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Serra-Burriel, Miquel ; Aebersold, Helena ; Foster-Witassek, Fabienne ; Coslovsky, Michael ; Rodondi, Nicolas ; Blum, Manuel R ; Sticherling, Christian ; Moschovitis, Giorgio ; Beer, Jürg H ; Reichlin, Tobias ; Krisai, Philipp ; Aeschbacher, Stefanie ; Paladini, Rebecca E ; Kühne, Michael ; Osswald, Stefan ; Conen, David ; Felder, Stefan ; Schwenkglenks, Matthias

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Economic Evaluation

Real-World Cost-Effectiveness of Pulmonary Vein Isolation for Atrial Fibrillation: A Target Trial Approach

Miquel Serra-Burriel, PhD, Helena Aebersold, MSc, Fabienne Foster-Witassek, MSc, Michael Coslovsky, PhD, Nicolas Rodondi, MD, MAS, Manuel R. Blum, MD, MSc, Christian Sticherling, MD, Giorgio Moschovitis, MD, Jürg H. Beer, MD, Tobias Reichlin, MD, Philipp Krisai, MD, Stefanie Aeschbacher, PhD, Rebecca E. Paladini, PhD, Michael Kühne, MD, Stefan Osswald, MD, David Conen, MD, MPH, Stefan Felder, PhD, Matthias Schwenkglenks, PhD, MPH, for the Swiss-AF investigators

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 patients with AF between 2014 and 2017. Resource utilization and cost information were collected through claims data. Quality of life was measured with EQ-5D-3L utilities. We estimated incremental cost-effectiveness ratios (ICERs) from the perspective of the Swiss statutory health insurance system.

Results: Patients undergoing PVI compared with medical therapy had a 5-year overall survival advantage with a hazard ratio of 0.75 (95% CI 0.46-1.21; $P = .69$) and a 19.8% SD improvement in quality of life (95% CI 15.5-22.9; $P < .001$), at an incremental cost of 29 604 Swiss francs (CHF) (95% CI 16 354-42 855; $P < .001$). The estimated ICER 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 ICER 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 CHF 100 000 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 randomized controlled trial settings.

Keywords: causal inference, target trial, cost-effectiveness, atrial fibrillation, pulmonary vein isolation.

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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 2 decades.[1,2] High-quality evidence regarding its impacts on health outcomes has recently been established thanks to the proliferation of randomized controlled trials (RCTs).[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]

Nevertheless, high-quality evidence regarding the real-world effectiveness and health economic outcomes of PVI is scarce. Most published cost-effectiveness results stem directly from either 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 such as the CABANA study excluded patients who had already undergone ablation before enrollment or patients younger than 65 years 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 aimed to approximate the incremental cost-effectiveness ratio (ICER) of PVI compared with 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 use 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 patients with AF in Switzerland, Swiss-AF.[15–17] Swiss-AF enrolled 2415 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 1013 (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 a written informed consent to participate in the study before taking part.

Outcomes

The primary outcome of the present analysis is the 5-year empirical 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 (LYs), measured as the difference in area between the overall survival curves of PVI and 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 and medical therapy, where HRQoL was measured as utilities derived from the EQ-5D-3L questionnaire. Incremental direct medical costs were assessed from the

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

Component	Target trial	Emulated trial using Swiss-AF 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 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 December 31, 2020, whichever occurs first.	Same
Outcome	1. LY 2. QALY 3. Cost 4. ICER	Same
Causal contrast	Intention-to-treat effect, ie, the effect of being assigned to PVI vs control at baseline; per-protocol effect, ie, the effect of receiving PVI vs 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 postbaseline covariates when adjusting for loss to follow-up)	Same as per-protocol analysis

AF indicates atrial fibrillation; ECG, electrocardiogram; ICER, incremental cost-effectiveness ratio; IPTW, inverse probability treatment weighting; LY, life-year; PVI, pulmonary vein isolation; QALY, quality-adjusted life-year.

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 after the intervention to estimate the ICER for a 10-year period.

