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TRANSLATIONAL PERSPECTIVE

# Overcoming Barriers to Development of Novel Therapies for Cardiovascular Disease

## Insights From the Oncology Drug Development Experience

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**SUMMARY**

Despite the fact that cardiovascular disease (CVD) is the number 1 cause of death globally, investment in drug development and new drug approvals for CVD are precipitously declining. In contrast, the trajectory of both investment in development as well as new drug approvals for oncology have been increasing steadily over the same time frame. The factors that have spurred drug development in oncology may be applicable to new efforts to overcome barriers to drug development for CVD. Greater investment in basic research and application of expedited regulatory pathways have contributed to a lowering of development barriers in oncology. Barriers in implementation are also critical. More rapid adoption of guideline-based therapies and lower access barriers by payers have contributed to fewer implementation barriers for oncology therapeutics. There is substantially greater advocacy among patients and physicians for new oncology therapeutics, and such advocacy efforts are likely to have had a meaningful impact on lowering barriers to develop new oncology therapeutics. Broad support of patient and physician advocacy efforts directed towards CVD may help overcome existing development and implementation barriers to new drug development, thereby spurring more rapid progress in the fight to eradicate cardiovascular disease. (J Am Coll Cardiol Basic Trans Science 2019;4:269–74)


Cardiovascular disease (CVD) is the number 1 cause of death globally and has been the leading cause of death in the United States for almost 100 years. It also results in substantial impairment of health status, disability, and increased health care expenditures. Because of improvements in lifestyle and treatments, the United States experienced a 60% reduction in age-adjusted death rates for CVD from 1950 to 1999 (1). Despite this extraordinary advancement for public health, recent data show that CVD mortality rates are no longer declining and, in fact, are increasing for some groups (2). The need to develop new therapies for CVD remains high. There have also been remarkable

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**ABBREVIATIONS AND ACRONYMS**

**ARNI** = angiotensin receptor neprilysin inhibitor

**ASCVD** = atherosclerotic cardiovascular disease

**CVD** = cardiovascular disease

advances in cardiovascular (CV) basic and translational sciences with a plethora of promising targets for new therapies. Notwithstanding this potential for new therapies and great public health need, it is well recognized that over the past couple of decades there have been proportionally fewer CVD therapeutic candidates in all stages of drug development, including fewer new CVD drug approvals (3-6). Although substantial investments in large scale trials for CVD research continue, more investment seem to be shifting toward other therapeutic classes, such as oncology (3,4). CVD and oncology are the first and second leading causes of death, respectively, yet the investment trajectories are completely different. During the time that CVD drug approvals were declining, new drug approvals and investment in oncology increased significantly (3-6). Understanding the differences in trends and reasons for those differences may be informative and provide strategic insights into approaches used in oncology that can be applied in the treatment of CVD.

Several recent articles have thoroughly reviewed different reasons for the recent reduction in CVD drug development and compared it with the growing investment in oncology (3,4,7). Many factors contribute to more uncertainty and a lower near-term return on investment for CVD relative to oncology. Some factors are related to aspects of drug development and regulatory approval whereas others are related to market dynamics once a drug has been approved. For clarity, this paper will group similar barriers together and refer to the former as development barriers and the latter as implementation barriers (**Central Illustration**). Rather than discussing all these reasons in detail, this paper will focus on the barriers that seem to have been lowered for oncology to suggest similar strategies that may be used to overcome barriers and increase investment in CVD.

