WORLDWIDE CLINICAL TRIALS

SECTOR INSIGHT | SEPTEMBER 2017

FIVE EMERGING TRENDS WITHIN CARDIOVASCULAR RESEARCH

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Over the past 50 years, dramatic changes in the treatment of cardiovascular disease, accompanied by marked declines in morbidity and mortality have occurred. Nonetheless, cardiovascular disease remains the leading cause of death and disability in the world. With increasingly permissive science providing new insights into pathophysiology, innovative drug discovery methods now engage more specific targets of cardio pathophysiology and drug development occurs in a highly internationalized environment.

FIVE EMERGING TRENDS

Five emerging trends within the drug discovery/drug development paradigm are highlighted in this review—each reinforcing the need for therapeutically focused, methodologically rigorous, and highly efficient project teams for product evaluation and commercialization. These trends are:

1. Recognition of pleiotropic drug effects;
2. Emergence of personalized/precision medicine;
3. Impact of epigenetics and miRNA antisense oligonucleotide therapeutics;
4. Development of innovative trial methods for innovative Interventions; and
5. Academic, CRO, and pharmaceutical collaboration as a natural extension of emerging science.

1 - CARDIOVASCULAR RESEARCH IN AN AGE OF PLEIOTROPY

Drugs treating metabolic aberrations such as dyslipidemias and type 2 diabetes mellitus are on the current wave of treatments which demonstrated multiple effects frequently subsumed under the concept of "pleiotropy," a well-established phenomenon of a single gene affecting multiple traits[1]. The impact of type II diabetic therapy on the cardiovascular system specifically prompts scrutiny. Until recently, the target was dipeptidyl peptidase 4 (DPP-4) enzyme. DPP-4 inhibitors are currently approved to lower glucose levels in Type 2 Diabetes Mellitus through the incretin hormones, glucagon like peptide (GLP-1), and glucose dependent insulin trop peptide (GIP).

Yet the substrates for DPP-4 inhibitors are varied and extensive with the potential to mediate a wide range of effects, independent of those mediated through GLP-1 modulation. For example, DPP-4 inhibitors exert cardiac effects through stromal cell derived factor-1 (SDF-1) potentiation. It's not clear if SDF-1 augmentation is due to the effects of GLP-1 increase or a direct effect of DPP-4 inhibition leading to improved circulating stem cell signaling through SDF-1. Yet, more research is underway to understand these cardiac effects because large scale trials have indicated conflicting information which is critically relevant clinically.

By contrast, the sodium glucose cotransport 2 (SGLT2) inhibitors and the GLP agonists are less controversial in their improvement of the off-target effects of cardiovascular outcomes. In particular, empagliflozin (EMPA-REG OUTCOMES trial) and canagliflozin (CANVAS trial) have been successful in showing a reduction in cardiovascular death and heart failure hospitalization. And the GLP agonists, liraglutide (LEADER trial) and semaglutide (SUSTAIN-6 trial) have also been convincing in improvement in cardiovascular outcomes. Empagliflozin has cardioprotection labeling and liraglutide has just been aproved for similar labeling. Several DPP-4 inhibitors are now approved for the treatment of hyperglycemia but these agents can have variable selectivity for enzymes with DPP-4-like activity; i.e., "off-target" effect. This would support the notion that the cardiovascular effects, whether positive or negative, may not be a class specific phenomenon of DPP-4 inhibitors. Indeed, a large, population-based study with data from the FDA-funded mini Sentinel program failed to find an increase in heart failure hospitalizations relative to other diabetic agents contradicting the SAVOR and EXAMINE trials. Further research into understanding the cardiovascular effects of these diabetic drugs may well demonstrate a class effect in the pleitropic effects of SGLT2 inhibitors and GLP1 agonists. These off-target effects will soon be considered just "effects".

2 - PERSONALIZED/PRECISION MEDICINE

Accelerating interest in personalized and precision medicine is changing the way the pharmaceutical industry, as well as physicians approach therapeutic novelty in cardiovascular disease.

