Supplementary material

Cost-effectiveness of Early Rhythm-Control versus Usual Care in Atrial Fibrillation Care: An analysis based on data from the EAST-AFNET 4 trial

Table S1 CHEERS 2022 Checklist

Topic	No.	Item	Location where item is reported
Title			
	1	Identify the study as an economic evaluation and specify the interventions being compared.	Provided in the title.
Abstract			
	2	Provide a structured summary that highlights context, key methods, results, and alternative analyses.	Provided in the Abstract, including sensitivity analyses.
Introduction			
Background and objectives	3	Give the context for the study, the study question, and its practical relevance for decision making in policy or practice.	Introduction.
Methods			
Health economic analysis plan	4	Indicate whether a health economic analysis plan was developed and where available.	No health economic analysis plan as reported in the methods section.
Study population	5	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).	Provided in the results section.
Setting and location	6	Provide relevant contextual information that may influence findings.	Detailed in the methods section.
Comparators	7	Describe the interventions or strategies being compared and why chosen.	Title, introduction and methods.
Perspective	8	State the perspective(s) adopted by the study and why chosen.	Provided in methods and discussion.
Time horizon	9	State the time horizon for the study and why appropriate.	Provided in methods and based on trial.
Discount rate	10	Report the discount rate(s) and reason chosen.	Provided in the methods.
Selection of outcomes	11	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	Provided in the methods.
Measurement of outcomes	12	Describe how outcomes used to capture benefit(s) and harm(s) were measured.	Provided in the methods and based on trial.
Valuation of outcomes	13	Describe the population and methods used to measure and value outcomes.	Based on trial, in the methods.
Measurement and valuation of resources and costs	14	Describe how costs were valued.	Provided in the methods.
Currency, price date, and conversion	15	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	Provided in the methods.
Rationale and description of model	16	If modelling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed.	No modelling.
Analytics and assumptions	17	Describe any methods for analysing or statistically transforming data, any	Provided in the methods.

		extrapolation methods, and approaches for validating any model used.	
Characterising heterogeneity	18	Describe any methods used for estimating how the results of the study vary for subgroups.	Discussed in discussion section, no subgroup analysis.
Characterising distributional effects	19	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	Not applicable, trial based.
Characterising uncertainty	20	Describe methods to characterise any sources of uncertainty in the analysis.	Provided in methods, results, discussion.
Approach to engagement with patients and others affected by the study	21	Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (such as clinicians or payers) in the design of the study.	No engagement of stakeholders. Trial-based.
Results			
Study parameters	22	Report all analytic inputs (such as values, ranges, references) including uncertainty or distributional assumptions.	In the Tables and Figures.
Summary of main results	23	Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure.	In Results, Discussion and Conclusion.
Effect of uncertainty	24	Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.	Provided in Tables S5-S6, Figures S2-S5.
Effect of engagement with patients and others affected by the study	25	Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study	Trial-based, not applicable.
Discussion			
Study findings, limitations, generalisability, and current knowledge	26	Report key findings, limitations, ethical or equity considerations not captured, and how these could affect patients, policy, or practice.	In the discussion.
Other relevant information			
Source of funding	27	Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	Provided after conclusion.
Conflicts of interest	28	Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	Provided after conclusion.

From: Husereau D, Drummond M, Augustovski F, et al[1]

Assignment of diagnoses and procedures to hospital stays (detailed description)

Hospitalizations were recorded along the study as part of the documentation of serious adverse events (SAEs). Events were classified as SAEs if they resulted in death, were life-threatening, required or prolonged inpatient hospitalization, resulted in persistent or significant disability/incapacity, or were judged as medically important. Among other information, the type of event, the date of onset/admission/discharge, the interventions performed, and the outcome were specified for each SAE. Diagnosis-related groups (G-DRG catalogue 2021) were assigned to the individual hospital stays based on the initial diagnosis that led to admission into hospital (International Statistical Classification of Diseases and Related Health Problems, 10th revision, German modification, ICD-10-GM) and the performed cardiovascular procedures during the hospital stay (German Operation and Procedure Classification, OPS). For reported SAEs, ICD-10 and OPS codes were assigned to the types of events and cardiovascular procedures specified in the electronic case report form (Table S1 & S2). When the type of event was classified as "any type of cardiovascular surgery" or "other cardiovascular event" (which is not specific enough to derive a particular diagnosis or procedure), ICD-10 and OPS codes were assigned based on free-text entries. "Other events" that resulted in the performance of a cardiovascular procedure were also assigned ICD-10 and OPS codes based on the information provided in the electronic case report form and as free text.

