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ORIGINAL RESEARCH

Setting priorities in the health care sector – the case of oral anticoagulants in nonvalvular atrial fibrillation in Denmark

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Aim: Resources devoted to health care are limited, therefore setting priorities is required. It differs between countries whether decision-making concerning health care technologies focus on broad economic perspectives or whether focus is narrow on single budgets ("silo mentality"). The cost perspective as one part of the full health economic analysis is important for decision-making. With the case of oral anticoagulants in patients with nonvalvular atrial fibrillation (NVAF), the aim is to discuss the implication of the use of different cost perspectives for decision-making and priority setting.

Methods: In a cost analysis, the annual average total costs of five oral anticoagulants (warfarin and non-vitamin K oral anticoagulants [NOACs; dabigatran, rivaroxaban, apixaban, and edoxaban]) used in daily clinical practice in Denmark for the prevention of stroke in NVAF patients are analyzed. This is done in pairwise comparisons between warfarin and each NOAC based on five potential cost perspectives, from a "drug cost only" perspective up to a "societal" perspective.

Results: All comparisons of warfarin and NOACs show that the cost perspective based on all relevant costs, ie, total costs perspective, is essential for the choice of therapy. Focusing on the reimbursement costs of the drugs only, warfarin is the least costly option. However, with the aim of therapy to prevent strokes and limit bleedings, including the economic impact of this, all NOACs, except rivaroxaban, result in slightly lower health care costs compared with warfarin. The same picture was found applying the societal perspective.

Conclusion: Many broad cost-effectiveness analyses of NOACs exist. However, in countries with budget focus in decision-making this information does not apply. The present study's case of oral anticoagulants has shown that decision-making should be based on health care or societal cost perspectives for optimal use of limited resources. Otherwise, the risk is that suboptimal decisions will be likely.

Keywords: atrial fibrillation, oral anticoagulants, priority setting, drug costs, total costs, silo thinking

Introduction

Resources devoted to health care and to improvement of patients' health and quality of life are limited. Therefore, setting priorities for use of resources between different sectors as well as between different activities within a sector, eg, the health care sector, is required. Health economics and health economic analyses aim to assist decision-makers in rational prioritization of health care resources by taking the costs as well as the health improvement of a health technology, ie, drug, device, or medical procedure, into account.[1]

Decision-making in health care may be based on narrow or broad economic perspectives potentially influencing the treatment recommendations. Consequently, health

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care resource spending may result in less health improvement than would be achievable, if decisions were based on more appropriate analyses. Decision-making made with the sole purpose of optimizing within one budget, eg, the drug budget, is an example of a narrow cost perspective that may lead to a suboptimal priority setting. This is especially the case when costs and disease outcomes of the compared alternative health interventions differ. Health economists have named this kind of budgetary focus with potential suboptimal priority setting and use of resources as "silo thinking".[1,2] From affordability point of view with focus upon keeping a specific budget, the narrow cost perspective may make sense and is in principle understandable. However, the problem comes when a decision based on a narrow budget perspective has immediate cost implications for other budgets or can be followed by potential additional costs in the future shifting within the health care budget, budgets outside the health care sector, as well as costs at the societal level. In such a case, the narrow cost perspective should not be left alone while taking the decision regarding implementing and using a health technology.

A societal perspective of a health economic analysis is the broadest possible perspective. Ideally, it includes all relevant costs in the health care sector, costs outside the health care sector (eg, social care), patients' and possible caregivers' expenses (eg, transportation expenses), as well as production loss for the society due to disease and/or early death – a perspective that in principle covers all costs in the society.

Whether the decisions regarding implementation and use of health technologies, including coverage decision-making, are taken with inputs from broad health economic perspectives or whether they are narrower differs between countries. Some countries base their economic input to decision-making on broader cost-effectiveness evidence either performed from the broad societal perspective or from broader public sector or health care sector perspectives depending on the purpose of the health care sector in the countries. Panteli et al have recently shown that this is the case in some European countries like the United Kingdom, Ireland, Spain, Switzerland, Sweden, Finland, and Norway.[3] In other countries, this cost-effectiveness approach has not been adopted or is not a prerequisite, hence decision-making regarding the use of health care technologies is often based on more narrow cost perspectives, eg, the price of the drug. This is primarily the case in Denmark and predominantly in the hospital setting. At the hospital level, decision-making concerning the use and recommendation of specific drugs mainly focuses on cost information of the drug. In such a system, one could argue that decision-makers tend to focus more on a specific budget ("silo thinking") rather than on the overall economy in the health care sector or in the society.

The prevalence of nonvalvular atrial fibrillation (NVAF) is increasing. Today, around 11 million people in the United States and Europe suffer from NVAF, and the number of patients will increase substantially during the next 30–35 years.[4–6] Patients diagnosed with NVAF are often treated with oral anticoagulants in order to reduce the risk of stroke. Currently available oral anticoagulants differ in terms of their ability to reduce outcomes in NVAF like stroke and all-cause mortality, and the implicit treatment complications like major bleeding, as well as they do also differ with respect to the need for treatment monitoring.[4–7] Reducing the occurrence of these outcomes and the need for monitoring will result in reduced costs for the health care sector and other sectors (eg, social care) and may potentially result in productivity gains. Hence, these aspects should be included when analyzing the costs of alternative oral anticoagulants and thereby enable optimal priority setting and decision-making.

The aim of this study was to focus upon the cost side of the health economic analysis in order to illustrate and discuss the implications of different cost perspectives for decision-making, priority setting, and consequently for the optimal use of limited resources. A budget impact model was used as a tool for the cost analyses. The case presented was treatment with oral anticoagulants in patients with NVAF in Denmark.

