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Cardiovascular Outcomes Research

A Clinician's Guide to Cardiovascular Epidemiology and Clinical Outcomes Trials

Humana Press

Contemporary Cardiology

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ISSN 2196-8969 ISSN 2196-8977 (electronic)
Contemporary Cardiology
ISBN 978-3-031-54959-5 ISBN 978-3-031-54960-1 (eBook)
https://doi.org/10.1007/978-3-031-54960-1

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

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Foreword

Translation and implementation of evidence-based medical research into every day clinical practice is a global priority because of its potential impact on health services delivery and patient-centered outcomes. Nearly 20 years ago, the U.S. Institute of Medicine in partnership with the National Institutes of Health proposed initiating a new model for re-engineering clinical research and healthcare delivery so that evidence is available when it is needed, and applied in healthcare settings that is both more effective and more efficient than exists presently. This movement became known as a "Learning Health System" (LHS) wherein the pace, uptake, and integration of medical evidence derived from randomized clinical trials and observational studies can be accelerated more expeditiously at the point of clinical care. Because it is generally estimated that it takes an average of 17 years for published research evidence to reach clinical practice, translating scientific discoveries into patient benefit more quickly is a policy priority of many "Learning Health Systems."

Against this backdrop, most physicians, research scientists, nurse practitioners, physician assistants, and other healthcare providers are besieged with ever-expanding evidence base derived from randomized clinical trials and observational studies that challenge how such important information can be applied to bedside clinical decision-making. Yet, little time is devoted during provider training about how to read and critically interpret clinical research data and reports published from cardiovascular outcomes studies. As an academic preventive cardiologist in a teaching institution who has also been a lead investigator and Study Chair for the Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) and the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trials, Study Co-Chair of the Atherothrombosis Intervention in Metabolic Syndrome with Low High Density Lipoprotein/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial, and a national Co-Principal Investigator for the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial, these experiences have underscored both the critical importance of testing hypotheses in clinical medicine and the slow pace at which new results from such studies are incorporated into clinical practice (the so-called "T2 lag" in translational biomedical research, cited above).

Accordingly, it is abundantly clear that there is a critical, unmet need among clinicians for guidance on interpreting the medical literature surrounding cardiovascular outcomes studies and how this knowledge can be best applied to clinical decision-making. While clinical practice guidelines and recommendations can be helpful for summarizing and rating the quality of available evidence, new trial results and meta-analyses of existing pooled data with important treatment implications for clinical practice arrive with regularity, such that clinicians need to be familiar with the implications of new findings and how best to interpret them in order to provide the best care for their patients.

Cardiovascular Outcomes Research: A Clinician's Guide to Cardiovascular Epidemiology and Clinical Outcomes Trials, the latest book in Springer's Contemporary Cardiology series, edited by Maki and Wilson, is a welcome resource that busy clinicians should find as an extremely helpful guide to becoming better and more knowledgeable consumers of the medical literature relevant to prevention and management of cardiovascular diseases. In their new book, Drs. Maki and Wilson provide insightful coverage of foundational concepts in biostatistics, study design, and guideline development. In addition, an overview is provided of our current understanding of the key roles of cardiovascular risk factors, as well as both lifestyle and pharmacologic interventions for achieving optimal residual cardiovascular risk reduction related to dyslipidemias, inflammation, hypertension, obesity, diabetes, thrombosis, arrhythmias, and chronic kidney disease. This is a book that will occupy a prominent position on the bookshelf in my office and will be a valuable educational resource to advance learning for me and other readers for years to come.

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William Edward Boden

Preface

It has been just over 75 years since the initiation of the Framingham Heart Study, which was the first study to demonstrate that risk factors, particularly elevated serum cholesterol, diabetes mellitus, hypertension, and cigarette smoking, were associated with increased incidence of myocardial infarction in a group of adults in the United States. When the Framingham Heart Study was initiated, the general view in the medical community was that "hardening of the arteries" was an unavoidable consequence of the aging process. In the space of one lifetime, a great deal of progress has been made in the identification of additional risk factors, as well as reliable methods of determining whether strategies to modify risk factors lower incidence of cardiovascular morbidity and mortality. Clinicians now have an array of tools available for reducing cardiovascular event risk and improving outcomes in both primary and secondary prevention, including lifestyle therapies and pharmacologic and surgical approaches.

The randomized controlled trial (RCT) has become the gold standard for evaluating the benefits and risks of interventions intended to affect human health. While observational studies are important for hypothesis generation, they are more subject to certain types of bias and confounding than RCTs. Due to random application of treatment, a large-scale RCT has the advantage that the treatment groups can be assumed to have similar prognoses because both known and unknown determinants of the outcome will be approximately equally distributed across treatment conditions.

