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FIGARO-DKD Finds Finerenone Offers CV Benefits in Mild to Moderate Kidney Disease With T2D

Results Show Risk of HF Hospitalization Reduced 29%

Mary Caffrey

AFTER A PREVIOUS STUDY SHOWED finerenone (Kerendia) slowed chronic kidney disease (CKD) progression and cut cardiovascular (CV) events in the highest-risk patients, a new study unveiled August 28 found the drug also offered benefits to patients with mild to moderate CKD and type 2 diabetes (T2D).

The phase 3 study, FIGARO-DKD, was presented during the European Society of Cardiology (ESC) Congress 2021, taking place in a virtual format for the second year because of COVID-19. Results were published simultaneously in the *New England Journal of Medicine (NEJM)*.¹

CONTINUED ON PAGE 3

SGLT2 Inhibitors Added to ESC Guidelines for Treatment of Chronic HFrEF

Mary Caffrey

TWO SODIUM GLUCOSE CO-TRANSPORTER 2 (SGLT2) inhibitors, empagliflozin (Jardiance) and dapagliflozin (Farxiga), are now recommended for treatment of chronic heart failure (HF) with reduced ejection fraction (HFrEF), according to the latest 5-year update of the European Society of Cardiology (ESC) Guidelines in acute and chronic HF. They were

CONTINUED ON PAGE 5

ALSO IN THIS ISSUE:

- 5 Studies Address Cardiac, Heart Failure Outcomes Affected by COVID-19, [page 7](#)
- Dr Bertram Pitt: Finerenone Works "Across the Spectrum of Cardiovascular Disease," [page 10](#)
- Experts Discuss the Potential for Combination Therapy, [page 12](#)
- Salt Substitute Offers an Inexpensive Way to Cut Stroke Risk at Scale, Study Finds, [page 13](#)
- STEP Trial Findings Build on SPRINT Results, With a Twist, [page 14](#)

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FIGARO-DKD Finds Finerenone Offers CV Benefits in Mild to Moderate Kidney Disease With T2D

(CONTINUED FROM COVER)

Finerenone, a nonsteroidal mineralocorticoid receptor antagonist (MRA) sold by Bayer, is designed to target overactivation of the mineralocorticoid receptor that leads to renal decline. It offers potent anti-inflammatory and antifibrotic effects and reduces the urinary albumin-to-creatinine (UACR) ratio with fewer adverse effects than steroidal MRAs.²

During Kidney Week in October 2020, the FIDELIO-DKD study reported that finerenone slowed CKD progression by 18% and cut CV events 14% in patients with advanced kidney disease (stage 3 or 4 CKD with severely elevated albuminuria) and T2D.² Results reported for FIGARO-DKD involved patients who fell into 1 of 2 categories: stage 2 to 4 CKD with moderately elevated albuminuria or stage 1 or 2 CKD with severely elevated albuminuria.¹

Among these patients with mild to moderate kidney disease and T2D, finerenone produced a 13% reduced risk in the primary outcome, a composite of death from CV causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure (HF). The risk of hospitalization for HF was reduced 29% for patients taking finerenone.

Understanding the Renal End Point

To be eligible for the study, patients with stage 2 to 4 CKD had to have a UACR of 30 to 300 mg/g and those with stage 1 or 2 CKD had to have a UACR of 300-5000 mg/g.

A secondary outcome was a composite of kidney failure, a sustained decrease from the baseline of at least 40% estimated glomerular filtration rate (eGFR), or renal death. Lead study author Bertram Pitt, MD, of the University of Michigan School of Medicine, discussed the renal outcome with *The American Journal of Managed Care*® (AJMC)® (see page 10).

“We had a secondary outcome, which was renal progression of disease, and the primary outcome was reduction of eGFR by 40% that was sustained. This trended positive, but it wasn’t significant,” Pitt said. “We picked that end point because the FDA and the [European Medicines Agency] at one point thought that was a very good renal end point. Subsequently, we’ve learned it’s not very sensitive, and the more sensitive renal end point is a 57% reduction in eGFR, and that was significantly reduced.

“But most importantly, we reduced the need for dialysis. We reduce the progression to end-stage renal disease,” he said. “That is really important.”

All patients in the study had to be treated with drugs to optimize the renin-angiotensin system blockade; 98% were taking glucose-lowering therapy, 70% were taking statins, 55% were taking insulin, 47% were taking a diuretic, and smaller numbers were taking a sodium-glucose co-transporter 2 (SGLT2) inhibitor (8.5%) or a glucagon-like peptide-1 (GLP-1) receptor agonist (8.4%).

Because finerenone raises serum potassium levels, patients’ serum potassium levels had to be 4.8 mmol/L or below during screening visits (but not at randomization) so that levels could be maintained around 5.0 mmol/L or below.

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Results showed the following:

- In the study, 7437 patients were randomized and 7352 ended up in the analysis.
- Follow-up over a median of 3.4 years was affected by COVID-19, with the trial being discontinued early for 27% in each arm because of the pandemic.
- A primary outcome event occurred in 458 of 3686 patients (12.4%) of the finerenone group and 519 of 3666 (14.2%) of the placebo group, for an HR of 0.87 (95% CI, 0.76-0.98; $P = .03$).
- Lower incidence of HF hospitalization was the most important driver of the primary outcome benefit (HR, 0.71; 95% CI, 0.56-0.90).
- Secondary composite outcomes occurred in 350 patients (9.5%) in the finerenone group compared with 395 (10.8%) in the placebo group (HR, 0.87; 95% CI, 0.76-1.01).
- The frequency of adverse events did not differ between the 2 groups overall; there was more hyperkalemia-related discontinuation of the study drug in the finerenone group (1.2%) than the placebo group (0.4%), but Pitt said more hyperkalemia is to be expected, and this rate is actually low.

Finerenone in the Treatment Regimen

The findings are important for other reasons, Pitt said. Not only does a nonsteroidal MRA offer physicians and patients an option to avoid dialysis with a treatment that is better tolerated than steroid therapies, but it also gives cardiologists a reason to look for albuminuria, something that may not be on their radar.

Patients might have a normal eGFR, but an increase in UACR, Pitt said. “Most of us neglect these patients,” he said. “Now, we know we can do something about that—the patient should be started on therapy.... I think that’s a really important message.”

