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STATE-OF-THE-ART REVIEW

The Imperative to Enhance Cost-Effectiveness for Cardiovascular Therapeutic Development

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HIGHLIGHTS

- **Novel cardiovascular disease drug development is declining despite high incidence.**
- **A high-cost and high-risk environment is an increasing deterrent to drug innovation.**
- **Cardiovascular outcomes trials are lengthy and a major cost.**
- **Cost-effective solutions are needed to promote cardiovascular therapeutic progress.**

SUMMARY

Cardiovascular disease (CVD) is the leading cause of mortality worldwide. Therapeutic agents, such as those that lower low-density lipoprotein cholesterol, have been a critical factor in mitigating CVD event risk and demonstrate the important role that drug discovery plays in reducing morbidity and mortality. However, rapidly rising development costs, diminishing returns, and an increasingly challenging regulatory environment have all contributed to a declining number of cardiovascular (CV) therapeutic agents entering the health care marketplace. For pharmaceutical companies, a traditional cardiovascular outcomes trial (CVOT) can be a major financial burden and impediment to CV agent development. They can take as long as a decade to conduct, delaying potential investment return while carrying risk of failure. For patients, lengthy CVOTs delay drug accessibility. Without cost-effective CVOTs, drug innovation may be compromised, with CV patients bearing the consequences. This paper reviews potential approaches for making CV drug development more cost-effective. (JACC Basic Transl Sci 2024;9:1029-1040) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Cardiovascular disease (CVD) continues to be the leading cause of mortality worldwide, accounting for 17.9 million deaths in 2019,[1] and heart disease remains the number one cause of mortality in the U.S. with just under 700,000 deaths in 2022.[2] These statistics are despite the decades of effective cardiovascular (CV) therapeutics, such as those for lowering atherogenic lipoproteins and blood pressure.[2-5] While these therapies remain a core part of primary and secondary CVD prevention, significant scientific and technologic therapeutic advances continue to be needed to improve quality and quantity of life. Examples of recent advances include breakthrough device therapies for heart failure,

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ABBREVIATIONS AND ACRONYMS

BLA = Biologics License Application

CCTA = coronary computed tomographic angiography

CVOT = cardiovascular outcomes trial

IRA = Inflation Reduction Act

IVUS = intravascular ultrasound

MACE = major adverse cardiovascular events

NDA = New Drug Application

PCSK9 = proprotein convertase subtilisin/kexin type 9

clinical implementation of epigenomics, and the potent low-density lipoprotein cholesterol (LDL-C)-reducing proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor biologics.[6-8] However, compared with other therapeutic areas, there is significant underinvestment by the pharmaceutical industry and across biotechnology (biotech) companies where most innovation originates in the development of agents for CVD. Without an environment that promotes drug innovation, it is ultimately the patients, not the pharmaceutical industry, who pay the price.

Critical to the development of any novel therapeutic agent is the conduct of clinical trials; among most CV therapeutics, this includes at least 1 cardiovascular outcomes trial (CVOT). A CVOT is a large clinical trial that evaluates the effect of a therapeutic agent or intervention on clinical CV outcomes, which most often include CV death, myocardial infarction, and stroke (major adverse cardiovascular events [MACE]), and sometimes revascularization, hospitalization for unstable angina, and heart failure.[9,10] CVOTs also provide the opportunity to further assess the safety and tolerability of a new agent and evaluate its cost-effectiveness. The ideal design for a CVOT is double blind, randomized, placebo controlled, and statistically powered to achieve at least a 15% relative reduction of adjudicated MACE. Inherent to the current CVOT design is the need for large patient cohorts, years of intervention and follow-up, and numerous clinic visits, all under the risk umbrella that the agent being studied may never enter the health care market. In short, a CVOT is a high-cost, high-risk hurdle that may impede new drug development.

