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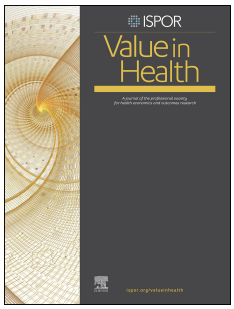

Real-world cost-effectiveness of pulmonary vein isolation for atrial fibrillation: *a target trial approach*

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Highlights

i) What is the real-world cost-effectiveness of pulmonary vein isolation compared to standard medical therapy for atrial fibrillation patients?

ii) In this economic evaluation designed with a target trial approach including 2,379 patients with real-world clinical, quality-of-life, and costing data, we estimate the incremental cost-effectiveness ratio of pulmonary vein isolation compared to standard medical therapy to be 158,612 Swiss Francs (CHF) per QALY gained (USD1~CHF0.93) at 5 years, and 82,195 per QALY at 10 years.

ii) In our target trial emulation-based cost-effectiveness assessment, PVI for the management of AF might be cost-effective over a 10-year period.

Abstract

Objectives: Randomized controlled trials of pulmonary vein isolation (PVI) for treating atrial fibrillation (AF) have proven the procedure's efficacy. Studies assessing its empirical cost-effectiveness outside randomized trial settings are lacking. We aimed to evaluate the effectiveness and cost-effectiveness of PVI versus medical therapy for AF.

Methods: We followed a target trial approach using the Swiss AF cohort, a prospective observational cohort study that enrolled AF patients between 2014 and 2017. Resource utilization and cost information was collected through claims data. Quality-of-life was measured with EQ-5D-3L utilities. We estimated incremental cost-effectiveness ratios from the perspective of the Swiss statutory health insurance system.

Results: Patients undergoing PVI compared to medical therapy had a 5-year overall survival advantage with a hazard ratio of 0.75 (95%CI 0.46-1.21, p=0.69), a 19.8% standard deviation improvement in quality-of-life (95%CI 15.5-22.9%, p<0.001), at an incremental cost of 29,604 (95%CI 16,354-42,855, p<0.001) Swiss Francs (CHF). The estimated incremental cost-effectiveness ratio was CHF 158,612 per quality-adjusted life-year (QALY) gained within a 5-year time horizon. Assuming similar health effects and costs over 5 additional years changed the incremental cost-effectiveness ratio to CHF 82,195 per QALY gained. Results were robust to the sensitivity analyses performed.

Conclusions: Our results show that PVI might be a cost-effective intervention within the Swiss healthcare context in a 10-year time horizon, but unlikely to be so at 5-years, if a willingness-to-pay threshold of CHF100,000 per QALY gained is assumed. Given data availability, we find target trial designs are a valuable tool for assessing the cost-effectiveness of healthcare interventions outside of RCT settings.

Introduction

Catheter ablation based on pulmonary vein isolation (PVI) is a key intervention to achieve rhythm control in patients with atrial fibrillation (AF). The use of PVI as a procedure has grown exponentially over the past two decades.[1,2] High-quality evidence regarding its impacts on health outcomes has recently been established thanks to the proliferation of randomized control trials (RCT).[3–6] There is RCT evidence regarding the effects of PVI on all-cause mortality,[7] cardiac hospitalization rates,[8] quality-of-life,[5] and cost-effectiveness.[9]

However, high-quality evidence regarding the real-world effectiveness and health economic outcomes of PVI is scarce. Most published cost-effectiveness results either stem directly from RCTs[9] or modeling studies, and the use of real-world data is currently limited to complementing trial-based or modeling-based economic evaluations.[10] Moreover, trials like the CABANA study excluded patients who had already undergone ablation prior to enrollment, or patients under age 65 with a lone AF diagnosis. Hence, there is a need for observational studies aiming to identify the real-world, empirical health effects and costs of PVI outside of modeling studies and trial-eligible populations.

