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SYSTEMATIC REVIEW

A systematic literature review of methods of incorporating mortality in cost-effectiveness analyses of lipid-lowering therapies

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ABSTRACT

Aims: Cost effectiveness analysis (CEA) is a useful tool for estimating the value of an intervention in relation to alternatives. In cardiovascular disease (CVD), CEA is especially important, given the high economic and clinical burden. One key driver of value is CVD mortality prevention. However, data used to inform CEA parameters can be limited, given the difficulty in demonstrating statistically significant mortality benefit in randomized clinical trials (RCTs), due in part to the frequency of fatal events and limited trial durations. This systematic review identifies and summarizes whether published CVD-related CEAs have incorporated mortality benefits, and the methodology among those that did.

Materials and methods: A systematic literature review was conducted of CEAs of lipid-lowering therapies published between 2000–2017. Health technology assessments (HTA) and full-length manuscripts were included, and sources of mortality data and methods of applying mortality benefits were extracted. Results were summarized as proportions of articles to articulate common practices in CEAs of CVD.

Results: This review identified 100 studies for inclusion, comprising 93 full-length manuscripts and seven HTA reviews. Among these, 99% assumed a mortality benefit in the model. However, 87 of these studies that incorporated mortality differences did so despite the trials used to inform model parameters not demonstrating statistically significant differences in mortality. None of the 12 studies that used statistically significant findings from an individual RCT were based on active control studies. In a subgroup analysis considering the 60 CEAs that incorporated a direct mortality benefit, 48 (80%) did not have RCT evidence for statistically significant benefit in CVD mortality.

Limitations and conclusions: The finding that few CEA models included mortality inputs from individual RCTs of lipid-lowering therapy may be surprising, as one might expect that treatment efficacy should be based on robust clinical evidence. However, regulatory requirements in CVD-related RCTs often lead to insufficient sample sizes and observation periods for detecting a difference in CVD mortality, which results in the use of intermediate outcomes, composite end-points, or meta-analysis to extrapolate long-term mortality benefit in a lifetime CEA.

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Introduction

Healthcare expenditures in the US have been increasing, with spending in 2014 estimated at $3 trillion, or 17.5% of GDP[1]. Efforts are underway to control spending, with the focus ranging from systemic changes in payment and insurance design to more careful assessment of the value of technologies being utilized. One such method of assessing the value of an innovation compared with existing alternatives is cost-effectiveness analysis (CEA).

CEA is a well-established framework for estimating the costs per unit of incremental benefit provided by a new technology[2]. In CEA, the incremental economic impact of therapeutic options is estimated and divided by the incremental clinical benefit, with the result referred to as the incremental cost-effectiveness ratio and used as a measure of value, often over the course of a lifetime. As real-world costs are often not sufficiently captured through clinical trials, and many long-term clinical outcomes are not observable due to the limited time horizons of trials, simulation models are commonly used to conduct CEAs assessing the lifelong impact of trial-tested interventions. Model-based CEAs are used to inform decision-making throughout the world, despite their more recent adoption in the US[3]. The need for such analyses is driven by the increasing discussion around rising healthcare costs. Bibliographic analyses performed by researchers using the Tufts Cost Effectiveness Registry have shown that CEA publications both in the US and internationally have grown dramatically over the past 25 years[4], along with a corresponding increase in healthcare providers and administrators utilizing the information.

A clinical area where CEA is frequently performed is cardiovascular disease (CVD), due to its significant clinical, economic burden, and the emergence of high cost and high

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value therapies. In 2015, 41.5% of US citizens, and over 90% of those over the age of 80, had some form of CVD[5] (defined as hypertension, coronary heart disease, stroke, congestive heart failure, or atrial fibrillation). Given the aging population in the US, the impact of CVD is only expected to increase. Of similar concern is the trend of increasing costs. Direct healthcare spending in CVD prevention and treatment was recently estimated at $231 billion, and, when including indirect costs, it was estimated at more than $650 billion in 2015[6]. The high burden and high costs associated with CVD have led to an increase in published CEAs that aim to inform decision-makers on how best to allocate valuable resources to manage this disease.

As CEAs are increasingly used by non-health economists such as clinicians, payers, and policy-makers to inform value assessments, it is important to ensure that modeling approaches are well-established and understood by this expanded audience. One aspect that may not be sufficiently transparent is how efficacy, a main driver of economic analyses, is incorporated into models, as often times the limited data from RCTs need to be extrapolated to estimate a lifetime treatment benefit. A specific area of potential confusion related to efficacy is the methodology for incorporating the impact of interventions on mortality, when the treatment benefit is not independently assessed in RCTs.

