New anticoagulant drugs *versus* warfarin in atrial fibrillation: economic evaluation and cost-effectiveness analysis

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ABSTRACT

Health care resources available for medical procedures, including pharmaceuticals, are limited worldwide. Health economic evidence is now accepted as an essential component of health technology appraisal, realizing the importance of value for money considerations for a more efficient (cost-effective) prescribing. Regulatory agencies in more and more countries perform economic evaluation and cost-effectiveness analysis in order to decide about reimbursement of a new and almost always more expensive drug. Pharmacoeconomy is now acknowledged as a science. Cost-effective analysis is just one of its approaches, measuring cost in money and benefit in terms of Quality Adjusted Life Year, a new outcome measure which combines quantity/quality of additional life-years gained with the new drug/technology. A growing body of pharmacoeconomic evidence about new anticoagulant drugs (dabigatran, rivaroxaban, apixaban) for stroke prevention in atrial fibrillation is now available. Most of this evidence comes from the National Institute of Health and Clinical Excellence (NICE) in the United Kingdom, the most referenced regulatory agency in the world. Compared to current standard therapies (warfarin), dabigatran, rivaroxaban and apixaban are cost-effective treatments for the whole population of patients with atrial fibrillation, independently of poor/good international normalized ratio control (time in therapeutic range) and risk stratification for stroke (CHADS2 score). Significant innovation and the lower rate of intracranial hemorrhage/hemorrhagic stroke coupled with the new drugs are the key drivers of these results.

Introduction

Worldwide, warfarin is one of the most prescribed drugs. The main indication for oral anticoagulant therapy is atrial fibrillation (AF). Given the high prevalence of AF in older individuals and the aging population an ever-increasing number of people are expected to start warfarin. The drawbacks in its use are well known and are well reviewed elsewhere in this journal.[1] Dabigatran, rivaroxaban and apixaban are new anticoagulant drugs with the potential of replacing oral anticoagulant therapy, as clearly demonstrated by several randomized controlled trials (RCT).

Substituting a new anticoagulant for warfarin will result in an additional burden to the pharmacy budget for anticoagulation therapy due to the increased drug costs.[2] The current acquisition cost of a new anticoagulant drug is 2-3 euros/day *versus* 0.07 euros/day for warfarin. Such a policy for the entire Italian AF population (650,000 patients) would result in an incremental cost of 0.5 billion euros. The importance of an evidence based health policy has now been acknowledged worldwide, given the limited healthcare resources available. Reimbursement of new medicines is subjected to economic evaluation to improve efficient allocation of public resources.[3,4]

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Cost-effectiveness analysis

Briefly, economic evaluation is a formal comparison of alternative actions in terms of costs and benefits. Cost-effectiveness analysis (CEA) is one of the four types of full economic evaluation (Table 1) in which costs are measured in monetary terms and outcomes are measured using a common unit of effect.[3] This common unit is a clinical measurement when evaluating alternatives that produce the same effect (*e.g.* anti-hypertensive drugs and mm Hg values reduction in blood pressure). If the alternatives do produce multiple effects, a more general measure is needed. This measure is the Quality Adjusted Life Year (QALY): CEA is also

known as cost-utility analysis, when QALY is used to measure effectiveness. The QALY combines and weighs quantitative and qualitative data about life improvements, where 1 is the weight of full health and 0 is the weight of dead-equivalent.[3-5] Various methods for determining weights are available; of course, CEA including these methods are considered superior to others that do not.[6,7]

Cost-effectiveness analysis considers all the costs associated with a new technology/drug, not merely acquisition costs. Costs and savings accruing on the patients, their families and even the impact upon economic activities, have to be considered. Again, methods for these types of evaluation are well established.[3] There are several different approaches to assess cost-effectiveness according to the data collection methods used (Table 2). CEA can be conducted alongside RCTs that provide evidence for efficacy and safety of a new technology/drug. This approach, often called *piggy-back analysis*, has several drawbacks that limit its application. These include: limited time-horizon, selected patient populations, economic data/analysis conducted for registration, not for pharmacoeconomic purposes. Economic modeling on the basis of the results of RCTs is perhaps the most accepted approach by decision makers to substantiate a reimbursement decision on a new drug; the decision tree, Markov and discrete event simulation are the most frequently applied. Clinical data from RCT are put together with information from epidemiological and cost-of-illness studies and other retrospective data sources, thus allowing a longer time horizon, and re-

Table 1. Classification of full economic evaluations according to the measurement of health gain.