In the present study, we aim to approximate the incremental cost-effectiveness ratio of PVI compared to medical therapy by combining clinical data from the Swiss-AF prospective observational cohort study, health insurance claims, and health-related quality of life (HRQoL) information. To do so, we employ a novel methodological approach, the target trial emulation [11] to approximate the causal effect of PVI on the previously described outcomes and combine them into comparative cost-effectiveness results. The target trial approach addresses common biases that arise in traditional observational studies when trying to establish causal estimates.[12] The approach consists

of analyzing an observational study as if it was a trial, explicitly stating the treatment assignment strategy, patient eligibility, and the assumptions that lead to the identification of the effects. It has been applied in a wide range of applications in medical research, ranging from the effects of statins on cancer incidence[13] to the comparative effectiveness of COVID-19 vaccines.[14]

Methods

Patient population and data sources

This project uses data from an ongoing, multicentric prospective observational cohort study of AF patients in Switzerland, Swiss-AF.[15–17] Swiss-AF enrolled 2,415 patients between April 2014 and August 2017. The present analysis used a 2014-2021 data cut. Additional economic data were obtained through statutory health insurance claims data, available for a subset of 1,013 (43%) of the study population and covering all inpatient, outpatient, pharmaceutical, and other reimbursed expenses. The Swiss statutory health insurance is compulsory for all residents, with a comprehensive benefits package.

The study was approved by the ethics committee of Northwest and Central Switzerland (2014-067, PB_2016-00793). Participants gave written informed consent to participate in the study before taking part.

Outcomes

The primary outcome of the present analysis is the 5-year empirical incremental cost-effectiveness ratio (ICER) for PVI versus medical therapy, measured as the ratio of incremental costs and incremental quality-adjusted life years (QALYs).

Secondary outcomes include incremental life years (LY), measured as the difference in area between the overall survival curves of PVI versus medical therapy, plus the

components of the primary outcome. Namely, incremental QALYs were determined as the HRQoL-weighted difference in area between the overall survival curves of PVI versus medical therapy, where HRQoL was measured as utilities derived from the EQ-5D-3L questionnaire. Incremental direct medical costs were assessed from the perspective of the Swiss statutory health insurance system, a universal coverage health system. All outcomes were primarily assessed for a 5-year follow-up period and discounted at a 3% yearly rate for both costs and health effects.[18] To assess longer-term economic effects, we assumed a similar rate of health effects and costs for up to 10 years post-intervention to estimate the ICER for a 10-year period.

Target trial, statistical analysis, and economic modeling

Our analytical approach combines elements from a trial-based economic evaluation[19] and a target trial study design [11] applied to the Swiss-AF cohort. A target trial is an attempt to emulate a randomized experiment that would answer a causal question of interest.[20] In our case, we aim to assess the comparative cost-effectiveness of PVI versus medical therapy (defined as standard rhythm and/or rate control drugs, guided by European clinical guidelines as used in Swiss clinical practice)[21]. We explicitly emulated a target randomized controlled trial comparing PVI to medical therapy for AF to empirically estimate the effects of interest in our outcomes. The protocol of the target trial is specified in **Table 1**.

To successfully emulate the target trial specified in **Table 1**, we required an adequate definition of time zero of follow-up in the data. We defined time zero as the time when an eligible individual initiated a treatment strategy. For PVI patients, the intervention date was thus used, and for medical therapy (as defined in Supplementary Table S2) patients, the time point they met the eligibility criteria for inclusion in the trial. Patients were not censored if they required a repeated PVI procedure for any outcome.

To emulate the random assignment, we assumed that the treatment strategy initiation was as good as randomly distributed in the Swiss-AF cohort, conditional on a set of potential confounders (specified in **Table 2**).[12] We use these potential confounders to create inverse probability treatment weights (IPTW) by fitting a logistic regression model with PVI treatment as the dependent variable. To model the per-protocol all-cause survival effect of PVI, we estimated a Cox regression weighted with the IPTW. Then, a natural spline of survival was integrated for both treatment arms over the follow-up horizon.

