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VICTORIA Trial Results: Vericiguat Demonstrates Benefit in Patients With Heart Failure and Reduced Ejection Fraction

LAURIE ANNE WALDEN, DVM

The investigational drug vericiguat may be a beneficial treatment option for high-risk patients with heart failure, according to study results presented at the American College of Cardiology's Annual Scientific Session Together With World Congress of Cardiology virtual conference on March 28, 2020.[1]

Patients with chronic heart failure are at risk of death or heart failure hospitalization after an episode of worsening heart failure even if they receive treatment based on current guidelines, said presenter Paul Armstrong, MD.[1]

The VICTORIA (Vericiguat Global Study in Subjects With Heart Failure With Reduced Ejection Fraction) trial investigated the efficacy and safety of vericiguat, a novel oral soluble guanylate cyclase (sGC) stimulator, in patients with chronic heart failure, reduced

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ODYSSEY HoFH: Alirocumab Reduces LDL in Adults With Homozygous Familial Hypercholesterolemia

NICOLA PARRY, DVM

Alirocumab, a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, lowered low-density lipoprotein (LDL) cholesterol (LDL-C) in adults with homozygous familial hypercholesterolemia (HoFH), according to new data from the Alirocumab Efficacy and Safety in Adults With Homozygous Familial Hypercholesterolemia (ODYSSEY HoFH) trial that were presented at the American College of Cardiology's Annual Scientific Session Together With World Congress of Cardiology virtual conference.[1]

"This is the largest randomized controlled interventional trial in patients with homozygous familial hypercholesterolemia," said Dirk J. Blom, MD, PhD, head of

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VICTORIA Trial Results (Continued from page 1)

ejection fraction, and a recent episode of decompensated heart failure. In the trial, compared with placebo, vericiguat reduced the incidence of the composite outcome of death from cardiovascular causes or first hospitalization because of heart failure. Full results were simultaneously published in the *New England Journal of Medicine* on the day of presentation.[2]

The VICTORIA trial represents "another win in the treatment of heart failure," said Clyde W. Yancy, MD, in the panel discussion following Armstrong's presentation. "Hospitalization for heart failure generates a major inflection point in the natural history of this condition, with a marked change in the risk for rehospitalization and death. Now we have a therapy that may be the first one to change that natural history after a person with heart failure has had a worsening event."

Background

Heart Failure

Heart failure is associated with substantial health care burden in the United States. The CDC reports that about 6.5 million adults in the United States currently have heart failure, with an estimated annual national cost of more than $30.7 billion in 2012.[3]

The VICTORIA trial enrolled patients with heart failure with reduced ejection fraction.[1] Patients in the trial also had a recent episode of decompensated heart failure and elevated levels of natriuretic peptides, which are indicators of heart muscle damage.[1]

"Patients with recent heart failure hospitalization for decompensation have been actively excluded from all the trials that have shown benefit," said Lynne Warner Stevenson, MD, in the panel discussion. "Recent trials that do focus on this population have consistently shown no benefit. VICTORIA finally addresses this population of decompensated patients."

Therapeutic Target

Nitric oxide (NO) and sGC are part of the NO-sGC pathway that produces cyclic guanosine monophosphate (cGMP); this pathway is important in normal cardiovascular function. In patients with heart failure, oxidative stress and endothelial dysfunction disrupt this pathway by reducing the bioavailability of NO, resulting in lower levels of sGC and cGMP. Vericiguat directly stimulates sGC, thereby increasing cGMP production. Vericiguat also restores sGC's sensitivity to NO.[1,2]

Yancy commented, "There are a number of cardiovascular disease states, especially heart failure, where nitric oxide bioavailability is reduced. We tried to target this before with exogenously administered nitrates, with phosphodiesterase inhibitors, but [they've] not been very effective." Vericiguat, unlike some of the other heart failure treatments, successfully targets the NO-sGC pathway.[1,2]

Methods

The VICTORIA trial was a multinational, double-blind, randomized, placebo-controlled phase 3 trial.[2] Its main objective was to assess the effect of vericiguat on the primary outcome, a composite of cardiovascular death or first hospitalization for heart failure. Secondary outcomes were individual components of the primary composite outcome, total heart failure hospitalizations (first plus recurrent), all-cause mortality, and the composite of all-cause mortality or first heart failure hospitalization. The investigators also assessed the safety and tolerability of vericiguat.[1]

Patients enrolled were adults with chronic heart failure (New York Heart Association class II, III, or IV), left ventricular ejection fraction less than 45%, and elevated natriuretic peptide levels. All enrolled patients had received guideline-based treatment for heart failure but had experienced an episode of worsening heart failure, defined as receipt of intravenous diuretic therapy or hospitalization due to heart failure. Patients were excluded if they were clinically unstable; were receiving a long-acting nitrate, phosphodiesterase

type 5 inhibitor, sGC stimulator, or intravenous inotrope; were awaiting a heart transplant; or had certain comorbidities.[1,2]

All patients received guideline-based heart failure therapy and were randomized to also receive either vericiguat or placebo. The initial dose of vericiguat was 2.5 mg once daily, and this dose was increased every 2 weeks to a target dose of 10 mg once daily. Patients were assessed every 16 weeks until the end of the trial, after which a 14-day safety follow-up was conducted.[1]

> "Vericiguat significantly reduced the incidence of the composite primary outcome of cardiovascular death or first heart failure hospitalization versus placebo, with a 10% relative difference between groups."

Results

Patients

The trial enrolled 5050 patients at 616 international sites between September 25, 2016, and December 21, 2018. The median follow-up time was 10.8 months. Of the 5050 patients, 2526 received vericiguat and 2524 received placebo. Baseline characteristics were not significantly different between the groups. The mean age was 67 years; almost one-fourth were women. Two-thirds of the patients had a heart failure hospitalization within 3 months of beginning the study. Almost one-third had an implantable cardiac device, biventricular pacemaker, or both. The mean ejection fraction in the study population was 29%, and the median N-terminal pro-brain natriuretic peptide level was elevated at 2816 pg/mL.[2]

Primary Outcome

The incidence of the primary composite outcome, death from cardiovascular causes or first hospitalization for heart failure, was significantly lower in the vericiguat group (897 of 2526 patients; 35.5%) than in the placebo group (972 of 2524 patients; 38.5%) (hazard ratio [HR], 0.90; 95% CI, 0.82-0.98; $P = .02$).[2]

