

Pharmacoeconomics of anticoagulation therapy for stroke prevention in atrial fibrillation: a review

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Summary. *Introduction:* Atrial fibrillation (AF) increases the risk of ischemic stroke 5-fold and may not only be responsible for as many as 15% of all strokes that occur but also for larger and more disabling strokes than those attributable to other causes which increase the associated costs of care. Anticoagulation with warfarin in the target INR of 2.5 is a major clinical challenge in real-life practice, given that the complex relationship between warfarin dosage and response is readily altered by a variety of factors such as concurrent medications, illnesses, genetic influences, and dietary/lifestyle changes. Consequently, INR values are out of the target range approximately half of the time in real-life studies compared to clinical trial setting. Current anticoagulation therapies are less likely to be cost-effective in routine clinical practice and need improvement. The aim of this review is to discuss the pharmacoeconomic consequences of this management strategy by analysing the optimal treatment option within specific age and risk groups, confirming current guidelines for a health economic perspective and considering the economic impact on health care policy. *Methods:* An electronic search of the Medline/PubMed database from 1966 to 2005 was performed to identify articles dealing with all pharmacoeconomic aspects of stroke prevention in atrial fibrillation. The following search terms were used: 'atrial fibrillation', 'stroke', 'cost', 'warfarin'. *Results:* Treatment with warfarin is cost-effective (versus aspirin or no therapy) in patients with AF at moderate-to-high risk of stroke. The cost-effectiveness of anticoagulation therapy is driven by the achieved risk reduction rather than the potential benefits estimated from clinical trials. Failure to maintain optimal anticoagulation places patients at risk of complications, the management of which is a significant cost

driver. *Conclusion:* Improvement could be achieved by optimising physicians and patient's knowledge driven through prevention campaigns by health care policy.

Keywords: anticoagulation therapy, atrial fibrillation, cost-effectiveness, stroke, vitamin K antagonists, warfarin.

Introduction

Atrial fibrillation (AF) is a common cardiac arrhythmia that predisposes to the formation of thrombi and hence increases the risk of stroke, a leading cause of morbidity and death in the developed world [1]. The presence of AF increases the risk of ischemic stroke 5-fold [2] and may be responsible for as many as 15% of all strokes that occur [2,3]. Thromboembolic events among patients with AF are usually responsible for larger and more disabling strokes than those attributable to other causes and may increase the associated costs of care [2,5]. In a recent French study, for example, the mean cost for severe stroke was €34 809 (\$45 948)¹ per patient, more than three times higher than the mean cost for a patient with mild stroke (€10 530 [\$13,900]¹) [6]. Similar findings were apparent in a Swedish study, in which a severe stroke was estimated to cost SKr58 392–SKr397 951 (€8642–58 897)² for the first year of care compared with a cost of SKr42 350–SKr133 261 (€6268–19 723) for a mild stroke [7]. Notably, 70% of the costs were for inpatient care.

Stroke is also associated with substantial long-term costs. In this regard, survivors of AF-related stroke are more likely to have longer hospital stays and increased likelihood of disability with need for long-term care [4]. In a Danish study, the duration of hospitalization after stroke was significantly greater for patients with AF (50 days) compared with patients without AF (40 days), while the European Community Stroke Project found that the presence of AF increased the probability of becoming disabled or handicapped after a stroke by almost 50% [8,9]. This is underscored by the observation in a recent German study that almost half of

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¹Exchange rate: € 1 = \$1.32, November 2004.

²Exchange rate: SKr10 = €1.48, November 2004.

patients who suffered a stroke were not discharged home but required additional treatment in alternative settings such as nursing homes [10]. Indeed, the need for subsequent nursing home care has been shown to increase the management costs of stroke by 11% [11]. Not surprisingly, therefore, the significant medical and monetary burden that AF-related stroke places on society has prompted healthcare systems to develop strategies aimed at tackling this problem, notably closer attention to effective stroke prophylaxis. The aim of this review was to discuss the pharmacoeconomic consequences of this management strategy. An electronic search of the Medline/PubMed database from 1966 to 2005 was performed to identify articles dealing with all pharmacoeconomic aspects of stroke prevention in AF. The following search terms were used: 'AF', 'stroke', 'cost', and 'warfarin'. All peer-reviewed published Medline/PubMed papers were included. No omissions have been made.