Methods

At present, there are five oral anticoagulants used in daily clinical practice in Denmark for the treatment of patients with NVAF – the vitamin K antagonist warfarin and the four non-vitamin K oral anticoagulants (NOACs): dabigatran, rivaroxaban, apixaban, and edoxaban. Each of the NOACs has been evaluated and compared with warfarin in large Phase III randomized controlled trials (RCTs) leading to their market authorization.[8–11] Table 1 summarizes the RCT study data regarding the relative risk (hazard ratio [HR]) of stroke and bleeding of each NOAC versus warfarin.

Cost perspectives

The costs related to treatment of NVAF with oral anticoagulants includes the costs of the oral anticoagulant drug itself, the costs of visits to monitor INR (international normalized ratio) levels in warfarin patients, the costs of follow-up visits for NOAC patients, the costs of having a stroke as well as the costs of having a bleeding event following the oral anticoagulant treatment. The number of cost elements included

in the cost analysis will depend on the cost perspective, as illustrated in Figure 1.

The broadest cost perspective, ie, the total costs of oral anticoagulant treatment, includes all or most of the cost elements being either a societal perspective or a public sector perspective (health care and social care sectors). The narrowest perspective only focuses on the costs of the drug itself.

Costs estimates

To analyze the cost side of a full health economic analysis, a budget impact model was used when analyzing the costs of oral anticoagulants. This model analyzes the annual average costs of treating NVAF patients with either warfarin or one of the four NOACs. The cost model was based on the clinical evidence of absolute risk and relative risk (HR) for stroke and bleeding comparing warfarin with each of the four NOACs as found in the Phase III randomized controlled trials (Table 1),[8–11] price per day of using oral anticoagulants based on pharmacy selling prices (PSP), average cost estimates of monitoring and follow-up visits based on available published Danish studies, as well as the costs of a stroke or bleeding event based on Danish registry studies. Costs are reported in US dollars (1 US$ is equal to 6.64 DKK [June 15, 2017]).

The current price per day (PSP, including 25% value added tax [VAT]) for the five available anticoagulants in Denmark varies from US$ 194 for warfarin (3 tablets/day of 7.5 mg warfarin equals US$ 0.53 per day, incl VAT), US$ 1,180 for dabigatran (2 tablets/day equals US$ 3.23 per day, incl VAT), US$ 1,194 for rivaroxaban (1 tablet/day equals US$ 3.27 per day, incl VAT), US$ 1,343 for apixaban (2 tablets/day equals US$ 3.68 per day, incl VAT), and finally US$ 1,149 for edoxaban (1 tablet/day equals US$ 3.15 per day, incl VAT) (www.medicinpriser.dk, accessed June 15, 2017).[12] Part of these costs are reimbursed in the primary care setting by the universal Danish public tax-financed health insurance – roughly 20% for warfarin and around 70–72% for NOACs (see Figures 2–5 for exact figures). The remaining part is paid by the patient as out-of-pocket expense. Patients may, however, have other drugs prescribed, leading to lower copayment share.

Treatment with warfarin requires regular INR monitoring of the patient. A report from the Danish Health Authorities as well as two other publications have estimated the average costs of INR monitoring at both the general practitioner (GP) setting and the hospital setting as well as with telemedicine solutions in Denmark.[13–15] The average of these estimates, depending on the mode of delivery, can be calculated to an annual average cost of US$ 895 for the health care sector of INR monitoring for warfarin patients and US$ 1,212 at the societal level (Table 2).