Secondary Outcomes

In the vericiguat group, 414 patients (16.4%) died from cardiovascular causes, as did 441 patients (17.5%) in the placebo group (HR, 0.93; 95% CI, 0.81-1.06). A total of 691 patients (27.4%) in the vericiguat group and 747 patients (29.6%) in the placebo group were hospitalized due to heart failure (HR, 0.90; 95% CI, 0.81-1.00).[2]

Fewer total hospitalizations for heart failure occurred in the vericiguat group (1223 hospitalizations; 38.3 events per 100 patient-years) than in the placebo group (1336 hospitalizations; 42.4 events per 100 patient-years) (HR, 0.91; 95% CI, 0.84-0.99; $P = .02$). All-cause mortality was lower among patients who received vericiguat compared with those who received placebo (512 patients [20.3%] vs 534 patients [21.2%]; HR, 0.95; 95% CI, 0.84-1.07; $P = .38$). The composite secondary outcome of all-cause mortality or first heart failure hospitalization occurred in significantly fewer patients in the vericiguat group than in the placebo group (957 patients [37.9%] vs 1032 patients [40.9%]; HR, 0.90; 95% CI, 0.83-0.98; $P = .02$).[2]

Safety

The incidence of serious adverse events was similar in the 2 treatment groups (vericiguat vs placebo: 32.8% vs 34.8% of patients). Symptomatic hypotension and syncope, adverse events of clinical interest, tended to occur in more patients in the vericiguat group than the placebo group (vericiguat vs placebo: symptomatic hypotension, 9.1% vs 7.9% of patients [$P = .12$]; syncope, 4.0% vs 3.5% of patients [$P = .30$]). More patients in the vericiguat group (7.6%) than in the placebo group (5.7%) had anemia.[2]

Discussion

Compared with placebo, vericiguat significantly reduced the incidence of the composite primary outcome of cardiovascular death or first heart failure hospitalization, with a 10% relative difference between groups.[1,2] This difference between groups emerged about 3 months after treatment began and lasted for the duration of the trial.[2] Vericiguat therapy reduced the absolute event rate by 4.2 events per 100 patient-years.[1] Vericiguat was also generally well tolerated. The investigators noted that adherence to vericiguat may be high because vericiguat is administered once a day and is easy to titrate.[1,2]

In conclusion, the VICTORIA trial evaluated a high-risk population with substantial unmet needs, and the results showed that vericiguat conferred a clinically meaningful reduction in the absolute primary event rate. Vericiguat may be a useful treatment option for patients with a recent episode of decompensated heart failure, Armstrong said.[1] Merck Sharp & Dohme Corp and Bayer AG supported the VICTORIA trial. ●

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ODYSSEY HoFH (Continued from page 1)

the Division of Lipidology and associate professor at the University of Cape Town in South Africa. HoFH is associated with markedly elevated LDL-C levels and accelerated atherosclerotic cardiovascular disease, despite use of conventional lipid-lowering drug therapies. "Treating these patients with alirocumab resulted in a statistically very significant, but also clinically meaningful LDL reduction of about 63 mg/dL," said Blom.[1]

ODYSSEY HoFH was a randomized, double-blind, placebo-controlled, parallel-group, phase 3 trial in patients with HoFH who were 18 years or older. A total of 69 participants were randomized 2:1 to receive 150 mg of alirocumab every 2 weeks (n = 45) or placebo (n = 24). During the trial, patients also continued on the maximally tolerated lipid-lowering therapy that they were receiving at the time of screening.[1]

The study's primary end point was the percentage change from baseline in LDL-C in patients receiving alirocumab compared with placebo at week 12. At baseline, the mean LDL-C levels were 295.0 mg/dL for patients in the alirocumab group and 259.6 mg/dL for those in the placebo group.[1]

Alirocumab treatment resulted in a statistically significant mean lowering of LDL-C levels by 35.6% at 12 weeks. LDL-C levels fell by a mean of 26.9% (amounting to a mean of 62.8 mg/dL) in the alirocumab group and rose by a mean of 8.6% (amounting to a mean of 8.9 mg/dL) in the placebo group, meeting the trial's primary end point. The results showed that 57.1% of patients receiving alirocumab achieved a reduction in LDL-C levels of 30% or more (P = .0010), whereas 26.7% achieved a reduction of 50% or more (P = .0017).[1]

Thus, treating patients with alirocumab in addition to maximally tolerated lipid-lowering therapy can provide "a clinically meaningful further reduction in LDL cholesterol in those difficult-to-treat cohorts of patients," said Blom. "We're not getting most patients to goal, but we're certainly getting them closer to goal," he added, explaining that many patients will still need further therapies that don't rely on upregulation of the LDL receptor, such as lipoprotein apheresis.[1]

Alirocumab treatment also resulted in significant lowering from baseline of other atherogenic lipids compared with placebo. This included mean reductions in total cholesterol (–26.5%; P <.0001), apolipoprotein B (–29.8%; P <.0001), non–high-density lipoprotein cholesterol (–32.9%; P <.0001), and lipoprotein(a) (–28.4%; P <.0001).[1]

However, as studies have shown with statins, the overall LDL response with alirocumab is more variable in patients with HoFH than in those with other forms of hypercholesterolemia, Blom noted. He also noted that alirocumab was generally well tolerated by study participants, and its safety profile was found to be similar to what has been previously reported for the drug in other patient populations.[1]

The rates of treatment-emergent adverse events (TEAEs) were similar in the alirocumab and placebo groups (n = 20 [44.4%] vs n = 12 [50.0%], respectively). The most common TEAEs included upper respiratory infection (n = 2 [4.4%] vs n = 2 [8.3%]), headache (n = 2 [4.4%] vs n = 2 [8.3%]), and diarrhea (n = 3 [6.7%] vs n = 0 [0%], respectively). Local injection-site reaction and general allergic events were each reported in 1 patient in the alirocumab group. No serious TEAEs, deaths, or discontinuations due to TEAEs occurred in either group during the study.[1]

During a panel discussion after the presentation, Raul Santos, MD, MSC, PhD, director of the Lipid Clinic at the Heart Institute of the University of São Paulo, Brazil, stressed that PCSK9 inhibitors should be the next treatment step for these patients, after statins and ezetimibe, to see how much cholesterol levels can be further reduced. "Certainly, [PCSK9 inhibitors] have an advantage compared with lipoprotein apheresis and lomitapide because they have better availability and they are a lot less expensive than the other treatments," he noted.