Target Trial, Statistical Analysis, and Economic Modeling

Our analytic 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 aimed to assess the comparative cost-effectiveness of PVI versus medical therapy (defined as standard rhythm or rate control drugs, guided by European clinical guidelines as used in Swiss clinical practice).[21] We explicitly emulated a target RCT comparing PVI with 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 patients with PVI, the intervention date was thus used, and for medical therapy patients (as defined in Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.08.008), 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 (IPTWs) 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 2 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. Given that 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 US dollar exchange rate for the study period was 1.042. Inverse probability weighting was also used to adjust for differential censoring across

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

	Before IPTW	
	Medical therapy	PVI
n	2134	247
Demographics and 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 and 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)

AF indicates atrial fibrillation; BMI, body mass index; CRT, cardiac resynchronization therapy; CRT-ICD, cardiac resynchronization therapy with implantable cardioverter-defibrillator; ICD, implantable cardioverter-defibrillator; IPTW, inverse probability treatment weighting; NOAC, nonvitamin K antagonist oral anticoagulant; PVI, pulmonary vein isolation.
*Measured as weekly standardized units.

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	8311	7625	8998	11 469	9763	13 174
2	19 514	17 730	21 298	8677	7993	9361	10 837	9384	12 289
3	18 185	16 394	19 976	8992	8257	9727	9193	7783	10 602
4	19 122	17 174	21 070	9717	8829	10 605	9405	7900	10 910
5	16 276	14 409	18 144	8427	7607	9247	7850	6431	9268

Note. Panel A presents the utilities and B presents the costs. Utilities are based on the EQ-5D-3L quality of life questionnaire combined with the German, European, and French value sets.
*Expressed in Swiss francs (2022).

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,[23] because of 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 nonparametric bootstrapping with 1000 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 were derived using the bootstrapped estimates of incremental costs and effects. Cost-effectiveness acceptability curves demonstrate the probability of an intervention being cost-effective at different ceiling ratios of decision-makers' willingness to pay per QALY gained. In the absence of an explicit Swiss willingness to pay, we assumed CHF 100 000 per QALY to be cost-effective.[24]

We performed several sensitivity analyses, namely (1) the use of propensity score matching on the PVI-treated patients to compute average treatment effects on the treated, meaning the effect on those that received PVI, (2) varying the utility estimates by using the French and European EQ-5D-3L value sets instead of the German one,[25,26] and (3) 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 5 years after the intervention. To estimate longer-term economic effects and to extend the basis for comparison with the RCT-based CABANA cost-effectiveness analysis, we assumed and modeled a similar rate of health effects and costs up to 10 years after the intervention.

Finally, we also compared the estimates of our analytic approach, target trial emulation, with those obtained with a standard observational approach not following the target trial protocol. This naive 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 approximately 1100 patients per treatment arm comparing PVI with medical therapy and including all endpoints relevant to a comprehensive economic evaluation, that is, mortality, HRQoL, and costs.

All analyses were performed in R version 4.1.2, R Foundation for Statistical Computing, Vienna, Austria., the project complies with the Consolidated Health Economic Evaluation Reporting Standards reporting guidelines,[28] and the checklist is available as a supplementary document. The code can be accessed via a collaborative agreement on GitHub.

