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STATE OF THE ART REVIEW

Economic analyses in cardiac electrophysiology: from clinical efficacy to cost utility

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Abstract

Cardiac electrophysiology is an evolving field that relies heavily on costly device- and catheter-based technologies. An increasing number of patients with heart rhythm disorders are becoming eligible for cardiac interventions, not least due to the rising prevalence of atrial fibrillation and increased longevity in the population. Meanwhile, the expansive costs of healthcare face finite societal resources, and a cost-conscious approach to new technologies is critical. Cost-effectiveness analyses support rational decision-making in healthcare by evaluating the ratio of healthcare costs to health benefits for competing therapies. They may, however, be subject to significant uncertainty and bias. This paper aims to introduce the basic concepts, framework, and limitations of cost-effectiveness analyses to clinicians including recent examples from clinical electrophysiology and device therapy.

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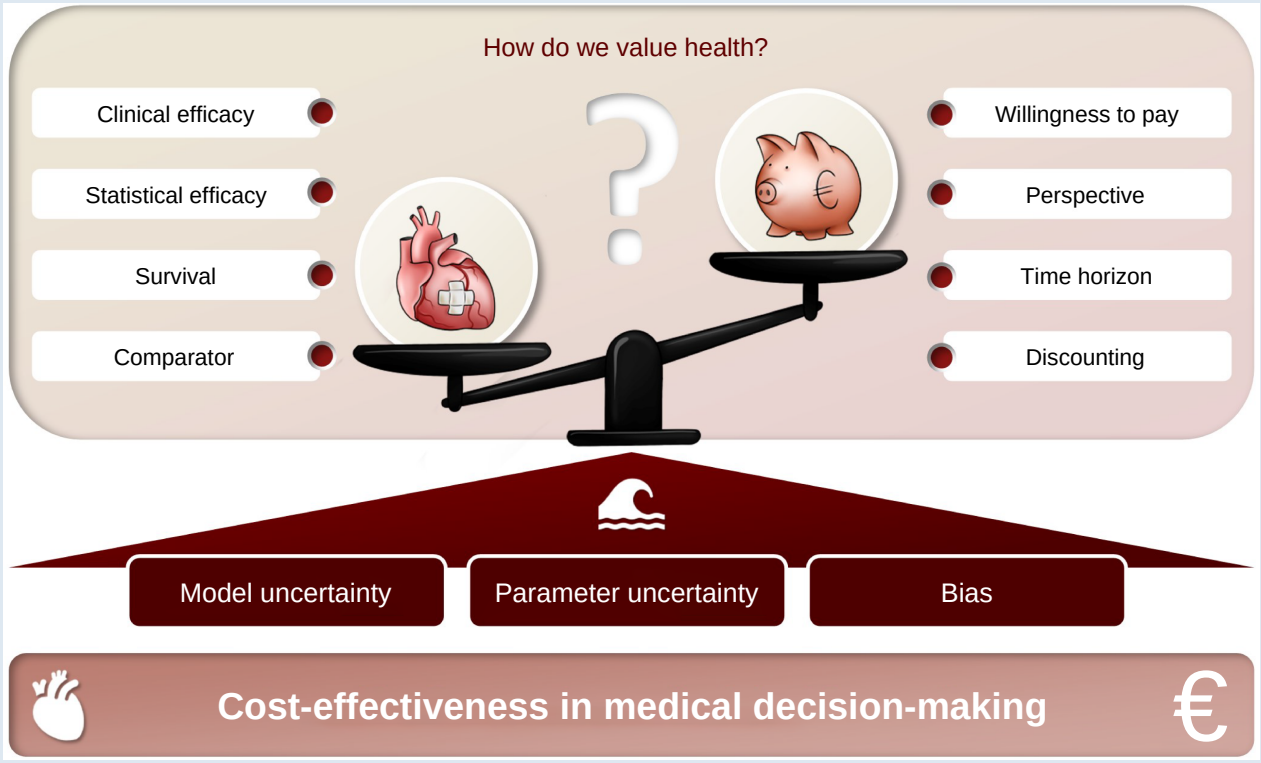
Graphical Abstract



Keywords Cost-effectiveness analysis • Quality-adjusted life year • Cardiac electrophysiology • Economy • Cost utility • Early rhythm control • Cardiac implantable electronic devices • Antibacterial envelope

Introduction

In a recent analysis from the European Society of Cardiology and Oxford University, the costs of cardiovascular care in Europe were estimated at €282 billion in 2021 alone[1]—and costs continue to ascend. This looming imbalance between societal resources and the costs of healthcare has heightened the demand for health economic evaluations. This implies that new interventions need not only be assessed within a context of clinical efficacy but also economic efficiency to ensure that healthcare is provided evenly, appropriately, and ingeniously.[2,3] Cost-effectiveness analyses (CEAs) are gaining awareness among healthcare professionals and acceptance into *clinical* scientific journals. To guide resource allocation, CEAs evaluate the comparative monetary costs of new interventions over the assumed health effects. The overall goal is to maximize value (i.e. health) for money. As such, they may facilitate or impede new treatments from being adopted into clinical care. This may occur at national health policy level but results from CEAs may also influence clinical practice guidelines,[4,5] and for many interventions in electrophysiology, the decision to accept or discard new technologies is taken at an institutional level. Hence, results from CEAs inform policymakers and clinicians alike. Despite their general appeal, CEAs may be subject to significant uncertainty and bias, which is easily obscured when results are presented. Moreover, the methodological principles underlying these models are unfamiliar to most non-economists. The aim of this paper is therefore to briefly introduce the basic concepts, framework, and limitations of CEAs including examples from recent applications within clinical electrophysiology and device therapy.

Economic models

This review will focus on CEAs, but common types of economic models are briefly outlined in *Table 1*. Cost-effectiveness analyses can be model based or performed directly from or alongside clinical trials. In many cases, trial data are insufficient for economic analyses, and it may be appropriate to source data from literature (e.g. survival with and without the intervention) to incorporate into decision models. The most common models are decision trees and Markov models (*Figure 1*).[6] In a decision tree, the flow of events is unidirectional: each sequential health state is assigned a probability, and each possible outcome is populated with specific costs.[7] The tree ends in a terminal node at which point the individual may die or return to the original health state (healthy). Markov models, in turn, are cyclic, and transitions from any (non-fatal) health state to another is allowed to occur in successive cycles with a fixed duration (often 1 year) until all cases reach the absorption state (often death). For this reason, Markov models are especially suited for diseases that involve *ongoing* risk. Important assumptions in the Markov model are that each state retains no memory of the previous state meaning that the probability of transitioning depends on the current state only, and the transition probabilities remain constant over time.

Costs and effects

Although effect estimates used in CEAs are ideally obtained from randomized clinical trials (RCTs), several limitations may arise. The intervention under investigation in a CEA is always compared to usual care. Conversion of trial data, which are obtained under strictly

Table 1 Four main types of economic analyses

Model	Purpose	Comments
Cost-effectiveness analyses (CEAs)	Measures differences in outcomes (costs and health benefits) of one or more health interventions compared to another (the *status quo*). Outcomes are measured in single, natural units (e.g. life years).	Comparisons across different health conditions and interventions are not straightforward.
Cost–utility analysis (CUAs)	Type of cost-effectiveness analysis that measures differences in outcomes of one or more health interventions compared to another (the *status quo*) in multiple dimensions of health (e.g. QALYs or DALYs).	Health outcomes are aggregated into a single index, which allows comparisons across different health conditions and interventions.
Cost–benefit analysis (CBA)	Measures differences in costs of one or more health interventions compared to another (the *status quo*), where both costs and outcomes (benefits) are assigned monetary values. In principle, CBAs assume that all health effects can be valued based on people's willingness-to-pay preferences.	Uses a single unit of measurement, which eases comparisons across different health conditions and interventions. However, individual willingness to pay is subjective and sensitive to external factors and can therefore be highly variable.
Cost–minimization analysis (CMAs)	Compares costs related to two interventions (including downstream costs) that are assumed equivalent in terms of health effects. The purpose is to ascertain the least costly alternative.	Can only be applied for interventions that infer identical outcomes. It is pivotal for these analyses that costs are determined accurately.

