ANTI-COAGULATION, ANTI-PLATELETS OR NO THERAPY IN HAEMODIALYSIS PATIENTS WITH ATRIAL FIBRILLATION: A DECISION ANALYSIS

INTRODUCTION

Atrial fibrillation (AF) is relatively common among maintenance haemodialysis patients with most studies reporting a prevalence of between 12% and 17%.(1-6) Haemodialysis patients with AF are at increased risk of ischemic stroke, thromboembolism, hospitalisation and premature death as compared to those without AF.(7-9)

The decision to anti-coagulate or use anti-platelet therapy in a patient with AF requires consideration of potential risks versus benefits. Such risks and benefits have been established for the general population through multiple large randomised controlled trials (RCTs).(10-12) These data have been used to power predictive scores, the $CHADS_2$ (Cardiac failure, Hypertension, Age, Diabetes and Stroke) score and more recently the CHA_2DS_2-VASc (Cardiac failure, Hypertension, Age, Diabetes, Stroke, Vascular disease and gender) scores, which use patient risk factors to estimate stroke risk and guide treatment decisions in the general population.(13, 14) Patients with impaired kidney function were excluded from these trials, and it is not certain whether or not their findings are applicable to the haemodialysis population. Haemodialysis patients have a different risk-benefit profile for anti-coagulation and anti-platelet agents than the general population due to factors including platelet dysfunction from uraemia, altered pharmacokinetics and increased falls risk.(15, 16) There are also concerns that the use of warfarin in haemodialysis patients may increase vascular calcification and hence, ischemic stroke risk.(15, 17)

No RCTs of anti-coagulation or anti-platelet interventions in haemodialysis patients with AF have been conducted. Thus, the evidence base consists largely of small observational studies reporting conflicting results.(2, 3, 7, 8, 18-20) Informed clinical decision-making is

challenging in the face of this inadequate evidence base and there is considerable controversy over when, and if, anti-coagulation and anti-platelet therapy should be used in the haemodialysis population.

The aim of this study was to incorporate the most recent evidence into a decision analysis offering an up to date perspective of the treatment of AF in haemodialysis patients. It seeks to answer the question: Does warfarin offer superior Quality Adjusted Life Years (QALYs) to aspirin and/or no anti-thrombotic therapy in haemodialysis patients with AF?

METHODS

We constructed a Markov model using decision analytic software (TreeAge Pro 2012, Williamstown, USA) to compare the benefits of anti-coagulation (warfarin), anti-platelet agents (aspirin) and no therapy in haemodialysis patients with AF. Our base case was a 72 year old man on haemodialysis with non-valvular AF, reflecting the mean age of patients on haemodialysis with AF in the literature.(1, 6, 7, 18, 21)

Markov model design

Markov models represent the natural history of a disease and use hypothetical patients with disease courses that reflect those found in the literature. Disease courses are characterised by predefined mutually exclusive health states. Patients transition between these states in each 'Markov cycle' according to probabilities drawn from the literature.(22) Expected outcomes per hypothetical patient are determined by summing all the expected costs and benefits in each health state that the patient experiences.(22)

Our model followed 1000 hypothetical patients split into three cohorts by treatment option (warfarin, aspirin, no therapy). We built the model to run 3 monthly Markov cycles for 20 cycles (five years). The time horizon reflects the older age of haemodialysis patients with AF,

the chronic nature of the disease and its life-long complications. The structure of our model and the health states are outlined in Figure 1.

Clinical data and health outcomes

We performed a comprehensive literature search to determine the best available estimates for clinical data and health outcomes. The search strategy is outlined in Appendix 1.

The clinical data included transition probabilities (the probability of transitioning between health states) and the relative risks of transitioning between health states on different treatments (see Table 1). Where there were multiple sources of probabilities or relative risks these were meta-analysed in Stata software version 12 (StataCorp, College Station, Texas USA).