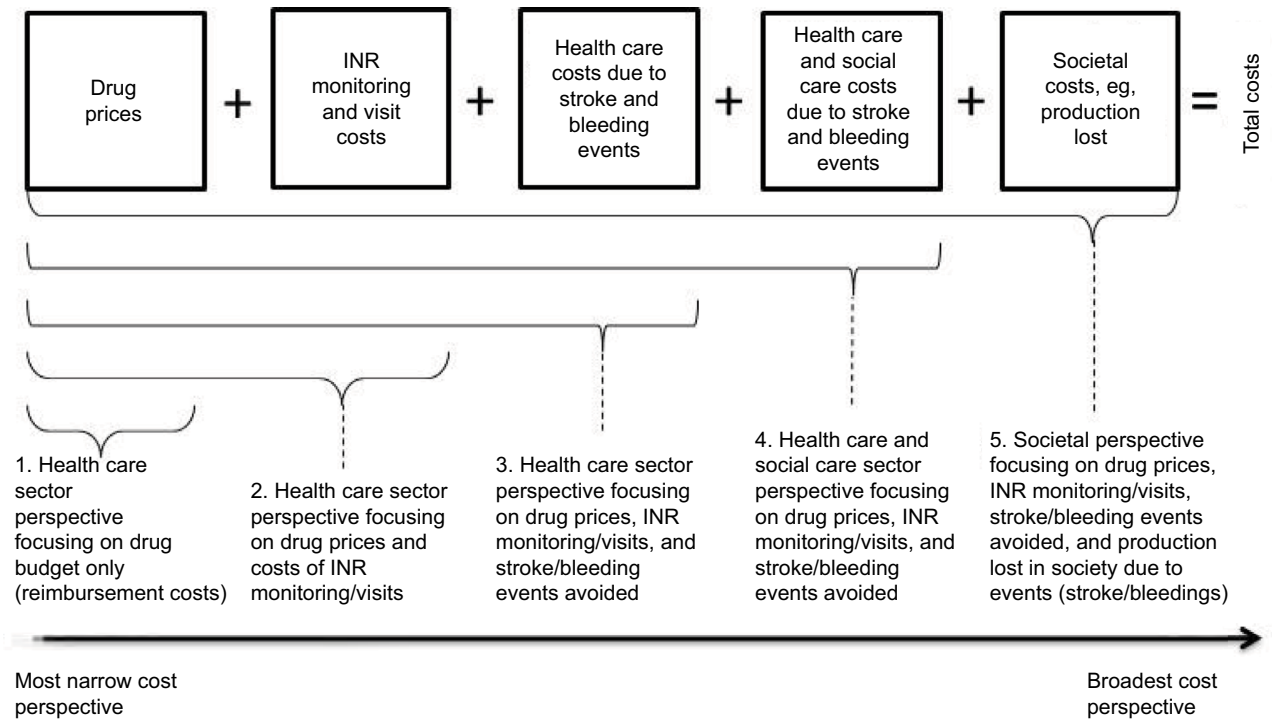

Figure 1 Different cost perspectives in oral anticoagulant therapy.
Abbreviation: INR, international normalized ratio.

Table 1 Risk reduction in stroke and bleeding events* using NOACs compared with warfarin

RCT study data	Stroke	Intracranial bleeding	Gastrointestinal bleeding	Other bleedings
Dabigatran (Connolly et al, 2009)[8]				
1-year event risk among warfarin patients	1.69%	0.74%	1.02%	1.60%
Relative risk (HR) in events using dabigatran 110 mg/150 mg compared with warfarin (CI)	1.00**/0.66 (NS: 0.91; CI: 0.74–1.11 /0.66; CI: 0.53–0.82)	0.31/0.40 (0.31; CI: 0.20–0.47/0.40; CI: 0.27–0.60)	1.00**/1.50 (NS: 1.10; CI:0.86–1.41/ 1.50; CI: 1.19–1.89)	1.00**/1.00** (0.85; CI: NA / 0.83; CI: NA)
Rivaroxaban (Patel et al, 2011)[9]				
1 year event risk among warfarin patients	2.40%	0.73%	1.33%	1.28%
Relative risk (HR) in events using rivaroxaban compared with warfarin (CI)	1.00** (0.88; CI: 0.75–1.03)	0.67 (CI: 0.30–0.58)	1.45 (CI: NA)	1.00 (0.78; CI: NA)
Apixaban (Granger et al, 2011)[10]				
1 year event risk among warfarin patients	1.60%	0.80%	0.86%	2.27%
Relative risk (HR) in events using apixaban compared with warfarin (CI)	0.79 (CI: 0.66–0.95)	0.42 (CI: 0.30–0.58)	1.00** (CI:0.7–1.15)	0.79 (CI: 0.68–0.93)
Edoxaban (Giugliano et al, 2013)[11]				
1-year event risk among warfarin patients	1.80%	0.85%	1.23%	
Relative risk (HR) in events using edoxaban 60 mg compared with warfarin (CI)+	1.00** (NS: 0.87; CI: 0.73–1.04)	0.47 (CI: 0.34–0.63)	1.23 (CI: 1.02–1.50)	

Notes: *"Other bleedings" are reported in some of the clinical trials. These are severe bleedings together with intracranial bleedings and gastrointestinal bleedings and summed up in these clinical trials as "major bleedings" following treatment. Because "other bleedings" were not reported in all four trials, these bleeding types were omitted from the present analysis; **all relative risks (HR) that were not found significant in the clinical trials (NS = not significant) were set to 1.0 in the cost analysis; ; +only the 60 mg dose is included for edoxaban as this is the only approved dosage according to their SmPC.
Abbreviations: NA, not applicable; NOAC, non-vitamin K oral anticoagulants; RCT, randomized clinical trial; SmPC, Summary of Product Characteristics; CI, confidence interval; HR, hazard ratio.

Table 2 Annual average costs of INR monitoring of warfarin patients (US$)

INR monitoring at:	Share of type of monitoring[13]	Danish Health Authorities[13] – adjusted to 2015 charges*	Langkilde et al[14] – adjusted to 2015 charges*	Vestergaard et al (2015)[15]	Average annual costs of INR monitoring
The general practitioner	60%	US$ 492	US$ 728	US$ 750	US$ 657
Hospital, ambulatory visit**	39%	US$ 1,269			
Self-monitoring at home	1%	US$ 654			
Tele-medicine monitoring	0.4%	US$ 680			
Distributed total costs of INR monitoring		US$ 799	US$ 941	US$ 954	US$ 898‡

Notes: *Cost calculations in Danish Health Authorities (Sundhedsstyrelsen, 2012)[13] and in Langkilde et al. (2012)[14] have for the INR monitoring in the GP setting been adjusted to 2015 charges[16] (2015 prices); **12 annual visits assumed (one visit per month); ‡the societal annual costs of INR-monitoring are calculated to US$ 1,212. The extra costs come from the patients transporting direct expenses and time used visiting the clinic for INR-monitoring following calculations by the Danish Health Authorities.[13]
Abbreviation: INR, international normalized ratio.