At times it may not be ethical or feasible to test an intervention using an RCT to evaluate the impact on cardiovascular outcomes (e.g., bariatric surgery or cigarette smoking cessation). In such instances, clinical recommendations must rely on the best available evidence, which might include results from observational studies, short-term investigations to evaluate effects of the intervention on biomarkers of cardiovascular risk, and animal models, as well as other types of evidence such as that from Mendelian randomization. Mendelian randomization uses genetic variants to determine whether an observational association between a risk factor and an outcome is consistent with a causal effect. It relies on the natural random distribution of genetic variants in a population. Because these genetic variants are typically unassociated with confounders, differences in the outcome between those who carry

the variant and those who do not can be attributed to the difference in the risk factor. Recommendations for the use of interventions that have not been rigorously tested using adequately powered RCTs should be qualified to alert clinicians to the lower quality of evidence compared with interventions that have been demonstrated to reduce cardiovascular morbidity and/or mortality in RCTs.

Clinical training typically involves a greater focus on the application of interventions than on the process by which the evidence is produced to support the use of those interventions. The focus of this book is on the process by which such evidence is generated and the basics of interpreting reports in the medical/scientific literature from observational and intervention studies to assess relationships of risk factors and interventions to cardiovascular outcomes, particularly major adverse cardiovascular events, such as myocardial infarction, stroke, revascularization, and cardiovascular death.

The book is divided into two parts. Part I describes the history and evolution of cardiovascular outcomes studies and the major roles such studies play, including pharmaceutical development, regulatory approval, and the formation of guidelines for cardiovascular disease risk reduction and clinical management of cholesterol and dyslipidemia. The challenges associated with developing evidence-based recommendations for non-pharmacological interventions for cardiovascular risk reduction, and the emerging field of implementation science, which aims to accelerate the adoption and integration of evidence-based clinical practice guidelines, are also discussed. Chapters regarding the statistical methods used in cardiovascular outcomes trials and their interpretation, and biomarkers and imaging modalities for detecting subclinical atherosclerotic disease are also included. Part II provides an overview of the evidence for categories of interventions affecting cardiovascular outcomes including chapters on lifestyle therapies and interventions affecting lipids and lipoproteins, inflammation, thrombosis and hemostasis, blood pressure, obesity, diabetes mellitus, cardiac rhythms, and chronic kidney disease.

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Acknowledgments

There are many people who contributed in various ways to bringing this book to fruition, and it would be impossible to properly acknowledge all who did so. However, the Editors would like to thank Peter Toth, MD, PhD (series Editor), who encouraged us to take on this project, and Swathiga Karthikeyan from Springer, who provided logistical and technical support. We are grateful for our colleagues who generously shared their knowledge and expertise as authors. Also, the Editors are particularly indebted to Mary R. Dicklin, PhD, Midwest Biomedical Research, for her assistance with editing the chapters and communicating with the contributors throughout the publication process. Mary has been a long-time friend and colleague and has contributed in innumerable ways to this and many other projects.

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Part I
Background and Process

Evolution of Cardiovascular Outcomes Studies

Liana L. Guarneiri, Mary R. Dicklin, and Kevin C. Maki

Key Points

- The Framingham Heart Study was the first large-scale cardiovascular epidemiology study in the USA, and observations from it pioneered the notion of cardiovascular risk factors.
- Observational studies like Framingham led to the testing of strategies to reduce cardiovascular event risk by modifying risk factors.
- Observational studies are effective at evaluating research questions that are not appropriate for an experimental design, but they are vulnerable to bias and confounding.
- Mendelian randomization is an observational method that uses genetic variation to investigate the relationship between a risk factor and a disease outcome.
- Cardiovascular outcome intervention trials have increased in size, complexity, and cost in recent decades.
- Explanatory trials are designed to test the efficacy of an intervention in optimized conditions, while pragmatic trials favor study design choices that maximize the applicability of study findings to usual care settings.
- Registry-based randomized controlled trials use patient registries to collect data and follow up with patients, which reduces the cost and enhances the generalizability of findings.

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K. C. Maki, D. P. Wilson (eds.), *Cardiovascular Outcomes Research*, Contemporary Cardiology, https://doi.org/10.1007/978-3-031-54960-1_1

- In cardiovascular research, major adverse cardiovascular events (MACE) are common composite endpoints, traditionally including cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke, although other endpoints are often included such as revascularization procedures, unstable angina, and hospitalization for heart failure.
- Adaptive study designs use interim statistical analyses to inform decisions on the modification of study design elements (e.g., sample size, randomization ratio, number of treatment arms, dose, and population).
- The blinding of participants/researchers, comparator groups, population, outcome variables, and follow-up duration are important considerations when designing cardiovascular outcome studies.

