Pharma VOICE

THERAPEUTIC DIGEST

CARDIOLOGY

ADVANCES AND CHALLENGES

IN COLLABORATION WITH thinkgen

MAY 2021

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CARDIOLOGY

Advances and Challenges

Biomedical innovation in cardiovascular care is important given the significant burden of cardiovascular diseases (CVDs) in America. Over 18 million people have CVD; CVDs cause roughly a quarter of deaths nationally[1,2] and unmet need remains in CVD care (especially risk reduction[3]). Furthermore, there are significant sociodemographic inequities, with older adults, those with lower education, racial or ethnic minority groups, and rural residents disproportionately affected. For example, individuals living in rural settings have higher age-adjusted CVD death rates relative to urban counterparts[4,5].

The pipeline of new cardiovascular drugs in the United States is relatively limited compared with many other specialties, partially due to the complexity and cost of evidence generation[6]. There has been substantial growth in the pipeline for cardiovascular medical devices, however, with products for minimally invasive surgery, heart health tracking, interventional products for restoring heart rhythm and reviewing blockages, and wearables.

ADVANCES IN CARDIOLOGY

▶ Nexletol (bempedoic acid)

In February 2021, the FDA has approved[7] Esperion's Nexletol (bempedoic acid), oral, once-daily non-statin LDL cholesterol (LDL-C)-lowering medicine for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or established atherosclerotic cardiovascular disease (ASCVD) who require additional lowering of LDL-C. The drug is the first oral, non-statin, LDL-lowering medication approved since 2002.

Shortly after its approval, the FDA also cleared a fixed-dose combination containing bempedoic acid and ezetimibe (Nexlizet). The novel agent is an inhibitor of ATP citrate lyase, a key enzyme involved in the cholesterol biosynthesis pathway. "This approval delivers upon a commitment we've made to millions of patients for a new treatment alternative if they struggle with bad cholesterol and have ASCVD or HeFH," says Tom Mayleben, president and chief executive officer of Esperion in a press release statement[8]. "Even with maximally tolerated statins, which may mean no statin at all, some of these patients can't achieve their LDL-C goals. [This] approval provides them with a new medicine to go along with a healthy diet."

SGLT2 Inhibitors

In patients with heart failure with reduced ejection fraction, the placebo-controlled EMPEROR-Reduced trial of Boeringer Ingelheim's empagliflozin[9] largely confirmed the benefits seen with dapagliflozin in DAPA-HF, also known as chronic heart failure.

EMPEROR found a statistically significant 25% reduction in the combined endpoint of cardiovascular (CV) death and hospitalization for heart failure. A meta-analysis[10] of the two trials confirmed a benefit for the drugs in all-cause death, CV death. Heart failure, hospital admissions, and a composite renal outcome. And both sodium-glucose transport protein (SGLT) 2 inhibitors produced similar benefits in patients with and without diabetes.

The novel inhibitor of both SGLT1 and 2, Sanofi's sotagliflozin, was also shown to prevent CV outcomes in two trials: SOLOIST[11] enrolled patients with diabetes and worsening heart failure, and SCORED[12] comprised patients with diabetes and chronic kidney disease (CKD).

There was more good news for CKD when the DAPA-CKD[13] trial showed that dapagliflozin reduced a composite renal outcome by 39% compared with placebo. These findings were similar to those seen in the CREDENCE[14] and CANVAS[15] studies.

Aortic Valve Disease

Until January 2021, standard practice for patients with severe aortic stenosis (AS) was to wait for symptoms to develop before intervening. This year, however, a South Korean group published a randomized controlled trial[16] comparing early aortic valve surgery vs conservative therapy in asymptomatic patients with severe AS and found a massive 91% reduction in death with early surgery.

That trial only added to the enthusiasm of treating patients with AS. At the European Association for Cardio-Thoracic Surgery (EACTS) annual meeting in October 2020, Dr. Joseph Bavaria, director of the Thoracic Aortic Surgery Program at PennMedicine, reported that the number of transcatheter aortic valve replacement (TAVR) procedures performed in the United States has not surpassed the number of surgical aortic valve replacement (SAVR) procedures in all its forms[17].

Yet 2020 brought sobering data on TAVR relative to SAVR. The PARTNER 2 study authors reported 5-year data in "intermediate risk" patients with AS[18]. The results are complicated, but the early advantage of TAVR clearly decreased over longer follow-up.

This catch-up effect was also seen in the 2-year results of PARTNER 3, a trial that compared TAVR vs SAVR in "lower risk" patients. Unlike all other TAVR trials, PARTNER 3 included rehospitalization in its primary endpoint. This led to markedly positive results for TAVR at 1 year; but in the 2-year results[19], the rates of stroke and death did not differ significantly in the two groups. Valve thrombosis was significantly higher in the TAVR arm (2.6% vs 0.7% for SAVR; P = .02).

History has shown that many cardiac procedures begin in a surgeon's hands (revascularization, ablation, pacing, etc.) but transition to the cardiologist with the aid of technology. The thing about TAVR is that despite substantial iterations in the procedure, real-world data only add to the concern raised from trial results. Bavaria noted at EACTS that over the past 5 years, the 30-day rates of stroke and need for pacemaker have not budged. "We have to do better," he said.

