Health economic impact of medication non-adherence to direct oral anticoagulants in Austria

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Objectives

Medication non-adherence is a common and costly problem. EU-wide, non-adherence may lead to almost 200,000 deaths and excess cost of €80–125 billion [1]. Atrial fibrillation (AF) is the most frequent cardiac arrhythmia, increasing the risk of stroke from three to fivefold and being a leading cause of cerebrovascular mortality and morbidity [2]. Oral anticoagulant medication is recommended to reduce this risk, but medication non-adherence leads to considerable health-risks and avoidable cost. The aim of the present cost-utility analysis (CUA) is to analyze the estimated impact of medication non-adherence to direct oral anticoagulants (DOACs) compared to vitamin K antagonists (VKAs) in terms of clinical outcomes, direct medical cost, and cost-utility.

Methods

A previously published model was used to assess the impact of medication non-adherence to DOACs compared to VKAs (Warfarin) for adult AF-patients using a lifetime horizon, a 5% discount rate, and an Austrian healthcare perspective [3] (Table 1). Real-world evidence (RWE) on patient non-adherence and treatment discontinuation was identified through a systematic literature review (SLR), integrated into the model, and varied in a series of deterministic sensitivity analyses to assess changes in incremental cost, health effects, and cost-utility.

Table 1. Methods

Population	• **Patients with atrial fibrillation in Austria**
	  • Age: 70 years (median), gender: 63.3% male, BMI: 28.0 (mean)
	  • Comorbidities: stroke (20.2%), hypertension (73.8%), chronic heart insufficiency (32.0%)

Intervention	• **Direct oral anticoagulants (DOACs)**
	  • Apixaban 5mg, 2*daily
	  • Edoxaban 60mg, 1*daily
	  • Rivaroxaban 20mg, 1*daily
	  • Dabigatran 110mg & 150mg, 2*daily

Comparator	• **Vitamin K antagonists (Warfarin)**
Outcomes	• **Future health events avoided** • intracranial haemorrhage (ICH); ischaemic stroke; myocardial infarction (MI); clinically relevant or major (extracranial) bleed (MB) • **LYs saved; QALYs saved** • **Cost; ICURs**
Perspective	• **Austrian healthcare system**
Study type	• **Cost-effectiveness analysis (CEA)** • **Cost-utility analysis (CUA)**
Model type	• **Discrete time Markov multistate model**
Time horizon	• **Lifetime**
Cycle lengths	• **3 month**
Discount rate	• **Cost: 5%** • **Effects: 5%**
Timing	• **2021**

Source: own table based on Walter et al. 2021
BMI: body mass index; ICUR: incremental cost-utility ratio; LYs: life years; QALYs: quality adjusted life years

- The SLR of RWE-studies on patient adherence to DOACs included studies published between 2015 and 2021 searching Medline, EMBASE, Cochrane, Science Direct and Pubmed databases and comprising both English and German language articles. Studies were selected if they included data for non-adherence and treatment discontinuation.
- For the base-case analysis, 1st year patient adherence was based on Giner-Soriano et al. (2020) and estimated at 49% for Dabigatran and Edoxaban, 65% for Rivaroxaban and 66% for Apixaban and VKAs (Warfarin) [4]. For the second and subsequent years, average patient adherence for each alternative was estimated at 67% and 80% respectively.
- For assessing the impact of treatment discontinuation on cost and health effects, patient adherence was altered between 30% and 100% and respective comparisons were made assuming identical adherence rates for all treatment alternatives.

Clinical Data

- An indirect treatment comparison based on a network meta-analysis (NMA) provided clinical inputs for the model.
- The NMA included 23 randomized trials involving a total of 94,656 patients (see López-López et al. 2017) [5].

Resource Use and Costs

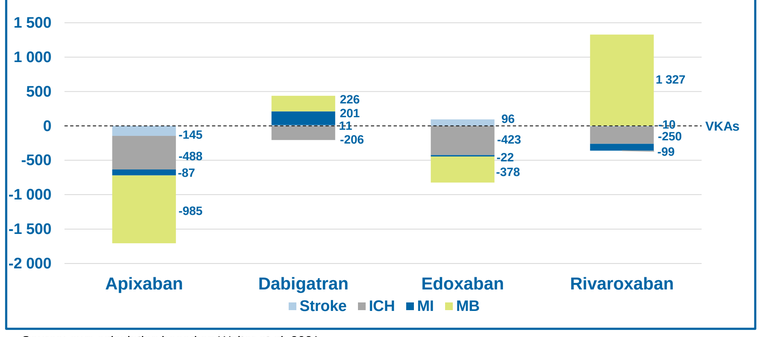
- Cost of oral anticoagulants are based on Austrian reimbursement prices.
- Cost of future health events include inpatient cost rehabilitation cost, outpatient cost and drug costs.
- First year event cost of stroke and MI are based on a SLR and were updated to 2021. For ICH and MB, first year event cost are calculated based on resource use reported in Belisari et al. (2016) [6].
- For dabigatran, idarucizumab was also considered.