Results

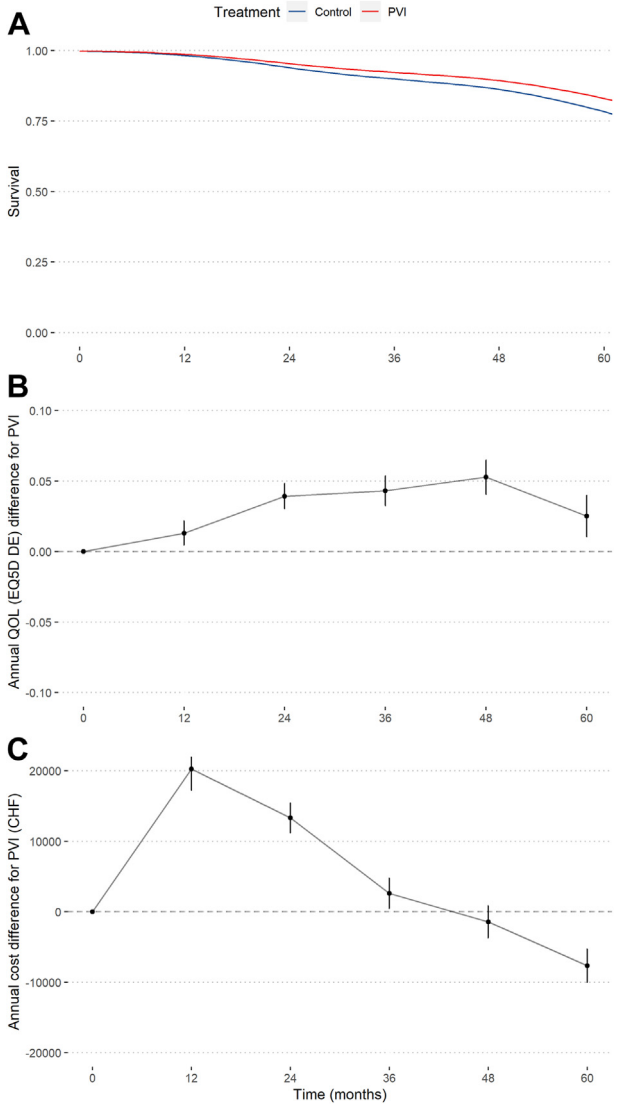
Study Population

A total of 2381 patients who met the eligibility criteria were included in our analytic sample; 247 patients (10.4%) 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 presented in Table 2.

Before weighing, there were notable differences in almost all baseline characteristics. After weighting, these differences were attenuated (Appendix Figs. 1 and 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.08.008). A total of 1013 patients had available claims data. Both patients with and without claims data were comparable (Appendix Table 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.08.008).

The evolution of EQ-5D-based utilities for the European, German, and French utility sets, alongside the distribution of

Figure 1. Overall survival, quality of life, and cost estimates. (A) The all-cause survival model estimates. (B) The QoL model estimates. (C) The costs model estimates.



CHF indicates Swiss francs; PVI, pulmonary vein isolation; QoL, quality of life.

outpatient, inpatient, and total costs over the follow-up period, is presented in Table 3.

Target Trial and Cost-Effectiveness Results

Our primary estimates indicate that patients undergoing PVI had an overall 5-year relative survival advantage of approximately 23% (hazard ratio 0.77; 95% CI 0.46-1.21) (Fig. 1A). With discounting, this led to an increment of 0.11 LYs. Patients with PVI accrued 4.22 LYs 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 SD 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 fifth year after the intervention (Fig. 1B). With discounting, this translated into 0.187 QALYs gained over the 5-year observation period in the patients undergoing PVI versus medical therapy (Appendix Fig. 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.08.008). Patients with PVI accrued 3.90 QALYs and medical therapy patients accrued 3.71.

Incremental costs, cumulated over 5 years and discounted, were CHF 29 604 (95% CI 16 354-42 855) (Fig. 1C). Patients undergoing PVI experienced a substantial cost increase over the first year after the intervention, with the estimates decreasing continuously up to the point of becoming negative in the fourth and fifth years of follow-up. Absolute 5-year costs amounted to CHF 97 197 for the patients with PVI and 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 (Fig. 2B). The corresponding cost per LY 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 CHF 82 195 per QALY gained and CHF 84 206 per LY gained (Appendix Fig. 4 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.08.008).

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 hazard ratio of 0.36 versus 0.77, the average 5-year HRQoL effect with an improvement of 3.5% versus 19.8% of a SD, and the 5-year incremental cost increase with CHF 7700 versus CHF 29 600 (Appendix Figs. 5 and 6 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.08.008). In contrast, our main, target trial emulation-based estimates are comparable with 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 United States, the CABANA-based analysis also yielded 5-year and 10-year cost differences in a similar range and comparable ICER results.