For quality of life, we estimated a longitudinal linear regression model weighted with the IPTW, while including baseline utilities, over the 5-year follow-up period, with the coefficients of interest representing the difference in utilities, calculated from the EQ-5D-3L questionnaire answers in each year; utilities were estimated using the German EQ-5D-3L valuation algorithm.[22] Because utility information was only available at planned study visits, we assumed that the utility in dates between visits followed a linear relationship between the two closest visits, before and after. Patients were censored if they had missing HRQoL information despite being alive, and those who died during the follow-up were censored to avoid double counting of survival effects. Finally, the difference in survival and between utilities was combined to estimate the QALYs in each year, with yearly discounting at a baseline rate of 3%.

We estimated a longitudinal regression model weighted with the IPTW over the 5-year follow-up period for costs. The coefficients of interest represent the yearly total cost differences between treatment arms. The difference estimate for each year was also discounted with a baseline rate of 3% per year. Because costs were available on a daily basis, there were no additional assumptions required regarding costs and time 0. As the study's temporal window fell in a period of very low inflation in Switzerland, we used

all costs as reported, without adjustment for inflation. For reference, the mean Swiss Franc (CHF) to USD exchange rate for the study period was 1.042. Inverse probability weighting was also used to adjust for differential censoring across all analyses. To obtain the ICERs in terms of cost per QALY gained, we divided the incremental cost estimates by the incremental quality-adjusted survival estimates. The resulting estimates reflect an average treatment effect (ATE)[23], due to the creation of a pseudo population through IPTW that measures the effect of PVI versus medical therapy that would have occurred if all patients in the sample had received PVI.

Because all parameters in our economic analysis were empirically estimated from the available patient-level data, uncertainty was characterized in the form of non-parametric bootstrapping with 1,000 random draws with replacement. The estimates were used to assess uncertainty for the mean incremental costs and effects, and to summarize the uncertainty surrounding the ICERs. To further illustrate this uncertainty, cost-effectiveness acceptability curves (CEACs) were derived using the bootstrapped estimates of incremental costs and effects. CEACs demonstrate the probability of an intervention being cost-effective at different ceiling ratios of decision-makers' willingness to pay (WTP) per QALY gained. In the absence of an explicit Swiss WTP, we assumed CHF100,000 per QALY to be cost-effective.[24]

We performed several sensitivity analyses, namely: (i) the use of propensity score matching on the PVI-treated patients to compute average treatment effects on the treated (ATT), meaning the effect on those that received PVI, (ii) varying the utility estimates by using the French, and European EQ-5D-3L value sets instead of the German one,[25,26] and (iii) using only the subset of the population for which claims data were available, to estimate the whole model.

Our preferred empirical approach is limited to the follow-up of patients in the database, and hence only allows to assess the costs and health effects during the first five years post intervention. In order to estimate longer term economic effects and to extend the basis for comparison with the RCT-based CABANA cost-effectiveness analysis, we assumed and modelled a similar rate of health effects and costs up to 10 years post intervention.

Finally, we also compared the estimates of our analytical approach, target trial emulation, with those obtained with a standard observational approach not following the target trial protocol. This naïve approach, still using IPTW weighting but ignoring immortal time bias, reflects the results that would have been obtained if treatment assignment had happened after the start of follow-up. We also compared our results with those from a previously published economic evaluation of the CABANA randomized trial of PVI versus medical therapy.[9] Our choice of anchoring trial is motivated by the trial design.[27] More specifically, CABANA was the largest international trial in the field to-date, including around 1,100 patients per treatment arm comparing PVI versus medical therapy, and including all endpoints relevant to a comprehensive economic evaluation, i.e. mortality, HRQoL, and costs.

All analyses were performed in R version 4.1.2, and the project complies with the CHEERS reporting guidelines,[28] and the checklist is available as a supplementary document. The code can be accessed via a collaborative agreement on GitHub.

Results

Study population

A total of 2,381 patients met the eligibility criteria were included in our analytic sample. 247 (10.4%) patients underwent at least one PVI procedure. Patients undergoing PVI

were relatively younger and healthier, albeit with a higher degree of AF-specific symptoms. Their characteristics are outlined in **Table 2**.

