Review: Clinical Trial Methodology

CLINICAL INVESTIGATION

New considerations in the design of clinical trials for anti-atherosclerotic drugs

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The purpose of this article is to review the current landscape of new therapeutic targets, advances in biomarkers and imaging technologies, regulatory sciences, and their collective potential impact on the development of novel anti-atherosclerosis drugs. Current development challenges such as the design of pharmacodynamic (indicative or surrogate biomarker) and 'hard' end point studies are reviewed. The reader can also expect to learn about advanced collaborative efforts that will likely have an impact on future initiatives.

Keywords: atherosclerosis • biomarkers • clinical development plan • high-density lipoprotein • hypercholesterolemia • low-density lipoprotein

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Atherosclerosis is a progressive condition with enormous worldwide implications for economic, social and physical health. At the beginning of the 20th Century, cardiovascular disease was only the fourth leading cause of death in the USA. Today, coronary heart disease causes approximately one of every six deaths, and stroke causes approximately one in every 18 deaths in the USA. The total direct and indirect cost of cardiovascular disease and stroke in the USA for 2010 was estimated to be US$503.2 billion [1]. Furthermore, hospitalization rates categorized by age groups indicate that acute myocardial infarction and ischemic heart disease become important diseases by the time a person is in their fourth or fifth decade of life.

Pathophysiology & therapeutic targets

Risk factors have been uncovered and diligent efforts have unraveled the etiology of atherosclerosis. Known risk factors include smoking, high blood pressure, high cholesterol, diabetes, inflammation, obesity, male gender, age, genetic predisposition and inactivity [2]. Many of these risk factors are modifiable with lifestyle changes, but resistance to change behaviors have blunted efforts to reduce hypertension, obesity and hypercholesterolemia, which has led to an increasing reliance on pharmacologic intervention. Biomarkers and potential disease surrogates have been discovered, and novel therapeutic agents have emerged. Therefore, the need is great for new, cost-effective, therapeutic options.

Progressive vascular disease has been recognized for more than 150 years, but our understanding of the process has evolved significantly over that time. In the mid 19th Century, the German pathologist, Rudolf Virchow, recognized that fatty deposits in the blood vessels cause blockages leading to strokes and heart attacks. Atherosclerosis is characterized by the excess accumulation of lipid-laden macrophages within the arterial wall. It is now recognized that multiple small lesions in the coronary circulation wax and wane during adulthood. The ultimate fate of these lesions (either in regression or in a clinical event) involves inflammatory response including endothelial expression of adhesion molecules, release of cytokines and chemokines, involvement of reactive oxygen species, macrophage accumulation in the arterial wall and

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incorporation of oxidized low-density lipoprotein (LDL) cholesterol (LDL-C) [3]. Lesions that become fragile may rupture, causing a catastrophic abrupt closure of a major vessel and substantial myocardial or neuronal cell death, manifesting as a myocardial infarction or stroke [4].

Targeted therapies that lower LDL-C, primarily the statins, have reduced morbidity and mortality in the broad population very cost-effectively. Since these drugs lose patent protection, an even greater percentage of the global population is likely to be benefited. In the large controlled trials, statins (and other LDL-lowering methods) have reduced cardiovascular morbidity by approximately 30%. Various researchers are seeking to address the remaining risk by investigating new targets. The most-studied potential contributors include:

- Raising high-density lipoprotein (HDL) cholesterol (HDL-C) via biologicals or small molecules;
- Other lipid fractions, lipoproteins;
- Modulators of inflammation.

Drugs that are targeted for novel mechanisms often require new drug-development paradigms. Each drug-development strategy will be discussed below, along with the primary methods to monitor response.