Type of evaluation	Measurement of health gain	Measurement of cost	Applicability
Cost-minimization analysis	Non-specified (equal health gain)	Monetary value	Comparison of medical procedures with equal health gain
Cost-effectiveness analysis	Natural units (traditional clinical trial end points)	Monetary value	Comparison of medical procedures with non-equal health gain measurable in the same health dimension
Cost-utility analysis	Quality-adjusted life-years	Monetary value	Comparison of any medical procedures
Cost-benefit analysis	Monetary value	Monetary value	Comparison of any medical and non-medical procedures and investment options

Modified from Bodrogi et al., *2010.*[3]

Table 2. Classification of economic evaluations according to the data collection method used.

	Advantages	Disadvantages
Economic evaluation alongside clinical trials	Randomization (internal validity) Low cost of economic data collection Economic results are available before reimbursement decisions	Selected patient population Protocol-induced costs Limited time horizon Monitoring of economic data is less strict than of clinical variables Calculation of statistical power is based on efficacy end points Economically meaningful events after clinical end point and study drug discontinuation
Naturalistic pharmacoeconomic studies	Non-selected ordinary patients in routine care settings (external validity) *Real world* resource utilization and costs independently of the study protocol Easy monitoring if individual patient records in payers' or managed care database can be linked based upon individual patient ID Large patient population	Unpredictable data collection, complicated study administration, lack of data monitoring Selection bias (if no randomization) Limited time horizon Economic results available only after reimbursement decisions
Economic modeling on the basis of prospectively collected clinical trial data	Economic modeling results available before major decisions (*e.g.* reimbursement) Results can be generalized, adjusted to local medical practice and patient population	Results depend on appropriateness of modeling assumptions (*e.g.* model structure) Known uncertainty in input parameters reduces the clarity of conclusions

Modified from Bodrogi et al., *2010.*[3]

sults that can be generalized and adjusted to local medical practice and patient population. The level of appropriateness of modeling assumptions (*i.e.* model structure, time horizon, sophistication of the model to differentiate clinically and economically meaningful outcomes) is of paramount importance in determining accuracy of CEA estimates. Input parameters are subject to considerable uncertainty both qualitatively and quantitatively, thus making conclusions less clear.[3-5]

Once the costs (money) and effects (QALY) of a new technology/drug have been established, they have to be paired with a comparator, usually the current gold standard in order to calculate the incremental cost effectiveness ratio (ICER). The ICER is calculated by dividing the difference in the expected costs by the difference in the expected QALY (Figure 1). This acquisition is very important from the perspective of a decision maker, because a threshold (*i.e.* maximum ICER value) could be established in order to accept/reject reimbursement for a new drug.[3-5] The World Health Organization developed the CHOICE project (choosing interventions that are cost-effective) with the objective of providing policy makers with the evidence needed to allow them to decide on the interventions and programs which maximize health for the available resources.[8] CHOICE uses gross domestic product (GDP) as a readily available indicator from which to derive the following three categories of cost-effectiveness: i) highly cost-effective (<GDP *per capita*); ii) cost-effective (1-3 times GDP *per capita*); and iii) not cost-effective (>3 times GDP *per capita*).

The National Institute of Health and Clinical Excellence (NICE) in the United Kingdom is perhaps the most famous regulatory agency dealing with decision making to accept or refuse to make new drugs available on the market based on CEA. When a NICE technology appraisal recommends use of a drug, treatment or other technology, the UK National Health Service must usually provide funding and resources for it within three months of the guidance being published.