CBA, cost-benefit analysis; CEA, cost-effectiveness analysis; CMA, cost-minimization analysis; CUA, cost-utility analysis; DALY, disability-adjusted life year; QALY, quality-adjusted life year.

controlled settings, into real-world scenarios in cost-effectiveness models is not always straightforward. Trial populations are typically subject to selection and therefore not necessarily representative of their target populations. Moreover, the comparator arm in clinical trials may not reflect routine clinical practice, and this can cause discrepancy between the effect estimate and the calculated costs. Aside from selection, appropriate clinical outcomes used in RCTs may not be appropriate for CEAs. Examples might be freedom from device-detected atrial fibrillation (AF) recurrence in an ablation study, use of surrogate endpoints such as reduction in left ventricular ejection function (LVEF), or composite clinical endpoints including both fatal and non-fatal events (e.g. major cardiovascular events). Another challenge is to choose an appropriate time horizon. This needs to be sufficiently long to capture all relevant consequences in terms of costs and effects associated with the intervention—even if this is rarely the case when using RCT data. Again, the primary appeal of composite endpoints in RCTs is to increase statistical power, reduce follow-up duration, and limit trial-related costs.

Once the basic outline of the model has been established, costs must be estimated based either on direct medical costs (the healthcare payer perspective) or all costs including indirect non-medical costs (the societal perspective).[5] Although seemingly straightforward, it is often challenging to undertake: first, to identify which resources are relevant to include and, second, to accurately estimate the resources consumed.[8] Independent costs are rarely available, and many CEAs rely on less accurate reference costs or national tariffs based on diagnosis-related group (DRG) codes. When the time horizon extends beyond 1 year into the future, it is common practice to apply discounting to adjust for future costs and health effects. Annual discount rates of 3–3.5% per year are usually applied.[9] For example, the present value of €1000 in Year 2 would be €971 assuming a 3% discount rate [€1000 · $(1/1.03)^1$], or €863 in Year 6 [€1000 · $(1/1.03)^5$]—and so forth. The rationale behind discounting is to account for opportunity costs (*Figure 2*) and positive time preference, i.e. present benefits are generally preferred over future benefits. However, the relevance and/or level of discounting (including whether uniform or differential discounting on health and effects are more appropriate) has been heavily debated. This is because the dynamics of how costs and health are valued over time are complex, and discounting can have substantial impact on the outcomes when the time horizon is long.[10,11] Costs also vary significantly across healthcare systems, and this further complicates comparability and transferability of results from one healthcare system to another.

The incremental cost-effectiveness ratio

Cost-effectiveness analyses evaluate the *incremental* monetary costs per unit of *incremental* benefit; this defines the incremental cost-effectiveness ratio (ICER):

$$\text{ICER} = \frac{\Delta\ \text{Costs}}{\Delta\ \text{Health}},$$

where Δ indicates the difference in costs/health with the new intervention vs. usual care. The ICER thus estimates the proportional relationship between costs and different dimensions of health gained. The denominator may comprise single natural units (i.e. life-years gained or lives saved) or composites of two or more factors [i.e. quality-adjusted life years (QALYs) or disability-adjusted life years (DALYs)]. When the denominator incorporates multiple domains of health (quantity and quality), it is typically referred to as a cost–utility analysis (CUA), which can be considered a specific type of CEA. As such, the ICER does not constitute a single entity but a ratio of parameters that may on several levels be influenced by uncertainty. Inherently, if the denominator is small, the ICER becomes highly sensitive even to minute changes. Negative ICERs are not usually presented due to ambiguity; they may result from two possible scenarios: (i) the intervention is cheaper and more effective (negative incremental costs) or (ii) the intervention is more costly and less effective than the comparator (negative incremental health). Rather, in scenario i, the intervention is referred to as 'dominant' over the comparator, and in scenario ii, the intervention is 'dominated' by the comparator. Likewise,

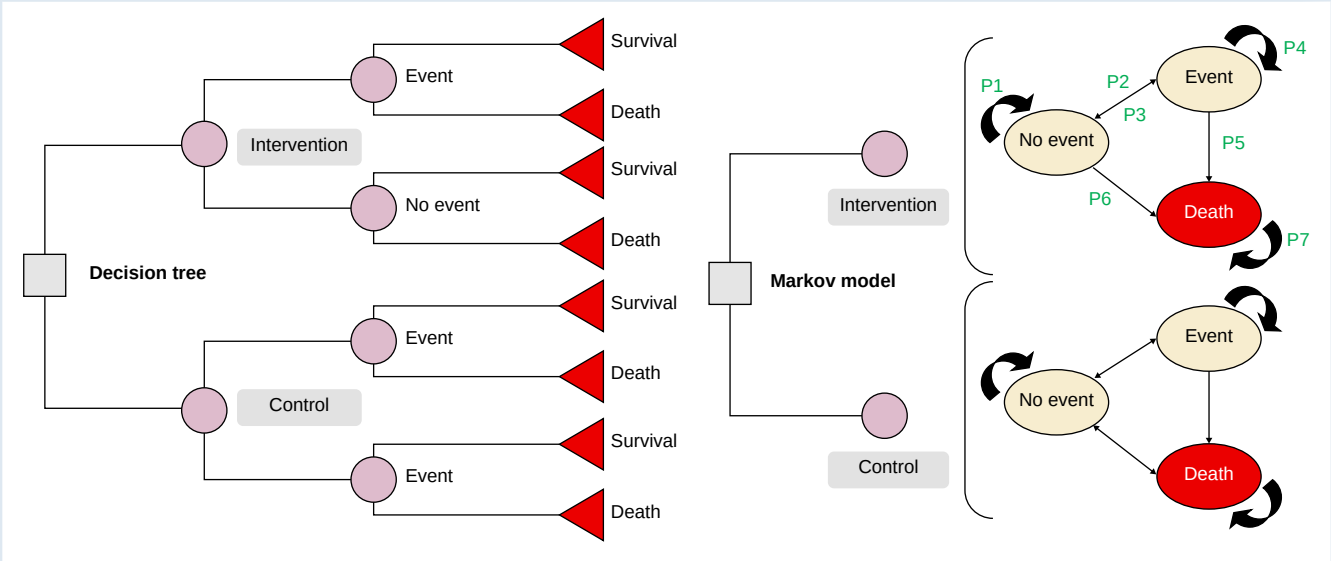


Figure 1 Example of a decision tree (left) and a simplified three-state Markov model (right). An important distinction between these two models is that decision trees are unidirectional, whereas Markov models are cyclic. The different disease states in the models should represent significant events both clinically and economically. Squares indicate decision nodes. Triangles indicate terminal nodes. P's indicate transition probabilities, which are usually estimated from literature. P7 is an absorptive state (death) for which the transition probability will always be 1.

interpretation of the ICER becomes counterintuitive if the intervention is both less effective and cheaper than its comparator.