Drugs that lower LDL-C

The results of the Lipid Research Council study of the late 1970s established LDL-C as a modifiable risk factor and a prime target for anti-atherosclerotic intervention. However, total mortality reduction was not achieved until more powerful statins were used in the mid-1980s [5]. The determination of effect was easily demonstrated; the Lipid Research Council had established qualified laboratories to test cholesterol efficiently, noninvasively and cheaply, and allowed for the promulgation of 'know your cholesterol' efforts of the American Heart Association. The explosion of interest made clinical studies straightforward, as plenty of patients knew their risk factors and were willing to participate in studies. The efficacy of the agents was recognizable after a few days of dosing, and results of the effect on LDL (which was assumed to be a surrogate of risk for heart disease) was available to subjects immediately after a study concluded. The regulatory authorities stated that a reduction of LDL of 15% was required for approval of a systemically absorbed agent, and the required safety experience was approximately 700–2500 subjects exposed to the agent, for up to 2 years. All of the statin labels were essentially the same. The sponsors quickly sought to differentiate their products by performing regression studies using quantitative coronary angiography (QCA), B-mode ultrasound and peripheral vascular imaging. The early methodology for these tests were awkward, but persistence lead to greater reproducibility. By March 1990, the US FDA advisory committee agreed that QCA and B-mode ultrasound were useful methods for assessing the progression or regression of atherosclerosis. In the early 1990s, the Cholesterol and Recurrent Events trial and the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) studies demonstrated reductions in morbidity in primary and secondary populations , and in 1997 the Scandinavian Simvastatin Survival Study demonstrated a reduction on all-cause mortality. All subsequent statin-development plans have followed a similar course; with the assessment of LDL followed by changes in atherosclerosis and finally at least one end point study. The end point studies were turned to virtuous ends by exploring new populations: for instance, patients considered at low-to-moderate risk but with an elevation in an inflammatory marker (e.g., the high-sensitivity C-reactive protein [hs-CRP]). The correlation of change in LDL to vascular changes to cardiovascular risk allowed for the rapid assessment of many new statins, as well as other LDL-lowering strategies. The use of placebos has become much more difficult with the success of new drugs, so new statins must be compared with available drugs of the class.

Drugs that increase HDL

Similarly to high LDL, low HDL-C is a strong independent risk factor for cardiovascular disease. However, the extrapolation to drugs that increase HDL has been more problematic. In 1990, the FDA advisory committee proposed that a positive change in HDL, along with a change in vascular pathology (as measured by QCA or intima-media thickness [IMT]), would be sufficient for approval of a new drug. However, the late 1990s and 2000s saw several compounds that increased HDL fail to significantly reduce cardiovascular outcomes. In one instance, a cholesterol ester transfer protein (CETP) inhibitor increased major adverse cardiovascular events. However, the detrimental effects may not be class-related and currently several new CETP inhibitors are under development. Other HDL strategies in earlier stage development include short-term infusion of reconstituted HDL or apolipoprotein (apo) AI, and vaccines targeting CETP [6]. In the development plans for these compounds, change in total HDL (or HDL subfractions) are used as the marker for dose-selection. Subsequent studies with imaging, primarily carotid IMT, intravascular ultrasound (IVUS) or MRI, provide greater confidence that a positive effect in the vessel may lead to a reduction in cardiovascular events, as well as increased exposures to subjects to build a strong safety database. Finally, a cardiovascular end point study is required.

Drugs that effect inflammation or other soluble parameters

The third category of anti-atherosclerotic drugs includes agents that target inflammatory modulators such as P-selectin, TNF-α, IL-1, leukotriene, lipoprotein-associated phospholipase-A2 and matrix metalloproteinase. Other strategies include altering the form of LDL, either oxidized or small-dense LDL or effecting the lipid composition of the vessel wall (e.g., acyl coenzyme A: cholesterol acyltransferase inhibitors). All of these programs are in early stages of development [7]. These programs are challenged to find soluble markers that will allow for the characterization of an adequate dose response. Once a dose has been selected, most programs have moved directly to imaging studies to document regression as well as a robust safety profile. The imaging modalities employed for these programs may be more esoteric, such as spectroscopy, thermography, elastography or other methods that may correlate with the purported mechanism-of-action of the new therapeutic candidate. Once again, cardiovascular end point studies are required to define the risk–benefit ratio and to gain registration of the product.

Imaging modalities & soluble biomarkers in drug development

An improved understanding of atherosclerosis pathophysiology has improved with the advancement of various high-technology tools. Diagnostic tools and biomarkers have also played a critical role in the development of anti-atherosclerosis agents and their importance will likely continue to increase. The biomarkers that have historically played a key role in the development of anti-atherosclerosis drugs include lipid assays and imaging technologies such as QCA. Drug-development tools such as genomics, proteomics, soluble plasma markers and advanced imaging technologies, such as IVUS, PET, CT scan, B-mode ultrasound and MRI, are already being applied to current development programs and will likely play an increasingly important role in future programs.