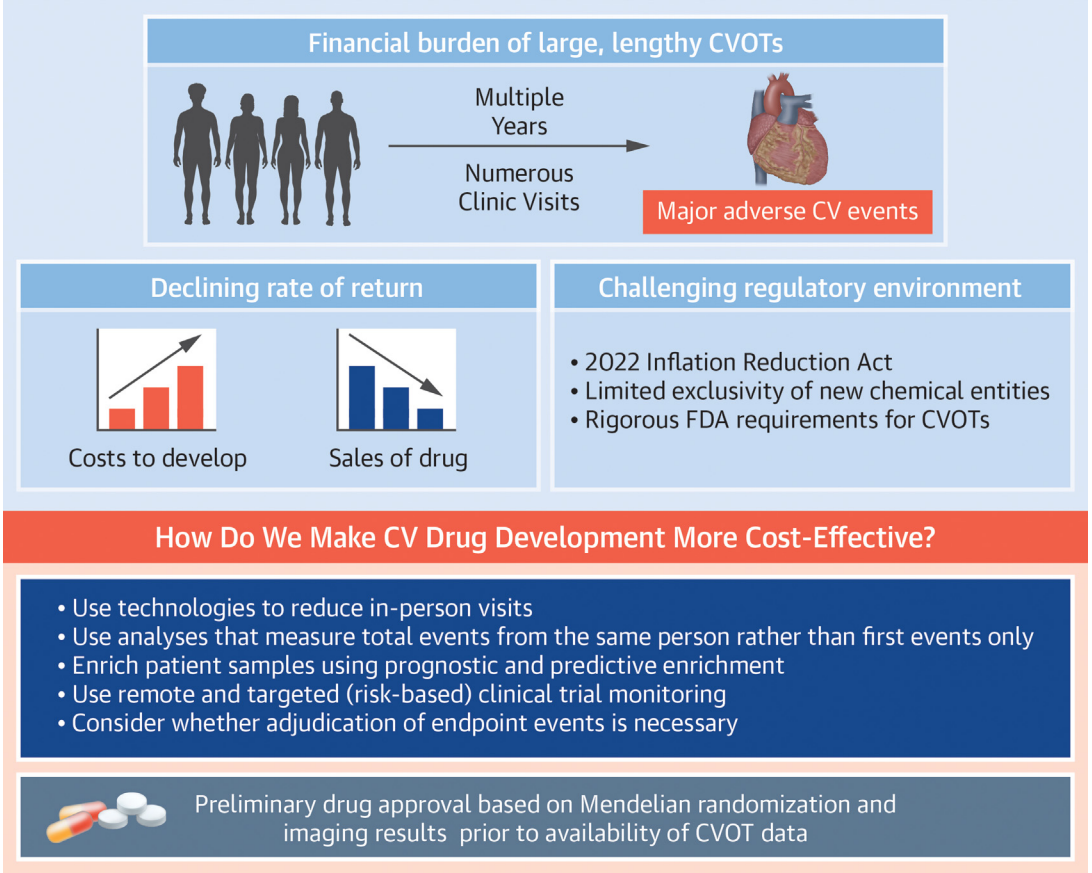
CVOTs are a significant portion of the total financial burden required for novel drug commercialization. CVOT costs are driven, in part, by the stringent regulatory requirements for conducting such a trial. Current legislation in the U.S. also dampens the ability for companies to recover this investment. Due to stringent exclusivity limitations on new chemical entities and, most recently, the Inflation Reduction Act (IRA) (described in detail later in this review), pharmaceutical and biotech companies may find the cost-benefit ratio of investing in a novel therapeutic agent development to be unfavorable, particularly for CV agents.[11,12]

Change is a natural component of the scientific process; thus, the drug development process, including its regulation, must evolve and adapt to ensure a balance between promotion of innovation while ensuring a favorable balance among the benefits, risks, and costs of a novel therapeutic approach. Various opportunities exist to enhance pharmaceutical agent innovation. There are potential regulatory incentives that could rebalance and improve the risk and return on investment for CV drugs that have demonstrated benefits on MACE. In our view, marked changes to the regulatory pathway for development of novel CV therapies, such as complete removal of the CVOT requirement for certain drug classes, are unlikely and would not be desirable. Therefore, this review focuses on potential strategies to reduce cost and time, and thus improve the efficiency and cost-effectiveness of CVOTs, without jeopardizing the quality of the development process (**Central Illustration**). The approaches discussed have the potential to reduce the number of participants required to show efficacy, shorten trial duration, and streamline processes related to trial monitoring and endpoint assessment. The inclusion of expanded cardiovascular endpoints beyond a standard 3- or 4-point MACE, as well as the use of selected surrogate endpoints to increase confidence in the likely efficacy of the therapeutic agent under development before undertaking the investment required for a CVOT and potentially to support interim approval of an agent while a CVOT is underway, are also discussed.

OVERVIEW OF THE PROCESS

Assessing CVOT cost-effectiveness first entails understanding the drug development process in the U.S., which is overseen by the Food and Drug Administration (FDA). The development process comprises: 1) discovery research and development aimed at identifying a therapeutic agent; 2) characterizing the agent's administration, absorption, distribution, metabolism, and excretion through preclinical studies; and 3) assessing its delivery, dose-response, pharmacokinetics, and efficacy in phase 1-3 clinical trials conducted in humans.[13] Phase 3 clinical trials are aimed at demonstrating efficacy and safety. CVOTs occur during phase 3, the clinical trial phase with the largest participant cohort, which is intended to be representative of the end users for the therapeutic agent. A New Drug Application (NDA) or a Biologics License Application (BLA), depending on the type of therapeutic agent, is submitted to the FDA to start the application process of drug approval for the health care market and commercialization.[14] The application process may be undertaken after the phase 3 program has been completed or, in some

CENTRAL ILLUSTRATION **Obstacles in Developing CV Therapeutic Agents**



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CV = cardiovascular; CVOT = cardiovascular outcomes trial.

instances, when a CVOT is underway and substantially enrolled.

