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Global Challenges in Cardiovascular Drug Discovery and Clinical Trials

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Abstract

Despite major advancement in drug development heart disease and stroke remain major public concern due to primary cause of death. In developing nations, more than 20-25 million peoples are projected to die due to cardiovascular disease by 2020. The burden of cardiovascular disease clearly remains both a major public health concern and growing global challenge.

The number of cardiovascular drugs in the research pipeline has declined across all phases of development in the last 20 years even as cardiovascular disease has become the No. 1 cause of death worldwide. The reason for this trend is multifactorial but primary reason is cost of conducting cardiovascular outcome trials in the current regulatory environment that demands a direct assessment of risks and benefits. It is difficult to prove treatment benefits in cardiovascular space compared with other therapeutic areas like Neuroscience and oncology. The Global challenges to bring new cardiovascular drugs in to the market go beyond scientific breakthroughs and innovation. The key challenges are:

- Rising cost
- Regulatory uncertainty
- Decline in new drug targets
- Late-stage failures
- Complexity in clinical trial design

End point studies having surrogate markers are the pivotal for the cardiovascular drug development. Innovative technology, web based conduct and global participation is needed to overcome global challenges.

Keywords: Global challenge; Cardiovascular drug development; Clinical trials

Introduction

Drug development - Key facts

The pathway for drug development is becoming more complex and costly for industry. Currently it takes around 10-12 years and investment over $3-5 billion to bring single innovative drug in to market (Figure 1) [1]. In regulated countries, pre marketing approval, clinical investigations and post marketing procedures are heavily regulated. Testing of every potential new therapy independently from the currently available therapies seeking to treat same disease or conditions is must which adds lot of extra cost and efforts to complete drug development [1-3]. In addition, there is huge concern about the ability and willingness, of societies to pay for the novel treatment [4].

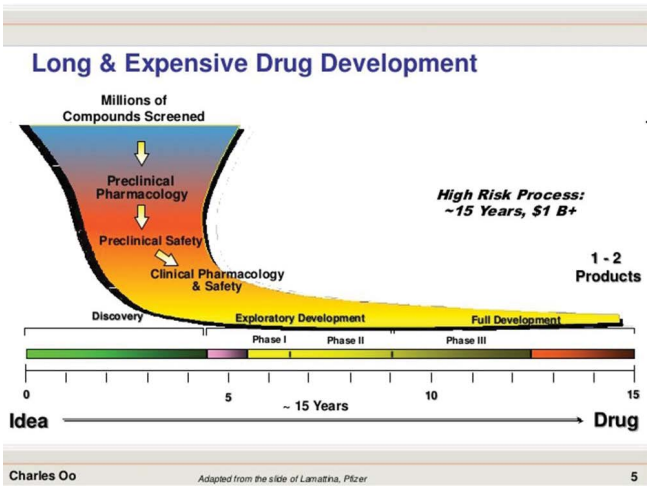

Figure 1: Drug development process.

Reasons for the rising drug development cost

There are several reasons for the rising drug development cost. Key reasons are as under.

High failure rate: Drug development is very long, risk and expensive process. It is required to do screening of 5,000 to 10,000 compounds to get one FDA approved product. The success rate is around 12-16% for the compound that entering in to clinical trial [1,2].

Complexity of clinical trials: Regulations are constantly evolving across globe. To incorporate these changes, clinical trial protocols are having more and more procedure to generate data. Most of the protocols are having long trial duration and difficult eligibility criteria's for the patient enrolment. Personalized medicine and diagnostics add lot of cost to perform clinical trials [1,3,5].

Volunteers/patients enrolment: It is difficult to get suitable volunteers/patient for conducting clinical trials. There are numerous factors responsible for it. One of the major barriers is lack of awareness about clinical trials. Below is a detailed list of enrollment obstacles [1,2,6,7].

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Fear of being a guinea pig.

Concern about cost and coverage by the insurance:

- Protocol design and stringent inclusion/exclusion and procedure requirements.
- Preference for alternative and holistic treatments.
- Belief that clinical trial treatment is more invasive compared to standard treatment.
- Informed consent procedure.
- Concerned about lack of continuity in treatment and care.

Global disease burden: The global burden of disease has dramatically shifted from communicable, maternal, perinatal and nutritional causes to non-communicable diseases (NCDs) (Figure 2) [4,8,9].

It is estimated that, the people die due to ischemic heart disease will increase by around 50% in developed countries and by over 100% in developing and undeveloped countries. Similar increase will also found in stroke by 2020.