Prophylaxis of stroke in patients with AF

Stroke prevention in patients with AF is aimed at reducing not only the frequency of ischemic stroke, but also the severity of such events and the associated risk of death. In this regard, international guidelines such as those of the American College of Chest Physicians, the American College of Cardiology/American Heart Association/European Society of Cardiology, and the American Academy of Family Physicians/American College of Physicians are unanimous in their recommendation of oral anticoagulation therapy with warfarin [a vitamin K antagonist (VKA)] in patients with persistent AF and at moderate-to-high risk of stroke [12–14] (Table 1). This recommendation is based on published evidence that warfarin substantially reduces the risk and severity of stroke in patients with AF, such benefits being optimized with an INR (a measure of blood-clotting ability) in the range of 2.0–3.0 (target 2.5) [12–16].

Table 1 Recommended treatment options for patients with persistent atrial fibrillation (AF) [12]

Clinical features	Risk of stroke	Recommended therapy
Prior ischemic stroke, transient ischemic attack, or systemic embolism Age > 75 years Moderately or severely impaired left ventricular systolic function and/or congestive heart failure History of hypertension or diabetes	High	Warfarin*
Age 65–75 years, in the absence of other risk factors	Moderate	Warfarin* or aspirin (325 mg day ⁻¹)
Age < 65 years, and with no other risk factors	Low	Aspirin (325 mg day ⁻¹)

*Dose-adjusted to achieve a target international normalized ratio of 2.5 (range 2.0–3.0).

Pharmacoeconomics of anticoagulation therapy for stroke prophylaxis

A number of studies have been conducted to evaluate the economic consequences of anticoagulation therapy for the prevention of stroke in patients with AF. This includes cost-minimization studies, which only compare the direct costs of treatment, that is, the costs of medical resources consumed, physician visits, surgical procedures, and medical supplies as well as hospitalizations; cost-effectiveness studies which compare the cost per unit of clinical outcome, such as years of life saved or strokes prevented and cost-utility studies, which compare the costs per quality-adjusted life-year [QALY] gained [17–20]. This last method assigns a preference weight to each health state, determines the time spent in each state, and estimates life-expectancy as the sum of the products of each preference weight and time spent for each state [21–25]. While all these types of pharmacoeconomic assessments are valuable, cost-utility assessments (a specific type of cost-effectiveness analysis using quality-adjusted life-years as the effectiveness endpoint) are particularly useful because the results of these studies can be compared with other healthcare activities (e.g. screening for hypertension and prevention campaigns) and even non-healthcare interventions (e.g. transportation safety and environmental protection activities). These analyses allow societies to decide if the intervention is worth the cost and assist in prioritizing options. In a US cost-minimization study that modeled patients with AF, warfarin therapy was associated with lower direct medical costs [\$2599 per patient-year (1995 values)] compared with no therapy (\$4113 per patient-year), based on an annual probability of a thromboembolic event of 14.3 per 1000 anticoagulated patients compared with 46.7 per 1000 patients not receiving warfarin (69% risk reduction) [17]. Cost-effectiveness studies have also demonstrated the benefit of VKA therapy over no stroke prophylaxis in patients with AF. A modeling study (1997 values), conducted from the UK National Health Service perspective and based on the rates of stroke reported in the Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators study, for example, reported that the discounted 10 years direct costs of anticoagulation were £4760 (\$8996)³ per patient whereas the average discounted cost (i.e. future costs converted to their present value) for the treatment of a stroke over the same time frame was £17 820 (\$33 680)³ [19,26]. Similarly, a Swedish study found that for patients with AF and at moderate risk for stroke, VKA therapy was associated with a net cost saving as long as the risk of major hemorrhage remained low ($\leq 1.2\%$) [18]. More recently, a UK study by Abdelhafiz and Wheeldon reported that the total cost of warfarin therapy to prevent one stroke per year was £5260 (\$9941)³ (1999–2000 values), based on an attributable risk reduction of 3% vs. untreated patients. This real-life study

³Exchange rate: £1 = \$1.89, November 2004.

of costs relating to stroke prophylaxis with warfarin among patients referred to a hospital anticoagulation clinic, also revealed that INR monitoring and hospital admission for bleeding complications were the major cost drivers, accounting for 35% and 29% of annual costs of care per patient, respectively [20].