CVOTs consist of randomized controlled trials where the primary efficacy endpoints are MACE that include CV-related mortality, myocardial infarction, and stroke, and may include other outcomes such as revascularization procedures and hospitalization for heart failure.[10] CVOTs also provide the opportunity to investigate the safety and tolerability of the agent under study in a larger number of patients treated for a longer duration than most other trials. However, a lower-cost option to further evaluate the long-term safety and tolerability of an agent after its efficacy has been established is through an open-label extension following the double-blind treatment period in a randomized controlled trial. Such an extension typically involves less frequent visits and is thus less costly than the double-blind phase. Most CVOTs use an explanatory design to test the intervention in optimized, highly controlled conditions.[15] However, some CVOTs are designed as pragmatic trials, which aim to inform a clinical decision in the context of real-world practice and focus on patient-centered outcomes such as survival.[15,16] Pragmatic trials offer a wider pool of participants and require fewer specialized staff than explanatory trials, but they also require a larger sample size to allow for statistical power owing to nonadherence, dropout, confounding of other medications or diseases, and crossover.[15,16] Because they mimic real-world conditions, they may offer more tangible and concrete data on what patients and their health care providers can expect from the therapeutic agent regarding safety and efficacy. Pragmatic trials are often more cost-effective than explanatory trials, but they still require significant investment, in both time and

resources, for drug development. Even within the context of an explanatory trial design, using real-world data to assist in the identification of potential trial participants and for the collection of some data may help to reduce costs.

The FDA has provided guidance documents for CV therapeutic agent development, including those to treat hyperlipidemia, hypertension, and heart failure.[17-20] The FDA recognizes LDL-C reduction as a surrogate for the reduction of CVD risk, and as such, it may not be necessary to have a completed CVOT before initial approval of agents for which LDL-C reduction is the primary target. For such agents, a CVOT must typically be in progress and substantially enrolled before starting the FDA's NDA or BLA process. For therapies that affect lipoprotein metabolism through novel mechanisms, such as lowering lipoprotein(a) or inhibiting cholesteryl ester transfer protein, apolipoprotein C3, or angiopoietin-like 3, current regulations indicate that a CVOT must generally be completed before initiation of the NDA or BLA process.

Therapeutics for the treatment of heart failure also require a CVOT for initial approval,[20] however, therapeutic agents developed for hypertension fall under the CV outcome benefits claim that covers all classes of antihypertensive agents, and therefore they do not require a CVOT as part of their development process.[17-19] CVOTs are not only required for CV therapeutics. CVD is a common comorbidity of type 2 diabetes mellitus (T2DM), and in 2008 the FDA recommended that clinical trials evaluating the efficacy of T2DM agents not only assess their effect on glycemic control, but also demonstrate that the novel agent does not increase CV risk.[21] This recommendation was withdrawn in March 2020, when the FDA released a new draft guidance document.[22] The new guidance was released because no CVOT conducted since 2008 as part of T2DM therapeutic drug development showed an increased risk of ischemic CV events. In fact, some CVOTs with novel T2DM therapeutics demonstrated a reduced risk of CV events.[22] Arguably, without the 2008 CVOT requirement for diabetes agents, there would likely not have been a pathway for using sodium-glucose cotransporter 2 inhibitors for the treatment of heart failure in patients without diabetes.[23] Because T2DM is a chronic condition, novel T2DM therapeutic agents require safety data addressing chronic exposure (eg, at least 4,000 patient-years of exposure of new drugs in phase 3 clinical trials) and trials enriched in those with established CVD.[22] It is now recommended that sponsors of antihyperglycemic medications use rigorous methods to collect adverse CV events and assess them by adjudication. However, a dedicated CVOT is no longer required.

The drug development process in the U.S. can extend for several years to several decades, depending on its technologic maturation.[24] A significant portion of this time is allotted to the new technology's initiation, defined as the exponential growth in its publication activity. For example, this period includes characterizing molecular pathways and potential small molecule targets. Once exponential growth ends, it is considered an established technology.[24] The median lengths of time between a technology's initiation to its establishment, first clinical trial, and first FDA approval are 25 years, 29 years, and 36 years, respectively. Although not as lengthy as the technologic discovery and maturation phases, clinical trials account for a significant portion of the time it takes to develop a drug.

Once clinical trials commence, the average length of time from the start of phase 1 to completion of phase 3 was 6.1 years in 2022 in the top 20 pharmaceutical companies by spending for CV therapeutics.[25] Using strategies that reduce the temporal load for completion of clinical trials is helpful for controlling costs and shortening the time required to deliver therapeutic benefits to patients in clinical practice.