Furthermore, hospital stays due to events classified as "other events" for which no cardiovascular procedure was performed were monetarily valued based on standardized unit costs and inflated to the year 2021 according to the consumer price index.[2, 3]

Table S2 ICD-10 codes assigned to the SAEs specified in the e-CRF

Type of SAE as specified in the e-CRF	ICD-10 code	ICD-10 description
TIA	G45.99	Transient cerebral ischemic attack, unspecified
Ischemic stroke (including transient events with matching lesion on cerebral imaging)	I63.9	Cerebral infarction, unspecified
Hemorrhagic stroke	I61.9	Intracerebral hemorrhage, unspecified
STEMI, anterior	I21.0	Acute transmural myocardial infarction of anterior wall
STEMI, posterior	I21.1	Acute transmural myocardial infarction of inferior wall
STEMI, not classifiable	I21.9	Acute myocardial infarction, unspecified
NSTEMI	I21.4	Acute subendocardial myocardial infarction
Unstable AP	I20.0	Unstable angina
Stable AP or atypical chest pain	I20.9	Angina pectoris, unspecified
Worsening of heart failure, decompensated	I50.9	Heart failure, unspecified
Worsening of heart failure, not decompensated	I50.9	Heart failure, unspecified
Ventricular tachycardia	I47.2	Ventricular tachycardia
Ventricular fibrillation	I49.9	Cardiac arrhythmia, unspecified
Drug-induced bradycardia	R00.1	Bradycardia, unspecified
AV nodal block	I44.3	Other and unspecified atrioventricular block
Ablation-induced or drug-induced atrial flutter/atrial tachycardia	I48.9	Atrial fibrillation and atrial flutter, unspecified
Syncope	R55	Syncope and collapse
Bleeding caused by catheter intervention or antithrombotic therapy	T81.2	Accidental puncture and laceration during a procedure, not elsewhere classified
Pericardial tamponade	I31.9	Disease of pericardium, unspecified
Drug toxicity of AF-related drug therapy	T88.7	Unspecified adverse effect of drug or medicament
Non-fatal cardiac arrest	I21.9	Acute myocardial infarction, unspecified
Implantation of a pacemaker, ICD, CRT or any other cardiac device	I48.9	Atrial fibrillation and atrial flutter, unspecified
Percutaneous coronary (e.g. PCI), cerebrovascular or peripheral procedure	I70.9	Generalized and unspecified atherosclerosis
	I25.19[1]	Atherosclerotic heart disease, unspecified
Blood pressure related (hypotension, hypertension; except syncope)	I10.90[2]	Essential (primary) hypertension, unspecified

Cardiovascular infection (e.g. endocarditis, pericarditis, infectious myocarditis)	I38[3]	Endocarditis, valve unspecified
Major bleeding	R58[4]	Hemorrhage, not elsewhere classified
Pulmonary embolism or deep vein thrombosis	I26.9[5]	Pulmonary embolism without mention of acute cor pulmonale
	I80.28	Phlebitis and thrombophlebitis of other deep vessels of lower extremities
Hospitalization for AF	I48.9	Atrial fibrillation and atrial flutter, unspecified
Any type of cardiovascular surgery	[Manual assignment of diagnoses and procedures based on free text entries]	
Other cardiovascular event	[See above]	
Other event	[If cardiovascular procedure was performed, manual assignment of diagnoses and procedures based on free text entries; monetary valuation via unit costs]	
Death as primary event (sudden death)	[If cardiovascular procedure was performed, manual assignment of diagnoses and procedures based on free text entries; monetary valuation via unit costs]	

Abbreviations: SAE, serious adverse event; e-CRF, electronic case report form; ICD-10, International Statistical Classification of Diseases and Related Health Problems 10th Revision – German Modification 2021; STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; AP, angina pectoris; AV, atrioventricular; AF, atrial fibrillation; ICD, implantable cardioverter-defibrillator; CRT, implantable cardiac resynchronization therapy defibrillator; PCI, Percutaneous coronary intervention

[1] If PCI is documented as procedure

[2] Assumption: hypertension (more likely)

[3] All events assumed to be endocarditis because long length of hospital stay or event resulted in death (=indicator for severe course of disease)

[4] Used as initial diagnosis when cardiovascular procedure was performed (procedure is DRG-determining); otherwise, monetary valuation via unit costs since not further specified