With many new therapies for CKD, where will finerenone fit in to the existing standard of care? If a cardiologist finds that a patient also has diabetes with albuminuria greater than 30 mg/g, then they should be started on finerenone, according to Pitt.

The drug’s tolerability, as seen in the safety data in FIGARO, shows a clear benefit over steroidal MRAs. Patients taking finerenone should be on an angiotensin-converting enzyme inhibitor and likely a glucose-lowering therapy.

“Now, the SGLT2 inhibitors and the GLP-1 receptor agonists have also shown benefits, and we had less than

10% each of these [patients] in our trial. And all we can say is that on top of those drugs, finerenone seems to be equally beneficial, but these were small numbers, and we need more,” Pitt said.

As for making the case for payers, Pitt does not have a formal cost analysis, but he said, “I think this is going to be a cost-effective therapy—you save patients from heart failure and dialysis.”

Where will finerenone fit into the existing standard of care? If a cardiologist finds that a patient also has diabetes with albuminuria greater than 30 mg/g, then they should be started on finerenone, according to Bertram Pitt, MD.

Filling a Need in HFpEF?

Preclinical data show promise in combining finerenone with empagliflozin, an SGLT2 inhibitor.

“It appears in the preclinical models at least, there was an additive effect on fibrosis, inflammation, and survival. So our expectation is that if we do the right trials, we will show this,” Pitt said. “The patients would benefit by being on an SGLT2 inhibitor, an MRA, and maybe a GLP-1 receptor agonist,” with the last therapy being added to reduce the risk of stroke.

There has been discussion how finerenone will be used alongside other new therapies for HF and CKD, and renal results from another major trial presented during the ESC Congress, EMPEROR-Preserved for empagliflozin, may increase the talk of combination therapy (see **interviews, page 12**).

Empagliflozin was found to have significant cardiovascular benefits, driven by a reduction in HF hospitalization, for patients with HF with preserved ejection fraction

(HFpEF).³ However, the renal benefits seen previously in HF with reduced ejection fraction (HFrEF) were not present.⁴

In correspondence in *NEJM*, the investigators reported that the HR for serious renal outcomes was 0.51 (95% CI, 0.33-0.79) in the EMPEROR-Reduced trial and 0.95 (95% CI, 0.73-1.24) in the EMPEROR-Preserved trial. In each trial, “the effect of empagliflozin was consistent across the components of the primary outcome and across all prespecified subgroups, including patients with and without diabetes,” the EMPEROR study investigators said.⁴

In his presentation of the FIGARO-DKD results, Pitt noted that patients with symptomatic HFrEF with NYHA Class II-IV were excluded from both the FIDELIO-DKD and FIGARO-DKD trials.

In a follow-up email to *AJMC*[®], Daniela Esser, DPhil, communications business partner in cardiology for Bayer, explained that information about ejection fraction was not collected, and thus, it is not possible to clearly identify

the distribution of asymptomatic HFrEF, HFpEF, and those with HF with mildly reduced ejection fraction at baseline.

“Subgroup analyses including more details on kidney and heart benefits as well as comedications are planned to be presented at upcoming congresses,” Esser said. ♦

REFERENCES

1. Pitt B, Filippatos G, Agarwal R, et al, for the FIGARO-DKD investigators. Cardiovascular events with finerenone in kidney disease and type 2 diabetes. *N Engl J Med*. Published online August 28, 2021. doi:10.1056/NEJMoa2110956
2. Bakris GL, Agarwal R, Anker SD, et al, for the FIDELIO-DKD investigators. Effect of finerenone on chronic kidney disease outcomes on type 2 diabetes. *N Engl J Med*. 2020;383(23):2219-2229. doi:10.1056/NEJMoa2025845
3. Anker SD, Butler J, Filippatos G, et al; EMPEROR-Preserved Trial Investigators. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med*. Published online August 27, 2021. doi:10.1056/NEJMoa2107038
4. Packer M, Butler J, Zannad F, et al. Empagliflozin and major renal outcomes in heart failure. *N Engl J Med*. Published online August 27, 2021. doi:10.1056/NEJMc2112411

SGLT2 Inhibitors Added to ESC Guidelines for Treatment of Chronic HFrEF

(CONTINUED FROM COVER)

released August 27. ESC typically updates guidelines in various treatment areas on 5-year cycles, and guidelines are released throughout the annual Congress. Other guidelines released during the 2021 meeting were updates for valvular heart disease, cardiac pacing, and cardiovascular disease prevention. The HF guidelines were simultaneously published in the *European Heart Journal*.¹

Chronic HF is a condition where the heart is unable to pump blood around the body properly. It usually occurs because the heart has become too weak or stiff. Ejection fraction, which is the percentage of the blood within the ventricles that is ejected during the cardiac cycle, is the most important measure in HF.

HF with preserved ejection fraction (HFpEF), also called diastolic HF, involves impaired relaxation of the left ventricle. HFrEF, or systolic HF, involves impaired contraction of the left ventricle.

HFpEF is on the rise in the United States and worldwide,² given that its likelihood rises with age and high blood pressure. According to ESC, prevalence rises from 1% among those 55 years and under to more than 10% among those 70 years and older.³ Symptoms include breathlessness, ankle swelling, and tiredness. Once diagnosed, patients

are typically hospitalized once each year and 50% die within 5 years.^{2,3}

HF is linked to hospitalization and has been a major source of rising health care costs; in 2014, the mean cost of a hospitalization was pegged at \$11,552, with total costs nationwide estimated at \$11 billion.⁴ Under the Affordable Care Act, Medicare has begun penalizing hospitals that readmit too many patients for HF within 30 days of discharge, thus further fueling the need for therapies to treat this condition.

The ESC update recognizes that patients with HF typically have other conditions, such as atrial fibrillation and valvular heart disease, and it makes treatment recommendations accordingly. “It is crucial to treat the underlying causes of heart failure and its comorbidities,” said task force chairperson Marco Metra, MD, of the University of Brescia, Italy. “Proper treatment of high blood pressure, diabetes, and coronary artery disease can prevent the development of heart failure. Atrial fibrillation, valvular heart disease, diabetes, chronic kidney disease, iron deficiency, and other comorbidities frequently coexist with heart failure and the adoption of specific treatments may have a major impact on the clinical course of our patients.”³

The Rise of SGLT2 Inhibitors in Heart Failure

Several evidence-based treatments have been developed to improve survival in HFrEF, such as angiotensin-converting enzyme inhibitors, angiotensin-receptor neprilysin inhibitors, beta-blockers, and mineralocorticoid receptor antagonists. But in recent years, SGLT2 inhibitors, first introduced in 2013 to treat type 2 diabetes (T2D), have reshaped cardiometabolic care across diabetes, heart failure, and renal disease.