Treatment with NOACs does not require INR monitoring. However, the patient is expected to come to hospital ambulatory clinics or to their GP for follow-up visits, including for blood sample testing, with four visits in the first year after initiation of treatment and two visits the following years.[17] In the present analysis, three annual visits are conservatively assumed on average for the patients prescribed a NOAC at a cost of US$ 28 per visit.[16]

Oral anticoagulant treatment reduces the risk of stroke in patients with NVAF. At the same time, it may increase the risk of bleeding, thus the safety profile of the drug is equally important as the efficacy profile. A Danish national registry study covering all Danish AF patients in the period 2002–2012 found the first 3-year total attributable societal average costs of a first incident stroke to be as high as US$ 30,925 (present value).[18] Similarly, the 3-year total attributable societal average costs of a first incident episode of intracranial bleeding were US$ 30,950, US$ 20,019 for a gastrointestinal bleeding episode, and US$ 13,874 for other bleeding events in the same AF population (present values).[19] Given that this study analyzed all AF patients over a 10-year period, mortality was taken into account in the analyses when estimating the attributable costs due to stroke or bleeding events.[18,19] The cost estimates found in this study are further split into the relevant different sectors in the budget impact analysis (health care, municipalities, society), and thereby the budgets that they impose. The risk of having stroke and bleeding events in NVAF patients during anticoagulation therapy as well as

Table 3 Total extra costs of first-incident stroke and first-incident bleeding events in AF patients – 3-year present values (US$)

Cost elements	Stroke[18,19]	Intracranial bleeding[19]	Gastrointestinal bleeding[19]
Health care sector costs	20,507	20,234	16,235
Municipality social care costs	8,080	8,429	3,428
Lost production costs	2,338	2,288	355
Total societal costs	30,925	30,950	20,019

Abbreviation: AF, atrial fibrillation.

their associated costs (as presented in Table 3) are included in the present study's estimation of the total costs related to treatment of NVAF with oral anticoagulants.

Results

In the cost analysis, the different alternatives from the narrowest perspective (drug costs only) to the broadest perspective (societal) are analyzed, including all treatment costs, social care costs, and production lost. Figures 2–5 show the total costs per patient receiving oral anticoagulant therapy in Denmark for each of the four NOACs compared with warfarin for the five different cost perspectives in Figure 1.

All comparisons (Figures 2–5) show that the cost perspective of the analysis based on total costs per patient per year is central for the choice of therapy. If the cost perspective focuses on the reimbursement costs of the drugs only (drug prices minus out-of-pocket payment), ie, the drug budget of the public health care sector (first option in the figures), then warfarin is clearly the least costly option. When adding the costs of INR monitoring and follow-up visits to the drug budget expenses (second option in the figures), all four NOACs, more or less, reach the cost level of the warfarin alternative. The aim of oral anticoagulants is to prevent strokes, while at the same time limiting bleeding events. Referring to the