> "Treating patients with HoFH with alirocumab in addition to maximally tolerated lipid-lowering therapy can provide a clinically meaningful further reduction in LDL cholesterol."

Santos stressed the need to also focus on younger patients with HoFH. "This study enrolled patients older than 18 years and we need studies in younger people—in children," he said, noting that 2 trials are currently ongoing in younger populations with this condition. "It's going to be very important to expand these treatments to younger patients with HoFH because they have to start very early."

Santos also emphasized that additional newer treatments will be necessary to address the very high LDL levels that persisted in these patients. "And, finally, we have to guarantee access to these treatments for HoFH patients because they really can make a difference," he concluded. ●

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TAILOR-PCI Fails to Meet Goal but Does Provide Insight on Genotype-Guided Therapy

PATRICK CAMPBELL

The TAILOR-PCI study failed to meet its primary end point of halving the rate of cardiovascular events through the use of genetic testing–guided therapy after percutaneous coronary intervention (PCI).[1] The trial results were discussed in the presentation "Clinical Implementation of Clopidogrel Pharmacogenetics: the TAILOR-PCI Trial" at the American College of Cardiology's Annual Scientific Session Together With World Congress of Cardiology virtual conference on March 28, 2020.

Although the trial failed to reduce the rate of cardiovascular events by 50%,[1] the results still proved valuable because they indicated that using genetic testing to guide antiplatelet therapy post PCI reduced adverse events by 34% in the first year and total events by 40%.[2]

> "A post hoc analysis revealed a 79% reduction in adverse events in the first 3 months of treatment for carriers in the genotype-guided therapy group."

"Although these results fell short of the effect size that we predicted, they nevertheless provide a signal that offers support for the benefit of genetically guided therapy, with approximately one-third fewer adverse events in the patients who received genetically guided treatment compared with those who did not," said Naveen L. Pereira, MD, a professor of medicine at Mayo Clinic in Rochester, Minnesota, and co-principal investigator of the study, who presented at the virtual meeting.[2]

Because an estimated 30% of the US population carries a genetic variant that inhibits the ability to metabolize clopidogrel, TAILOR-PCI was designed to assess whether genetic testing to identify *CYP2C19*2/*3* carriers could improve outcomes for patients with acute coronary syndrome or stable coronary artery disease undergoing PCI. The largest genotype-based cardiovascular trial ever conducted, the 2-arm, open-label, international, multicenter, randomized superiority trial enrolled 5302 patients who had undergone treatment for an arterial blockage with 1 or more stents.[1,2]

The participants were randomized 1:1 to either conventional or genotype-guided therapy. Patients in the conventional therapy group received clopidogrel 75 mg daily, whereas *CYP2C19*2/*3* carriers in the genotype-guided group received ticagrelor 90 mg twice daily.[1]

Exclusion criteria included being less than 18 years of age, failure of index PCI, known *CYP2C19* genotype, and planned revascularization of any vessel within 30 days or of the target vessel within 12 months post index procedure.[1]

The trial's primary end point was a composite of cardiovascular death, myocardial infarction, stroke, definite or probable stent thrombosis, and severe recurrent ischemia within 1 year of the index PCI. The secondary end point was major or minor bleeding defined by Thrombolysis in Myocardial Infarction (TIMI) criteria. Assessments took place at hospital discharge and at 1, 6, and 12 months post PCI through phone interview or medical record review.[1]

Of the 2641 patients randomized to genotype-guided therapy, 903 were *CYP2C19*2/*3* carriers. In the 2635 randomized to conventional therapy, 946 were retrospectively identified as carriers.[1]

At the end of the trial, the composite end point occurred in 35 carriers (4%) in the genotype-guided group and 54 (5.9%) in the conventional therapy group, correlating to a 34% lower risk (adjusted HR, 0.66; 95% CI, 0.43-1.02; $P = .056$). Results indicated that TIMI major or minor bleeding was observed in 16 carriers (1.9%) in the guided-treatment group and 14 (1.6%) in the conventional treatment arm at 1 year.[1,2]

Investigators noted that a post hoc analysis revealed a 79% reduction in adverse events in the first 3 months of treatment for carriers in the genotype-guided therapy group (HR, 0.21; $P = .001$). A sensitivity analysis examining total events found that carriers receiving genotype-guided therapy had a 40% lower risk of events than those in the conventional therapy group (HR, 0.60; 95% CI, 0.41-0.89; $P = .011$).[1]

"We now know from clinical practice and other studies that antiplatelet drug therapy is critical during the first 3 months after PCI," Pereira said in a statement. "This finding suggests that the lion's share of the benefit of genetically guided therapy may occur during this high-risk period. Because this wasn't a preplanned analysis, we can't draw firm conclusions from it, but it merits further study."[2]

The study was funded by the National Heart, Lung, and Blood Institute (NHLBI) and Mayo Clinic. The statement noted that the NHLBI has funded an extended follow-up study to further evaluate the impact of genotype-guided therapy beyond the 12-month period, including in TAILOR-PCI.[1]

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VICTORIA: Q&A With the Investigators

JAVED BUTLER, MD, MPH, MBA, is the Patrick H. Lehan Chair in Cardiovascular Research, the chair of the Department of Medicine, and a professor of physiology at the University of Mississippi Medical Center in Jackson, Mississippi. His research interests focus on clinical trials in patients with heart failure.

JUSTIN EZEKOWITZ, MBBCh, MSc, is codirector of the Canadian VIGOUR Centre at the University of Alberta in Edmonton, Alberta, Canada. He is also a professor in the Division of Cardiology and the director of cardiovascular research at the University of Alberta. His research interests include novel interventions for patients with chronic heart failure.

The VICTORIA study, which was cosponsored by Merck and Bayer, was conducted in collaboration with the Canadian VIGOUR Centre and the Duke Clinical Research Institute in more than 600 centers in 42 countries.

THE AMERICAN JOURNAL OF MANAGED CARE® (AJMC®): Can you discuss the burden of heart failure in the US population? Do some groups have a greater burden than others?

BUTLER: There are about 6 million people in the United States [who] have heart failure—the annual incidence is about three-quarters of a million or a little bit higher than that. The burden is quite extensive, and unfortunately, the trends are such that this will increase by about 25% by the year 2030. So, not only is the burden quite high right now, it is expected to go up pretty substantially as well.