The 2015 EMPA-REG OUTCOME trial, designed to meet FDA requirements for empagliflozin's approval in T2D, stunned both the diabetes and cardiology community when the drug showed cardiovascular (CV) benefits, and soon separate trials in HF and renal disease were underway across the drug class.⁵

Two of these trials were EMPEROR-Reduced⁶ and EMPEROR-Preserved,⁷ which examined empagliflozin in HFrEF and HFpEF, respectively. Both EMPEROR-Reduced and the DAPA-HF⁸ trial in dapagliflozin showed significant reductions in a composite of CV death or HF hospitalization, leading to the new ESC guidelines.

Findings for EMPEROR-Preserved were unveiled later on August 27, showing a 21% reduced risk in CV death and hospitalization for HF.⁷ As noted during a news conference held ahead of the presentation on EMPEROR-Preserved, the new HF guideline update would be outdated literally within hours. The 2021 ESC Guidelines state, "To date, no treatment has been shown to convincingly reduce mortality and morbidity in patients with HFpEF, although improvements have been seen for some specific phenotypes of patients within the overall HFpEF umbrella."

"Every guideline we write is out of date a few days after it's published," said Milton Packer, MD, of Baylor University Medical Center, who presented pooled results from the EMPEROR trials in renal outcomes.

Acknowledging that he was exaggerating a bit, Packer continued, "The guidelines are dynamic documents. They represent what we know at the time that they're written. And then new information comes out, and they have to be updated. And that takes time. It's a process and we all understand that process; there is no real concept of finality here. We do the best we can with the data we have."

Changes From 2016

The ESC guidelines in HF were last updated in 2016. The authors highlight several concepts incorporated across the guidelines, including as follows:

- a change from the term "heart failure with mid-range ejection fraction" to "heart failure with mildly

reduced ejection fraction" to describe patients with left ventricle ejection fraction of 41% to 49%

- a modified classification for acute HF
- the addition of key quality indicators

Therapies

The updated guidelines recommend empagliflozin, dapagliflozin, canagliflozin, ertugliflozin, and sotagliflozin for patients with T2D who are at risk of CV events "to reduce hospitalizations for HF, major CV events, end-stage renal dysfunction, and CV death." Separately, dapagliflozin, empagliflozin, and sotagliflozin were recommended for those with T2D and HFrEF to reduce hospitalizations for HF and CV death. Sotagliflozin, which is an SGLT1/2 inhibitor, has not yet been approved by the FDA.⁹

Of note, new Level 1 recommendations—which means there is evidence or general agreement that a treatment or procedure is beneficial, useful, and effective—call for giving patients evidence-based oral medications, including SGLT2 inhibitors, before discharge from the hospital. Guidelines call for patients to be evaluated for congestion before they are discharged so that physicians can find optimal oral therapy regimens. Follow-up visits are recommended at 1 to 2 weeks to increase doses if necessary.

Strategies

Beyond the recommendations for the use of specific therapies, other updates—if embedded into clinical practice—could have a major impact on patient care. Additional Level 1 recommendations cover the following:

- *HFpEF Screening* for, and treatment of, etiologies, and CV and non-CV comorbidities, are recommended in patients with HFpEF
- *Prevention and screening.* (a) Self-management strategies are recommended to reduce the risk of HF hospitalization and mortality. (b) Either home-based and/or clinic-based programs improve outcomes and are recommended to reduce the risk of HF hospitalization and mortality.
- *Management for advanced HF* (a) Patients being considered for long-term mechanical circulatory support must be able to handle the device and have support systems in place. (b) Heart transplants are recommended for those with advanced HF who are refractory to medical/device therapy and who do not have absolute contraindications.
- *Management of patients with HF and valvular heart disease.* (a) Aortic valve intervention, transcatheter

aortic valve implantation (TAVI), or surgical aortic valve replacement (SAVR) is recommended in patients with HF and severe high-gradient aortic stenosis to reduce mortality and improve symptoms. (b) The choice between TAVI and SAVR should be made based on individual patient preference and features that include age, surgical risk, and clinical, anatomical, and procedural aspects, weighing the risks and benefits of each approach.

- **Patients with HF and iron deficiency.** Patients with HF must be screened for anemia and iron deficiency with analyses of a full blood count, serum ferritin concentration, and transferrin saturation.
- **Patients with HF and cancer.** Those with cancer who are at increased risk for cardiotoxicity, defined by a history of or risk factors for CV disease, previous cardiotoxicity, or exposure to cardiotoxic agents, should undergo CV evaluation before scheduled anticancer therapy, preferably by a cardiologist with experience in cardio-oncology.
- **HF and amyloidosis.** The guidelines recommend tafamidis (Vyndamax) for patients with (a) transthyretin (TTR) amyloidosis–cardiac amyloidosis (CA), NYHA Class I or II symptoms, and genetic testing that has shown hereditary TTR-cardiomyopathy; or (b) patients with wild-type TTR-CA and NYHA Class I or II symptoms, to reduce symptoms, CV hospitalization, and mortality. ♦

