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Editorial

BVS, RDN, IABP: The Afghanistan of interventional cardiology trials

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ABSTRACT

In the field of medicine and cardiology newer therapy and devices have been launched with a huge promise and a lot of hype. Unfortunately, over the course of time, a good many of them like biovascular scaffold, renal denervation and intra-aortic balloon pump have failed to live up to their initial promise so much so that some of them have been withdrawn. The reason for this downfall may be multifold from incomplete understanding of the patho-physiology of disease, incomplete understanding of mechanism of action of the therapy, in-appropriate application in clinical practice, in-efficient therapy development related to flawed trial design, regulatory impediments placed on the trials or deficits in application of scientific techniques. Here-in we investigate the specific reason for failure for some of these therapies and attempt to suggest a way forward.

We need to appreciate that the success we have today can be taken away tomorrow

1. Introduction

1.1. The BVS fiasco

It was year 2009 when bioresorbable scaffolds (BRSs) were announced as the fourth revolution in interventional cardiology due to a unique ability of these devices to provide a temporary support while maintaining the patency of the vessel immediately after percutaneous coronary intervention (PCI) before gradually decomposing themselves, releasing the treated vessel from surrounding scaffold. While the technology was primarily targeted to reduce the risk of stent thrombosis (ST) particularly the late ST, restitution of vessel integrity and function was purported as another possible advantage. The early "childhood" of this technology was almost dream-like; in the year 2011, Abbott Vascular's Absrorb™, Abbott Vascular, Santa Clara, CA, USA received CE Mark approval. In October 2012, it was released in Europe for commercial use and in December 2012 in India. In July 2016 it received US FDA approval. Trials so far had shown equivalent results with scaffold while having the added advantage of no late complications and late restoration of vessel function. Nearly 20 companies all over the world jumped into BRS bandwagon and were in various stages of its development. However, after achieving this high, began a downward spiral for this technology. Within a few months of its FDA approval, in October 2016 at TCT, ABSORB II trial was presented by Patrick Serruys and simultaneously published in Lancet. For the first time it was shown that not only the BVS was not non-inferior to the "best-in-class Xience™, Abbott Vascular, Santa Clara, CA, USA (everolimus DES); the co-primary end point of late lumen loss (for this was less with the Xience), but there was no superiority in vascular restoration, and the secondary device-oriented composite end point {cardiac death, myocardial infarction (MI) attributable to target vessel, plus clinically indicated target lesion revascularization (TLR)} was 10% in Absorb™ group versus 5% in the Xience™ group (hazard ratio 2.17; 95% CI 1.01–4.70), a difference mainly driven by target vessel MI (6% vs 1%, $p = 0.01$), including periprocedural MI (4% vs. 1%, $p = 0.16$). Eight biovascular scaffold (BVS) thromboses had occurred versus none in the Xience™ group.[1] In September 2017, Abbott Vascular discontinued the global sale of its 1st generation Absorb device. Thus within a span of 1 year a device heralded as the 4th revolution had become a failed revolution.[2]

1.2. The RDN story

Hypertension is one of the most common maladies affecting the human-kind (afflicting nearly a third of the population) as also a leading cause of cardiovascular morbidity and mortality. It is estimated that >10% of hypertensive adults are resistant to pharmacological treatment. The etiology of hypertension is multi-factorial but sympathetic nervous system (SNS) is a well-known contributor, at least in younger individuals and seems to play a pivotal role in resistant hypertension. Surgical transaction of the SNS (thoraco-lumbar sympathectomy, renal nerve resection etc.) was attempted nearly a century ago, even before anti-hypertensive medication was available to treat patients with hypertension but was ultimately given up due to prohibitively high morbidity, mortality and issues of orthostatic hypotension with this

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modality.[3] Percutaneous radiofrequency (RF) ablation has become gold standard in treatment of several arrhythmias, effective by mediating focused tissue destruction of unwanted conduction tissue. Not only in cardiac electrophysiology, it has also been found useful in oncology and interventional radiology. Catheter based technologies can also be effectively applied to target the SNS much more safely and non-invasively compared to surgical resection. Indeed this concept seemed so attractive that renal denervation (RDN) was considered the "next breakthrough" in anti-hypertensive armamentarium. The first patient was treated in 2009 and since then numerous clinical trials including Symplicity HTN-1 and 2 envisaged a highly efficacious and safe therapy for resistant hypertension, so much so that it seemed poised to be applied not only to less severe stages of HT but even to other clinical syndromes featuring excessive SNS activation such as heart failure, diabetes mellitus, sleep apnea and chronic renal disease.[4,5] This therapy seemed particularly valuable because drug therapy in hypertension had seemingly reached a plateau and certainly there were concerns regarding tolerability of available drugs especially in context of resistant HT. A flurry of devices got approved in Europe; Symplicity ™ Renal Denervation System (Medtronic/Ardian; CE mark approval in 2010); EnligHTN TM Multi-Electrode Renal Denervation System (St. Jude Medical; CE mark approval in 2012); V2 ™ Renal Denervation System (Vessix Vascular; CE mark approval in 2012); OneShot ™ System (Covidien; CE mark approval in 2012); and Paradise ™ System (Recor; CE mark approval in 2012). Moreover, work started on numerous other devices all over the world. And then came the damper; the failure of the pivotal SYMPLICITY HTN-3 study to meet its primary efficacy endpoint.[6]