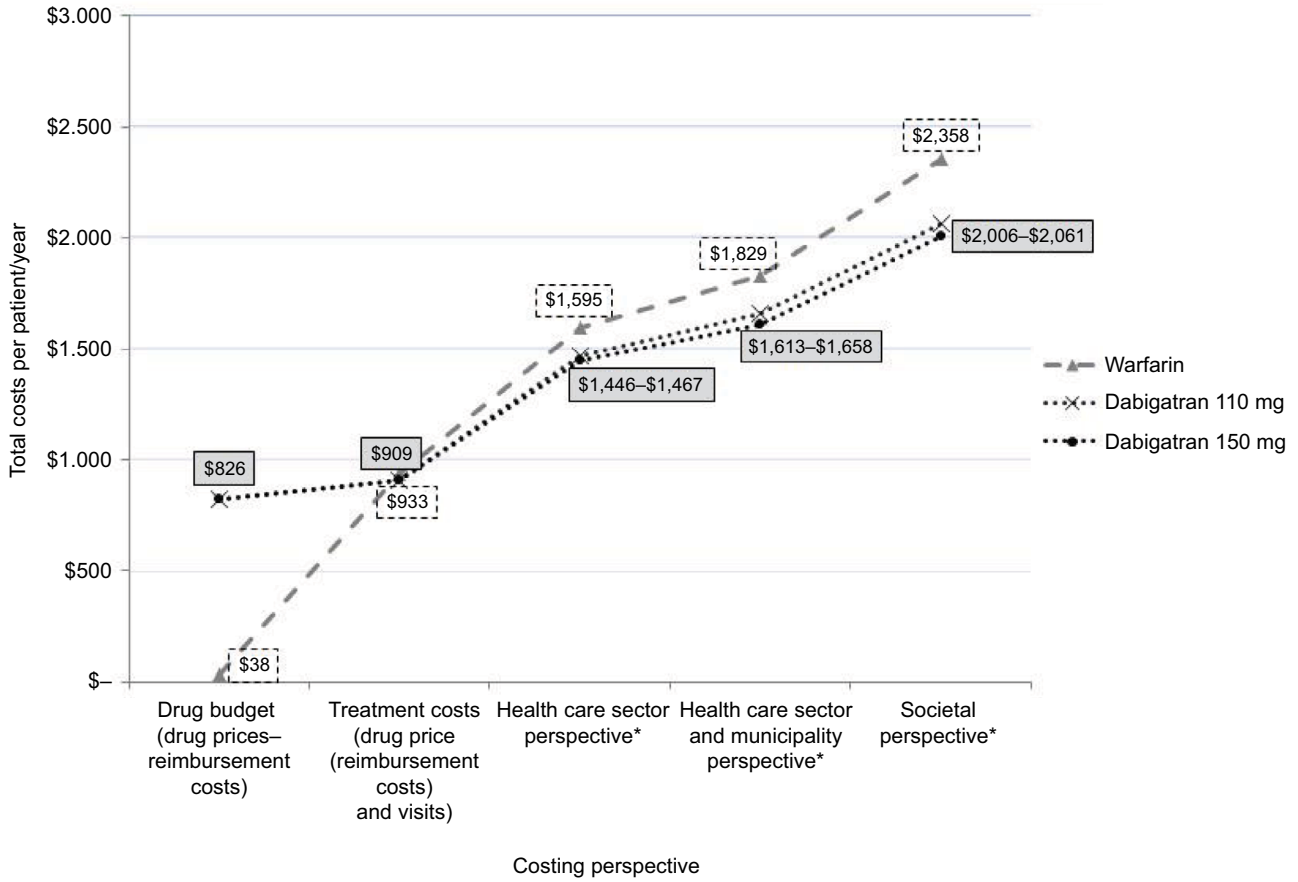

Figure 2 Annual costs per NVAF patient receiving warfarin versus dabigatran 110 mg and 150 mg (US$).**
Notes: *Including the costs of stroke and bleedings; **annual costs for the warfarin alternative are presented in the white boxes in the figure, whereas the annual costs in the dabigatran alternative are presented in the gray shaded boxes.
Abbreviation: NVAF, nonvalvular atrial fibrillation.

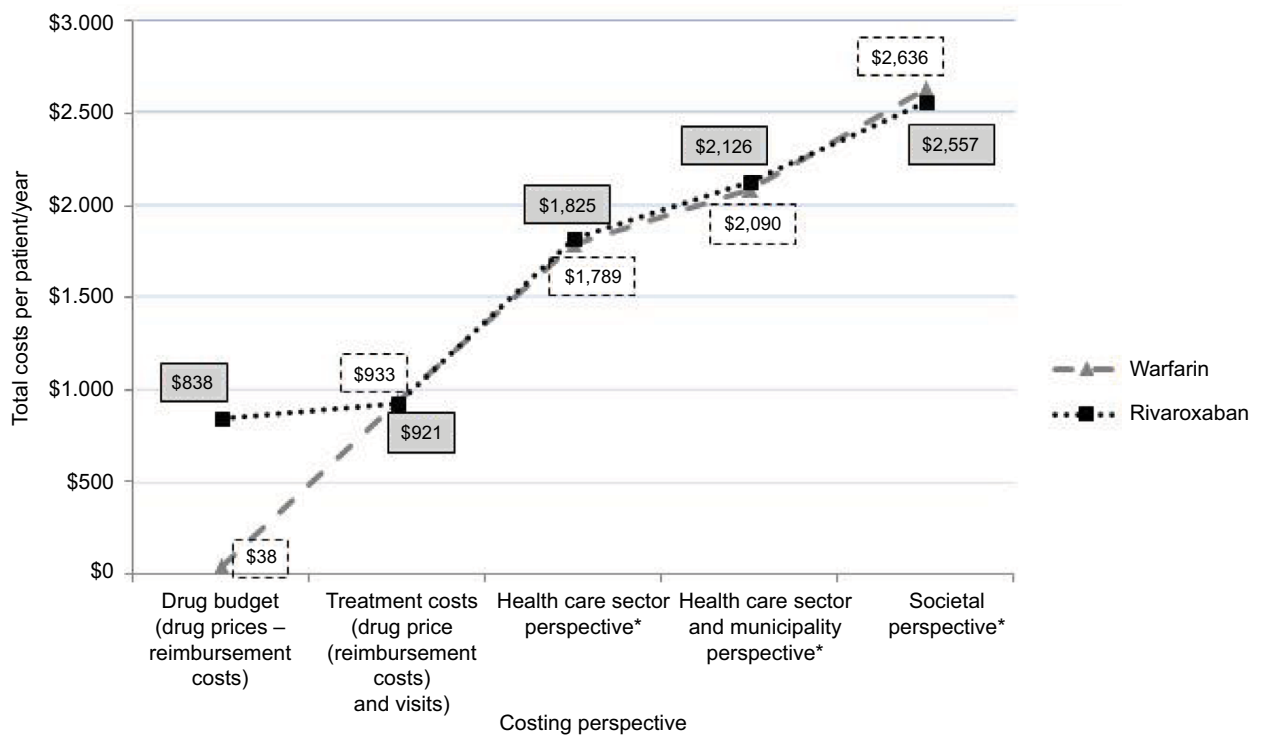

Figure 3 Annual costs per NVAF patient receiving warfarin versus rivaroxaban 20 mg (US$).**
Notes: *Including the costs of stroke and bleedings; **Annual costs for the Warfarin alternative are presented in the white boxes in the figure, whereas the annual costs in the rivaroxaban alternative are presented in the gray shaded boxes.
Abbreviation: NVAF, nonvalvular atrial fibrillation.

