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THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Cardiovascular Drug Development

Is it Dead or Just Hibernating?

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ABSTRACT

Despite the global burden of cardiovascular disease, investment in cardiovascular drug development has stagnated over the past 2 decades, with relative underinvestment compared with other therapeutic areas. The reasons for this trend are multifactorial, but of primary concern is the high cost of conducting cardiovascular outcome trials in the current regulatory environment that demands a direct assessment of risks and benefits, using clinically-evident cardiovascular endpoints. To work toward consensus on improving the environment for cardiovascular drug development, stakeholders from academia, industry, regulatory bodies, and government agencies convened for a think tank meeting in July 2014 in Washington, DC. This paper summarizes the proceedings of the meeting and aims to delineate the current adverse trends in cardiovascular drug development, understand the key issues that underlie these trends within the context of a recognized need for a rigorous regulatory review process, and provide potential solutions to the problems identified. (J Am Coll Cardiol 2015;65:1567–82) © 2015 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AD = adaptive design

NME = new molecular entity

PFS = progression-free survival

ROI = return on investment

Despite significant improvements in cardiovascular mortality over the last several decades, cardiovascular disease remains the leading cause of death both in the United States and the rest of the world (1–3). Heart disease and stroke will result in an estimated 24 million deaths/year worldwide by 2030, and will continue to represent the dominant cause of death among the most prevalent chronic diseases (4–6) (**Figure 1**). Furthermore, mortality and morbidity due to cardiovascular events continue to climb globally as a result of rising cardiovascular disease rates in low-income countries, resulting in increasing disparities in outcomes as a function of wealth and education (7). The burden of cardiovascular disease clearly remains both a major public health concern and growing global challenge.

Notwithstanding this increase in cardiovascular disease prevalence worldwide, investment in cardiovascular drug development has stagnated over the past 2 decades, with relative underinvestment compared with other therapeutic areas (8–13). This alarming trend appears to reflect the business strategy in the pharmaceutical industry of maximizing return on investment (ROI) by focusing on areas currently felt to be most lucrative (8,9). As discussed in the following text, the reasons for these trends are multifactorial. However, a particularly important factor is the high cost of conducting cardiovascular outcome trials in the current regulatory environment that demands a direct assessment of risks and benefits using clinically-evident cardiovascular endpoints for approval rather than biomarkers or putative surrogates. These realities suggest that although the cardiovascular disease burden continues to grow and innovative scientific discoveries continue to occur, investors have concerns regarding what they describe as regulatory uncertainty and high development costs, leading to negative effects on ROI for novel cardiovascular therapies.

To work toward consensus on improving the environment for cardiovascular drug development, stakeholders from academia, industry, and government convened in July 2014 in Washington, DC. This paper summarizes the proceedings of this "think tank" meeting, the specific aims of which were to:

1. Delineate the current adverse trends in cardiovascular drug development;
2. Understand the key issues that underlie these trends within the context of a rigorous regulatory review process that is a key aspect of drug development; and
3. Provide potential solutions to the problems identified.

CURRENT TRENDS IN CARDIOVASCULAR DRUG DEVELOPMENT

Between 2000 and 2009, U.S. Food and Drug Administration (FDA) approvals for new cardiovascular drug therapies declined by approximately 33% compared with the prior decade (11). During the discussions, FDA representatives reported parallel adverse trends in investigational new drug applications to the

Cardiorentis, Janssen, Novartis, Pfizer, and St. Jude Medical. Dr. Wasserman is an employee of Amgen, Inc. Dr. Braunstein is an employee of Regeneron Pharmaceuticals and a retired employee of Merck; and owns stock in both Regeneron Pharmaceuticals and Merck. Dr. Pitt is a consultant for Pfizer, Bayer, AstraZeneca, scPharmaceuticals, Relypsa, Aurasense, Da Vinci Therapeutics, Stealth Peptides, and Tricida; has stock options in Relypsa, scPharmaceuticals, Aurasense, Tricida; has a patent pending for site-specific delivery of eplerenone to the myocardium; has served on data monitoring boards of Novartis, Johnson & Johnson, Oxygen Biotherapeutics, and Cytopherx; and has served on the events committee of Juventis. Dr. DeMets is a consultant to the National Institutes of Health, the Food and Drug Administration, and the pharmaceutical and medical device industry on the design, monitoring, and analysis of clinical trials; and receives compensation for serving on several industry-sponsored data and safety monitoring committees, including AstraZeneca, Amgen, Actelion, GlaxoSmithKline, Merck, Sanofi, Boehringer Ingelheim, Teva, and AbbVie. Dr. Armstrong received research grants from Boehringer Ingelheim, Merck Sharp & Dohme in conjunction with Duke Clinical Research Institute (DCRI), GlaxoSmithKiline, Amylin Pharmaceutical, Inc. in conjunction with DCRI, Merck & Co., Inc., Sanofi-aventis Research and Development, and Regado Bioscience; and received consulting fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Merck & Co., Inc., F. Hoffmann-La Roche Ltd., Axio/Orexigen, Merck, Eli Lilly, and Bayer. Dr. Berkowitz is an employee of Bayer HealthCare. Dr. Scott is an employee of and shareholder of Amgen, Inc. Dr. Prats is an employee of The Medicines Company. Dr. Stockbridge is an employee of the Food and Drug Administration. Dr. Peterson has received research grants from the American College of Cardiology, American Heart Association, Eli Lilly & Co., Janssen Pharmaceutical Products, and the Society of Thoracic Surgeons; and has received consulting fees from AstraZeneca, Bayer AG, Boehringer Ingelheim, Genentech, Janssen Pharmaceutical Products, Merck & Co., and Sanofi-Aventis. Dr. Califf has received research grants from Amylin, Bristol-Myers Squibb, Eli Lilly & Co., Janssen Research and Development LLC, Merck, and Novartis; and received consulting fees from Amgen, Bayer Healthcare, BMEB Services LLC, Medscape LLC/heart.org, Merck, Novartis, Regado NJ, and Roche; and has equity in N30 Pharma and Portola. The views expressed are those of the authors and do not necessarily reflect official National Heart, Lung, and Blood Institute positions. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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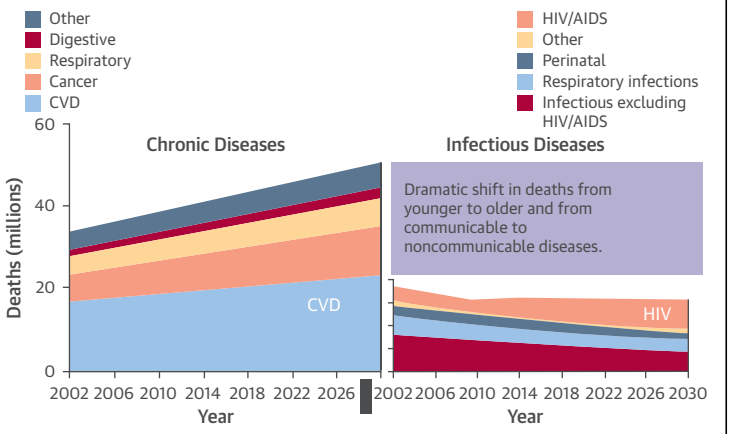
Division of Cardiovascular and Renal Drugs for new molecular entities (NMEs) seeking approval for marketing (with no change in investigational new drugs and a relative decline in new marketing applications), including NMEs for cardiovascular disease, from 1991 to 2013 (personal communication, N. Stockbridge, December 6, 2014) (**Figure 2**). Parallel analyses that evaluated regulatory approvals for cardiovascular therapies demonstrated a similar temporal decline, but showed that approvals in several other therapeutic areas, including oncology, rose substantially during the same time frame (11).

CARDIOVASCULAR DRUG DEVELOPMENT COMPARED WITH OTHER THERAPEUTIC AREAS. The application of genomic technologies, as well as systems biology approaches, have collectively identified multiple potential new cardiovascular drug targets, as well as actual molecules with potential cardiovascular applications. Unfortunately, these scientific advances have not stimulated an increase in new cardiovascular drug development. Early-phase research and development appear to have stagnated, with fewer molecules in the cardiovascular research pipeline compared with other therapeutic areas. In an analysis comparing the number of drugs undergoing early-phase development at 2 separate intervals (1990 to 1999 vs. 2000 to 2007), the development of antineoplastic agents grew from 16.55% to 23.43% (+6.88%), whereas the development of cardiovascular agents experienced the strongest contraction of any therapeutic area (-4.57%) (9). Furthermore, the success rate for antineoplastic drug approvals increased during this time interval (10). An analysis of all FDA NMEs from 2000 to 2012 found that oncology drugs had not only the greatest number of NME applications (n = 61), but also the highest rate of first-cycle FDA approvals of all therapeutic classes (72%) (12). In contrast, cardiovascular drugs had significantly fewer NME applications (n = 21) and a much lower rate of first-cycle approvals (32%). The current portfolio of drugs being evaluated in clinical trials reflects these trends, with a steep rise in cancer drugs being tested over the last 2 decades (**Figure 3**) (13).

RISING DRUG-DEVELOPMENT COSTS AND THE CONCEPT OF REGULATORY UNCERTAINTY. Notwithstanding the issues that appear to be impeding cardiovascular drug development, during the last decades, the overall pharmaceutical research and development processes have become less efficient in converting promising therapies into actual approved and marketed agents (**Figure 4**) (14). In 2005, the average capitalized cost to bring 1 new biopharmaceutical product to market, including the cost of failures, was $1.24 billion (14). These high drug-development costs caused overall research and development spending to exceed $50 billion in the United States in 2008.

