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Patients on vitamin K treatment: is switching to direct-acting oral anticoagulation cost-effective? A target trial on a prospective cohort

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ABSTRACT

Aims Direct-acting oral anticoagulants (DOACs) have, to a substantial degree, replaced vitamin K antagonists (VKA) as treatments for stroke prevention in atrial fibrillation (AF) patients. However, evidence on the real-world causal effects of switching patients from VKA to DOAC is lacking. We aimed to assess the empirical incremental cost-effectiveness of switching patients to DOAC compared with maintaining VKA treatment.

Methods The target trial approach was applied to the prospective observational Swiss-AF cohort, which enrolled 2415 AF patients from 2014 to 2017. Clinical data, healthcare resource utilisation and EQ-5D-based utilities representing quality of life were collected in yearly follow-ups. Health insurance claims were available for 1024 patients (42.4%). Overall survival, quality-of-life, costs from the Swiss statutory health insurance perspective and cost-effectiveness were estimated by emulating a target trial in which patients were randomly assigned to switch to DOAC or maintain VKA treatment.

Results 228 patients switching from VKA to DOAC compared with 563 patients maintaining VKA treatment had no overall survival advantage over a 5-year observation period (HR 0.99, 95% CI 0.45, 1.55). The estimated gain in quality-adjusted life years (QALYs) was 0.003 over the 5-year period at an incremental costs of CHF 23 033 (€ 20 940). The estimated incremental cost-effectiveness ratio was CHF 425 852 (€ 387 138) per QALY gained.

Conclusions Applying a causal inference method to real-world data, we could not demonstrate switching to DOACs to be cost-effective for AF patients with at least 1 year of VKA treatment. Our estimates align with results from a previous randomised trial.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Randomised trials have shown advantages of direct-acting oral anticoagulants (DOACs) over vitamin K antagonist (VKA) for the anticoagulation of atrial fibrillation (AF) patients.

⇒ Recent trial-based evidence has challenged the safety of switching VKA-treated patients to DOACs.

WHAT THIS STUDY ADDS

⇒ We applied target trial emulation, a causal inference method, to study cost-effectiveness using real-world prospective cohort and insurance claims data.

⇒ We could not demonstrate switching to DOACs to be cost-effective for patients with at least 1 year of VKA treatment.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Switching AF patients well-treated with VKA to DOACs should be considered cautiously.

INTRODUCTION

In atrial fibrillation (AF) patients, oral anticoagulation is used to prevent strokes effectively.[1] Vitamin K antagonists (VKAs) have been the gold standard before direct-acting oral anticoagulants (DOACs), including dabigatran, rivaroxaban, apixaban and edoxaban, were introduced more than 10 years ago. DOACs were developed to overcome the limitations of VKA treatments, such as constant anticoagulation monitoring or drug interactions. The advantages of DOACs were shown in many trials, leading to their recommendation over VKA in the European Society of Cardiology Guidelines.[2]

Since the introduction of DOACs, their use has gradually increased, substituting VKAs.[3] Real-world evidence on safety and

effectiveness is increasingly available,[4–6] and most recently also on cost-effectiveness,[7–9] comparing patients treated with VKAs versus patients treated with DOACs. However, none of the studies based on real-world data have used an explicit causal method to estimate costs and effects. Moreover, there have been few efforts so far to investigate the effects of patients switching from VKA treatment to DOAC while being on VKA treatment. Using data from the prospective Swiss-AF cohort study, we aimed to assess the causal empirical incremental cost-effectiveness and quality-of-life effects in patients switching from VKA treatment to DOAC compared with patients maintaining VKA.

We employed a relatively novel methodological approach, the target trial emulation.[10] This approach combined clinical data, health-related quality of life (HRQoL) information, and health insurance claims to approximate the causal effect of switching patients' anticoagulation treatment from VKA to DOAC. The target trial approach provides a basis for addressing biases that may emerge from conventional analyses of observational studies when trying to establish causal estimates.[11] Analysing observational studies as randomised controlled trials (RCTs), has been succesfully applied in various medical fields, for example, to study the effects of statins on colorectal cancer risk[12] or the comparative effectiveness of COVID-19 vaccines.[13] Moreover, it has been recently shown to be a valuable tool for assessing the cost-effectiveness of healthcare interventions outside of RCT settings.[14]

METHODS

Study design and data sources

This study is based on data from Swiss-AF, an ongoing prospective observational cohort study of AF patients across 14 clinical centres in Switzerland.[15 16] 2415 patients with a history of documented AF and mostly aged >65 years were enrolled between April 2014 and August 2017. 228 patients were enrolled in the age range 45–64 years to enable the study of socioeconomic aspects in potentially professionally active patients. Patients underwent an extensive assessment at enrolment and yearly follow-up data collection. Details of the design have been reported previously.[14] Additional economic data were obtained from statutory health insurance claims for 1024 patients (42.4% of the study population, reflecting the market share of four large, contributing health insurers), covering inpatient and outpatient services and medication. In Switzerland, statutory health insurance is compulsory for all residents with a broad, uniform benefit package defined by law. We used a 2014–2021 data cut.