1.3. Has intra-aortic balloon pump popped off?

Intra-aortic balloon pump (IABP) counterpulsation is another case in point. Since the concept was proposed by Moulopoulos and co-workers in 1962, it emerged as one of the most effective and most frequently employed methods of mechanical circulatory support for the failing ventricle, whether it was decompensated heart failure or ischemia induced failure. Mechanistically it relies on the twin support by diastolic augmentation (and increasing coronary flow) and afterload reduction (reducing myocardial demand) which led to improved myocardial hemodynamics. Over the period of last 5 decades or so the use increased so much that >70,000 IABP devices were annually used US alone in a wide variety of situations: cardiogenic shock, persistent and intractable angina, high-risk angioplasty, and peri-CABG setting. Unfortunately the enthusiasm of using this device was not matched by evidence in its support, the bad news emanating from most unlikely quarter; cardiogenic shock and patients with poor left ventricular function undergoing coronary artery bypass surgery (CABG). IABP-SHOCK II trial revealed that in patients of acute MI (AMI) complicated by cardiogenic shock, the use of IABP did not reduce 1-year all-cause mortality.[7] A meta-analysis investigating patients presenting with AMI also revealed no improvement in these patients regardless of cardiogenic shock status.[8] In non-emergent CABG setting another trial revealed no benefit of IABP use in a patient with stable hemodynamic profile and a low ejection fraction (LVEF < 35%). The only solace for this device was the realization that there could still be some benefit if this device was employed just prior to actual ventricular decompensation; one such application being prophylactic use in high risk PCI but not in a bail-out situation when the patient had already decompensated.[9]

These trials are just 3 examples. Numerous trials in cardiology and interventional cardiology; trans-myocardial laser, thrombus extraction devices, bivalirudin have failed to show a benefit after initial promise and huge hype. Why did this happen?

2. Why do prestigious trials fail?

There are several reasons for the failure of a trial but the most important is that there was not enough information/clarity of situation before embarking upon the trial or "the battle-field was not entirely known before the invasion;" Afghanistan of clinical trials or something akin to Abhimanyu entering the Chakravyu but being unable to safely exit. However, this situation is not unusual in research environment, there is ample proof that clinical translation cannot succeed without failure. As a matter of fact there may be attrition at every level of a drug/device development. Nearly 90% of drugs that reach clinical stage development never make it to FDA or other approvals.[10] Even in later stages of development the failure is quite common; it is estimated that >40% of drugs fail phase III clinical trials and many drugs have to be withdrawn following post-marketing surveillance.[11]

There could be several reasons for this failure (Table 1). The most important reason is that currently science works by a process of differentiation, treating the human body as a machine and disease as a defective machine part. It breaks down the patho-physiology of the disease, really a complex mystery, in individual parts (like a machine), then these parts are individually understood, and finally these parts are fixed back like some jig-saw puzzle, instead of trying to understand the whole. The same principle is applied to the pharmacology of a drug or device, breaking its mechanism of action into a flow-chart and then acting on a specific part of the algorithm[12] Unfortunately, in real world, mere Cartesian reductionism cannot explain the human body or its disease process. Furthermore, the medical practitioner cannot behave as a technician trying to fix an individual part of the machine.[13]

Another related mistake is excessive focus in identifying the cause or etiology. Modern medical scientist firmly believes that the key to any therapy is to identify a cause. Once the cause is identified, it is then just a web of related events which defines the disease process and the therapy involves intervention at any level of this web of patho-physiology or better stills the final common mediator i.e. the cause. In current scientific parlance cause/etiology is identified by statistical co-relation with a part of the disease. Statistically, the "significance" of any co-relation (etiology) is established if it would be produced by chance <5% of time. However, as we go along the algorithm (web), this >95% chance gets diluted by another >95% chance at the next step, and so on. Thus by the time we reach the end of the flow chart, the actual statistical correlation between the first "etiology" and the "final outcome" may be much less, and may not actually be co-relative at all. To explain this apparent paradox we bring around the concept of negative and positive feedbacks, which makes the overall picture very complex. Again the statistical model mathematically points out to the common fallacy of medical science, that sum of parts cannot be the whole part. Thus in reality all etiologies are actually mental short-cuts, many a times they work well enough but when it comes to complex and dynamic systems these short-cuts can famously fail from being highly efficient to downright misleading.[12]

Table 1
Reasons for failure of landmark trials.

