CURBSIDE CONSULT

The Biggest Clinical Trial Innovation Needs in…

Physicians consider priorities for future clinical trials in their respective interventional cardiology areas of focus, with responses spanning from a need for data informing treatment benefit and decision-making for current and future therapies to broader changes needed in the approach to research.

With Mirvat Alasnag, MD, FACC, FACP, FSCAI, FRCP; Salvatore Brugaletta, MD, PhD; Jay Giri, MD, MPH, FACC, FAHA, FSCAI; Rasha Al-Lamee, MA, MBBS, FRCP, PhD; Rishi Puri, MD, PhD, FRACP; and Gagan D. Singh, MD

WOMEN'S HEALTH

Mirvat Alasnag, MD, FACC, FACP, FSCAI, FRCP

We currently have a paucity of data defining outcomes of women with multivessel coronary artery disease undergoing physiology- or image-guided complete revascularization. There are varying results in trials evaluating physiology-guided revascularization, whether percutaneous or surgical. Trials such as FLOWER-MI and FAME 3 primarily enrolled men (> 80%), making it difficult to draw conclusions in women specifically. Furthermore, at the heels of recently presented meta-analyses reviewing hyperemic and resting functional testing,[1,2] it is particularly difficult to extract meaningful recommendations in women. With respect to intravascular imaging, landmark studies such as the COMPLETE-OCT substudy remain small; only a total of 93 patients were enrolled, of whom 83% were men, making it impossible to draw conclusions for women undergoing percutaneous coronary intervention (PCI).[3] However, although the study did identify features of vulnerable plaque in nonculprit vessels with obstructive disease, we cannot presume that plaque features in women are similar. I anticipate plaque volume, burden, and consistency need further investigation in the future, presenting an opportunity for the interventional community to address response to plaque-modifying medical therapies, such as lipid-lowering agents and antiplatelet regimens.

1. Berry C, McClure JD, Oldroyd KG. Coronary revascularization guided by instantaneous wave-free ratio compared to fractional flow reserve: pooled 5-year mortality in the DEFINE-FLAIR and iFR-SWEDEHEART trials. Eur Heart J. Published online August 27, 2023. doi: 10.1093/eurheartj/ehad552
2. Eftekhari A, Holck EN, Westra J, et al. Five-year major cardiovascular events are increased when coronary revascularization is guided by instantaneous wave-free ratio compared to fractional flow reserve: a pooled analysis of iFR-SWEDEHEART and DEFINE-FLAIR trials. Eur Heart J. Published online August 27, 2023. doi: 10.1093/eurheartj/ehad582
3. Pinilla-Echeverri N, Mehta SR, Wang J, et al. Nonculprit lesion plaque morphology in patients with ST-segment-elevation myocardial infarction: results from the COMPLETE trial optical coherence tomography substudys. Circ Cardiovasc Interv. 2020;13:e008768. doi: 10.1161/CIRCINTERVENTIONS.119.008768

ACUTE CORONARY SYNDROME

Salvatore Brugaletta, MD, PhD

Over the last 2 decades, we have made substantial improvement in terms of drugs and devices to treat acute coronary syndromes, especially ST-segment elevation myocardial infarction (STEMI). However, there are still two main unmet needs to be answered. The first need is regarding microvascular obstruction after primary PCI. Data show that microvascular obstruction after a STEMI matters if we want to improve further long-term prognosis and quality of life for our patients, but we are still looking for the best way to treat it and need a trial that demonstrates the benefit of such a treatment. The second need is related to cardiogenic shock. Trials have failed so far to demonstrate superiority of hemodynamic supportive devices, but this does not mean that we don't need to cut down the high mortality of these patients either with new devices on the block or new trials.

TRICUSPID

In structural interventions, there have been many innovations during the last 10 years, with several different new devices launched into the market without clear clinical evidence. I particularly think about the tricuspid valve—or the "forgotten" valve. Although data are coming from registries and regarding the various devices available for this valve, we're still missing a well-done trial that shows a real clinical benefit of early stage percutaneous tricuspid intervention versus sham control arm in terms of hard clinical endpoint, such as cardiovascular death or worsening heart failure.

RENAL DENERVATION

Jay Giri, MD, MPH, FACC, FAHA, FSCAI

Over the past decade, since an initial failed clinical trial with older technology, a series of randomized trials designed with rigorous, sham-controlled methods have demonstrated the efficacy of renal denervation (RDN) for reducing blood pressure in a wide array of patient populations with uncontrolled hypertension. Simultaneously, in both these clinical trials and in real-world commercial use outside the United States, RDN has demonstrated an excellent safety profile.

Experience thus far has demonstrated substantial treatment-related heterogeneity in individual patients undergoing the procedure, with some patients experiencing "hyper-response," others demonstrating "nonresponse," and a larger portion somewhere in between. Identifying the phenotypic, biomarker, or genotypic factors influencing this heterogeneity should be a priority of future research. Additionally, work to date has been successful in demonstrating the efficacy of RDN for reducing blood pressure. Future work will ideally take the next step in tying these reductions in blood pressure (a surrogate endpoint) to cardiac and renal outcomes, similar to what has been done in past research for antihypertensive pharmacotherapies.