## DRUG APPROVAL TRENDS AND DEVELOPMENT BARRIERS

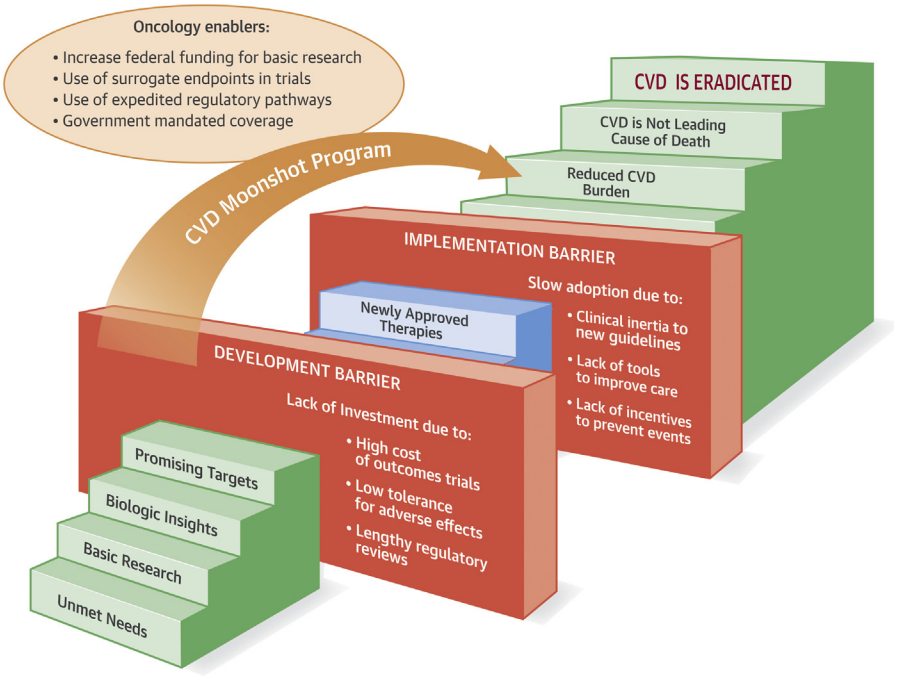
In the 1980s, approximately 1 in 4 approvals for all new drugs and biologics were in the CVD therapeutic class whereas ~1 in 10 was in the oncology class (5). In relative terms, in the 1980s U.S. Food and Drug Administration (FDA) approvals for oncology therapies were approximately 20% of new CVD approvals; however, this has changed rapidly over the past few decades. Between 2010 and 2017, there were almost 2.5 times as many oncology FDA approvals as CVD approvals (**Figure 1**) (8).

One factor contributing to drug approvals is investment in basic research. A recent article shows that the speed of clinical and regulatory development is significantly shorter if basic science in the field reaches a point of scientific establishment (7). When comparing levels of federal funding, oncology has significantly more funding than CVD. In 2017, there was more than $6 billion in funding for cancer between the National Cancer Institute funding ($5.9 billion) and the Beau Biden Cancer Moonshot funding from the 21st Century Cures Act ($300 million) (9,10). The National Heart Lung and Blood Institute received one-half that amount of funding ($3.1 billion) in 2017 (9). In fact, among all the institutes at the National Institutes of Health, the National Cancer Institute has held the largest proportion of the budget since at least 1980 (3).

Even after this early-stage investment, the cost of clinical development is substantial. Development cost for a drug or class is a critical factor in return on investment calculations. A recent study analyzed cost data from more than 100 compounds beginning human testing from 1995 to 2007 and estimated the cost of developing a new drug at more than $2.5 billion (in 2013 dollars) (11). This cost estimate was almost 1.5 times higher than they had previously estimated for drugs that were approved a little more than a decade earlier (12). These data are consistent with the so-called "Eroom's law" (Moore's law spelled backwards) used to describe the phenomenon of the increasing cost of drug development over time (4). To our knowledge, there are no studies that compare the development costs for oncology and CVD; however, it has been shown that the registration-enabling trials for CVD are, in general, larger and longer trials than oncology trials (3).

Size and duration are 2 of the main determinants of clinical trial costs. Some of the reasons that CVD trials take longer include: 1) the need to show clinically significant improvement in clinical outcomes on a background of guideline-directed therapies instead of relying on surrogate markers; and 2) a very low tolerance for adverse effects. Potentially because of the success in treating large populations and the sheer number of people treated, there is, with few exceptions, a need to show clinically significant improvement in hard outcomes instead of relying on surrogates in CVD. Also, cardiologists are skeptical of surrogates because many have not successfully predicted CV-related outcomes. For example, the promise of high-density lipoprotein increases as a surrogate for CVD outcomes was not fulfilled when the outcomes trials were conducted. In addition, for drugs that have an impact on more-established

**CENTRAL ILLUSTRATION** **The Development and Implementation Barriers That Impede the Generation of Novel Therapies for Cardiovascular Disease Could Be Overcome by a Cardiovascular Disease "Moonshot Program"**




**Khakoo, A.Y. et al. J Am Coll Cardiol Basic Trans Science. 2019;4(2):269–74.**

The generation of novel cardiovascular therapeutics is impeded by a lack of investment due to barriers that limit investment in research in development as well as barriers that slow adoption of safe and effective therapies that limit their implementation. A "CVD Moonshot Program," consisting of elements that have fueled the rapid development of new cancer therapeutics- increased research funding, novel surrogate endpoints in clinical trials, expedited regulatory pathways, and government mandated coverage- could pave a road towards eradication of CVD. CVD = cardiovascular disease.