We measured health outcomes by life years and QALYs. QALYs are used in economic evaluations because they incorporate both the expected number of years lived as well as the quality of life (measured in utilities) during those years. Preference based utilities on a 0-1 scale where 0 is death and 1 is full health were preferred (e.g. EQ-5D, time trade off, and standard gamble).(22) Where utilities specific to patients on haemodialysis with AF were not available, utilities from the general population were used. Health states required the use of multiple utilities (e.g. a hypothetical patient on haemodialysis with AF taking warfarin and who suffered a stroke). To create these utilities we used the haemodialysis utility as our base and then created disutilities that were each subtracted from the base case. Disutilities captured all aspects of treatment, including requirements to take medication and undergo monitoring in addition to side-effects such as bleeding. All outcomes were discounted at an annual rate of 5% which is a standard practice in economic evaluations.(23)

For both clinical and health outcomes we determined plausible ranges for each probability or relative risk to be the 95% confidence interval calculated in our meta-analysis, the published

95% confidence interval when only one published study was used, or half and double the probability (i.e. using a standard multiplier formula) if a confidence interval was not available.

Model assumptions

We made the following assumptions in constructing our Markov model: 1) the outcomes of ischemic and haemorrhagic strokes were the same; 2) stroke outcomes of haemodialysis patients (i.e. the probability of disability or death) with AF were the same as patients in the general population with AF; 3) the relative risk of haemorrhagic stroke in patients on aspirin versus no therapy was 1; 4) the anti-coagulation and anti-platelet agents of patients who experienced either a haemorrhagic stroke or an extracranial bleed were immediately and permanently ceased; 5) the disutility associated with AF, warfarin use, aspirin use, and stroke outcomes were the same in haemodialysis patients as in the general population.

Sensitivity analyses

We conducted multiple sensitivity analyses to determine the impact of uncertainty on model results. One-way sensitivity analyses were performed on each variable over the range specified in Table 1 while holding all other variables constant. Unless otherwise specified, the range represented the highest and lowest values we identified in the literature. We further investigated the key variables of extracranial bleeding, haemorrhagic stroke and ischemic stroke by two-way sensitivity analyses for warfarin, aspirin and no therapy. This was done by simultaneously varying both stroke rates and bleeding rates for each treatment type over the range specified in Table 1.

Probabilistic sensitivity analysis enabled us to evaluate the impact of uncertainty across all key parameters simultaneously and so provide a more accurate estimate of outcomes. To perform this analysis we modelled our input variables as distributions following standard methods.(24) The probabilities of moving between health states and the utilities were

modelled as beta distributions (bounded by 0 and 1), while the relative risks (of warfarin and aspirin versus no therapy) were modelled as log-normal distributions and 500,000 monte carlo simulations were conducted.(24)

RESULTS

The clinical data and utilities used in the model are presented in Tables 1 and 2.

Base-case analysis. The mean life expectancy of a 72 year old man on haemodialysis and with AF was 9.55 cycles (2.39 years) treated with warfarin, 9.59 cycles (2.40 years) with aspirin, and 9.58 cycles (2.39 years) with no therapy. Incorporating quality of life led to a mean QALY of 5.94 cycles (1.49 years) treated with warfarin, 6.47 cycles (1.62 years) with aspirin, and 6.48 cycles (1.62 years) with no therapy. Thus, warfarin led to 0.14 fewer QALYs or 1.6 fewer months of life lived in full health, than either aspirin or no therapy (see Table 3).

One-way sensitivity analyses. The base case was only sensitive to the relative risk of death from other (non stroke, non bleed) causes as shown in Table 4.

Two-way sensitivity analyses. 'No therapy' was the preferred treatment strategy under all scenarios.