The quality-adjusted life year and cost–utility analyses

To allow comparisons of cost-effectiveness across treatments and health conditions, it is necessary to aggregate health outcomes in a single index. This is needed because the concept of 'health' ideally encompasses more domains than simply 'absence of disease'. The QALY is an internationally recognized standard metric in CEAs, and several countries use 'costs per QALYs' as benchmarks for cost-effectiveness. For example, in the UK, use of QALYs is required by the National Institute for Health and Clinical Excellence (NICE) for health technology assessments. The QALY attempts to integrate survival with quality-of-life measures.[5,12] It is expressed in a scale ranging from 0 to 1, where 1 corresponds to utility of the best possible outcome (optimal health) and 0 is an arbitrary value that corresponds to the utility of being dead. To exemplify, if the health-related QALY year is 0.5 for a particular condition, 1 year of living with this condition will correspond to 0.5 years in perfect health. Quality-adjusted life years thus operate on an interval scale, and this implies that all QALYs are valued equally, e.g. a change from 0.1 to 0.2 is assumed equal to a change from 0.8 to 0.9.[13] This specific feature of the QALY has raised both moral and ethical debate, as well as operational concerns since quantity (survival time) is measured on a ratio scale.[12,13]

The concept behind QALYs is based in utilitarianism, and to estimate the QALY, you simply multiply the utility value of a given health condition with the years spent in this state (*Figure 3*). As such, the QALY represents quality-adjustment weights ('utilities') that when applied to 'time' provide a measure of 'health'.[14] There are various strategies to obtain these weights. Most commonly, responses from clinical quality-of-life questionnaires [usually using the EuroQol five-dimension questionnaire (EQ-5D)] administered to trial participants are used to estimate disease-specific quality of life.[12] These are then matched to national preferences obtained from general surveys. As previously addressed, quality of life will often vary over time, and for assessments over extensive time horizons, it is usual to discount QALYs by 3–3.5%[5,12] per year, assuming that immediate health benefits are generally preferred over longer-term effects.

Cost-effectiveness thresholds

Most new health interventions impose costs, and it remains a matter of judgement to decide whether the new intervention provides sufficient benefits to justify the added costs. To guide decision-makers, results from CEAs are often interpreted in relation to arbitrary cost-effectiveness thresholds, i.e. the fixed maximum amount a decision-maker is willing to pay for a new intervention. Incremental cost-effectiveness ratios that fall below the cost-effectiveness threshold are considered cost-effective and *vice versa* (*Figure 4*). Since they are not context specific and there is no scientific justification for determining these thresholds, they have fostered great debate.[15] Willingness-to-pay (WTP) thresholds vary considerably across healthcare systems, and not all countries have established thresholds for cost-effectiveness—such is the case for Denmark and Germany.[16,17] Moreover, they encourage simplistic interpretations of complex issues. To exemplify the substantial variation in *acceptable* costs, NICE in the UK proposed a threshold range of £20–30 000,[18] the World Health Organization (WHO) promotes a threshold of three times the gross national product per capita as a guide (in Denmark, this would imply an upper bound of ~€200 000), and in the USA, thresholds ranging from $50 000 to $150 000 per QALY have been considered economically acceptable.[19]

Sensitivity analyses

It is common to define a base case (or reference case) based on the best available data. However, as can be deduced from the above, uncertainty may arise from multiple levels.[20] To quantify the level of uncertainty, probabilistic sensitivity analyses (PSAs) apply repeated random sampling to generate a distribution of ICER estimates that can be graphed

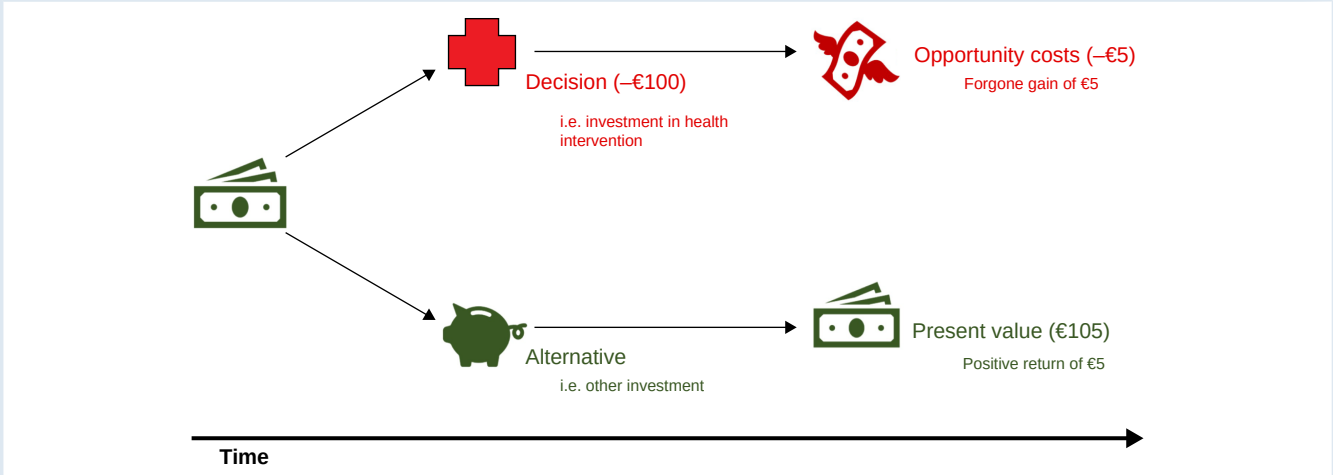


Figure 2 Opportunity costs are the potential profits forgone by choosing one alternative over the other.

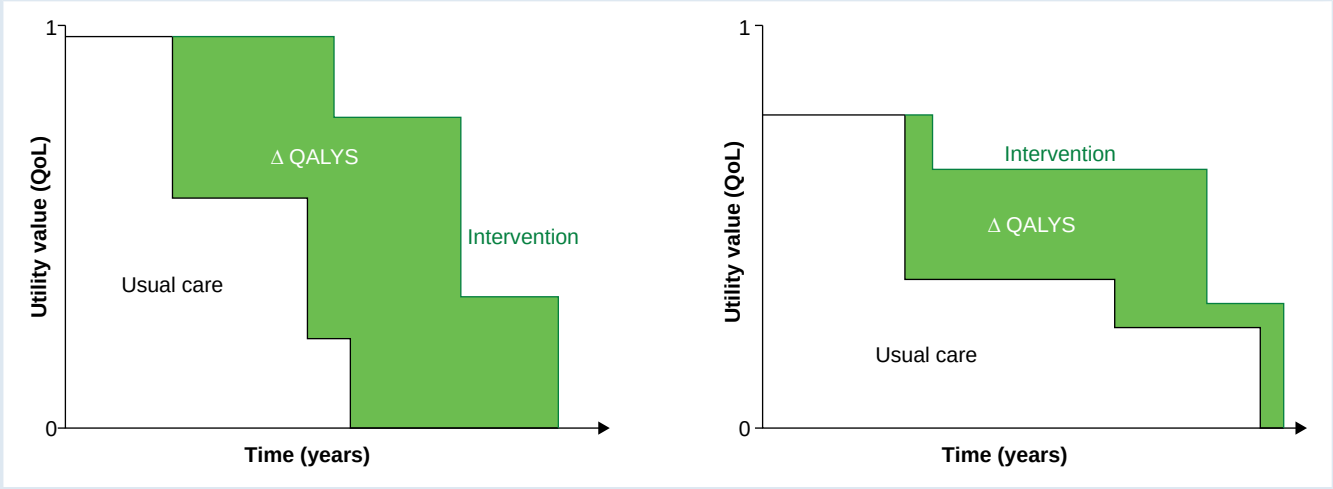


Figure 3 Two simplified schematic overviews of calculation of QALYs with usual care vs. the intervention under investigation. Quality-adjusted life years are estimated by multiplying utility weights associated with a given health condition with the time spent in this state. ΔQALY indicates QALY gained. A utility value of 0 corresponds to the utility of being dead. QALYs, quality-adjusted life years; QoL, quality of life.

on the cost-effectiveness plane (*Figure 4*) or used to construct cost-effectiveness acceptability curves (CEACs). Cost-effectiveness acceptability curves graphically relate the uncertainty of results (or the probability of cost-effectiveness) over a range of possible cost-effectiveness thresholds (*Figure 4*), whereas the cost-effectiveness plane is used to display differences in costs and health effects in two planes. Uncertainty in the cost-effectiveness plane can be deduced from the dispersion of points, 'the cloud' (each point representing one iteration), in the plot. In PSAs, model parameters are presented as distributions (normal, Weibull, gamma etc.) around the point.