[5] If resulted in death or duration of hospitalization >9 days (assumption: severe course of disease = pulmonary embolism)

Table S3 OPS codes assigned to cardiovascular procedures specified in the e-CRF

Cardiovascular procedure as specified in the e-CRF	OPS code	OPS - description
Heart valve surgery or percutaneous valve replacement or repair	5-354.y[1]	Other operations on heart valves, unspecified
Atrial fibrillation (AF) ablation	8-835.y	Ablation procedures for cardiac arrhythmias, unspecified
	5-371.y[2]	Surgical ablation procedures for cardiac arrhythmias, unspecified
Catheter ablation for other arrhythmias (not AF)	8-835.y	Ablation procedures for cardiac arrhythmias, unspecified
Coronary bypass surgery	5-361.y	Placement of an aortocoronary bypass, unspecified
Implantation of an ECG monitor device	5-377.8	Implantation of a pacemaker, defibrillator and event recorder; event recorder
Percutaneous coronary intervention	8-837.y	Percutaneous transluminal vascular intervention on heart and coronary vessels, unspecified
Percutaneous cerebrovascular or peripheral intervention	8-836.y	(Percutaneous) transluminal vascular intervention, unspecified
Implantation of a pacemaker, ICD, CRT or any other cardiac device	5-377.y	Implantation of a pacemaker, defibrillator and event recorder, unspecified
Electrical cardioversion	8-640.y	External electrical defibrillation (cardioversion) of the heart rhythm, unspecified
Vascular surgery	5-399.y	Other operations on blood vessels, unspecified
Cerebrovascular surgery or interventions for stroke or bleeding events		[Too unspecific. Assignment of DRGs depending on length of hospital stay and/or outcome after stroke or hemorrhage (DRGs for complex stroke treatments)]
Other cardiovascular intervention		[Manual assignment of OPS code(s) based on free text entries]
Cardiac transplantation[3]	5-375.y	Heart and heart-lung transplantation, unspecified

Notes & Abbreviations: The description of the procedures was freely translated from German. e-CRF, electronic case report form; AF, atrial fibrillation; ECG, electrocardiogram, ICD, implantable cardioverter-defibrillator; CRT, implantable cardiac resynchronization therapy defibrillator; DRG, diagnosis-related group; OPS, Operation and Procedure Classification System

[1] Since the majority of cases had "Pacemaker implantation" or "Any type of Cardiovascular surgery" as serious adverse event (SAE) type, it was assumed to be a cardiac surgery procedure

[2] If ablation was documented as "surgical" or SAE type was specified as "Any type of cardiovascular surgery"

[3] Not performed on any of the EAST-AFNET 4 participants

Table S4 Sensitivity analyses – Adjusted[a] incremental costs, effects and cost-effectiveness ratio for early rhythm-control (n=832) vs. usual care (n=832) in patients with early atrial fibrillation at 6 years follow-up

	Base case[b]	Variation of discount rate[b]		Including cost of rehabilitation and care post stroke/acute coronary syndrome[b]			Subsample (follow-up 72 < end of study)[c]	Hospitalizations monetarily valued via unit costs[b 2]
		0% discount rate	5% discount rate	Minimum scenario	Maximum scenario	Extreme scenario		
	Mean	Mean	Mean	Mean	Mean	Mean	Mean	Mean
	(95% CI[d])	(95% CI[d])	(95% CI[d])	(95% CI[d])	(95% CI[d])	(95% CI[d])	(95% CI[d])	(95% CI[d])
Total costs	2194	2158	1864	1855	1727	1313	3094	1353
	(-152, 4539)	(-269, 4585)	(-363, 4091)	(-493, 4203)	(-673, 4127)	(-1673, 4299)	(-149, 6337)	(-1090, 3797)
Years to primary outcome	0.19	0.20	0.17	0.18	0.18	0.18	0.20	0.19
	(0.03, 0.35)	(0.02, 0.37)	(0.02, 0.32)	(0.02, 0.34)	(0.02, 0.34)	(0.02, 0.34)	(-0.01, 0.42)	(0.03, 0.34)
Years survived	0.10	0.09	0.08	0.09	0.09	0.09	0.07	0.09
	(-0.01, 0.22)	(-0.03, 0.22)	(-0.02, 0.19)	(-0.03, 0.20)	(-0.03, 0.20)	(-0.03, 0.20)	(-0.08, 0.23)	(-0.02, 0.19)
ICER (€per year without a primary outcome)	11736	10895	10907	10243	9521	7179	15425	7248
ICER (€per life year gained)	21626	23050	23153	21727	20229	15401	42480	15505

Costs are reported in 2021 euros (€).