Decision problem and outcome measures

The primary outcome of the analysis was the 5-year empirical incremental cost-effectiveness ratio (ICER) for patients switching from VKA to DOAC versus maintaining VKA treatment after having been on VKA treatment for at least 1 year. The ICER was measured as the ratio of incremental costs and incremental quality-adjusted life years (QALYs).[4] Costs represented total direct medical costs from the perspective of the Swiss statutory health insurance system, considering the total costs of all healthcare services principally reimbursable by the statutory health insurance, irrespective of their relationship with AF.

Secondary outcomes included the individual components of the primary outcome, that is, incremental costs, incremental QALYs and incremental life years (LYs). Incremental LYs were measured as the difference in area between the overall survival curves of switching versus maintaining. Incremental QALYs were calculated as the HRQoL-weighted difference in area between the overall survival curves of switching versus maintaining. HRQoL was measured as utilities derived from the EQ-5D-3L questionnaire.[17]

All outcomes were assessed for a 5-year follow-up period and discounted at 3% per year.

Complementary analyses were run on clinical event occurrence, enabling us to assess the risk of residual confounding better. We considered stroke/transient ischaemic attack (TIA), major bleeding and myocardial infarction (MI).

Target trial and statistical analysis

We combined elements from a trial-based economic evaluation employing a statistical analysis-based (as opposed to decision-analytic modelling-based) approach[18] and a target trial study design.[10] The target trial attempts to emulate a randomised trial that would answer the causal question of interest.[19] We explicitly emulated a target RCT to estimate the empirical average treatment effects of interest in our outcomes. The specification and emulation protocol of the target trial are shown in table 1.

An adequate definition of time zero of follow-up was required to emulate the target trial successfully. We defined time zero as the time when an eligible individual initiated a treatment strategy: for patients switching from VKA to DOAC, the date of the switch was used. For patients maintaining VKA treatment, the time point of meeting the eligibility criterion for inclusion in the trial was used, that is, being on VKA treatment for at least 1 year.

The random assignment was emulated by assuming the treatment strategy initiation to be as good as randomly distributed conditional on a set of potential confounders (specified in table 2).[11] These were used to create inverse probability weights (IPW) for the whole study sample by fitting a logistic regression model with switching as the dependent variable. IPW were also used to adjust for differential censoring in the longitudinal outcomes across all analyses.

A Cox regression weighted with the IPW was run to model the modified intention-to-treat all-cause survival effect. A longitudinal linear regression model weighted with the IPW was used for quality of life over the 5-year follow-up period. The difference in utilities between

Table 1 Specification and emulation of the target trial of switching from VKA to DOAC versus maintaining VKA treatment using data from the Swiss-AF study

Component	Target trial	Emulated trial using SAF data
Aim	To estimate the incremental cost-effectiveness of switching from VKA to DOAC vs maintaining VKA treatment over a 5-year time horizon	Same
Eligibility	Swiss-AF eligibility criteria. Eligible patients must be ≥45 years old and have either paroxysmal AF defined as: self-terminating AF lasting <7 days that does not require cardioversion and that was documented at least two times within the last 60 months; persistent AF defined as AF sustained ≥7 days and/or requiring cardioversion, documented within the last 60 months by ECG or rhythm monitoring devices; or permanent AF (cardioversion has failed or not been attempted). In addition, patients must have been on VKA treatment for at least 1 year	Same
Treatment strategies	1. Switching from VKA to DOAC at trial baseline 2. Maintaining VKA treatment at trial baseline	Same
Treatment assignment	Patients are randomly assigned to either strategy	Patients are assigned to switching from VKA to DOAC if they are no longer taking VKA but DOAC at Swiss-AF FU1-5. Randomisation is emulated via adjustment for baseline covariates, as described in the variables section
Follow-up	Follow-up starts at treatment assignment and ends at their last follow-up or 30 June 2021, whichever occurs first	Same
Outcome	1. LY 2. QALY 3. Cost 4. ICER	Same
Causal contrast	Intention-to-treat effect, that is, effect of being assigned to switching from VKA to DOAC vs maintaining VKA treatment at trial baseline	Observational analogue of modified intention-to-treat, that is, the effect of being assigned to switching from VKA to DOAC and taking the first prescription vs maintaining VKA treatment
Statistical analysis	Intention-to-treat analysis	Modified intention-to-treat analysis. Randomisation is emulated via adjustment for baseline covariates, as described in the variables section

AF, atrial fibrillation; DAOC, direct-acting oral anticoagulant; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year; VKA, vitamin K antagonist.

treatment arms represented the coefficients of interest. Utilities were estimated using the European EQ-5D-3L valuation algorithm. Information on utility was only available at planned study visits, so utilities on dates between visits were assumed to follow a linear relationship. Patients were censored if they had missing HRQoL information. Finally, the difference in survival and between utilities was combined to estimate the QALYs.