COSTS OF DEVELOPMENT

The cost associated with drug development from discovery through commercialization is a key determinant of which therapeutic area, and its respective therapeutic agent(s), warrant investment. The average cost to bring a novel therapeutic agent to the market was $2.284 billion in 2022, and, collectively, the top 20 pharmaceutical companies by spending spent $139.2 billion in 2022 on research and development.[25] Meanwhile, the forecast value of approved therapeutic agents' peak sales has declined from $340 million in 2021 to $284 million in 2022 (excluding COVID-19 emergency use authorization assets). Collectively, the internal rate of return on late-stage pipeline therapeutic agents has consistently declined since 2013 and fallen to 1.2%, the lowest internal rate of return in the past decade, and to 0.6% when excluding COVID-19 emergency use authorization assets.[25]

Clinical trials are notoriously expensive with a median cost of $19 million per trial in the U.S., as assessed in a cross-sectional assessment from 2015 to 2017.[26] CV therapeutic development is particularly costly, with the estimated cost of trials per drug being $141 million (Q1-Q3: $74-$183 million). The next most

expensive therapeutic area was respiratory, which cost substantially less at $91 million (Q1-Q3: $73-$110 million).[26] CVOTs have some of the highest enrollment requirements, with participant numbers commonly in the tens of thousands.[26] There are several reasons why CV therapeutic development drives up clinical trial costs. One analysis suggested that the number of patients needed to establish efficacy is the largest single influence on cost.[26] From 2015 to 2017, the median cost per patient in a trial was $34,857 (Q1-Q3: $22,922-$50,540).

The declining internal rate of return of drug development, combined with increasing research and development costs, has led the pharmaceutical industry to scrutinize investment portfolios and determine which therapeutic areas to pursue and which potentially promising agents must be terminated. For example, although early phase development of antineoplastic therapeutic agents grew by 6.88% from 1990 to 2007, early phase development of CV agents within this same period decreased by 4.57%.[27,28] Once an agent reaches the clinical trial phase of drug development, the odds are still strong that it will be discontinued. According to the Congressional Budget Office, only 12% of drugs entering clinical trials are approved by the FDA.[29] Furthermore, the rate of discontinuation appears to be on the rise; a recent analysis found that among the top 20 pharmaceutical companies by spending, the number of terminated therapeutic agents doubled from 15 in 2021 to 30 in 2022.[25] Among potential CV agents, 12 candidates were terminated in the years 2016 to 2018 within the clinical trials phase of development: 3 candidates in phase 1, 6 in phase 2, and 3 in phase 3.[30] Half were discontinued owing to lack of efficacy and the other half owing to strategic or unspecified reasons. Overall, the later the development phase of the agent, the greater the financial burden of its failure.[31] Given the high stakes of drug development, it is not surprising that therapeutic target selection and development are likely driven by financial investment risk at least as much as the potential ability to meet a therapeutic need.

Additional investment considerations before therapeutic target selection include market saturation and the regulatory environment, the latter including both patent regulations as well as approval and commercial regulations. First-to-market pharmaceutical manufacturers are awarded 5 years of regulatory exclusivity for new chemical entities in the U.S. and 10 years in the European Union.[11,32] Once exclusivity is gone, the market can quickly become saturated and profit margins dwindle. Five years of exclusivity may not provide enough time to recover development costs, particularly for CV drugs. This can result in either failure to initiate a promising therapeutic agent or a significant price increase to offset projected losses attributed to shortened market exclusivity, both of which ultimately affect the patient.

REGULATORY ENVIRONMENT

CV therapeutic agent developers now face another challenge beyond the costly CVOT. The IRA was signed into U.S. law in 2022. Provisions included in it were intended to increase drug access and simultaneously decrease drug spending for millions of Americans on Medicare or Medicaid.[12,33] The federal government is the largest purchaser of prescription drugs in the U.S., with more than 25% of its health care costs attributable to prescription drugs.[34,35] The 3 critical components aimed to mitigate drug pricing in the IRA are: 1) redesigning Medicare Part D benefits to limit out-of-pocket spending; 2) penalization of pharmaceutical companies if they raise drug prices faster than inflation; and 3) mandatory price negotiations on high-cost drugs.[33,36] Mandatory price negotiations will affect any high-priced, small-molecule, single-sourced drugs that have been approved for marketing by the FDA for at least 9 years and any biologic approved for at least 13 years.[33] Advocates of the IRA predict that users could save thousands of dollars each year. For example, at least one simulation predicted that Medicare would save 5% on spending in the first 3 years of the act's implementation simply via the mandatory price negotiations.[33,36]

Critics of the IRA fear that its enactment discourages pharmaceutical and biotech companies from investing in drug discovery for new treatments and limits exploration of new uses for currently available medications.[33,37] This argument expands even to the generics market, traditionally viewed as a means to reduce drug costs. Generic competition can lower drug prices by 50% to 90%, and generic producers generally operate at a narrow profit margin. Implementation of the IRA may erase any profit margin for some generics, which could ultimately reduce competition and availability of some generic options.[33] An example of the importance of generic competition on drug prices is colchicine. A cohort study of 2,723,327 patient-years of individuals with gout from 2007-2019, designed to examine the implications of the 2010 FDA decision to remove lower-priced versions of colchicine from the market, showed that the price of colchicine prescriptions increased 15.9-fold and the out-of-pocket price increased 4.4-fold.[38]