[a] results from seemingly unrelated regressions

[b] cost differences adjusted for peripheral artery disease at baseline; effect difference adjusted for age and peripheral artery disease at baseline (time to primary outcome) or age, peripheral artery disease, chronic obstructive pulmonary disease, malignant diseases, and valvular disease at baseline (years survived).

[c] cost differences adjusted for peripheral artery disease, hypertension, heart rhythm, and EQ-5D index at baseline; effect difference adjusted for age, peripheral artery disease, hypertension, and EQ-5D index at baseline (time to primary outcome) or age, heart rhythm, chronic obstructive pulmonary disease, and EQ-5D index at baseline (years survived).

[d] based on 1,000 bootstrapped replications

Table S5 Sensitivity analysis – Unadjusted costs (hospitalizations monetarily valued via unit costs) for early rhythm-control (n=832) vs. usual care (n=832) in patients with early atrial fibrillation at 6 years follow-up

	Early Rhythm Control	Usual Care	Difference	
	Mean	Mean	Mean	95% CI[a]
Medication	9870	8637	1233	73, 2392
Hospitalization	15210	14820	390	-1765, 2544
Total costs	25079	23457	1622	-846, 4090

Costs are reported in 2021 euros (€).

[a] based on 1,000 bootstrapped replications
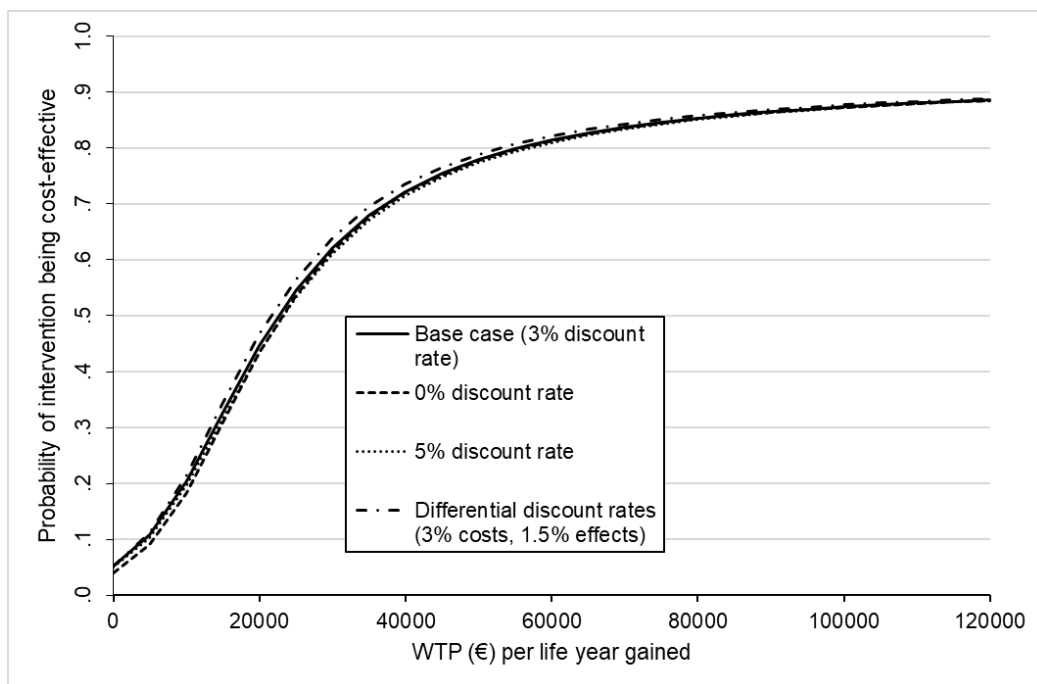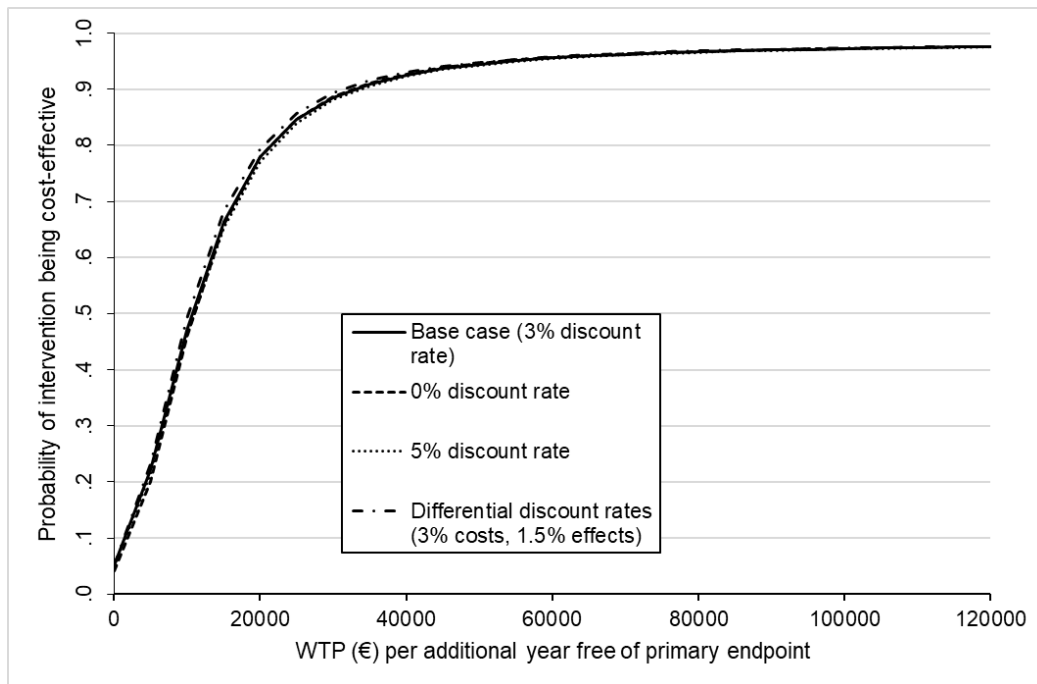
Figure S1 Sensitivity analyses – Cost-effectiveness acceptability curves for early rhythm-control (n=832) vs. usual care (n=832) in patients with early atrial fibrillation at 6 years follow-up. The probability that early rhythm-control is cost-effective compared to usual as the willingness to pay for each additional year without a primary outcome or life year gained is varied from €0 to €120 000.