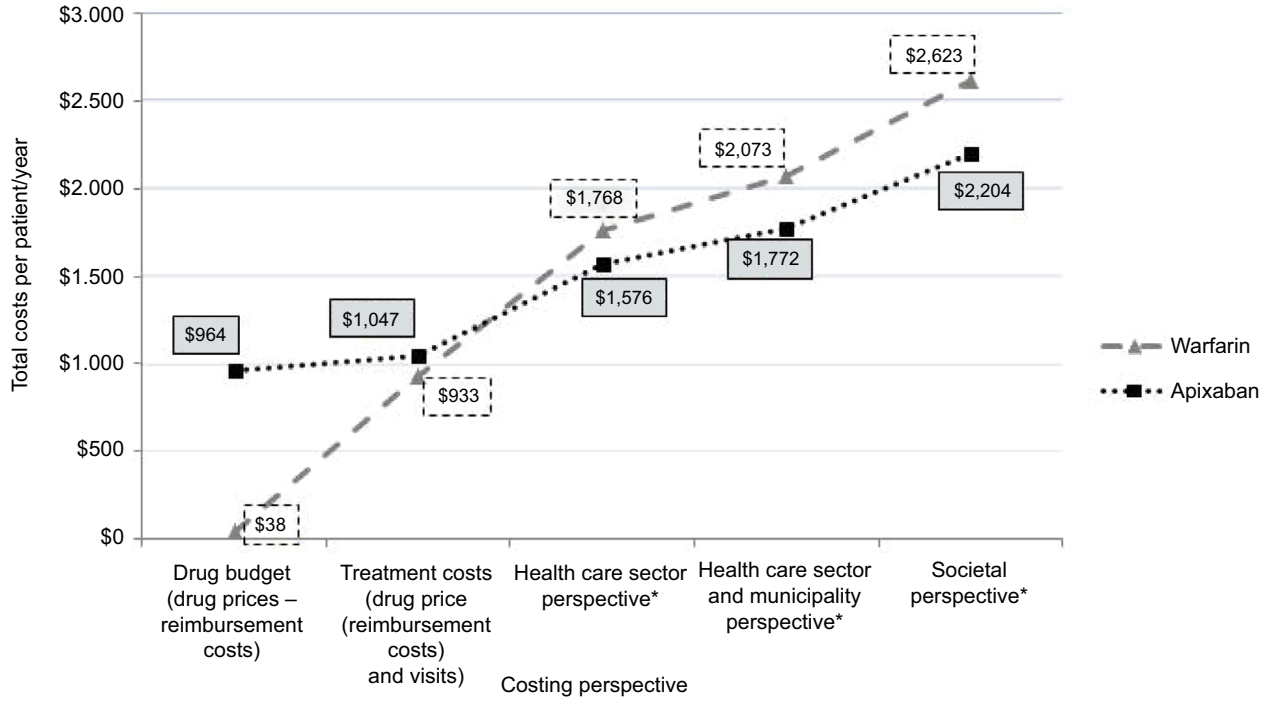

Figure 4 Annual costs per NVAF patient receiving warfarin versus apixaban 5 mg (US$).**
Notes: *Including the costs of stroke and bleedings; **annual costs for the warfarin alternative are presented in the white boxes in the figure, whereas the annual costs in the apixaban alternative are presented in the gray shaded boxes.
Abbreviation: NVAF, nonvalvular atrial fibrillation.