NICE uses a standard approach to calculate cost and benefits: medicines whose ICER fall below the range of £20,000-30,000 per QALY gained are more likely to be approved than medicines whose ICER exceeds this national threshold. Nevertheless, the decisions of NICE are not wholly related to this unique parameter. Special circumstances if applicable, are considered and medicines with threshold-exceeding ICER are sometimes approved.[9-11] Such special circumstances could include severity of underlying illness, end-of-life treatments, stakeholder pressure, significant innovation, disadvantaged population, or children.

New anticoagulant drugs: economic evaluation

Emerging health-economic evidence is available in the literature about new anticoagulant drugs. Most of this evidence is related to dabigatran, the first drug to generate evidence and to be introduced on the market.

Dabigatran

The most extensive and accurate CEA for dabigatran *versus* warfarin in AF has been produced by 2012 NICE technology appraisal document, on the basis of RELY trial results.[12] The committee concluded that the most plausible ICERs for the whole population eligible for dabigatran were within the range normally considered a cost-effective use of National Health Service resources, *i.e.* less than £20,000 *per* QALY gained. Apart from this, some comments must be made about a number of controversial issues.

$$ICER = \frac{C_{new} - C_{old}}{B_{new} - B_{old}} = \frac{money}{QALY} = money\ per\ QALY$$

	Highly cost effective	Cost effective	Not cost effective
WHO	<GDP *per capita*	1-3 GDP *per capita*	>3 GDP *per capita*
UK	<£30,000	£30-60,000	>£60,000

C, cost; B, benefit; GDP, gross domestic product; ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year.

Figure 1. Incremental cost effectiveness ratio (ICER) calculation and ICER thresholds.

1. Effectiveness of dabigatran compared with warfarin according to international normalized ratio (INR) control on the evidence that people with good INR control with warfarin may not gain additional clinical benefit by taking dabigatran. The clinical specialists *emphasised the importance of the significantly lower rates of intracranial haemorrhage and haemorrhagic stroke associated with both doses of dabigatran compared with warfarin in the RE-LY trial, and that this effect is maintained in people with good INR control. The Committee heard that haemorrhagic stroke and intracranial haemorrhage have devastating and life-threatening consequences and concluded that the lower rates associated with dabigatran represent an important advance in the treatment of atrial fibrillation alongside reduction in ischaemic stroke*.[12]
2. Restriction of dabigatran to patients with poor INR control. A time on therapeutic range (TTR) of more than 75% was calculated for warfarin in order to obtain an ICER for dabigatran above the threshold of £30,000 *per* QALY. This is well above the TTR of RELY (72%) and of UK practice (67%), and perhaps of the general *real world*, given the high standards of the UK anticoagulation service. *The Committee was satisfied that the technology was a cost-effective treatment for the whole patient group. It noted that robust evidence of differential clinical effectiveness and cost effectiveness, with clear justification of the threshold level chosen, would be needed to select out a subgroup, based on INR control, for whom dabigatran would not be recommended.*[12]

Dabigatran CEA in AF have been conducted in other countries by local health services. Three studies demonstrated the cost-effectiveness of abigatran across the USA. Freeman and Homan yielded an ICER less than 50,000 US dollars (USA ICER threshold) in the whole AF population and in patients with previous stroke/transient ischemic attack, respectively, while Shah documented a cost effectiveness only in people at high risk of hemorrhage or high risk of stroke unless international normalized ratio control with warfarin was excellent. From the perspective of Canadian Health Services, dabigatran *versus* warfarin is cost-effective with an ICER of 10,440 Can dollars/QALY.

Cost-effectiveness analyses have also been conducted across the European Union. According to national health services, dabigatran is considered cost-effective *versus* warfarin in AF patients in Belgium, Denmark, Sweden, UK and Spain. A recent paper extends the same results to Switzerland[13-23] (Table 3).