Cardiovascular disease

Cardiovascular disease burden is major concern across globe. Key diseases of cardiovascular system are:

1) Hypertension
2) Myocardial infarction
3) Congestive heart failure
4) Cardiac arrhythmias
5) Coronary artery disease

Currently, around 80% of cardiovascular deaths are reported in low and middle income countries due to widespread urbanization that has seen during recent times. There are changes seen in type of food consumed and increasing sedentary life style as societies shift to urban setting. It is estimated that by 2020, heart disease and stroke will become the main cause for the worldwide death and disability [1-4,10-12].

Cardiovascular drug development:

a. History: Cardiovascular drug development program was aggressive enough during 1980s/90s. This led to development of several blockbusters such as Beta blockers, statins, ACE inhibitors and anti-platelet agents [1-9].

b. Current scenario: Investment in cardiovascular drug development has stagnated over the past 2 decades compared with other therapeutic areas.

- 1990-95: 16% (Phase-I) 21% (Phase-III)
- 2005-12: 05% (Phase-I) 07% (Phase-III)

It has been reported that, the number of new cardiovascular drugs approved by the U.S. Food and Drug Administration (FDA) has declined. Several high-profile failures of clinical development have contributed to this. For example, in 2012, a large Phase 3 trial of varespladib, a secretory phospholipase A2 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.

Global challenges and reasons for decline in cardiovascular drug development

There are several reasons for the slowdown of cardiovascular drug development. Important reasons are as under:

1. Patent cliff (phenomenon of patent expiration dates) - The cardiovascular drug market is severely impacted by the scarcity of new agents and the loss of patent protection. Several blockbusters having high revenue for the companies saw patent expiry. It was started in 2011 when Pfizer's biggest anti-cholesterol blockbuster, Lipitor®, went off patent. It was followed by Sanofi's best-seller anticoagulant Plavix® in 2012. This phenomenon led to a 135 billion $ loss for the pharmaceutical industry in 2013 which represents nearly 20% of its turnover [1,6,9] (Figure 3).
2. The bar has been raised significantly for the regulatory approval in US. There is greater focus on pre-approval safety requirements and post marketing obligations which makes cardiovascular drug development more difficult.
3. Most of the low hanging fruits have been plucked and current drug development process is very long, risky and complex for cardiovascular drug development.

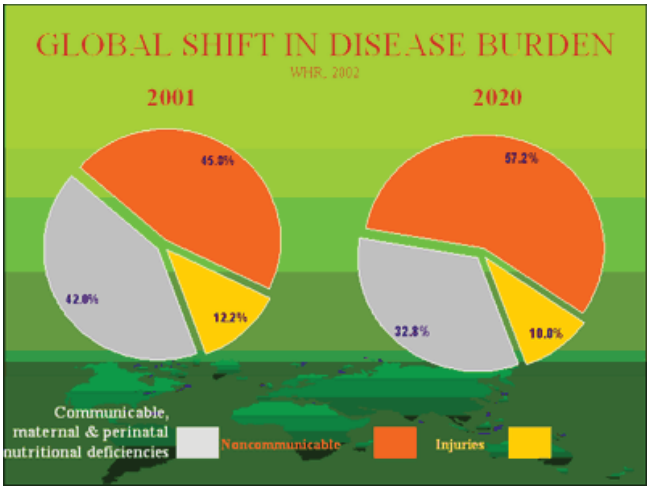

Figure 2: Global disease burden.

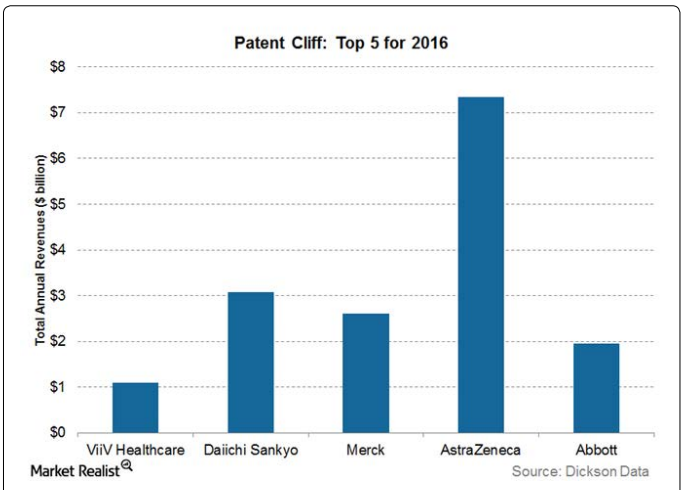

Figure 3: Patent cliff.

