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Cost-effectiveness of direct acting oral anticoagulants in the prevention of thromboembolic complications: limits and concerns of economic evaluations

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Corresponding Author:	Giuseppe MC Rosano, M.D., Ph.D King George's Medical University Londra, UNITED KINGDOM
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	King George's Medical University
Corresponding Author's Secondary Institution:	
First Author:	Pierluigi Russo
First Author Secondary Information:	
Order of Authors:	Pierluigi Russo
	Giuseppe MC Rosano, M.D., Ph.D
	Giampiero Favato
	Tommaso Staniscia
	Ferdinando Romano
Order of Authors Secondary Information:	
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Cost-effectiveness of direct acting oral anticoagulants in the prevention of thromboembolic complications: limits and concerns of economic evaluations

Pierluigi Russo[1], Giuseppe M.C. Rosano[2-3*], Giampiero Favato[4], Tommaso Staniscia[5], Ferdinando Romano[6]

[1]Department of Medicine and Aging, University "G. d'Annunzio", Chieti-Pescara, Italy, and Italian Medicines Agency, Rome, Italy

[2]Cardiovascular Clinical Academic Group - St George's Hospitals NHS Trust University of London

[3]Department of Medical Sciences, IRCCS San Raffaele Roma

[4]Institute of Leadership and management of Health, Kingston Business School, Kingston University London

[5]Department of Medicine and Aging, University "G. d'Annunzio", Chieti-Pescara, Italy

[6]Department of Public Health and Infectious Diseases, University La Sapienza, Rome, Italy

***Corresponding author**

Giuseppe M.C. Rosano

Department of Medical Sciences - IRCCS San Raffaele Pisana,

via della Pisana, 235, 00163 Rome, Italy

tel. +39 06 52252409 Fax +39 06 52252465

giuseppe.rosano@gmail.com

Abstract

Economic evaluations have a widespread application in many areas of clinical research and play a key role in clinical decision-making process. However, economic analyses have been sometimes used to produce new "evidence" that is not adequately tested in the target population. This is the case of data arising from a systematic review of clinical trials evaluating the use of direct acting oral anticoagulants (DOACs) for the prevention of stroke in patients with atrial fibrillation. Taking into account this example, here we discuss the concerns raised by the improper interpretation of the results. Our conclusions are threefold. Data from economic analyses should not be shifted to a clinical recommendation. Simulation models should not be used to generate new "evidence", that is not supported by experimental data and is misleading. Clinical judgment is therefore pivotal to interpret results emerging from economic analyses.

Keywords

cost-effectiveness analysis, network meta-analysis, warfarin, direct acting oral anticoagulants, atrial fibrillation

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Author contributions

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Conflicts of interest

The authors have no conflicts of interest relevant to the development of the current publication to declare.

Perspective Article

Since the publication of the foundations of cost-effectiveness analysis (CEA) for health and medical practices in the 1970s,[1] this approach has been widely applied to health technologies and pharmaceuticals. However, criticism has emerged regarding the influence of conflicts of interest,[2,3] the varying degrees of precision, power of data and analytic methods,[4] and the difference between clinical evidence obtained in randomized controlled trials (RCTs), which aim to receive regulatory approval, and clinical effectiveness in real-world practice.[5,6] The main concerns are that these economic analyses could be used to produce new evidence that is often not adequately tested in the target population, instead of using available evidence that emerges from clinical trials to add useful information for the efficient allocation of resources.

In 1996, O'Brien noted that although RCTs provide the highest level of clinical evidence, these trials are designed to measure efficacy in a restricted population (i.e., using drugs in clinical practice).[5] Thus, applying the results of RCTs to assessments of clinical effectiveness in real-world practice may be challenging. If RCTs are not the optimal source of efficacy measures in assessing clinical effectiveness, compared to that of data published twenty years ago, the strength of clinical evidence is currently lower in several therapeutic areas. Furthermore, many registrative trials are not comparative (i.e., single arm, particularly among orphan drugs), are based on surrogate markers that may not correlate well with the outcome of interest,[7] or are designed as a non-inferiority trial; the frequency of such trials has increased by a factor of 6 during the past decade.[8]

According to currently available efficacy data from registrative clinical trials, the risk that CEA may generate new evidence that is not supported in the clinical setting is high. Thus,

alternative options that do not differ in clinical efficacy likely differ in models comparing effectiveness and cost-effectiveness.