Since atherosclerosis is a disease affecting the vasculature, imaging the vasculature remains the most direct way of measuring atherosclerosis progression and regression. There are a variety of cardiovascular imaging technologies currently in use, all with some advantages as well as limitations.

Quantitative coronary angiography has been used for over three decades to assess progression and regression of atherosclerosis in coronary vessels by permitting determination of the minimum luminal diameter and the percentage diameter stenosis [8]. QCA is an invasive procedure in which a catheter is advanced through a large artery and into the coronary arteries to inject contrast material. The images are then analyzed for presence of atherosclerotic narrowing or percentage stenosis as compared with 'reference' segments. Good correlations between QCA findings and established risk factors such as hypertension and hypercholesterolemia have been established. In addition, when QCA has been used as a tool in the evaluation of anti-atherosclerotic therapies, good correlations were found to exist between the reduction in cardiovascular disease risk and coronary artery stenosis [9]. Many drug-development programs in Phase II–IV continue to incorporate coronary QCA assessments as indicators of efficacy. QCA measures are not considered as a 'surrogate' for morbidity and mortality determinations, and therefore, do not replace the need for definitive, large-scale studies for registration. Results from angiography studies have been the basis of new indications for currently marketed drugs, and will continue to have utility in defining potential effects of new products.

Intravascular ultrasound is an invasive imaging technique providing high-resolution cross-sectional tomographic images. The precise and accurate measurement of coronary atherosclerosis with IVUS has resulted in its increasingly common use in clinical trials assessing anti-atherosclerosis drugs, which in turn has resulted in improvements in standardized image acquisition, analysis and interpretation of the resulting data. Phase II IVUS clinical trials have provided useful insights into potential efficacy or lack thereof, serving a critically important role in determining if investment in large Phase III clinical trials are justified [10]. Accumulating evidence suggests that changes in IVUS measurements correlate with changes in clinical outcomes [11]. However, large-scale trials such as those being conducted by national and international research networks will be needed to understand the relationship conclusively.

As compared with coronary arteries, carotid arteries are more easily imaged noninvasively because they are superficial, relatively stationary and have a large diameter. The anatomy is also particularly well suited to reproducible serial imaging because of easily identifiable landmarks (e.g., the bifurcation and carotid bulb). Atherosclerotic deposits in the carotid arteries are fairly common and are linked to atherosclerosis in other vascular beds including the coronary arteries [12,13]. Carotid atherosclerosis has also been correlated with major cardiovascular adverse outcomes such as stroke and myocardial infarction [14]. Measurement of carotid IMT with B-mode ultrasound has been a favored noninvasive method for assessing the effect of new therapies on atherosclerosis. Beginning with the Cholesterol Lowering Atherosclerosis Study in the 1980s, many potential and proven anti-atherosclerotic agents have been evaluated using this method [15–19].

Experience in multicenter trials with this technology, in both standardized image acquisition, as well as image analysis, has increased the reliability of carotid IMT as a tool used for anti-atherosclerosis drug development and its use continues in both early as well as late-stage clinical trials. Additional refinements in this technology may allow for the morphologic assessment of plaques, providing incrementally more utility in drug development. In order to include an assessment of carotid IMT in a study include: at least four vessels need to be imaged (internal and external carotids on the left and right side) and the intervention difference needs to be defined and must be clinically relevant. Most trials have used the change in carotid IMT over a period of 18–24 months as the primary outcome. Additional refinements include the use of microbubbles and other contrast agents, 3D imaging, as well as stratified gray-scale median analysis and color mapping of the carotid plaque.

PET is a noninvasive imaging technique in which a biologically active radionuclide is introduced into the body and the emitted γ-rays are detected by a tomographic device. PET may become a very useful tool for locating lesions, as well as assessing the response to new anti-atherosclerosis therapies that work by an anti-inflammatory mechanism. Novel PET agents are also being developed to more precisely evaluate the inflammatory activity of plaques [20].

MRI is a commonly used diagnostic imaging procedure for evaluating structures of the heart including the myocardium, pericardium, valves and congenital abnormalities. Further development of targeted contrast agents may enhance the utility of MRI to provide valuable information about the effect of an intervention. Trials designed to validate the use of advanced MRI techniques for the characterization of atherosclerosis are under way. Several single- and multi-center clinical trials using MRI have demonstrated lipid-lowering therapy to have a beneficial effect on the carotid plaque morphology and plaque regression [21,22].

