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TRANSLATIONAL PERSPECTIVES

Temporal Trends and Factors Associated With Cardiovascular Drug Development, 1990 to 2012

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SUMMARY

Cardiovascular disease remains a leading cause of death, but stakeholders have recently raised concerns about the pace of innovation and investment in developing new therapeutics. Here, the authors characterized temporal trends in cardiovascular research and development over the past 2 decades and the likelihood of successful completion of pre-approval clinical trials. The authors also evaluated the reasons for discontinuation, novelty, and rates of trial results publication for cardiovascular therapies in late-stage development. Between 1990 and 2012, the number of new cardiovascular drugs entering clinical trials declined across all stages of development ($p < 0.001$ for linear trends). There was no evidence for a difference in probability of successful progression to the next stage of development between cardiovascular and noncardiovascular drugs. Small and medium-sized companies sponsored 43%, 38%, and 31% of new Phase 1, Phase 2, and Phase 3 trials, respectively. Roughly one-half of the drugs in Phase 3 trials were categorized as targeting a novel biological pathway. The number of cardiovascular trials sponsored by small and medium-sized companies and the number of novel drugs entering Phase 3 trials increased over time. Most drugs were discontinued in Phase 3 due to inadequate efficacy (44%) or safety issues (24%), but the Phase 3 trial results for only one-half of the discontinued drugs were published in peer-reviewed journals. These results shed light on important shifts in research and development activity and confirm the perceived challenges in cardiovascular translational research. (J Am Coll Cardiol Basic Trans Science 2016;1:301–8) © 2016 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

The development of new prescription drugs and their adoption into clinical practice have been associated with significant reductions in cardiovascular mortality over the past 2 decades (1). Despite this progress, cardiovascular disease is a leading cause of death in the developing world and still accounts for 1 in 3 deaths in the United States (1–5). The productivity of translational research in this field has recently come under scrutiny amidst concerns over the declining pipeline of novel therapies (6). Proposed explanations for the discrepancy between the slowdown in innovation and burden of disease include the rising cost of conducting large cardiovascular outcome trials, stagnating financial investment, and diminished commercial attractiveness of the cardiovascular field owing to availability of

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ABBREVIATIONS AND ACRONYMS

ATC = Anatomical Therapeutic Chemical

CI = confidence interval

CNS = central nervous system

FDA = Food and Drug Administration

HR = hazard ratio

LDL = low-density lipoprotein

PCSK9 = proprotein convertase subtilisin/kexin type 9

low-cost generic medications (6,7). Several high-profile failures of clinical development have contributed to this perception. For example, in 2012, a large Phase 3 trial of varespladib, a secretory phospholipase A_2 inhibitor hypothesized to improve cardiovascular outcomes, was halted when an interim analysis found that the drug was in fact associated with an increased risk of myocardial infarction (8).

There are limited data on trends in cardiovascular research and development and the factors associated with the success of new therapies in clinical trials. It has been previously reported that the number of new cardiovascular drugs approved by the U.S. Food and Drug Administration (FDA) has declined in recent years (6,9). A contraction in the pool of cardiovascular drugs under development has also been reported (10), but trends in new drugs that have entered clinical testing or those that have been discontinued remain undefined.

SEE PAGE 309

In this study, we describe temporal trends in cardiovascular drug development over the past 2 decades, analyze the likelihood that investigational cardiovascular drugs successfully complete preapproval clinical trials, and characterize the novelty of drug pathways, reasons for discontinuation, and rates of publishing trial results for new drugs in late-stage development.

METHODS

DATA SOURCES AND EXTRACTION. We analyzed data from a large commercial database of drug development activity (Citeline Pharmaprojects, Informa plc, London, United Kingdom), which tracks in real time the pipeline of pharmaceutical research and development projects. This database covers more than 50,000 products for all diseases from pre-clinical to commercialization stage and is widely used by industry and researchers to analyze trends in drug development (11–15). Using methods described previously (16), we selected for analysis all products that had entered Phase 1 clinical trials between January 1, 1990, and December 31, 2012 (N = 4,715). For each product, we extracted key information, including generic and proprietary names, sponsor, primary indication, mechanism of action (if known), start and end dates of each phase of clinical testing, date of regulatory approval (if applicable), and date and reason for discontinuation (e.g., failure to demonstrate efficacy, safety concerns, commercial/financial). On the basis of the primary indication, each product was mapped to an Anatomical Therapeutic Chemical (ATC) code, which categorizes drugs according to the organ or system on which they act and their therapeutic and chemical characteristics. We focused on drugs intended to treat disorders of the cardiovascular system (ATC code C), such as antihypertensive, antiarrhythmic, antianginal, and lipid-lowering agents, and disorders of blood and blood-forming organs (ATC code B), such as blood fraction and plasma substitutes, and anticoagulant, antithrombotic, antifibrinolytic and antianemic agents. We also compared rates of cardiovascular drugs entering clinical trials with those of cancer drugs (ATC code L01) and central nervous system (CNS) drugs (ATC code N, except N01 and N02) (11). We categorized all sponsors in our study cohort into large pharmaceutical companies, defined as companies with gross revenues >$1 billion, and small and medium-sized companies. Next, we searched Medline, EMBASE, and Web of Science for peer-reviewed publications of trial results, and search engines, press releases, and other publicly available sources for the stated reasons (if any) for discontinuation of drug development.

Finally, 2 investigators (T.J.H. and J.C.L.) categorized cardiovascular drugs that entered Phase 3 trials during our study period as targeting a "novel pathway" or "other target." Consistent with prior studies by the FDA and others (17–19), we defined a novel pathway as a target or biological pathway for which the FDA had not yet approved a therapeutic agent by the pivotal trial start year. Changes in formulation (e.g., the first oral alternative to existing intravenously administered products) and new combinations of existing drugs (with or without a new agent) were considered novel pathways. Changes in chirality (e.g., a purified single enantiomer form of an already-approved racemic drug) were not considered to be a novel pathway. Any disagreements (representing ~5% of cases) were resolved by consensus.

All data were initially downloaded on June 28, 2013, and information on publication status and novelty was updated through March 1, 2016. This study was not submitted for institutional review board review, because it is based on publicly available data and involved no patient health records.

OUTCOME MEASURES. We first studied temporal trends in the number of new Phase 1, 2, and 3 clinical trials started for investigational cardiovascular drugs over time and compared these trends to those for drugs intended to treat cancer and CNS disorders. We also evaluated the proportion of such trials started by small and medium-sized companies. Because the