Past the wall in cardiovascular R&D

Cardiovascular drug development seems to have 'hit the wall' in recent years, with multiple high-profile trial failures and declining industrial interest. How can the field be revitalized?

In the 1980s and 1990s, cardiovascular drug development programmes led to multiple blockbusters, such as statins, angiotensin-converting enzyme (ACE) inhibitors, anti-platelet agents and beta-blockers. However, after this long run of successful mega-trials — often involving more than 10,000 patients — progress has stalled, with only rare positive results in recent years and many disappointing failures, owing to unexpected toxicity (for example, torcetrapib) or lack of efficacy (for example, the combination of ACE inhibitors with angiotensin receptor blockers). The previous successes also raised the bar for trials of new drugs, necessitating active controls and the use of non-inferiority trials.

With the cost of mega-trials in cardiovascular medicine reaching US$400–500 million, such as the recent comparison of prasugrel to clopidogrel in over 16,000 patients, the willingness of sponsors to take the necessary investment risk has greatly diminished. Moreover, such trials typically have 'hard' efficacy end points, such as reducing death, heart attack and stroke. So, with the lower bar for regulatory approval for new drugs in oncology and neurodegenerative disease, and the likelihood of higher reimbursement, interest in pursuing new paths in cardiovascular medicine has faded. This is perhaps best exemplified by the recent announcement from Pfizer — a company whose cardiovascular drugs have long been among the most successful — that it was exiting the field.

Such decisions, and the general shift of the pharmaceutical industry to pursue non-cardiovascular indications, are deeply concerning. The number one cause of death and disability is still cardiovascular disease, despite the therapeutic progress that has been made. Moreover, its worldwide importance is rapidly increasing owing to the ageing population and the 'diabesity' epidemic in the developed world, and its increasing prevalence in the developing world. How can this mismatch of unmet, soaring clinical need and lack of interest from, and incentive for, the pharmaceutical industry be rectified?

A complete rethink of the current model of cardiovascular clinical development seems warranted. Instead of programmes that culminate in large trials for a broad indication, it is time to consider a new path, which has already shown some success in anticancer drug development. By capitalizing on '-omics' knowledge, future cardiovascular trials have an opportunity to seek high levels of efficacy, reduction of serious adverse events, or both.

The potential of this concept in cardiovascular medicine can be illustrated by the example of anti-platelet drugs that target the $P2Y_{12}$ receptor, which have been highly successful in the prevention of arterial thrombosis. Indeed, clopidogrel, the leading drug in this class, is the second best-selling prescription drug. However, for several years, it has been known that at least 30% of patients receiving clopidogrel have a diminished response. A key reason is that clopidogrel requires hepatic metabolism to an active metabolite, relying predominantly on cytochrome P450 CYP2C19, and loss-of-function variant alleles for *CYP2C19* are common, being present in at least 30% of individuals of European ancestry, 40% of those of African ancestry and 55% of those of Asian ancestry. Indeed, in three large clinical studies, individuals with the *CYP2C19* loss-of-function variants had at least a threefold increase in risk of death, heart attack or stroke compared with individuals with the wild-type sequence.

With this background, an attractive clinical programme for a new $P2Y_{12}$ inhibitor that does not require metabolism to the active drug can be mapped out. Following genotypic screening, only patients with loss-of-function *CYP2C19* alleles would participate in the trials, with clopidogrel serving as the control. However, instead of requiring tens of thousands of patients to demonstrate the 15–20% reduction of major end points that is typical in pivotal trials of cardiovascular drugs, the expectation of a higher efficacy of this targeted therapy should allow for reduced sample sizes and more rapid recruitment, but still a relatively large population for everyday clinical use.

There are many other instances in cardiovascular medicine in which such '-omics'-oriented development programmes might prove beneficial, such as screening for single-nucleotide polymorphisms in genes that encode β-adrenoceptors to guide the use of beta-blockers in congestive heart failure. Proof of concept for this strategy will rely on the willingness of the pharmaceutical industry to design and execute clinical research programmes that embrace individualized medicine, rather than the current, untenable blockbuster model. In this way, it should be possible to provide new energy to take cardiovascular medicine past the wall and back on track to reducing the toll of some of the most important and life-threatening diseases.

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