FIGURE 1 Global Burden of Disease: Chronic and Infectious Diseases 2002 to 2030

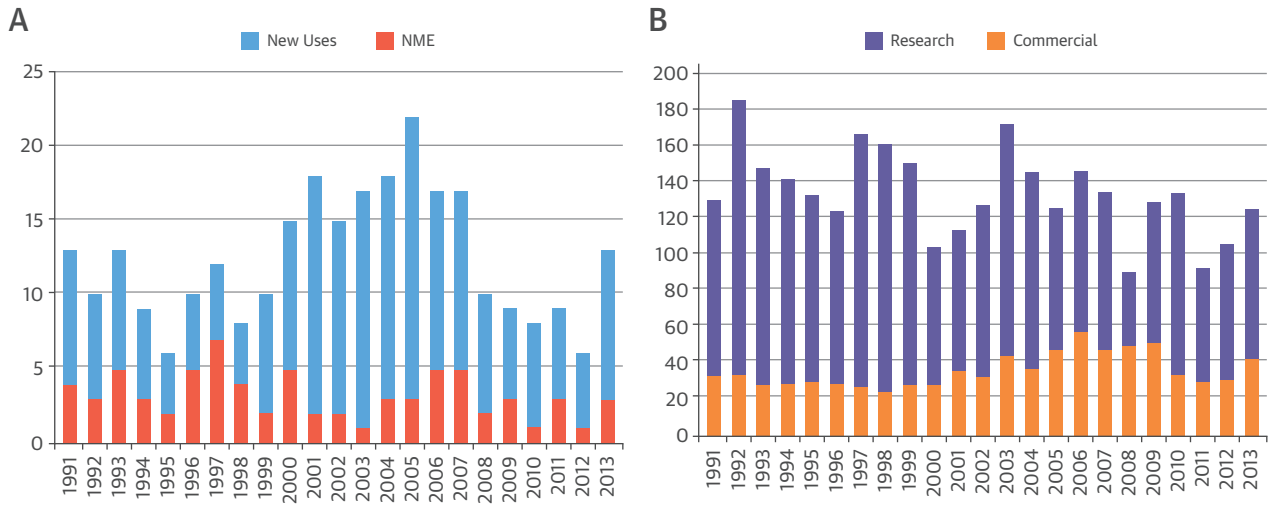


AIDS = acquired immune deficiency syndrome; CVD = cardiovascular disease; HIV = human immunodeficiency virus. Reprinted with permission from Fuster et al. (4) and adapted with permission from and Mathers and Loncar (6).

The high costs of drug development were considered by meeting participants to include the perceived complexities and obstacles in navigating the regulatory drug approval process. Although the critical role of the FDA and other regulatory agencies to balance the timely approval of effective therapies with the need to protect the public from harmful drugs was discussed and strongly endorsed, the concept of "regulatory uncertainty" appears to be deep-seated in the pharmaceutical industry.

The pathway for drug development is becoming more complex and costly for industry, but given multiple prior instances of drugs receiving regulatory approval that eventually resulted in patient harm through post-market analyses, there is intense government and public scrutiny on the regulatory drug approval process (15). Nonetheless, the reality is that the pharmaceutical industry will always be the dominant funding source for drug discovery—a finding reinforced by recent analyses that found that between 40% to 80% (16,17) of randomized controlled trials published in top-tier medical journals were funded by industry sponsors. Pharmaceutical representatives at the meeting cited regulatory uncertainty as not only a common concern across industries (18,19), but also a key influence on decisions regarding the specific development of innovative cardiovascular drugs given the high cost of regulatory failures during drug discovery. Despite these concerns, the FDA representatives expressed a strong willingness to meet early with industry representatives to discuss plans for a

FIGURE 2 Marketing Applications for New Uses and NMEs and Research and Commercial IND Applications Received by the FDA by Year

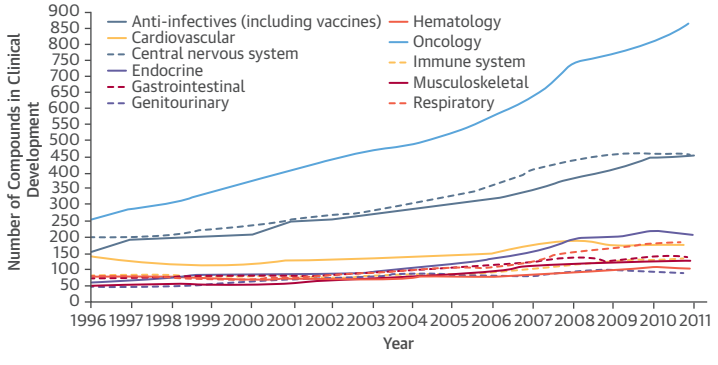


(A) Marketing applications received by the FDA Division of Cardiovascular and Renal Drugs for new uses and new molecular entities (NMEs) by year; **(B)** investigational new drug (IND) applications received by the FDA for both research and commercial by year. New use applications are for previously approved drugs that are reviewed for a new indication in future transactions. NME refers to a new drug application reviewed for its first approved indication. Commercial IND applications are those intended to be marketed for therapeutic use. Research IND applications are those not intended to be marketed for therapeutic use, but for research purposes.

drug-development program to provide guidance and feedback regarding the potential regulatory pathways for a promising therapy before the launch of pivotal registration trials.

Studies in economics and finance have found regulatory uncertainty to be potentially a major source of unpredictable variation in the return on business investment (20). The regulatory state is often perceived as a key component of the "external environment" that pharmaceutical companies must take into account when making capital investments or deciding whether to enter competitive markets (18). Some therapies may follow a known regulatory pathway, which may decrease the time to drug approval. For other therapies, the pathway for regulatory approval has not been defined or has been influenced by prior regulatory decisions for therapies in a similar class, so the timeline for drug approval may be expected to be prolonged or difficult to predict. The FDA also recognizes that although innovative drugs are more difficult and costly to develop, they may also be more difficult to review given the lack of experience with a new therapy or indication (21). Thus, although regulatory uncertainty may be a key factor influencing the trends in cardiovascular drug development, the path forward may involve early, in-depth discussions with industry representatives and regulatory agencies that would be expected to guide decisions about how to structure a development program that addresses an unmet need in clinical practice, but also appears viable within the context of a rigorous but fair regulatory review process.

FIGURE 3 Innovative Compounds Between Phase I and III Development Over Time



Adapted with permission from Berggren et al. (13).

REGULATORY ISSUES ASSOCIATED WITH THE GLOBALIZATION OF CLINICAL TRIALS. From a contemporary United States perspective, the globalization of cardiovascular clinical trials has resulted in increased regulatory complexity at both the FDA and European Medicines Agency (EMA) (22). Although recent efforts have been made to standardize regulatory reporting in Europe (23), the EMA remains a decentralized organization, with each European nation still having its own drug agency and regulations. Because cardiovascular drug registration

trials typically involve many countries to meet enrollment goals, a large and experienced pool of cardiovascular site investigators is critical to the success of these trials. However, over the past decade, the number of FDA-regulated investigators based outside of the United States has grown by 15% annually, whereas United States–based investigators have declined 5.5% annually over the same interval (24). Nonetheless, studies have shown that the FDA approves drugs faster than the EMA and Health Canada (median: 303, 366, and 352 days, respectively) (25), but enrollment in cardiovascular registration trials has appeared to shift to non-Western countries with perceived greater enrollment potential and lower operational costs. Although difficulty in patient recruitment has contributed to this shift of trial enrollment to non-Western countries (26), the perceived bureaucratic and expensive regulatory environments in Western countries is another strong influence (22).

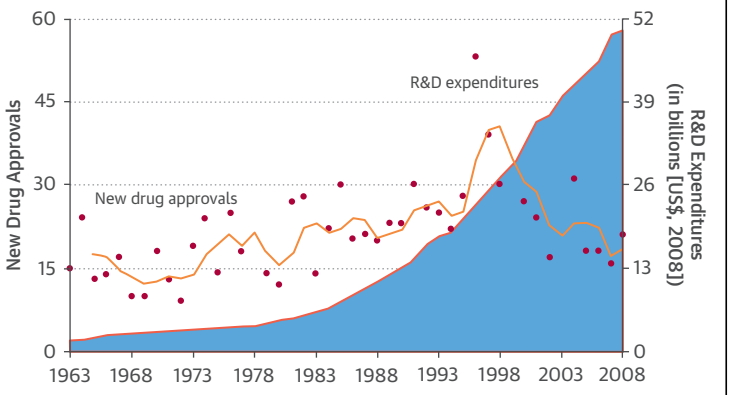
Although globalization of trial conduct and enrollment could theoretically reduce upfront costs for pivotal registration trials, growing concern exists over the geographical variation in patient selection and results in cardiovascular outcomes trials (27,28). The recent TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) trial demonstrated clear differences in patient selection for heart failure with preserved ejection fraction amongst patients in Russia and Georgia, which highly confounded the overall trial results (29). Additionally, low enrollment of patients in the United States in pivotal registration trials can also introduce confounding, as was demonstrated in the PLATO (Study of Platelet Inhibition and Patient Outcomes) trial with the antiplatelet agent ticagrelor (30). The treatment results were discordant in the United States compared with other geographic regions, with <10% of the patients enrolled in the United States. Therefore, the globalization of clinical trials appears to contribute to regulatory uncertainty and to complicate the regulatory review process for therapies with pivotal trials that showed geographical differences in patient selection/features as well as treatment results.

