of stroke varies from 1 percent to 18 percent or higher.[29,9,30,6,31,32]Treatment with ASA has been shown to reduce the risk of thromboembolic events by 19 percent compared with no treatment, but it also slightly increases the risk of bleeding. [29,7,33,6] The risk of thromboembolic events with ASA or no treatment used in the present calculation was based largely on the scientific basis underlying the Swedish National Board of Health and Welfare's guidelines for the treatment of AF. [6] The risks of warfarin-related complications were taken from the recent RE-LY trial, which compared the new anticoagulation drug dabigatran with warfarin .[16] As dabigatran is not yet used in patients with AF, its associated costs were not considered here. The warfarin-related risk of haemorrhagic stroke was taken from the intracranial bleeding estimates in the RE-LY study. One sub-study from RE-LY presented the risks of complications divided by the background risk of stroke according to CHADS2. [34] The annual absolute risks of complications arising with different anticoagulation treatments are presented in [Table 3].

Another subgroup analysis from the RE-LY trial studied the risks for complications divided by the different study centres' average INR level.[35]Centres were divided into quartiles according to their mean time in therapeutic range (TTR). The quartile with the maximum TTR had more than 72.6 percent of the INR within therapeutic range. In our calculation, we assumed that this corresponds to well-controlled warfarin patients. The second-worst quartile was used for non-controlled warfarin patients; here, TTR ranged between 57.1 percent and 65.5 percent. The reason for using this method was that Sweden has a higher rate of INR within therapeutic range than the mean in the RE-LY trial. Risks for stroke and major bleeding divided by well-controlled and non-controlled warfarin therapy are presented in [Table 4]. A weighting of well-controlled and non-controlled warfarin was used for warfarin-naïve patients, in line with the proportion of warfarin patients in Östergötland (77 percent).

Results

Among the 9 340 682 inhabitants of Sweden, we estimated that there are 117 827 patients with AF and at least one more risk factor of stroke, comprising 1.26% of the population. Of the patients, 43.3% are treated with warfarin, 28.3% use acetylsalicylic acid, and 28.3% are assumed to have no anticoagulation treatment. The largest cost was incurred in the patients not given anticoagulation with warfarin, as these patients have a higher risk of stroke. The lowest cost per patient was incurred by those with well-controlled warfarin therapy (see Figure 1).

The total cost of thromboembolic events and their prevention among AF patients in Sweden was estimated at €437 million for 2010 (see Table 5), corresponding to €3 712 per AF patient per year. The highest cost was caused by stroke, and the second highest by the cost of monitoring the warfarin treatment.

Discussion

In this study, we estimated the costs of thromboembolic events and their prevention among AF patients in Sweden. The total societal cost was estimated at €437 million per year. Even though our calculation did not include AF treatments such as antiarrhythmic drugs or ablation, we believe that thromboembolic events and their prevention constitute the major costs related to AF. Most of the data used for the calculation of the costs are confirmed by published studies, but some presumptions have been made which can be seen as a limitation to the quality of the study. For example, the exact prevalence of AF patients in Sweden is not known and the TTR among patients monitored in primary care is not verified. All these presumptions are presented in the material and methods section.

A recent Swedish study [12] estimated the total cost of AF in Sweden to be about SEK6.6 billion (€708 million), which is higher than the total presented in our study. The main reason for this is probably that the other study used a top-down approach including all medical costs faced by patients with AF. However, this will probably be an overestimate since many patients with AF also have other cardiovascular diseases, and shares of these costs could be traced to diseases other than AF. Another reason for the differing totals is that our study did not include any treatment of the AF. Another study has estimated the AF related cost per AF patient in Sweden to €4 866 and in Germany to €3 891 .[36] Another study, which included the costs of social services and productivity loss, estimated the costs directly related to AF in the UK at £1 307 million .[14] Translated to Sweden, this corresponds to a total cost of approximately €380 million, which is roughly in line with the cost estimates in the present article. Another study, which estimated the per-patient cost of AF in five European countries, [37] found that the cost was lowest in Poland (€1 010) and highest in Italy (€3 225). Le Heuzey et al. [38] found that the two highest costs associated with AF were hospital admissions (52%) and pharmaceuticals (23%); these results are also in line with those found in this study. All studies have concluded that the cost for AF will increase significantly in the future, due to the increasing prevalence of AF.

We used a societal perspective in calculating the costs. This includes all costs and effects that occur in the society, whether for the patient (or relatives providing informal care), hospital (county), social services (municipality), or productivity losses (state). However, there are some costs that we were not able to include. Informal care provided by relatives to the patient is not included due to lack of data. Furthermore, the relatives of a patient with AF are often also affected in terms of decreased quality of life due for example to worries, and these costs (or loss of quality of life) are not included either in our calculations.