REFERENCES

1. McDonagh TA, Metra M, Adamo M, et al; ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Published online August 26, 2021. *Eur Heart J*. doi:10.1093/eurheartj/ehab368
2. Upadhyya B, Kitzman DW. Heart failure with preserved ejection fraction in older adults. *Heart Fail Clin*. 2017;13(3):485-502. doi:10.1016/j.hfc.2017.02.005
3. ESC Guidelines on heart failure launched today. News release. European Society of Cardiology; August 27, 2021. Accessed August 27, 2021. <https://www.escardio.org/The-ESC/Press-Office/Press-releases/ESC-Guidelines-on-heart-failure-management-launched-today>
4. Jackson SL, Tong X, King RJ, Loustalot R, Hong Y, Ritchey MD. National burden of heart failure events in the United States, 2006 to 2014. *Circ Heart Fail*. 2018;11(12):e004873. doi:10.1171/CIRCHEARTFAILURE.117.004873
5. Zinman B, Wanner C, Lachin JM, et al; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373(22):2117-2128. doi:10.1056/NEJMoa1504720
6. Packer M, Anker SD, Butler J, et al. EMPEROR-Reduced Trial Investigators. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med*. 2020;383(15):1413-1424. doi:10.1056/NEJMoa2022190
7. Anker SD, Butler J, Filippatos G, et al; EMPEROR-Preserved Trial Investigators. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med*. Published online August 27, 2021. doi:10.1056/NEJMoa2107038
8. McMurray JJV, Solomon SD, Inzucchi SE, et al; DAPA-HF Trial Committees and Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;381(21):1995-2008. doi: 10.1056/NEJMoa1911303
9. Caffrey M. Can heart failure results create an alternate path for sotagliflozin? *The American Journal of Managed Care*® website. Published May 19, 2021. Accessed September 3, 2021. <https://www.ajmc.com/view/can-heart-failure-results-create-an-alternate-path-for-sotagliflozin>

5 Studies Address Cardiac, Heart Failure Outcomes Affected by COVID-19

Maggie L. Shaw

IN A SESSION THAT TOOK PLACE on August 27 during the European Society of Cardiology Congress 2021, 5 clinicians from around the world presented their findings on how the COVID-19 pandemic has and hasn't affected cardiac care, in particular for patients with heart failure. The session was co-chaired by cardiologist Mikhail N. Kosiborod, MD, vice president of research at Saint Luke's Health System, Kansas City, Missouri, and Michele Senni, MD, chief of the Cardiovascular Department at Papa Giovanni XXIII Hospital in Bergamo, Italy.

The clinicians' mixed findings indicate that much remains to be learned on the complex interactions among COVID-19 infection, cardiovascular care, and heart failure.

Unplanned Admissions¹

Nur Adawiyah Yusoff, RN, from Changi General Hospital in Singapore, addressed unplanned admissions for heart failure. She emphasized that although globally there is a high burden on health care systems from the COVID-19 pandemic, admissions for acute heart failure have actually

dropped and that this decrease may be the result of lockdowns, “potentially leading to adverse outcomes, such as increased morbidity and mortality.”

With few data available on the effect of the pandemic on heart failure–related care in multiethnic Southeast Asian countries, her single-center study examined admissions for acute heart failure, hypothesizing that totals were influenced by both the pandemic and its related lockdown restrictions. The study compared outcomes from before (January 23–July 31, 2019, the control period; $n = 164$) and during the pandemic (January 23–July 31, 2020, the study period; $n = 183$).

In both groups, all patients were 67 years or older; most were male and of Chinese ethnicity. Their average hospital stay was 4 days. However, a subgroup analysis of the periods April 7 to June 1, 2019, and April 7 to June 1, 2020, showed that patients were sicker upon admission during the pandemic, with mean (SD) Charlson Comorbidity Index scores of 2.88 (2.1) vs 1.97 (1.8) ($P < .05$). Despite this, overall admissions were shown to be down in the beginning of the pandemic (daily average dropped from 2.44 to 1.39) compared with the same period in 2019 (January 23–April 6). They didn’t rise again, to a daily average of 2.28 admissions, until after reopening, at which point they were shown to be higher compared with the same period in 2019 (June 2–July 31).

Yusoff noted the importance of seeking medical attention, adding that “the lockdown measures implemented may have influenced a patient’s decision to step out of the house for medical treatment, leading to serious adverse effects from acute heart failure.” Patient education is essential, she emphasized, and telehealth can be used to advance care, but further studies need to examine patient behavior as it affects medication adherence, diet/fluid restriction, and other lifestyle modifications brought on by the pandemic.

Heart Transplant Recipients²

Daniel Miklin, MD, from the University of Southern California, discussed outcomes among heart transplant recipients, who face an even greater risk from COVID-19 because of immunosuppression. This “provides a significant risk for morbidity and mortality” among this patient population, he stated. In addition, data are few and far between on the initial management of this patient population. Data do show, however, a 20% to 30% mortality among those infected with COVID-19, Miklin said.

His retrospective review included 235 patients who were an average of 7 years post heart transplant and almost all (97%) on an immunosuppression regimen including tacrolimus. They had a median (interquartile range) age of 56.0

(41.0–63.5) years; 71% were male, 55% had nonischemic/dilated cardiomyopathy, and their most common comorbidity was hyperlipidemia (58%). Upon hospital admission, most presented with upper respiratory infection or acute hypoxic respiratory failure (29% each) or dyspnea (26%).

Most received supportive care (55%), but those requiring further care received steroids (19%), remdesivir (Veklury) (19%), or antibiotics (23%). The most common change to immunosuppression regimens was to decrease mycophenolate (29%).

“Interestingly, our outcomes demonstrated only 7% mortality, with a 93% survival rate,” Miklin stated. Most patients (55%) received outpatient care, and of the 45% requiring hospitalization who did not succumb to their illness, all were discharged successfully.

The findings are in great contrast to those of other studies, he added, which show mortality ranging from 20% in Israel to 37% in Italy. This may be because the patients in his study were younger and not as far out from their transplant, he hypothesized. Additionally, those on triplet immunosuppression therapy may be reaping protective benefits in the form of limited cytokine storm.

Miklin, too, emphasized the need for additional research, especially into long-term outcomes and therapy optimization for this particular patient group.

Cardiac Complications³

Gianluca Rigatelli, MD, PhD, of the Division of Cardiology at General Hospital of Rovigo, in Italy, summarized findings on acute heart failure related to COVID-19 infection. His systematic review and meta-analysis aimed to gauge “the pooled incidence of acute heart failure as a cardiac complication of COVID-19 disease, and to estimate the related mortality risk in these patients.”

He and his team used a cutoff of December 26, 2020, searching MEDLINE, Scopus, and Web of Science. Their analysis ultimately focused on a 1064-patient cohort, representing 6 studies, among whom 6.9% to 63.4% of patients hospitalized for COVID-19 had complications brought on by acute heart failure. Pooled incidence analysis showed that 20.2% (95% CI, 11.1%–33.9%; $P < .0001$) of patients with COVID-19 had complications from acute heart failure and they had a significantly increased mortality risk (odds ratio, 9.36; 95% CI, 4.76–18.4; $P < .0001$).