1 Evolution of the Study of Cardiovascular Outcomes

Prior to the mid-1900s, cardiovascular (CV) practices were based on tradition [1]. Recognizing the need to invest in research on CV disease (CVD) prevention, the U.S. Public Health Service initiated the Framingham Heart Study (FHS) in 1948 [2]. The FHS was the first large-scale CV epidemiology study in the USA; it involved 5209 mostly white men and women who were evaluated biennially through physical examinations, laboratory tests, and questionnaires. Results from the FHS were instrumental in pioneering the notion that CV risk factors could be identified that predicted risk for CVD events and that some risk factors are modifiable, which has revolutionized the prevention of CVD [3, 4]. The four key modifiable risk factors for CVD identified in the FHS were elevated levels of blood pressure, cholesterol, glucose (diabetes mellitus), and cigarette smoking.

Today, large studies that evaluate the impact of an intervention on CV outcomes (e.g., CV death, myocardial infarction (MI), stroke, and heart failure hospitalization) are termed cardiovascular outcomes trials (CVOTs) [1]. The first outcomes trial in CVD conducted in the late 1960s, the Department of Veterans Affairs (VA) Cooperative trial, evaluated the effects on the morbidity of antihypertensive treatments and laid the foundation for the management of hypertension today [1, 5]. Another instrumental study was the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) which was conducted in men with hypercholesterolemia in the 1970s and 1980s [6]. This randomized, double-blind, placebo-controlled trial demonstrated that lipid-lowering therapy with cholestyramine (a bile acid sequestrant) reduced total cholesterol and low-density lipoprotein cholesterol (LDL-C) concentrations more than placebo, which translated into reduced risk of coronary heart disease (CHD). In 2008, in response to concerns about the CV safety of certain antidiabetes compounds, the Food and Drug Administration mandated that all new hypoglycemic drugs must demonstrate CV safety, which led to the initiation of numerous CVOTs [7]. This guidance was modified in 2020 by a new approach that continued to stress the importance of CV safety data (not limited to atherosclerotic events) in the evaluation of diabetes medications but recommended

basing the safety evaluation on signals of risk identified in the development program, rather than using a one-size-fits-all approach [8]. Nevertheless, CVOTs remain a key step in the evaluation of the safety and efficacy of numerous drug classes, such as those that target lipoproteins and related variables, blood pressure, glycemia, inflammation, and platelet function.

There are several challenges associated with conducting CV outcomes investigations. As medicines with the potential to improve CV risk factors and reduce CVD risk have become more effective and widely used, the level of evidence required to support the introduction of a new drug into the marketplace has increased immensely [1]. Additionally, the cost of conducting a CVOT has increased markedly due to the large sample sizes and long durations that are required. Furthermore, the importance of inclusivity in CVOTs is now recognized. To be able to generalize the results of CVOTs, the population studied needs to reasonably represent the population that will receive the drug therapy. Women and racial/ethnic minorities are disproportionately impacted by CVD, yet these participants are continually underrepresented in CVOTs, including those for lipid-lowering and hypoglycemic therapies [9–13]. For example, Avgerinos et al. systematically reviewed CVOTs that investigated the effect of hypoglycemic medications on major adverse cardiovascular events (MACE) in adults with type 2 diabetes [11]. Although women and African Americans represent 47.5% and 15.7% of patients with type 2 diabetes in the USA, only 35.1% and 4.6% of the trial participants, respectively, were drawn from these populations. Similarly, Grant et al. demonstrated that among 40 randomized controlled trials (RCTs) of lipid-lowering therapies with proven atherosclerotic cardiovascular disease (ASCVD) benefits, non-Hispanic Black participants comprised just 7.3% (median) of the total number of subjects per trial [13]. Furthermore, the calculation of the ratio of the percentage of non-Hispanic Black enrollees among trial participants to the percentage of non-Hispanic Black persons among the disease population (i.e., the participation-to-prevalence ratio [PPR]) indicated a marked underrepresentation compared with their disease burden in studies of persons with diabetes (PPR, 0.18), hypercholesterolemia (PPR, 0.33), stable coronary artery disease (PPR, 0.20), and acute coronary syndrome (PPR, 0.08). Selecting broad inclusion criteria, hiring multilingual staff, and providing flexibility in participation hours to accommodate work schedules are a few strategies to increase the enrollment of underrepresented populations in CVOTs.

2 Types of Observational Studies and Clinical Trials

Observational studies evaluate the relationship between exposures and disease outcomes in free-living populations [14]. Although useful for answering research questions that are not appropriate for experimental designs and generating hypotheses about potential interventions, observational studies are vulnerable to bias and confounding. The two main types of observational studies are case–control and cohort study designs.