Results

Preventable Events

Figure 1 depicts future health events avoided due to the use of DOACs instead of VKAs. Whilst Apixaban has the highest potential to avoid future health events, some DOACs may even increase the risk of intracranial haemorrhages, ischaemic strokes, and/or clinically relevant or major (extracranial) bleedings when compared to VKAs.

Figure 1. Future health events avoided by DOACs versus VKAs
(eligible population: 187,500 patients in Austria)

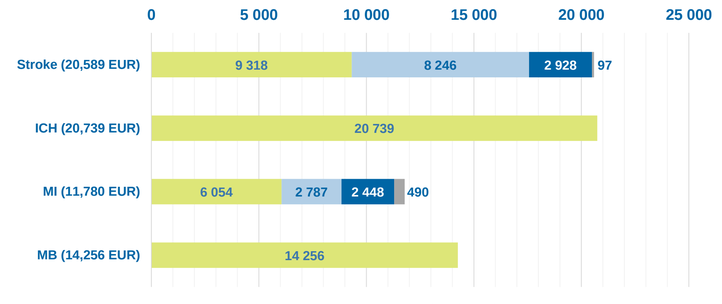


Source: own calculation based on Walter et al. 2021
DOACs: direct oral anticoagulants; ICH: intracranial haemorrhage; MB: clinically relevant or major (extracranial) bleed; MI: myocardial infarction; VKAs: vitamin K antagonists

First year event cost

First year event cost of stroke and MI were estimated at 20,589 EUR and 11,780 EUR. Based on Belisari et al. (2016), first year event cost for ICH and MB were estimated at 20,739 EUR and 14,256 EUR respectively (Figure 2).

Figure 2. 1st year event cost in Austria (2021)



Source: own calculation based on Walter et al. 2021
ICH: intracranial haemorrhage; MB: clinically relevant or major (extracranial) bleed; MI: myocardial infarction

Cost-utility analysis

Apixaban is highly cost-effective compared to VKAs with an ICUR of 12,891 EUR/QALY, and it dominates other DOACs (Table 2).

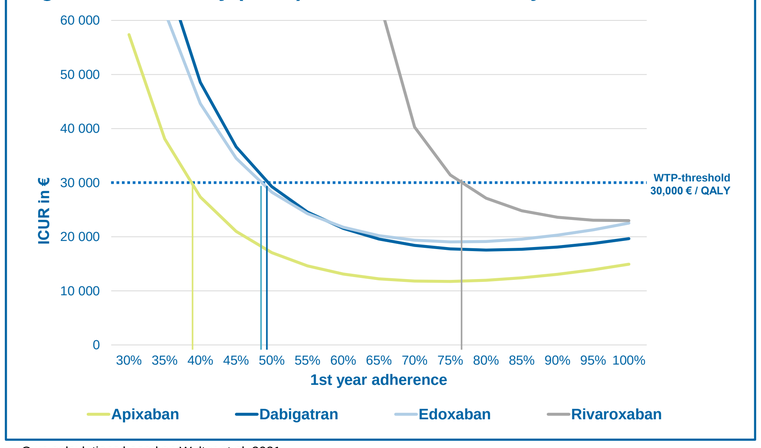
Table 2. Cost-utility analysis of DOACs vs. VKAs (base case)

	Apixaban	Dabigatran	Edoxaban	Rivaroxaban	VKAs (Warfarin)
Cost (EUR) Δ Cost (EUR)	**14,446** 740	**14,861** 1,156	**14,649** 943	**15,202** 1,496	**13,706** --
QALYs ΔQALYs	**4.633** 0.057	**4.623** 0.047	**4.614** 0.038	**4.578** 0.002	**4.576** --
LYs ΔLY	**6.001** 0.07	**5.990** 0.06	**5.978** 0.05	**5.937** 0.01	**5.928** --
ICUR ΔCost/ΔQALYs	**12,891** EUR/QALY	**24,486** EUR/QALY	**24,705** EUR/QALY	**600,701** EUR/QALY	**--**

Source: own calculations based on Walter et al. 2021
ICUR: incremental cost-utility ratio; LYs: life years; QALYs: quality adjusted life years; VKAs: vitamin K antagonists

- Assuming a willingness to pay (WTP)-threshold of 30,000 EUR/QALY, Apixaban is cost-effective at a first year adherence rate of 38.6% (Figure 3).
- For Dabigatran and Edoxaban versus VKAs, adherence rates of around 48.5% and 49.4% would be required for the ICUR to fall below the WTP-threshold value (Figure 3).
- For Rivaroxaban versus VKAs, adherence would have to reach 76.3% respectively (Figure 3).

Figure 3. Cost-utility (ICUR) of DOACs vs. VKAs by adherence



Own calculations based on Walter et al. 2021
DOACs: direct oral anticoagulants; ICUR: incremental cost-utility ratio; VKAs: vitamin K antagonists; WTP: willingness to pay

In the entire population (187,500 patients in Austria), an improvement in medication adherence of Apixaban from 60% to 70% would prevent an additional 1,155 health events (intracranial haemorrhage; ischaemic stroke; myocardial infarction; clinically relevant or major [extracranial] bleed) versus VKAs (Figure 4).