Left Main Coronary Artery Disease

In January, NOBLE investigators published 5-year results[20] of their trial comparing percutaneous coronary intervention (PCI) with drug-eluting stents versus coronary artery bypass grafting (CABG) for patients with left main coronary artery disease. PCI was inferior to CABG for the primary endpoint of death, nonprocedural myocardial infarction (MI), and repeat revascularization.

The clarity of NOBLE stands in contrast to the opacity of EXCEL[21], the larger trial comparing PCI to CABG in patients with left main disease. The 5-year results of EXCEL may have been published in late 2019, but the discussion surrounding this trial and how to manage patients with left main disease continued in earnest this year.

The clinical issue of treating patients with left main disease is easier. In June, Dr. James Brophy PhD of McGill University published a Bayesian reanalysis of the EXCEL trial. Bayesian analyses are useful because they offer the probability of a hypothesis (benefit or harm) given the data.

Using EXCEL data alone, Brophy calculated a 95% probability that the 5-year primary outcome difference was increased with PCI vs CABG and a 99% probability that there was excess mortality with PCI. When he incorporated previous trials of PCI vs CABG, the estimated probability of excess mortality with PCI decreased to 85%[22].

Isolated left main disease is uncommon, but when it occurs, patients ought to be counseled that outcomes with PCI are inferior over the long run.

Early Rhythm Control in AF

The EAST-AFNET 4 trial[23] was a pragmatic but unblinded trial comparing early rhythm control with either drugs or ablation vs usual care in patients with atrial fibrillation (AF). Early rhythm control led to a statistically significant 21% reduction in the composite primary outcome of CV death, stroke, heart failure admission, or acute coronary syndrome.

The STOP AF[24] and EARLY-AF[25] trials both compared ablation with a cryoballoon vs antiarrhythmic drugs in patients who had not previously received rhythm control. Ablation beat drugs in the surrogate endpoint of arrhythmia episodes in both trials.

Statin Nocebo Effects

Researchers at Imperial College London have once again shown that advances in knowledge do not always require mega-trials. In 2017, their 200-patient ORBITA trial showed that PCI resolved ischemic myocardium but was no better at improving exercise time than a placebo or sham procedure. The obvious conclusion: the improvement in quality of life that patients feel after a PCI may stem in large part to the positive expectations of being cared for or being "fixed."

The opposite of the placebo effect is the nocebo effect—when negative expectations lead to negative effects. If people think a statin will make them feel poorly, they may be more apt to feel poorly.

The SAMSON trial enrolled 60 patients who had previously stopped statins. Using an of N-of-1 design, the researchers elegantly showed that, yes, patients do have significant side effects from statins, but it is not due to the statin chemical but from the act of taking a statin pill.

The importance of this work is twofold: If we use the results of SAMSON to teach patients, many will restart a beneficial drug—as did 30 of the 60 patients in the trial. The second benefit is that it confirms the importance of our words and actions at the bedside. Our ability to help or harm transcends biochemistry and physiology.

INNOVATION CHALLENGES FOR CARDIOVASCULAR DRUGS

Patient participation in cardiovascular trials is low[26]. One study found trial participation by eligible acute myocardial infarction patients in a national registry declined from 5.2% in 2008 to 3.4% in 2011[27], and another of the same population has even lower estimates, most recently 0.8% participation through 2014[28]. Enrollment is especially limited for high-risk groups such as elderly and rural patients[29, 30] because these groups face multiple logistical barriers to participating in trials.

Low patient participation can also lead to unmet enrollment targets, which can contribute to the failure of a trial, either from a lack of participants or the inability to demonstrate efficacy due to a small sample size[31]. For example, in the AleCardio trial (a large, international, phase III cardiovascular clinical trial), only 18.2% of sites met enrollment targets, and 10% closed before the end of recruitment, mostly because they failed to enroll a single patient[32]. The trial was ultimately terminated when a futility analysis showed it was subsequently unlikely to prove clinical efficacy[33].

One explanation for low rates of patient participation may be limited clinician engagement. Another is lack of hospital and health system participation in clinical trials (only about 5% of acute care hospitals consistently participate in clinical trials[34]), with many hospitals not properly trained in conducting clinical research[35].

Low patient participation may also reflect limited patient engagement in development of the trials themselves. For example, patients and families are often not involved in developing the trial operational plan to help ensure trial procedures are convenient for patients. Patients are often interested in how therapies may affect quality of life[36], but this information is often not represented in trial end points.

CONCLUSION

CVD continues to be the leading cause of death and disability and remains highly costly, complicated, and burdensome. Despite this, drug innovation is lagging and US enrollment in drug and device trials is limited. New strategies are needed to streamline and reduce the costs of clinical trials, all the while placing greater emphasis on the patient voice and experience. New technologies offer a promising path forward and can help improve upon current patient participation, generate high-quality evidence in real-world settings, and ensure evidence meets the needs of all stakeholders.

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