There are subgroups of people who have a higher risk of developing heart failure. People who have diabetes, obesity, high blood pressure, valvular heart disease—these are the people [who] have a higher risk of developing heart failure. But I think probably the biggest reason why the incidence and the prevalence of heart failure is increasing is because of the aging population, as most heart failure cases are older patients—older patients are at a higher risk.

AJMC®: Can you describe the mechanism of action of vericiguat? What is the potential to address an unmet need?

BUTLER: Heart failure is a state in which you have generalized endothelial dysfunction and decreased nitric oxide [NO] production. NO is the molecule that goes into the cell and binds to an enzyme called soluble guanylate cyclase. This binding leads to increased production of cyclic GMP [cGMP].

cGMP signaling further down in multiple organs of the body has a lot of beneficial effects. In the cardiovascular system, [cGMP signaling] causes vasodilation, improves endothelial function, and decreases fibrosis and remodeling of the heart. There are all these beneficial effects that occur in the cardiovascular system, but in the presence of oxidative stress, there is substantial reduction in NO and subsequently the action of the soluble guanylate cyclase. Vericiguat is a novel medication that sort of bypasses that NO step and just directly binds and stimulates the soluble guanylate cyclase, directly increasing cGMP production and all the downstream beneficial effects on the cardiovascular system.

EZEKOWITZ: Vericiguat modulates how soluble guanylate cyclase acts with NO in both a normal and low-NO scenario. Most patients with heart failure are in a low-NO scenario. Vericiguat differs from nitrates, phosphodiesterase inhibitors, and sacubitril/valsartan, which all indirectly act on the NO or cGMP pathway. Sacubitril/valsartan modifies the cGMP pathway but acts on a different part of the pathway and location; hence, they are complementary. Other medications do not work on this area.

There are many, many unmet needs in this patient population. We still see a strikingly high mortality rate in the treatment group despite best therapy. Vericiguat can be added on to reduce the risk, but no medication, device, or surgery eliminates the risk completely. Improved integrated care, as well as nonpharmaceutical and pharmaceutical therapies, are all needed. Focusing on what is best for individual patients versus all patients is the next frontier.

AJMC®: Given that the results met their primary end point, what are the most important takeaways, in your view?

BUTLER: There is currently an unmet need in patients who have heart failure with reduced ejection fraction. If you look at the past 3 decades or so, there have been a lot of good medications that have come out to show benefits and [improve] outcomes for these patients, but remember, we started at such a bad point—people had 30% to 35% 1-year mortality. Even with all those therapies, the reduction in mortality even in disabled patients, we're talking about 10% or so.

Now, there's a special high-risk group of patients [with] worsening heart failure. These are the patients who have been stable in the outpatient setting on whatever medication you were giving them, but now that therapy is not enough, and they're developing worsening heart failure symptoms requiring escalation of therapy or hospitalization in many cases. Once these patients [are] hospitalized, we're talking about [a] 25% to 30% 1-year mortality—so, a much higher-risk group of patients. So, that's where vericiguat was tested in the VICTORIA trial, and what we found was that [with regard to] the primary end point for combined heart failure hospitalization and cardiovascular mortality, [there] was a benefit.

Now, what is the magnitude of benefit? It has to be looked at in [terms of] both relative risk reduction and absolute risk reduction. The amount of benefit is actually related to not only how efficacious the drug is, but [also] what was the baseline patient population in the clinical trial, [what were] the inclusion/exclusion criteria.

So, as mentioned, this was a high-risk group of patients. The primary end point was statistically significant; it was a 10% relative risk reduction, but it was a very short follow-up of about 10 months on average because these patients had such a high risk—about 3 times higher risk than [patients in] some of the recent heart failure trials that we have seen. Therefore, the event accumulation was much faster. Thus, if you look at the absolute risk reduction, there was about a 4% absolute risk reduction, which is the same or better than some of the recent trials that we've seen.

EZEKOWITZ: VICTORIA met its primary end point (a composite of cardiovascular death or heart failure hospitalization [HFH]) with a hazard ratio of 0.90 (95% CI, 0.82-0.98), with an absolute event-rate reduction of 4.2 events per 100 patient-years. The secondary end points were also met for HFH and directionally aligned for both cardiovascular death and all-cause death. Importantly, vericiguat was well tolerated, safe, and did not change electrolytes or renal function.

***AJMC®*:** What are some of this study's strengths and limitations?

EZEKOWITZ: Strengths include the rigor in which this was conducted efficiently in a patient population that is often harder to have participate in trials. Limitations would include the relatively short follow-up time with a median of 10.8 months, and that all patients had to have a recent event (within 6 months).

***AJMC®*:** What is the relevance of these results for managed care professionals, and how could this information be used?

EZEKOWITZ: Vericiguat was tested on top of excellent standard of care including sacubitril/valsartan and devices, and as such, [the VICTORIA patient population] reflects a real-world patient population. A second key issue is that we enrolled patients with a broad range of renal function (estimated glomerular filtration rate >15 mL/min/1.73 m^2) and ejection fraction up to 45%, leading to broad applicability. Critical for health systems was that vericiguat reduced HFH, which is an important driver of healthcare expenses.

***AJMC®*:** Based on the results of this study, what are the next steps? For example, should additional research be done?

EZEKOWITZ: First steps, of course, will be helping this medication get to the patients who need it via initial regulatory and payor approval and clinician and patient education. After that, broad dissemination and integration into national and international guidelines is next. Finally, additional work would involve evaluating vericiguat in different patient populations—for example, those with higher ejection fractions, those without a recent event, or those with other cardiac disease.