Before weighting, there were notable differences in almost all baseline characteristics. After weighting, these differences were attenuated (Supplementary Figure S1 and S2). A total of 1,013 patients had available claims data. Both patients with and without claims data were comparable (Supplementary Table S1).

Table 3 displays the evolution of EQ-5D-based utilities for the European, German, and French utility sets, alongside the distribution of outpatient, inpatient, and total costs over the follow-up period.

Target trial and cost-effectiveness results

Our primary estimates indicate that patients undergoing PVI had an overall 5-year relative survival advantage of around 23%, hazard ratio (HR) 0.77 (95%CI 0.46-1.21), **Figure 1, panel a**. With discounting, this led to an increment of 0.11 life years. PVI patients accrued 4.22 life years and medical therapy patients accrued 4.11.

In terms of HRQoL, PVI was associated with an average overall improvement of 19.8% (95%CI 12.31-27.29) of a standard deviation in utility, or 0.033 (95%CI 0.028-0.039) points on a 0 to 1 utility scale, where 0 represents death and 1 perfect health. Annual estimates showed the effect to be relatively constant across the observation period, albeit slightly increasing over time, with only a crease in the 5^{th} year after the intervention, **Figure 1, panel b.** With discounting, this translated into 0.187 QALYs gained over the 5-year observation period in the patients undergoing PVI versus medical therapy (Supplementary Figure S10). PVI patients accrued 3.90 QALYs and medical therapy patients accrued 3.71.

Incremental costs, cumulated over 5 years and discounted, were Swiss Francs (CHF) 29,604 (95%CI 16,354-42,855), **Figure 1, panel c**. Patients undergoing PVI experienced a substantial cost increase over the first year post-intervention, with the estimates decreasing continuously up to the point of becoming negative in the 4th and 5th years of follow-up. Absolute five-year costs amounted to CHF 97,197 for the PVI patients CHF 67,593 for the medical therapy patients.

The resulting base case ICER amounted to CHF 158,612 per QALY gained, discounted by 3% per year over the 5-year time horizon, **Figure 2, panel b.** The corresponding cost per life year gained was CHF 169,247.

Assuming the same average health effects and incremental costs over a 5-year additional time period, implying an overall time horizon of 10 years, reduced the ICER to 82,195 CHF per QALY gained and 84,206 CHF per life year gained (Supplementary Figure S5).

Impact of target trial approach and comparison with anchoring trial

The differences in estimated health effects and costs between the target trial emulation and a standard observational approach were substantial. The latter estimated the 5-year survival benefit with a HR of 0.36 versus 0.77, the average 5-year HRQoL effect with an improvement of 3.5% versus 19.8% of a standard deviation, and the 5-year incremental cost increase with CHF 7,700 versus CHF 29,600 (supplementary Figures S3 and S4). In contrast, our main, target trial emulation-based estimates are comparable to those obtained in the within-trial cost-effectiveness analysis of the CABANA trial, with almost equal HRQoL effects albeit a smaller survival benefit, **Table 4.**[9] Although performed for the USA, the CABANA-based analysis also yielded 5-year and 10-year cost differences in a similar range and comparable ICER results.

Sensitivity analyses

We found no substantial differences in estimated results between our preferred specification and using a propensity score matching approach (Supplementary Figure S6). Notably, the latter achieved an even better covariate balance (Supplementary Figure S7). Our HRQoL estimates did not vary substantially when calculating utilities using the French or European value set (Supplementary Figure S8). When using only patients with claims data available, our results were not substantially impacted for the calculation of survival, HRQoL, cost, and ICER (Supplementary Table S1 and Supplementary Figure S9).

Discussion

To the best of our knowledge, this is one of the first studies to combine trial-based economic evaluation elements with a target trial approach. Each parameter in the economic model stems from an approximated causal relationship of PVI versus medical therapy, which was intended to be identified through the specified target trial protocol and explicit assumptions. Our study assessed the economic and clinical effects of PVI versus medical therapy in an observational cohort of AF patients. Clinically significant effects on overall survival and quality of life were estimated using a target trial emulation approach. Economically significant cost impacts were estimated using the same approach. Overall, our results suggest that PVI is unlikely to be cost-effective within a 5-year time horizon, but likely to be so when a 10-year time horizon is considered.