Rivaroxaban

Evidence from the ROCKET trial was the basis for a NICE technology appraisal document on rivaroxaban.[24] The most plausible ICER for rivaroxaban *versus* warfarin lies between £2870 and £29,500 per QALY gained, given that the principle driver of CEA and the main source of uncertainty was the cost of anticoagulation monitoring. However, this ICER value is not above the threshold of £30,000 and rivaroxaban is considered a cost-effective option in AF patient management in the UK.

No clinically relevant subgroups for which there is evidence of differential effectiveness were identified. Rivaroxaban is a cost-effective treatment for the whole population of patients with AF, independently of risk stratification (CHADS2 score) and poor/good INR control (TTR).

Rivaroxaban has been evaluated for cost-effective-

Table 3. Dabigatran: cost-effectivess analysis data.

Study	Country	Treatment	Year of costing	ICER/QALY gained
Markov model				
Freeman[13]	USA	Dabigatran 150 mg	2008	$US 45.372
Kamel[14]	USA	Dabigatran 150 mg	2010	$US 25.000
Kansal[15]	UK	Dabigatran 150 mg	2010	£4.831
Langkilde[16]	Denmark	Dabigatran 150 mg	2011	€6.950
NICE[12]	UK	Dabigatran 150 mg	2011	£6.264
Sha and Gage[17]	USA	Dabigatran 150 mg	2010	$US 86.000
Sorensen[18]	Canada	Dabigatran 150 mg	2010	$Can 10.440
Pletscher[19]	Switzerland	Dabigatran 150 mg	2011	CHF10.215
Wouters[20]	Belgium	Dabigatran 150 mg	2011	€5296
Gonzales-Juanatey[21]	Spain	Dabigatran 150 mg	2010	€17.581
Davidson[22]	Sweden	Dabigatran 150 mg	2011	€12.449
Discrete-event-simulation model				
Pink[23]	UK	Dabigatran 150 mg	2009	£23.082

ICER, incremental cost effectiveness ratio; QALY, Quality Adjusted Life Year.

ness from the perspective of the US health services. The ICER for rivaroxaban was $27,498 per QALY, well below the US-ICER threshold of $50,000 per QALY. Again, the major driver of CEA was the lower hazard of intracranial hemorrhage with rivaroxaban.[25]

Apixaban

Very recently, NICE evaluated apixaban for cost-effectiveness on the data from the ARISTOTLE randomized clinical trial.[26] The same standard approach used for dabigatran and rivaroxaban appraisal was used. The Committee concluded that apixaban had been shown to be cost-effective compared with warfarin, the most plausible ICER being less than £20,000 *per* QALY gained. Again, apixaban is a recommended option for the whole AF population, independently of CHADS2 score and TTR.

A comment was made about the different calculated ICERs for new anticoagulants. The ICER for apixaban was lower than that for dabigatran that was in turn lower than that for rivaroxaban, giving rise to the possibility of a different cost effectiveness among the drugs. There is, however, considerable uncertainty about the relative treatment effects of the drugs, arising from the base-line characteristics of people included in the trials and no firm conclusion can really be drawn on this issue. The Committee concluded that, for the moment, there was insufficient evidence to distinguish between the cost effectiveness of apixaban, dabigatran and rivaroxaban.

Conclusions

Economic evaluation and CEA conducted in European and North American countries have demonstrated the cost effectiveness of dabigatran, rivaroxaban and apixaban compared to warfarin for stroke prevention, in atrial fibrillation. In other words, the expected benefits, progressively increasing over time, far outweigh the higher initial acquisition cost. From the perspective of a regulatory agency, responsible for reimbursement of the cost of the drug, the number of patients subjected to treatment is of paramount importance for cost estimation. While no restriction to subgroup is applied to the population of patients with AF in Europe, Canada or the US, in Italy, the national local regulatory agency (*Agenzia Italiana del Farmaco*, AIFA) has still not made such a decision.

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