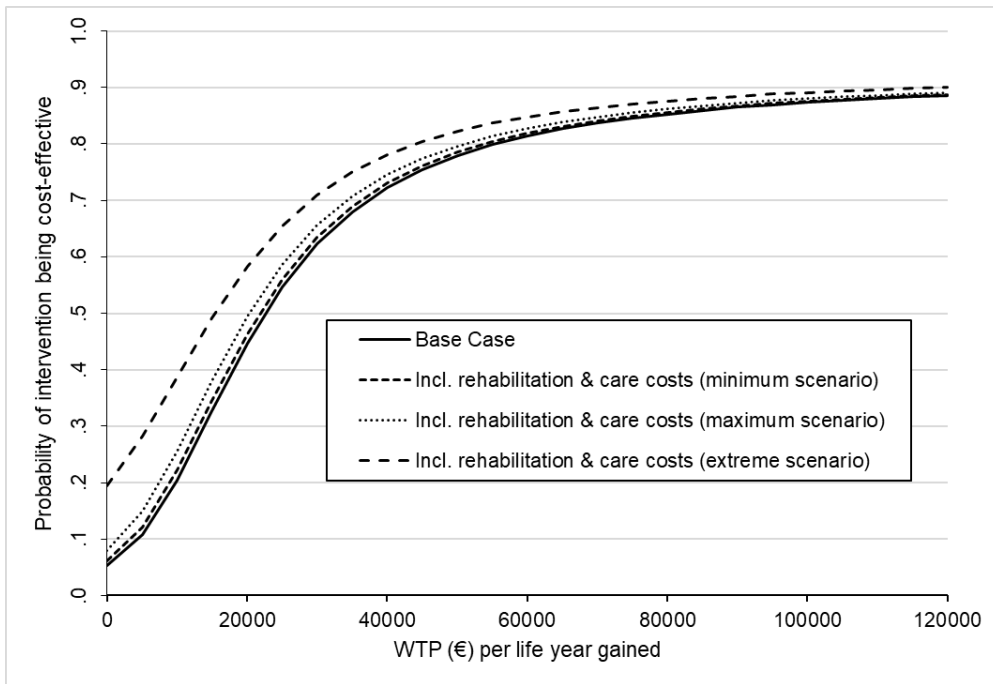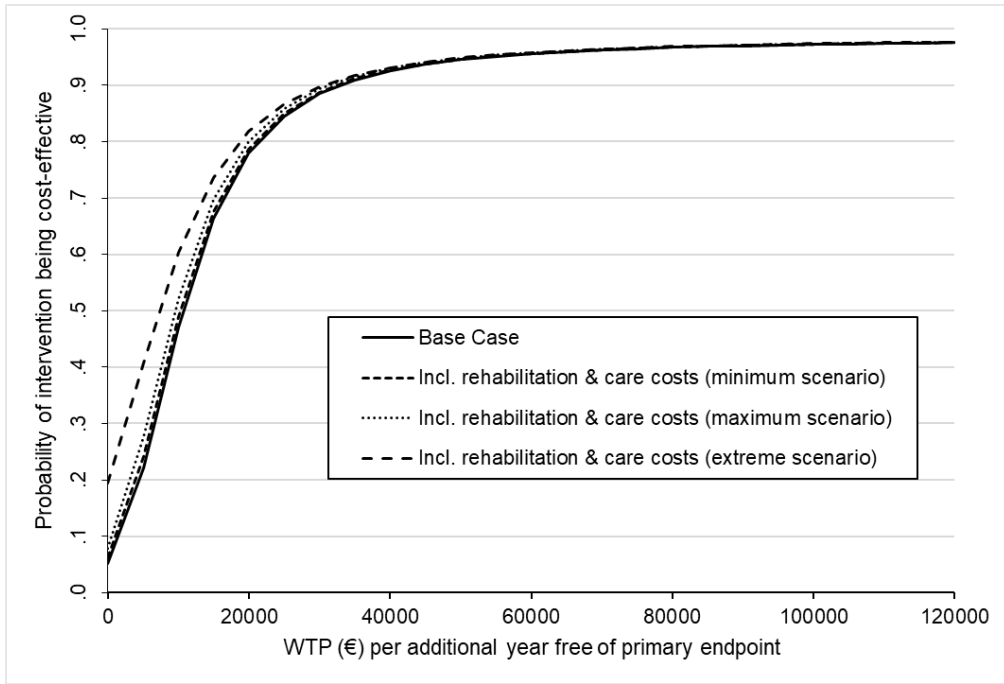
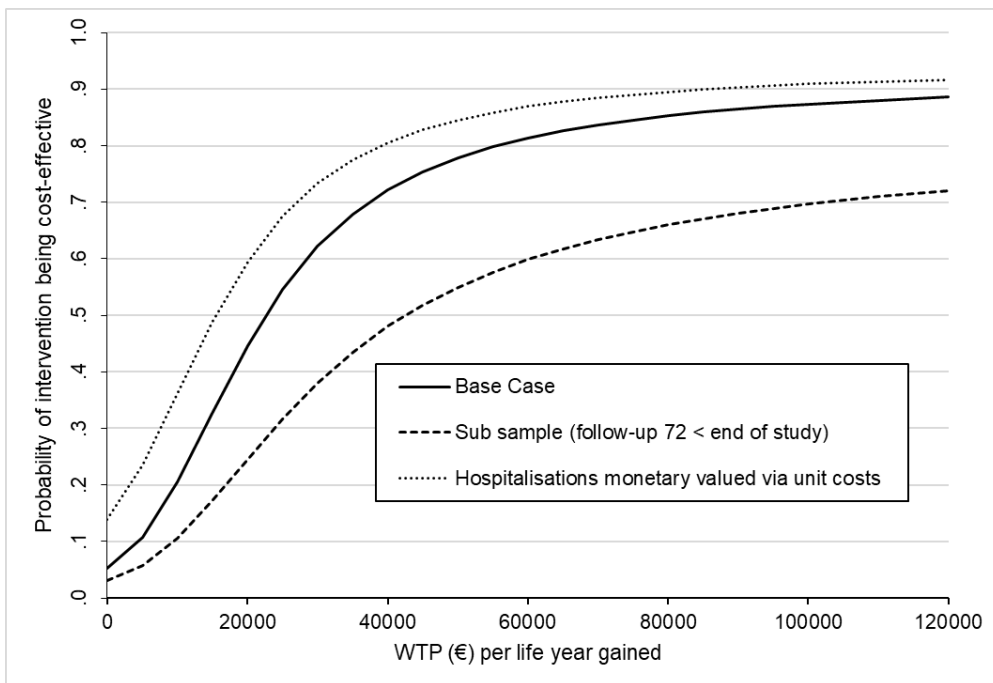**Figure S2** Sensitivity analyses – Cost-effectiveness acceptability curves for early rhythm-control (n=832) vs. usual care (n=832) in patients with early atrial fibrillation at 6 years follow-up. The probability that early rhythm-control is cost-effective compared to usual as the willingness to pay for each additional year without a primary outcome or life year gained is varied from €0 to €120 000. Minimum/maximum scenario: minimum/maximum reported rehabilitation and care costs in the literature. Extreme scenario: the typical care allowance for the highest care level for a person in an inpatient care facility in Germany is modelled to the total costs after an event.