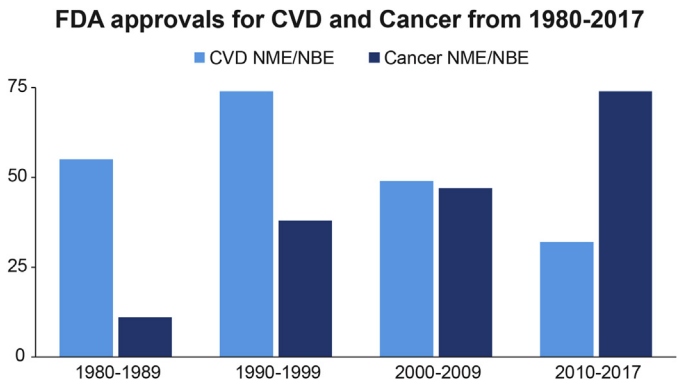
surrogate endpoints for CVD such as lowering of low-density lipoprotein cholesterol, large outcomes trials were needed to obtain approval from regulatory and reimbursement authorities. On the other hand, in oncology, because of the recognized importance of getting promising new therapeutics to cancer patients as quickly as possible, there is greater acceptance of drugs being approved based on clinically meaningful surrogate endpoints (13). In addition, there is much greater acceptance of side effects and serious adverse events in oncology. The time for clinical development of new therapies for CVD indications has not changed much since the 1970s (7). Oncology drugs, on the other hand, have taken advantage of expedited regulatory pathways to reduce development times. Of the 4 expedited programs offered by the FDA (orphan, priority review, accelerated approval, and fast track), the greatest number of applications were for oncology drugs. In fact, the proportion of oncology applications for each of these programs ranged from about one-third to more than one-half compared to <10% for CV applications (3).

There is a need to re-envision the development pathways for CVD drugs considering the public health importance of CVD. If this can be accomplished, it will help improve the return on investment and provide more incentive to invest in CVD and further improve public health.

## IMPLEMENTATION BARRIERS

Another key factor in return on investment is how rapidly the innovation is adopted into clinical practice. Although there is evidence of geographic differences in the speed of adoption of new cancer drugs (14), there does not seem to be the same general reluctance to adopt new therapies as there is in CVD. For CVD, even when new drugs are adopted into

**FIGURE 1 U.S. Food and Drug Administration Approvals for Cardiovascular Disease and Cancer From 1980 to 2017**




Adapted from Tufts Center for the Study of Drug Development Impact Report 2016 (5). NBE = new molecular entity; NME = new molecular entity.

treatment guidelines, there seems to be clinical inertia regarding adherence to the guidelines. This may be due to the previous success in reducing morbidity and mortality which creates an impression that sufficient progress had been made and underestimates the true burden of CVD. Also, identifying patients at imminent risk of an event is difficult in clinical practice due to a lack of near-term risk prediction tools, particularly for asymptomatic patients (15). Another issue may be that preventing future events is not considered a priority in a system that has a short-term budget view. The current structure of our health care system incentivizes treating conditions that have impact in the short run but does not provide sufficient incentive to prevent or treat conditions that could have enormous long-term impact (e.g., atherosclerotic CVD [ASCVD]).

Even with CV conditions that do have short-term impact and a strong immediate value proposition, such as heart failure (HF), adoption of new therapies is slow. Even though HF has mortality rates comparable to several common cancers (16), when a drug in a new class of HF therapeutics, angiotensin receptor neprilysin inhibition (ARNI), showed a 20% reduction in CV death and similar or better tolerability compared with standard of care, only ~2% of eligible patients were prescribed the drug 1 year after approval (17). This was close to 2 years after the initial report of the benefit of ARNI (18). An analysis by Fonarow et al. (19) estimated that optimal adoption of ARNI therapy could have saved almost 30,000 lives in the United States annually. These better clinical results may actually result in lower total health care costs. Recent analysis of real-world data has shown that, despite the higher pharmacy costs, ARNI reduced total health care costs by 28% compared to standard-of-care because of the much lower medical costs for ARNI-treated patients (20).