PERCUTANEOUS CORONARY INTERVENTION

Rasha Al-Lamee, MA, MBBS, FRCP, PhD

A great deal of scope remains for improving clinical trials in PCI. We are often too focused on clinical trials of novel therapies or treatment strategies. Perhaps it is time to redirect some of our energy to considering how we encourage implementation of the knowledge we already have. Notably, the delivery of clinical trials is expensive and cumbersome. We need to find ways to make research design and delivery more nimble and cost-effective. We owe it to our patients to effectively use clinical trials to answer the clinical questions that matter to them.

Finally, many global disparities in coronary care remain. We need to consider strategies to address this inequity in care. It is time to ensure that we conduct clinical research that has the widest possible clinical application across the globe so that we can improve health care for the many, not just the privileged few.

TRANSCATHETER AORTIC VALVE REPLACEMENT

Rishi Puri, MD, PhD, FRACP

Transcatheter aortic valve replacement (TAVR) has matured tremendously during the past decade such that it is now the dominant means of treating severe aortic stenosis. We have witnessed several iterations of transcatheter heart valve (THV) designs across both the balloon- and self-expanding spectrum. Intermediate (4-5 year) durability outcomes in low-risk patients aged on average in their mid-70s will soon become available, enabling us to more reliably project 7- to 10-year durability relative to surgical aortic bioprostheses. As several more THV platforms will emerge for commercial use in the United States in the coming years (all with a stock standard trial design based around a small early feasibility study and a larger pivotal trial—a process taking 5-6 years and approximately $100 million), the smoldering volcano that will erupt in 5 to 7 years will be how to deal with failed THVs. Patients are living longer and outliving their current THV platforms. Most, if not all, current THV platforms were not specifically designed with a view to undertake a second TAVR procedure. Operators are constantly straddling implant depth (vs conduction system damage) and commissural/coronary alignment (for coronary reaccess) to achieve optimal hemodynamics and durability.

The future of TAVR will not only lie in adaptive THV designs for meeting these aforementioned technical challenges across a broad age and range of anatomic characteristics but also in our ability to modify/resect bioprosthetic leaflets (akin to the surgeons removing leaflets during surgical aortic valve replacement) to enable subsequent TAV-in-TAV procedures with minimal risk to the patient, applied broadly across the TAVR community. Transcatheter aortic annular/left ventricular outflow tract modification of bulky calcium is also an unmet need for optimizing valve sealing and frame expansion while minimizing the risk of annular trauma.

Although we will continue to see a range of trials designed specifically for assessing longer-term performance of newer valve platforms aiming to penetrate the market, adjunctive leaflet and annular modification technologies will ultimately play an important role in our ability to comfortably treat younger patients with aortic valve disease via a transcatheter approach who are likely to need more than one TAVR procedure in their lifetime.

MITRAL

Gagan D. Singh, MD

The established therapy for mitral and tricuspid pathology is transcatheter edge-to-edge repair (TEER). In select operators and published series, TEER has been used to treat a wide array of pathologies, with acceptable durability out to 1 and 2 years—albeit in higher-risk populations. Billions of dollars, years of development and testing, and countless hours have been spent on non-TEER technologies to treat mitral regurgitation (MR) and tricuspid regurgitation. However, no other therapy has been approved or become standard of care for commercial use. Industry and research and development teams need to develop systems that can first match the safety of TEER therapy. The next priority of any system in development is to ensure complete eradication of MR (to 1+ or less) and have sustained durability out to a minimum of 5 years. For regulatory approval and adoption, clinical trial design should focus on matching safety against TEER, reproducible and streamlined procedural times/demand, and sustained durability.

Mirvat Alasnag, MD, FACC, FACP, FSCAI, FRCP
King Fahad Armed Forces Hospital
Jeddah, Saudi Arabia
mirvat@jeddacath.com

Salvatore Brugaletta, MD, PhD
Cardiovascular Institute; Hospital Clínic
Barcelona, Spain
sabrugaletta@gmail.com

Jay Giri, MD, MPH, FACC, FAHA, FSCAI
Hospital of the University of Pennsylvania
Philadelphia, Pennsylvania
jay.giri@pennmedicine.upenn.edu

Rasha Al-Lamee, MA, MBBS, FRCP, PhD
Imperial College London
London, United Kingdom
r.al-lamee13@imperial.ac.uk

Rishi Puri, MD, PhD, FRACP
Cleveland Clinic
Cleveland, Ohio
purir@ccf.org

Gagan D. Singh, MD
UC Davis Medical Center
Sacramento, California
drsingh@ucdavis.edu

Disclosures

Dr. Alasnag: None.

Dr. Brugaletta: Advisory board for Boston Scientific and Zoll; receives speaker fees from Abbott Vascular and GE.

Dr. Giri: Consultant to and receives research funds to the institution from Recor Medical; receives research funds to the institution from Medtronic.

Dr. Al-Lamee: Receives speaker honoraria from Philips, Abbott, and Medtronic.

Dr. Puri: Consultant to Medtronic and Abbott TAVI.

Dr. Singh: Consultant to Abbott Structural Heart, Philips, Boston Scientific, and Gore Medical.