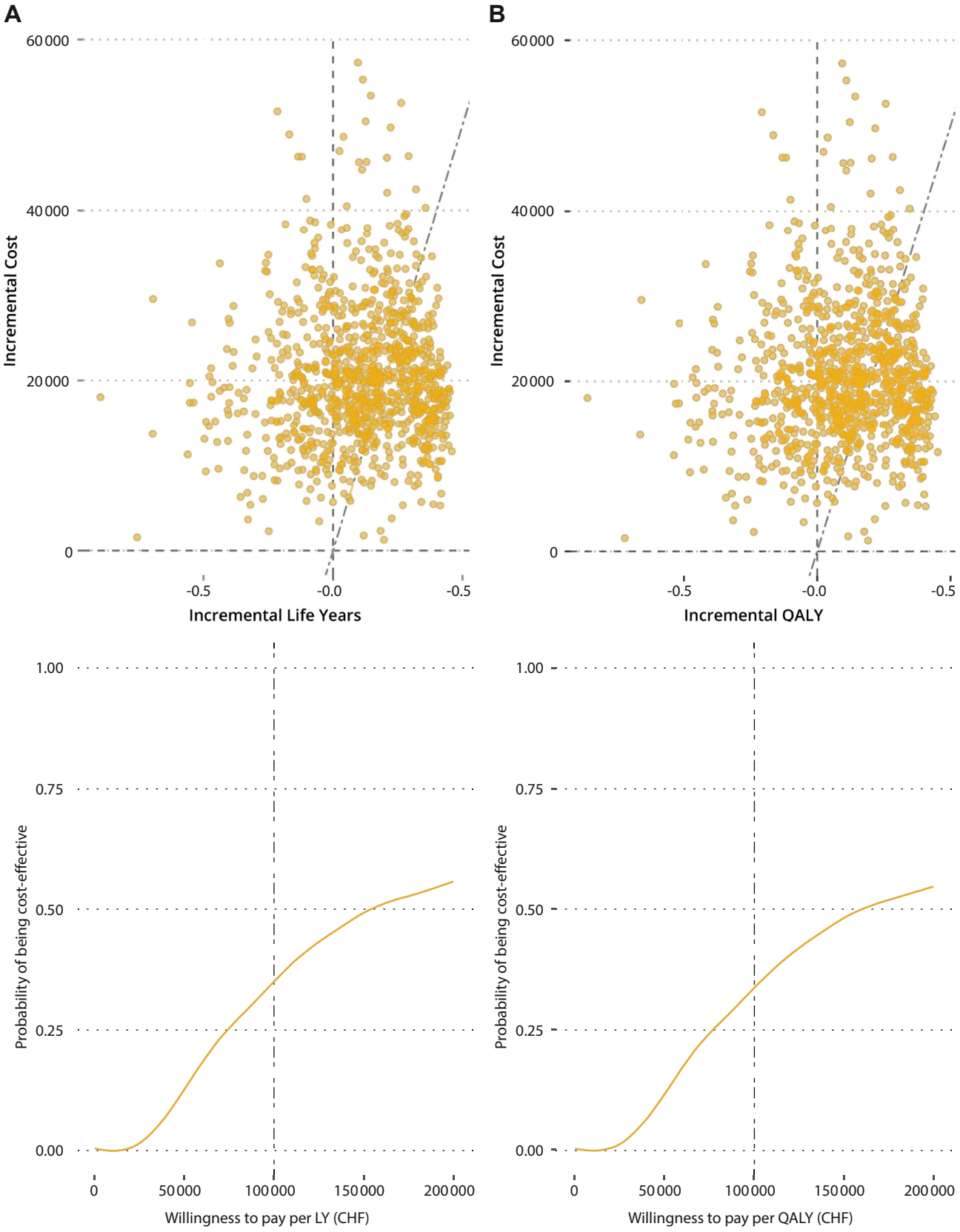
Sensitivity Analyses

We found no substantial differences in estimated results between our preferred specification and using a propensity score matching approach (Appendix Fig. 7 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.08.008). Notably, the latter achieved an even better covariate balance (Appendix Fig. 8 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.08.008). Our HRQoL estimates did not vary substantially when calculating utilities using the French or European value set (Appendix Fig. 9 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.08.008). When using only patients with claims data available, our results were not substantially impacted for the calculation of survival, HRQoL, cost, and ICER (Appendix Table 2 and Appendix Fig. 10 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.08.008).

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

Figure 2. Probabilistic sensitivity analyses results. (A) The scatter plot of the 1000 bootstrap simulations of incremental LYs and incremental cost (upper) and its corresponding cost-effectiveness acceptability curve (lower). (B) The scatter plot of the 1000 bootstrap simulations of incremental QALYs and incremental cost (upper) and its corresponding cost-effectiveness acceptability curve (lower).



CHF indicates Swiss francs; LY, life year; QALY, quality-adjusted life-year.