For pharmaceutical companies, a 2015 study estimated that, on average, at least $2.5 billion in additional revenue is required to support novel therapeutic innovation.[39] Requiring price negotiations may affect the ability to achieve the minimum funding required to motivate novel drug-producing companies to innovate. Some have predicted that drug price controls will lower U.S. pharmaceutical revenues up to 60% by 2039 and result in up to 342 fewer novel drugs entering the marketplace over that timeframe.[40] On the other hand, increased government spending by Medicare on outpatient drugs, as observed with the implementation of Medicare Part D, has traditionally resulted in significantly greater investment in research and development by private pharmaceutical companies.[41]

Penalizing price increases beyond inflation rates may halt companies from pursuing novel indications for existing drugs, including conducting CVOTs to demonstrate new uses. After initial FDA approval, companies will often continue research to confirm that the therapeutic agent can work in the long term and to explore its potential use for new indications.[33] However, research shows that without pricing premium incentives, conducting confirmatory or follow-up studies is likely to be reduced.[42]

Finding a way to mitigate excessive prescription drug costs without compromising innovation investment will be critical as the IRA provisions are phased in over the coming years. For example, linking drug prices directly to their value may offset the consequences of capped prices. The IRA currently targets diseases that disproportionately affect elderly Americans, including CVD, and thus innovation for these treatments might be viewed as less profitable and therefore less favorable for innovative pursuits.[33]

There are potential regulatory incentives that could rebalance and improve the return on investment for CV drugs that demonstrate MACE improvements. The new chemical entity regulatory exclusivity is 5 years in the U.S. and 10 years in Europe.[11] A reasonable incentive is to grant 10 years of exclusivity in the U.S. to a CV therapy that demonstrates MACE reduction, or at least an additional 5 years of patent life extension to improve the return on investment.

The IRA allows the Centers for Medicare and Medicaid Services (CMS) to initiate price negotiations at postapproval year 9 for oral dugs (year 12 year for biologics).[12] Recently, CMS announced the first 10 drugs to be reviewed for price negotiations, including 6 oral CV drugs with proven benefits established by CVOT-based evidence.[43] Because the majority of CV therapeutics are oral, another potential incentive is to postpone price negotiations on oral CV drugs that have demonstrated MACE benefits to postlaunch year 12, similarly to the timeline for biologics. The cost of drug development is part of the consideration for how price negotiations are determined by CMS, but a special carve-out for CV drugs to allow the extra 3 years and provide parity to biologic therapies is a significant incentive to fund a CVOT.

In addition, because the IRA will very likely limit the pursuit of new indications for existing drugs, implementing a pricing structure framework for payers based on the amount of treatment efficacy, indications, and safety, in place of a one-size-fits-all approach, could keep pharmaceutical companies encouraged to continue to find the most efficacious therapeutics and to investigate additional indications.[33] For example, because CV therapeutics often require lengthy and expensive MACE-based CVOT data, having increased payer reimbursement for the continuation of these rigorous studies may incentivize pharmaceutical companies to continue to conduct CVOTs and to innovate around new indications. Payers requiring prior authorization may also indirectly increase drug costs because they cause significant delays and reduce treatment access.[44] Therefore, reducing this commonly encountered obstacle would likely lower costs for both drug developers and patients.

Risk of failure is another major financial factor considered in novel drug development. For example, among CV therapeutics, 2 monoclonal antibody PCSK9 inhibitors, evolocumab and alirocumab, entered the market in 2015 as potent well tolerated agents that decrease LDL-C, and both were subsequently shown to reduce MACE risk in CVOTs.[8] Evolocumab initially cost $14,300 per year,[45] no doubt priced to cover the millions of dollars invested for its development. However, bococizumab, a third PCSK9 inhibitor, was discontinued owing to lack of efficacy during its phase 3 clinical trial.[30] Although the high costs of medications such as these may make them unaffordable for some patients, nevertheless it should also be considered that, given the high cost of development accompanied by the high risk of failure, the pursuit of this efficacious drug class may not have occurred if the IRA policies had been in place at that time.