Probabilistic sensitivity analyses. The mean life expectancy for the base case via probabilistic sensitivity analysis was 2.39 years for no therapy, 2.40 years for aspirin and 2.39 years for warfarin. For the outcome of life expectancy 77% of simulations favoured aspirin, 18% of simulations favoured no therapy and 5% of simulations favoured warfarin. The mean QALYs for the base case via probabilistic sensitivity analysis were 1.62 years for no therapy, 1.62 years for aspirin and 1.48 years for warfarin. For the outcome of quality-adjusted life expectancy, 60% of simulations favoured aspirin, 40% of simulations favoured no therapy and 0.2% of simulations favoured warfarin. In summary, in 95% of simulations for survival

and 99.8% of simulations for QALYs, warfarin was not the preferred treatment choice for AF in haemodialysis patients given the current evidence base in the literature.

DISCUSSION

We found that for our base case patient, a 72 year old male haemodialysis patient with atrial fibrillation there was no difference in life expectancy between warfarin, aspirin and no treatment but that warfarin provided 1.6 fewer months lived in full health. The one-way, two-way and probabilistic sensitivity analyses did not alter the base case findings.

Our results suggest that the decision to use warfarin in a haemodialysis patient with AF should be considered very carefully and that for patients that resemble our base case patient, a 72 year old man, warfarin may not be the preferred treatment option. We caution that our findings cannot be applied to patients that differ from this base case, e.g. are much younger, and note that the difference between each treatment option, warfarin, aspirin and no therapy is small and is overshadowed by the poor prognosis of these patients regardless of anti-coagulation / anti-platelet therapy.

A decision analysis has been previously conducted by Quinn et al.(25) They found that warfarin produced an additional 0.1 years of life expectancy and an additional 0.09 years of QALY versus no therapy and was superior to both no therapy and aspirin.(25) Since this publication, a number of important studies looking at stroke and bleeding rates in haemodialysis patients with AF patients have been published, and these are incorporated into our transition probabilities which consequently differ from Quinn et al's.(26-28)

The strengths of this paper include its use of the most current evidence available, that it draws utilities from all possible sources, both directly measured and transformed from SF-36 data, and our use of sensitivity analysis, particularly probabilistic sensitivity analysis. However, the study also has several limitations. First, the evidence base underpinning the decision analysis

is limited to retrospective, observational studies of small patient populations and where AF may not have been the primary indication for warfarin use. Second, we could not adequately account for demographic differences such as age and sex, nor for clinical differences such as comorbidities, because of the incompleteness of reported data and our reliance on the aggregated, rather than patient-level, data provided by published studies. Third, we had to use some data (such as stroke outcomes) that were not drawn from the haemodialysis population.

Areas for further research include large well-designed epidemiological studies and, crucially, a prospective RCT where haemodialysis patients with AF are randomised to receive warfarin, aspirin, or placebo. Large epidemiological studies are needed to ensure that the RCT draws from the right patient subsets and so provides clinically meaningful results to guide treatment decisions.

CONCLUSIONS

Our results suggest that warfarin should not be the default choice for haemodialysis patients with non-valvular AF. We found that warfarin provided the fewest QALYs compared to aspirin and no therapy. However, we note that the evidence base underpinning our decision analysis is sub-optimal and further research is required to definitively delineate the role, if any, of anti-coagulation and anti-platelet agents in haemodialysis patients with AF.

Appendix 1: Search strategy

The literature search was conducted in Medline, EMBASE and the Cochrane Database of Systematic Reviews from database inception until October 2012 and through a manual search of the reference lists from relevant studies. For transition probabilities and relative risks we used the following text words or medical subject headings (MeSH): "atrial fibrillation" plus one or more of "renal failure", "kidney failure", "end stage kidney disease", "end stage renal disease", "end stage kidney failure", "end stage renal failure", "dialysis", "haemodialysis", "hemodialysis". For utilities we added the text words "utility" or "utilities" or "quality of life" and MeSH heading "quality-adjusted life years".

Randomised controlled trials, observational series, case series and population-based registry studies were all included. We excluded review articles, comments, editorials, letters and case reports.