POTENTIAL CAUSES OF RELATIVE UNDERINVESTMENT IN CARDIOVASCULAR DRUG DEVELOPMENT

FEW INCENTIVES TO PROMOTE CARDIOVASCULAR DRUG DEVELOPMENT. Cardiovascular drug development currently suffers from a lack of "push-pull" incentives relative to other fields, particularly oncology, which tends to dominate contemporary drug development. "Push" funding policies aim to incentivize the pharmaceutical industry by reducing costs during the research and development stages, whereas "pull" mechanisms create incentives for the pharmaceutical industry by creating viable market demand for novel therapies that address unmet clinical needs (31). Push mechanisms may partially offset research and development by underwriting a portion of the costs, whereas pull mechanisms may reward positive trial results for novel therapies.

At the federal funding level, the field of oncology has several push mechanisms that may accelerate the discovery of novel therapies by academic researchers that could potentially be commercialized through academic-industry collaborations. First, the 2013 National Institutes of Health (NIH) budget was approximately $29.3 billion, with $4.8 billion allocated to the National Cancer Institute (NCI), the largest proportion among all institutes and a distinction held by the NCI since at least 1980 (32,33). In comparison, despite the relative proportional increase in the budget of the National Heart, Lung, and Blood Institute (NHLBI) compared with the NCI during this time period (32), the allocation in the 2013 budget to the NHLBI was significantly lower at $2.9 billion (34). Second, the FDA has several special-designation programs designed to expedite and facilitate the authorization and approval of new medications for unmet medical needs. A detailed

FIGURE 4 New Drug Approvals and Pharmaceutical R&D Expenditures in the United States From 1963 to 2008



Dots and orange line indicate new drug approvals and **periwinkle shaded area** indicates pharmaceutical research and development (R&D) expenditures. R&D expenditures are presented in terms of constant 2008 dollar value. The trend line is a 3-year moving average. The source of drug approval data is the Tufts Center for the Study of Drug Development. The source of R&D expenditure data is the Pharmaceutical Research and Manufacturers of America; Industry Profile 2009. Conversion of actual expenses to constant dollars was performed by the Tufts Center for the Study of Drug Development. Adapted with permission from Kaitin (14).

analysis found that the greatest percentage of applications to each of these programs was for oncology therapies (35). In comparison with oncology drugs, cardiovascular drug applications were far fewer in all programs: orphan (9% vs. 38%), priority review (4% vs. 53%), accelerated approval (8% vs. 32%), and fast track (1% vs. 56%). Finally, as a result of the FDA's orphan program and the increasing focus of the pharmaceutical industry on novel "first-in-class" therapies, the number of NMEs targeting orphan indications has risen 3-fold over the past 3 decades (36). However, there are few cardiovascular disease conditions that would qualify for orphan drug programs, so the interest for novel therapies has naturally shifted to the oncology field.

Advocacy and fundraising, major push mechanisms, are also dominated by oncology. In 2011, charitable donations raised during the Susan G. Komen Race for the Cure for breast cancer ($258 million) and Movember for prostate cancer ($147 million) were over 7-fold greater than that of the American Heart Association (AHA) Jump Rope for Heart campaign ($54 million) (37). Furthermore, the AHA raised $509 million in 2010, compared with $903 million raised by the American Cancer Society (38). The oncology field has also dominated crowdfunding initiatives—ventures that raise small amounts of money from a large number of people (typically via the Internet). A recent analysis of 97 crowdfunding campaigns aimed at cancer research found that the average amount raised per campaign was $45,629 (average donation: $186), including 5 rare-disease campaigns raising between $17,217 and $248,734 (39). In contrast, few crowdfunding campaigns have involved cardiovascular disease, although a new initiative to fund early-stage products was introduced at the AHA 2014 Scientific Sessions (40). Finally, an example of the consequences of philanthropic discrepancies affecting future drug development is reflected in the number of young investigator awards available for fellows in either subspecialty: the AHA had 0 research grants of at least 1 year in duration for fellows in 2012, the American College of Cardiology had 4, and the American Society of Clinical Oncology had 38 (41).

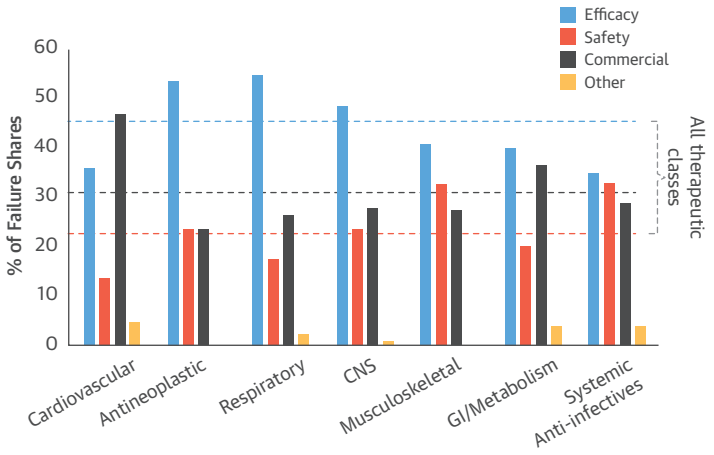
What drives successful cancer fundraising campaigns? It is possible that certain organizations are better organized to raise funds. However, fear may also explain the documented discrepancy between public perception of disease severity and reality (42). For example, a 2011 survey conducted by the MetLife Foundation found that 41% of responders named cancer as the disease they feared most; only 8% named heart disease, and another 8% feared stroke (43). Surveys of women conducted by the AHA show many believe cancer to be the number 1 cause of death for females, not heart disease, as annual mortality statistics consistently confirm (44). Given that the diagnosis of cancer typically elicits a much greater emotional response than that of cardiovascular disease, the disparities in the breadth and success of fundraising and advocacy campaigns for cancer versus cardiovascular disease likely reflect societal opinions on the "unmet needs" for medical conditions, despite the aforementioned global burden of cardiovascular disease.

DIVERTING INVESTMENT AWAY FROM CARDIOVASCULAR THERAPIES. Even though the biotechnology sector continues to show interest in drug development, trends for venture capital funding priorities demonstrate a shift away from cardiovascular disease. Between January 2005 and June 2012, acquisitions of venture-backed life science companies with 1 or 2 products in the pipeline remained strong (45). However, companies with oncology and infectious disease products had the greatest acquisitions, with approximately double the money spent compared with acquisitions that focused on cardiovascular disease products. Similarly, biotechnology companies with either an oncology or a neurology focus had the most licensing agreements during the same time period (2005 to 2012)—4-fold higher than the cardiovascular arena. The consensus opinion expressed at the meeting was that although it appears that venture capital investor interest in biotechnology remains strong, the appetite for risk is lower compared with historical trends, so investment firms typically are less interested in cardiovascular drug-development programs given the uncertain ROI for the previously mentioned reasons. Compared with the blockbuster therapies that were previously developed from biotechnology companies, investors are now prepared to accept a lower ROI (i.e., an orphan drug for a defined and small population) in exchange for a lower risk of drug-development failure (46,47). In fact, global sales of oncology drugs in 2013 topped $67 billion, the highest of any class of medications (48). These findings highlight the interest of investment firms in oncology therapies that typically have a clear regulatory pathway and a strong degree of advocacy from patient groups.

COMMERCIAL VIABILITY OVER EFFICACY OR SAFETY AS A DRIVER OF CARDIOVASCULAR DRUG-DEVELOPMENT FAILURE. In addition to a lack of push incentives, a lack of pull incentives currently hinders cardiovascular drug development due mainly to industry concerns regarding ROIs. A recent analysis demonstrated that cardiovascular drug failures following pivotal registration trials most often result from a lack of commercial viability rather than from efficacy or safety

issues (10) (**Figure 5**). Failure from commercial viability for cardiovascular therapies occurred for several reasons, including cases where expected future costs rise or expected revenues fall (perhaps due to increased competition or that testing suggests the target profile should be narrowed) to the point where the project is no longer perceived to be financially viable, or when pharmaceutical firms abandon a development program for strategic reasons (J.A. DiMasi, personal communication, December 9, 2014). For cardiovascular therapies, physicians, payers, and regulatory agencies demand large trials that are adequately powered to show a difference in clinical outcomes for approval. In general, and apart from some conditions such as heart failure, the progression of cardiovascular disease to "hard" natural history outcomes is relatively prolonged compared with the more rapid accumulations of such outcomes in oncology. Therefore, cardiovascular outcomes trials require large sample sizes and must continue for many years to accumulate enough endpoints to be adequately powered. Additionally, new cardiovascular medications must be tested on a background of a multitude of guideline-recommended therapies that comprise the "standard of care." Because patients selected for most cardiovascular outcomes trials on background medical therapy have relatively low event rates, trials have become larger, prolonged, and costlier with each new therapeutic modality (49).

FIGURE 5 Drug Failures by Therapeutic Class, 2000 to 2009



The **dashed lines** represent the rates of failure among all therapeutic classes. Adapted with permission from DiMasi (10). CNS = central nervous system; GI = gastrointestinal.

NECESSITY OF MEASURING VALIDATED CLINICAL OUTCOMES OVER SURROGATE ENDPOINTS. The use of putative surrogate endpoints to bring potentially beneficial treatments to patients many years before the availability of clinical outcomes at relatively lower cost appeals to investors, scientists, and patients who hope to seek access to beneficial therapies (50). Yet, such shortcuts can have several well-documented unintended consequences, demanding direct measures of clinical outcomes that matter to patients. In cardiovascular medicine, both blood pressure and low-density lipoprotein levels have served as surrogates of important clinical outcomes under specific circumstances, but only after validation in multiple randomized clinical trials involving tens of thousands of patients (51,52). Success of the IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial), which demonstrated that low-density lipoprotein lowering with a combination of ezetimibe and simvastatin versus simvastatin alone resulted in improved long-term clinical outcomes, provides further impetus for the development of novel agents, including PCSK9 inhibitors (53). Yet, alpha-adrenergic blockers lower blood pressure but appear to be inferior in reducing cardiovascular events compared with other blood pressure-lowering treatments (54). Torcetrapib and long-acting niacin increased high-density lipoprotein cholesterol considerably, but provided no cardiovascular outcome benefits in multiple large trials and, conversely, were associated with significant harm due to off-target drug effects (55,56). Other cardiovascular clinical trials have exposed harms after showing positive results with surrogate outcomes, including morbidity from the utilization of inotropes in cardiogenic shock despite improved hemodynamic parameters or death associated with the use of class IC antiarrhythmic agents despite successful suppression of premature ventricular contractions post-myocardial infarction (57–59).