For costs, a longitudinal linear regression model weighted with the IPW was used over the 5-year follow-up period based on the patients with claims data available. The yearly total cost differences between treatment arms represented the coefficients of interest. Because costs were available daily, no additional assumptions were required regarding costs and time zero. Given the relative stability of prices over the observation period, we used all costs as reported, without adjustment for inflation. For reference, the mean Swiss francs (CHF) to Euros (€) exchange rate for the study period was 1.1.

To obtain the ICERs in terms of cost per QALY gained, the incremental cost estimates were divided by the incremental quality-adjusted survival estimates. Non-parametric bootstrapping with 1000 random draws with replacement was used to assess uncertainty for the mean incremental costs and effects and to summarise the uncertainty surrounding the ICERs. Using the bootstrapped estimates of incremental costs and effects, this uncertainty is further illustrated with cost-effectiveness acceptability curves (CEACs). CEACs show the probability of a treatment being cost-effective at different ceiling ratios of decision-makers' willingness to pay per QALY. Switzerland has no official willingness-to-pay threshold, but the benchmark of CHF 100 000 per QALY gained is sometimes used tentatively.[20 21]

Sensitivity analyses included the use of an alternative analytical method, namely 1:2 nearest neighbour propensity score matching, to estimate the average treatment effect on the treated, the use of alternative EQ-5D-3L valuation algorithms (German and French value sets instead of the European one), and the estimation of the main results, including clinical results, using only the subset of patients with available claims data. To enable comparison, we also performed a conventional regression-based cohort analysis of clinical effects and costs, adjusting for the same potential confounders used to create the IPW but not using the target trial approach. This analysis

Table 2 Baseline characteristics of patients maintaining vitamin K antagonist or switching to direct-acting oral anticoagulant, before and after inverse probability weighting (IPW)

	Before IPW		After IPW	
	Maintaining	Switching	Maintaining	Switching
N	563	228	794.95	759.88
Characteristics				
Age mean (SD)	77.63 (7.63)	77.99 (6.96)	77.73 (7.41)	77.92 (7.05)
Sex Female, N (%)	139 (24.7)	63 (27.6)	201.5 (25.4)	197.5 (26.0)
BMI median (IQR)	27.45 (24.74, 30.26)	26.90 (24.48, 30.43)	27.35 (24.68, 30.24)	26.85 (24.31, 30.36)
Type of AF, N (%)				
Paroxysmal	172 (30.6)	95 (41.7)	266.4 (33.5)	258.0 (34.0)
Permanent	240 (42.6)	71 (31.1)	314.1 (39.5)	302.4 (39.8)
Persistent	151 (26.8)	62 (27.2)	214.5 (27.0)	199.5 (26.3)
AF symptoms, N (%)	235 (41.7)	96 (42.1)	331.3 (41.7)	318.0 (41.9)
Years since AF Dx, mean (SD)	10.08 (9.39)	9.41 (7.12)	9.87 (8.76)	9.58 (7.71)
CHA2DS2-VASc, mean (SD)	3.81 (1.57)	4.28 (1.53)	3.97 (1.62)	3.99 (1.49)
Prev. major bleeding, N (%)	48 (8.5)	32 (14.0)	76.5 (9.6)	69.4 (9.1)
Prev. stroke or TIA, N (%)	117 (20.8)	59 (25.9)	178.9 (22.5)	165.6 (21.8)
Prev. Sys. embolism, N (%)	40 (7.1)	19 (8.3)	59.6 (7.5)	52.6 (6.9)
Prev. heart failure, N (%)	196 (34.8)	88 (38.6)	294.2 (37.0)	283.2 (37.3)
Prev. myocardial Inf., N (%)	109 (19.4)	51 (22.4)	163.2 (20.5)	145.2 (19.1)
Diabetes, N (%)	99 (17.6)	57 (25.0)	159.7 (20.1)	154.1 (20.3)
Hypertension, N (%)	395 (70.2)	180 (78.9)	578.9 (72.8)	546.6 (71.9)
Renal insufficiency, N (%)	166 (29.5)	58 (25.4)	227.5 (28.6)	205.6 (27.1)
Sleep apnoea, N (%)	102 (18.1)	43 (18.9)	149.1 (18.8)	145.6 (19.2)
Prev. PTCA or CABG, N (%)	199 (35.3)	98 (43.0)	304.1 (38.3)	299.2 (39.4)
Prev. electroconversion, N (%)	197 (35.0)	93 (40.8)	292.0 (36.7)	285.8 (37.6)
Prev. PVI, N (%)	81 (14.4)	43 (18.9)	122.8 (15.5)	122.5 (16.1)
Implanted device, N (%)				
No device or loop recorder	423 (75.1)	178 (78.1)	606.5 (76.3)	575.9 (75.8)
PM	84 (14.9)	33 (14.5)	112.8 (14.2)	112.3 (14.8)
ICD	19 (3.4)	14 (6.1)	35.8 (4.5)	38.8 (5.1)
CRT (ICD)	37 (6.6)	3 (1.3)	39.9 (5.0)	32.8 (.3)
Medication, N (%)				
Antiplatelet	21 (3.7)	10 (4.4)	29.6 (3.7)	29.8 (3.9)
Aspirin	80 (14.2)	31 (13.6)	109.5 (13.8)	94.2 (12.4)
Statins	295 (52.4)	143 (62.7)	444.1 (55.9)	443.9 (58.4)
Diuretics	310 (55.1)	132 (57.9)	449.4 (56.5)	426.0 (56.1)
Beta-blockers	397 (70.5)	160 (70.2)	555.6 (69.9)	533.9 (70.3)
Digoxin	31 (5.5)	17 (7.5)	52.9 (6.7)	64.4 (8.5)
Socioeconomic				
Education, N (%)				
Basic	79 (14.0)	28 (12.3)	106.5 (13.4)	87.6 (11.5)
Middle	290 (51.5)	115 (50.4)	407.2 (51.2)	376.5 (49.5)
Advanced	194 (34.5)	85 (37.3)	281.3 (35.4)	295.8 (38.9)
Mother tongue, N (%)				
German	399 (70.9)	173 (75.9)	578.5 (72.8)	559.2 (73.6)
French	96 (17.1)	26 (11.4)	123.1 (15.5)	120.7 (15.9)