***AJMC®*:** Is your team involved in additional research in this area?

EZEKOWITZ: We're pleased to continue the academic–industrial partnership along the lines of scientific knowledge generation and helping patients. Watch this space! ●

Poster and Abstract Roundup

SARAH MACMILLAN

Characteristics and Outcomes of Patients With Heart Failure With Reduced Ejection Fraction

Heart failure (HF) is a progressive disease occurring in roughly 6.5 million Americans older than 20 years. In patients older than 65 years, HF is the most common diagnosis of those discharged from the hospital.[1,2] The number of Americans with HF is expected to increase 46% by 2030.[1,2] About half of patients with HF have HF with reduced ejection fraction (HFrEF), and those with worsening chronic HF (WCHF) experience symptoms that require inpatient or outpatient treatment.[2] The 2 studies described here evaluated HF-related and all-cause healthcare resource utilization (HRU) of patients with commercial insurance and on Medicare to help inform healthcare policies and identify unmet needs within this patient population. Posters of these studies were presented at the American College of Cardiology's Annual Scientific Session Together With World Congress of Cardiology virtual conference, March 28-30, 2020.[1,2]

The first was a retrospective observational cohort study in which clinical and demographic data for patients with stable HFrEF were compared with data for patients with worsening disease. All patients in this study were fully commercially insured, and HRU between the 2 groups was evaluated.[1]

(Continued on page 10)

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MYOKARDIA

Poster and Abstract Roundup (Continued from page 8)

Using IBM MarketScan Research Databases, patients aged 18 to 64 years with inpatient and outpatient claims for HFrEF were identified and indexed from January 1, 2015, to December 31, 2016 (N = 16,646). Their medical history for 12 months before the index date (baseline period) was evaluated, and patients were then followed for 12 months after index.[1]

The mean age of patients with WCHF was 56.1 years (SD, 8.0), and for patients with stable HFrEF, it was 55.4 years (SD, 8.2). Across groups, the population was mostly men: 63.7% of patients with WCHF and 64.6% of patients with stable disease.[1]

Study results showed that 26.8% of patients experienced WCHF within 12 months. These patients had more comorbidities compared with patients whose HFrEF remained stable. At baseline, patients with WCHF had lower use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers compared with patients with stable HFrEF (51% vs 58%, respectively), although use of other HF medications was similar between the groups. During the 12-month follow-up period, those with WCHF had more all-cause and HF-related HRU compared with patients with stable HFrEF, including outpatient visits, emergency department (ED) visits, and hospitalizations.[1]

"These preliminary results suggest [that] new therapies are needed to help prevent WCHF and help reduce burden of disease in this patient population," the authors concluded. "Additional analyses adjusting for patient characteristics (such as baseline demographic and clinical characteristics) are needed to confirm these findings."[1]

A second retrospective observational study was conducted in patients with HFrEF to evaluate the differences in outcomes between those with WCHF and those whose disease did not worsen. In this study, all patients were covered by Medicare Advantage.[2]

Patients were identified from October 2015 through September 2017 based on inpatient and outpatient claims for HFrEF and had continuous enrollment for 12 months before the index date (baseline period) and 12 months after (N = 28,645).[2]

WCHF occurred in 32.5% of patients during the 12-month follow-up period, more frequently in patients who were older; the mean age at index of patients with WCHF was 78.1 (SD, 12.9) versus 76.7 (SD, 12.5) for those with stable disease. Although more patients with HFrEF overall were women, more men experienced WCHF. Patients with WCHF also had more comorbidities than patients whose disease did not worsen.[2]

During the follow-up period, the rate of all-cause hospitalizations for patients with WCHF was more than twice the rate for those without worsening disease (94.8% vs 38.3%, respectively), and ED visits were also significantly higher (63.4% vs 41.0%, respectively). HF-related outpatient visits, ED visits, and hospitalizations were also higher for patients with WCHF than for those without.[2] At 90 days, the HF-related readmission rate for patients with WCHF was 24.5%. All-cause readmissions at 90 days were 50.2% for patients with WCHF versus 11.7% for patients without worsening diease.[2]

The authors concluded, "WCHF patients had more all-cause and HF-related healthcare resource utilization. This underscores the need for better clinical management or innovative approaches in this high-risk population."[2]

Sodium-Glucose Cotransporter 2 Inhibitors Underprescribed in Patients With Diabetes and Cardiovascular Disease

High blood glucose from diabetes can damage blood vessels and is linked to increased risk for cardiovascular disease (CVD), and people with diabetes are more likely to have risk factors for CVD, such as high cholesterol.[3] In patients with diabetes, studies have shown improvements in CVD outcomes with sodium-glucose cotransporter 2 inhibitor (SGLT2i) treatment.[4] The following study aimed to evaluate prescribing patterns of SGLT2i treatment in patients with diabetes. A poster of the study was presented at the American College of Cardiology's Annual Scientific Session Together With World Congress of Cardiology virtual conference, March 28-30, 2020.[4]

> "In patients with diabetes, studies have shown improvements in CVD outcomes with sodium-glucose cotransporter 2 inhibitor treatment."

This retrospective analysis was conducted using IBM's Explorys electronic medical records database to identify adult patients who had diabetes and CVD (a history of coronary artery disease, myocardial infarction, or stroke) and were taking metformin, between 2016 and 2019. Patients were excluded if they had chronic kidney disease or end-stage renal disease. Multivariable analyses were conducted to assess factors including age, sex, race, insurance coverage, and specialist visits.[4]

The authors noted that, for patients with diabetes and CVD, "Previous studies have shown that in this population, SGLT2i [was associated with] lower rates of primary composite cardiovascular outcome and death from any cause when added to standard care."[4]

However, results from this study showed that just 9.3% of patients with diabetes and CVD were prescribed an SGLT2i (35,590 of 383,750 patients).[4] Among patients who were prescribed an SGLT2i, 49% were 65 years or younger, compared with 30% of patients who were not prescribed an SGLT2i. Of patients receiving an SGLT2i, 64% were men compared with 50% of patients who were not prescribed an SGLT2i. Patients prescribed an SGLT2i were also more likely to be Caucasian (86% vs 82%) and have

commercial insurance (62% vs 51%). Differences were significant (P <.001) for all measures.[4]

Investigators concluded that SGLT2i medications are underprescribed in patients with diabetes and CVD, and they identified statistically significant prescribing disparities according to race and sex.[4] In particular, women are inadequately represented among patients who receive these therapies. The authors also noted that because SGLT2i medications are currently unavailable in generic formulations, prescribing disparities due to insurance coverage may become less pronounced in the future.[4]

Guideline-Recommended Statin Therapy Underused in the Elderly

Treatment guidelines for elderly patients who have atherosclerotic CVD (ASCVD) recommend moderate-intensity statin use, although it is not clear that real-world prescribing is in line with these guidelines.[5] In this study, researchers used a Northern California multispecialty health system in conjunction with state mortality records to gather electronic health records data from 2006 to 2018 for adults with ASCVD who were older than 75 years. In this retrospective cohort analysis, associations between statin therapy and low-density lipoprotein cholesterol, predictors of statin use, and likelihood of death were evaluated. A poster of the analysis was presented at the American College of Cardiology's Annual Scientific Session Together With World Congress of Cardiology virtual conference, March 28-30, 2020.[5]