In this systematic review, we identified and summarized how published CVD-related CEAs have modeled mortality benefits. We specifically assessed how many published CEAs included a mortality difference between comparators, and, among those, the sources and methods for how treatment effect was incorporated. This was not an attempt to advocate for a particular methodology, given the extensive research that has been conducted around the appropriateness of using intermediate outputs[7–9]. Rather, we aimed to provide quantitative measures of what was done in previously published analyses. It was hypothesized that, because of limitations in RCTs of lipid-lowering therapies, the majority of CEA would model a mortality impact that was not found to be statistically significant in individual RCTs. These findings can help illustrate a practical challenge in CEAs, highlight the need to develop better, more precise recommendations from CEA experts on modeling inputs, describe approaches when encountering a lack of hard end-points to provide insights into common practices to readers of CEA literature, and aid in designing future research.

Methods

Search strategy

We conducted a thorough search of the literature in compliance with the National Institute for Health and Care Excellence (NICE) and the Institute for Quality and Efficiency in HealthCare (IQWiG) standards to identify relevant cost-effectiveness studies of lipid-lowering therapies (statins or ezetimibe). The following databases were searched: MEDLINE (Ovid); Embase; Econlit; and NHS Economic Evaluation Database (EED). Medical Subject Headings (MeSH) and keyword searches were used and edited as necessary (Supplemental Tables 1a–d). Health technology assessment (HTA) documents assessing cost-effectiveness models of lipid-lowering therapies were identified through a search of the Center for Reviews and Dissemination (CRD) electronic bibliographic database and country-specific HTA websites. In total, 19 agencies across 16 countries were included and searched manually. Conference proceedings were excluded from the search, as the word limits for abstracts led to insufficient details for abstraction of relevant modeling methods. The search was conducted for articles published in the English language between January 2000 and February 2017.

Study selection

A multi-stage process was used for identifying relevant articles for abstraction. Initially, each title and abstract from the peer-reviewed literature was screened by two researchers. Among those chosen for full-text review, each publication was reviewed by multiple members of the research team to determine inclusion eligibility, and disagreements were resolved via consensus. HTA documents were similarly assessed for eligibility against inclusion/exclusion criteria. Eligibility is shown in Table 1, and was limited to studies of lipid-lowering therapies in adults >18 years of age for whom treatment is recommended.

Data abstraction

For included CEA, bibliographic data and mortality-specific details were abstracted. In cases where the CEA publication did not provide sufficient detail, the original trials (sources) informing mortality parameters were also reviewed.

Table 1. Study inclusion criteria applied when screening articles and abstracting data.

Component	Inclusion	Exclusion
Population	Adults with hypercholesterolemia and mixed dyslipidemia	Children <18 years of age
Publication date	2000–2017	Prior to 2000
Language restrictions	English	Non-English
Intervention and comparators	Statins	Surgical procedures
	Ezetimibe	Lifestyle or dietary modifications
Outcome	Cardiovascular event reduction	Costs alone (no efficacy)
	LYs gained	
	QALYs gained	
	Cost-effectiveness and/or cost-utility results	

LY, life year; QALY, quality-adjusted life year.

After data was extracted from all sources, relevant information was then reviewed again by a third, more senior researcher to ensure that all data had been collected and correctly categorized. A quality-assurance process was undertaken by external clinical and methodological experts to verify all abstracted data and classifications. Discrepancies were resolved by consensus.

For each CEA, we categorized the source of mortality data as direct (from an RCT or meta-analysis) or indirect (based on a risk equation, such as the Framingham Risk Score, or using a difference in intermediate end-points, such as incidence of a CVD event that increased the risk of mortality post-CVD event). Within the source RCTs, we determined whether the trials compared the studied intervention to an active control or to a placebo, had demonstrated a differential risk of cardiovascular mortality between treatments, and whether that difference had been shown to be statistically significant in a trial. We also assessed whether the mortality effect had been measured in the source study as an individual end-point or as a composite end-point that included both fatal and non-fatal cases. Findings were reported for the entire collection of abstracted articles, and a sensitivity analysis was conducted assessing those studies that used a mortality benefit as directly reported from the source.