Continued

Table 2 Continued

	Before IPW		After IPW	
	Maintaining	Switching	Maintaining	Switching
N	563	228	794.95	759.88
Italian	68 (12.1)	29 (12.7)	93.3 (11.7)	79.9 (10.5)
Smoking, N (%)				
Never	251 (44.6)	104 (45.6)	355.0 (44.7)	322.3 (42.4)
In the past	279 (49.6)	112 (49.1)	393.0 (49.4)	384.3 (50.6)
Active	33 (5.9)	12 (5.3)	47.0 (5.9)	53.2 (7.0)
Alcohol, mean (SD)	0.97 (1.42)	0.91 (1.35)	0.94 (1.39)	1.02 (1.48)
Greater region, N (%)				
Zurich	51 (9.1)	23 (10.1)	73.2 (9.2)	74.2 (9.8)
Lake Geneva Region	53 (9.4)	14 (6.1)	65.4 (8.2)	61.4 (8.1)
Espace Mittelland	145 (25.8)	56 (24.6)	211.0 (26.5)	213.9 (28.2)
Northwestern Switzerland	198 (35.2)	71 (31.1)	267.2 (33.6)	246.3 (32.4)
Eastern Switzerland	29 (5.2)	20 (8.8)	51.2 (6.4)	50.7 (6.7)
Southern Switzerland	66 (11.7)	28 (12.3)	90.8 (11.4)	78.2 (10.3)
Central Switzerland	21 (3.7)	16 (7.0)	36.1 (4.5)	35.2 (4.6)

Alcohol in drinks per day.
AF, atrial fibrillation; CABG, coronary artery bypass grafting; CHA2DS2-VASc, risk of stroke (for non-valvular atrial fibrillation); CRT, cardiac resynchronisation therapy; Dx, diagnosis; ICD, implantable cardioverter defibrillator; PM, pacemaker; Prev., previous history of; PTCA, percutaneous transluminal coronary angioplasty; PVI, pulmonary vein isolation; TIA, transient ischaemic attack.

treated the point of being on VKA treatment for at least 1 year as time zero for all patients. In order to assess the degree to which the inclusion of patients switched after a clinical event may have influenced the results, we performed a sensitivity analysis excluding patients who experienced a treatment switch within 1 month of an event. Events included stroke, systemic embolism, bleeding, heart failure and MI.

All analyses were conducted using R V.4.2.1, and the project adheres to the reporting guidelines of Consolidated Health Economic Evaluation Reporting Standards.[22]

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of our research.

RESULTS

Patient population

Figure 1 shows the patient selection. Of 873 eligible patients in the target trial, 791 were included in the survival analysis, 783 had complete data on QoL and 351 patients had available claims data for cost analysis. Baseline characteristics are shown in table 2. Before weighting, patients switching from VKA to DOAC had more paroxysmal AF and were likelier to have had a clinical event, such as major bleeding or stroke/TIA. After IPW, differences between the two treatment arms were attenuated (online supplemental figures S1 and S2).