Results showed that, compared with low-intensity statins or no statin therapy, treatment with moderate- or high-intensity statins was linked to a decrease in all-cause mortality (HR, 0.86; 95% CI, 0.80-0.93). In this study, only 45% of patients received moderate- or high-intensity statins. Certain patients were less likely to receive such therapies; among them were patients with dementia (objective response rate [ORR], 0.88; 95% CI, 0.82-0.95), women (ORR, 0.77; 95% CI, 0.74-0.80), those who were underweight (ORR, 0.64; 95% CI, 0.57-0.73), and those who had HF (ORR, 0.69; 95% CI, 0.65-0.74).[5]

"Guideline-recommended moderate-/high-intensity statins are underused in elderly patients with ASCVD despite associations with lower mortality," the authors concluded. "Future studies are needed to understand barriers to recommended statin use for secondary prevention in the elderly."[5] ●

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Effects of Renal Denervation in the Absence of Antihypertensive Medications: SPYRAL HTN-OFF MED Pivotal Trial

LAURIE ANNE WALDEN, DVM

Catheter-based renal denervation safely lowered blood pressure (BP) for 3 months in patients with uncontrolled hypertension who were not taking antihypertensive medications, according to results of the SPYRAL HTN-OFF MED pivotal trial.[1] Primary results from the trial were presented on March 29, 2020, at the American College of Cardiology's Annual Scientific Session Together With World Congress of Cardiology virtual conference and simultaneously published in *Lancet*.[2]

Because hypertension remains uncontrolled in many patients, "there is a great unmet clinical need for new hypertension treatments," said presenter Michael Böhm, MD. Renal denervation is a nondrug antihypertensive option that uses radiofrequency nerve ablation to decrease sympathetic activity in renal nerves, thereby reducing BP. During the procedure, a catheter advanced into a renal artery delivers an electric current to nerve endings in the walls of renal arteries.[2]

Earlier studies of renal denervation showed that the procedure could lower BP. However, the first sham-controlled trial (SYMPLICITY HTN-3) did not show that renal denervation lowered BP more than a sham procedure. Because of inconsistencies in the methods and procedures of that trial, further studies were conducted. These studies again showed that renal denervation could reduce BP.[2]

Methods

The SPYRAL HTN-OFF MED trial was conducted in 2 parts.[1] A pilot proof-of-concept trial showed that renal denervation lowered BP,[3] and the pivotal trial reported here investigated

renal denervation independent of the effects of antihypertensive drugs. The analysis used a Bayesian adaptive study design to include data from both the pilot and pivotal trials.[1]

The pivotal trial was a prospective, single-blind, randomized, sham-controlled trial conducted at 44 international study sites. Patients included in the study were either not taking antihypertensive drugs or agreed to discontinue these drugs during the trial. BP measurements were obtained in a medical office and with 24-hour ambulatory BP monitoring. Patients included were aged 20 to 80 years, had office systolic BPs ranging from 150 to less than 180 mm Hg, had office diastolic BPs of at least 90 mm Hg, and had mean 24-hour systolic BPs ranging from 140 to less than 170 mm Hg. Patients were excluded if they had angina or myocardial infarction within 3 months of enrollment, renal artery anatomy ineligible for catheter-based denervation, a history of certain cardiovascular conditions, relevant comorbidities, or secondary causes of hypertension.[1,2]

> "Renal denervation reduced office and 24-hour systolic BP measurements in patients who were not taking antihypertensive medications."

All patients underwent renal angiography and were randomly assigned to receive either renal denervation or a sham procedure. The renal denervation procedure used a multielectrode renal denervation catheter (Symplicity Spyral, Medtronic) and a radiofrequency generator (Symplicity G3, Medtronic). The renal denervation catheter can deliver energy for up to 60 seconds to 4 quadrants of an artery and can access arteries between 3 and 8 mm in diameter. In the trial, ablation times of 45 seconds or longer were considered successful, and ablations were advised for all accessible renal and branch arteries.[2]

Patients received safety follow-ups every 2 weeks for 3 months. BP measurements and screens for antihypertensive drugs were obtained at baseline and at 3 months. Patients who met escape criteria—an office systolic BP measurement of at least 180 mm Hg or BP-related symptoms or complications—resumed antihypertensive medications.[2]

The primary efficacy end point was the change in mean 24-hour systolic BP from baseline to 3 months. The secondary efficacy end point was the change in office systolic BP from baseline to 3 months. Predefined major adverse events were all-cause mortality, end-stage renal disease, end-organ damage resulting from embolism, renal artery perforation or dissection requiring intervention, vascular complications, and hospitalization because of a hypertensive crisis.[1]

Results

The analysis included 331 patients (80 in the pilot trial and 251 in the pivotal trial) enrolled from June 25, 2015, to October 15, 2019. A total of 166 patients received renal denervation; 165 received the sham procedure.[1,2] Baseline characteristics were similar in the 2 groups.[2]

Patients in the renal denervation group received a mean of 46.9 (SD, 15.6) ablations in 2.2 (SD, 0.6) main renal arteries and 5.8 (SD, 2.7) branch arteries.[1] The main results were as follows:

- The change in 24-hour systolic BP from baseline to 3 months was significantly larger in the renal denervation group than in the sham procedure group (treatment difference, −3.9 mm Hg; Bayesian 95% credible interval, −6.2 to −1.6).[2]
- The change in office systolic BP from baseline to 3 months was also significantly larger in patients receiving renal denervation than in those receiving the sham procedure (treatment difference, −6.5 mm Hg; Bayesian 95% credible interval, −9.6 to −3.5 mm Hg).[2]
- Analysis yielded a greater than 99.9% probability that renal denervation was superior to the sham procedure for 24-hour and office systolic BP reduction.[2]
- Systolic and diastolic BPs were consistently reduced across the entire 24-hour measurement period in the renal denervation group.[2]
- By 3 months after intervention, 1 major adverse event had occurred in each group. Neither of these was attributed to the device or procedure.[1,2]
- More patients in the sham procedure group (28 of 165, 17%) than in the renal denervation group (16 of 166, 9.6%) met the safety escape criteria ($P = .049$).[1]
- Most patients (85%-95%) complied with the direction not to take antihypertensive medications during the trial.[1]

Discussion

Both the primary and secondary efficacy end points of the study were met. Renal denervation reduced office and 24-hour systolic BP measurements in patients with uncontrolled hypertension who were not taking antihypertensive medications. BP reduction was clinically meaningful 3 months after the procedure, and no major device- or procedure-related safety events occurred.[1]

The effect of renal denervation therapy is continuous regardless of whether patients adhere to medications, said Böhm. This therapy also provides consistent BP reduction over 24 hours, "particularly at times of the day when high blood pressure is most closely associated with cardiovascular complications," he added.