The findings of cost-utility studies, which convert effects into personal preferences (or utilities) and describe the costs for additional gains in quality adjusted life-years of anticoagulation therapy for the prevention of AF-related stroke, are summarized in Table 2. Overall, these studies demonstrate that, in most cases, VKA therapy is associated with a low cost per QALY gained or is superior (associated with both increased QALYs and a reduced cost) compared with no antithrombotic intervention, particularly among those at moderate-to-high risk of stroke. For example, in an early US study, Eckman *et al.* calculated a cost per QALY of \$2732 (1991 values) for a base-case scenario of a 35-year-old woman with AF caused by mitral stenosis [21]. Another North American modeling study in patients with non-valvular AF found that treatment with a VKA performed better than no antithrombotic therapy in patients at moderate-to-high risk of stroke (non-valvular AF plus ≥ 1 additional risk factor). Among those at low risk (non-valvular AF alone), the cost per QALY gained (\$14 000) compared with no therapy was very competitive. This study

also found that VKA therapy was dominant over aspirin therapy in high-risk patients. In 65-year-old patients without risk factors (low to moderate risk group), the cost-utility of VKA therapy would amount up to \$370 000 per QALY gained compared with aspirin treatment, but would decline to reasonable \$8000 per QALY gained if only high-risk patients (one risk factor present, see also Table 1) were treated with VKA (1994 values) [22]. For comparative purposes, screening adults for essential hypertension result in costs of \$10 000–50 000 per QALY [27]. In a US study in elderly patients with non-rheumatic AF, VKA therapy was dominant over no antithrombotic therapy for those at high risk (prior stroke or transient ischemic attacks, diabetes mellitus, and hypertension) [25]. However, the cost-utility of VKA therapy decreased with an increasing age with a cost per QALY of \$30 000 for high-risk patients who were 95 years of age. In another US study, Eckman *et al.* demonstrated that VKA therapy was predominant over no antithrombotic therapy in high-risk elderly patients; the marginal cost-utility remained $< \$50 000$ per QALY gained as long as the risk for major hemorrhage remained $\leq 8.5\%$. In contrast, no treatment yielded better results among patients at low risk for stroke. The authors calculated that the rate of hemorrhage must be $< 3.5\%$ for VKA therapy to be preferred to no therapy in low-risk patients [23]. One study has found that patient preference-based therapy (VKA

Table 2 Summary of cost-utility studies of anticoagulation therapy vs. no stroke prophylaxis (or aspirin) in patients with AF

Study	Indication	Comparison	Patient subgroups	Cost-utility of VKA	Currency
Eckman <i>et al.</i> [21]	AF caused by mitral stenosis	VKA vs no ATT	Base-case (35-year-old woman)	\$2732/QALY	\$\$ (1991 values)
Gage <i>et al.</i> [22]	Non-valvular AF	VKA vs no ATT	High-risk	VKA dominates* (saves \$2800 and adds 0.50 QALYs)	\$\$ (1994 values)
			Medium-risk	VKA dominates* (saves \$500 and adds 0.37 QALYs)	
			Low-risk	\$14 000/QALY	
Eckman <i>et al.</i> [23]	AF	VKA vs no ATT	Elderly, low risk	No treatment dominates* (saves \$1093 and adds 0.02 QALYs)	\$\$ (1998 values)
			Elderly, high risk	VKA dominates* (saves \$288 and adds 0.09 QALYs)	
Gage <i>et al.</i> [24]	Non-valvular AF	VKA vs PPBT (ASA or VKA)	High-risk	PPBT costs \$110 more but adds 0.01 QALYs	\$US (1995 values)
			Medium-risk	PPBT dominates* (saves \$90 and adds 0.02 QALYs)	
			Low-risk	PPBT dominates* (saves \$670 and adds 0.05 QALYs)	
Desbiens <i>et al.</i> [25]	Non-rheumatic AF	VKA vs no ATT	High-risk (age 65 years)	VKA dominates* (saves \$1434 and adds 2.2 QALYs)	\$\$ (2000 values)
			High-risk (age 85 years)	VKA dominates* (saves \$1767 and adds 0.5 QALYs)	
			High-risk (age 95 years)	\$30 000/QALY	

*Increased QALYs and cost saving.

VKA, vitamin K antagonist; AF, atrial fibrillation; ATT, antithrombotic therapy; QALY, quality-adjusted life-year; ASA, aspirin; PPBT, patient preference-based therapy (ASA or VKA).

or aspirin) is a cost-effective alternative to use VKA therapy for all patients with non-valvular AF, particularly in those at low-to-moderate risk of stroke [24].