While personalized medicine has had success in oncology, it faces different challenges in cardiovascular disease where complex genetics, the environment, and patient lifestyle combine to create a unique clinical presentation for each patient. Much more than simply genotype, it is the interplay of environmental factors with patient risk factors that dictate therapeutic decisions, and hence factors which either confound or mediate beneficial therapeutic effects. As an example, the prevalence of traditional therapies like angiotensin-converting enzyme (ACE) inhibitors, beta blockers, and various interventions to reduce modifiable risk factors (e.g. exercise, smoking) means that many patients are receiving these and other therapies as a management stratagem which must be accounted for in trial design, methods of execution and analysis. The complex interplay of genes and environmental influences means that new therapies may work extremely well, but only in a subset of patients adding emphasis to a frequently voiced axiom that while **"researchers live at the mean, physicians live within the standard deviations."** The challenge becomes defining the boundaries of that subset.

As an example, **regenerative therapies** touted to repair and replace damage tissue in conditions as diverse as myocardial infarction, vasculogenesis, ventricular function, and ischemic heart disease are still in their early stages, with allogeneic and autologous therapies under development. In this case, medicine "personalized" by the use of a patient's own stem cells also can be a disadvantage commercially because it requires that the patient's cells be harvested and then converted into a therapeutic agent, often by culturing and expanding donor cells into mesenchymal stem cells that can improve damaged heart tissue. In contrast, the use of allogeneic cells (e.g., derived from genetically non-identical donors) shortens the time to administration of a therapy for a specific patient and can be used in an "off-the-shelf" manner, although with the potential for decreased compatibility with a patient's immune system.

Precision medicine such as one-dose **gene therapy** treatments are also making their mark. In this stratagem, a vector is designed to introduce genetic material into cells to compensate for abnormal genes or to make a beneficial protein. The application, which has recently been introduced for heart failure patients has profound implication for trial design and commercialization. For example, one dose gene therapy based interventions in heart failure could result in a reevaluation and ranking of the importance of outcomes with impact on milestones, timelines and expenditures for trials. Additionally, payer perspectives gain ascendancy because gene therapy treatments have a disproportionate impact on formulary placement and reimbursement decisions given the transformative benefit of the therapy, the number of patients possibly affected, and the "interaction" effects which will exist between this novel therapy and existing pharmacotherapy. In addition, lifestyle modification must be considered.

An integrated, highly effective project team which can provide insights on medical diagnoses, measures, analysis, and outcomes, all of which potentially inform "value" as well as clinical utility, provide a differentiated solution in this setting.

3 - EPIGENETICS AND miRNA ANTISENSE OLIGONUCLEOTIDE THERAPEUTICS

The large amount of basic science research regarding epigenetic effects on RNA biology has greatly expand knowledge of their role in the progression and prevention of disease across therapeutic areas. Scientific discoveries regarding epigenetic changes in DNA methylation, histone modification, and how RNA biology affects the cardiovascular system are opening up the potential for new therapeutic avenues.

For example, the methylation status for certain genes has been linked to increased risk of cardiovascular disease in discrete populations, such as F2RL3 in smokers, PLA2G7 in females, and locus 9p21 within the Chinese population.[2] Promising antisense oligonucleotide technologies suggest that oligonucleotides themselves may soon emerge in the therapeutic armamentarium as has been illustrated by mipomersen, an antisense oligonucleotide approved for treatment of hyperlipidemia.

However promising these therapeutic strategies appear, there are still encumbrances that must be addressed before any clinical potential can be realized. For example, in antisense therapeutic strategies, one challenge frequently addressed is how to specifically target antisense oligonucleotide products to the organs of interest. Delivery mechanisms under evaluation include cell-penetrating peptides, nanoparticles, viral vectors, liposomes, polymers, dendrimers, micelle, and ultrasound-targeted microbubble destruction.[3] Research and development implications thus are formidable. In addition to creating the antisense technology, a sponsor must also co-develop or otherwise account for differences in methods of delivery.

Overall, these innovative disciplines have the potential to bring about the next generation of cardiovascular therapeutics, and the design and execution of the trials that will evaluate them must also be equally innovative.

