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An analysis of FDA-approved drugs for cardiovascular diseases

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Following the introduction of antibiotic therapy and widespread inoculations, cardiovascular diseases have leapt ahead of infectious diseases in terms of prevalence in much of the developed and developing world. Herein, we assess FDA-approved drugs for the treatment of cardiovascular diseases. The drug development enterprise around cardiovascular diseases has remained stable in contrast to turbulent changes in other therapeutic indications. However, upon closer inspection, the results identify narrow scope in terms of the breadth of targets and the mechanistic actions of new drugs. From the public health point of view, it is important to balance incremental change with orthogonal innovations that are needed to combat a leading cause of morbidity and mortality.

Background

Human beings have constantly struggled to find new treatments for heart disease. The diagnosis of 'hard pulse disease' (today known as hypertension) was addressed more than four millennia ago in ancient China through the use blood letting or leeches to reduce blood volume [1]. The seminal publication of *Anatomica de Motu Cordis et Sanguinis in Animalibusin* by William Harvey provided the framework for the modern understanding of heart function and, consequently, a new means to target cardiovascular diseases [2].

Modern attempts to address heart diseases in their various manifestations have led to an accumulation of new drugs to address age-old challenges [3]. Burroughs Wellcome received the first FDA approval for a cardiovascular new molecular entity (NME), digoxin, in January 1937. Since that time, the FDA has approved 201 different NMEs through to the end of 2013 (Fig. 1a). When viewed over time, the average rate of introduction of NMEs has remained relatively steady since the 1950s, with an average of 2.7 NMEs per year (Fig. 1b).

Likewise, the number of companies active in the cardiovascular NME research and development space has grown steadily over time (Fig. 1c). The number of organizations with active cardiovascular research and development shrank as a consequence of mergers and acquisitions but recently stabilized at a range of 35–45 companies. This relative constancy is somewhat surprising given the number of mergers of major pharmaceutical companies in the 1980s and 1990s. We evaluated the volatility by evaluating the number of active and independent companies that entered (as a result of gaining at least one FDA approval for a cardiovascular indication) and exited (as a result of a merger, acquisition or bankruptcy) the field. Indeed, there has been a large number of exits in recent years but this has been offset by the introduction of new organizations (Fig. 1d). This steadiness differs dramatically from the impact that volatility has had upon infectious diseases but lacks the growth of companies in the oncology space [4,5].

Unlike the situation with all other disease areas evaluated to date, the pharmaceutical industry continues to dominate cardiovascular diseases. Biotechnology companies (defined herein as those founded after 1971) remain in the minority in terms of contributing the first patent, investigational new drug (IND) applications or participation in clinical trials. This could be explained at least in part by our recent findings that biotechnology companies tend to favor orphan indications and biologics. Indeed, only seven biologics (from a total of 94 biologics ever approved) were approved with an initial indication being in the field of cardiovascular disease. Moreover, only five cardiovascular NMEs have ever been approved with an initial orphan

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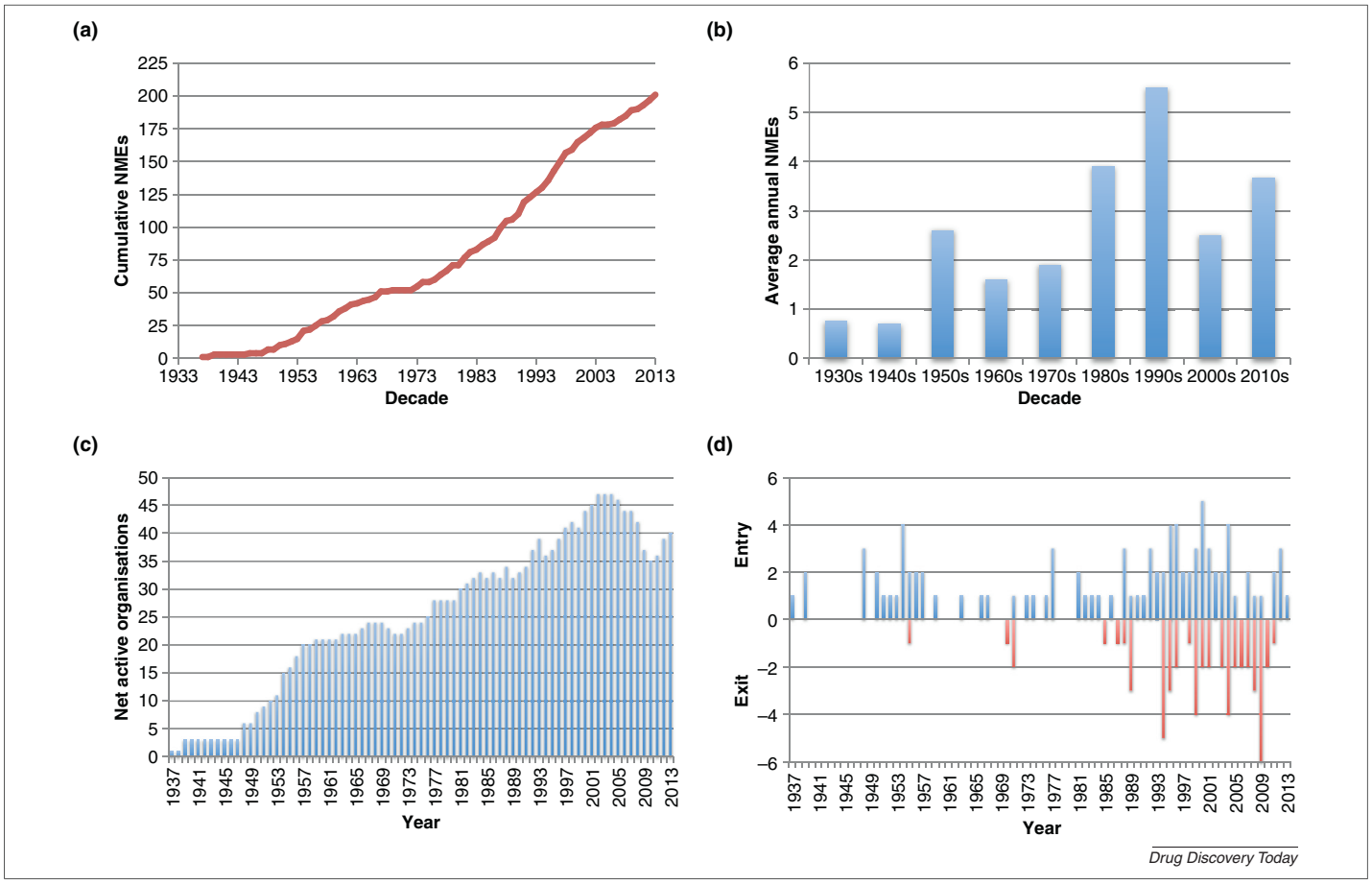