With this regard, Lopez-Lopez *et al.*[9] performed a systematic review of RCTs evaluating the use of direct acting oral anticoagulants (DOACs), vitamin K antagonists, or antiplatelet drugs for the prevention of stroke in patients with atrial fibrillation. The systematic review included 23 randomized trials involving 94656 patients, and the authors performed a network meta-analysis. Then, a CEA was performed based on a discrete-time multistate Markov model. The main aim of the analysis was to indirectly compare the use of DOACs and warfarin for the prevention of stroke in patients with atrial fibrillation and recommend a rank order for the use of DOACs based on efficacy, safety and cost. The first conclusion of this systematic review was that DOACs, as a class, reduce the risk of stroke and all-cause mortality and are safer than warfarin in terms of major and intracranial bleeding at doses that maintain an international normalized ratio (INR) of 2.0 to 3.0. This result was unexpected since DOACs have been authorized by both the European Medicine Agency and Food and Drug Administration based on evidence that DOACs are not inferior to warfarin.

The second conclusion was that since 5 mg apixaban twice daily ranks the highest in the balance of efficacy, safety, and cost, thus policy makers, healthcare providers, and patients should consider apixaban the first choice among DOACs for the prevention of stroke in most patients with atrial fibrillation.

According to these conclusions, the translation of the results of Lopez-Lopez *et al.*'s[9] CEA into clinical recommendations indicates that 5 mg apixaban twice daily should be considered as first choice in the prescription of DOACs, while the first conclusion is already included in the main clinical guidelines.[10] No clinical guideline supports the use of any specific

DOAC as the first choice[11] due to several therapeutic reasons; for instance, different DOACs may be more appropriate than others in different settings; therefore, each DOAC may be more appropriate according to the individual patient profile, i.e., impaired renal function, history of ischaemic heart disease, peripheral arterial disease, etc.

Overall, a first-choice drug other than apixaban could be selected for several therapeutic reasons, and this alternative is likely equally cost effective for patient subgroups; consequently, the CEA on DOACs generated new evidence that is not supported by experimental data, which is a critical issue; thus, identifying the step in the analysis that could affect the CEA's conclusions and result in potentially misleading clinical recommendations is relevant.

The first step is the indirect comparisons among the DOACs using a network meta-analysis. Tables 1 and 2 show the results of the network meta-analysis performed to indirectly compare the use of DOACs in regard to the outcomes of stroke, myocardial infarction, mortality, and bleeding in patients with atrial fibrillation (data published by Lopez-Lopez et al.[9]; the data reported in the tables only reflect the indirect comparisons, i.e., the direct comparison with warfarin was excluded). Based on the indirect comparison using a network meta-analysis, no DOAC is better than another in terms of efficacy in stroke prevention and risk of adverse events (Tables 1 and 2). In a few cases, the odds ratios were statistically significant; however the significant differences highlighted may have had a high probability of occurring by chance, the so-called family-wise error. Indeed, these estimates were obtained without adjusting for multiple comparisons, therefore, the observed statistically significant odds ratios may be not due to systematic differences among DOACs. This could be a critical issue for the network meta-analysis performed giving rise to false positive results.[12] As a whole, this finding is not unexpected based on the recommendation of the main clinical guidelines.[10,13]

Table 3 shows the results of the CEA of licensed products for the prevention of stroke in patients with atrial fibrillation from Lopez-Lopez *et al*.[9] First, the Markov model predicted insignificant differences among DOACs in the expected mean quality-adjusted life years (QALYs). This result is consistent with the results of the network meta-analysis. However, whether meta-analysis of RCTs supports a favourable risk–benefit profile of DOACs compared to warfarin,[14] no significant differences were obtained from the modelling of the expected QALYs in patients treated with DOACs and warfarin.

DOAC anticoagulation treatment is easier to manage than that of warfarin, thus providing greater opportunities to improve the quality of life[15] due to the possibility of not periodically monitoring the INR, which is the main reason for the reimbursement of DOACs by public healthcare. Furthermore, a product that only requires administration once daily may provide certain advantages in terms of medication adherence compared with products that require twice daily administration. In contrast, a twice daily administration schedule of molecules with a shorter half-life may provide an advantage in managing the risk of bleeding during the waiting period for emergency surgery.

Overall, more than 80% of the variability in the point estimates of the QALYs with all DOACs overlapped with that of warfarin (i.e.: percentage of 95% CI overlapped with that of warfarin). According to the overall results of both the network meta-analysis and the Markov model, no healthcare benefit can be attributed more to one DOAC molecule than to another.