4 - INNOVATIVE TRIAL METHODS FOR INNOVATIVE INTERVENTIONS

Regional heterogeneity in treatment outcomes emphasizes the necessity of reevaluating traditional trial designs and methods of execution. Even if trials may not differ in treatment intervention, eligibility criteria, or imaging assessments, it is commonly observed that patient response in different geographical regions can exhibit marked variation. These differences exist as a reflection of differences in standards of care, and either genotypic or phenotypic variation in patient presentation significantly impacting inferences which are possible based upon overall statistical analyses. Indeed, overall trial results may not generalize fully across the entire population of patients who might ultimately be eligible for treatment.

Regional heterogeneity in treatment outcome therefore accentuates the need to plan for examination of **subgroups** in a fashion permitting valid analyses and clinical interpretation. For example, both quantitatively and qualitatively different treatment effects across subgroups are fraught with challenges in interpretation given that the outcome of one subgroup may not be anticipated to be materially better or worse than the others in a new trial a priori. Nevertheless, these differences can be discerned particularly in the larger clinical trial databases produced in later phase clinical investigations. Because assessments of the benefit may vary by subgroups (eg. risk ratio for novel CV therapeutics) large international trials are a better way to assess potential new treatments across many countries versus the alternative of separate smaller trials in each region. Managing scale, process, staffing and dataflow in the context of multiple countries and multiple vendors demands the highest operational acumen.

The combination of **transformative therapeutics** in cardiovascular disease and the international expansion of the clinical trial environment also mandate examination of different strategies in clinical trial design that extend across a program of research. For example, designing a program of research in which learning phase paradigms are maximally utilized prior to launching confirmatory studies become mandatory, and thus the entire panoply of **adaptive study design methodology** becomes a part of the clinical trial portfolio. Concepts as diverse as sample size re-estimation procedures, adaptive randomization based on observed response, adaptive randomization based an acknowledged covariate, enrichment designs, adaptive treatment switching designs, and an adaptive seamless phase 2/3 program provide the basis for a “21st” century toolbox.[4]

And because study results based upon adaptive trial methodology may not intuitively translate into changes in clinical care, it becomes equally important to evaluate therapeutic potential on the other end of the explanatory/pragmatic continuum. Pragmatic clinical trials use inclusive rather than restrictive patient eligibility requirements, approach sites delivering clinical care for research participation rather than centers specializing in clinical research, modify data ascertainment techniques to be compatible with busy practice environments and focus on outcomes impacting healthcare utilization with the objective of informing clinical and policy decisions to influence real world practice.

5 - ACADEMIC, CRO, AND PHARMACEUTICAL AGREEMENTS: A NATURAL EXTENSION OF THE SCIENCE

Basic research (predominately academic), drug discovery (predominately industry) and drug development (CRO dominated) are too often viewed as being at opposite ends of the research and development continuum. However, within an increasingly complex scientific and medical environment these research cultures are complementary and heavily enmeshed. Serving as a mediator of process, the contract research organization (CRO) must exemplify an ability to facilitate, manage, and support the interests of diverse stakeholders and in the process transform the way clinical trial research can be conducted.

For example, large cardiovascular trials provide an exemplary case study of the need for collaboration between research interests, although the relationship is applicable even within the earliest phases of translational research. These long, large, and complex programs require the financial support and drug discovery expertise of industry sponsors, the management acumen and efficiency of clinical trial operations within a CRO, and the oversight and expertise of academic specialists who inform patient diagnostics, assessments, and methods of analyses.

Finally, there is an additional benefit. Academic industry/CRO collaborations also create a niche environment for the next generation of trialists who have a pedigree in either basic or clinical research. Strong collaboration between these unique groups, each with their own goals and expectations requires clinicians and scientists who can navigate across environments, using a common substrate of clinical trial methodology as a basis for reciprocal support. Through a combination of didactic and experiential learning academic, CRO, and pharmaceutical collaborative efforts provide an "incubator" for the next generation of investigators.

CONCLUSION

Highly innovative science, increasingly nuanced patient phenotypes, and a compelling unmet clinical need now converge to drive explosive growth in innovative technology and clinical research in diverse cardiovascular indications. Although this selection of only a few potentialities reflect the arbitrary sentiments of authorship, the "five emerging trends" highlighted serve to illustrate the exciting era of therapeutic possibilities developing within cardiovascular research.

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