Our estimates are consistent with those previously reported from randomized controlled trials, albeit with slightly smaller health effects at a slightly higher cost, likely reflecting a wider spectrum of patients with AF in our real-world cohort, given more restricted

eligibility for clinical trials.[7] Our 5-year incremental cost estimate of about CHF 30,000 compares to an approximate cost of a PVI procedure of CHF 25,000 in terms of DRG reimbursement.

The study period comprises a time horizon in which there were no major changes in the pharmacological management of AF patients.[29] Only the introduction of edoxaban in 2015 presents a major change. Hence, our estimates are likely to be generalizable to other settings and the management of patients in the standard medical therapy group is an updated representation of the current standard of care.

Compared with not using the proposed framework, our estimates of an empirical economic evaluation make it appear likely that traditional estimates overestimate the cost-effectiveness of PVI, due to conditioning on post-treatment variables[13] and confounding on a set of economic results.[12]

The strengths of our study relate to the high-quality data sources used, (including quality-of-life and detailed resource utilization), and the analytical approach in the explicit emulation of a hypothetical trial. The estimates from the battery of sensitivity analyses are also in line with the interpretation of our primary modeling approach, and add to the credibility of our results.

Our cost-effectiveness study is not without limitations, first, our estimated effects could suffer from unobserved confounding that we could not account for with our current clinical data availability. Second, while our study had enough precision in identifying effects on quality of life and cost, there was substantial uncertainty around the all-cause survival point estimate to confirm a benefit due to the limited number of events. Third, as PVI may impact long-term HRQoL and length of life, a lifetime horizon would principally be appropriate. Our purely empirical results are only valid within a 5-year

follow-up window for which data was available. Our ICER estimate for the 10-year time horizon is based on a sensitivity analysis extrapolating beyond the time period we had empirical data for. It is, however, supported by the observation of a very similar ICER change between 5 and 10 years as reported in the cost-effectiveness analysis of the CABANA trial, (see Table 4).[9] Extension to a lifetime horizon using additional modelling steps might also have yielded similar results. Given our focus on a novel approach to directly data-based cost-effectiveness analysis, we did not undertake such further extension. The issue of limited follow-up times affects most cost-effectiveness analyses directly based on prospective clinical data collections, including RCTs. Fourth, our real-world economic estimates might not be generalizable to a setting outside of Switzerland, and our results warrant replication in other countries, especially in those with a lower socio-economic level. Fifth, we have assumed that HRQoL measures between follow-up visits can be approximated with a linear interpolation between time points.

Conclusions

Our economic evaluation of PVI versus medical therapy based on a target trial approach showed that PVI might be cost-effective at a cost-utility threshold of CHF 100,000 per QALY gained, as it is sometimes assumed for Switzerland, over a 10-year time horizon, but not within a 5-year time horizon. Moreover, this study warrants further application of the target trial approach to cost-effectiveness evaluations.

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Figures

Figure 1. Overall survival, quality of life, and cost estimates.

Notes: panel a) presents the all-cause survival model estimates, panel b) presents the QoL model estimates, and panel c) presents the costs model estimates.

Figure 2. Probabilistic sensitivity analyses results

Notes: panel a) presents the scatter plot of the 1,000 bootstrap simulations of incremental life-years and incremental cost, (upper) and its corresponding cost-effectiveness acceptability curve (lower), panel b) presents the scatter plot of the 1,000 bootstrap simulations of incremental quality-adjusted life-years and incremental cost, (upper) and its corresponding cost-effectiveness acceptability curve (lower).

Tables

Table 1. Specification and emulation of the target trial of PVI versus Medical therapy.