Many studies also present results from deterministic sensitivity analyses (DSAs). Here, individual or sets of model parameters are allowed to vary across a prespecified range (keeping the rest constant) to assess the relative influence of misspecification in the base case on the outcome, including whether this would have been sufficient to alter the study conclusions. The range of possible outcomes can be determined based on expert opinion or often simply according to the 95% confidence intervals of the point estimates. Because DSAs are typically univariate (one way), these may be more likely to underestimate uncertainty.[20] Multiway DSAs are rarely reported as they are both difficult to present and to interpret, especially if included parameters correlate. Results from DSAs can be visualized using line or bar charts and sometimes summarized in tornado diagrams (*Figure 5*).

Examples from clinical electrophysiology

Below we briefly showcase two examples of economic analyses in clinical electrophysiology. First, we introduce a protocolled subanalysis to The Early Treatment of Atrial Fibrillation for Stroke Prevention Trial (EAST-AFNET 4). Atrial fibrillation affects approximately one-third of individuals of European ancestry, and the prevalence of AF is projected to increase. Hence, AF represents a major clinical and health economic

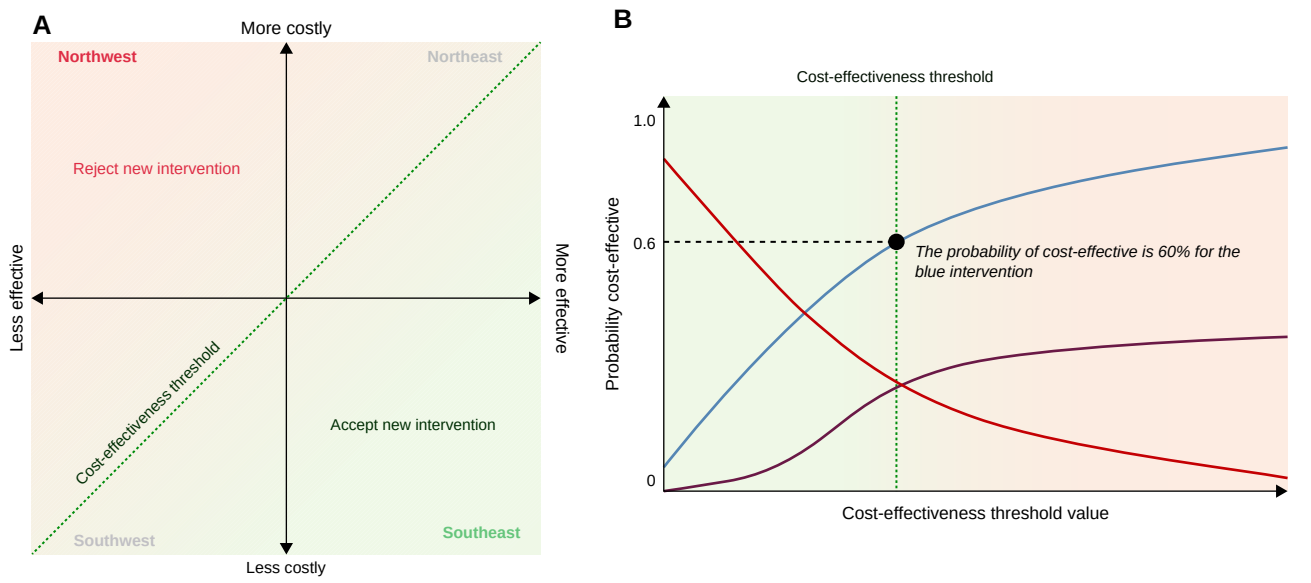


Figure 4 (*A*) The cost-effectiveness plane. The *Y*-axis indicates incremental cost. The *X*-axis indicates incremental health benefits of the new intervention. (*B*) The CEAC. Note that the CEAC also provides information about the error rate (1-p). Solid lines indicates an intervention. As shown, the probability of cost-effective is 60% at the given cost-effectiveness threshold, and accordingly, the probability of not being cost-effective is 100% – 60% = 40%. CEAC, cost-effectiveness acceptability curve.

challenge.[21] Early intervention and risk factor control are believed to reduce incident AF,[21,22] and economic analyses of AF interventions carry significant societal interest. Second, we present an economic evaluation of the antibiotic-eluting envelope. While clinical efficacy is well established, the economic efficiency of the envelope became the pivot of debate and a central argument against its uptake into clinical care at many centres. Finally, we evaluate the role of catheter ablation for ventricular tachycardia (VT) in coronary artery disease.[23] A series of moderately sized RCTs demonstrated that VT ablation reduces VT recurrence and appropriate implantable cardioverter defibrillator (ICD) therapy but with no significant effect on mortality or quality of life.[24] Meanwhile, ablation is associated with high economic costs and a non-negligible risk of complications.

Early rhythm control in atrial fibrillation

In a study recently published in *Europace*, Gottschalk *et al.*[17] completed a planned trial-based economic evaluation of early rhythm control compared to usual care in AF based on data from EAST-AFNET, a multinational randomized controlled trial.[25] The main trial demonstrated that an early rhythm control strategy (pharmacological or ablation) reduced the risk of the primary outcome (a composite of cardiovascular death, stroke, or hospitalization for worsening heart failure or acute coronary syndrome) by ~20%. Observational cohort studies demonstrated consistent results.[26–28] The cost-effectiveness study was based on the German patient subsample comprising nearly 60% of the total population and was conducted from the German healthcare payer perspective over a 6-year time horizon. Costs were restricted to hospitalizations and medication costs estimated based on DRG taxes with deductions and surcharges according to length of hospital stay and considering the individual revenue of each hospital. Correction for baseline imbalances was obtained using regression-based methods. Incremental cost-effectiveness ratios were reported per life gained and per year free from the primary outcome, and the study assumed a WTP value of €55 000 per year. Quality of life did not differ between treatment groups in the main study and was not assessed in the CEA. The study was reported in accordance with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS).[29] To evaluate robustness of the base-case results, scenario analyses, univariate DSAs, and PSAs were performed. Appropriate measures of uncertainty were reported throughout. Probabilistic sensitivity analysis results were visually displayed on the cost-effectiveness plane and using CEACs. The estimated ICERs for early rhythm control were €10 638 per year free of the primary outcome and €22 536 per life year gained. The probabilities of cost-effectiveness at a WTP ≥€55 000 were estimated at 95 and 80%, respectively. Hence, the study indicated that an early rhythm control strategy is associated with increased costs, but—assuming a WTP of ≥€55 000—they concluded that this strategy has a high probability of being cost-effective in the German healthcare system.