In case–control designs, individuals with the outcome of interest are identified as the cases, and individuals without the outcome of interest in the population are identified as the controls. The level of historical exposure is compared between the cases and controls. Case–control designs are generally cost-effective and are most useful for studying rare outcomes and diseases for which little is known about potential causative factors [15].

In cohort designs, patients with varying levels of exposure and without the disease/outcome of interest are followed over time to evaluate the incidence of the outcome in each exposure group [14]. Cohort designs clearly establish a temporal relationship between exposure and disease, which is less clear in case–control designs since the exposure and disease have already occurred at the time of enrollment. In addition, multiple disease outcomes can be studied for a given exposure. One key limitation of cohort study designs for behavioral exposures is the self-selection of the exposure. For example, individuals who choose to exercise regularly, use dietary supplements, consume whole grains, use oral contraceptives, smoke cigarettes, and numerous other lifestyle choices may differ in material respects with relevance to disease risk from those who make different choices.

Confounding occurs when a factor is related to both the exposure and the disease under study. Although statistical methods are available to investigate potential confounding, these are far from perfect, and it is difficult to rule out residual confounding. Bias is a particular type of confounding that occurs when there are systematic differences that result in a difference in the likelihood of the outcome of interest between those with and without an exposure (or with different degrees of exposure), resulting in an inaccurate estimate of the relationship between the exposure and the outcome.

3 Mendelian Randomization Studies

Mendelian randomization is an observational method that uses genetic variation to investigate the relationship between a risk factor and a disease outcome; it is an important way to identify and validate potential targets of therapy [16]. During meiosis, offspring receive a random assortment of genetic variants from the parents. Individuals with and without genetic variants that affect risk factors (e.g., a gene variant that increases LDL-C) are observed over time for the occurrence of the outcome of interest (e.g., CHD). Because genetic variants are not affected by confounders, differences in the outcome between individuals with and without the genetic variant are more likely to be attributable to the difference in the risk factor (e.g., higher LDL-C), providing strong evidence for a causal relationship despite the study's observational nature. For example, results from a Mendelian randomization study reported that individuals with mutations in the gene for proprotein convertase subtilisin/kexin type 9 (PCSK9) that are associated with lower LDL-C throughout life had lower ASCVD risk [17].

4 Types of Cardiovascular Outcomes Trials

4.1 Randomized Controlled Trials

RCTs are prospective investigations used to examine cause-and-effect relationships between an intervention and an outcome [18]. They are considered the highest level of evidence to establish causal associations in clinical research. Because randomization balances participant characteristics between groups, including known and unknown predictors of the outcome, it generally allows the attribution of differences in the outcome to the intervention being studied. There are many RCT designs and features, some of which are described in more detail below.

4.1.1 Explanatory and Pragmatic Trials

In the late 1960s, two French statisticians proposed a distinction between trials aimed at confirming a physiological hypothesis (explanatory) and trials aimed at informing a clinical or policy decision (pragmatic) [19]. More specifically, explanatory trials are designed to test the efficacy of an intervention in optimized conditions. They include highly specific eligibility criteria and strict protocols for the assessment of safety and efficacy [20]. The interventions are often delivered by specialized research personnel with expertise in research implementation, and the trial is carefully monitored and followed up. Establishing efficacy via an explanatory trial is a hurdle that needs to be overcome before an intervention can be approved by regulators and introduced into the market. Conversely, pragmatic trials are focused on providing evidence for an intervention in the context of real-world clinical practice and often inform clinical or policy decisions [21]. Pragmatic trials were developed in response to concerns that explanatory trials are not relevant to clinical practice due to their frequent lack of generalizability, and that they may overestimate the benefits of interventions [20, 21]. Therefore, pragmatic trials combat these issues by utilizing simple study designs with minimal trial procedures and data collection (e.g., mailed questionnaires, web-based forms, etc.) [21]. The interventions are delivered by staff with typical clinical experience to a large, unselected patient population. The primary endpoints of explanatory trials are usually surrogates of physiological endpoints that indicate the efficacy of an intervention, whereas primary endpoints of pragmatic trials often focus on patient-centered outcomes (e.g., survival, quality of life, and functional status) [20].

There are several benefits to using a pragmatic approach. First, pragmatic trials optimize recruitment efforts by reducing the burden of the study protocol on practitioners and patients and including a wider pool of participants [20]. The reduced burden of the trial increases the accessibility of participation in research to historically marginalized groups with limited transportation, finances, or time. Oftentimes, pragmatic trials include entire practices or registries, resulting in large and diverse study populations that improve the generalizability of the results. Second,

pragmatic trials are often cheaper to conduct than explanatory trials because fewer resources and specialized staff are required. Third, less frequent contact with participants in pragmatic trials minimizes the Hawthorne effect, in which participants change their behavior in response to their awareness of being observed [22]. However, there are also limitations to pragmatic trials. There may be more missing data in pragmatic vs. explanatory trials since follow-up in pragmatic trials is often conducted via mailed questionnaires or web-based forms, resulting in challenges for analysis and interpretation [21]. Additionally, pragmatic trials require a larger sample size for adequate statistical power due to increased nonadherence, dropouts, and crossover between groups compared to explanatory trials [20]. Since explanatory and pragmatic approaches exist on a continuum, it is important for researchers to consider design choices that will support applicability while preserving the ability to understand efficacy [23].