Intermediate endpoints, such as progression-free survival (PFS), are more commonly used in oncology. The use of PFS among all systemic-therapy randomized controlled trials of breast, colorectal, and non-small-cell lung cancers published in the *Journal of Clinical Oncology* increased from 0% (1975 to 1984) to 26% more recently (2005 to 2009), whereas 23% of new FDA drug approval indications from 2005 to 2007 were on the basis of trials with PFS as the primary endpoint (60–62). Therefore, there has not only been a clear increase in the use of intermediate endpoints over time, but the prevalence of intermediate endpoint use has been consistent across studies. Justification for the use of PFS as a valid outcome for drug approval relates to the extended patient follow-up and to being confounded by causes of mortality unrelated to cancer. Furthermore, as novel therapies demonstrate

effectiveness along the treatment continuum for cancers such as breast and colorectal, survival may be influenced by the use of such therapies when trials have been completed (63,64). However, the use of PFS as a primary endpoint in many randomized controlled trials of advanced solid tumors, including breast cancer, has not been on the basis of evidence of its surrogacy for either overall survival or quality of life (60,65). Despite approving many therapies on the basis of PFS, the FDA has long acknowledged that tumor responses may not necessarily equate with clinical benefit, because nonresponding patients may benefit from a delay in tumor progression and tumors may recur more aggressively if they regress quickly in some cases (66,67). Taken together, despite their appeal to make trials more efficient, putative surrogate endpoints do not fully predict the true balance of risk and benefit of interventions. This failure usually is a result of incomplete coupling between the biomarker of interest and the array of clinical outcomes and the unknown and unintended pharmacological actions of an intervention that are independent of the disease process (68).

Notwithstanding the different types of outcomes that meet the thresholds for approval in cardiovascular disease versus cancer, the quality of clinical trial evidence used for recent approvals of novel therapeutic agents varies widely across indications. An analysis of the pivotal clinical trial evidence required for FDA approval between 2005 and 2012 is striking: cardiovascular disease, diabetes mellitus, and hyperlipidemia trials were larger than those in other therapeutic areas (median sample size = 651 subjects), were of longer duration (median = 24 weeks), were mostly randomized (98.6%), were typically conducted in a double-blind fashion (93.2%), and almost uniformly used a placebo or an active control in the comparator arm (97.2%) (**Table 1**) (69). In contrast, trials used to support cancer drug approvals were small (median sample size = 266 subjects), were of shorter duration (median = 18.5 weeks), were less frequently randomized (47.3%), were less frequently conducted in a double-blind manner (27.3%), and less than one-half used a placebo or active control in the comparator arm (47.3%). The consensus at the meeting was that cardiovascular medicine must continue to rely on proven clinical outcomes in the new era of drug development, especially in light of the previously-mentioned failures of putative surrogate endpoints (54–59).

"MISCLASSIFICATION" OF CARDIOVASCULAR DISEASE: IMPLICATIONS FOR DRUG DISCOVERY. Traditionally, cardiovascular drug development has focused on systemic therapies centering on large populations, such as hypertension and heart failure. However, these conditions result from multiple heterogeneous influences and pathways and have several potential therapeutic biological targets. Relatively few new drug targets for cardiovascular disease exist that can be completely separated from potential overlap with existing targets, because there are often multiple effective drugs in any given class (i.e., statins, antiplatelet agents, novel anticoagulants), which often renders distinction from existing therapies difficult. This setting presents considerable challenges to the development of new therapies. Yet, recent scientific advances, including harnessing genetic and systems biology approaches, promise to yield many novel drug targets in the multiple pathways involved in cardiovascular diseases such as thrombosis,

TABLE 1 Design of Pivotal Efficacy Trials Providing the Basis for Approval of Novel Therapeutic Agents by the FDA Between 2005 and 2012, Stratified by Therapeutic Agent

Therapeutic Agent (Pivotal Trials)	Patients	Duration, Weeks	Randomized	Double-Blinded	Placebo or Active-Control Comparator
CVD, DM, hyperlipidemia (n = 72)	651 (406–926)	24.0 (10.0–26.0)	98.6	93.2	97.2
Cancer (n = 55)	266 (84–610)	18.5 (8.9–29.2)	47.3	27.3	47.3
Infectious disease (n = 57)	585 (319–697)	5.0 (2.5–24.0)	93.0	78.9	91.2
Neurology (n = 38)	358 (234–613)	16.0 (12.0–21.0)	100.0	100.0	94.7
Dermatology (n = 29)	233 (121–491)	4.3 (2.0–13.0)	93.1	75.9	86.2
Autoimmune/MSK (n = 36)	525 (362–749)	24.0 (24.0–28.0)	100.0	94.4	100.0
Psychiatry (n = 43)	432 (275–590)	6.0 (6.0–8.0)	100.0	100.0	100.0

Values are median (interquartile range) or %. Adapted with permission from Downing et al. (69).
CVD = cardiovascular disease; DM = diabetes mellitus; MSK = musculoskeletal.

myocardial relaxation and strain, lipid metabolism, and atherosclerosis. The traditional "lumping" of heterogeneous disease—on the basis of taxonomy established by the International Classification of Diseases that seldom incorporated rapidly-emerging molecular data, incidental patient characteristics, or socio-environmental influences on disease (70)—should give way to a subclassification on the basis of biological signatures that better represents the underlying pathophysiology and permits more precise targeting of treatments (71). This approach mimics the now well-established strategy of targeted therapies in oncology (receptor level) and infectious diseases (organism level) and provides enticing drug targets. As opposed to cancers, common cardiovascular diseases do not arise from single gene mutations, but rather reflect interactions of risk factors with multiple genes that each contribute a small portion of risk. This complexity currently furnishes fewer appealing biological targets in cardiovascular medicine than in cancers (9). Nonetheless, in a recent industry survey, most large pharmaceutical companies (14 of 16) have still expressed an interest in partnering regarding cardiovascular disease (44).

STRATEGIES TO ADVANCE CARDIOVASCULAR DRUG DEVELOPMENT

REDUCE OPERATING COSTS OF CLINICAL TRIALS. Well-intentioned efforts to minimize the risk of harm or undesirable outcomes in patients enrolled in clinical trials have introduced numerous inefficiencies in the conduct of trials, particularly in pivotal registration trials that result in rigorous regulatory review (72). Meeting participants uniformly agreed that reducing the amount of extraneous data collected for a cardiovascular clinical trial offers an important cost savings opportunity. The typical clinical trial in 2012 involved 13 endpoints, had 169 case report form pages, and required study volunteers to make 11 visits over an average of 175 days (49). To advance discussions about reducing the amount of extraneous data collected for a large cardiovascular outcomes trial, the participants recommended that pharmaceutical industry sponsors meet early with key stakeholders (regulators, academic collaborators) to omit collection of unessential data and to simplify case report forms. Furthermore, there was a clear recommendation from FDA representatives to the pharmaceutical industry to meet with the FDA to gain a commitment early during the drug-development process to limit the amount of data to be collected. Academic collaborators should be encouraged to support the scientific legitimacy of this approach, with the goal of emphasizing quality by design (discussed in the following text). Adopting FDA guidance with respect to centralized monitoring practices and risk-based monitoring is a strategy that should continue to ensure subject protection and overall study quality while increasing efficiency (73). Other strategies to reduce costs include the use of centralized institutional review boards (74,75) and improving the system of reporting and interpreting unexpected serious adverse events through decreasing the review of uninterpretable case reports (76). The Clinical Trials Transformation Initiative (CTTI)—a public-private partnership founded by the FDA and Duke University to identify barriers to the conduct of large, simple trials—has recognized other important impediments to clinical research involving regulatory bodies, sponsor-imposed delays, academic impediments, and health system and clinical practice site impediments (72). Finally, harnessing the massive National Patient-Centered Clinical Research Network (PCORnet) program to centralize and organize clinical data will not only augment our understanding of risk and outcomes for people with specific diseases, but should also provide answers that are vital to patients more quickly, efficiently, and at a lower cost than previously possible (77).

INCREASE FOCUS ON PRACTICAL, STREAMLINED TRIALS. Despite a temptation to use surrogate endpoints to decrease sample sizes and shorten the duration of clinical trials (ostensibly to reduce the likelihood of drug-development failures), it was agreed that we must continue to promote large, pragmatic trials to measure clinical outcomes when evaluating new cardiovascular therapies. Larger trials also help resolve conflicting data. After post-approval analyses of data from small, randomized trials suggested that use of nesiritide was associated with a rate of worsening renal function and death, the ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure) demonstrated the safety of nesiritide but demonstrated no efficacy benefits with this agent (78). Finally, if conducted properly, large, simple trials can prove to be successful despite high rates of background, guidelines-recommended therapies that are known to improve outcomes when used widely. A prime example of the contemporary success of a novel agent studied in a large trial is PARADIGM-HF (Prospective Comparison of ARNI [Angiotensin Receptor-Neprilysin Inhibitor] with ACEI [Angiotensin-Converting-Enzyme Inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial), which compared LCZ696 versus enalapril in heart failure with reduced ejection fraction (79). This trial was stopped early due

to efficacy in the LCZ696 arm. Finally, integrating quality by design principles during the planning of large, simple trials is a key ingredient for trial streamlining. CTTI promotes quality by design with the goal that clinical trials will be more streamlined, fit for purpose, and quality driven (80). Trials with adequate sample sizes to assess benefits and risks using cardiovascular events should, therefore, remain the reference standard for cardiovascular drug development.