Component	Target trial	Emulated trial using SAF data
Aim	To estimate the incremental cost-effectiveness of PVI vs. medical therapy over a 5-year time horizon.	Same
Eligibility	Swiss AF eligibility criteria. Eligible patients must be ≥65 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 twice 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).	Same
Treatment strategies (arms)	1. PVI at baseline and repeated ablation for recurrent AF if necessary. 2. Medical therapy at baseline. Patients receive usual care after the intervention.	Same
Treatment assignment	Patients are randomly assigned to either strategy.	Patients are assigned to PVI if they receive a PVI during follow-up and their start of follow-up starts there. Patients in the control group's baseline point is when they meet the PVI eligibility criteria. Randomization is emulated via adjustment for baseline covariates via IPTW.
Follow-up	Follow-up starts at treatment assignment and ends at their last follow-up or 31 December 2020, whichever occurs first.	Same
Outcome	1. LY 2. QALY 3. Cost 4. ICER	Same

Causal contrast	Intention-to-treat effect, i.e., the effect of being assigned to PVI versus control at baseline. Per-protocol effect, i.e., the effect of receiving PVI versus control at baseline.	Observational analog of per-protocol effect.
Statistical analysis	Intention-to-treat analysis. Per-protocol analysis: comparison of 5-year all-cause mortality, quality of life, and cost between groups receiving each treatment strategy with adjustment for baseline covariates (and post-baseline covariates when adjusting for loss to follow-up).	Same as per-protocol analysis

Notes: abbreviations: PVI: pulmonary vein isolation, ECG: electrocardiogram, IPTW: inverse probability treatment weighting, LY: life-years, QALY: quality-adjusted life years, ICER: incremental cost-effectiveness ratio.

Table 2. Baseline characteristics of patients with and without PVI.

	Before IPTW Medical Therapy	PVI
n	2134	247
Demographics & Behavioral		
Age (mean (SD))	73.94 (8.16)	66.94 (8.02)
Sex Male (%)	1547 (72.5)	182 (73.7)
Smoking (%)		
Former	1056 (49.5)	107 (43.3)
Active	150 (7.0)	21 (8.5)
Never	928 (43.5)	119 (48.2)
Alcohol consumption* (mean (SD))	1.05 (1.47)	1.22 (1.74)
BMI (mean (SD))	27.64 (4.78)	28.01 (4.81)
Education level (%)		
Advanced	798 (37.4)	118 (47.8)
Basic	255 (11.9)	25 (10.1)
Middle	1081 (50.7)	104 (42.1)
Baseline Disease & comorbidities		
AF type (%)		
Paroxysmal	927 (43.4)	141 (57.1)
Permanent	576 (27.0)	11 (4.5)
Persistent	631 (29.6)	95 (38.5)
AF symptoms (%)	1270 (59.5)	203 (82.2)
Years since diagnosis (mean (SD))	6.29 (7.89)	5.03 (4.98)
CHA_2DS_2-VASc (mean (SD))	3.60 (1.69)	2.38 (1.38)
Stroke (%)	449 (21.0)	25 (10.1)
Heart failure (%)	577 (27.0)	38 (15.4)
Diabetes (%)	391 (18.3)	23 (9.3)
Baseline Treatments		
Previous PVI (%)	372 (17.4)	107 (43.3)
NOACs (%)	1038 (48.6)	176 (71.3)
Antidepressants (%)	138 (6.5)	9 (3.6)
Aspirin (%)	367 (17.2)	29 (11.7)
Statins (%)	367 (17.2)	29 (11.7)
Diuretics (%)	1038 (48.6)	74 (30.0)
Beta-blockers (%)	1492 (69.9)	180 (72.9)
Digoxin (%)	102 (4.8)	6 (2.4)
Implanted device (%)		
CRT N (%)	28 (1.3)	1 (0.4)
CRT-ICD N (%)	42 (2.0)	3 (1.2)
ICD N (%)	68 (3.2)	6 (2.4)
Loop recorder N (%)	16 (0.7)	8 (3.2)

None N (%)	1681 (78.8)	224 (90.7)
Pacemaker N (%)	299 (14.0)	5 (2.0)
Electroconversion *N* (%)	727 (34.1)	118 (47.8)