4.1.2 Registry-Based Randomized Controlled Trials

Registry-based RCTs use patient registries to collect data, randomize, and follow-up [24]. Eligible patients are identified prior to intervention selection when the registry is used for reporting, then the randomization service embedded in the registry randomizes participants to a treatment strategy [25]. Data in registries are typically obtained from patients, physicians, medical charts, electronic health records (EHRs), or other databases [24]. Benefits of registry-based RCTs include rapid consecutive enrollment of patients, improved completeness of follow-up, reduced cost of implementation, and enhanced generalizability. These trials tend to be pragmatic in nature since the eligibility criteria are less stringent, and the patient monitoring and follow-up reflect real-world circumstances rather than a controlled environment. The Thrombus Aspiration during ST-segment Elevation MI (TASTE) trial was one of the first registry-based trials [26]. This trial demonstrated that intracoronary thrombus aspiration plus primary percutaneous coronary intervention (PCI) vs. PCI alone did not reduce 30-day mortality in patients with ST-segment elevation MI; the cost was approximately US $50 per patient [24, 26]. Another example is the Bivalirudin Versus Heparin in ST-Segment and Non-ST-Segment Elevation MI in Patients on Modern Antiplatelet Therapy in the Swedish Web System for Enhancement and Development of Evidence-based Care in Heart Disease Evaluated According to Recommended Therapies Registry (VALIDATE-SWEDEHEART) trial. This was an open-label, registry-based RCT that demonstrated no difference in the primary composite endpoint of death, MI, and major bleeding events in patients receiving bivalirudin vs. heparin during a PCI [27].

Despite the benefits, registry-based RCTs also have challenges such as poor registry data quality, ethical issues, and methodological difficulties [24]. An example of an ethical concern is the level of informed consent that needs to be documented when all treatments administered are established and used in routine clinical practice. A methodological concern is that the registry may not include blinding,

standardized implementation procedures, and/or fixed follow-up duration. Trialists should acknowledge the challenges associated with registry-based RCTs and attempt to mitigate the impact of these challenges on study quality.

4.1.3 Electronic Health Record-Enabled Trials

EHR-enabled trials are large pragmatic RCTs that are conducted through the routine clinical setting [28]. Enhanced technology allows the RCT to be embedded in the EHR without disrupting clinical workflows [29]. The result is the full integration of knowledge generation and health-care delivery. Eligibility for the RCT may be assessed in real time as data are entered into the EHR or retrospectively by backward querying of the database [28, 29]. Additionally, randomization can be programmed to occur within the EHR system, and follow-up occurs naturally when patients interact with their health-care provider [29]. The strengths of an EHR-enabled trial are similar to registry-based RCTs (rapid consecutive enrollment, low cost, and enhanced generalizability) [28]. However, there are several limitations, including the initial cost of implementing EHR infrastructure that is appropriate for research facilitation; privacy and ethical considerations; and poor standardization and quality of data. Clinical staff typically use free-text boxes to record electronic health data, which can be challenging to translate into quantifiable data for an RCT. Furthermore, the interval of contact between patients and providers is not standardized like it would be in a traditional clinical trial protocol. Finally, the detail and accuracy of the data recorded will likely vary between staff members. These limitations must be addressed to ensure high-quality data collection.

4.1.4 Time-to-Event Outcome Studies

In time-to-event (TTE) outcome studies, subjects are followed longitudinally with a clearly defined start time and end time (usually until the event of interest or the last follow-up occurs) [30]. TTE endpoints are a measure of treatment efficacy. The TTE analysis simultaneously evaluates whether an event happened (i.e., a binary outcome) and when the event happened (e.g., a continuous outcome) [31]. It is important that the event is clearly defined and mutually exclusive (e.g., alive vs. dead, or hospitalized vs. not hospitalized). If the event is not mutually exclusive (e.g., becoming symptomatic), then a threshold must be defined to differentiate an event vs. no event.

Composite endpoints are often used to increase the number of primary outcome events [32]. In CV research, MACE is used as a common composite endpoint. Traditional (3-point) MACE includes CV death, nonfatal MI, and nonfatal stroke; thus, a TTE outcome study would capture the time to any one of these events. Other MACE composites (e.g., 4- or 5-point) may include outcomes such as revascularization procedures, unstable angina, and hospitalization for heart failure.