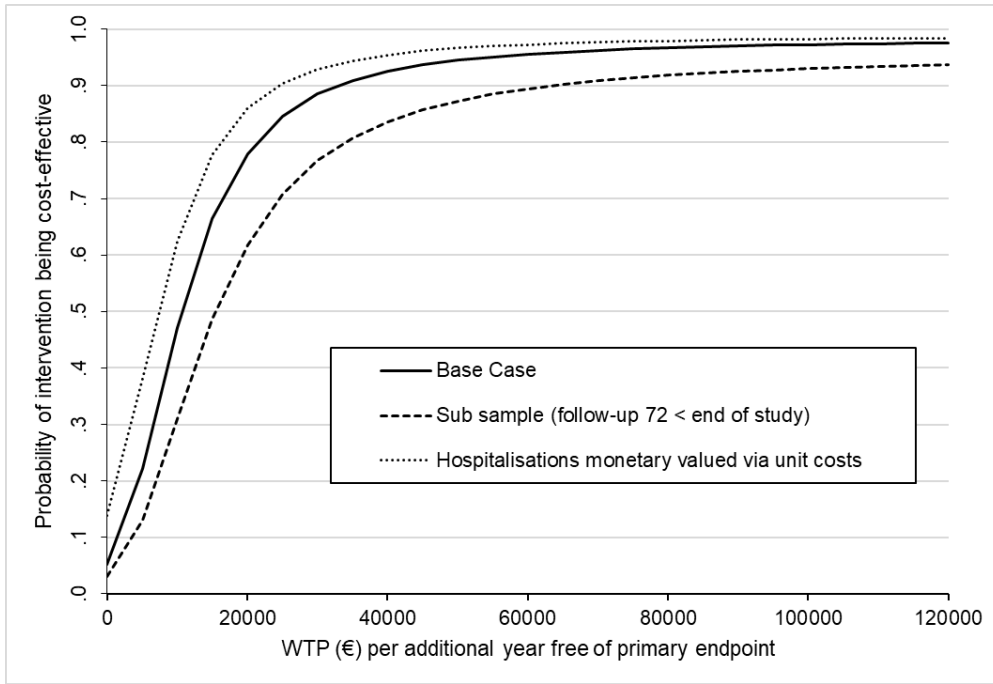
Figure S3 Sensitivity analyses – Cost-effectiveness acceptability curves for early rhythm-control (n=832 [n=423 in subsample]) vs. usual care (n=832 [n=429 in subsample]) in patients with early atrial fibrillation at 6 years follow-up. The probability that early rhythm-control is cost-effective compared to usual as the willingness to pay for each additional year without a primary outcome or life year gained is varied from €0 to €120 000.
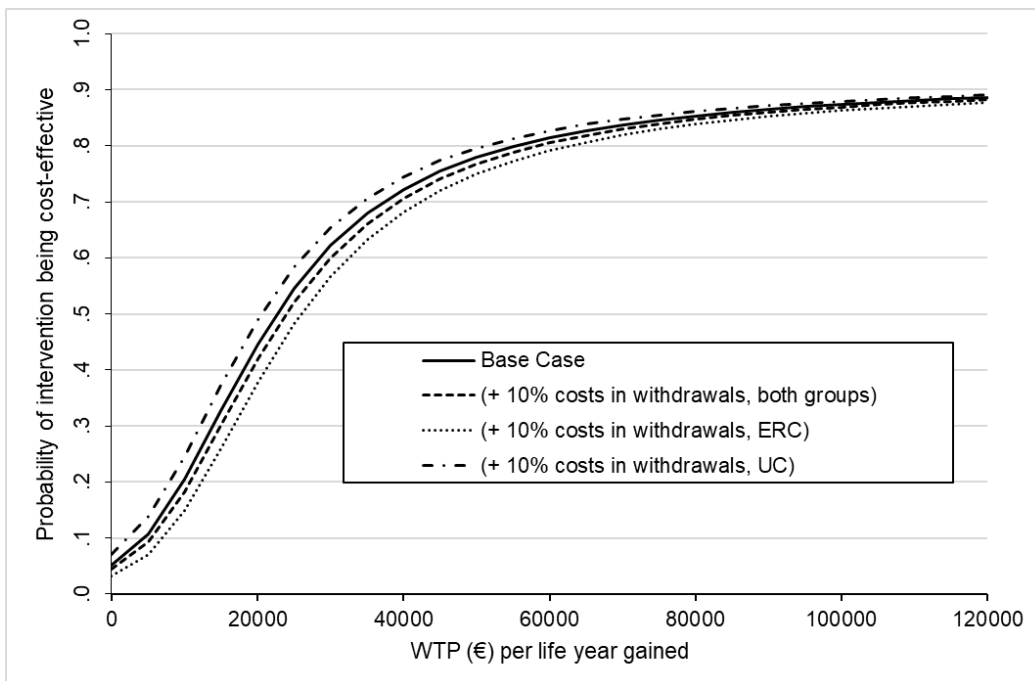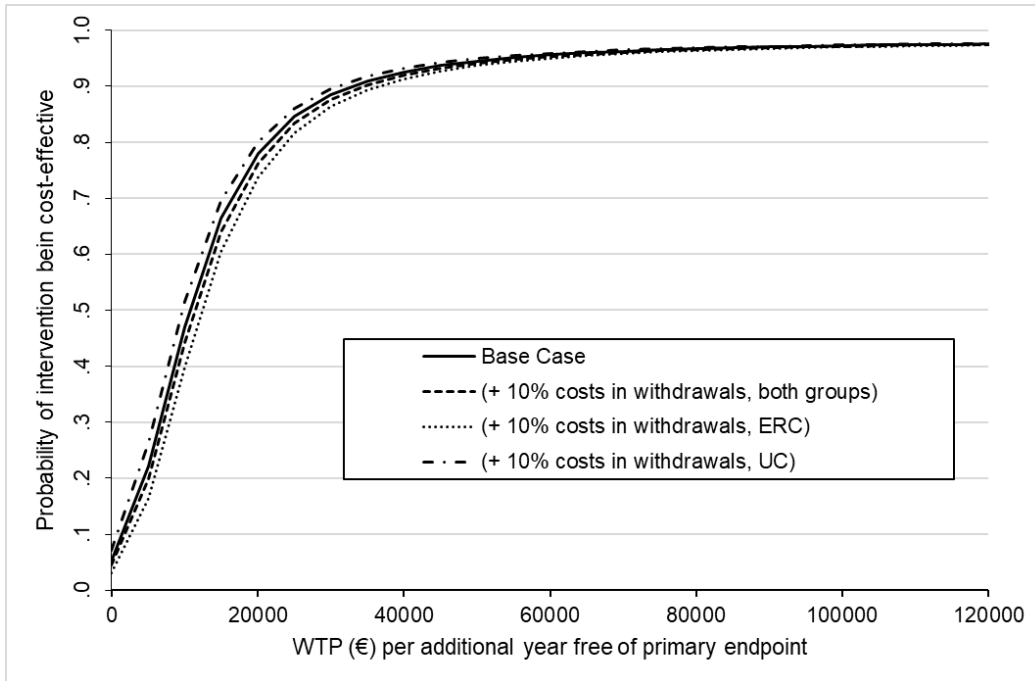
Figure S4 Sensitivity analysis – Cost-effectiveness acceptability curves for early rhythm-control (ERC, n=832) vs. usual care (UC, n=832) in patients with early atrial fibrillation under different missing not at random (MNAR) assumptions. Imputed total costs of withdrawals have been modified. Participants with missing values due to censoring at the end of the study were assumed to be missing at random (MAR).

References

1. Husereau D, Drummond M, Augustovski F, de Bekker-Grob E, Briggs AH, Carswell C, Caulley L, Chaiyakunapruk N, Greenberg D, Loder E, Mauskopf J, Mullins CD, Petrou S, Pwu RF, Staniszewska S. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 2022 Explanation and Elaboration: A Report of the ISPOR CHEERS II Good Practices Task Force. Value Health 2022;25(1):10-31.

2. Bock JO, Brettschneider C, Seidl H, Bowles D, Holle R, Greiner W, König HH. [Calculation of standardised unit costs from a societal perspective for health economic evaluation]. Gesundheitswesen 2015;77(1):53-61.

3. OECD. Inflation (CPI) (indicator) In; 2020.