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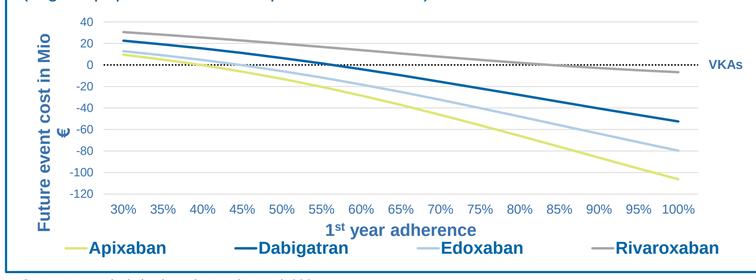
This improvement in medication adherence to Apixaban would save €17.9 million in related treatment cost (Figure 4), compared to VKAs.

Figure 4. Future event cost avoidable by DOACs vs. VKAs in Mio EUR
(eligible population: 187,500 patients in Austria)

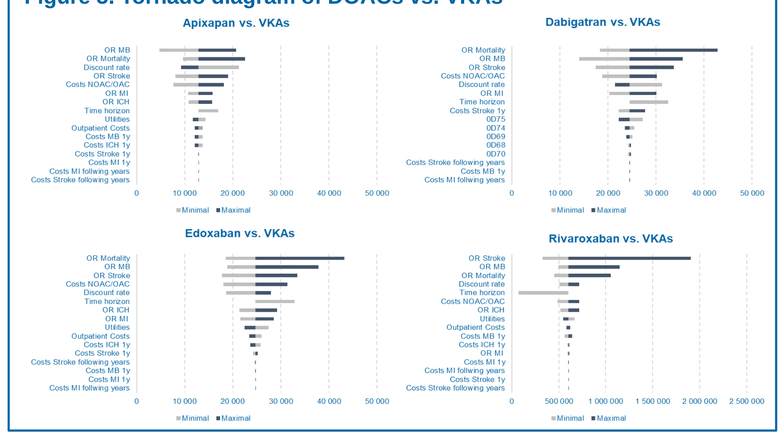


Source: own calculation based on Walter et al. 2021
DOACs: direct oral anticoagulants; VKAs: vitamin K antagonists

Sensitivity Analyses

Probabilistic (PSA) and deterministic (DSA) sensitivity analyses were carried out to examine the robustness of the model. DSA results are depicted in Figure 5.

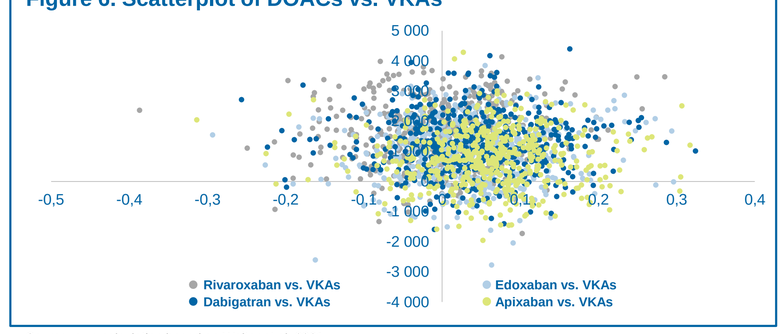
Figure 5. Tornado diagram of DOACs vs. VKAs



Source: own calculation based on Walter et al. 2021
DOACs: direct oral anticoagulants; ICH: intracranial haemorrhage; MB: clinically relevant or major (extracranial) bleed; MI: myocardial infarction; OR: odds ratio; VKAs: vitamin K antagonists

Monte-Carlo PSA-results of 500 second-order simulations plotting incremental cost versus incremental effects are depicted in Figure 6. At a threshold of 30,000 EUR/QALY, all DOACs were cost-effective vs. VKAs in around 82.5% of simulations.

Figure 6. Scatterplot of DOACs vs. VKAs



Source: own calculation based on Walter et al. 2021
DOACs: direct oral anticoagulants; VKAs: vitamin K antagonists

Discussion

Many approaches have been suggested to improve patient adherence to medicines. Though there is still some ambiguity as to which of those may work best, this analysis has shown that the investment in adherence programmes can lead to significant benefits for both patients and the healthcare system.

Improving patient adherence to DOACs directly improves health outcomes and increases both life expectancy and health related quality of life. It also reduces future healthcare spending by avoiding AF-related health events.

It is therefore unsurprising that improving patient adherence to DOACs further improves their cost-effectiveness, not even taking into account the potential impact on societal cost (such as work loss and long-term care cost) following an avoidable health event.

Conclusions

Increasing medication adherence to DOACs results in better patient-related outcomes, higher life expectancy and improved health related quality of life.

It also further improves the cost-utility of DOACs for patients with AF in Austria.

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Disclosures

Evelyn Walter, PhD, Gerald Eichhober, MSc as well as Marco Voit, MSc are employees of the Institute for Pharmaeconomic Research. The Institute for Pharmaeconomic Research was a paid consultant to Pfizer and Bristol Myers Squibb in connection with the development of this abstract and poster.

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