The power needed to analyze TTE data is dependent on the number of events instead of the total sample size, and the trial may be stopped early when a prespecified minimum number of events is reached [33, 34]. When calculating sample size, first the number of events needed to detect a minimum clinically important effect size with a preselected power and alpha level (*p*-value to declare statistical significance) is calculated [33]. Next, the proportion of patients who are expected to experience the event is estimated. The length of follow-up is based on the frequency of events, which may result in longer than anticipated follow-up if the event rate observed is below that projected during planning or vice versa [30].

In the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial, the median follow-up period was planned to be 4 years, but the actual follow-up was 2.2 years due to a higher than postulated event rate [35]. The trial demonstrated that treatment with evolocumab resulted in a 15% reduction in the risk for the primary composite endpoint (CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization). Following the "parent trial," patients were eligible to be enrolled in the FOURIER open-label extension (FOURIER-OLE) in which all patients were treated with evolocumab, regardless of their original treatment assignment in FOURIER [36]. After a median follow-up of 5 years, patients who had been originally randomized to evolocumab in the parent trial had a 15–20% lower risk of MACE, and a 23% lower risk of CV death, compared to the patients who were originally randomized to placebo. These data suggest that there is a delay in observing the full clinical benefit of LDL-C lowering. This illustrates the importance of utilizing a sufficiently long follow-up period in CVOTs.

Patients who do not experience the event of interest prior to their last follow-up and patients that do not complete their scheduled follow-up for reasons independent of the event of interest are described as censored patients [30]. It is not appropriate to exclude censored patients from the analysis since the event might occur at an unknown future time, so TTE analysis methods must be used to account for censoring. One example is the Kaplan–Meier method, which includes data from patients who had the event of interest and those being censored to estimate the probability of survival at different time points [30, 31]. Another challenge of analyzing TTE data is that not all participants are followed for an equal amount of time. For this reason, the log-rank test is the most popular method for comparing the survival of groups since it considers the entire observed follow-up using person-time units of observation (e.g., person-years) for all participants rather than selecting an arbitrary point in time [37].

4.1.5 Adaptive Designs

Adaptive designs use accumulating data, such as those from interim statistical analyses, to inform decisions on the modification of study design elements (e.g., sample size, randomization ratio, number of treatment arms, dose, and population) [38]. Adaptive designs increase the efficiency of RCTs and improve the likelihood of

identifying a benefit of the intervention, if one exists, while maintaining the integrity and validity of the trial [39]. There are two common adaptations that are applied to CVOTs [40]. First, the sample size may be re-estimated without changing the total number of events after a blinded interim review of the event rate. Second, the targeted number of events may be modified based on an unblinded review of the interim data. One strategy is to power the CVOT to demonstrate superiority, but to include an interim analysis to determine whether the trial should be continued or stopped early due to noninferiority or futility. Another strategy is to power the trial for noninferiority and then to update the study objective to superiority by increasing the total number of events and/or subjects if the interim analysis yields promising results for superiority.

There are several obstacles to implementing an adaptive design [39, 41]. Since adaptive designs are less conventional, funding and regulatory agencies often scrutinize proposals for adaptive designs more closely and require additional explanation for the rationale of the design. Additionally, the interim analyses should be conducted with care to avoid introducing bias into the trial [41]. It is best practice for an unblinded independent data monitoring committee to review interim data and then make recommendations to a blinded steering committee. All adaptation rules should be specified in the protocol prior to trial initiation. Finally, the interpretation of results from an adaptive trial will require extra care. A statistician with experience in adaptive designs should be consulted when creating the statistical analysis plan, and the trial processes and procedures that will be used to minimize potential operational bias should be described in detail.

4.2 Considerations for Designing Cardiovascular Outcomes Trials

4.2.1 Blinding

Blinding of study participants, care providers, research investigators, and outcome assessors is used in RCTs to minimize post-randomization bias (mainly performance bias and ascertainment bias) [42]. Performance bias occurs when care providers inadvertently administer different care to participants in the intervention arm. Ascertainment bias occurs when a researcher is influenced by group assignment during outcome measurement, verification, or recording. Blinding is optimal for RCTs but not always feasible due to methodological, technical, or ethical reasons. In open-label outcome trials, an external blinded outcome adjudication committee can be used to prevent differential classification of outcomes between interventions and controls [43]. In CVOTs, these committees are especially important for evaluating nonfatal endpoints such as unstable angina or revascularization procedures, which are more vulnerable to subjective evaluation [44]. However, some question whether the benefits of blinded outcome adjudication committees always outweigh the high cost and loss of efficiency in these trials.