*Notes: *measured as weekly standardized units, ¥ Weighted pseudo-populations.*

Abbreviations: IPTW: inverse probability treatment weighting, PVI: pulmonary vein isolation, SD: standard deviation, BMI: body mass index, AF: atrial fibrillation, NOACs: non-vitamin K antagonist oral anticoagulant, CRT: cardiac resynchronization therapy, CRT-ICD: cardiac resynchronization therapy with implantable cardioverter-defibrillator, ICD: implantable cardioverter-defibrillator

Table 3. Average health-related quality of life and cost evolution.

a)

Time (year)	Utility (German set)	95%CI		Utility (European set)	95%CI		Utility (French set)	95%CI	
Baseline	0.90	0.89	0.90	0.83	0.82	0.83	0.84	0.84	0.85
1	0.90	0.89	0.90	0.83	0.82	0.84	0.85	0.84	0.86
2	0.90	0.89	0.91	0.83	0.83	0.84	0.85	0.84	0.86
3	0.90	0.89	0.91	0.83	0.82	0.84	0.85	0.84	0.86
4	0.90	0.89	0.91	0.83	0.82	0.84	0.85	0.83	0.86
5	0.89	0.88	0.91	0.83	0.82	0.85	0.85	0.83	0.87

b)

Time (year)	Total costs*	95%CI		Outpatient costs*	95%CI		Inpatient costs*	95%CI	
1	19,780	17,799	21,761	8,311	7,625	8,998	11,469	9,763	13,174
2	19,514	17,730	21,298	8,677	7,993	9,361	10,837	9,384	12,289
3	18,185	16,394	19,976	8,992	8,257	9,727	9,193	7,783	10,602
4	19,122	17,174	21,070	9,717	8,829	10,605	9,405	7,900	10,910
5	16,276	14,409	18,144	8,427	7,607	9,247	7,850	6,431	9,268

Notes: Panel a) presents the utilities and b) presents the costs expressed in Swiss Francs (2022). Utilities are based on the EQ-5D-3L quality of life questionnaire combined with the German, European, and French value sets.*

. **Table 4.** Comparison of 5-year estimates of survival, quality of life and cost, between the target trial approach (current study), CABANA trial estimates, and standard analysis estimates.

	Overall survival		
Source	HR	95%CI	
Target trial	0.77	0.46	1.21
CABANA results*	0.68	0.47	0.99
Standard analysis	0.36	0.14	0.89
	Quality of Life		
	QoL (% SD)	95%CI	
Target trial	19.81	12.31	27.29
CABANA results*	20.02	12.38	28.44
Standard analysis	3.51	-0.12	0.19
	Cost		
	Cost	95%CI	
Target trial	CHF 29,604	CHF 16,354	CHF 48,855
CABANA results*	USD 19,245	USD 11,360	USD 27,170
Standard analysis	CHF 7,785	CHF -5,061	CHF 20,779
	5-year empirical ICER**		
	ICER		
Target trial	158,612 CHF/QALY		
CABANA results*	165,991 USD/QALY		
Standard analysis	40,974 CHF/QALY		
	10-year modelled ICER**		
	ICER		
Target trial	82,195 CHF/QALY		
CABANA results*	85,117 USD/QALY		
Standard analysis	21,233 CHF/QALY		

*Notes: HR: hazard ratio, ICER: incremental cost-effectiveness ratio, QoL: quality of life (EQ-5D-3L; results are presented as % of a standard deviation in the outcome). During the study period, the exchange rate of USD to CHF was 0.93. The inverse probability treatment weighting in both the standard analysis and the target trial approaches included the following baseline parameters.: age, sex, smoking status, alcohol consumption, body mass index, education level, type of atrial fibrillation, years since diagnosis, CHA_2DS_2-VASc, history of stroke, heart failure, diabetes, pulmonary vein isolation, device implantation, electroconversion, non-vitamin K antagonist oral anticoagulant use, antidepressant use, aspirin use, statin use, diuretics use, beta-blocker use, digoxin use, and EQ-5D-3L quality of life. * Based on Chew et al., Table 4.[9] ** The ICER estimates do not include confidence intervals due to being unable to obtain those from the CABANA trial.*