Highlights From the American College of Cardiology's Scientific Sessions—New Heart Failure Management Guidelines, Alirocumab After a Myocardial Infarction, and Treating Mild Chronic Hypertension in Pregnancy

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Shortly after the American College of Cardiology's Annual Scientific Sessions wrapped in early April, JAMA sat down with the conference's cochair to talk about research presented during the meeting. Pamela Morris, MD, a preventive cardiologist and a professor of medicine in cardiology at the Medical University of South Carolina, discussed new heart failure management guidelines—the first comprehensive update since 2013—and results from several important clinical trials. The following is an edited version of that conversation.

JAMA: What changes were introduced in the new heart failure management guidelines?

DR MORRIS: The emphasis on prevention of heart failure was a key feature of this new guideline, with revised definitions of stage A and stage B heart failure intended to identify risk factors early and provide treatment before any evidence of structural changes or signs of decreased heart function.

The guidelines now have a category called heart failure with improved ejection fraction. It includes those individuals who previously had reduced ejection fraction less than 40%, but with therapy their left ventricular ejection fraction is now above 40%.

Also, the guidelines redefine the treatment strategies for patients with heart failure with reduced ejection fraction. There are 4 classes of medications that now have demonstrated benefit in addition to the diuretics, which are used really for decongestion. The guidelines recommend focusing first on the angiotensin receptor–neprilysin inhibitors, or ARNIs. Then, if not feasible, use an ACE [angiotensin-converting enzyme] inhibitor, or the angiotensin receptor blockers for those who can’t take ACE inhibitors. The second class recommended are the mineralocorticoid receptor antagonists.

Next are the β-blockers. Then finally, the new kid on the block, the SGLT2 [sodium-glucose cotransporter 2] inhibitors, which are now recommended for individuals with symptomatic chronic heart failure with reduced ejection fraction, regardless of whether they have type 2 diabetes.

I think all of these changes together are really major steps forward in reducing the morbidity or mortality in the vulnerable heart failure population.

JAMA: Let’s turn to the PACMAN-AMI (Effects of the PCSK9 Antibody Alirocumab on Coronary Atherosclerosis in Patients With Acute Myocardial Infarction) randomized clinical trial, published in JAMA.

DR MORRIS: This is an incredibly important study looking at the optimal management strategy of dyslipidemia or of LDL [low-density lipoprotein] cholesterol in very high-risk patients who just had an acute myocardial infarction and were undergoing a stent placement. About 300 patients received high-intensity statin therapy with rosuvastatin. Within 24 hours after urgent stent placement of the culprit lesion they were randomized to biweekly doses of alirocumab or placebo.

The primary efficacy end point was the change in the amount of plaque volume at 52 weeks. There was a 2-fold regression of coronary atherosclerosis and a stabilization of those high-risk plaques when compared with treatment with statins alone.

My takeaway from this study is, number 1, begin early therapy for these very...
high-risk patients. And also implement aggressive lowering of LDL cholesterol in patients who’ve had an acute coronary syndrome and are at very high risk for a recurrent cardiovascular event. I think that this trial may end up having important clinical implications in terms of how we follow and treat patients with dyslipidemia for cardiovascular risk reduction.

**JAMA:** Have the costs improved at all for proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors?

**DR MORRIS:** That’s a great question. The 2018 multisociety cholesterol guideline included a value statement because at that time the 2 PCSK9 monoclonal antibodies, alirocumab and evolocumab, had just been approved by the US Food and Drug Administration (FDA), and the retail pricing at that time was quite costly. Within weeks to months after the release of the guideline, the costs were significantly reduced. Over the subsequent years, these drugs have become increasingly more affordable, though still certainly more expensive than generic oral statin therapy. The cost has come down considerably, making them a more attractive option.

**JAMA:** Let’s talk about 1 more trial published in JAMA, a study of a short interfering RNA (siRNA) targeting lipoprotein(a) (Lp(a)) production in people with elevated plasma Lp(a) levels.

**DR MORRIS:** This was the APOLLO trial. As a prevention enthusiast, this trial was of incredible importance. Elevated Lp(a) levels are an important recognized causal risk factor in atherosclerotic cardiovascular disease—particularly premature cardiovascular disease—and aortic stenosis. It’s a heritable risk factor, and you may see multiple members of a family who have had a very premature atherosclerotic cardiovascular disease event.

This risk factor oftentimes goes unrecognized and undiagnosed. It is not routinely measured, despite the fact that a number of societies do recommend at least a single measurement of Lp(a) in one’s lifetime. It is relatively stable over a lifetime, so repeated measurements are generally not necessary unless you have some other risk factors. In high-risk individuals, this is a risk factor that should be measured.

Previously, we have not had any pharmacological therapies that significantly, or clinically significantly, lowered Lp(a). There’s a modest reduction with niacin, and the 2 PCSK9 monoclonal antibodies do reduce Lp(a). But it’s uncertain if the degree of lowering would end up being clinically significant in cardiovascular outcomes trials.

That is why this APOLLO study was so important. This siRNA, SLN360, was tested in patients with very high levels of Lp(a). What they found is that patients receiving the highest 2 doses had a maximum of a 96% to 98% reduction in Lp(a) levels and a reduction of about 70% to 80% that persisted out to 5 months compared to baseline. Those patients who were on placebo had no lowering of Lp(a) levels. The highest doses also reduced LDL cholesterol, but only by about 20% to 25%. Importantly, there were no serious safety concerns. I think the APOLLO trial indicates that this therapy is worth pursuing in phase 2 and phase 3 trials as well.