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

Source	Overall survival		
	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
	QoL		
	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 7785	CHF −5061	CHF 20 779
	5-year empirical ICER†		
	ICER		
Target trial	CHF 158 612/QALY		
CABANA results*	USD 165 991/QALY		
Standard analysis	CHF 40 974/QALY		
	10-year modeled ICER†		
	ICER		
Target trial	CHF 82 195/QALY		
CABANA results*	USD 85 117/QALY		
Standard analysis	CHF 21 233/QALY		

Note. EQ-5D-3L; results are presented as % of a SD 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, nonvitamin K antagonist oral anticoagulant use, antidepressant use, aspirin use, statin use, diuretics use, beta-blocker use, digoxin use, and EQ-5D-3L QoL.
CHF indicates Swiss franc; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; QoL, quality of life; USD, US dollar.
*Based on Chew et al[9] (Table 4).
†The ICER estimates do not include confidence intervals because of being unable to obtain those from the CABANA trial.

target trial protocol and explicit assumptions. Our study assessed the economic and clinical effects of PVI versus medical therapy in an observational cohort of patients with AF. 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 RCTs, 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 approximately CHF 30 000 compares with an approximate cost of a PVI procedure of CHF 25 000 in terms of diagnostic-related groups reimbursement.

The study period comprises a time horizon in which there were no major changes in the pharmacological management of patients with AF.[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 seem likely that traditional estimates overestimate the cost-effectiveness of PVI, because of 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 analytic 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 have unobserved confounding that we could not account for with our current clinical data availability. Second, although 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 because of the limited number of events. Third, given that PVI may

affect 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 were 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. Nevertheless, it is 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 modeling 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 socioeconomic 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.

Author Disclosures

Links to the individual disclosure forms provided by the authors are available here.

Supplemental Materials

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2023.08.008.

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Author Affiliations: Epidemiology, Biostatistics, and Prevention Institute, University of Zurich, Zurich, Switzerland (Serra-Burriel, Aebersold, Foster-Witassek, Schwenkglenks); Department of Clinical Research, University of Basel, University Hospital, Basel, Switzerland (Coslovsky); Cardiovascular Research Institute Basel, University of Basel, University Hospital, Basel, Switzerland (Coslovsky, Sticherling, Krisai, Aeschbacher, Paladini, Kühne, Osswald); Department of General Internal Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland (Rodondi, Blum); Institute of Primary Health Care (BIHAM), University of Bern, Bern, Switzerland (Rodondi, Blum); Department of Cardiology, University Hospital Basel, University of Basel, Basel, Switzerland (Sticherling, Krisai, Aeschbacher, Paladini, Kühne, Osswald); Department of Medicine, University Hospital Basel, University of Basel, Basel, Switzerland (Sticherling, Krisai, Aeschbacher, Paladini, Kühne, Osswald); Division of Cardiology, Ente Ospedaliero Cantonale, Regional Hospital of Lugano, Lugano, Switzerland (Moschovitis); Department of Medicine, Cantonal Hospital of Baden and Molecular Cardiology, University Hospital of Zürich, Zurich, Switzerland (Beer); Department of Cardiology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland (Reichlin); Population Health Research Institute, McMaster University, Hamilton, Canada (Conen); Department of Business and Economics, University of Basel, Basel, Switzerland (Felder); Health Economics Facility, Department of Public Health, University of Basel, Basel, Switzerland (Schwenkglenks).

Correspondence: Miquel Serra-Burriel, PhD, Epidemiology, Biostatistics, and Prevention Institute, University of Zurich, Hirsengraben 84, Zurich 8001, Switzerland. Email: miquel.serraburriel@uzh.ch

Author Contributions: *Concept and design:* Serra-Burriel, Aebersold, Foster-Witassek, Reichlin, Krisai, Schwenkglenks
Acquisition of data: Foster-Witassek, Coslovsky, Rodondi, Blum, Sticherling, Moschovitis, Beer, Reichlin, Krisai, Aeschbacher, Paladini, Kühne, Osswald, Conen, Schwenkglenks
Analysis and interpretation of data: Serra-Burriel, Aebersold, Foster-Witassek, Coslovsky, Rodondi, Blum, Sticherling, Reichlin, Conen, Felder, Schwenkglenks
Drafting of the article: Serra-Burriel, Aebersold, Rodondi, Blum, Sticherling, Schwenkglenks
Critical revision of the article for important intellectual content: Serra-Burriel, Aebersold, Foster-Witassek, Coslovsky, Rodondi, Blum, Sticherling, Moschovitis, Beer, Reichlin, Krisai, Aeschbacher, Paladini, Kühne, Osswald, Conen, Felder, Schwenkglenks
Provision of study materials or patients: Rodondi, Blum, Sticherling, Moschovitis, Beer, Reichlin, Krisai, Aeschbacher, Paladini, Kühne, Osswald, Conen
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