“Acute heart failure represents a frequent complication of COVID-19 infection,” Rigatelli noted, “and it is associated with a higher risk of mortality in the short-term period.” However, meta-regression analysis did not find a statistically significant relationship between age and incidence of acute heart failure from COVID-19 infection ($P = .062$) or overall mortality risk ($P = .053$).

Prognostic Biomarkers⁴

Patients with COVID-19–related pneumonia and no history of heart failure were the focus of an abstract from Tufan Cinar, MD, of Sultan Abdulhamid Han Training and Research Hospital in Istanbul, Turkey. Specifically, he focused on the potential of N-terminal pro-brain type natriuretic peptide (NT-proBNP), a nonactive prohormone, as a prognostic indicator of mortality from possible heart failure. NT-proBNP levels are known to be higher than average in patients with heart failure vs those without heart failure.⁵

Among the 137 patients included in Cinar's analysis, for which the primary outcome was in-hospital death, overall mortality was 18.9%. The most common comorbidities among those who died were hypertension, chronic kidney disease, coronary artery disease, stroke, and dementia. Elevated levels of white blood cells (WBC), glucose, creatinine, troponin I, and NT-proBNP were also seen, but only NT-proBNP, WBC, and troponin I levels, in addition to age, were linked to increased in-hospital mortality following multivariable analysis.

Further receiver operating characteristic analysis showed an ideal NT-proBNP predictive level of 260 ng/L, at a sensitivity of 82% and specificity of 93% (area under the curve, 0.86; 95% CI, 0.76-0.97), for in-hospital mortality. This “clearly shows that the NT-proBNP levels are independently linked with in-hospital mortality rates in subjects with COVID-19 pneumonia and without heart failure,” Cinar noted, adding that the biomarker holds value as a prognostic parameter in these cases.

Device Therapy⁶

Presenter Rimma Hall of the Department of Cardiology, Cambridge University Hospital NHS Foundation Trust, and her fellow investigators examined the effects of the COVID-19 pandemic on device therapy for patients with heart failure. They compared the practice of defibrillator implantation and cardiac resynchronization for patients with arrhythmias and heart failure against National Institute for Health and Care Excellence guidelines.

“The study period coincided with the COVID-19 pandemic,” Hall said, “This allowed us to assess its impact on device therapy.”

Hall's team found that, for infection-control purposes, care for patients admitted to the hospital was redistributed to ward-based care and away from specialty care, and the investigators particularly wanted to examine the impact of this change on patients who required specialty care but were not receiving it. Outcomes from March to August 2020 were compared with the same period in 2019; 18 patients in each group were eligible for device therapy.

Although device therapy was consistently prescribed in both periods—in particular for those patients with serious ventricular arrhythmia, a familial cardiac condition with high risk of sudden cardiac death, or a history of surgical repair of congenital heart disease—the team did see a reduction in the proportion of patients with heart failure who were eligible for device therapy: It dropped from 94% in 2019 to 79% in 2020 ($P = .03$).

Additional findings showed an 8% reduction in admissions for heart failure patients during the pandemic and a trend toward patients being considered too frail for device therapy. In 2020, 26 of 31 patients not receiving cardiology-directed care were deemed too frail for device therapy.

Possible reasons for their findings, Hall noted, included physicians being pressured to quickly discharge patients, a greater perception of potential patient frailty, and nonspecialty physicians having a lack of knowledge of indications for device therapy.

“Cardiac services should actively look for heart failure patients who may have missed out on life-saving therapies during the pandemic,” she concluded. ♦

REFERENCES

1. Yusoff NA. The effect of the COVID-19 pandemic on heart failure unplanned admission: a single center study. Presented at: European Society of Cardiology Congress 2021; August 27-31, 2021; virtual.
2. Miklin D. Outcomes of COVID-19 infection in heart transplant recipients. Presented at: European Society of Cardiology Congress 2021; August 27-31, 2021; virtual.
3. Rigatelli G. Heart failure as a complication of covid-19 infection: systematic review and meta-analysis. Presented at: European Society of Cardiology Congress 2021; August 27-31, 2021; virtual.
4. Cinar T. Prognostic significance of N-terminal pro-BNP in patients with COVID-19 pneumonia without previous history of heart failure. Presented at: European Society of Cardiology Congress 2021; August 27-31, 2021; virtual.
5. NT-proB-type natriuretic peptide (BNP). Cleveland Clinic. Accessed August 27, 2021. <https://my.clevelandclinic.org/health/diagnostics/16814-nt-prob-type-natriuretic-peptide-bnp>
6. Hall R. Impact of the COVID-19 pandemic on the device therapy for patients with the heart failure. Presented at: European Society of Cardiology Congress 2021; August 27-31, 2021; virtual.



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Dr Bertram Pitt: Finerenone Works “Across the Spectrum of Cardiovascular Disease”

BERTRAM PITT, MD, PROFESSOR OF MEDICINE emeritus at the University of Michigan School of Medicine, presented results for the FIGARO-DKD study involving finerenone (Kerendia, Bayer) during ESC Congress 2021. In an interview with *The American Journal of Managed Care*® (AJMC®), Pitt discussed the findings of FIGARO-DKD and how they relate to earlier findings of FIDELIO-DKD, which were presented during Kidney Week in October 2020.

Patients in FIDELIO-DKD had more advanced chronic kidney disease than patients in FIGARO-DKD; in both trials, nearly all patients were taking an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB).

This interview has been edited lightly for clarity.

AJMC®: Can you discuss the relationship between the FIGARO and the FIDELIO studies and the primary results of FIGARO?

Pitt: The FIDELIO trial, which was published in [the December 3, 2020] issue of the *New England Journal of Medicine*, involved about 5700 patients with severe kidney disease and diabetes. These patients were randomized to the nonsteroidal mineralocorticoid receptor antagonist [MRA] finerenone at a dose of 10 to 20 mg, and they were followed over more than 2 years. And they found that patients who were randomized to finerenone on top of excellent care—almost 100% had an ACE inhibitor or an ARB—had a significant reduction in the progression of renal disease, which was the primary outcome. They also had a reduction in cardiovascular outcomes, including hospitalization for heart failure. Now, FIGARO-DKD is a companion trial, also in people with type 2 diabetes and kidney disease; there was overlap in the population. But the FIGARO trial has many patients who have a normal eGFR [estimated glomerular filtration rate] but have an increase in urinary albumin-to-creatinine ratio [UACR].