Target trial and cost-effectiveness results

Figure 2 shows the all-cause survival, HRQoL and cost model estimates. Patients who switched from VKA to DOAC had the same overall 5-year survival as those who maintained VKA treatment. The HR was 0.99 (95% CI 0.45, 1.55). In HRQoL, switching was associated with an average overall effect of −0.01 (95% CI −0.03, 0.01) points on a utility scale of 0–1, where 0 is death and 1 is perfect health. The effect was relatively constant across the observation period. With discounting, these findings translate into 0.003 QALYs gained over the 5-year observation period in patients switching from VKA to DOAC. Switchers accrued 3.984 LYs (3.296 QALYs), and maintainers accrued 3.981 LYs (3.294 QALYs). Cumulated and discounted incremental costs were CHF 23 033 (95% CI −8681, 63 442); € 20 940 (95% CI −7892, 57 675); yearly increments remained relatively stable across the 5-year observation period. Absolute 5-year costs amounted to CHF 92 239 for switchers and CHF 69 206 for maintainers. Additional inverse probability weighted time-to-event analysis of clinical events of stroke/TIA, major bleeding and MI showed no difference between the treatment arms (online supplemental figures S3 and S4). Average yearly drug costs for DOAC were roughly CHF 1000, while average annual costs for VKA were CHF 80 across the observation period.

The resulting base-case ICER (figure 3) was CHF 425 852 (€ 387 138) per QALY gained, discounted by 3% per year across the 5-year observation period. The

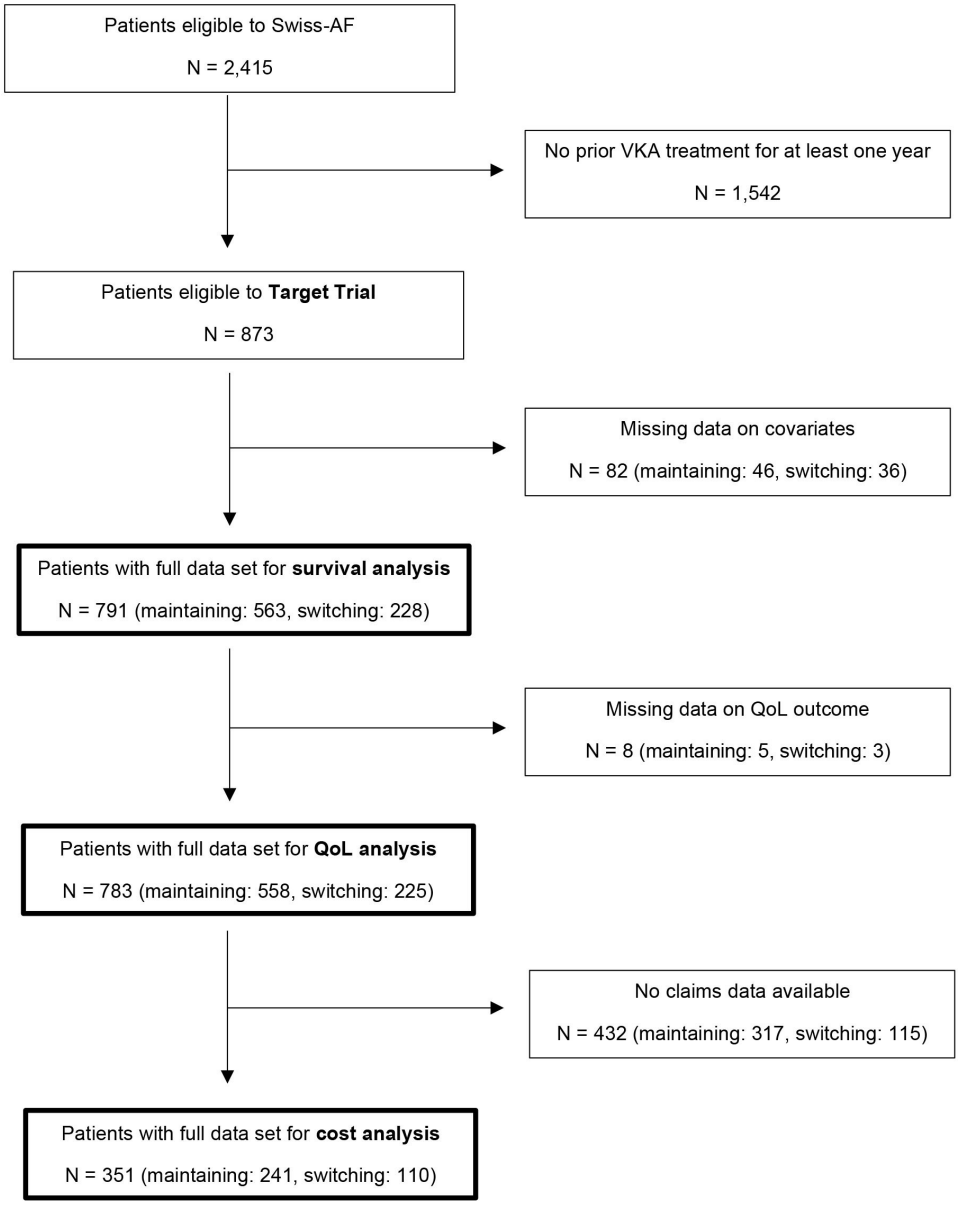

Figure 1 Patient selection flow chart. AF, atrial fibrillation; QoL, quality of life; VKA, vitamin K antagonist.

corresponding cost per LY gained was CHF 424 925 (€ 386 296).