Other intravascular technologies currently being developed for research and clinical use include near-infrared spectroscopy, thermography, elastography, optical-coherence tomography and radiofrequency backscatter. Near-infrared, which is based on the absorption of light by organic molecules, has been used to identify the lipid content of biological specimens and may help in the detection of plaques vulnerable to rupture [23]. The identification of these 'weak' spots may be useful in predicting clinical events and measuring the effect over time of an anti-atherosclerotic agent expected to stabilize plaques, rather than change overall plaque volume. Optical-coherence tomography is a technique utilizing back-reflected infrared light to distinguish vessel wall components (e.g., calcium, fibrosis, lipid and necrosis) based on their optical properties, or the optical attenuation coefficient of the tissue. Software has been developed to provide 'virtual histology' as compared with atherectomy specimens. These technologies are currently being used to assess changes in plaque composition over time and correlations with changes in lipid levels in clinical trials [24,25].

Compared with imaging biomarkers, blood biomarkers in drug development have advantages and disadvantages. Blood biomarkers are usually easier to obtain, less expensive to measure, require less technical expertise to collect and pose no or minimal risk to the patient. The blood biomarker for atherosclerosis that has been most extensively discussed during the past decade is the inflammatory marker hs-CRP. hs-CRP is an important marker of risk, which adds prognostic information across a wide group of patients. Many drug-development programs include hs-CRP within their bank of soluble markers to assess potential drug effects. LDL-C-reducing therapies have consistently demonstrated an ability to decrease hs-CRP levels over time [26]. However, it is unknown whether the isolated reduction in inflammation will translate into a decreased risk for cardiovascular events, or if reductions in inflammation are simply the result of anti-atherosclerosis effects by other mechanisms. Therefore, inflammatory biomarkers remain useful tools to assess biological activity of novel anti-atherosclerotic agents, but are not considered surrogate markers for therapeutic effectiveness.

End point studies

Most cardiovascular drug programs include provision for an event-driven end point study. Following the results of studies such as the Hypertension Optimal Treatment [27], Scandinavian Simvastatin Survival Study [28] and Cholesterol and Recurrent Events trials [29], the medical community was prepared to accept decreases in blood pressure and LDL-C as a surrogate end point for overall improvement in mortality. The belief in surrogates was extended to other areas such as diabetic control, based upon hemoglobin A1c, and heart failure medications (positive ionotropes) based on exercise tolerance. However, several notable failures, likely resulting from 'off-target' activity, lead to a reversion to the requirement for stronger evidence – proof of a reduction in cardiovascular events. Further concerns about competing mechanisms leading to possible negative effects has even lead to some calls for requiring a reduction in total mortality to obtain drug approval.

Sample size is a critical factor in the design of end point trials and deserves careful attention, especially as it is difficult to determine the appropriate end point incidence. Several factors affect this. One is the selection bias towards healthier patients enrolling in

clinical trials as compared with the general population. Another is that advances in medicine are continuously reducing morbidity, such that a study that is based on data/outcomes may be 10 years behind the 'true' rate of events by the time that the 'new' study has completed. Further difficulty lies in predicting how large a 'risk' reduction would be plausible given the mechanism of action and specific agent under evaluation. Other end point trial design considerations include the use of large simple studies that may be cost effective, particularly in European countries where end point data is available to government agencies, as seen in the Helsinki Heart Study [30], and the use of adaptive design where data is reviewed rapidly and protocol modification decisions are made based on algorithms defined *a priori*.

Two important and related elements of an end point study include the Data Safety Monitoring Board (DSMB) and the End point Committee. These committees frequently report their findings to a Steering Committee, which is responsible for the overall conduct and scientific integrity of the trial. In 2006 the FDA issued a 'Guidance for Industry' regarding the use of DSMBs [101]. The increasing use of DSMBs has resulted from the growing number of industry-sponsored trials with mortality or major morbidity as an end point, Institutional Review Board/Ethics Committee concerns regarding trial monitoring and patient safety in large multicenter trials and increased awareness of the need for approaches to protect against inaccurate and/or biased results. The constitution of the DSMB should be independent of any investigators that enter patients into the study and include physicians with a clear understanding of the anti-atherosclerotic agent under evaluation, including its mechanism of action, safety profile and the know effects of other similar agents. DSMB membership should include at least one statistician, with significant clinical trial experience, and should have an absence of serious conflicts of interest.