FIGURE 1

Growth of cardiovascular new molecular entities (NMEs) over time. **(a)** The accumulation of NMEs was evaluated on a year-to-year basis, revealing a total of 201 NMEs targeting cardiovascular diseases as their initial indication. **(b)** The average number of annual NMEs was assessed on a decade-by-decade basis. **(c)** The net number of organizations active and awarded at least one NME for a cardiovascular indication is shown, as is **(d)** the annual number of organizations entering or exiting the field.

disease indication, which is well below the average of more than one-third of all FDA-approved NMEs during the current decade.

Having established the players and overall trends in the field, we began dissecting the indications and the mechanistic basis of NME approvals over the years. In terms of indications, drugs focused on blood pressure have dominated the field (Fig. 2a). One-hundred-and-five NMEs target blood pressure (primarily hypertension), which represents more than half (52.2%) of all cardiovascular medicines. At its peak in the 1950s, more than 80% of all cardiovascular-disease-focused NMEs targeted blood pressure. These numbers have been trending downwards and, today, the level of NMEs targeting blood pressure stands at 36.4%. Despite this decline, this level still represents more than one-third of all cardiovascular NMEs.

The past few decades have witnessed increases in targeting of coagulation and thrombosis-related indications. Together, these indications currently represent over one-third of NMEs approved for cardiovascular diseases in the current decade (Fig. 2b). Drugs targeting hyperlipidemia, first introduced in the 1960s, surged in the 1990s as a result of the development of statins targeting 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase. By contrast, emphasis on new arrhythmia drugs, which were first introduced in the 1940s and remained relatively prominent through the 1980s, has dropped in recent years.

Changing trends in indications led us to ask about the classes of targets selected for intervention (Fig. 3a). Historically, G-protein-coupled receptors (GPCRs) represent the most common family of targets, accounting for 41% of all cardiovascular NMEs. These are followed by drugs targeting channels (21%: primarily sodium and potassium and calcium) and proteases (21%). Together, these three target types encompass more than four out of five NMEs approved for cardiovascular diseases.

The disproportionate emphasis on a small subset of target types raised important questions about potential bias. Follow-on (also known as 'me-too') drugs might have limited the breadth of cardiovascular targets emphasized by the biopharmaceutical industry [6,7]. For example, Merck gained FDA approval for the first HMG-CoA reductase inhibitor, lovastatin, in 1987. This was followed by pravastatin (Bristol-Myers Squibb, 1991), simvastatin (Merck, 1991), fluvastatin (Sandoz, 1993), atorvastatin (Warner-Lambert, 1996), cerivastatin (Bayer, 1997), rosuvastatin (Astra-Zeneca, 2003) and pitavastatin (Kowa, 2009). Moreover, it is increasingly accepted that proof-of-concept from the standpoint of sales and marketing (i.e. demonstrating profitability) has favored the development of multiple generations of statins and antihypertensives, a trend that continues today.

What is perhaps less well known is that unintentional bias might be introduced by past success. For example, the composition of screening libraries or investigator expertise with certain molecule types might favor emphasis on structures with which there is greater

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