Methodological considerations

One limitation of these pharmacoeconomic studies is that they are based on the results of controlled clinical trials that were performed in selected patients and generally achieved high levels of anticoagulation control. Maintaining optimal anticoagulation, particularly at levels recommended by international guidelines, is much more clinically challenging in routine practice because of the heterogeneity of patients and, in turn, greater variability of the hard-to-predict impact on warfarin pharmacokinetics and pharmacodynamics of factors (such as genetic variation in warfarin metabolism by hepatic cytochrome P450 2C9 and drug–drug interactions), concomitant illness such as fever and diarrhea, and dietary/lifestyle effects such as alcohol and food intake, and the model of care used [28–31]. These factors, along with issues such as poor compliance with drug therapy, probably explain why INR values are out of the target therapeutic range approximately half of the time in real-life practice, which is much lower than the level of anticoagulation control typically observed in the clinical trial setting [32]. The risk of hemorrhage is approximately 2-fold higher in patients receiving anticoagulant therapy outside experimental trials [33]. There is a significant underuse of thromboembolic prophylaxis in patients presenting AF at high risk for events [34]. Furthermore, there are further investigations focusing on the reasons why patients with AF did not receive warfarin. It has been shown that only 15–44% of patients with AF without any contraindications to warfarin therapy receive warfarin. Health care-, patient- and physician-related barriers to warfarin therapy were identified. Perceived embolic and hemorrhagic considerations and age were identified as patient-related factors influencing the decision of prescribing anticoagulation [35]. Physicians with better experience in warfarin treatment were more likely to prescribe it, but nonetheless still did not prescribe for half of their patients, and some physicians reported difficulty in maintaining therapy within the therapeutic range, stating that further training, the ability of consultation, or guidelines would increase the willingness [36]. 97% of physicians cited a lack of patient reliability as a contraindication to therapy, and more than 90% did not prescribe warfarin to patients with history of alcohol abuse. Among physicians who were aware of clinical practice guidelines, many believed the guidelines were not applicable to their patients [37]. Patients in health maintenance organizations were found to have a significantly greater incidence of angina, previous myocardial infarction, congestive heart failure, and diabetes than patients in clinical trials [38]. Thus, although optimal stroke prophylaxis with warfarin is cost-effective compared with no treatment in clinical trials, the patterns of INR control actually achieved in real-life practice mean that current anticoagulation therapy is less likely to be cost-effective in routine clinical practice. A lack of resources and experienced

Table 3 Treatment costs and number of patients who would be needed to be treated with anticoagulation therapy to prevent one ischemic stroke, in relation to annual risk of intracerebral hemorrhage. Gustafsson *et al.* [18]

	Annual risk of intracerebral hemorrhage		
	0.3%	1.3%	2.0%
Number of patients treated to prevent one ischemic stroke	31	31	31
Net number of patients required to prevent one ischemic stroke	34	53	83
Treatment costs per ischemic stroke prevented (SKr, thousands)	171	267	417
Net cost per ischemic stroke prevented (SKr, thousands)*	–9	87	237

*Based on direct cost of SKr180 000 per stroke.

SKr, Swedish Krona.

Exchange rate: SKr10 = \$1.48 (November 2004).

personnel within the community to adopt practice recommendations to a level reported in clinical trials needs a carefully planned service. Appropriate resources need to be made available to meet patients' demand and measures should be put into place to ensure quality control in the primary care setting [39]. There is a positive example using low intensity warfarin anticoagulation in elderly patients (76 ± 7 years) who have more risk factors for stroke compared with those in clinical trials. However, the annual event rate of stroke and systemic embolism in this practice were comparable with those of patients receiving warfarin in clinical trials (2.0% vs. 1.4% and 0.7% vs. 0.3%) [40].