Results

Search and screening overview

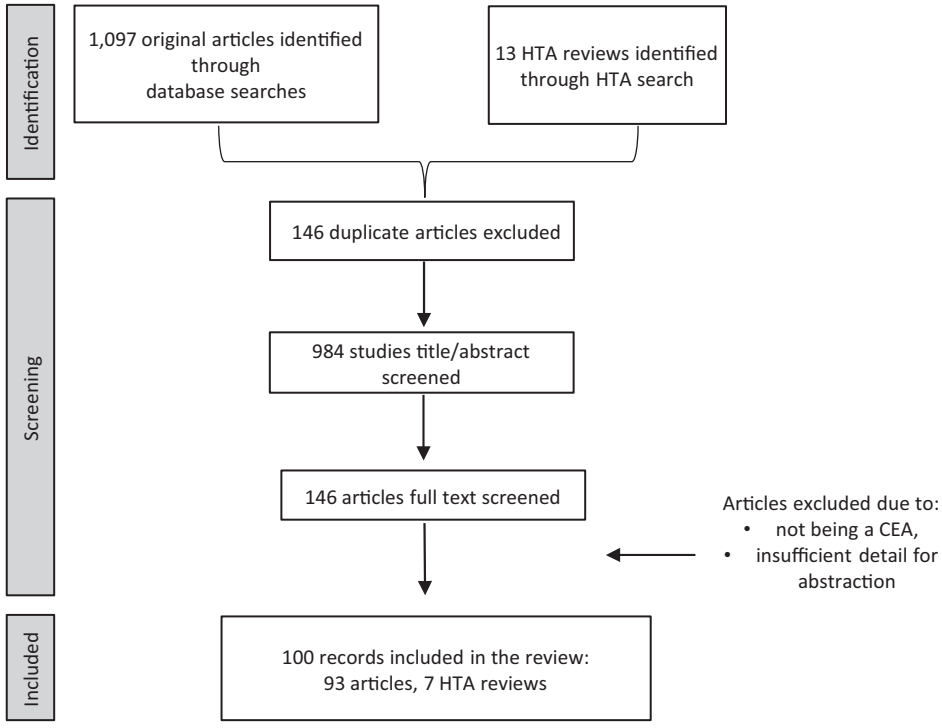
The search of all relevant databases yielded 1,110 studies including published literature and formal HTAs identified through individual agency websites (Figure 1). After screening the literature, 133 full text articles and 13 HTA were accepted for abstraction. Among those abstracted, 46 studies were further excluded, with the primary reason being a lack of details regarding methodology to extract necessary components. A final set of 100 articles were included in the review, with details found in Supplemental Table 2[10–109].

Summary of included articles

Included studies ranged in publication date from 2000–2016, with 30 published in 2010 or more recently. Fifty-nine studies assessed lipid-lowering therapy against placebo, while 41 compared the benefits from intensification of lipid-lowering therapy or active controlled studies. There were a wide variety of model outcomes predicted, with some strictly estimating all-cause mortality, whereas others considered multiple separate CVD-related causes of mortality (e.g. coronary heart disease, stroke).

Studies applying mortality benefit, direct or indirect

Among the 100 included CEAs, 99 assumed a CVD mortality benefit in their analysis. Of these, only 12 CEAs were based on an individual RCT with mortality benefit that was shown to be statistically significant, while 87 of the studies incorporated mortality differences despite the trials used to inform model parameters not demonstrating statistically significant mortality differences. When stratifying by whether the source study had an active vs placebo control arm, none of the CEA that were based on trials using active controls had RCT evidence for statistically significant CVD mortality benefit.



HTA, health technology assessment

Figure 1. Flow diagram depicting the literature review process and studies identified. HTA, health technology assessment.

Table 2. Results: frequency of statistically significant mortality data utilized within cost effectiveness analyses of lipid-lowering therapies.

	n (%)	
	Assumed CVD mortality benefit in the model	No RCT evidence for statistically significant benefit in CVD mortality[a]
All ($n = 100$)	99/100 (99%)	87/99 (88%)
Active controlled studies[b] ($n = 41$)	40/41 (98%)	40/40 (100%)
Placebo controlled studies ($n = 59$)	59/59 (100%)	47/59 (80%)

[a]Defined as individual RCTs that did not demonstrate statistically significant benefit in CVD mortality, even though, in certain cases, statistical significance can be achieved through ad-hoc sub-group analysis, non-RCTs, or meta-analysis of RCTs.
[b]Includes dose intensification studies.