REDUCING COST FOR CVOTS

The criterion standard for a phase 3 CVOT is a randomized, double-blind, placebo-controlled, time to first event design, with a composite of MACE as the primary outcome.[10,46] A lengthy trial, lasting years, is

inherent to this type of study design. The longer the trial duration, the more that study visits, laboratory work, monitoring, data collection, and patient incentives cost.[26,47] Furthermore, whereas earlier clinical trial phases focus on isolating the effects of the intervention and therefore require a more homogeneous and less variable study group, phase 3 CVOTs enroll a larger, more heterogeneous study population to ensure that the results are generalizable to the group for which the drug would be expected to be used.[47] The primary cost driver of clinical trials is the number of patients needed to establish a treatment effect, but CVOT costs are further compounded by the second greatest cost influencer, the number of study visits, which is directly proportional to study duration.[26] Large patient cohorts, lengthy study duration, and, subsequently, a multitude of clinic visits, all significantly contribute to CVOTs being the most expensive trials to conduct during drug development.[26]

Lowering CVOT cost is not only in the best interest of the pharmaceutical industry, but also in the best interest of patients and payers, both private and public. Aside from the overt financial savings, patient health would benefit from reduced CVOT duration and a faster timeline to market, particularly in the development of novel therapies that are highly efficacious in preventing MACE. Reducing CVOT cost can be achieved by decreasing the sample size, reducing trial length, reducing the number of clinic visits, and streamlining trial monitoring. Also, as appropriate, consideration of adjunctive data from other sources, such as imaging studies, may help to increase confidence in the efficacy of an agent.

REDUCTION IN SAMPLE SIZE REQUIREMENTS. One way to reduce sample size and attenuate clinical trial costs is to use population enrichment. Enriching a patient population with those at highest risk for an event allows the study to be conducted with a smaller sample size for a given level of power. The FDA advocates the inclusion of prognostic enrichment for endpoint-driven studies.[48,49] In addition, in some instances, it may be possible to use predictive enrichment to focus on recruiting patients most likely to respond to the therapy being tested.[50,51] Data from previous trials with an agent in the same class or from mendelian randomization studies may be used to develop a scoring model to categorize individuals based on expected response for the endpoint under study or the biomarker being targeted (eg, LDL-C) in order to enrich the study sample with participants who have a larger predicted response.[50] Together, these two types of enrichments can increase the rate of accumulation of endpoint events in the control group and the magnitude of the effect. However, the trade-off of enrichment strategies is that more strict entry criteria limit the generalizability of the results and may result in a narrow indication for the agent once approved. Accordingly, additional testing may be required to expand the indication to a broader patient population.

REDUCTION IN NUMBER OF CLINIC VISITS AND TRIAL DURATION. Reducing the duration of CVOTs lowers the cumulative number of clinic visits, as well as the associated logistical considerations and costs, which can yield millions of dollars in savings. In a study assessing pivotal clinical trials supporting the approval of 101 new therapeutic agents, including 6 CV drugs, conducted from 2015 to 2017, the average number of clinic visits was 11 (Q1-Q3: 8-17), and each additional trial visit added $2 million to the estimated trial cost.[26] Reducing the overall length of a CVOT or the number of clinic visits can each contribute to cost savings and can be achieved through a variety of strategies. For example, newer technologies such as telehealth visits may be used in clinical trials to reduce the frequency of in-person visits. Routine safety assessments such as blood collection can be obtained through partnerships with large laboratory companies so that participants are able to have blood drawn more locally for some visits.

However, shortening the duration of a CVOT is associated with a potentially higher risk of failure to demonstrate efficacy, particularly for LDL-C–lowering agents. For example, although the cholesteryl ester transfer protein (CETP) inhibitor evacetrapib significantly reduced LDL-C by 31.1% (compared with a 6% increase with placebo), in the ACCELERATE (Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibitor With Evacetrapib) trial it failed to demonstrate a significant effect on the primary composite endpoint (HR: 1.01; 95% CI: 0.91-1.11; $P = 0.91$).[52] This was likely because the trial was terminated early for futility at a median follow-up of just 26 months, after 82% of the planned primary composite endpoint events had occurred. In contrast, in the REVEAL (Randomized Evaluation of the Effects of Anacetrapib Through Lipid Modification trial of another CETP inhibitor, LDL-C was reduced by 41% with anacetrapib vs placebo, and there was a significantly lower incidence of major coronary events (RR: 0.81; 95% CI: 0.85-0.97; $P = 0.004$) after a median follow-up of 4.1 years.[53] The IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial), which evaluated the effects of ezetimibe combined with simvastatin, reduced LDL-C by 16.7 mg/dL vs simvastatin alone (at 1 year), and significantly reduced the primary endpoint at 7 years

of follow-up (median 6 years) (HR: 0.936; 95% CI: 0.89-0.99; $P = 0.016$). Notably, a clear separation in event rates between treatment groups was not evident until approximately 3 years.[54] These results demonstrate the importance of not only the absolute reduction in LDL-C, but also its duration, for reducing MACE. Based on the Cholesterol Treatment Trialists' Collaboration's meta-regression of statin trials demonstrating a linear and predictable relationship between absolute LDL-C lowering and MACE reduction, and subsequent meta-analysis of CVOT duration, it is estimated that a CVOT with a median follow-up of around 3.5 years optimizes the probability of seeing a maximal MACE reduction benefit.[55,56] Designing a CVOT for lipid-lowering agents with this minimum follow-up duration may enable stakeholders to increase their return on investment in a CVOT.