Sensitivity analysis

We did not observe substantial differences in the results estimated with the target trial and propensity score matching approach (online supplemental figures S5 and S6). The HRQoL estimates did not vary substantially when using the German and French EQ-5D-3L valuation algorithms instead of the European ones (online supplemental figure S7). The estimates were not materially altered when we restricted the analysis to the subsample with claims data available (online supplemental figure S8).

In the conventional regression-based cohort analysis performed for comparison, the HR of overall survival was 0.71 (95% CI 0.19, 1.22, online supplemental figure S9), QALYs gained was 0.17 and discounted incremental costs were CHF 23 734.

Excluding 24 patients having a treatment switch within 1 month of a clinical event increased the uncertainty but did not alter the results materially (online supplemental figure S10).

DISCUSSION

To our knowledge, this is the first study to apply a causal inference method in a real-world cost-effectiveness analysis of DOAC. We have used the target trial approach, a novel analytical methodology,[10 11] to analyse prospective observational cohort data, thus addressing bias risks inherent in the conventional regression-based cohort analysis of observational studies. Overall survival, quality of life and costs were estimated, emulating a hypothetical

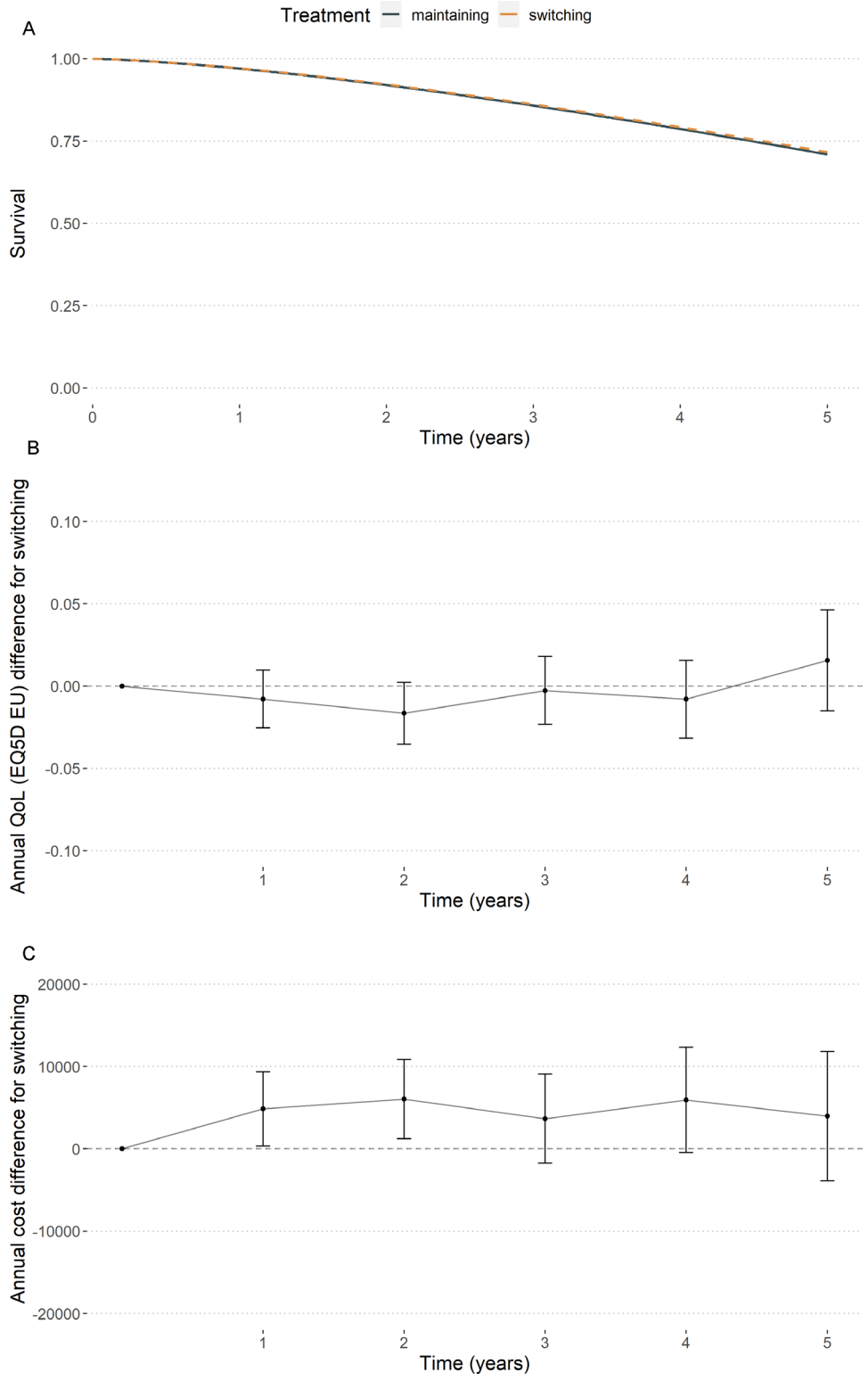

Figure 2 Estimates of incremental overall survival, quality of life (QoL) and costs.