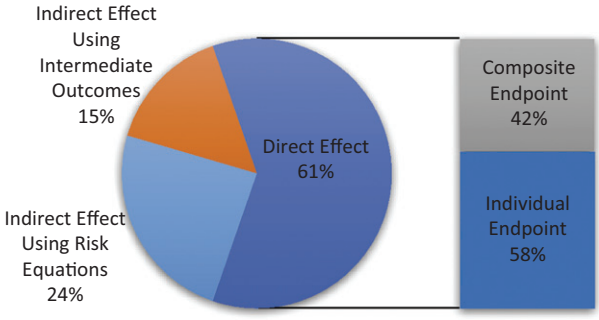


Figure 2. Results: source of mortality data and use of composite and individual end-points within CEA that incorporated a direct effect.

The majority of placebo controlled studies used to inform CEA inputs also did not find statistically significant mortality evidence (Table 2).

Studies applying a direct mortality benefit

Of the 99 CEAs that included a mortality benefit, 61% used direct information (RCT or meta-analysis) as the source for this benefit. Among the 60 studies using direct mortality information, 35 (58%) used a source trial that reported an individual end-point of death, whereas 25 (42%) used a composite end-point, such as the combined rate of fatal and non-fatal events. Of the CEA that used indirect information, 24 used trial findings (such as a decrease in LDL-C) entered into a risk calculator (e.g. Framingham Risk Score, SCORE Risk Equation) to model CVD mortality. The remaining 15 used trial findings of differences in intermediate outcomes, such as incidence of stroke or CHD, and applied a case-fatality rate from a separate source to indirectly model a mortality benefit (Figure 2). Among the 60 CEA that used direct information, the majority used individual trials as opposed to meta-analyses. For those that used individual trial data for CVD mortality benefit, 20 of 43 studies (47%) applied a composite end-point (Table 3).

Sensitivity analysis considering only studies that directly incorporated CVD mortality benefit

Sixty CEAs (60%) directly incorporated CVD mortality benefits in the model, out of which 48 studies (80%) included mortality benefit that did not have RCT evidence to support a statistically significant benefit between treatments. Of these studies, 19 relied on source trials that used active controls, while 41 were based on trials that were placebo controlled. Similar to the main analysis, none of the 19 studies with active controlled comparators had RCT evidence for CVD mortality benefit, and only 12 of 41 studies (29%) of the placebo controlled comparators had evidence of CVD mortality supported by clinical trial (Table 4).

Table 3. Results: quantitative assessment of mortality data sources and format of data used among studies modeling a direct mortality effect.

Parameter	*n* (%)	
	Among studies based on meta-analysis	Among studies based on individual trials
All studies that used a direct effect on mortality	17/60 (28%)	43/60 (72%)
End-point applied:		
Individual end-point (e.g. CHD death)	12/17 (71%)	23/43 (53%)
Composite end-point (e.g. fatal and non-fatal CHD)	5/17 (29%)	20/43 (47%)

CHD, coronary heart disease.

Table 4. Sensitivity analysis of studies that incorporated a direct CVD mortality benefit.

Parameter	*n* (%)	
	Used direct evidence of CVD mortality benefit in the model among all studies	No RCT evidence for statistically significant benefit in CVD mortality[a] among studies using direct evidence
All ($n = 100$)	60/100 (60%)	48/60 (80%)
Active controlled studies ($n = 41$)	19/41 (46%)	19/19 (100%)
Placebo controlled studies ($n = 59$)	41/59 (69%)	29/41 (71%)

[a]Defined as individual RCTs that did not demonstrate statistically significant benefit in CVD mortality, even though, in certain cases, statistical significance can be achieved through ad-hoc sub-group analysis, non-RCTs, or meta-analysis of RCTs.

Discussion

This systematic review of the literature identified 100 English-language CEAs that fulfilled the inclusion criteria of assessing lipid-lowering therapies in adults for prevention of CVD mortality. The reviewed articles, including manuscripts and HTA reports, primarily relied on data from meta-analyses or trials that did not find a statistically significant mortality difference between comparators. The articles were published in a wide range of peer-reviewed journals, and provided insights that could be used in driving important payer decisions.

Most likely, published CEAs did not rely strictly on statistically significant mortality findings, because it can be difficult, costly, and time consuming to design a trial that is powered to detect a statistically significant impact on mortality. A recent meta-analysis of clinical trials of lipid-lowering therapies reported that, of 27 studies assessed, only three showed statistically significant mortality outcomes[110]. All three trials (LIPID, 4S, and HPS) were older (published between 1997–2002), had longer duration (>5 years), and

were placebo-controlled[111–113]. Among the six recent trials that compared more or less intensive LDL cholesterol lowering therapy, none found a statistically significant impact on mortality associated with treatment[114–119].