Other factors that need to be considered when interpreting the cost-effectiveness of warfarin therapy for prevention of AF-related stroke include the frequency of anticoagulation monitoring, the costs of which may include equipment, reagents, nursing, and administration staff time. In the study of Caro *et al.*, for example, the cost of regular monitoring accounted for 22% of the total cost of anticoagulation care [17]. Not surprisingly, therefore, the results of the cost-effectiveness analysis by Lightowers and McGuire were sensitive to alteration in the frequency of INR monitoring [19]. The base-case analysis assumed that anticoagulation checks were performed every 3 weeks, costing £35 (\$66)⁴ per visit. Decreasing the frequency of monitoring to every 6 weeks therefore improved cost-effectiveness, although the authors assumed that this change did not affect the level of INR control. Further, this is not in agreement with current guidelines (e.g. American College of Cardiology) that recommend monitoring of anticoagulation be performed no less than every 4 weeks once the patient's INR level has stabilized.

Another factor that may impact on the cost-effectiveness of warfarin therapy is the risk of bleeding complications such as intracerebral hemorrhage. Table 3 illustrates the effect of hemorrhagic risk on the cost-effectiveness of anticoagulation

⁴Exchange rate: £1 = \$1.89, November 2004.

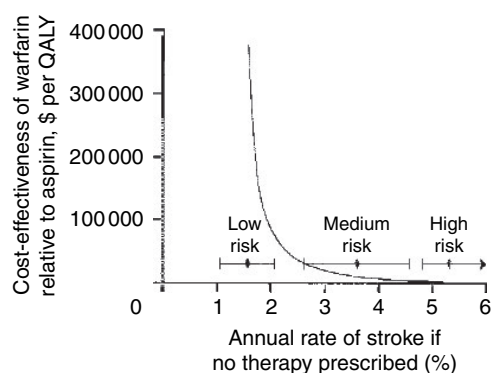


Fig. 1. Sensitivity analysis of the cost-effectiveness of warfarin relative to aspirin in a 65-year-old patient with atrial fibrillation; QALY, quality-adjusted life-years gained (1994 values). Reproduced with permission from Gage *et al.* [22]. *JAMA* 1995; **274**: 1839–45.

therapy for the primary prevention of AF-related stroke [18]. Such sensitivity analyses are appropriate because the low rates of hemorrhagic complications reported in clinical trials are probably not representative of routine clinical practice. Nevertheless, even when much higher rates of major hemorrhage are assumed (i.e. doubling of risk), the cost per QALY saved can still be within accepted values for reimbursement.

Finally, the patient's intrinsic risk of stroke is an important consideration. In the study of Gage *et al.*, for example, warfarin cost \$8000 per QALY gained vs. aspirin in those at moderate risk of stroke [22]. In those at low risk, however, warfarin provided only minor improvements in quality-adjusted life-expectancy leading to a marked increase in cost per QALY gained (Fig. 1). This is explained by fewer stroke-related costs to offset those of anticoagulation therapy in such patients. Such findings therefore are in consensus to the current clinical guidelines, in that warfarin prophylaxis is the preferred (and cost-effective) treatment option for those at moderate-to-high risk of stroke whereas aspirin is appropriate for those at low risk.

Conclusions

The occurrence of ischemic stroke in patients with AF accounts for a major socioeconomic burden that can be addressed by appropriate anticoagulation therapy with warfarin. Indeed, based on the findings of controlled clinical trials, treatment with warfarin is cost-effective (vs. aspirin or no therapy) in patients with AF at moderate-to-high risk of stroke, such findings are confirmed by the recommendations of current clinical guidelines. However, the cost-effectiveness of anticoagulation therapy is driven by the achieved risk reduction rather than the potential benefits estimated from clinical trials. The practical difficulties associated with maintaining INR within the optimal range during warfarin therapy (i.e. because of genetic diversity in drug metabolism; drug, food, and alcohol interactions; concomitant disease, changes in lifestyle, and

compliance problems) may result in anticoagulation therapy being less cost-effective in real-life practice. Indeed, failure to maintain optimal anticoagulation places patients at risk of complications and the management of which is a significant cost driver. Improvement could be achieved by optimizing physician and patient's knowledge driven through prevention campaign by healthcare policy. Further, it is important to realize that the results of pharmacoeconomic studies are not necessarily generalizable to different practice settings and healthcare systems because economic analyses are very sensitive to such perspectives. In addition, as these studies are time-sensitive, the findings of one study may not be relevant in other settings or time periods. Clearly, these factors warrant consideration when evaluating the published reports on the pharmacoeconomics of anticoagulation therapy with warfarin for the prevention of AF-related stroke.

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Disclosure of conflicts of interest

The authors declare that they have no conflicts of interest to disclose regarding this study.

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