**JAMA:** Who would this medication potentially be appropriate for?

**DR MORRIS:** The simple answer is patients with very high levels of Lp(a). But first we have to get the message out there that it’s important to measure Lp(a) levels so that we can identify these patients earlier and treat them earlier to prevent cardiovascular outcomes.

**JAMA:** Let’s move on to a trial of antihypertensive therapy for mild chronic hypertension that looked at pregnancy outcomes.

**DR MORRIS:** This was the CHAP [Chronic Hypertension and Pregnancy] trial, which was a landmark trial with a definitive outcome. Ithad practice-changing results.

Typically, when women are pregnant and develop hypertension, you allow what we would call permissive hypertension. Routinely, you would not implement antihypertensive therapy unless the blood pressure levels were over 160/110 mm Hg. The hypothesis was that this higher perfusion pressure would be better for fetal growth and development, but it had never been tested in a randomized controlled fashion in pregnant women.

This was an open-label randomized controlled trial enrolling about 2400 women who had known mild chronic hypertension. Their blood pressures were less than 160/110 mm Hg but they were elevated above 140/90 mm Hg. They were randomized to receive treatment with first-line medications or no treatment unless their blood pressure went above 160/105 mm Hg. Labetalol or nifedipine were the primary medications, but they could also use other medications such as methyldopa or hydralazine.

There were significantly lower rates of a composite outcome of preeclampsia
with severe features, preterm birth before 35 weeks, [placental] abruption, and neonatal or fetal death among those women who received treatment compared to those who did not. Importantly, there was no difference in the rate of babies who were small for gestational age between the 2 groups, indicating that antihypertensive therapy beginning at a blood pressure level of 140/90 mm Hg was safe for the fetus. The results support the need for clinical guidance to be more aggressive in treating not only severe chronic hypertension in pregnancy but also mild hypertension in pregnancy.

**JAMA:** Now let’s talk about a trial of mavacamten as an alternative to surgical septal myectomy or alcohol ablation in patients with severely symptomatic obstructive hypertrophic cardiomyopathy, the VALOR-HCM (Evaluation of Mavacamten in Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy Who Are Eligible for Septal Reduction Therapy) trial.

**DR MORRIS:** This trial was another important first. Mavacamten is an agent that reduces cardiac muscle contractility. This is important because there’s never before been a pharmacological agent that has demonstrated benefit in randomized controlled trials for patients with severe hypertrophic obstructive cardiomyopathy.

This study was performed in 112 adults with severely symptomatic obstructive hypertrophic cardiomyopathy despite other medical therapies. They were candidates for invasive septal reduction therapy, either by surgical myectomy or by alcohol septal ablation.

At 16 weeks, those patients who received mavacamten had a much lower rate of eligibility for surgical reduction therapy. Only 18% remained eligible for intervention, compared with 77% of those who were still eligible for either myectomy or alcohol septal ablation. No patients experienced serious adverse cardiac events.

This really is the first pharmacotherapy that offers a viable medical option for people with obstructive hypertrophic cardiomyopathy, short of needing an invasive procedure. Mavacamten is currently under review with the US Food and Drug Administration for use in patients with obstructive hypertrophic cardiomyopathy, and we expect to see a decision by the end of April.

**JAMA:** Next we’re going to talk about 2 trials that were surprising: EDIT-CMD (Efficacy of Diltiazem to Improve Coronary Microvascular Dysfunction) and TRANSLATE-TIMI 70 (Targeting ANGPTL3 With an Antisense Oligonucleotide in Adults With Dyslipidemia).

**DR MORRIS:** EDIT-CMD was a very interesting study of the role of diltiazem, one of the calcium channel blockers, in patients who have ANOCA, or angina with no obstructive coronary disease. Rather, what they may have is either epicardial coronary vasospasm or microvascular disease. We have historically used a variety of agents. Diltiazem was used with the hypothesis that it would help in reducing microvascular dysfunction or coronary vasospasm and would improve angina in nonobstructive coronary disease.

In this study, patients with ANOCA were randomized to treatment with placebo or diltiazem, with an incredibly surprising result. There was no benefit in reduction in symptoms of angina in patients who received the drug. There did appear to be a slight reduction in coronary vasospasm but no reduction in angina and no improvement in quality of life.

**TRANSLATE-TIMI** looked at a medication that I’ve been very enthusiastic and excited to learn about. Vupanorsen is an ANGPTL3 [angiopoietin-like protein 3] inhibitor of lipoprotein lipase and endothelial lipase, which are very important in lipoprotein metabolism. Vupanorsen has been shown to reduce levels of LDL cholesterol and triglycerides. In this trial, it was evaluated for its ability to reduce non-HDL [non-high-density lipoprotein] cholesterol, which is an excellent measure of all atherogenic lipoproteins, including LDL cholesterol and VLDL [very low-density lipoprotein] cholesterol.

With use of vupanorsen, there was a reduction in non-HDL cholesterol, although perhaps not as dramatic as was anticipated. Unfortunately, there was a significant increase in adverse treatment effects, particularly injection site reactions, leading to a number of patients discontinuing or having difficulty with therapy. As a result of that, this medication is no longer moving forward as a potential therapy for reducing non-HDL cholesterol.

This trial, much like the EDIT-CMD trial, is an example that we must do randomized controlled trials. A hypothesis is not enough and surrogate end points are not enough. We actually need to do the trials, so we have a good understanding of not only the efficacy of potential therapies but also the safety of these therapies.

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**Conflict of Interest Disclosures:** Dr Morris reported that she is an advisory board participant for Amgen, Esperion, and Novartis and a local principal investigator on the CLEAR Outcomes trial, sponsored by Esperion Therapeutics Inc, evaluating the bempedoic acid tablet on cardiovascular risk reduction.

**Note:** Source references are available through embedded hyperlinks in the article text online.

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