In fact, 62% of the people in FIGARO have a normal eGFR, they have type 2 diabetes, but their kidney disease is defined not by a reduction in eGFR, but by an increase in urinary albumin to creatinine ratio. And this is a group that we, frankly, as cardiologists haven't paid too much attention to. Often, when [cardiologists] see a normal renal function, they don't go any further; a lot of diabetologists certainly know this, but the cardiovascular community and internists—a lot of us have not [tested UACR].

These patients are at increased risk. In fact, people that have type 2 diabetes and renal disease have a 3-fold risk of increased cardiovascular events than people with type 2 diabetes alone.

These patients went into run-in where we maximize ACEs and ARBs. And we very carefully excluded those that had heart failure with reduced ejection fraction because we know they have a Class I indication for an MRA, so we didn't want to include them. There were about 7% to 8% of patients who got into [the trial] with heart failure, but that was probably heart failure with preserved ejection fraction where there's no clear indication, but they were a very small minority...

What we found is a reduction in the primary end point. The primary end point was cardiovascular death, nonfatal infarction, nonfatal stroke, and hospitalization for heart failure, and that was reduced significantly by 13%. But the really important news is, this was driven primarily by a 29% reduction in heart failure hospitalization. As I mentioned, 62% had a normal eGFR, but they had an increase in urinary albumin-to-creatinine ratio.

AJMC®: What is the significance of the results on the renal end points?

Pitt: We had a secondary outcome, which was renal progression of disease, and the primary outcome was a reduction in eGFR by 40% that was sustained. This trended positive, but it wasn't significant. We picked that end point because the FDA and EMA [European Medicines Agency], at one point, thought that was a very good renal end point. Subsequently, we've learned it's not very good. It was sensitive, and the more sensitive renal end point is a 57% reduction in eGFR, and that was significantly reduced.

Most importantly, we reduced the need for dialysis; we reduced the progression to end-stage renal disease. That is really important, that we save people dialysis and that we showed that. Now, finerenone is a nonsteroidal mineralocorticoid receptor antagonist. And as a mineralocorticoid receptor antagonist, you would expect hyperkalemia. We got hyperkalemia—twice as much on finerenone as placebo. But what was really amazing to me is this was really well tolerated. Only 1.2% of the patients on finerenone had to stop because of hyperkalemia vs 0.4% on the control group. So that's less than 1% [that] had to stop.

We know from all of our experience with the steroidal MRAs, spironolactone and eplerenone, that they're really poorly tolerated. In fact, there's a recent paper in *JACC* [Journal of the American College of Cardiology], from the Get With the Guidelines-Heart Failure registry [from the American Heart Association] on over 100,000 patients, where they looked at the use of the steroidal MRAs in people with heart failure and a reduced ejection fraction by that baseline renal function.¹ And the use was pretty dismal, especially when you got to an eGFR less than 45%. And here we have a drug we've shown is effective in reducing heart failure, prevents end-stage renal disease, and is well tolerated.

“Not only did we have very little hyperkalemia, we significantly reduced hypokalemia, which is also very important....The latest data suggest that hyperkalemia is really a risk marker and not a risk factor, whereas hypokalemia is both a risk marker and a risk factor.”

This is a great success for our patients. When you look at the FIDELIO trial and FIGARO together, we have over 13,000 patients. We can pretty confidently say that this drug works in people with diabetes across the spectrum of cardiovascular disease.

AJMC®: Can you elaborate on the safety results for FIGARO?

Pitt: Not only did we have very little hyperkalemia, we significantly reduced the incidence of hypokalemia, which is also very important. People often don't pay too much attention to it, [because] people get frightened about hyperkalemia. But the latest data suggest that hyperkalemia is really a risk marker and not a risk factor; it reflects the underlying renal disease, whereas hypokalemia is both a risk marker *and* a risk factor. And we did lower blood

pressure about 2 to 3 mm. We had some hypotension, but it was very well tolerated.

AJMC®: In a real-world setting, this therapy would most likely be given alongside standard of care. How would it be added to an existing treatment regimen?

Pitt: Let me emphasize, as I did before, that a lot of us [in cardiology] aren't paying attention to people [with] diabetes with a normal renal function. But one of the important take home messages [is] if you see someone with diabetes regardless of their eGFR, you should be looking to see whether they have albuminuria greater than 30 [mg/g]. If they do, they have an increased risk, [and] then I would be starting finerenone. Now, they should be on good anti-diabetic drugs as well, because we didn't have any effect on [glycated] hemoglobin A1c. They need to be taking metformin, and they probably need to be on a [sodium-glucose cotransporter-2 (SGLT2)] inhibitor, or maybe insulin depending on their level of A1c. But in addition to that, they should be on an ACE inhibitor or an ARB.

Now, the SGLT2 inhibitors and the [glucagon-like peptide-1 (GLP-1)] receptor agonists have also shown benefits. And we had less than 10% [of our patients] on each in our trial. All we can say is that on top of those drugs, finerenone seemed to be equally beneficial. But these are small numbers, and we need more.

We have some preclinical data, where finerenone was combined with empagliflozin—and it appeared in the preclinical models at least, there was an additive effect on fibrosis, inflammation, and survival. Our expectation is that if we do the right trials, we will show this, but we don't have it yet—that the patients would benefit by being on an SGLT2 inhibitor, and an MRA, and maybe a GLP-1 receptor agonist. We didn't reduce stroke or infarction; the SGLT2 inhibitors don't do that either. But the GLP-1 receptor agonists do, and maybe that will be a combination to the future. We just don't have the data.

AJMC®: If we're talking to payers, how do you make the case that finerenone is cost-effective?