4.2.2 Comparator Group

Placebo-controlled interventions blind participants and investigators to the allocated treatment by simulating the experience of receiving an experimental intervention without administering a therapeutic intervention [45]. The incorporation of a placebo arm controls for response bias (patients report outcomes that they believe will please the investigators) and the placebo effect (participants experience symptoms differently when receiving an intervention). Although administering a placebo is optimal for establishing the efficacy of a drug, the ethics of administering a placebo to patients with diseases for which an effective treatment has already been established come into question [46].

One option to mitigate the ethical concerns of placebos is to use historical control data to replace concurrent control data [47]. Data for historical controls often come from medical charts, published data of off-label use, registries, and previously completed trials. Using historical data is cost-efficient but requires robust justification and heavy involvement of regulatory bodies. Historical controls are most often used in trials studying rare diseases when a standard of care has not been established. A more common approach to mitigate ethical concerns of placebos in CV research is to administer a drug with established therapeutic benefits as an active control and then to test whether the new drug is noninferior to the established drug [46, 48]. The following section describes the difference between trials evaluating superiority, equivalence, and noninferiority among treatments.

4.2.3 Superiority Vs. Noninferiority Trials

The objective of a superiority (comparative) trial is to demonstrate that an investigative treatment is better than an active control or placebo [48]. The objective of equivalence trials is to show that treatment with either therapy does not differ by more than a predefined threshold in either direction, which is referred to as the equivalence margin and denoted by Δ [49, 50]. If the confidence interval that is computed around the difference between the two treatments lies within the equivalence margin ($-\Delta$ to $+\Delta$), then the two treatments are deemed equivalent [49]. The purpose of a noninferiority trial is to demonstrate that the new treatment is not worse than the active control [48]. Noninferiority trials employ one-sided hypothesis testing toward $-\Delta$ (also referred to as the noninferiority margin), while equivalence and superiority trials employ two-sided testing, highlighting the need to establish the trial goals *a priori*. Two treatments are determined to be noninferior if the lower bound of the confidence interval that is computed around the differences between the two treatments does not exceed $-\Delta$. Noninferiority trials are popular in CV research since, as described previously, it is often unethical to include a placebo arm in RCTs when a "gold standard" therapy for the disease being studied has already been established. When the efficacy of a new therapy is determined to be noninferior to the "gold standard" therapy, the new therapy should ideally have an alternative benefit such as lower cost, fewer side effects, or improved convenience.

Noninferiority testing should be designed and conducted with rigor because less rigor makes it easier to show noninferiority [49]. "Biocreep" or "technology creep" describes when an inferior therapy is erroneously deemed noninferior and becomes an active control group in a future trial, resulting in degradation over time in the efficacy of the investigational treatment. Defining the noninferiority margin is an important step in designing a rigorous noninferiority trial [50]. The margin should be based on one or more placebo-controlled trials of the active comparator or a meta-analysis of several placebo-controlled trials. Researchers must also apply clinical judgment to determine what level of loss of efficacy in a new treatment would become clinically meaningful. Selecting an unreasonably wide margin will yield a lower sample size requirement, resulting in an underpowered trial that is more likely to show noninferiority [48]. Additionally, rigorous noninferiority trials should be designed similarly to previous trials to fulfill the constancy assumption, which states that the effect of the active comparator is consistent with the effect that was previously observed [51]. It is not appropriate to draw conclusions about noninferiority when the constancy assumption is not met. Altogether, noninferiority trials provide an exceptional opportunity to advance CV research and impact clinical practice, but these trials must be expertly designed and conducted, rigorously analyzed, and carefully interpreted to avoid bias toward noninferiority [48].

4.2.4 Population

When designing a clinical trial, it is important that researchers consider the study objective, the safety of participants, the feasibility of the eligibility criteria, and the target population [52]. The purpose of early phase trials is to isolate the effects of the intervention; thus, a more homogenous population will reduce response variation. However, later phase trials should target more heterogeneous populations to ensure the trial is generalizable to the entire population in which the intervention will be utilized in clinical practice. Researchers should also consider the feasibility of eligibility criteria. Although strict eligibility criteria may be desirable, the criteria may need to be relaxed to ensure completion of the trial within a reasonable time frame. Furthermore, studies should be designed to enroll a group of participants with an increased risk that is attributable to a pathophysiological state that might be mitigated by the administration of the intervention under investigation.

4.2.5 Outcome Variables

When selecting outcome variables to measure in clinical trials, researchers should consider the clinical relevance, interpretability, sensitivity to the intervention, practicality, and affordability of the measurement [52]. In addition, clinical trials frequently use composite outcomes, which combine two or more variables into a single measure that is used to assess a treatment's efficacy, tolerability, and/or safety [53]. Composite outcomes may also be used in CVOTs to provide a more comprehensive

evaluation of the variables being studied, but they can also make the interpretation of clinical trial results more difficult. A positive result for a composite outcome does not equate to positive results for all variables that make up that composite outcome. Another limitation of composite outcomes is that the time-to-first occurrence of any event in the composite is often evaluated, thus later events, that may be more severe, are ignored [54]. Therefore, the effect of the intervention on the individual components should also be evaluated as a sensitivity analysis and, ideally, total events (as opposed to the first events) should also be evaluated.