This cost calculation cannot be used to help decision-makers prioritize in this field, as it only estimates the costs and does not evaluate different treatments. The purpose of this type of analysis is rather to show the economic burden of AF and its consequences. However, this analysis can be used as a basis for future cost-effectiveness analyses. Several new anticoagulation treatments are expected to be available within the near future, and this calculation can be used in future comparative studies of different anticoagulation treatments. These new treatments do not need monitoring or patient-specific adjustments, which may reduce the total costs. On the other hand, the prices of the treatments are expected to be higher than for warfarin making the total influences on the costs unpredictable. Most important for the costs is however the treatments' effectiveness in preventing stroke, as stroke is the main cost driver. Dabigatran (Pradaxa®) is the first of the new upcoming anticoagulation treatments, and once the price of dabigatran is known its cost-effectiveness can be analysed.

Conclusions

Thromboembolic events and its prevention cause high costs in the society, and stroke is the main

cost driver. New and easily-administered treatments that could reduce the risk of stroke have a potential to be cost-effective.

Financial Disclosure

Grants for this study were received from Boehringer Ingelheim (producer of dabigatran/Pradaxa®) and from the county council of Östergötland.

References

1. Majeed, A., Moser, K., Carroll, K., Trends in the prevalence and management of atrial fibrillation in general practice in England and Wales, 1994-1998: analysis of data from the general practice research database. Heart. 86: p. 284-288 (2001).
2. Heeringa, J., van der Kuip, D., Hofman, A., Kors, J., van Herpen, G., Stricker, B., Stijnen, T., Lip, G., Witteman, J., Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. Eur Heart J. Apr;27(8): p. 949-953 (2006).
3. Berg, J., Lindgren, P., Nieuwlaat, R., Bouin, O., H., C., Factors determining utility measured with the EQ-5D in patients with atrial fibrillation. Qual Life Res. 19: p. 381-390 (2010).
4. Reynolds, M.R., Lavelle, T., Essebag, V., Cohen, D.J., Zimetbaum, P., Influence of age, sex, and atrial fibrillation recurrence on quality of life outcomes in a population of patients with new-onset atrial fibrillation: The Fibrillation Registry Assessing Costs, Therapies, Adverse events and Lifestyle (FRACTAL) study. Am Heart J. 152(6): p. 1097-1103 (2006).
5. van den Berg, M., Hassink, R., Tuinenburg, A., van Sonderen, E., Lefrandt, J., de Kam, P., Quality of life in patients with paroxysmall atrial fibrillation and its predictors: importance of the autonomic nervous system. Eur Heart J. 22: p. 247-253 (2001).
6. The National Board of Health and Welfare (Socialstyrelsen), Nationella riktlinjer för hjärtsjukvård 2008 - beslutsstöd för prioriteringar, Socialstyrelsen: Stockholm, access: http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/8592/2008-102-7_20081028.pdf (2010-12-30), (2008).
7. Hart, R.G., Benavente, O., McBride, R., Pearce, L.A., Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. Ann Intern Med. 131: p. 492-501 (1999).
8. The National Board of Health and Welfare (Socialstyrelsen), Open comparison and assessment 2009 - Cardiac care: Stockholm, access: http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/18108/2010-9-2.pdf (2010-12-30), (2010).
9. Gage, B.F., Waterman, A.D., Shannon, W., Boechler, M., Rich, M.W., Radford, M.J., Validation of clinical classification schemes for predicting stroke - Results from the national registry of atrial fibrillation. JAMA. 285: p. 2864-2870 (2001).
10. SBU ALERT nr 2007-05, Självtestning och egenvård vid användning av blodproppsförebyggande läkemedel, SBU: Stockholm (2007).
11. Statistics Sweden, Access: http://www.scb.se/Pages/TableAndChart____262459.aspx (2010-12-30), (2010).
12. Ericson, L., Bergfeldt, L., Björholt, I., Atrial fibrillation: the cost of illness in Sweden. Eur J Health Econ. Published online: 01 July 2010 (2010).
13. Furberg, C., Psaty, B., Manolio, T., Gardin, J., Smith, V., Rautaharju, P., Prevalence of atrial fibrillation in elderly subjects (the Cardiovascular Health Study). Am J Card. 74: p. 236-241 (1994).
14. Stewart, S., Hart, C., Hole, D., McMurray, J., Population prevalence, incidence and predictors of atrial fibrillation in the Renfrew/Paisley study. Heart. 86: p. 516-521 (2001).
15. Rietbrock, S., Heeley, E., Plumb, J., van Staa, T., Chronic atrial fibrillation: incidence, prevalence, and prediction of stroke using the Congestive heart failure, Hypertension, Age>, Diabetes Mellitus, and prior Stroke or transient ischemic attack (CHADS2) risk stratification scheme. Electrophysiology. 156(1): p. 57-64 (2008).
16. Connolly, S., Ezekowitz, M., Yusuf, S., Eikelboom, J., Oldgren, J., Parekh, A., Pogue, J., Reilly, P., Themeles, E., Varrone, J., Wang, S., Alings, M., Xavier, D., Zhu, J., Diaz, R., Lewis, B., Darius, H., Diener, H., Joyner, C., Wallentin, L., Dabigatran versus warfarin in patients with atrial fibrillation. N Eng J Medicine. 361(12): p. 1139-1151 (2009).
17. Arbring, K., Lindahl, T., Snapshot of warfarin treatment in different settings: a cross ection study in Swedish primary health care centers vs anticoagulation clinics. J Thromb Haemost. 5(Supplement 2): p. P-M-651 (2007).
18. FASS, www.fass.se/LIF/home/index.jsp, (2010-06-11).
19. Sydöstra sjukvårdsregionen, Priser och ersättningar för Sydöstra sjukvårdsregionen 2009: access: http://www.lio.se/upload/16047/20081209Prislista2009.pdf (2010-12-30), (2009).
20. Laboratoriemedicinskt centrum i Östergötland, Prislista 2010. Access http://www.lio.se/upload/80565/LMC%20prislista%202010%20(2).pdf (2010-12-30), (2010).
21. Andersson, S., Resurskonsumtion och kostnad för kontroll av behandling med wararin på antikoagulationsmottagningar i Sverige 2004, AstraZeneca, Sweden (2005).
22. Svensson, P., Andersson, S., Ovanfors, A., Westlund, A., Patientpreferenser för olika behandlingsegenskaper vid antikoagulationsbehandling hos patienter med förmaksflimmer - Resultat från en svensk multicenter studie. Poster presented at "Riksstämman 2004", Sweden. (2004).
23. Björholt, I., Andersson, S., Nilsson, G., Krakau, I., The cost of monitoring warfarin in patients with chronic atrial fibrillation in primary care in Sweden. BMC family practice. 8(6) (2007).
24. Ghatnekar, O., Persson, U., Glader, E., Terént, A., Cost of stroke in Sweden: an incidence estimate. Int J Tech Ass Health Care. 20(3): p. 375-380 (2004).
25. Luengo-Fernandez, R., Gray, A., Rothwell, P., Population-based study of determinants of initial secondary care costs of acute stroke in the United Kingdom. Stroke. 37: p. 2579-2587 (2006).
26. O'Brien, C., Gage, B., Costs and effectiveness of ximelagatran for stroke prophylaxis in chronic atrial fibrillation. JAMA. 293: p. 699-706 (2005).
27. Cameron, C., van Zanten, S., Skedgel, C., Flowedew, G., Moayyedi, P., Sketris, I., Cost-utility analysis of proton pump inhibitor and other gastro-protective agents for prevention of