The study is well performed, transparently reported, and draws on the advantages of having large-scale trial data available, albeit also its limitations. Composite endpoints are not ideal for CEAs as non-fatal and fatal events can rarely be considered equal, and the time horizon was restricted to 6 years. Again, Germany has no established threshold for cost-effectiveness,[30] although ranges between €50 and €55 000 per QALY are often assumed for reporting purposes. As also addressed by the authors, costs per QALY were not used as an outcome measure, which limits comparability across studies including the applicability of a threshold commonly used with reference to QALYs. Considering results from the quality-of-life assessments in the main study, application of QALY weights to the reported ICERs would likely produce substantially higher ICERs. Furthermore, the treatment intervention in EAST-AFNET 4 comprises a composite of multiple possible treatment modalities [different types of antiarrhythmic drug (AAD), cardioversions, and/or AF ablation], and a change in the ratio of pharmacological rhythm control to ablation procedures could have substantial impact on the estimated costs—and perhaps also on the observed effects. Moreover, since AF is a chronic condition, longer-term

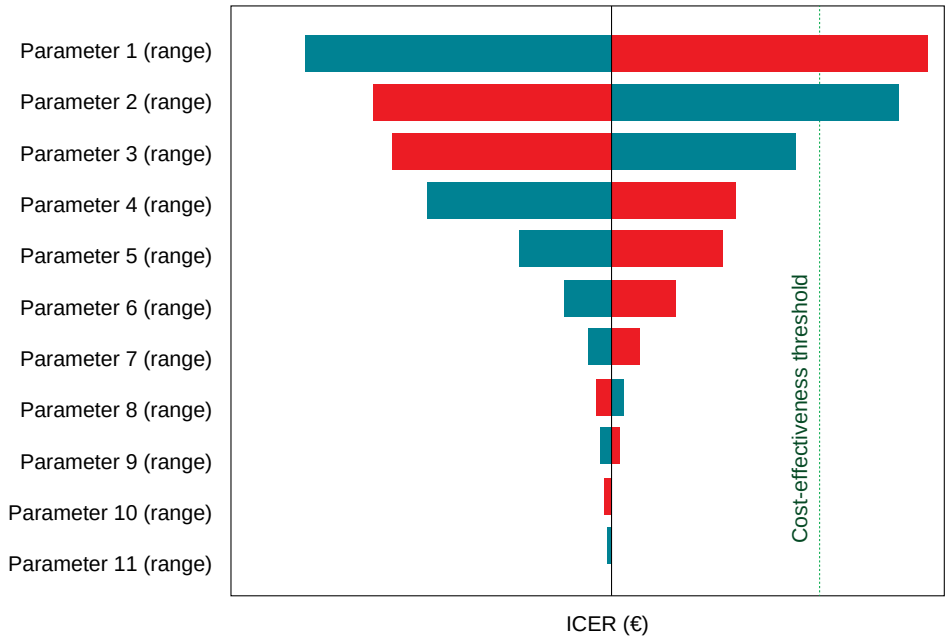


Figure 5 Example of tornado diagram. Tornado diagrams are used to depict results from one-way sensitivity analyses. The parameters in a tornado diagram are sorted from the highest (top) to the lowest range. The bars visually display which parameters have the strongest influence on the outcome; as shown, a change in Parameters 1 and 2 could potentially influence the conclusions of the analyses. Red and turquoise colours indicate the highest vs. the lowest values of each range.

effects and costs are of interest, and these were not assessed. Patients included in the EAST-AFNET 4 had a mean age of 70 years, and many patients presenting with early AF are <65 years and can expect a relatively long duration of therapy. Pharmacological rhythm control often requires ambulatory follow-up visits throughout the duration of treatment, and AF recurrence is not uncommon even after AF ablation. Insufficient follow-up time could therefore both under- and overestimate the downstream benefits of an early rhythm control strategy.

The antibiotic-eluting envelope

Cardiac implantable electronic device (CIED) infections are feared complications to CIED therapy. They are associated with high patient morbidity, mortality, and substantial economic costs as they generally warrant prolonged hospitalization, an inherent requirement for CIED extraction and (usually) a later reimplantation, and patients retain higher complication rates in the aftermath of CIED infections—on the short and on the long term.[16,31–34] The issue with CIED infections is that they are in nature iatrogenic, which only increases the incentive for prevention. Aside from sterile surgical technique and pre-procedural antibiotic prophylaxis, few preventive measures are evidence based.[35] In 2019, the Worldwide Randomized Antibiotic Envelope Infection Prevention Trial (WRAP-IT) demonstrated clinical efficacy of the antibiotic-eluting envelope for selected moderate- to high-risk CIED procedures (HR 0.60, 95% CI 0.36–0.98),[36] however, at an absolute risk reduction of only 0.5% corresponding to a number needed to treat of 200. This raised cost-effectiveness concerns[37–39] and speculations about whether results from WRAP-IT were transferable to higher risk settings, which would imply a more attractive cost-effectiveness profile as the envelope represents a costly intervention to prevent rare, but serious events.[40,41] Several studies since evaluated the economic efficiency of an envelope in various subpopulations of CIED patients and across different healthcare settings[16,39,42–48]; *Table 2* provides an overview of results from published cost–utility assessments of the absorbable antibacterial envelope, excluding two studies that did not estimate cost utility.[48,49]

Four of six studies used effect estimates derived from WRAP-IT[39,42,43,46] and/or the same basic decision tree model,[16,42–44] and five of six used utility estimates from WRAP-IT.[16,39,42,43,46] It was consistent that inclusion of all patients eligible for WRAP-IT was associated with high costs (112 000 USD to 274 000 CDN per QALY) whereas analyses based on patient subgroups with higher infection risk estimated ICERs below most established cost-effectiveness thresholds. The key limitations of these studies were, however, that they were based on effect estimates obtained from observational data,[16] from which causality cannot be inferred, or from the complete and multinational WRAP-IT population and, hence, not the subpopulation under investigation.[42,46] Despite this, multiple observational studies support that an envelope reduces infection risk after high-risk CIED implantations by 30–70% in various CIED subpopulations. Of interest, across settings and subgroups, the costs of a CIED were highly variable according to local context and to whether an extraction procedure was performed, and model uncertainty was high. Thus, even when comparable outcomes measures are applied (here, costs per QALY), straightforward comparisons are seldom possible, and when the outcome is rare, the uncertainty in the economic models is often also substantial. Finally, both examples included in this review take on a healthcare payer perspective, and hence, consequences to these interventions beyond the healthcare sector were not explored, although these may be of crucial importance for decision-making.

Ventricular tachycardia ablation in coronary artery disease

Guidelines recommend catheter ablation over escalated AAD therapy in ICD carriers with coronary artery disease and recurrent sustained

Table 2 Published papers evaluating the cost utility of the antibiotic-eluting envelope for the prevention of cardiac implantable electronic device infections

Study and country	Target population	Effect estimate	Model	Time horizon	Perspective	Infection-related costs Base case	Cost-effectiveness threshold per QALY gained	ICER (costs/QALY gained) Base case
Kay *et al.*[44] 2018 UK	Patients receiving an IPG, ICD, CRT-P, or CRT-D device	Observational data	Decision tree model	1 year	UK national health service perspective	Not reported	£30 000	Combined: £7 IPG: £46 548 ICD: dominant CRT-P: £21 768 CRT-D: dominant
Wilkoff *et al.*[43] 2020 USA	Patients undergoing CIED reoperation procedures or *de novo* CRT-D implantation	WRAP-IT	Decision tree model	Lifetime	US integrated payer–provider network perspective	No extraction: $16 592 Extraction without replacement: $45 694 Extraction with replacement: $67 586	$150 000	$112 603
Boriani *et al.*[42] 2021 UK, Germany, Italy	High-risk subgroups from WRAP-IT stratified by device type (high- vs. low-power devices)[a]	WRAP-IT	Decision tree model	Lifetime	UK, Italian, and German healthcare sector perspectives	Depending on scenario: UK: £14 466–37 633 Italy: €27 235–45 560 Germany: €23 429–42 921	UK: £30 000 Italy: €40 000 Germany: €50 000	Depending on subgroup: UK: £4067–57 270 Italy: €522–62 381 Germany: €4430–66 179
Rennert-May *et al.*[39] 2021 Canada	Patients undergoing CIED reoperation procedures or *de novo* CRT-D implantation	WRAP-IT	Decision tree model	1 year	Canadian healthcare sector perspective	$91 957 (over a year) + $1386 (envelope)	None defined	Combined: $274 416
Modi *et al.*[46] 2022 USA	Patients with heart failure and reduced ejection fraction undergoing ICD or CRT *de novo* or replacement procedures	WRAP-IT	Markov model	Lifetime	US healthcare sector perspective	$43 047 (hospitalization) + $320 173–32 810 (generator replacement)	$100 000	*De novo*: $112 000 CIED reoperation: $54 000
Frausing *et al.*[16] 2023 Denmark	Patients undergoing CRT reoperations	Observational data	Decision tree model	Lifetime	Danish healthcare sector perspective	CRT-P: €40 765 CRT-D: €50 366 (total costs)	€34 125	Combined: €12 022 CRT-P: €29 177| CRT-D: €6277