Thus, the less expensive DOAC molecule should be considered a better option since it can provide the same healthcare benefit at a lower cost. Dabigatran had the lowest mean cost (Table 3); however, this conclusion could be incorrect for two reasons. First, no statistically significant differences were observed for the mean expected cost of each DOAC and that of

warfarin (the 95% confidence interval of the incremental expected cost of each DOAC crossed zero). Second, more than 90% of the variability in the point estimates of the cost of each DOAC overlapped that of warfarin. Based on the results obtained from the analysis performed by Lopez-Lopez *et al*.,[9] the main conclusion should be that the analysis confirms the suggestions of the main clinical guidelines,[10-11;13] which do not support the preferential use of a DOAC over another in the same class. Furthermore, no evidence supports the lower total cost of a molecule compared to others.

Notably, the cost difference among the DOACs depends on the listed price of the product. Thus, the rank order and magnitude of the cost differences among the DOACs may change considering the final prices that institutional payers actually pay,[16] which could also affect the transfer of cost-effectiveness results from one country to another in a healthcare context.

Regardless of the limitations related to price and the transfer of cost-effectiveness results among different countries, the analysis included a step that computed the incremental net benefit (INB) of each DOAC compared to that of warfarin by combining cost data and QALYs from distributions that almost completely overlapped, which did not permit the identification of a better alternative option in regard to QALYs or total cost. Due to this methodological approach, the authors drew an incorrect conclusion regarding the use of 5 mg apixaban twice daily based on the 95% confidence interval of the INB, which did not cross zero. The lower limit was 93.5% lower than the mean estimate (£7 533, 95% CI: £490-18228, considering a threshold of £20 000 per QALY), and the upper limit was 142% higher than the mean estimate. Furthermore, the probability that 5 mg apixaban was the most cost-effective option always remained under 60% of any value of willingness to pay.[9]

In conclusion, economic evaluation has gained a widespread application in many areas of clinical research. In particular, health economics help address clinical decision-making process. However, the example described here concerning the use of DOACs in the prevention of thromboembolic complications suggests the need to avoid both misleading interpretations in transferring results into clinical recommendation and the generation (by the mean of simulation models) of new evidences, that are not supported by experimental data. This criticism has been already highlighted in the oncological context, where the acceptance by national health authorities of modelled data for reimbursement purpose may create a biased incentive for pharmaceutical companies to substitute RCTs that directly assess hard endpoints.[17] In this way, it is essential that the clinician acquires skills to critically evaluate the information and results emerging from economic modelling.

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Table 1. Indirect comparisons using a network meta-analysis of recommended doses of DOACs evaluated in a phase III trial investigating stroke, myocardial infarction, and mortality outcomes in patients with atrial fibrillation.

Comparison of recommended doses of DOACs evaluated in a phase III trial	**Stroke or systemic embolism** **Odds ratio* (95% CI)**	**Ischaemic stroke** **Odds ratio* (95% CI)**	**Myocardial infarction** **Odds ratio* (95% CI)**	**All-cause mortality** **Odds ratio* (95% CI)**
Dabigatran 150 mg twice daily and apixaban 5 mg twice daily	*0.82 (0.62 to 1.08)*	*0.83 (0.59 to 1.16)*	*1.48 (0.98 to 2.22)*	*1.00 (0.84 to 1.19)*
Edoxaban 60 mg once daily and apixaban 5 mg twice daily	*1.09 (0.87 to 1.39)*	*1.10 (0.83 to 1.46)*	*1.10 (0.76 to 1.58)*	*1.03 (0.89 to 1.20)*
Rivaroxaban 20 mg once daily and apixaban 5 mg twice daily	*1.11 (0.87 to 1.41)*	*1.01 (0.74 to 1.38)*	*0.92 (0.63 to 1.34)*	*0.94 (0.76 to 1.17)*
Edoxaban 60 mg once daily and dabigatran 150 mg twice daily	**1.33 (1.02 to 1.75)**	*1.33 (0.97 to 1.83)*	*0.74 (0.50 to 1.09)*	*1.03 (0.87 to 1.22)*
Rivaroxaban 20 mg once daily and dabigatran 150 mg twice daily	**1.35 (1.03 to 1.78)**	*1.22 (0.87 to 1.73)*	**0.62 (0.41 to 0.93)**	*0.94 (0.74 to 1.18)*

Rivaroxaban 20 mg once daily and edoxaban 60 mg once daily	*1.01 (0.80 to 1.27)*	*0.92 (0.69 to 1.23)*	*0.84 (0.59 to 1.20)*	*0.91 (0.73 to 1.13)*

Modified from Lopez-Lopez et al.[9]; *statistically significant odds ratios are shown in bold

Table 2. Indirect comparisons using a network meta-analysis of recommended doses of DOACs evaluated in a phase III trial investigating bleeding outcomes in patients with atrial fibrillation.