gastrointestinal complications in elderly patients taking non-selective non-steroidal anti-inflammatory agents. Alimentary pharmacology & therapeutics. Postprint(doi: 10.1111/j.1365-2036.2010.04305.x) (2010).
28. Health costing in Alberta: 2006 annual report, Alberta Health and Wellness: Edmonton (2006).
29. Atrial Fibrillation Investigators, Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. Arch Intern Med. 154(13): p. 1449-1457 (1994).
30. Mant, J., Hobbs, F., Fletcher, K., Roalfe, A., Fitzmaurice, D., Lip, G., Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. Lancet. 370(9586): p. 493-503 (2007).
31. van Walraven, C., Hart, R., Wells, G., Petersen, P., Koudstaal, P., Gullov, A., A clinical prediction rule to identify patients with atrial fibrillation and a low risk for stroke while taking aspirin. Arch Intern Med. 163(8): p. 936-943 (2003).
32. Wang, T., Massaro, J., Levy, D., Vasan, R., Wolf, P., D'Agostino, R., A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation in the community: the Framingham Heart Study. JAMA. 290(8): p. 1049-1056 (2003).
33. Hart, R.G., Pearce, L.A., Aguilar, M., Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med. 146(12): p. 857-867 (2007).
34. Oldgren, J., Alings, M., Darius, H., Eikelboom, J., Ezekowitz, M., Parekh, A., Pogue, J., Reilly, P., Yusuf, S., Wallentin, L., Connolly, S. Dabigatran versus warfarin in atrial fibrillation patients with low, moderade and high chads2 score: A Re-ly subgroup analysis. in American College of Cardiology. 2010. Georgia.
35. Wallentin, L., Yusuf, S., Ezekowitz, M., Alings, M., Flather, M., Grazia Franzosi, M., Pais, P., Dans, A., Eikelboom, J., Oldgren, J., Pogue, J., Reilly, P., Yang, S., Connolly, S., Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. Lancet. Sep 18;276(9745): p. 975-983 (2010).
36. Jönsson, L., Eliasson, Å., Kindblom, J., Almgren, O., Edvardsson, N., Cost of illness and drivers of cost in atrial fibrillation in Sweden and Germany. Appl Health Econ Health Policy. 8(5): p. 317-325 (2010).
37. Ringborg, A., Nieuwlaat, R., Lindgren, P., Jönsson, B., Fidan, D., Maggioni, A.P., Lopez-Sendon, J., Stepinska, J., Cokkinos, V., Crijns, H.J.G.M., Costs of atrial fibrillation in five European countries: results from the Euro Heart Survey on atrial fibrillation. Europace. 10: p. 403-411 (2008).
38. Le Heuzey, J., Paziaud, O., Piot, O., Said, M.A., Copie, X., Lavergne, T., Guize, L., Cost of care distribution in atrial fibrillation patients: the COCAF study. Electrophysiology. 147: p. 121-126 (2004).