Figure 1: Model structure showing health states Patients enter the model on haemodialysis (HD) and with AF. During each 3 monthly cycle patients can either remain in their current state (recursive arrow) or progress to a new health state (straight arrow).
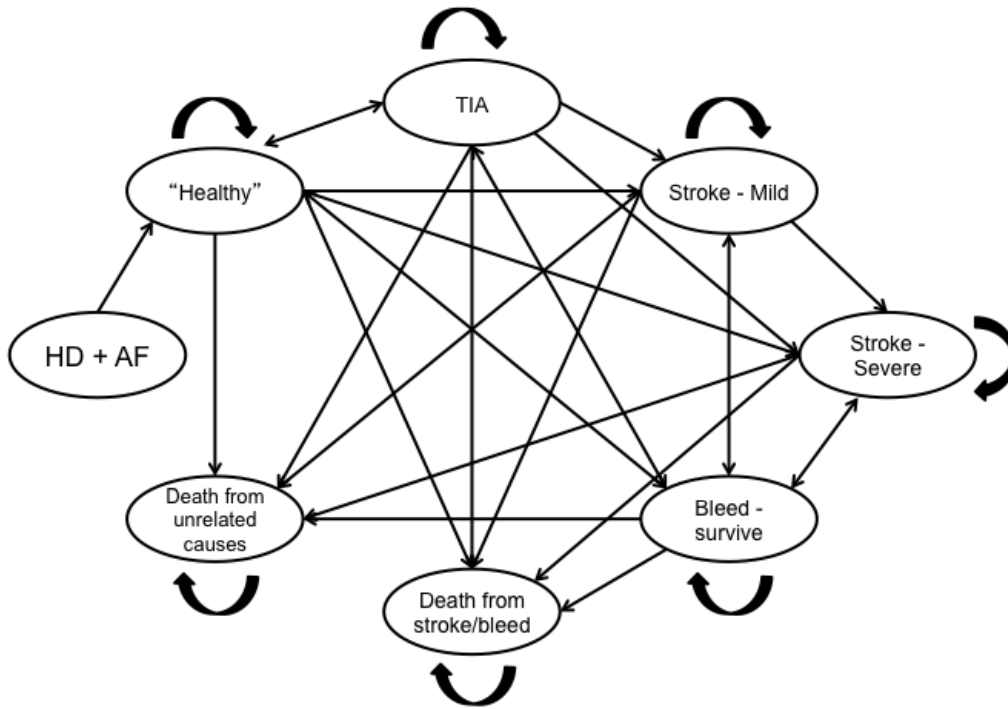
Table 1: Clinical data

Variable	Base case	Low	High	Sources
Probabilities per 3 month cycle				
Ischemic stroke rate – No therapy	0.006	0.004	0.009	(19)
Haemorrhagic stroke rate – No therapy	0.0013	0.0005	0.0035	(19)
Major bleed – No therapy	0.002	0.00*	0.07	(27, 28)
Death from other causes	0.07	0.03*	0.17*	(19)
Outcome probabilities				
Stroke – Recover	0.22	0.11*	0.43*	(29)
Stroke – Mild disability	0.30	0.15*	0.60*	(29)
Stroke – Severe disability	0.23	0.12*	0.46*	(29)
Stroke – Death	0.26	0.19	0.47	(29-31)
Major bleed - Death	0.13	0.07*	0.26*	(19)
Relative risks				
Ischemic stroke – Warfarin	0.94	0.72	1.22	(19, 26, 32)
Ischemic stroke – Aspirin	0.92	0.67	1.26	(19, 26)
Haemorrhagic stroke - Warfarin	2.31	1.35	3.94	(19, 32)
Haemorrhagic stroke - Aspirin	1.00	0.50*	2.00*	
Major bleed - Warfarin	3.88	1.5	67.2	(19, 28, 33)
Major bleed - Aspirin	5.50	2.75*	20	(28, 33)
Death from other causes - Warfarin	1.03	.052*	2.06*	(19)
Death from other causes - Aspirin	1.00	0.50*	2.00*	(19)

* Estimates where a broad range of probabilities were not available in the literature. Estimates

are for half the base case for the low end and double the base case for the high end.