With the improved management of hypertension and other risk factors, an increase in use of anti-platelet therapies, and substantial progress in the acute management of MI/stroke, survival in CVD patients has increased. This longer survival presents challenges in demonstrating CVD mortality benefit within a trial, where follow-up is limited and the sample size is selected to assess intermediate or composite end-points rather than CVD mortality alone. The regulatory landscape is also evolving, as current registration trials in CVD are increasingly powered to assess composite end-points. It would be beneficial if regulatory agencies and others assessing trials and subsequent CEAs provided formal guidance into appropriate study designs and how to incorporate trial data into lifetime economic models. In certain disease areas, such as metastatic cancer, collecting mortality data within the timeframe of a clinical trial is plausible, given that median overall survival time can be within 1 year of diagnosis or initiation of treatment. In a subsequent study, it could be interesting to investigate the types of data that are used in CEAs of other disease areas, to assess whether this is specific to chronic conditions.

CEAs are used to inform decision-making, and decisions must be made with the best available evidence. Therefore, model-based analyses are often forced to weigh trade-offs in using different sources of information not originally designed for economic analysis to inform parameters. Published modeling guidelines suggest that there is no single source that is preferable in all situations, but rather that researchers should weigh potential biases and utilize the best available evidence[120]. In rare cases, there may be a single head-to-head clinical trial designed to answer all relevant questions. In other cases, combining findings from RCTs with real world evidence can reduce biases. It is recommended that, in the absence of an ideal data source, it is preferable to combine data from multiple sources or infer the potential impact beyond the scope of an observation period, as preliminary cost-effectiveness results using best available data can be informative to decision-makers. The benefits of transparency in describing methods and results is that, as new data become available, the model can be updated. In the case of CVD, the long-term survival benefits of lipid-lowering therapy have been repeatedly shown over the past 20+ years[110], providing support for the link between a benefit in intermediate outcomes (e.g. stroke or MI prevented) and a decrease in mortality.

This analysis was conducted to provide a preliminary quantitative estimate of how mortality is incorporated within CVD CEAs, as opposed to making a formal recommendation or advocating for use of a specific methodology. One could envision an additional analysis that builds off this work in which predicted outcomes from historic models that used RCT data showing statistically significant results could be compared with those using non-statistically significant results or other types of data. This may help identify whether the practices identified can provide reasonable estimates.

While efforts were taken to adhere to guidelines regarding best practices in conducting systematic literature reviews, this study should be viewed in light of its limitations. Due to the detailed nature of the study question being examined, there were some articles that were excluded, despite their apparent relevance, because they did not provide sufficient transparency into the methods. There is no reason to believe that this limitation would introduce bias in any direction. Additionally, this analysis summarized the methods for incorporating mortality, and did not consider additional methodological decisions required when conducting CEA of lipid-lowering therapies, such as the choice to include quality-adjustments or gauging the strength of evidence used; this could be a potentially beneficial area for future research. Our investigation of methods for incorporating mortality also focused solely on the base case methods and findings, and did not evaluate how these assumptions were assessed in sensitivity analyses. This could provide further insights into the implications of modeling methodology, and would be an interesting area for future studies. Finally, our goal was to summarize the current practice, as opposed to assessing the quality of included studies or conducting a meta-analysis.

Conclusions

We assessed the use of intermediate outcomes, composite end-points, and non-statistically significant findings from RCT in CEA, using lipid-lowering therapy for CVD prevention as an example. In this review of 100 studies, we found that nearly all CEA incorporated mortality benefit, but most were not informed by statistical significance directly based on clinical trials. Limitations in clinical trials to assess mortality in chronic diseases, such as CVD, include insufficient sample sizes and limited observation periods. The clinical experience with lipid-lowering therapies in the past 20 years has led to exercises including the use of intermediate outcomes and composite end-points when conducting CEA, which has become a standard practice when assessing the value of lipid-lowering therapies. Subsequent analyses could help in determining whether this approach is also used in other disease areas, and additional investigation into the optimal data sources to use in CEA in the absence of RCT evidence could be warranted.

Transparency

Declaration of funding

This study has been sponsored by Amgen.

Declaration of financial/other relationships

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