RCT in which patients on VKA treatment switch from VKA to DOAC or maintain VKA treatment. Results suggest that for patients under VKA treatment for at least 1 year, switching to DOACs is unlikely to be cost-effective.

Only a few studies have focused on patients switching from VKA treatment to DOAC so far,[23–25] mainly investigating effectiveness and safety. Recently, the results of an RCT (FRAIL-AF) explicitly focusing on VKA switching for frail patients have shown adverse effects of switching on event rates.[26] By employing a target trial approach, we estimated an HR of 0.99 for overall survival. In contrast, when we did not use the target trial approach and did not specify a valid time zero, the HR was 0.71 (online supplemental figure S9), which is

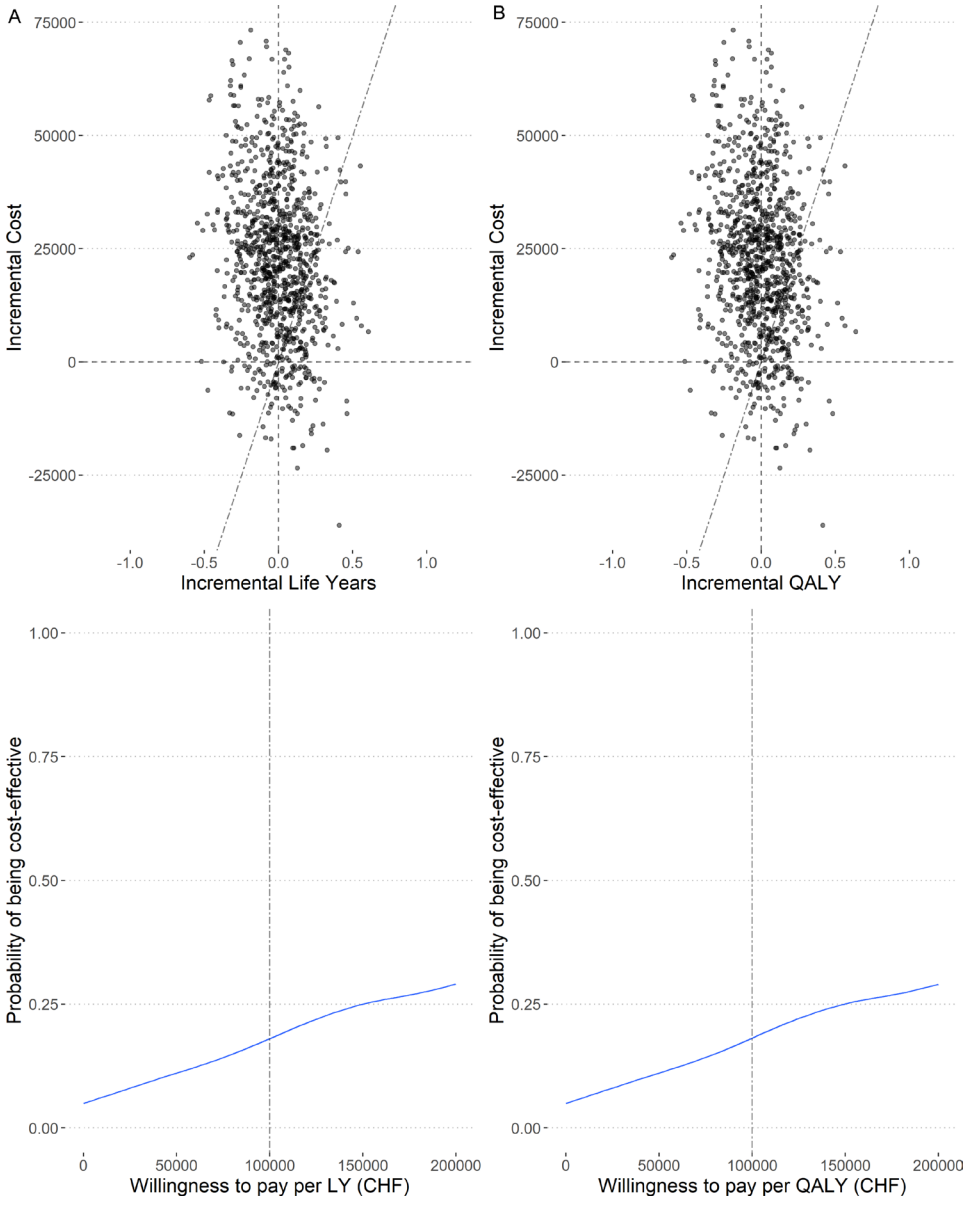

Figure 3 Probabilistic sensitivity analyses results. LY, life year; QALY, quality-adjusted life year.

similar to the OR of 0.76 found in Vaughan Sarrazin *et al*.[24]