Another related barrier for implementation is the reimbursement and access challenges that many new drugs face. When financing new therapies, 2 main questions are typically considered: 1) Can we afford to pay for the drug? 2) Is the drug worth the price? The concern about affordability and the impact of the drug on the budget is particularly relevant for drugs that treat large populations, such as CVD drugs. The most recent report from the American Heart Association (AHA) concludes that almost one-half of all Americans adults (>120 million individuals) have CVD (21). The prevalence of cancer is much lower (>14 million individuals in the United States) (22). The size of the population makes new CVD drugs potentially very difficult to afford. Beyond the budget impact concern, there is a need to convince insurance companies and other payers of the value of these drugs to ensure the drugs are placed onto insurance formularies and can be accessed by patients with an affordable out-of-pocket copayment or coinsurance amount. Often these 2 issues are conflated and what is described as a lack of value is really a concern about the ability to pay for the drug considering the large populations of potential patients.

To deal with financing concerns, payers can resort to erecting major access barriers and this has happened with several recently approved CVD drugs. For example, more than 1 year after proprotein convertase subtilisin/kexin type 9 inhibitors were FDA-approved for treating individuals with familial hypercholesterolemia and established ASCVD, analyses showed that insurance companies were rejecting claims for 63% of familial hypercholesterolemia patients and 58% of ASCVD patients (23). This high rejection rate is due to a failure in any number of steps towards reimbursement, including authorization paperwork that oftentimes requires documentation, and step therapy, often requiring trials of specific doses of medications for prespecified periods. If a patients' insurance rejects a claim, the physician's office may need to go through lengthy appeals processes with insurance companies (24). With oncology drugs, payers are much less likely to impose access restrictions. Government policies often mandate coverage for oncology drugs. For example, Medicare covers all FDA-approved indications for cancer and cancer is 1 of the 6 protected classes required to be covered under Medicare's Part

D drug benefit (25). Although they are not subject to these government mandates for commercially insured patients, payers have been reluctant to impose meaningful restrictions on cancer therapies. This reluctance may be related to previous backlash from advocacy groups when restrictions have been imposed in the past (25).

## OVERCOMING BARRIERS THROUGH STRONG ADVOCACY

A common thread in all the differences in oncology and CVD is the strong advocacy in oncology. The level of advocacy by physician groups and patients is not nearly as strong for CVD. For example, if survival outcomes for HF are similar to some cancers, why are people not wearing HF awareness bracelets? This lack of a strong advocacy voice may play into the complacency of payers and health care providers. Greater advocacy from patients and physicians shines the light on problematic barriers that can delay the time to life-changing therapies. There are several potential reasons for the difference in advocacy. Oncology patients tend to skew a little younger, so people are more concerned about life-threatening disease in younger patients. Also, CV patients may blame themselves and their lifestyle choices for their condition. Other than a few very specific conditions in oncology, such as lung cancer, this tends not to be the case for cancer.

With better advocacy for CVD, both development and implementation barriers could be better addressed and reduced. There would be substantial merit in a call to action with a CVD moonshot program and more research funding for CVD like there is for oncology to continue to catalyze innovation in CVD. There is a need for more proactive data-driven discussions with the FDA (as well as the Centers for Medicare and Medicaid Services and other payers) to ensure the right balance between speed and safety is found. Implementation barriers could be reduced through increased support for guideline-based performance improvement programs, systems of care, and training to aid health care systems with rapid adoption (26). Better physician and patient advocacy is critical to bring down payer access barriers. Multiple stakeholders including insurers still seem to underestimate the unmet need in CVD; hence, there is a need for more education about the impact of CVD on patients' health status, wellbeing, and quality of life (27).

Despite the compelling unmet need for additional therapies for CVD that provide meaningful patient-centered benefits, there is underinvestment in CVD compared to other therapeutic areas. However, there are reasons to be optimistic and strategies can be implemented to address these challenges. First, although recent approvals for CVD have declined, data suggests that we may be at a tipping point in basic research for CVD that could spur more successful drug development (7). Innovations in DNA sequencing methodologies have transformed the field of human genetics, holding the promise of identifying causal mechanisms and creating better drug targets for the treatment of common, complex diseases such as CVD (28). Second, as the focus on quality and patient-centered outcomes increases, providing treatments that improve patient outcomes in CVD is well aligned with quality incentive payment programs. Finally, we have seen how advocacy seems to have moved the needle in oncology. If we continue to work together and make a concerted effort to shine the light on the unmet need in CVD, we can help improve investment in this area. We already have large campaigns such as the Center for Disease Control's Millions Heart campaign (29) and the American Heart Association and Duke's Value in Health Care Initiative (30). If cardiologists champion these movements en masse, we will have great momentum. Like they have in oncology, we need to have a CV "moonshot" and we need to be advocates in the fight to eradicate CVD.

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**KEY WORDS** advocacy, cardiovascular disease, drug development, expedited regulatory pathways