LEVERAGE PHASE II TRIALS TO INFORM PHASE III TRIALS. Many participants in the meeting felt that the research and development community could more effectively leverage data collected from phase II trials to better plan for phase III trials. Although there is a need to use phase II trial data to predict phase III outcomes and to adequately design phase III trials for regulatory approval, it is equally important to use the data gathered to understand the impact of a novel therapy on biology and disease pathways to plan future development. Phase II studies should, thus, focus on informing and refining important variables such as dosing, population pharmacokinetic modeling, side effects, and the treatment effect on biomarkers before commencing pivotal phase III registration trials. In fact, biomarkers are most appropriately used in phase II trials to screen for promising new therapies through evaluation of biological activity (68). Embedding adaptive design (AD) within a single clinical trial may furnish a novel strategy as well. This approach allows a review of accumulating information during a trial that may suggest modification of trial characteristics, thus addressing uncertainty about choices made during planning (81). AD allows pre-specified updates to the maximum sample size, study duration, treatment group allocation, dosing, number of treatment arms, or study endpoints. AD could translate into more efficient therapy development by reducing trial size. In turn, this could lead to more viable studies, with less risk for sponsors. However, although some academic and industry representatives may be eager to use AD strategies, regulators have been rightfully cautious to accept all AD trials for approval due to the broad spectrum of potentially problematic adaptations involved (81,82).

USE NOVEL NIH PROGRAMS TO SUPPORT EARLY-PHASE DEVELOPMENT. Despite pre-clinical testing and selection, many drugs that enter human studies never make it to market because of failure between phases I and III (83). The NIH has initiated new programs in search of an effective approach to actively support early clinical development, hoping to provide a bridge to facilitate successful innovation. Although the majority of NIH funding goes to support non-human research, it is also committed to funding applied sciences (84). The newest NIH institute, the National Center for Advancing Translational Sciences, was created in 2010 to accelerate translation of ideas into treatments via different programs, including those that enable repurposing of existing drugs for new indications (85).

The NHLBI has also developed several new approaches to specifically facilitate the translation of basic cardiovascular discoveries into clinical applications. The goal is to continue to develop a variety of programs that create teams of academic investigators and industry partners (86) (**Figure 6**). The NIH Centers for Accelerated Innovations (NCAIs) aim to identify and advance the development of promising emerging technologies toward new commercial products for the prevention and management of medical conditions affecting the cardiovascular, pulmonary, and hematologic systems. The NCAIs are developing a centralized institutional approach to move basic science discoveries through the early stages of technology development to enable their subsequent commercialization. Inventors, especially those who are new to the product-development process, have access to relevant personal training and mentoring opportunities. The new Vascular Interventions/Innovations and Therapeutic Advances program (87) aims to address the need for new or better therapeutic interventions (drugs or devices) and diagnostic modalities in several medical conditions that have been traditionally neglected by industry. Strategies include: 1) no restrictions on the applicant's type of institutional affiliation or on geographic location (within the United States); 2) assistance with project management, regulatory issues, and expert industry advice; and 3) opportunities to leverage other existing NIH translational programs. Areas of recent funding include vascular disorders, thrombotic diseases, and pulmonary hypertension. The Small Business Innovation Research funding mechanism provides seed funding to support the development of a broad array of commercial products to detect, diagnose, treat, and prevent disease. Other current programs include the Science Moving Towards Research Translation and Therapy program and the Gene Therapy Research Program (GTRP). These new programs are unproven, but they do represent an effort by the NHLBI to encourage and enable cardiovascular drug research even in the risk-adverse capital environment that currently exists.

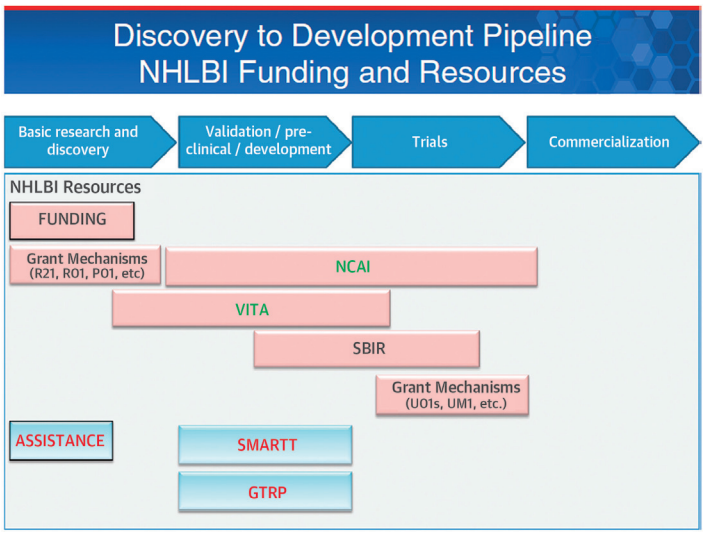
LEVERAGE ACADEMIC EXPERTS AS AN INTERFACE BETWEEN INDUSTRY AND REGULATORY BODIES. Optimal cardiovascular drug development depends on

true partnerships amongst academic representatives, regulatory officials, industry scientists, and clinical researchers, as well as practicing clinicians—all of whom represent the needs of patients with cardiovascular disease (**Central Illustration**). The use of academic clinical trialists is important in the design and conduct of pivotal cardiovascular registration trials where expertise on the cardiovascular disease condition, clinical trial operations, and established relationship with regulatory agencies are integrated attributes that are unique to academic researchers (88). Academic researchers can work with the pharmaceutical industry to help identify and define unmet clinical needs and to translate mechanisms of drug effect into clinical scenarios where the benefits may exceed the risks. Those qualifying as academic researchers are typically university-affiliated, have expertise in the field, and have prior clinical trial experience. Selected academic research organizations, especially in cardiovascular medicine, foster the "science of clinical operations" and stand well-positioned to enact and conduct efficient and streamlined clinical trials. However, academic clinical trials do not have to be affiliated with an academic research organization. Above all, with expertise and understanding of clinical practice, academic researchers can facilitate discussions between the regulatory bodies and the pharmaceutical industry from the perspective of expertise in disease therapeutics and patient-centered clinical care.

CONTINUE TO STRENGTHEN THE SCIENCE. Many cardiovascular drugs have been developed on the basis of proven biological activity in modifying a biomarker, hoping that the biomarker directly reflects disease outcomes. As discussed previously, many successful therapies have targeted biomarkers (specific lipid fractions and hypertension), resulting in improved clinical outcomes, but the definitive recommendation for therapy occurred only after vigorous testing in the form of multiple clinical trials with thousands of patients and valid clinical endpoints. In this setting, the effect sizes may be modest, and therefore, interventions require large trials to show benefit. At the meeting, there was general agreement that to improve efficiency from a scientific standpoint, development strategy should move away from targeting a directional change in biomarkers to: 1) use biomarkers to form enriched populations and further classify disease; and 2) learn more about the biologic targets and causal mechanisms that drive most cardiovascular diseases.

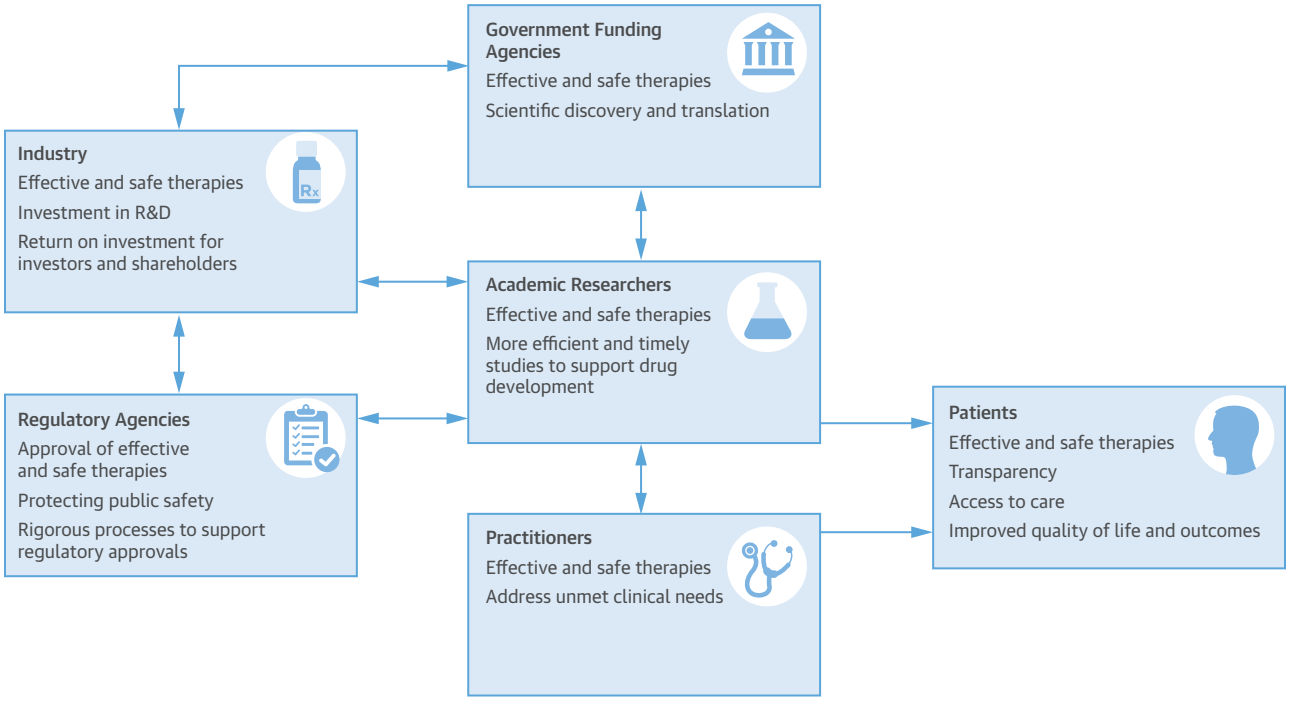
Using biomarkers to enrich study populations may help refine our definitions of disease and lead to successful drug development. Several examples already exist in the published data. In the COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure) trial, which demonstrated a 20% reduction in all-cause mortality or hospitalization with treatment with chronic resynchronization therapy (with or without an intracardiac defibrillator), the patient population was enriched by only including those with a QRS interval of ≥120 ms. The investigators widely acknowledge that if this therapy had been applied to the entire heart failure population, it almost certainly would have been negative (89). The JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) primary prevention trial, which demonstrated a reduction of major cardiovascular events with rosuvastatin, enriched an apparently healthy population by including only those with an elevation of an inflammatory marker, C-reactive protein (90). Finally, although the TOPCAT trial of spironolactone in patients with preserved ejection fraction was negative overall, a pre-specified subgroup of patients with elevated brain natriuretic peptide may have benefitted—a finding that must be regarded as exploratory and requires replication (91). Enrichment with biomarkers could help fuel studies to tackle several unmet cardiovascular research needs,