The study duration was only 3 months because of ethical considerations of withholding antihypertensive medications from the study population for a longer period of time, he said. However, other studies of renal denervation have shown a further decrease in BP after 3 months, so the trial could have underestimated the treatment effect. Other study limitations were that

more patients met safety escape criteria in the sham procedure group than in the treatment group and that some patients took antihypertensive drugs during the trial.[1] Device manufacturer Medtronic funded the SPYRAL HTN-OFF MED trial.

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Low-Dose Colchicine Is Cost-Effective for Improving Cardiovascular Outcomes After Myocardial Infarction

NICOLA PARRY, DVM

Adding colchicine to standard care therapy for patients after myocardial infarction (MI) is a cost-effective treatment and may lower per-patient costs by 69% over a lifetime period compared with standard care alone, based on the results of a new analysis of data from the randomized, double-blind, placebo-controlled Colchicine Cardiovascular Outcomes Trial (COLCOT) that were presented at the American College of Cardiology's Annual Scientific Session Together With World Congress of Cardiology virtual conference.[1]

Colchicine is a well-known anti-inflammatory drug that is frequently used to treat gout. In the COLCOT trial, patients were randomized to receive low-dose colchicine (0.5 mg/day) or placebo, and rhe primary composite end point included death from cardiovascular (CV) causes, resuscitated cardiac arrest, MI, stroke, and urgent hospitalization for angina leading to revascularization. The trial results, which were published in 2019 in *The New England Journal of Medicine*,[2] showed that low-dose colchicine significantly reduced post-MI ischemic CV events by 23% compared with placebo (HR, 0.77; 95% CI, 0.61-0.96; $P = .02$).[1]

Michelle Samuel, PhD, MPH, a postdoctoral fellow at Montreal Heart Institute in Montreal, Canada, and colleagues performed a cost-effectiveness analysis using data from COLCOT. "The objective was to assess the in-trial period and lifetime cost-effectiveness of low-dose colchicine compared to placebo in post-MI patients receiving standard care therapy," said Samuel.[1]

The researchers created a multi-state Markov model based on the intention-to-treat results of COLCOT and included the first and second events in the base case model. They calculated the incremental cost-effectiveness ratio (ICER) for the 2-year in-trial period, as well as for a 20-year lifetime period.[1]

In their model, the researchers included the components of the primary composite end point from COLCOT, death from any cause, and pneumonia, which was the only serious adverse event that was significantly different between the 2 treatment groups. They performed their primary analysis from the Canadian single-payer perspective and then replicated the base case from the US Medicare system and private insurance system perspectives. In the Canadian analysis, the researchers used the current cost of colchicine in Canada, which is $0.26 per pill.[1]

Treatment with colchicine was shown to be economically dominant, lowering average per-patient costs by 47% ($237) for the 2-year in-trial period and by 69% ($5647) for a 20-year lifetime period. It also increased quality-adjusted life-years by 0.04 for the in-trial period and by 2.86 for the lifetime period. This ICER dominance was maintained across multiple analyses that included all recurrent events.[1]

However, "the most important factor in the cost-effectiveness of any treatment is the cost of the treatment itself," said Samuel. So the researchers then changed the cost of colchicine in Canada to evaluate how the ICERs changed. They varied the cost from $0.26 to $4 per pill.[1]

The researchers noted that at a $50,000 willingness-to-pay threshold, ICER dominance was maintained up to a cost of $0.55 per pill for the 2-year in-trial period and that colchicine was cost-effective up to a cost of about $3.50. Dominance was also maintained to approximately $1.25 per pill for the lifetime period, and colchicine was cost-effective up to $4.[1]

The overall finding of economic dominance for treatment with colchicine was also seen when Samuel and colleagues replicated their analysis from the US perspective, where the cost of colchicine is about $4 to $6 per pill. In their Medicare model, colchicine was cost-effective at $4.50 per pill or less for the 2-year in-trial period and was dominant at $4.50 or less and cost-effective at up to $6 for the lifetime period. In the US private insurance system model, colchicine was economically dominant at a cost of $5 or less per pill for the in-trial period and again remained cost-effective up to $6 for the lifetime period. "For the lifetime perspective, all ICERs were dominant," said Samuel.[1]

"We talk a lot in the cardiovascular community about drugs that are both effective and that we can afford to pay for, and these data are obviously exceptional in that regard," said Paul Ridker, MD, MPH, director of the Center for Cardiovascular Disease Prevention at Brigham and Women's Hospital and Eugene Braunwald Professor of Medicine at Harvard Medical School, both in Boston, during a panel discussion about the study's findings. "I'm not a cost-effectiveness expert, but I do know that 'dominant' means you save money, and I think that's the message that you're getting here."

Commenting on the substantial per-pill price disparity for colchicine between the United States and Canada, Ridker noted that, even under the high US pricing, the data show "a dominant model for lifetime and probably a dominant model for the hospitalization period."

Jennifer Robinson, MD, MPH, a professor in the departments of Epidemiology and Medicine and director of the Prevention Intervention Center at the University of Iowa, in Iowa City, also emphasized that many of these newer trials are occurring in the background of optimal medical therapy, with many patients receiving high-intensity or at least moderate-intensity statins. Consequently, these new data must be considered against this backdrop in the context of statins, which are also cost-saving drugs. "[Statins are] really cost-saving as secondary prevention," she said. "So, I think putting the emphasis on that as the predominant therapy and then thinking about some of these other therapies—certainly colchicine looks like the next place to go—is kind of rising in the hierarchy of secondary prevention therapies."

Ridker highlighted the need to consider the relevance of both residual inflammatory risk and residual cholesterol risk. "My view is [that] these 2 things probably go together," he concluded. "I would predict that 5 to 10 years from now, we're going to be giving aggressive combination therapies that really dampen down both of these fundamental processes." ●

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Results of Additional Analysis Help Clarify Impact of EPA Levels on Outcomes in REDUCE-IT

PATRICK CAMPBELL

REDUCE-IT staked its claim as one of the most impactful trials in recent memory, yet the mechanism behind eicosapentaenoic acid (EPA) and how specific levels benefit cardiovascular health remain unclear.