A potential pitfall of using a shorter duration of follow-up in CVOTs of lipid-lowering therapies, which was experienced by the developers of the PCSK9 monoclonal antibody inhibitors, is that a shorter trial may result in a less-than-expected reduction in MACE compared with other lipid-lowering therapies for which the CVOT duration was longer. The CVOTs of evolocumab and alirocumab were ~2 years vs those for statins which extended to ~4 to 5 years. This affected the cost-effectiveness assessment of PCSK9 inhibitors used by insurance companies to implement payment plans, and thus reduced the use of PCSK9 inhibitors after their entry to the market.

REMOTE AND TARGETED (RISK-BASED) CLINICAL TRIAL MONITORING. Clinical trial monitoring is mandated by the FDA and represents another substantial portion of a clinical trial budget. As described by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice (GCP), monitoring aims to verify that: 1) the rights and well-being of the trial participants are protected; 2) the reported trial data are accurate, complete, and verifiable from source documents; and 3) the conduct of the trial is in compliance with the currently approved protocol/amendment(s), GCP, and applicable regulatory requirements.[57] Traditionally, monitoring is conducted on site and involves 100% verification of the source data for 100% of the participants. However, implementation of 2 alternative approaches, remote monitoring and targeted, or risk-based, monitoring, can reduce costs.[58,59] Centralized, remote monitoring of trial sites may actually improve trial oversight because it is ongoing and not limited in frequency, which enables earlier detection of issues. Targeted monitoring focuses on certain data points, sites, and events that have the highest impact on participant safety and credibility of the trial's results.[57] This generally requires less oversight and fewer monitoring visits, thereby providing the best value for the time and resources invested. The FDA has provided guidance on using remote and risk-based approaches to monitoring.[60,61]

TOTAL EVENTS VS FIRST EVENT. The use of composite endpoints that consider only first (index) CV events may underestimate the utility of a treatment and lengthen the time necessary to accumulate enough events to assess efficacy. After an initial nonfatal event there is high likelihood of a recurrent event.[62,63] In recent years, several analyses have been completed to assess total CV event incidence in CVOTs, including in trials of lipid-altering agents, including ezetimibe, PSCK9 inhibitors (evolocumab, alirocumab), bempedoic acid, and icosapent ethyl, and heart failure therapies, such as candesartan.[64-70] As an example, **Table 1** summarizes results from IMPROVE-IT that randomly assigned post-acute coronary syndrome patients to receive simvastatin plus placebo or simvastatin plus ezetimibe.[54,64] During the median follow-up period of 6 years, the difference in the number of primary outcome events was 170 fewer in the ezetimibe group.[54] However, there was a greater difference for additional events, with 251 fewer in the ezetimibe group. Had total events (ie, including first and additional events) been used for the primary outcome, both the cost and the length of the trial could likely have been reduced.[64] Power calculations using total events are conceptually more complicated than those for first events. However, as represented by the results from IMPROVE-IT, using total events allows accumulation of more events per unit of time, which would result in a smaller sample size needed to reach a specified number of endpoints.

Recurrent or total event analyses are not without limitations, such as selection bias, because randomization is not preserved after the first event, a potential overestimation of total events contributed by patients who experience MACE early in the trial, the inability to fully account for reduced compliance over time as a CVOT progresses, and confounding related to subjects who die from either CV death or non-CV death during the trial.[71] However, time to first event analyses are associated with problems of interpretation because less severe events that happen earlier in the study (eg, brief hospitalization for heart failure) would be counted, whereas more severe events (eg, death) that happen after an initial event would be censored. Total events analyses are generally accepted as valid, and a variety of approaches can be

used for such analyses.[72-75] An ongoing trial of evolocumab (Evolocumab Very Early After Myocardial Infarction trial; NCT05284747), is using the total (first and subsequent) composite of myocardial infarction, ischemic stroke, any arterial revascularization procedure, and all-cause death as the primary outcome measure.