CIED, cardiac implantable electronic device; CRT-P/-D, cardiac resynchronization therapy pacemaker/-defibrillator; ICD, implantable cardioverter defibrillator; ICER, incremental cost-effectiveness ratio; IPG, implantable pulse generator; QALY, quality-adjusted life year; WRAP-IT, Worldwide Randomized Antibiotic Envelope Infection Prevention Trial.

[a]Subgroups: Patients with a Prevention of Arrhythmia Device Infection Trial (PADIT) score ≥5, ≥6, or ≥7, a history of immunosuppressive therapy, ≥2 previous procedures, previous device infection, replacement device, or generator replacement with lead modification. All analyses were stratified by device type.

monomorphic VT despite chronic amiodarone therapy.[50] Although several moderately sized RCTs demonstrated that ablation reduces VT recurrence and appropriate ICD shock therapy, a recent meta-analysis indicated no effect on mortality or overall quality of life over AAD therapy in patients with ICDs, and this calls into question the cost utility of such intervention. Two recent CUAs based on RCTs evaluated the cost-effectiveness of VT ablation in this patient group—reaching conflicting conclusions. One was a trial-based CUA based on the Ventricular Tachycardia Ablation versus Escalated Antiarrhythmic Drug Therapy in Ischemic Heart Disease (VANISH) trial[51,52] and, the other, a Markov model based on data from multiple RCTs.[53]

In the CUA based on results from VANISH, Coyle *et al.*[52] determined that in patients with ICDs and coronary artery disease who had VT despite chronic AAD therapy, catheter ablation is likely to be cost-effective compared to escalated AAD therapy. In the main study, VT ablation reduced the rate of the primary composite endpoint (cardiac death, appropriate ICD therapy, and VT storm) by 28% (HR 0.72, 95% CI 0.53–0.98); however, there were no significant differences in mortality or overall health-related quality of life between groups.[51,54] For the CUA, results were weighted according to subgroup (amiodarone- or sotalol-refractory VT) as subgroup analyses indicated a significantly greater improvement with catheter ablation in patients with amiodarone-refractory VT. The study was completed taking the Canadian healthcare perspective, and the time horizon was 36 months. Information about quality of life (using the EQ-5D questionnaire) and resource expenditure was collected at each follow-up visit. Ablation produced greater QALYs than escalated AAD therapy (1.63 vs. 1.49, ΔQALY 0.14) and higher costs ($65 126 vs. $60 269, Δcost $4857). Probabilistic sensitivity analyses indicated that at a WTP of $50 000 per QALY, the probability of cost-effectiveness was only 57%, i.e. indicative of substantial uncertainty. Nevertheless, the overall ICER of $34 057 for the base-case analysis suggested that catheter ablation was cost-effective in this scenario.

On the contrary, Chen *et al.*[53] later evaluated the cost-effectiveness of VT ablation vs. AAD therapy concluding that the probability of cost-effectiveness was only 11% in the UK healthcare setting assuming a WTP of £30 000 per QALY. On this basis, cost-effectiveness was deemed unlikely. The study applied a decision-analytic Markov model with a 5-year time horizon (60 cycles with a duration of 1 month). There were five possible health states in each treatment arm: (i) death, successful ablation, successful ablation with adverse event, repeat ablation, and readmission or (ii) death, AAD maintenance, AAD maintenance with adverse event, readmission, and switch to ablation. Inputs for the model were predominantly informed by data from RCTs.[51,55–59] While the difference in costs between the two arms was modest (£5657), the difference in QALY was only 0.039 corresponding to an ICER of £144 150—far exceeding the acceptable WTP threshold in the UK. This result was unsurprising: no RCT has demonstrated a survival benefit with ablation over AAD therapy in patients with ICDs,[60] and the effects shown on quality-of-life measures have been marginal. Hence, the denominator of the ICER (ΔQALY) will be small and depend exclusively on sufficiency of the quality-of-life outcomes.

However, regardless of cost-effectiveness in the population at large, catheter ablation may be the only remaining treatment option for certain patients, and in VANISH, analyses indicated greatest benefit—clinically and economically—of early ablation in the subgroup of patients with amiodarone-refractory VT. Timing of ablation, duration of follow-up, and more meticulous assessment of quality-of-life measures can significantly influence the cost-effectiveness profile of this intervention. As the authors, Chen *et al.*,[53] specifically highlight in their final call for standardization and optimization of the collection of patient-reported outcomes in clinical trials, there remain considerable inaccuracies and knowledge gaps in the reporting of quality of life. This is a crucial parameter from the patient perspective and one that may critically influence CEAs and, consequently, whether or how new interventions are adopted into clinical care.

Limitations of cost-effectiveness analyses

Although CEAs are seemingly very simple (divide costs by health outcomes), many assumptions underlie these models, and the longer the time horizon, the greater potential for error. Model-based approaches usually require inputs from multiple sources; any bias (e.g. selection bias in RCTs or confounding in observational studies) and statistical uncertainty in the model parameters will be carried forward to the economic model. Moreover, it is important to recognize that all modelling essentially reduces clinical decision-making to a finite number of decisions, which will never reflect real-world scenarios. Therefore, it is important to recognize both model uncertainty (the simplified clinical case scenario) and parameter uncertainty, which is uncertainty related to the input we feed into the model. Non-homogenous cost data and differences in healthcare systems further imply that results from CEAs are not easily generalizable to other healthcare settings, and hence, they are mainly valid within the context of their conduct. Aside from imprecision or even bias in the model and modelling parameters, CEAs have also been subject to criticism directed towards their basic concepts of value: (i) their utilitarian approach to decision-making healthcare (i.e. the moral choice is that which 'produces the greatest good for the greatest number') and (ii) the validity (philosophical, moral, and ethical) of using QALYs to inform healthcare decisions.[12]

Finally, several studies associated industry sponsorship with more favourable outcomes in CEAs, and this was recently substantiated in a large registry-based analysis including almost 6000 published CEAs.[61] Specifically, sponsored model-based studies were significantly more likely to report lower ICERs and more likely to conclude the intervention was cost-effective than non-industry sponsored CEAs. Increased transparency in reporting from these models using standardized checklists (e.g. CHEERS as exemplified by Gottschalk)[29] or society recommendations (e.g. as proposed by Boriani *et al.*[3] under commission from the European Heart Rhythm Association), pre-registration of study protocols, or open-source analytical tools to further increase comparability and reproducibility of results are possible solutions—preferably combined with dedicated involvement from clinicians during modelling to ensure reliable and realistic model scenarios.