Pitt: I don't have a formal cost-effectiveness analysis. But I think it's going to be cost-effective if you prevent hospitalization for heart failure and dialysis. I think this is going to be a cost-effective therapy. Certainly, once you get end-stage renal disease, you're in big trouble. ♦

REFERENCE

1. Patel RB, Fonarow GC, Greene SJ, et al. Kidney function and outcomes in patients hospitalized with heart failure. *J Am Coll Cardiol*. 2021;78(4):330-343. doi:10.1016/j.jacc.2021.05.002

Experts Discuss the Potential for Combination Therapy

DIPTI ITCHHAPORIA, MD, FACC, FAHA, FESC, president of the American College of Cardiology, and the Eric and Sheila Samson Endowed Chair in Cardiovascular Health, Hoag Memorial Hospital, Newport Beach, California, discussed the results of FIGARO-DKD after presentation of the findings during ESC Congress 2021.

Why is it important to study different populations taking the same therapy as FIGARO/FIDELIO did for finerenone?

Itchhaporia: The data have to be generalizable to all our patients, so I think that's the main reason. And I think that particularly targeting lower-risk patients, hopefully, we can decrease long-term progression if the data are positive. We always want to reach patients early in the continuum so we can prevent disease progression.

Can these trial findings help build a case to add finerenone to an existing regimen, even if used with a sodium glucose co-transporter 2 (SGLT2) inhibitor?

Itchhaporia: This study had about 8.4% of the patients on an SGLT2 [inhibitor], and we know that mineralocorticoid receptor overactivation results in deleterious effects on the kidneys and the heart—really promoting inflammation and fibrosis, and progression of kidney and cardiovascular disease. I think that there's been consistent cardiovascular benefit with finerenone therapy, which was observed independent of, as well as in combination with, the use of an SGLT2 inhibitor agonist.

And I think the point estimates suggested a benefit with the combination used, and they saw that in the subgroup. The data are suggestive that maybe there's an additive cardiorenal and survival benefit if you do coadministration. Obviously, we need more data to look at this—and we'll need to take a look at that extra data to see—but I think that, hopefully, the data will establish whether the combination therapy finerenone and an SGLT2 inhibitor would really result in greater cardiorenal protection, whether the combination is better than each therapy alone.

Do you see cardiologists prescribing finerenone?

Itchhaporia: Absolutely. I think given the importance of cardiorenal protection, I see that. Also, another interesting thing about finerenone is that it's a targeted therapy with less hyperkalemia [than other options]. We believe in MRA [mineralocorticoid receptor antagonist] therapy for patients with heart failure, but I think what has prevented us from using it has been some of the hyperkalemia, which

we don't see as high a rating with this drug. Now, obviously, I would like to see trials that enroll patients with heart failure. I would also like to see the trial compare the current standard of care, which is spironolactone, with this drug; it's always nice to get those extra data. But I think in terms of utilizing MRAs, which we already believe in, in this type of patient, I think yes, we would—and I think for the cardiorenal protection—but I do think we need a little bit more data.

JAVED BUTLER, MD, MPH, MBA, is the Patrick H. Lehan Chair in Cardiovascular Research and professor and chairman of the Department of Medicine at the University of Mississippi Medical Center in Jackson. He is the co-principal investigator of EMPEROR-Preserved, which showed significant benefit for the SGLT2 inhibitor empagliflozin in heart failure with preserved ejection fraction (HFpEF) during ESC Congress 2021.

Many scientists have said they believe the solution to HFpEF is going to be a combination regimen—perhaps empagliflozin or SGLT2 inhibitors as an anchor, along with other therapies around it. What are your thoughts?

Butler: I completely agree with that mindset. That is the mindset we had for HFrEF [heart failure with reduced ejection fraction]; we were successful in HFrEF, and nobody questions what is the drug [used] in HFrEF if we give combination therapy. If you look [at] this now, we have data with empagliflozin all the way up to 65% [ejection fraction]. We'll see what happens above 65. As we know, valsartan/sacubitril with median EF of less than 57% showed benefit.

If you have some eye of faith and exclude the Russia and Georgia data from TOPCAT and all the heterogeneity that we saw, MRA seems to be benefiting as well.¹ And now, obviously, we have HFpEF-RAS (renin angiotensin system antagonists) going on with MRA. So I would say that HFpEF treatment, or at least a segment of HFpEF treatment, will start looking very much like HFrEF.

But certainly, with EMPEROR-Preserved empagliflozin all the way up to 65% is pretty much a straightforward answer. ♦

REFERENCE

1. Pitt B, Pfeffer MA, Assmann SA, et al. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med*. 2014;370:1383-1392. doi:10.1056/NEJMoa1313731

Salt Substitute Offers an Inexpensive Way to Cut Stroke Risk at Scale, Study Finds

Mary Caffrey

THE RESULTS OF A MASSIVE STUDY indicate that swapping out table salt for a substitute that is composed of at least one-fourth potassium can cut stroke risk by 14% among older adults and those at risk of cardiovascular events—offering an inexpensive, easy way to improve population health at scale.

The study, presented on August 29 during ESC Congress 2021, involved 20,995 residents of 600 villages in rural China. Most consumed diets high in salt; most had a history of hypertension and three-quarters had a history of stroke.

The ability of those who used the salt substitute to cut their risk of stroke with a simple intervention has implications for other developing countries with diets high in salt that have high rates of chronic disease.

Results were simultaneously published in the *New England Journal of Medicine (NEJM)*.¹

The idea that lowering salt intake improves health is nothing new. Multiple studies have shown that cutting back on salt lowers blood pressure. But tracking how a population-level intervention can reduce cardiovascular events is something else, wrote Julie R. Ingelfinger, MD, in an editorial in *NEJM*.²

“If the strategy is feasible over time, the salt-substitute approach might have a major public health consequence in China, and possibly elsewhere,” she wrote, while cautioning that the findings may not apply to other groups.

For this study, villages were assigned to receive either table salt or the substitute, which was 75% sodium chloride and 25% potassium chloride. In every village, about 35 people—each either 60 years or older or with high cardiovascular risk—were given one of the products in large

enough quantities for their entire household to use for cooking, seasoning, and food preservation. In rural China, families do their own cooking and there is no access to processed food.

Those in the salt-substitute group were encouraged to cut back on salt, as low-income groups are known to use more salt than needed in their food preparation. The table-salt group prepared food as usual.