Table 2: Utilities

Utilities	Base case	Low	High	Sources
Utility of haemodialysis patients	0.69	0.59	0.80	(34)
Disutility from AF	0	0	-0.15	(35, 36)
Disutility from taking warfarin	-0.05	-0.06	-0.01	(37, 38)
Disutility from taking aspirin	-0.002	-0.006	0	(37)
Disutility from minor disability following a stroke	-0.24	-0.42	-0.05	(38-42)
Disutility from severe disability following a stroke	-0.62	-0.81	-0.44	(39-42)
Disutility from surviving a major bleed	0.16	0.32*	0.08*	(38)
Death	0	0	0	Definitional

* Estimates where a broad range of probabilities were not available in the literature. Estimates

are for half the base case for the low end and double the base case for the high end.

Table 3: Life expectancy and quality-adjusted life expectancy for each of the four

treatment options

AF treatment	Life expectancy (years)*	Incremental life expectancy	QALY*	Incremental QALY
No therapy	2.39		1.62	
Aspirin	2.40	+0.01	1.62	0.00
Warfarin	2.39	0.00	1.49	-0.14

*All outcomes are discounted

Table 4: Influential variables from one-way sensitivity analyses

Variable	Threshold	Comments
Relative risk of death from other causes while treated with warfarin	0.83	Warfarin is the preferred treatment option when the relative risk of death from causes unrelated to stroke or bleeding is below 0.83 (compared to no therapy)
Relative risk of death from other causes while treated with aspirin	1.01	Aspirin is the preferred treatment option when the relative risk of death from causes unrelated to stroke or bleeding is below 1.01 (compared to no therapy)

REFERENCES

1.   Vazquez E, Sanchez-Perales C, Garcia-Garcia F, Castellano P, Garcia-Cortes M-J, Liebana A, et al. Atrial fibrillation in incident dialysis patients. Kidney Int. 2009;76(3):324-30.

2.   Wiesholzer M, Harm F, Tomasec G, Barbieri G, Putz D, Balcke P. Incidence of stroke among chronic hemodialysis patients with nonrheumatic atrial fibrillation. Am J Nephrol. 2001;21(1):35-9.

3.   Vazquez E, Sánchez-Perales C, Borrego F, Garcia-Cortes M, Lozano C, Guzmán M, et al. Influence of atrial fibrillation on the morbido-mortality of patients on hemodialysis. American Heart Journal. 2000;140:886-90.

4.   To AC, Yehia M, Collins JF. Atrial fibrillation in haemodialysis patients: do the guidelines for anticoagulation apply? Nephrology. 2007;12(5):441-7.

5.   Wizemann V, Tong L, Satayathum S, Disney A, Akiba T, Fissell RB, et al. Atrial fibrillation in hemodialysis patients: clinical features and associations with anticoagulant therapy. Kidney Int. 2010;77(12):1098-106.

6.   Genovesi S, Pogliani D, Faini A, Valsecchi MG, Riva A, Stefani F, et al. Prevalence of atrial fibrillation and associated factors in a population of long-term hemodialysis patients. Am J Kidney Dis. 2005;46(5):897-902.

7.   Vázquez-Ruiz de Castroviejo E, Sánchez-Perales C, Lozano-Cabezas C, García-Cortés M, Guzmán-Herrera M, Borrego-Utiel F, et al. Incidence of Atrial Fibrillation in Hemodialysis Patients. A Prospective Long-Term Follow-Up Study. Rev Esp Cardiol 2006;59(8):779-84.