As mentioned previously, the composite outcome of MACE is frequently used in CVOTs [55]. Although there is no standard definition for MACE, the classic definition focuses on the manifestation of ASCVD in the coronary and cerebral vessels (nonfatal MI, nonfatal stroke, and CV death), sometimes referred to as three-point MACE. Additionally, four-point MACE, which also includes hospitalization for unstable angina or revascularization procedures, and five-point MACE, which also includes heart failure, are commonly reported in the literature [56]. When choosing a composite outcome, the expected outcome of the intervention should be carefully considered. For example, in the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME), the primary outcome was the classic three-point MACE, but the trial demonstrated no effect of empagliflozin on two of the three key MACE components, MI or stroke [57]. Conversely, the risk of hospitalization for heart failure decreased by 35%, suggesting that the main effect of empagliflozin is on myocardial function, not atherosclerosis [55]. Similarly, in the Vitamin D and Omega-3 Trial (VITAL), there was no significant difference in the primary composite endpoint of MACE (MI, stroke, and CV mortality) between the marine-omega-3 fatty acids and placebo groups, but analyses of the individual components of the primary composite endpoint indicated a significant 18% reduction in MI [58]. Unfortunately, when the primary outcome is not significantly impacted, even if the secondary outcome(s) do show a significant effect, then regulatory approval for a new drug is improbable [59]. However, the findings for the secondary outcomes may contribute to the generation of new hypotheses that can be tested in subsequent RCTs.

4.2.6 Follow-Up Duration

Since CVOTs are driven by CV event occurrence, the length of follow-up is an essential component of the study design. Shorter follow-ups are more cost-effective but are vulnerable to overestimating the effect of the intervention since the estimated treatment effect varies randomly throughout the trial [60]. For example, Silverman et al. reported that the mean follow-up for CVOTs involving statins has been ~4.5 years, while other CVOTs involving nonstatin therapies have had even shorter follow-ups [61]. As described previously, the FOURIER trial was stopped after a median follow-up of 2.2 years when evolocumab demonstrated a 15% reduction in the primary composite outcome relative to placebo [35], but an even lower

risk of the primary endpoint was detected after the open-label extension when patients were followed for a median of 5 years (FOURIER-OLE) [36]. These data suggest that there is a delay in observing the full clinical benefit of LDL-C lowering, thus longer follow-up periods in CVOTs evaluating lipid-lowering therapies may be crucial.

In addition, stopping a trial early may limit evidence for important secondary and safety outcomes [60]. In the Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME 2) trial, in which PCI was compared with medical therapy alone, the trial was stopped after randomization of 54% of the initially planned study sample when PCI showed superiority for the primary outcome (all-cause death, MI, or urgent revascularization) [62]. However, the improvement with PCI was driven by fewer urgent revascularizations, which are arguably less clinically important than the other components of the primary outcome (all-cause death and MI) [60]. The results for death and MI were lower with PCI but did not reach statistical significance [62]. If the trial had continued longer, a significantly lower rate of death or MI may have materialized, improving the relevance and confidence of the trial findings.

4.2.7 Internal and External Validities

Internal validity evaluates whether the clinical trial was designed, conducted, and analyzed in a manner that answers the research question without bias [63]. Systemic error and random error are the two main factors that threaten internal validity of a trial. Systemic error results from four sources: selection bias, performance bias, detection bias, and attrition bias [64]. Effective randomization procedures, including appropriate allocation sequence generation and allocation concealment, reduce selection bias and balance known and unknown confounding factors [65]. Furthermore, performance bias occurs when there are systemic differences in the care provided to participants in different groups, and detection bias occurs when there are systemic differences in outcome assessment between groups [64]. Blinding participants, care providers, research investigators, and outcome assessors, and selecting objective outcome measures reduce the risk of performance bias and detection bias [66]. Finally, attrition bias occurs when there are systemic differences between groups in the loss of participants from the study [64]. Using an intention-to-treat analysis, which includes all randomized participants, minimizes the risk of overestimating the clinical effectiveness of the treatment.

External validity evaluates whether results from a clinical trial can be generalized to the "real world" population [64]. Results from a trial must have internal validity before being considered for external validity. Researchers may improve external validity by recruiting diverse populations, enrolling patients with a variety of clinical features and comorbidities, implementing interventions in a manner that is feasible in routine practice, and assessing a broad range of clinical outcomes.