FIGURE 6 NHLBI Programs That Exemplify the Opportunities Created to Support Translation Using Funding or Assistance-Type Mechanisms



Adapted with permission from Galis et al. (87). GTRP = Gene Therapy Resource Program; NCAIs = National Institutes of Health Centers for Accelerated Innovations; NHLBI = National Heart, Lung, and Blood Institute; SBIR = Small Business Innovation Research; SMARTT = Science Moving Towards Research Translation and Therapy; VITA = Vascular Interventions/Innovations and Therapeutic Advances.

CENTRAL ILLUSTRATION **Goals of Stakeholders Involved in New Cardiovascular Drug Development and Their Influence on Each Other**



Fordyce, C.B. et al. J Am Coll Cardiol. 2015; 65(15):1567–82.

Optimal drug development for patients with cardiovascular disease requires true partnerships among academic researchers, regulatory officials, industry representatives, government-funded researchers, and practicing clinicians.

including pulmonary hypertension, hypertrophic cardiomyopathy, and congenital heart disease. Therefore, although the use of biomarkers as surrogate endpoints can prove treacherous, they may be useful to enrich populations that may benefit from specific therapies.

To improve understanding of the causal mechanisms of disease, several novel approaches have been leveraged. A genome-wide association study identified 13 new susceptibility loci for coronary artery disease (92). Of the 13 loci, only 3 were associated with conventional, established cardiac risk factors, and all were found to be of greater significance than PCSK9, which missed the genome-wide significance level by a small margin. This analysis shows that there are many potential nonconventional targets associated with the pathogenesis of coronary artery disease available for mining. Next-generation sequencing found a strong association between titin and dilated cardiomyopathy (93), and the importance of systems biology approaches for drug discovery has now been recognized for over a decade (94). Other strategies include Mendelian randomization, proteomics, and metabolomics. New basic science technologies have helped further our understanding of some of the causal mechanisms of cardiovascular disease and have the potential to stimulate future drug development. Increasing transdisciplinary exchanges of knowledge between the basic and clinical research fields through training and collaborations will enhance efforts to identify new targets, pathologic mechanisms, and drugs to address the unmet need in cardiovascular disease.

STRATEGIES TO IMPROVE INDUSTRY-SPONSORED CARDIOVASCULAR DRUG DEVELOPMENT. The pharmaceutical industry is generally composed of 2 main industry groups: those from the top 15 largest pharmaceutical companies ("Big Pharma") and other companies considered small to medium-sized enterprises (95). From a drug-development process, this distinction may be important when evaluating research and development strategies. Small to medium-sized enterprises typically focus on the biology and potentially large effect sizes in serious cardiovascular illnesses. As discussed, leveraging human genetics or

known human pharmacology will be extremely valuable to identify drug targets with a higher likelihood of success, instead of investing in a multitude of targets and accepting that some will fail. An example of this was the identification of the PCSK9 protein as a compelling target to treat hypercholesterolemia (96,97). The convergence of deoxyribonucleic acid sequencing, computational biology, and statistical methods is uncovering new compelling targets that should lead to the next wave of therapies aimed at reducing cardiovascular morbidity and mortality. In addition, this new paradigm should mitigate investment risk and facilitate the acceleration of high-potential programs. As a corollary, some meeting participants felt that a move toward reduced investment in targets supported only by nonclinical genetics and disease models would be beneficial. Programs with the greatest risk of failure should be reserved for the most grievous illness, novel science, and potential biggest incremental advance for patients. Last, technological advances in small and large molecule generation and manufacturing as well as new insights into biology that allow for different therapeutic modalities have positioned the industry to address cardiovascular disease in ways previously not achievable.

From a "Big Pharma" industry perspective, simple randomized trial design could prove to be key. This pathway emphasizes clinical outcomes over putative surrogate endpoints. Trials must be sufficiently large to detect small but clinically-meaningful differences in mortality and other major outcomes important to both the individual and to society. Priority should be given to suspected unexpected serious adverse reactions and to limiting the recording of less impactful adverse and serious adverse events. Streamlined, risk-based, and remote monitoring would be beneficial. Big firms should continue to strive to improve trial efficiency and emphasize meaningful clinical outcomes.

TABLE 2 Key Issues Underlying Adverse Trends in Cardiovascular Drug Development and Potential Solutions

Issue	Solution
Rising costs	• Reduce extraneous data collected ○ Meet early with key stakeholders (regulators, academic collaborators) to set limits ○ Adopt quality by design ○ Implement centralized monitoring practices/risk-based monitoring ○ Prioritize the collection of suspected unexpected serious adverse reactions; limit collection of other adverse events • Centralize institutional review boards • Harness PCORnet to help centralize and organize clinical data
Regulatory uncertainty	• Ensure frequent and early communication with regulators • Leverage academic experts to interface between industry and regulatory bodies • Use NIH programs to mitigate financial risk in early phases • Consider novel trial design ○ Adaptive design ○ Pre- and post-marketing approval studies
Necessity of validated clinical outcomes over surrogate endpoints	• Increase focus on practical, streamlined trials ○ Adopt quality by design ○ Use phase II to inform phase III: dosing, pharmacokinetic modeling, side effects, and biomarkers • Use biomarkers to enrich populations, but continue to demand clinical outcomes
Apparent decline in new cardiovascular drug targets	• Strengthen novel scientific methods to further define the pathophysiology and create new "biological signature" ○ Genome-wide association studies ○ Next-generation sequencing ○ Mendelian randomization ○ Proteomics and metabolomics • Leverage NIH programs to facilitate translation of basic cardiovascular discoveries into clinical applications
Discord between cardiovascular burden and public perception	• Channel advocacy through the American Heart Association and American College of Cardiology

NIH = National Institutes of Health; PCORnet = National Patient-Centered Clinical Research Network.

PROMISING TRIAL DESIGNS TO IMPROVE DRUG DEVELOPMENT. A potential novel strategy to help streamline clinical trials in the future would be to perform a smaller pre-marketing study but agree to a larger post-marketing comparative effectiveness trial. Currently, post-marketing studies cannot be used to support approval and are primarily used to refine the labeling of an approved drug therapy. These are generally studies required of or agreed to by a sponsor that are conducted after the FDA has approved a product for marketing, and they typically serve to gather additional information about a product's safety, efficacy, or optimal use (98). By functioning as a more comprehensive extension of a typical post-marketing study, a "continuum" study design would pre-specify integrated, systematic, monitored data from pooled pre-market randomized and post-market registry (99). Gathering pre- and post-market "real world" safety data might both improve safety assessment and support the assurance of safety in smaller pre-market studies. From an industry perspective, smaller studies resulting in reduction of pre-market cost and time could provide incentive for a serious commitment to complete post-market registries that are larger and more rigorous than current post-market data collections. In 2012, the FDA released its vision for post-market surveillance for medical devices (100). Although this effort specifically covered medical devices, this system

could be adapted and implemented as a form of post-market enforcement to study novel drugs. These systems can and should be used to also assess efficacy (101). Furthermore, such post-marketing comparative effectiveness trials could align with 1 of several Patient-Centered Outcomes Research Institute initiatives, including PCORnet (discussed previously), whose goal is to build clinical research into the health care process by creating a national network for conducting clinical outcomes research (102,103). An example of a future clinical trial integrating an industry sponsor, the FDA, and patient-centered outcomes might be a post-marketing comparative effectiveness trial supported by the Patient-Centered Outcomes Research Institute, the data from which are then captured, integrated, and studied using PCORnet.

CONCLUSIONS: A CALL TO END THE HIBERNATION

Despite the growing global burden of cardiovascular disease, metrics indicate that cardiovascular drug development has steadily declined relative to the growth of scientific discovery and the expansion of development in other therapeutic areas. This trend is particularly concerning given the unprecedented effect of cardiovascular drugs on outcomes, particularly in high-income countries (104). Investment in cardiovascular drug development has shifted elsewhere. This trend seems driven primarily by economic factors, including ROI with increased reimbursement and the perceived reduction in investment risk in bringing noncardiovascular drugs to market.