4. Cardiovascular drug development was traditionally more focus on heart failure and hypertension; however these conditions resulted from multiple factors and pathways.
5. Late phase withdrawal due to cardiovascular toxicity is major concern during drug development.
6. Majority of CVD are caused due to several genetic factors and environment and each contribute to disease risk hence it's difficult to discover new cardiovascular drugs.
7. Public support remains low and willingness, of societies to pay for novel treatment.
8. Third party payers are demanding very high over period of time.
9. Market place is highly competitive.
10. There is perceived reduction in investment risk by focusing on other therapeutic areas (non-cardiovascular drugs) to marker by majority of drug development companies.

Complexity of cardiovascular clinical trials

- Cardiovascular trials needs operational expertise, deep medical understanding in order to prove efficacy of the new product over existing treatment.
- Majority of CVS trials are typically having 'hard' efficacy end points, like reducing death, heart attack and stroke with higher bar for the regulatory approval.
- It is required to do cardiovascular outcomes trials on large sample sizes and must continue for many years to accumulate enough endpoints.
- Patients needed for most cardiovascular outcomes trials are based on background medical history and having low event rate hence CVD trials are prolonged, costlier with new therapeutic modalities.
- It is necessary to do cardiovascular outcomes trials based on standard guideline recommended therapies having "standard of care". There are several cardiovascular drugs discontinued due to either safety or efficacy (Figure 4) [1-6,10-16].

Possible approaches/solutions to tackle the outlined challenges

Below are the probable solutions to tackle the outlined key challenges:

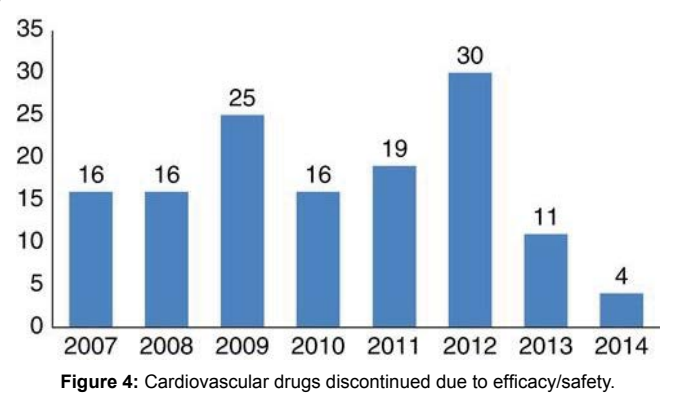

Figure 4: Cardiovascular drugs discontinued due to efficacy/safety.

Rising cost: Probable solutions:

- Reduce extraneous data collection
- Meet key stakeholders early during development
- Adopt quality by design approach
- Implement Risk based monitoring/Centralized monitoring
- Prioritize collection of SUSAR

Appoint centralize review board (DSMB/IRB)

Regulatory uncertainty: Probable solutions

- Consider novel trial design (Adaptive design)
- Ensure frequent/prompt communications with Regulatory agencies
- Involve academic expert to interface

Decline in new drug targets: Probable solutions:

- Strengthening novel scientific method to understand disease.
- Collaborate with academic institutions
- Create new biological signature
- Use next generation sequencing

Validate clinical outcome over surrogate endpoints: Probable solutions:

- Increase focus on practical, streamline trial
- Adopt quality by design
- Use biomarker but continue to demand clinical outcome

Discord between cardiovascular burden and perception: Probable solutions:

- Enhance awareness through Government funding
- Use NGO for the campaign

Conclusion

The cardiovascular drug market is severely impacted by the scarcity of new agents. There is decline in cardiovascular drug development due to limited funding, loss of patent protection of several block buster molecules, fewer validated targets, greater regulatory hurdles and requirements for the larger studies. It is difficult to prove treatment benefits in cardiovascular space compared with other therapeutic areas like Neuroscience and oncology. The incentive to develop cardiovascular agents has been reduced by increasing clinical development costs coupled with an augmented risk of failure due to the unprecedented nature of the promising drug targets and an increasingly challenging regulatory environment.

For the better management of cardiovascular disease, a coordinated effort is needed between academia, regulators, industry and Payers. This will foster better and more effective conduct of clinical cardiovascular trials, supporting earlier availability of innovative therapies.

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