Conclusions

To conclude, CEAs are performed to guide resource allocation in healthcare but are imperfect by nature. In CEAs, perspective matters, setting matters, scope matters, and imprecision matters; cautious interpretation of these analyses is strongly advised, and the level of confidence should be guided by the quality of information used to model these outcomes. For physicians especially, they invite reflections beyond clinical efficacy and utility; what is *value* in healthcare, how do we assess it, and importantly, what are the economic costs and downstream societal implications of the care at our disposal? Clinician involvement in the conduct of CEAs is key to determine the clinical framework within which results can meaningfully be interpreted.

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Data availability

No new data were generated or analysed in support of this research

References

1. Luengo-Fernandez R, Walli-Attaei M, Gray A, Torbica A, Maggioni AP, Huculeci R *et al.* Economic burden of cardiovascular diseases in the European Union: a population-based cost study. *Eur Heart J* 2023;**44**:4752–67.
2. Boriani G, Biffi M, Martignani C, Valzania C, Diemberger I, Bertini M *et al.* Is cardiac resynchronization therapy cost-effective? *Europace* 2009;**11**:v93–7.
3. Boriani G, Maniadakis N, Auricchio A, Müller-Riemenschneider F, Fattore G, Leyva F *et al.* Health technology assessment in interventional electrophysiology and device therapy: a position paper of the European Heart Rhythm Association. *Eur Heart J* 2013;**34**:1869–74.
4. Garbi M. National Institute for Health and Care Excellence clinical guidelines development principles and processes. *Heart* 2021;**107**:949–53.
5. Sanders GD, Neumann PJ, Basu A, Brock DW, Feeny D, Krahn M *et al.* Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: second panel on cost-effectiveness in health and medicine. *JAMA* 2016;**316**:1093–103.
6. Gupta N, Verma R, Dhiman RK, Rajsekhar K, Prinja S. Cost-Effectiveness analysis and decision modelling: a tutorial for clinicians. *J Clin Exp Hepatol* 2020;**10**:177–84.
7. Briggs A, Sculpher M. An introduction to Markov modelling for economic evaluation. *PharmacoEconomics* 1998;**13**:397–409.
8. Miners A. Estimating 'costs' for cost-effectiveness analysis. *PharmacoEconomics* 2008;**26**:745–51.
9. Severens JL, Milne RJ. Discounting health outcomes in economic evaluation: the ongoing debate. *Value Health* 2004;**7**:397–401.
10. O'Mahony JF, de Kok IMCM, van Rosmalen J, Habbema JDF, Brouwer W, van Ballegooijen M. Practical implications of differential discounting in cost-effectiveness analyses with varying numbers of cohorts. *Value Health* 2011;**14**:438–42.
11. Attema AE, Brouwer WBF, Claxton K. Discounting in economic evaluations. *PharmacoEconomics* 2018;**36**:745–58.
12. Wouters OJ, Naci H, Samani NJ. QALYs in cost-effectiveness analysis: an overview for cardiologists. *Heart* 2015;**101**:1868–73.
13. Prieto L, Sacristán JA. Problems and solutions in calculating quality-adjusted life years (QALYs). *Health Qual Life Outcomes* 2003;**1**:80.
14. Marseille E, Kahn JG. Utilitarianism and the ethical foundations of cost-effectiveness analysis in resource allocation for global health. *Philosophy, Ethics Hum Med* 2019;**14**:5.
15. Diamond GA, Kaul S. Cost, effectiveness, and cost-effectiveness. *Circ Cardiovasc Qual Outcomes* 2009;**2**:49–54.
16. Frausing MHJP, Johansen JB, Afonso D, Jørgensen OD, Olsen T, Gerdes C *et al.* Cost-effectiveness of an antibacterial envelope for infection prevention in patients undergoing cardiac resynchronization therapy reoperations in Denmark. *Europace* 2023;**25:**euad159.
17. Gottschalk S, Kany S, König HH, Crijns HJGM, Vardas P, Camm AJ *et al.* Cost-effectiveness of early rhythm control vs. usual care in atrial fibrillation care: an analysis based on data from the EAST-AFNET 4 trial. *Europace* 2023;**25**:euad051.
18. McCabe C, Claxton K, Culyer AJ. The NICE cost-effectiveness threshold: what it is and what that means. *PharmacoEconomics* 2008;**26**:733–44.
19. Anderson JL, Heidenreich PA, Barnett PG, Creager MA, Fonarow GC, Gibbons RJ *et al.* ACC/AHA statement on cost/value methodology in clinical practice guidelines and performance measures: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures and Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;**63**:2304–22.
20. Claxton K. Exploring uncertainty in cost-effectiveness analysis. *PharmacoEconomics* 2008;**26**:781–98.
21. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C *et al.* 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2021;**42**:373–498.
22. Joglar JA, Chung MK, Armbruster AL, Benjamin EJ, Chyou JY, Cronin EM *et al.* 2023 ACC/AHA/ACCP/HRS guideline for the diagnosis and management of atrial fibrillation: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2024;**149**:e1–156.
23. Kantharia BK. Implantable cardioverter defibrillator shocks from ventricular tachyarrhythmias in patients with ischemic heart disease: preventative measures, shortcomings, cost-effectiveness, and global practice perspectives. *J Cardiovasc Electrophysiol* 2021;**32**:2558–66.
24. Prasitlumkum N, Navaravong L, Desai A, Desai D, Cheungpasitporn W, Rattanawong P *et al.* Impact of early ventricular tachycardia ablation in patients with an implantable cardioverter-defibrillator: an updated systematic review and meta-analysis of randomized controlled trials. *Heart Rhythm* 2022;**19**:2054–61.
25. Kirchhof P, Camm AJ, Goette A, Brandes A, Eckardt L, Elvan A *et al.* Early rhythm-control therapy in patients with atrial fibrillation. *New Engl J Med* 2020;**383**:1305–16.
26. Kim D, Yang PS, You SC, Jang E, Yu HT, Kim TH *et al.* Early rhythm control therapy for atrial fibrillation in low-risk patients: a nationwide propensity score-weighted study. *Ann Intern Med* 2022;**175**:1356–65.
27. Dickow J, Kany S, Roth Cardoso V, Ellinor PT, Gkoutos GV, Van Houten HK *et al.* Outcomes of early rhythm control therapy in patients with atrial fibrillation and a high comorbidity burden in large real-world cohorts. *Circ Arrhythmia Electrophysiol* 2023;**16**:e011585.
28. Kany S, Cardoso VR, Bravo L, Williams JA, Schnabel R, Fabritz L *et al.* Eligibility for early rhythm control in patients with atrial fibrillation in the UK Biobank. *Heart* 2022;**108**:1873–80.
29. Husereau D, Drummond M, Augustovski F, de Bekker-Grob E, Briggs AH, Carswell C *et al.* Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) statement: updated reporting guidance for health economic evaluations. *Eur J Health Econ* 2022;**23**:1309–17.
30. Gerber-Grote A, Sandmann FG, Zhou M, Ten Thoren C, Schwalm A, Weigel C *et al.* Decision making in Germany: is health economic evaluation as a supporting tool a sleeping beauty? *Z Evid Fortbild Qual Gesundhwes* 2014;**108**:390–6.
31. Blomstrom-Lundqvist C, Ostrowska B. Prevention of cardiac implantable electronic device infections: guidelines and conventional prophylaxis. *Europace* 2021;**23**:iv11–9.
32. Olsen T, Jørgensen OD, Nielsen JC, Thøgersen AM, Philbert BT, Johansen JB. Incidence of device-related infection in 97 750 patients: clinical data from the complete Danish device-cohort (1982–2018). *Eur Heart J* 2019;**40**:1862–9.
33. Wilkoff BL, Boriani G, Mittal S, Poole JE, Kennergren C, Corey R *et al.* Impact of cardiac implantable electronic device infection: a clinical and economic analysis of the WRAP-IT trial. *Circ Arrhythmia Electrophysiol* 2020;**13**:e008280.
34. Eby EL, Bengtson LGS, Johnson MP, Burton ML, Hinnenthal J. Economic impact of cardiac implantable electronic device infections: cost analysis at one year in a large United States health insurer. *J Med Econ* 2020;**23**:698–705.
35. Frausing MHJP, Kronborg MB, Johansen JB, Nielsen JC. Avoiding implant complications in cardiac implantable electronic devices: what works? *Europace* 2021;**23**:163–73.
36. Tarakji KG, Mittal S, Kennergren C, Corey R, Poole JE, Schloss E *et al.* Antibacterial envelope to prevent cardiac implantable device infection. *N Engl J Med* 2019;**380**:1895–905.
37. Hillock N, Hillock R, Warner M. Antibacterial envelope to prevent cardiac implantable device Infection. *New Engl J Med* 2019;**381**:1782.
38. Lieberman RA, Olshansky B. Antibacterial envelope to prevent cardiac implantable device infection. *N Engl J Med* 2019;**381**:1782–3.
39. Rennert-May E, Raj SR, Leal J, Exner DV, Manns BJ, Chew DS. Economic evaluation of an absorbable antibiotic envelope for prevention of cardiac implantable electronic device infection. *Europace* 2021;**23**:767–74.
40. Frausing MHJP, Nielsen JC, Johansen JB, Jørgensen OD, Gerdes C, Olsen T *et al.* Rate of device-related infections using an antibacterial envelope in patients undergoing cardiac resynchronization therapy reoperations. *Europace* 2022;**24**:421–9.
41. Birnie DH, Wang J, Alings M, Philippon F, Parkash R, Manlucu J *et al.* Risk factors for infections involving cardiac implanted electronic devices. *J Am Coll Cardiol* 2019;**74**:2845–54.
42. Boriani G, Kennergren C, Tarakji KG, Wright DJ, Ahmed FZ, McComb JM *et al.* Cost-effectiveness analyses of an absorbable antibacterial envelope for use in patients at increased risk of cardiac implantable electronic device infection in Germany, Italy, and England. *Value Health* 2021;**24**:930–8.
43. Wilkoff BL, Boriani G, Mittal S, Poole JE, Kennergren C, Corey GR *et al.* Cost-effectiveness of an antibacterial envelope for cardiac implantable electronic device infection prevention in the US healthcare system from the WRAP-IT trial. *Circ Arrhythmia Electrophysiol* 2020;**13**:e008503.
44. Kay G, Eby EL, Brown B, Lyon J, Eggington S, Kumar G *et al.* Cost-effectiveness of TYRX absorbable antibacterial envelope for prevention of cardiovascular implantable electronic device infection. *J Med Econ* 2018;**21**:294–300.
45. Boriani G, Vitolo M, Wright DJ, Biffi M, Brown B, Tarakji KG *et al.* Infections associated with cardiac electronic implantable devices: economic perspectives and impact of the TYRX™ antibacterial envelope. *Europace* 2021;**23**:iv33–44.
46. Modi RM, Liu CL, Isaza N, Raber I, Calvachi P, Zimetbaum P *et al.* Cost-effectiveness of antibiotic-eluting envelope for prevention of cardiac implantable electronic device infections in heart failure. *Circ Cardiovasc Qual Outcomes* 2022;**15**:e008443.
47. Modi V, Shah K, Ferraro B, Gasimli-Gamache L, Nanda S, Stevens S *et al.* Cardiac implantable electronic device implantation and device-related infection. *Europace* 2023;**25**:euad208.
48. Shariff N, Eby E, Adelstein E, Jain S, Shalaby A, Saba S *et al.* Health and economic outcomes associated with use of an antimicrobial envelope as a standard of care for cardiac implantable electronic device implantation. *J Cardiovasc Electrophysiol* 2015;**26**:783–9.