New data presented by Deepak Bhatt, MD, MPH, at the American College of Cardiology's Annual Scientific Session Together With World Congress of Cardiology virtual conference help address these questions.[1] The REDUCE-IT findings indicate that on-treatment EPA levels correlate with the effect on first and total cardiovascular events seen with icosapent ethyl (Vascepa), Bhatt said during his presentation.[1]

The 8179-patient REDUCE-IT trial assessed the use of icosapent ethyl in 2 categories of patients: 1) those 45 years and older with a clinical history of coronary artery, cerebrovascular, carotid artery, or peripheral artery disease, and 2) those 50 years and older with diabetes and 1 additional risk factor for cardiovascular disease.[1,2] The results suggest that use of icosapent ethyl 4 g/day was associated with a reduction in relative risk of major adverse first (25%) and total (30%) cardiovascular events including cardiovascular death, stroke, myocardial infarctions (MIs), hospitalization for unstable angina, and revascularization.[2,3]

The substudy investigators examined the impact of both baseline and on-treatment EPA levels on outcomes. Results of the analysis revealed that on-treatment levels correlated strongly with reductions in cardiovascular death, MI, stroke, coronary revascularization, unstable angina, sudden cardiac death, cardiac arrest, new heart failure, and all-cause mortality.[1,2]

In an interview, Bhatt, the lead investigator of REDUCE-IT and executive director of Interventional Cardiovascular Programs at Brigham and Women's Hospital in Boston, said, "[When we looked] at the on-treatment EPA levels, what we found were extremely strong associations between higher EPA levels and lower rates of cardiovascular events. Cardiovascular death, all-cause mortality, sudden cardiac death, cardiac arrest, MI, stroke, hospitalization for unstable angina, revascularization—all these things were significantly associated with EPA levels; that is, higher EPA levels on treatment, lower rates of those events. For the first time, we also showed that in patients with the highest degrees of on-treatment EPA levels, there was actually a reduction in heart failure as an end point, so that's really exciting."

Bhatt noted that when the research team looked at the proportion of different biomarker changes that contributed

to the benefits seen in REDUCE-IT, changes in low-density lipoprotein and C-reactive protein appeared to have little effect. "[Also,] changes in triglycerides accounted for really a sliver of the benefits of the drug," he said. "Where the action was, it seemed, was [in] the 350% to 400% increase in EPA levels with icosapent ethyl driving the cardiovascular benefits. So, we did some statistical analysis that shows that really, it's EPA that's driving the benefit, not those changes in other biomarkers." ●

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COMPASS Diabetes Results Support Adding Rivaroxaban to Aspirin Regimen

PATRICK CAMPBELL

Even though the results of COMPASS solidified the role of rivaroxaban (Xarelto) 2.5 mg plus aspirin to treat coronary artery disease (CAD) and peripheral artery disease (PAD), many cardiologists and clinicians have questioned the real-world applicability of the findings.

Thanks to a prespecified subgroup analysis presented at the American College of Cardiology's Annual Scientific Session Together With World Congress of Cardiology virtual conference, clinicians now have more information on how the drug's impact might differ between patients with or without diabetes who also have CAD or PAD.[1]

The findings of COMPASS, which included 27,395 patients, indicated that using rivaroxaban 2.5 mg plus aspirin twice daily reduced the risk of a composite of cardiovascular death, stroke, or myocardial infarction better than aspirin alone (HR, 0.76; 95% CI, 0.66-0.86; *P* <.001). There was an apparent risk of major bleeding, but the investigators pointed out that there was no significant difference in intracranial or fatal bleeding between the 2 groups (HR, 1.70; 95% CI, 1.40-2.05; *P* <.001).[2]

The newest COMPASS subgroup analysis, presented by Deepak Bhatt, MD, MPH, executive director of Interventional Cardiovascular Programs at Brigham and Women's Hospital in Boston, examined the impact on the 10,341 patients with and 17,054 without diabetes at baseline. For the primary end point, results indicated a similar relative risk reduction for rivaroxaban plus aspirin compared with aspirin alone (HR, 0.74; *P* = .002 vs HR, 0.77; *P* = .005; *P* for interaction = .77) and all-cause mortality (HR, 0.81; *P* = .05 vs HR, 0.84; *P* = .09; *P* for interaction = .82).[1]

The findings also indicated greater absolute risk reductions for patients with diabetes than those without for the primary efficacy end point (2.3% vs 1.4%; *P* for interaction <.0001), all-cause mortality (1.9% vs 0.6%; *P* for interaction = .02), and major vascular events (2.7% vs 1.7%; *P* for interaction <.0001) at 3 years. The risk of bleeding hazards was similar between those with and without diabetes.

In an interview regarding the results, Bhatt said, "I think the take-home message is, first of all, [that] in the COMPASS trial, this regimen—some have called it a vascular protection regimen—rivaroxaban plus aspirin, is effective across the board. We studied high–ischemic risk, CAD, and/or PAD patients [who] are at low bleeding risk, but beyond that, now we see [that] those with diabetes are a particularly high-risk subgroup. Everybody knows that this is really a substantial advance, and the combination dual pathway inhibition of low-dose rivaroxaban and aspirin really is quite effective."

Bhatt advised exercising caution in patient selection. "In the diabetes subgroup, as in the nondiabetes subgroup, as in the overall trial, there was a significant increase in major bleeding, but fortunately, no significant excess in fatal or intracranial bleeding," he said. "It's only a strategy to consider in patients [at] low bleeding risk, but if they [are at] high ischemic risk and they [have] CAD or PAD and they have diabetes, that is a very appealing population in which to use this therapy."

According to Bhatt, "Bottom line: If they have high ischemic risk, a prime example of which is having diabetes, and otherwise fit the COMPASS CAD/PAD eligibility criteria, you've got to consider this regimen." ●

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TAKE A CLOSER LOOK

YOUR PATIENTS WHO HAVE HAD A WORSENING HEART FAILURE EVENT ARE AT INCREASED RISK FOR FUTURE EVENTS[1]

DESPITE A PERIOD OF STABILIZATION ON RECOMMENDED THERAPY.[2]

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