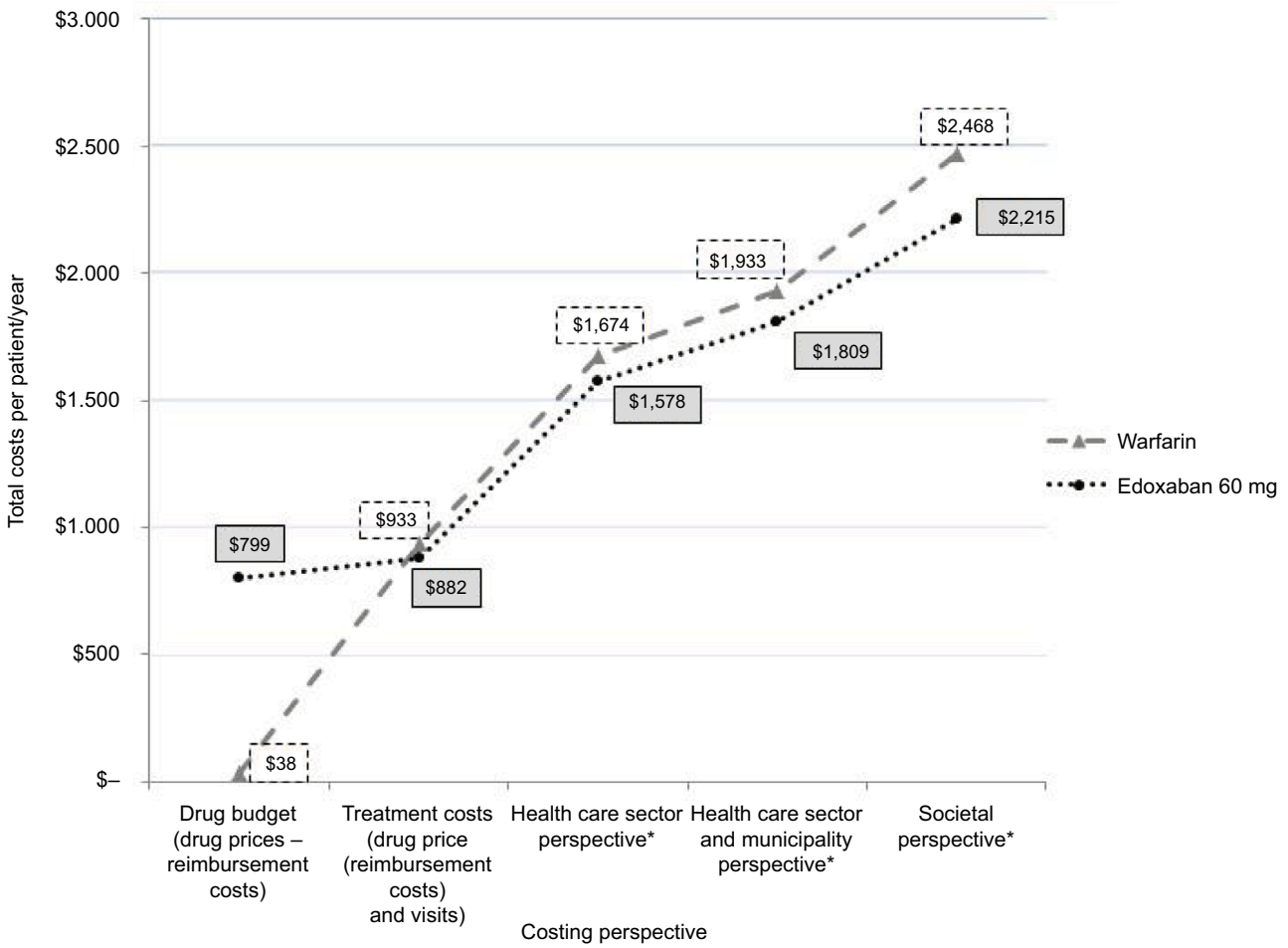

Figure 5 Annual costs per NVAF patient receiving warfarin versus edoxaban 60 mg (US$).**
Notes: *Including the costs of stroke and bleedings; **annual costs for the warfarin alternative are presented in the white boxes in the figure, whereas the annual costs in the edoxaban alternative are presented in the gray shaded boxes.
Abbreviation: NVAF, nonvalvular atrial fibrillation.

Phase III RCTs, dabigatran 150 mg and apixaban result in significantly less strokes than warfarin, whereas the other NOACs result in the same level of stroke prevention as warfarin (noninferiority). Furthermore, all NOACs reduce the risk of intracranial bleeding compared with warfarin, and some NOACs also reduce the risk of gastrointestinal bleeding, whereas other NOACs increase this particular risk (Table 1). When including the costs of strokes and bleeding events in the analysis (still with the health care sector and its budgets as the perspective, third option in the figures), all NOACs result in slightly lower health care costs compared with warfarin (Figures 2, 4, and 5) – except for rivaroxaban with costs close to the warfarin option (Figure 3). Enlarging the cost perspective to include costs related to social care at the municipality level (fourth option in the figures), selection of apixaban 5 mg, dabigatran 150 mg, and edoxaban 60 mg results in less annual costs (US$ 124 to US$ 301) compared with warfarin (Figures 2, 4, and 5). Finally, when analyzed from the societal perspective including the societal costs in terms of production loss and patients' own expenses and time (fifth option in the figures – societal perspective), selection of apixaban 5 mg, dabigatran 150 mg, and edoxaban 60 mg still result in less annual societal costs (US$ 253 to US$ 419) compared with warfarin (Figures 2, 4, and 5). For rivaroxaban 20 mg, the total costs including municipality costs are slightly higher than for warfarin, whereas rivaroxaban on the other hand results in slightly lower costs than for warfarin at the societal level, although close to being equal (Figure 3).

Discussion

Many analyses investigating the cost-effectiveness of the different NOACs have been carried out. Although it is out of scope of the present study to assess the quality of these analyses, they generally conclude that NOACs are cost-effective.[20–23] From a health economic perspective reimbursement, decision-making ought to be broad in terms of

evaluating both costs and outcomes of a given health intervention compared with relevant alternatives. However, in countries with no or limited use of broader cost-effectiveness evidence for reimbursement as well as local implementation, the decisions are instead predominantly based on more narrow cost perspectives and a single budget focus, and by that broader health economic information is often not taken into account, even though this may lead to decision-making that is not optimal either in terms of deciding upon reimbursement or in the use of the technology. The present study focuses only on the cost side of the health economic analysis and analyzes the total costs of the different NOACs, showing the implications of using different cost perspectives.

The case of oral anticoagulants demonstrates that choice of cost perspective is pivotal to the overall total cost results in the budget impact analysis when comparing alternative treatment options and thus important for decision-making and optimal priority setting. The potential recommendations for decision-making and priority setting in terms of the optimal treatment option with respect to the costs of the different alternatives differ depending on the perspective of the analysis. Having the narrowest cost perspective – costs of the drug only – warfarin compared to all NOACs is clearly the least expensive anticoagulant therapy. However, including visit costs as well as the costs of stroke and bleedings, and thereby broadening the cost perspective to that of the public sector or society, has the implication that NOACs are less expensive or comparable to warfarin, leading to cost savings or equal costs depending on the very NOAC of choice.

The present analyses show that the total annual costs of anticoagulation treatment in NVAF patients are between US$ 2,006 and US$ 2,557 using a NOAC compared with US$ 2,358 to US$ 2,636 using warfarin. The main reasons for these lower costs associated with NOACs are the reduced risk of having a stroke linked to some of the NOACs, the lower risk of intracranial bleeding linked to all NOACs, as well as a lower risk of gastrointestinal bleeding linked to some NOACs compared with warfarin treatment (Table 1).

Recently, Brunetti et al, as a proposal to the slow implementation of NOACs despite reimbursement, argued for the use of a budget impact approach as being more appreciated by the public payers, managers, and decision-makers instead of cost-effectiveness analyses.[24] Analyzing this with a broad perspective including direct and indirect health care and societal costs, mortality gains, gain in GDP, etc., brings the break even for the investment in NOACs in terms of costs spend down to 2.5 years.[24] Similarly, US budget impact and cost studies have also, as examples from the pespectives of the payer, compared the different NOACs versus warfarin specifically in terms of the costs of avoided stroke events and bleeding events induced.[25–28] These studies found similar results of savings in the 1-year costs of NOAC treatment compared with warfarin due to reduced risk of stroke and bleedings, although the magnitude of the savings varies. In some studies, though, different NOACs resulted in higher annual costs compared with warfarin, eg, rivaroxaban[27,28] and dabigatran[26] in patients ≥75 years of age. For rivaroxaban, this is also true in the present analysis with a perspective of the health care sector or the public sector, although cost differences are small (Figure 3). The US studies did not include either the costs of the oral anticoagulants itself or visit costs – cost elements that were both included in the analyses in the present study.