We did not find any differences in HRQoL for both treatment arms across the 5-year observation period, which aligns with the results from the GAInN study,[27] and the RE-LY trial.[28] Switching well-controlled VKA patients to DOAC has been shown to improve treatment convenience marginally but not to affect other parameters of quality of life,[27 29] resulting in stable HRQoL over time.[28]

Our estimated ICER was CHF 425 852 per QALY gained, suggesting that switching from VKA treatment to DOAC is not cost-effective. DOAC initiation was shown to be cost-effective in RCTs,[30–33] while effectiveness and safety results in a real-world setting were ambiguous.[6] These studies, however, did not account for patients who switched from VKA treatment lasting at least 1 year. Some studies only included patients who newly went onto anticoagulation and some excluded patients who switched. In contrast, some others allowed for mixed prior treatment histories but did not look at the specific effects. This hinders a direct comparison to our study. Irrespective of this, results from controlled clinical trial settings may not translate into equal effectiveness and cost-effectiveness in the real world. Treatment adherence may be one influencing factor that is not easy to assess. It has been shown that the risk of non-adherence to DOAC is high for patients with a low pre-switch time in the VKA therapeutic range (TTR).[34] Low TTR may indicate low therapy adherence to VKA, and switching to DOACs may shift the problem. Suboptimal adherence to DOAC may impact clinical outcomes and is associated with an increased risk of ischaemic stroke.[34] DOAC patients may not be regularly evaluated by their physicians, leading to unnoticed non-adherence, so other options for improvement of TTR or better guidance while using DOAC should be considered.

Our complementary analyses showed no effects on clinical events, consistent with our main findings. Systematic reviews[23 35] have found bleeding outcomes to be inconsistent after a switch of VKA-experienced patients, possibly confounded by the reason for switching. Other studies showed a reduced risk of stroke, systemic embolism and significant bleeding for DOACs.[36 37] However, their populations were not under prior VKA treatment for at least 1 year and they did not use causal methods. Our sensitivity analysis excluding patients in whom a clinical event may have triggered the switch to a DOAC did not alter the results materially (online supplemental figure S10).

The strengths of our study relate to the high-quality data sources used—including the prospectively collected multi-year data on quality-of-life and detailed resource utilisation and the methodological approach of emulating a hypothetical randomised trial. We have previously shown that using the target trial method can provide plausible, causal estimates in observational studies.[14] This approach offers a viable alternative to RCTs, especially in settings where RCTs are not ethical, feasible or available, such as in the case of our research question.

However, our study is not without limitations. First, while a set of time-updated cardiovascular event indicators was included in the calculation of the IPW, there may still be unmeasured factors we could not adjust for, influencing the rationale for switching patients from VKA to DOAC in clinical practice and outcomes. Such factors might, for example, be the emergence or worsening of conditions unrelated to AF, triggering a need or wish to simplify patient management. Further research on this is needed. Second, we treated all DOAC drugs as a class, not distinguishing the different drugs and their respective effects on clinical outcomes.[38 39] This reflects routine clinical practice, where all DOACs are available, and a broad spectrum of AF patients are treated differently. The pooling was a necessity to achieve the best possible statistical power. Third, while our study had reasonable precision in identifying effects on survival and quality of life, there was substantial uncertainty in the incremental cost estimates due to the limited number of patients with available claims data and the large variability of healthcare costs. Within wide CIs, these estimates showed a substantial cost disadvantage of the switching strategy. The higher medication costs of DOACs only explained this to a minor part, as reflected in the trajectories of median costs (online supplemental figure S11). We could not identify a systematic or specific (eg, a small number of outlying observations) reason for this observation. Patients who switched from VKA to DOAC did not experience more severe or frequent clinical events. With chance as a possible explanation, our estimates of incremental costs should be interpreted cautiously. Fourth, one disadvantage our empirical, within-cohort study approach shares with classical within-trial analyses is the restriction of the time horizon to the study observation period in the first instance. Extension to more desirable, longer time horizons required assumptions and extrapolation steps. Fifth, any generalisation of our real-world economic findings to individual DOAC drugs or populations with other demographic characteristics and socioeconomic status should be considered cautiously. Further research is warranted to explore different implementations of the target trial approach in economic evaluations.

In conclusion, we applied a target trial approach to analysing prospective observational cohort data of real-world AF patients. For patients on prior VKA treatment, we could not demonstrate switching to DOAC to be cost-effective in our setting.

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Data availability statement Data are available upon reasonable request. Data may be obtained from a third party and are not publicly available. The patient informed consent forms state that the data, containing personal and medical information, are exclusively available for research institutions in an anonymised form and are not allowed to be made publicly available. Researchers interested in obtaining the Swiss-AF data for research purposes can contact the Swiss-AF scientific lead. Contact information is provided on the Swiss-AF website (http://www.swissaf.ch/contact.htm). Authorisation of the responsible ethics committee is mandatory before the requested data can be transferred to external research institutions.

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