End point adjudication committees may be of particular value when end points are subjective and/or require the application of a complex definition such as is typical in the development of anti-atherosclerotic agents. Cardiovascular and noncardiovascular death, myocardial infarction, unstable angina, transient ischemic attack, stroke and hospitalization due to heart failure have collectively been known as major adverse cardiovascular events. Cardiovascular end point studies typically use major adverse cardiovascular events to define both efficacy and safety, with some minor variations depending on the mechanism of action. The Clinical Data Interchange Standards Consortium and the FDA have proposed standard definitions as of 17 November 2010 [102]. These standard definitions should serve to facilitate DSMB and End point Committee review, and help ensure adequacy and comparability of drug-development programs and end point studies across the board.

Recent advances in web-based systems have significantly improved the logistics involved in expediting End point Committee and DSMB review. In web-based systems, an adjudicator can access data relevant to a clinical event from a secure website via the Internet. All documents, including source documents such as x-ray film, CT scan and MRI images, are available for review. The adjudication form can also be completed online. The adjudicator remains blinded to the study treatment and unaware of any decisions reached by the other adjudicators. If the event package has been sent to two adjudicators and both agree in their end point assessment, the case is closed. If the experts disagree, a mismatch is recorded and either resolved at an expert committee meeting or allocated to a third adjudicator for a casting vote. In addition, randomization protocols can be incorporated into the system along with the allocation of events to separate committees. These recent advances when applied to drug-development programs help ensure that critical study assessments can be made efficiently and accurately.

Further advantages may be realized as the use of web-based systems and electronic medical records gain increased acceptance in clinical trial design. One example of innovative technology application is the Alliance study [31] in which databases of several large closed-panel Health Maintenance Organizations were used to select patients, and capture end points, and thereby reduce bias in clinical entry and expediting trial execution.

Globalization

Atherosclerosis is a global concern with some regional nuances. The USA and Europe have experienced decreasing mortality due to myocardial infarction and stroke over the past few years. While this is obviously a positive trend, fewer deaths has not resulted in a healthier population, but rather has resulted in a larger percentage of patients 'at risk'. Many patients experiencing a myocardial infarction that would have lead to death a few decades ago have now become patients with compromised myocardium or frank congestive heart failure. Other countries are experiencing an increase in both an 'at risk' population and cardiovascular deaths as relative affluence has lead to increased caloric intake and reduced activity. The so-called BRIC (Brazil, Russia, India and China) countries as well as Turkey and Mexico have experienced a significant growth in the middle-class [3], and the population at risk for glucose intolerance in these countries will outstrip that of the USA and Europe in the next few decades [32]. The practice of cardiology is expanding as well in these countries, but resources for cardiovascular disease will need to compete with other needs, such as infectious disease.

While the 'flattening' of the world, in terms of cardiovascular disease as well as economics, has increased the global burden of disease, medical practice has expanded to address the disease patterns. As a result, clinical trials have undergone globalization and the inclusion of patients from developing countries has rapidly expanded. Between 1995 and 2005, the number of clinical trial sites located outside the USA more than doubled, while the proportion of trials conducted in the USA and Western Europe significantly decreased. The benefits of this trend include shorter timelines for clinical testing, lower cost and improved translation of clinical trial results to local populations. In contrast, the globalization of clinical trials has raised some scientific and ethical concerns including potential lack of research experience at some investigational sites, inadequate protection of patient rights, disparity in healthcare standards, enticement of financial incentives in poorer populations and lack of availability of approved drugs in countries contributing to research efforts.

Pharmacoeconomics

The steady and insidious process of atherosclerosis progression, compounded by concerns that new medications should be assessed when administered with (and not instead of) optimal medical therapy, have placed great challenges in the path of those who strive to develop better, more effective therapies. Further adding to these challenges is the high cost of conducting randomized clinical trials designed to assess end points of cardiovascular morbidity and mortality. This cost is a significant risk to the company developing the product, particularly given the reality of late-stage drug failures. These challenges may be insurmountable for small biotechnology companies with limited resources and have discouraged even some large pharmaceutical companies from pursuing this line of development. Furthermore, if a novel agent is developed successfully, the high cost of development is eventually passed on to individual payers and governments, who are already burdened with the high cost of healthcare.