Limitations

Our analysis has a number of limitations. Firstly, our analyses are not based on head-to-head comparisons of the NOACs, but on pairwise comparisons of the individual NOACs and warfarin in Phase III registration trials (RCTs),[8–11] as no head-to-head trials of NOACs exist. However, indirect comparisons are generally accepted in health science when performing meta-analyses and systematic reviews, as well as in health economic analyses and technology assessments.[29] The aim of the present analysis was to focus upon within-trial comparison of warfarin to the specific NOAC in the trial and not to make conclusions across trials. Hence, we do not consider this limitation important and relevant in the present case.

Secondly, the present analysis relies on clinical evidence from Phase III RCTs.[8–11] The advantage is a high internal validity (proofs of concept), but potentially a low external validity, ie, it does not necessarily reflect current clinical practice. However, a number of recent real-world data studies based on retrospective information from different registries have in general complemented the data findings from the different NOAC RCTs in terms of risk reduction of stroke and bleeding events using these agents.[30–34] Thus, the results of the present study are not expected to be markedly different, if data from these real-world studies were used instead of those from the RCTs.

Thirdly, when compared with the different NOACs, the warfarin-treated patients in the present analyses utilized an average level of the time in therapeutic range (TTR), as found in the respective randomized clinical trials. However, applying subgroup analyses of warfarin treatment quality with respect to different TTR levels obtained show similar cost saving results for apixaban even for high TTR levels of warfarin treatment (TTR levels in percentages between

71.2 and 83.2) as found in the base case analysis.[35] Similarly, consistency is found on the comparison of apixaban with warfarin patients being less well controlled (TTR levels in percentages between 24.3 and 60.5).[35]

Fourthly, some NOACs (apixaban and edoxaban) have shown significantly lower risk of "other bleedings" compared with warfarin.[10,11] Due to missing data for some NOACs regarding this bleeding outcome and potentially derived costs, these bleeding events were not included. The inclusion of "other bleedings" in the cost calculation would, at least for one of the two NOACs, had resulted in even larger cost savings compared with warfarin. This is true for part of the NOAC group, in particular apixaban, where a reduction in all-cause mortality has been found.[8,11] Gains in mortality were, however, not included in the analyses of the present study. If all-cause mortality gains were included in the analyses this would have been a further upside for apixaban compared with warfarin, as also argued by Brunetti et al.[24]

Fifthly, the study only analyzed the annual costs of the different treatment options and not their long-term costs. Should the 1-year risk reductions in terms of stroke and bleedings found in the clinical trials for the different NOACs versus warfarin differ over a longer time horizon of treatment, this might influence the cost difference between the alternatives. This would likely have been the case if all patients included in these trials were newly diagnosed AF patients receiving their first anticoagulation treatment by inclusion in the trial. However, the clinical trials (eg, Granger et al[10]) did not have this requirement with patients to be included just fulfilling certain criteria for having an AF diagnosis. In this respect, the annual risk reductions found in terms of stroke and bleeding summarizes the average annual risk of events for a broader range of AF patients and not only newly diagnosed, eg, 40% in apixaban study.[10] Hence, the results found in the present study are expected to more or less represent the annual total costs in a given year, and thus in principle it should be possible to multiply this annual cost with number of years to estimate the long-term cost expression.

Sixthly, four follow-up GP visits are recommended in the first year after initiation of NOAC treatment.[17] In the present analyses, an average of three visits was assumed. The number of visits after the first year is typically reduced to 2–3 visits for NOAC patients, based on individual clinical judgment. The present analyses are based on a standard year and not the first year with more intense INR monitoring for warfarin patients. If considering only the first year of NOAC treatment with four visits, the total costs of NOACs come slightly closer to the costs of warfarin, although still being lower than that of warfarin in the analysis based on the societal perspective.

Seventhly, the present analyses only include those costs related to the municipality social care resource, which is available from the national registries in Denmark. It is, however, well-known that these registries do not include all resources used at the municipality level, hence the costs of social care, including both stroke and bleeding events, are an underestimation of the true costs.

Finally, VAT (25%) is included in the drug costs used in the analyses due to the focus upon budgets. However, in economic theory VAT is a transfer payment and not a true use of resources, thereby it can be argued that the VAT part should not be included in health economic analyses. Including VAT in the analyses is not an advantage for the NOAC alternatives due to their higher drug costs compared with warfarin, which makes the results of the analyses conservative. Omitting VAT on drug prices increases the difference in total costs between the NOACs and warfarin.

Conclusion

The analyses of the cost side in health economic analyses using a budget impact model approach have shown the importance of analyzing costs from a broader cost perspective than just a focus on drug prices. For optimal use of limited resources in society and/or the health care sector, priorities should be made at the broadest possible and most relevant perspective in terms of the overall aim of the health care sector. This implies that health economic analyses on the cost side should at least cover all relevant cost implicating activities in the health care sector, and may also have to include costs in other sectors that are affected as well. If the overall aim of the health care priorities is to keep citizens as healthy and productive as possible, the societal perspective ought to be chosen. Even though narrow cost perspectives and budget focus may well be relevant for decision-making at local levels, broader costs perspectives have to be considered to identify potential costs shifting within the health care budget, other budgets, as well as costs at the societal level. This will avoid the risk that priority setting may not be optimal, as illustrated with oral anticoagulants in the present analysis.

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