ADJUDICATED VS NONADJUDICATED MACE. The FDA typically requires central adjudication of complex or subjective efficacy and safety endpoints in randomized controlled trials supporting drug approval, including MACE in CVOTs.[76,77] Centralized adjudication is performed by a panel of experts who independently review and classify suspected endpoints in a blinded manner, and evaluate whether these meet the protocol definitions of endpoint criteria. This process can be quite complicated and costly because it involves identifying the cases to be adjudicated; collecting the data for adjudication (ie, case report forms, laboratory test results, radiography results, etc); ensuring that the data are anonymized and masked; identifying, inviting, and training members of the adjudication panel; and organizing and conducting consensus meetings among the panel members. Although adjudication can help to avoid misclassification of endpoint events, the significant investments in time and resources for using a central adjudication committee, particularly in blinded clinical trials conducted by qualified investigators who have access to technology enabling accurate on-site diagnosis, have called it into question.[78,79] A meta-analysis of data from 47 randomized controlled trials (N = 275,078), which were mainly large multicenter trials in cardiology, found, on average, no difference in the treatment effect estimates from on-site assessors compared with an adjudication committee, although results of a subgroup analysis showed an interaction according to the blinded status of the on-site assessors.[79] Another meta-analysis of 10 CVOTs that included more than 9,000 events from 95,038 patients failed to detect an effect of event adjudication; the OR for adjudicated vs reported events was 1.00 (95% CI: 0.97-1.02).[80] Based on these findings, it can be argued that centralized adjudication may not be necessary for all CVOTs. Eliminating or streamlining the adjudication process may be a way to reduce the costs of a CVOT without reducing the quality of the evidence.

CONSIDERING EXPANDED CARDIOVASCULAR ENDPOINTS AND SURROGATE ENDPOINTS. As mentioned previously, CVOTs often use a standard 3-point composite MACE as the primary endpoint, consisting of nonfatal myocardial infarction, nonfatal stroke, and CV death.

TABLE 1 Summary of Results From an Analysis of First and Total Primary Outcome Events in the IMPROVE-IT Trial

	Simvastatin + Placebo	Simvastatin + Ezetimibe	Difference	HR (95% CI)	*P* Value
First events	2,742	2,572	−170	0.94 (0.89-0.99)	0.016
Additional events	2,241	1,990	−251	-	-
Total events	4,983	4,562	−421	0.91 (0.85-0.97)	0.007

Sources: Cannon et al[54] and Murphy et al.[64]

However, 4- and 5-point MACE that include additional outcomes such as coronary revascularization (urgent or emergency), hospitalization for heart failure, or hospitalization for unstable angina have also been used in the primary composite MACE endpoint in selected CVOTs. History suggests that only the components that are part of the primary composite are candidates for a new agent's approved indication, which affects the return on investment in the CVOT. Therefore, it is important to select the most suitable cardiovascular endpoints, according to the putative biological effects of the therapeutic agent, to produce a robust clinically and statistically significant effect on the primary composite outcome.

Finding suitable surrogate non-MACE primary endpoints is another option that may reduce therapeutic agent development duration and cost. Atherosclerosis is the key underlying pathophysiologic driver of clinical CVD event risk.[81,82] A growing body of evidence supports the view that coronary atheroma volume progression and regression predict higher and lower incidence of MACE, respectively.[81,83] Intravascular ultrasound (IVUS) and coronary computed tomographic angiography (CCTA) can be used to quantify changes in atheroma volume. A systematic review and meta-regression analysis of IVUS studies recently published by Iatan et al demonstrated that a 1% reduction in mean percentage atheroma volume achieved with lipid-altering therapies was associated with a 14% to 25% reduction in the odds for MACE.[84] Fewer investigations have examined MACE and changes in atherosclerotic plaque with the use of CCTA, but in general the results appear to be consistent.[85,86] Studies that measured plaque volume in the same patients with the use of both IVUS and CCTA demonstrated a high correlation between these methods, with correlation coefficients in the range of 0.91 to 0.98.[87,88]

Development and validation of other surrogate measures of MACE risk, such as biomarkers of plaque stability, also have the potential to increase the confidence needed to invest in CVOTs for promising CV

therapeutics.[83,89] Independently from lipid lowering, statins and PCSK9 inhibitors have been shown to promote coronary atheroma calcification, reduce the lipid core burden index, and increase fibrous cap thickening, all changes that represent improved coronary plaque composition and stabilization.[90-92] Results from imaging studies showing regression or less progression of atheroma volume and/or increased plaque stabilization might justify approval of an agent on an interim basis while a CVOT is underway. Inclusion of atheroma volume progression as an "event" in a composite endpoint might be another way to enhance the efficiency of a CVOT. The composite endpoint might include fatal and nonfatal myocardial infarction and stroke, coronary revascularization, unstable angina, and total atheroma volume progression of at least 3.5% (or some other threshold). This is analogous to the composite outcomes in trials for renal function, which may include new cases of dialysis, renal transplantation, renal death, and a 40% (or some other threshold) reduction in estimated glomerular filtration rate.[93]

CONCLUSIONS

CVD is a leading cause of death in the U.S. and worldwide. Finding novel therapies to mitigate CV morbidity and mortality should be a high priority. Unfortunately, the current drug development requirements for CV therapeutics and limited exclusivity for new chemical entities in the U.S. compared with some other developed nations are deterring investment, owing to high costs and perceived risks. Finding ways to lower CV therapeutic development costs, particularly those associated with the conduct of CVOTs, without compromising the evaluation of drug efficacy and safety, is imperative for the promotion of continued investment in CV therapeutic discovery and development.

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