The success of future therapies will be dependent on the value for investment, and the assessment of value will be increasingly an objective assessment. The rule-of-thumb of benefit over the past 50 years has been similar to dialysis and kidney transplant, or approximately $50,000 per year of quality-adjusted life saved. The overall increase of the price of healthcare (10–20% of GDP in most economies) has placed a greater emphasis on reducing costs. The upshot has been a decrease in the number of diagnostic and interventional procedures in cardiology, as cardiovascular disease has received a disproportionate amount of resources over the past 20 years due to the death rates. As many drugs have become available as generic products, the incidence of severe disease has also been reduced in areas such as stroke and congestive heart failure related to hypertension. Whether these changes will, in the long run, result in reductions in vascular disease as well as the manifestations of microvascular disease including dementia and renal disease is not yet clear.

Regulatory sciences

There are currently no official regulatory guidelines for the development of anti-atherosclerosis drugs that work by a novel mechanism. However, in the USA, a Special Protocol Assessment prior to initiating a pivotal trial has been encouraged. Available therapies that reduce the impact of atherosclerotic cardiovascular disease are largely made up of LDL-lowering agents and antihypertensive agents, both of which have relied on biological markers of disease to detect drug effects and gain regulatory approval. In 1996, Aurecchia *et al*. from the Center for Drug Evaluation and Research (CDER), FDA, published a paper entitled 'Regulatory Concerns at Various Phases of Drug Development', which outlined views on the development of new drugs [33]. Considerations in the development of anti-atherosclerotic drug products with novel mechanisms including the modification of structure and/or functional properties, increasing HDL levels, modulating inflammation, inhibiting thrombosis at sites of plaque ulceration or altering vasomotor tone and reactivity, were outlined. While it was noted that the approach to clinical development should be tempered by the mechanism of action and may therefore not be generalizable, the expectation was that the trials be centered on clinical end points. At that time it was also recognized that QCA had value in drug-development programs, but not as a surrogate for clinical risk reduction, and that newer technologies including IVUS, CT scans and PET "may assume accepted roles in monitoring the impact of therapy and may provide support for marketing indications".

In 2004 the FDA outlined its concerns about development efficiencies in a document titled 'Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products' [103]. The Critical Path Initiative has subsequently been launched to identify key areas where scientific advances may best be applied to aid drug development. Current FDA efforts include:

- Development of validation pathways for biomarkers [104];
- Evaluation of pooled internal databases to provide guidance on markers of toxicity;
- Expansion of public–private partnerships for nonproprietary, common interests.

One example is the formation of the Predictive Safety Testing Consortium that submitted data to FDA in 2007 to qualify seven novel renal biomarkers of acute kidney injury. A FDA Renal Biomarker Qualification Team was formed to review the submission and provide recommendations for action to CDER. The objectives of this effort are to determine potential utility for novel biomarkers of renal toxicity in order to aid in initial dose selection in clinical studies, allow drugs with preclinical renal toxicity signals to be studies safely in the clinic and to select patients with early acute kidney injury to enrich clinical trials, among others. These markers are now being incorporated into several Phase II–III clinical trials.

Other FDA efforts to advance regulatory science include its collaboration with other government agencies, academic institutions and sponsors worldwide to standardize cardiovascular end points, definitions and case-report forms. These efforts are intended to improve the quality and efficiency of cardiovascular trials; to provide end point definitions so that events are clearly characterized by objective criteria and reported uniformly; to standardize data collection to capture key elements; to simplify analysis of events in drug-development programs or among different clinical trials; and to more easily identify trends and other safety signals. The benefits of this initiative will simplify the process and reduce the cost of conducting clinical trials, facilitate agreement on how to define end point events, provide for uniform reporting of end point events, simplify the analysis of cardiovascular events in drug-development programs or among clinical trials and allow access to this database in a way that allows academia to address other research questions [34].

The FDA Draft Guidance Document issued in 2010 entitled, 'Qualification Process for Drug Development Tools' was recently issued and is intended to provide a framework to identify data needed to support qualification of a drug-development tool (i.e., biomarkers or patient reported outcome instruments) [105]. This is another example of the initiatives undertaken by the CDER to help guide the use of drug-development tools. It is anticipated that this guidance will encourage individuals and companies with an interest in these drug-development tools to advance their development.