Nevertheless, the science of clinical therapeutics drives the continued requirement for the field of cardiovascular medicine to have large cardiovascular outcomes trials to demonstrate the balance of benefits and harms of potential novel therapies. Fortunately, despite the current perceived hibernation of cardiovascular drug development, most large pharmaceutical firms still have an interest in pursuing novel cardiovascular therapies should the right opportunity exist (45). The key issues and potential solutions are summarized in **Table 2**. Leveraging academic collaborations and novel governmental programs to identify, derisk, and develop potential therapeutic targets through pre-clinical and early-phase development appears to provide a positive path forward. By strengthening and refining the scientific questions and early-phase discoveries, cardiovascular drug development can rise once again by targeting enriched populations, using novel operational approaches to study design and conduct afforded by advances in the science of clinical trials, and emphasizing the pursuit of unmet clinical needs. Outcomes research and population health are coalescing around streamlining and simplification. As such, the "hibernation period" for cardiovascular drug development could draw to a close by application of the principles recommended in this paper.

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REFERENCES

1. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics—2014 update: a report from the American Heart Association. Circulation 2014;129:e28–292.

2. Gaziano TA. Cardiovascular disease in the developing world and its cost-effective management. Circulation 2005;112:3547–53.

3. Nabel EG, Braunwald E. A tale of coronary artery disease and myocardial infarction. N Engl J Med 2012;366:54–63.

4. Fuster V. Global burden of cardiovascular disease: time to implement feasible strategies and to monitor results. J Am Coll Cardiol 2014;64:520–2.

5. Fuster V, Kelly BB, Vedanthan R. Promoting global cardiovascular health: moving forward. Circulation 2011;123:1671–8.

6. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med 2006;3:e442.

7. Reddy KS. Cardiovascular disease in non-Western countries. N Engl J Med 2004;350:2438–40.

8. DiMasi JA, Feldman L, Seckler A, Wilson A. Trends in risks associated with new drug development: success rates for investigational drugs. Clin Pharmacol Ther 2010;87:272–7.

9. Pammolli F, Magazzini L, Riccaboni M. The productivity crisis in pharmaceutical R&D. Nat Rev Drug Discov 2011;10:428–38.

10. DiMasi JA. Causes of clinical failures vary widely by therapeutic class, phase of study. Tufts CSDD Impact Report 2013;15(5):1–4.

11. Kaitin KI, DiMasi JA. Pharmaceutical innovation in the 21st century: new drug approvals in the first decade, 2000–2009. Clin Pharmacol Ther 2011;89:183–8.

12. Sacks LV, Shamsuddin HH, Yasinskaya YI, Bouri K, Lanthier ML, Sherman RE. Scientific and regulatory reasons for delay and denial of FDA approval of initial applications for new drugs, 2000–2012. JAMA 2014;311:378–84.

13. Berggren R, Moller M, Moss R, Poda P, Smietana K. Outlook for the next 5 years in drug innovation. Nat Rev Drug Discov 2012;11:435–6.

14. Kaitin KI. Deconstructing the drug development process: the new face of innovation. Clin Pharmacol Ther 2010;87:356–61.

15. Eichler HG, Pignatti F, Flamion B, Leufkens H, Breckenridge A. Balancing early market access to new drugs with the need for benefit/risk data: a mounting dilemma. Nat Rev Drug Discov 2008;7:818–26.

16. Lundh A, Krogsbøll LT, Gøtzsche PC. Sponsors' participation in conduct and reporting of industry trials: a descriptive study. Trials 2012;13:146.

17. Lundh A, Barbateskovic M, Hróbjartsson A, Gøtzsche PC. Conflicts of interest at medical journals: the influence of industry-supported randomised trials on journal impact factors and revenue-cohort study. PLoS Med 2010;7:e1000354.

18. Whitford AB. The reduction of regulatory uncertainty: evidence from transfer pricing policy. Saint Louis University Law Journal 2010;55:269–306.

19. Hoffmann VH, Trautmann T, Schneider M. A taxonomy for regulatory uncertainty—application to the European Emission Trading Scheme. Environmental Science & Policy 2008;11:712–22.

20. Morgan DP. Rating banks: risk and uncertainty in an opaque industry. Am Econ Rev 2002;92:874–88.

21. Milne CP, Kaitin KI. FDA review divisions: performance levels and the impact on drug sponsors. Clin Pharmacol Ther 2012;91:393–404.

22. Glickman SW, McHutchison JG, Peterson ED, et al. Ethical and scientific implications of the globalization of clinical research. N Engl J Med 2009;360:816–23.

23. Berntgen M, Gourvil A, Pavlovic M, Goettsch W, Eichler HG, Kristensen FB. Improving the contribution of regulatory assessment reports to health technology assessments—a collaboration between the European Medicines Agency and the European Network for Health Technology Assessment. Value Health 2014;17:634–41.

24. Getz KA. Global clinical trials activity in the details: individual countries hold the key to finding hot spots in growth regions like Central and Eastern Europe. Appl Clin Trials 2009. Available at: http://www.appliedclinicaltrialsonline.com/appliedclinicaltrials/article/articleDetail.jsp?id=453243. Accessed October 14, 2014.

25. Downing NS, Aminawung JA, Shah ND, Braunstein JB, Krumholz HM, Ross JS. Regulatory review of novel therapeutics-comparison of three regulatory agencies. N Engl J Med 2012;366:2284–93.

26. Thiers FA, Sinskey AJ, Berndt ER. Trends in the globalization of clinical trials. Nat Rev Drug Discov 2008;7:13–4.

27. Mentz RJ, Kaski JC, Dan GA, et al. Implications of geographical variation on clinical outcomes of cardiovascular trials. Am Heart J 2012;164:303–12.

28. Fiuzat M, Califf RM. Conduct of clinical trials in acute heart failure: regional differences in heart failure clinical trials. Heart Fail Clin 2011;7:539–44.

29. Pfeffer MA, Claggett B, Assmann SF, et al. Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial. Circulation 2015;131:34–42.

30. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361:1045–57.

31. Grace C, Kyle M. Comparative advantages of push and pull incentives for technology development: lessons for neglected disease technology development. Global Forum Update on Research for Health 2009;6:147–51.

32. Sampat BN. Mission-oriented biomedical research at the NIH. Res Policy 2012;41:1729–41.

33. Mervis J. U.S. spending. Final 2014 budget helps science agencies rebound. Science 2014;343:237.

34. National Institutes of Health website. Appropriations history by institute/center (1938 to present). Available at: http://officeofbudget.od.nih.gov/approp_hist.html. Accessed October 6, 2014.

35. Milne CP. Prospects for rapid advances in the development of new medicines for special medical needs. Clin Pharmacol Ther 2014;95:98–109.

36. Kinch MS, Merkel J, Umlauf S. Trends in pharmaceutical targeting of clinical indications: 1930–2013. Drug Discov Today 2014;19:1682–5.

37. Belluz J. The truth about the Ice Bucket Challenge: viral memes shouldn't dictate our charitable giving. Available at: http://www.vox.com/2014/8/20/6040435/als-ice-bucket-challenge-and-why-we-give-to-charity-donate. Accessed August 29, 2014.

38. Wood S. Money—is cancer beating cardiovascular disease? Medscape. August 16, 2011. Available at: http://www.medscape.com/viewarticle/790999. Accessed October 16, 2014.

39. Dragojlovic N, Lynd LD. Crowdfunding drug development: the state of play in oncology and rare diseases. Drug Discov Today 2014;19:1775–80.

40. Heart Innovation Forum. Available at: http://www.heartinnovationforum.org/. Accessed November 14, 2014.

41. Ahmad T, Becker RC. The unmet need for philanthropic funding of early career cardiovascular investigators. J Thromb Thrombolysis 2014;37:527–31.

42. Siegel KR, Feigl AB, Kishore SP, Stuckler D. Misalignment between perceptions and actual global burden of disease: evidence from the US population. Global Health Action 2011;4.

43. Wood S. Glory—is cancer beating cardiovascular disease? Medscape. August 18, 2011. Available at: http://www.medscape.com/viewarticle/791006#vp_2. Accessed October 14, 2014.

44. Mosca L, Mochari-Greenberger H, Dolor RJ, Newby LK, Robb KJ. Twelve-year follow-up of American women's awareness of cardiovascular disease risk and barriers to heart health. Circ Cardiovasc Qual Outcomes 2010;3:120–7.

45. Giniatullina A, Boorsma M, Mulder GJ, van Deventer S. Building for big pharma. Nature Biotechnol 2013;31:284–7.

46. Mathieu MP. PAREXEL Biopharmaceutical R&D Statistical Sourcebook 2013/2014. Waltham, MA: Parexel International Corp, 2013.

47. Bioassociate Innovative Consulting website. 2013 Biotech & pharma IPO review-most popular therapeutic trends, trending clinical stages and post-IPO winners & losers. December 14, 2013. Available at: http://www.bioassociate.com/2013-biotech-pharma-ipo-review-most-popular-therapeutic-trends-trending-clinical-stages-and-post-ipo-winners-losers/. Accessed October 8, 2014.

48. IMS Health website. Top-line market data. December 2013. Available at: http://www.imshealth.com/portal/site/imshealth/menuitem.18c196991f79283fddc0ddc01ad8c22a/?vgnextoid=6521e590cb4dc310VgnVCM100000a48d2ca2RCRD&vgnextfmt=default. Accessed October 29, 2014.