49. Burnhope E, Rodriguez-Guadarrama Y, Waring M, Guilder A, Malhotra B, Razavi R *et al.* Economic impact of introducing TYRX amongst patients with heart failure and reduced ejection fraction undergoing implanted cardiac device procedures: a retrospective model based cost analysis. *J Med Econ* 2019;**22**:464–70.
50. Zeppenfeld K, Tfelt-Hansen J, de Riva M, Winkel BG, Behr ER, Blom NA *et al.* 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J* 2022;**43**:3997–4126.
51. Sapp JL, Wells GA, Parkash R, Stevenson WG, Blier L, Sarrazin JF *et al.* Ventricular tachycardia ablation versus escalation of antiarrhythmic drugs. *N Engl J Med* 2016;**375**:111–21.
52. Coyle K, Coyle D, Nault I, Parkash R, Healey JS, Gray CJ *et al.* Cost effectiveness of ventricular tachycardia ablation versus escalation of antiarrhythmic drug therapy: the VANISH trial. *JACC Clin Electrophysiol* 2018;**4**:660–8.
53. Chen Y, Gomes M, Garcia JV, Hunter RJ, Chow AW, Dhinoja M *et al.* Cost-effectiveness of ablation of ventricular tachycardia in ischaemic cardiomyopathy: limitations in the trial evidence base. *Open Heart* 2020;**7**:e001155.
54. Gula LJ, Doucette S, Leong-Sit P, Tang ASL, Parkash R, Sarrazin JF *et al.* Quality of life with ablation or medical therapy for ventricular arrhythmias: a substudy of VANISH. *J Cardiovasc Electrophysiol* 2018;**29**:421–34.
55. Reddy VY, Reynolds MR, Neuzil P, Richardson AW, Taborsky M, Jongnarangsin K *et al.* Prophylactic catheter ablation for the prevention of defibrillator therapy. *N Engl J Med* 2007;**357**:2657–65.
56. Kuck KH, Schaumann A, Eckardt L, Willems S, Ventura R, Delacrétaz E *et al.* Catheter ablation of stable ventricular tachycardia before defibrillator implantation in patients with coronary heart disease (VTACH): a multicentre randomised controlled trial. *Lancet* 2010;**375**:31–40.
57. Al-Khatib SM, Daubert JP, Anstrom KJ, Daoud EG, Gonzalez M, Saba S *et al.* Catheter ablation for ventricular tachycardia in patients with an implantable cardioverter defibrillator (CALYPSO) pilot trial. *J Cardiovasc Electrophysiol* 2015;**26**:151–7.
58. Di Biase L, Burkhardt JD, Lakkireddy D, Carbucicchio C, Mohanty S, Mohanty P *et al.* Ablation of stable VTs versus substrate ablation in ischemic cardiomyopathy: the VISTA randomized multicenter trial. *J Am Coll Cardiol* 2015;**66**:2872–82.
59. Kuck KH, Tilz RR, Deneke T, Hoffmann BA, Ventura R, Hansen PS *et al.* Impact of substrate modification by catheter ablation on implantable cardioverter-defibrillator interventions in patients with unstable ventricular arrhythmias and coronary artery disease: results from the multicenter randomized controlled SMS (Substrate Modification Study). *Circ Arrhythmia Electrophysiol* 2017;**10**:e004422.
60. Santangeli P, Muser D, Maeda S, Filtz A, Zado ES, Frankel DS *et al.* Comparative effectiveness of antiarrhythmic drugs and catheter ablation for the prevention of recurrent ventricular tachycardia in patients with implantable cardioverter-defibrillators: a systematic review and meta-analysis of randomized controlled trials. *Heart Rhythm* 2016;**13**:1552–9.
61. Xie F, Zhou T. Industry sponsorship bias in cost effectiveness analysis: registry based analysis. *BMJ* 2022;**377**:e069573.