8.   Genovesi S, Vincenti A, Rossi E, Pogliani D, Acquistapace I, Stella A, et al. Atrial fibrillation and morbidity and mortality in a cohort of long-term hemodialysis patients. Am J Kidney Dis. 2008;51(2):255-62.

9.   Abbott K.C. TFC, Taylor A.J., Agodoa L.Y. Atrial fibrillation in chronic dialysis patients in the United states: Risk factors for hospitalization and mortality. BMC Nephrology. 2003;4.

10.   Go A, Hylek E, Chang Y, Phillips K, Henault L, Capra A, et al. Anticoagulation therapy for stroke prevention in atrial fibrillation: how well do randomized trials translate into clinical practice? JAMA. 2003;290(20):2685-92.

11.   The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. N Engl J Med. 1990;323:1505-11.

12.   EAFT (European Atrial Fibrillation Trial) Study Group. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. Lancet. 1993;342:1255-62.

13.   Gage B, Waterman A, Shannon W, Boechler M, Rich M, Radford M. Validation of Clinical Classification Schemes for Predicting Stroke: Results From the National Registry of Atrial Fibrillation. JAMA. 2001;285(22):2864-70.

14.   Lip G, Nieuwlaat R, Pisters R, Lane D, Crijns H. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest. 2010;137(2):263-72.

15.   Yang F, Chou D, Schweitzer P, Hanon S. Warfarin in haemodialysis patients with atrial fibrillation: what benefit? Europace. 2010;12(12):1666-72.

16.   Reinecke H, Brand E, Mesters R, Schabitz W-R, Fisher M, Pavenstadt H, et al. Dilemmas in the management of atrial fibrillation in chronic kidney disease. J Am Soc Nephrol. 2009;20(4):705-11.

17.   Danziger J. Vitamin K-dependent proteins, warfarin and vascular calcification. CJASN. 2008;3(5):1504-10.

18.   Vazquez E, Sanchez-Perales C, Lozano C, Garcia-Cortes MJ, Borrego F, Guzman M, et al. Comparison of prognostic value of atrial fibrillation versus sinus rhythm in patients on long-term hemodialysis. Am J Cardiol. 2003;92(7):868-71.

19.   Chan KE, Lazarus JM, Thadhani R, Hakim RM. Warfarin use associates with increased risk for stroke in hemodialysis patients with atrial fibrillation. J Am Soc Nephrol. 2009;20(10):2223-33.

20.   Phelan PJ, O'Kelly P, Holian J, Walshe JJ, Delany C, Slaby J, et al. Warfarin use in hemodialysis patients: what is the risk? Clin Nephrol. 2011;75(3):204-11.

21.   Tsagalis G. BN, Manios E., Chouliaras I., Papagiannidou P., Stamellou E., Akrivos T., Makris F., Psimenou E., Koutroubas G., Xinos K., Vemmos K. Atrial fibrillation in chronic hemodialysis patients: Prevalence, types, predictors, and treatment practices in Greece. Artificial Organs. 2011;35(10):916-22.

22.   Briggs A, Sculpher M. An introduction to Markov modeling for economic evaluation. Pharmacoeconomics. 1998;13:397-409.

23.   Commonwealth Department of Health and Ageing. Guidelines for preparing submissions to the Pharmaceutical Benegits Advisory Committee (Version 4.3). In: Commonwealth Department of Health and Aging, editor. Canberra 2008. p. 273.

24.   Briggs A, Goeree R, Blackhouse G, O'Brien B. Probabilistic analysis of cost-effectiveness models: choosing between treatment strategies for gastroesophageal reflux disease. Medical Decision Making. 2002;22(4):290-308.

25.   Quinn RR, Naimark DMJ, Oliver MJ, Bayoumi AM. Should hemodialysis patients with atrial fibrillation undergo systemic anticoagulation? A cost-utility analysis. Am J Kidney Dis. 2007;50(3):421-32.