49. Eapen ZJ, Lauer MS, Temple RJ. The imperative of overcoming barriers to the conduct of large, simple trials. JAMA 2014;311:1397–8.

50. Temple R. Are surrogate markers adequate to assess cardiovascular disease drugs? JAMA 1999;282:790–5.

51. Turnbull F, Neal B, Ninomiya T, et al., for the Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults: meta-analysis of randomised trials. BMJ 2008;336:1121–3.

52. Mihaylova B, Emberson J, Blackwell L, et al., for the Cholesterol Treatment Trialists' (CTT) Collaborators. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet 2012;380:581–90.

53. Cannon CP. IMPROVE-IT trial: a comparison of ezetimibe/simvastatin versus simvastatin monotherapy on cardiovascular outcomes after acute coronary syndromes. Paper presented at: American Heart Association Scientific Sessions; November 14, 2014; Chicago, IL. Available at: http://my.americanheart.org/idc/groups/ahamah-public/@wcm/@sop/@scon/documents/downloadable/ucm_469669.pdf. Accessed December 3, 2014.

54. ALLHAT Collaborative Research Group. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). JAMA 2000;283:1967–75.

55. Barter PJ, Caulfield M, Eriksson M, et al. Effects of torcetrapib in patients at high risk for coronary events. N Engl J Med 2007;357:2109–22.

56. AIM-HIGH terol levels receiving intensive statin therapy. N Engl J Med 2011;365:2255–67.

57. O'Connor CM, Gattis WA, Uretsky BF, et al. Continuous intravenous dobutamine is associated with an increased risk of death in patients with advanced heart failure: insights from the Flolan International Randomized Survival Trial (FIRST). Am Heart J 1999;138 Pt 1:78–86.

58. Felker GM, Benza RL, Chandler AB, et al. Heart failure etiology and response to milrinone in decompensated heart failure: results from the OPTIME-CHF study. J Am Coll Cardiol 2003;41:997–1003.

59. Echt DS, Liebson PR, Mitchell LB, et al. Mortality and morbidity in patients receiving encainide, flecainide, or placebo. The Cardiac Arrhythmia Suppression Trial. N Engl J Med 1991;324:781–8.

60. Booth CM, Eisenhauer EA. Progression-free survival: meaningful or simply measurable? J Clin Oncol 2012;30:1030–3.

61. Kay A, Higgins J, Day AG, Meyer RM, Booth CM. Randomized controlled trials in the era of molecular oncology: methodology, biomarkers, and end points. Ann Oncol 2012;23:1646–51.

62. Sridhara R, Johnson JR, Justice R, Keegan P, Chakravarty A, Pazdur R. Review of oncology and hematology drug product approvals at the US Food and Drug Administration between July 2005 and December 2007. J Natl Cancer Inst 2010;102:230–43.

63. Hackshaw A, Knight A, Barrett-Lee P, Leonard R. Surrogate markers and survival in women receiving first-line combination anthracycline chemotherapy for advanced breast cancer. Br J Cancer 2005;93:1215–21.

64. Louvet C, de Gramont A, Tournigand C, Artru P, Maindrault-Goebel F, Krulik M. Correlation between progression free survival and response rate in patients with metastatic colorectal carcinoma. Cancer 2001;91:2033–8.

65. Saad ED, Katz A, Hoff PM, Buyse M. Progression-free survival as surrogate and as true end point: insights from the breast and colorectal cancer literature. Ann Oncol 2010;21:7–12.

66. Johnson JR, Williams G, Pazdur R. End points and United States Food and Drug Administration approval of oncology drugs. J Clin Oncol 2003;21:1404–11.

67. Johnson JR, Ning YM, Farrell A, Justice R, Keegan P, Pazdur R. Accelerated approval of oncology products: the food and drug administration experience. J Natl Cancer Inst 2011;103:636–44.

68. Fleming TR, DeMets DL. Surrogate end points in clinical trials: are we being misled? Ann Intern Med 1996;125:605–13.

69. Downing NS, Aminawung JA, Shah ND, Krumholz HM, Ross JS. Clinical trial evidence supporting FDA approval of novel therapeutic agents, 2005–2012. JAMA 2014;311:368–77.

70. Committee on a Framework for Development a New Taxonomy of Disease; National Research Council. Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease. Washington, DC: National Academies Press, 2011.

71. Ahmad T, Fiuzat M, Pencina MJ, et al. Charting a roadmap for heart failure biomarker studies. J Am Coll Cardiol HF 2014;2:477–88.

72. Kramer JM, Smith PB, Califf RM. Impediments to clinical research in the United States. Clin Pharmacol Ther 2012;91:535–41.

73. U.S. Department of Health and Human Services, Food and Drug Administration. Guidance for Industry: Oversight of Clinical Investigations—A Risk-Based Approach to Monitoring [draft guidance]. Silver Spring, MD: U.S. Department of Health and Human Services, August 24, 2011.

74. Menikoff J. The paradoxical problem with multiple-IRB review. N Engl J Med 2010;363:1591–3.

75. Flynn KE, Hahn CL, Kramer JM, et al. Using central IRBs for multicenter clinical trials in the United States. PloS One 2013;8:e54999.

76. Kramer JM, Vock D, Greenberg HE, et al. Investigators' experience with expedited safety reports prior to the FDA's final IND safety reporting rule. Ther Innov Regul Sci 2014;48:413–9.

77. Califf RM. The Patient-Centered Outcomes Research Network: a national infrastructure for comparative effectiveness research. N C Med J 2014;75:204–10.

78. O'Connor CM, Starling RC, Hernandez AF, et al. Effect of nesiritide in patients with acute decompensated heart failure. N Engl J Med 2011;365:32–43.

79. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371:993–1004.

80. Clinical Trials Transformation Initiative. QBD: project summary. Workshops on quality by design (QbD) and quality risk management (QRM) in clinical trials. Available at: http://www.ctti-clinicaltrials.org/what-we-do/investigational-plan/qbd-qrm. Accessed October 15, 2014.

81. Kairalla JA, Coffey CS, Thomann MA, Muller KE. Adaptive trial designs: a review of barriers and opportunities. Trials 2012;13:145.

82. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. Guidance for Industry: Adaptive Design Clinical Trials for Drugs and Biologics [draft guidance]. Rockville, MD: U.S. Department of Health and Human Services, February 2010.

83. Kola I, Landis J. Can the pharmaceutical industry reduce attrition rates? Nat Rev Drug Discov 2004;3:711–5.

84. Galis ZS, Hoots WK, Kiley JP, Lauer MS. On the value of portfolio diversity in heart, lung, and blood research. Circ Res 2012;111:833–6.

85. National Center for Advancing Translational Sciences. Available at: http://www.ncats.nih.gov/index.html. Accessed March 24, 2015.

86. Galis ZS, Black JB, Skarlatos SI. National Heart, Lung, and Blood Institute and the translation of cardiovascular discoveries into therapeutic approaches. Circ Res 2013;112:1212–8.

87. National Heart, Lung, and Blood Institute. VITA Program. Available at: http://www.nhlbi.nih.gov/research/resources/vita. Accessed March 24, 2015.

88. Brass EP, Hiatt WR. Improving the FDA's advisory committee process. J Clin Pharmacol 2012;52:1277–83.

89. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004;350:2140–50.

90. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008;359:2195–207.

91. Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med 2014;370:1383–92.

92. Schunkert H, Konig IR, Kathiresan S, et al. Large-scale association analysis identifies 13 new susceptibility loci for coronary artery disease. Nat Genet 2011;43:333–8.

93. Herman DS, Lam L, Taylor MR, et al. Truncations of titin causing dilated cardiomyopathy. N Engl J Med 2012;366:619–28.

94. Butcher EC, Berg EL, Kunkel EJ. Systems biology in drug discovery. Nat Biotechnol 2004;22:1253–9.

95. O'Connell KE, Frei P, Dev KK. The premium of a big pharma license deal. Nat Biotechnol 2014;32:617–9.

96. Blom DJ, Hala T, Bolognese M, et al. A 52-week placebo-controlled trial of evolocumab in hyperlipidemia. N Engl J Med 2014;370:1809–19.

97. Schwartz GG, Bessac L, Berdan LG, et al. Effect of alirocumab, a monoclonal antibody to PCSK9, on long-term cardiovascular outcomes following acute coronary syndromes: Rationale and design of the ODYSSEY Outcomes trial. Am Heart J 2014;168:682–689.e1.

98. U.S. Food and Drug Administration. Post-marketing requirements and commitments: introduction. Available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/. Accessed October 16, 2014.

99. Rao SV, Califf RM, Kramer JM, et al. Post-market evaluation of breakthrough technologies. Am Heart J 2008;156:201–8.

100. Center for Devices and Radiological Health, U.S. Food and Drug Administration. Strengthening our national system for medical device postmarket surveillance. September 2012. Available at: http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/UCM301924.pdf. Accessed October 16, 2014.

101. Vavalle JP, Ohman EM. Left ventricular support systems for high-risk percutaneous coronary interventions: how can we improve outcomes for rare procedures? Circulation 2013;127:162–4.

102. Frank L, Basch E, Selby JV. The PCORI perspective on patient-centered outcomes research. JAMA 2014;312:1513–4.

103. Fleurence RL, Curtis LH, Califf RM, Platt R, Selby JV, Brown JS. Launching PCORnet, a national patient-centered clinical research network. J Am Med Inform Assoc 2014;21:578–82.

104. Ford ES, Ajani UA, Croft JB, et al. Explaining the decrease in U.S. deaths from coronary disease, 1980–2000. N Engl J Med 2007;356:2388–98.

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APPENDIX For a list of think tank participants, please see the online version of this article.