The European perspective has been made much clearer by the recent promulgation of new guidelines for lipid-lowering agents [106]. The new gudelines reiterate that the goal of therapy is to reduce morbidity and mortality, but that other evidence, such as change in LDL-C (and to a lesser extent HDL and triglycerides), are important predictors of a drugs' success. Similarly, the imaging modalities – specifically mentioning carotid IMT, IVUS and MRI – have evolved to demonstrate vascular burden. The generation of data in two different vascular beds with two different methodologies – such as ultrasound/IMT of the carotids combined with IVUS of the coronaries – is robust. In addition, the guidance prefers regression to a lack of progression. Therefore, the European view of development of anti-atherosclerotic drugs is broadly similar to that in the USA (i.e., the need for an event-driven study in the appropriate population). It is difficult to predict what work will be required in Japan, although approvals in the USA, Europe and other countries (such as the Canadian Health Canada and Australian Therapeutic Goods Administration), are helpful.

Future perspective

Based on the continuing need, the expanding population at risk and the rapid advancement of technology, it may be entirely possible that the field will have evolved in a number of ways within the next 5–10 years. The broad application of antihypertensive and hypocholesterolemic agents has made a significant contribution to the overall reduction in mortality from vascular disease, even as obesity and glucose intolerance has been on the incline. While interventional procedures that 'fix' an identifiable lesion have resulted in reduced symptomatology, the benefits of pharmacological treatment have not been surpassed by mechanical means [35,36]. The need for further improvements in pharmacological therapy is clearly necessary, but the benefits of the present drugs have lead to a high threshold in terms of efficacy and safety.

Future advances will require diligent effort and careful planning. Health care economics will continue to play a significant role in the identification of new products for development. New classes of lipid-altering or hypotensive agents will need to prove a benefit in comparison with the best available therapy in terms of longevity – and still be cost effective. While several recent attempts to develop an agent that meets these stringent requirements have failed, costing hundreds of millions of dollars, there are several reasons to be hopeful about future endeavors. These include:

- The establishment of public-private partnerships to improve methods of detecting early signals of safety and efficacy;
- Globalization of healthcare and clinical trials;
- Increased knowledge about off-target effects;
- Improved understanding of pathophysiology.

The extension of the inflammatory model to vascular disease has already yielded multiple new targets. Recent failed attempts to effectively reduce total mortality

through the pharmacologic increase of HDL-C have lead to a better understanding of the complex physiology associated with 'good cholesterol' and many new agents have entered the development pipeline. The present paradigm of identifying safety concerns early in the development stages, using noncompetitive platforms, should help reduce late-stage attrition.

The total cost of development is unlikely to be reduced, as novel therapeutics will need to demonstrate efficacy and safety in broad, general populations in combination with the optimal therapy available. However, further advances in biomarkers and imaging technologies are expected to lend increasing levels of confidence in results from early-stage clinical trials, to make decisions about continued development or cancellation of drug-development programs. Alterations in trial design, such as iterative/adaptive designs and/or large simple studies that rely on advances in information technology may provide a cost-effective means of reducing costs in the future. These will be important considerations for companies with the interest and expertise to develop new cost-effective therapeutic options, despite the inherent risks.

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Executive summary

- Clinical and societal needs will continue to drive the search for new anti-atherosclerotic drugs in the years ahead.
- The successes of the past generation in producing treatments for cardiovascular disease has led to an increased percentage of the population on chronic therapy for known risk factors, to stave off a terminal event.
- Many new anti-atherosclerotic agents are under development and innovative efforts remain active.
- Technological advances in the development of biomarkers and imaging technologies will help improve the understanding of atherosclerotic disease and assess the effects of novel therapies on disease progression.
- Collaborative efforts will help reduce late-stage attrition by identifying safety concerns early in the development stages, using noncompetitive platforms.
- End point studies will remain pivotal to the most cardiovascular drug programs, and will rely on global participation, web-based technologies, standardized definitions and procedures, committee oversight and innovation.
- International regulatory agencies are aware of the need for new therapeutic options for a growing population with atherosclerotic disease, and are working to improve the regulatory framework to support the development of safe and efficacious products. While economics will remain a major factor in the development and success of new compounds, advances in the field have supported the continued investment in the search for better anti-atherosclerotic therapies.

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■■ **Latest information on the requirements for the approval of lipid-altering drugs in Europe.**