1. Incomplete understanding the patho-physiology of diseases
2. Excessive focus on identifying 1 etiology rather than understanding the complex web of interconnected mechanisms
3. Incomplete understanding of mechanism of action of the therapy
4. Inefficient therapy development
   –Flawed trial design
   –Regulatory impediments
   –Deficits in application of scientific methods
   –Excessive dependence on statistical methods
5. Inappropriate application in a clinical setting

There could be many other factors for individual failures; inefficient drug development related to flawed trial design, regulatory impediments placed on the trials or deficits in application of scientific techniques. Finally, how the previous positive trial is applied in the current trial or real-world healthcare practice can be another limitation.

3. How science failed us!

One of the limitations of current DES technology is that metallic stent is forever, subjecting the patient to a life-long risk of ST. It was thus felt that a technology that would allow dissolution of this scaffold and complete disappearance would overcome the problem of late thrombosis. This was a classical case of applying a solution to a part of the problem (in this case late ST) while ignoring the whole. Structurally, polymeric BRS has a low radial and tensile strength which translates into polymeric scaffold not getting properly imbedded into the vessel wall, rather, a lot of scaffold struts protrude into the vessel lumen, acting as a nidus for early and sub-acute ST (SAT).[2,14] Thus a minor advantage in late ST was overcome by more than many fold increase in SAT and post-procedural MI. Likewise, a faulty understanding of vessel function restoration was also in play. It was simplistically believed that impaired vessel function after stent implantation was due to the caging effect of a metallic scaffold and therefore once this cage was removed, the vessel functions would return back to normal. Alas that was not to be and clearly other factors were also involved in vascular restoration which had been incompletely understood in the first place. Thus the conceptual failure was many fold; incomplete understanding of patho-physiology but also the failure of device itself; it can be argued that a device with logarithmically inferior physical characteristics compared with metallic DES was already pre-destined for a failure. Another lacuna was improper application of this technology in real world practice. There here could have been a lot of learning curve involved with this "different" device, and a "different" way to properly implant it; optimal bed preparation, method of implantation, method of post-dilatation, use of imaging technology etc. It seems that in a haste to get an approval, perhaps these crucial design features and steps in understanding how to use the device were bypassed and randomized controlled trials (RCTs) started too soon. Finally, a faulty earlier trial design contributed; it looked at only intermediate follow-up whereas the beneficial effects were likely to be manifest only after 3-year follow-up. Thus it would have been ideal to have waited for at least 3–5 year before initiating the large RCT.

The case of RDN was also a case of faulty understanding of patho-physiology. Here the focus was on SNS which was thought to be causative factor in resistant hypertension, perhaps without realizing that hypertension is a multi-factorial disease with complex interaction between various organ systems and an interplay between numerous mechanisms of independent or interdependent pathways; renin angiotensin aldosterone system, salt intake, obesity, and neuro-hormonal system, SNS being just "a brick in the wall." Furthermore, in the haste to carry out an RCT, how to use the device was also incompletely understood. Even in the field of angioplasty, it is now a well known fact that 1st generation devices are not that successful, whether it is angioplasty balloon, bare metal stents or even gene therapy but in a haste to market an imperfect device, the hype created, ultimately spelled the doom for an entire technology.

For IABP it was a case of imperfect application in real world practice, probably the exact niche of IABP in failing ventricle environment was not properly understood. Improving coronary flow and reducing myocardial energy requirement rather than increasing contractility were the mechanism of action of this device. Thus, this device could be employed only in predominantly ischemic kind of dysfunction (and not hemodynamic) and that too in very early in the course of decompensation, or better even before the decomposition had set in; once cardiac power output (a product of cardiac output and mean blood pressure) becomes <0.6 there may be no benefit of this therapy. Beyond this point, devices which are more powerful in augmenting hemodynamics such as Impella device, Tandom Heart or extra-corporeal membrane oxygenator may be more useful.[15] Thus there is a very narrow therapeutic window for usefulness of IABP, which was not properly appreciated and device inappropriately used.

Likewise, trans-myocardial laser probably failed because the concept was too simplistic; how could just punching few holes in ventricle substitute for extensive coronary artery/arteriole/capillary network within the myocardium? For thrombus extraction devices probably their use caused more damage to an already fragile part of diseased coronary than benefit. Moreover, its application actually pushed the thrombus into distal bed more than extracting it. Use of bivalirudin suffered probably from lack of monitoring (possible with heparin), short duration of action and non-availability of antidote in case of excess.

4. The way forward

Failure of a trial should not be construed as an end-of-the-road for a therapy or a device. Rather it should be taken positively, as an understanding of a complex patho-physiology, understanding a mechanism of action of the therapy or its application in real world practice. The whole scientific process should lead to a better reporting on future trials. A failed trial should serve as a basis to further fine-tune the therapy and for better designing of future trials, learning from failed therapeutic trajectories, and searching for newer therapeutic modalities which will fix the existing lacuna.

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