Comparison of recommended doses of DOACs evaluated in a phase III trial	**Major** **Odds ratio (95% CI)**	**Intracranial** **Odds ratio (95% CI)**	**Gastrointestinal** **Odds ratio (95% CI)**	**Clinically relevant** **Odds ratio (95% CI)**
Dabigatran 150 mg twice daily and apixaban 5 mg twice daily	**1.33 (1.09 to 1.62)**	*0.96 (0.58 to 1.60)*	**1.71 (1.21 to 2.43)**	*2.32 (0.74 to 8.63)*
Edoxaban 60 mg once daily and apixaban 5 mg twice daily	*1.11 (0.92 to 1.35)*	*1.09 (0.69 to 1.70)*	**1.38 (1.00 to 1.92)**	**1.24 (1.09 to 1.42)**
Rivaroxaban 20 mg once daily and apixaban 5 mg twice daily	**1.45 (1.19 to 1.78)**	*1.55 (0.97 to 2.49)*	**1.66 (1.19 to 2.33)**	**1.53 (1.33 to 1.75)**
Edoxaban 60 mg once daily and dabigatran 150 mg twice daily	*0.84 (0.69 to 1.02)*	*1.13 (0.69 to 1.87)*	*0.81 (0.60 to 1.09)*	*0.54 (0.14 to 1.68)*
Rivaroxaban 20 mg once daily and dabigatran 150 mg twice daily	*1.10 (0.90 to 1.34)*	*1.61 (0.96 to 2.72)*	*0.97 (0.71 to 1.33)*	*0.66 (0.18 to 2.07)*
Rivaroxaban 20 mg once daily and	**1.31 (1.07 to 1.59)**	*1.43 (0.90 to 2.26)*	*1.21 (0.90 to 1.60)*	**1.23 (1.10 to 1.37)**

edoxaban 60 mg once daily				

Modified from Lopez-Lopez et al.[9]; *statistically significant odds ratios are shown in bold

Table 3. Cost effectiveness of licensed products used for the prevention of stroke in patients with atrial fibrillation from Lopez-Lopez et al.[9]

Expected (mean) values are reported (95% confidence intervals). Incremental values are relative to a warfarin international normalized ratio (INR) of 2.0-3.0.

	Warfarin INR (2.0-3.0)	**Apixaban 5 mg twice daily**	**Dabigatran 150 mg twice daily**	**Edoxaban 60 mg once daily**	**Rivaroxaban 20 mg once daily**
Total costs (£)					
Expected	24 418 (12 189 to 50 365)	23 340 (12 842 to 45 753)	23 064 (12 674 to 46 075)	23 985 (13 098 to 46 319)	24 841 (13 198 to 47 603)
incremental expected	NA	-1 078 (-7 626 to 2 568)	-1 354 (-8 049 to 2 273)	-433 (-6 430 to 3 619)	422 (-4 730 to 5 104)
QALYs					
Expected	5.166 (3.629 to 6.541)	5.488 (3.841 to 6.795)	5.416 (3.817 to 6.701)	5.405 (3.819 to 6.678)	5.451 (3.824 to 6.797)

incremental expected	NA	0.323 (-0.015 to 0.814)	0.251 (-0.080 to 0.703)	0.239 (-0.112 to 0.684)	0.285 (-0.068 to 0.810)
Expected incremental net benefit at threshold (£)					
£20 000	NA	7 533 (490 to 18 228)	6 365 (-168 to 17 039)	5 212 (-894 to 14 826)	5 279 (-1 097 to 15 180)
£30 000	NA	10 760 (576 to 25 861)	8 871 (-597 to 23 402)	7 601 (-1 556 to 20 987)	8 130 (-1 399 to 22 819)

Modified from Lopez-Lopez et al.[9]; NA=not applicable; QALY=quality-adjusted life year