26.   Olesen J, Lip G, Kamper A, Hommel K, Kober L, Lane D, et al. Stroke and bleeding in atrial fibrillation with chronic kidney disease. N Engl J Med. 2012;367(7):625-36.

27.   Elliott M, Zimmerman D, Holden R. Warfarin Anticoagulation in Hemodialysis Patients: A Systematic Review of Bleeding Rates. Am J Kidney Dis. 2007;50(3):433-40.

28.   Holden R, Harman G, Wang M, Holland D, Day A. Major Bleeding in Hemodialysis Patients. Clinical Journal of the American Society of Nephrology. 2008;3:105-10.

29.   Lin H, Wolf P, Kelly-Hayes M, Beiser A, Kase C, Benjamin E, et al. Stroke severity in atrial fibrillation. The Framingham Study. Stroke. 1996;27(10):1760-4.

30.   Iseki K, Fukiyama K. Clinical demographics and long-term prognosis after stroke in patients on chronic haemodialysis: The Okinawa Dialysis Study (OKIDS) Group. Nephrol Dial Transplant. 2000;15(11):1808-13.

31.   Gattellari M, Goumas C, Aitken R, Worthington J. Outcomes for patients with ischemic stroke and atrial fibrillation: the PRISM study. Cerebrovascular Diseases. 2011;32:370-82.

32.   Winkelmayer W, Liu J, Setoguchi S, Choudhry N. Effectiveness and safety of warfarin initiation in older hemodialysis patients with incident atrial fibrillation. Clinical Journal of the American Society of Nephrology. 2011;6(11):2662-8.

33.   Vazquez E, Sanchez-Perales C, Garcia-Cortes MJ, Borrego F, Lozano C, Guzman M, et al. Ought dialysis patients with atrial fibrillation be treated with oral anticoagulants? Int J Cardiol. 2003;87(2-3):135-9; discussion 9-41.

34.   Wyld M, Morton R, Hayen A, Howard K, Webster A. A Systematic Review and Meta-Analysis of Utility-Based Quality of Life in Chronic Kidney Disease Treatments. PLoS Medicine. 2012;9(9 e1001307. doi:10.1371/journal.pmed.1001307).

35.   Hagens V, Ranchor A, Van Sonderen E, Bosker H, Kamp O, Tijssen J, et al. Effect of rate or rhythm control on quality of life in persistant atrial fibrillation. J Am Coll Cardiol. 2004;43(2):241-7.

36.   Dorian P, Jung W, Newman D, Paquette M, Wood K, Ayers G, et al. The impairment of health related quality of life inpatients with intermittent atrial fibrillation: implications for the assessment of investigational therapy. J Am Coll Cardiol. 2000;36(4):1303-9.

37.   Gage B, Cardinalli A, Owens D. The effect of stroke and stroke prophylaxis with aspirin or warfarin on quality of life. Archives of Internal Medicine. 1996;156:1829-36.

38.   Thomson R, Parkin D, Eccles M, et al. Decision analysis and guidelines for anticoagulant therapy to prevent stroke in patients with atrial fibrillation. Lancet. 2000;355:956-62.

39.   Dorman P, Dennis M, Sandercock P. Are the modified "simple questions" a valid and reliable measure of health related quality of life after stroke? J Neurol Neurosurg Psychiatry. 2000;69:487-93.

40.   Duncan P, Lai S, Keighley J. Defining post-stroke recovery: implications for design and interpretation of drug trials. Neuropharmacology. 2000;39(5):835-41.

41.   Gore J, Granger C, Simoons M, Sloan M, Weaver W, White H, et al. Stroke after thrombolysis: mortality and functional outcomes in the GUSTO-I trial: Global Use of Strategies to Open Occluded Coronary Arteries. Circulation. 1995;92:2811-8.

42.   Shin A, Porter P, Wallace M, Naglie G. Quality of life of stroke in younger individuals: utility assessment in patients with arteriovenous malformations. Stroke. 1997;28:2395-9.