The primary outcome was stroke, and secondary outcomes were major adverse cardiovascular events and death from any cause. Investigators also measured clinical hyperkalemia as a safety outcome. After a follow-up of 4.74 years, results showed the following:

- The mean age of participants was 65.4 years; 49.5% were female, 72.6% had stroke history, and 88.4% had hypertension history.
- The rate of stroke was lower with the salt substitute, 29.14 vs 33.65 events per 1000 person-years; the rate ratio (RR) was 0.86 (95% CI, 0.77-0.96; $P = .006$).
- Rates of major cardiovascular events were also lower in the salt substitute group: 49.09 vs 56.29 events per 1000 person-years, for an RR of 0.87 (95% CI, 0.80-0.94; $P < .001$).
- The salt-substitute group had lower rates of cardiovascular death: 39.28 vs 44.61 events per 1000 person-years, for an RR of 0.88 (95% CI, 0.82-0.95; $P < .001$).
- Hyperkalemia was not significantly higher in the salt-substitute group: 3.35 vs 3.30 events per 1000 person-years, for an RR of 1.04 (95% CI, 0.80-1.37; $P = 0.76$).

The study’s principal investigator said the ability of those who used the salt substitute to cut their risk of stroke—and of other cardiovascular events—with a simple intervention has implications for other developing countries with diets high in salt that have high rates of chronic disease.

“The trial result is particularly exciting because salt substitution is one of the few practical ways of achieving changes in the salt people eat,” said lead study author Bruce Neal, MB, ChB, PhD, of the George Institute for Global Health in Sydney, Australia, in a statement. “Other

salt reduction interventions have struggled to achieve large and sustained impact.”³

Neal and his co-authors cited some important limitations of their study, such as the use of only 1 salt substitute preparation, which prevented the opportunity to grade decreases in salt consumption. They also noted the lack of measured serum potassium levels. However, the study’s method of implementation, which resembled how a public or nongovernmental organization salt-substitution program might be conducted at scale, offered proof of what health gains are possible.

The study proves that a simple intervention can be “taken up very quickly at very low cost,” he said.

Salt costs \$1.08 (US dollars) per kilogram in China; salt substitute is easily manufactured and costs \$1.62 per kilogram. Countries that adopt a policy of implementing salt substitute can quickly shift the health of their population, Neal said.

During a press presentation ahead of his formal presentation at ESC Congress 2021, Neal showed a world map of

countries with high salt consumption; developing countries were disproportionately represented. China offers a good example of what the stakes are, he said.

“A recent modeling study done for China projected that 365,000 strokes and 461,000 premature deaths could be avoided each year in China if salt substitute...proved to be effective,” Neal said. “We have now shown that it is effective, and these are the benefits for China alone. Salt substitution could be used by billions more [people] with even greater benefits.” ♦

REFERENCES

1. Neal B, Wu Y, Feng X, et al. Effect of salt substitution on cardiovascular event and death. *N Engl J Med*. Published online August 29, 2021. doi:10.1056/NEJMoa2105675
2. Ingelfinger J. Can salt substitution save at-risk persons from stroke? *N Engl J Med*. Published online August 29, 2021. doi:10.1056/NEJMe2112857
3. Low-sodium salt prevents stroke. News release. European Society of Cardiology; August 29, 2021. Accessed August 30, 2021. <https://www.escardio.org/The-ESC/Press-Office/Press-releases/Low-sodium-salt-prevents-stroke>

STEP Trial Findings Build on SPRINT Results, With a Twist

Maggie L. Shaw

RESULTS OF THE MULTICENTER RANDOMIZED STEP trial, presented on August 30 during ESC Congress 2021, show that intensive treatment for blood pressure (BP) control can reduce both mean systolic BP (SBP) and the risk of adverse cardiovascular (CV) outcomes, including heart failure.

These findings from STEP—Strategy of blood pressure intervention in the Elderly hypertensive Population—seemingly confirm 2015 results from the SPRINT (Systolic Blood Pressure Intervention) trial.¹ Both trials were stopped early due to clear CV benefit from intensive BP control: SPRINT at a median 3.26 years and STEP at a median 3.34 years vs original plans of 5 and 4 years, respectively.^{1,2}

However, the new results do deviate from those of SPRINT in that there was no perceived risk reduction for all-cause and CV-related mortality, with just a 28% drop (HR, 0.72; 95% CI, 0.39-1.32) seen for CV-related death but an 11% increase (HR, 1.11; 95% CI, 0.78-1.56) seen for all-cause death.² The SPRINT results, meanwhile, showed 42%

(HR, 0.58; 95% CI, 0.39-0.84) and 25% (HR, 0.75; 95% CI, 0.61-0.92) drops, respectively.

Results for STEP, which were published simultaneously in the *New England Journal of Medicine*, show that there was an overall 26% risk reduction for the primary composite outcome (HR, 0.74; 95% CI, 0.60-0.92; $P = .007$) in the intensive-treatment vs the standard-treatment group.²

This primary composite outcome for STEP included incidence of ischemic/hemorrhagic stroke, acute coronary syndrome (ACS; acute myocardial infarction or unstable angina hospitalization), acute decompensated heart failure, coronary revascularization, atrial fibrillation, and death from CV causes.

In-office BP measurements were taken via validated Omron electronic sphygmomanometer and home-based measures were self-collected through a smartphone app with Bluetooth connection to an Omron BP monitor. All patients had hypertension and were aged 60 to 80 years; they were recruited between January 10 and December

31, 2017, at 42 clinical centers throughout China. Then, they were assigned 1:1 to 2 cohorts, each with a different SBP target²:

- Intensive-treatment participants (n = 4243) had an SBP target range of 110 to < 130 mm Hg
- Standard-treatment participants (n = 4268) had an SBP target range of 130 to < 150 mm Hg

“Hypertension is a common risk factor for death from CV causes worldwide and in China,” the authors wrote. “Yet, current guideline-based recommendations for the SBP target in older patients remain inconsistent.”

An editorial accompanying the study results raised some questions about the research: Why were patients with a history of stroke excluded from the analysis? Any why was quality of life not evaluated?

In evaluating the primary outcome’s individual components, heart failure came out on top with an outstanding 73% reduced risk. This was followed by stroke and ACS, both of which saw a 33% risk reduction (stroke: 95% CI, 0.47-0.97; ACS: 95% CI, 0.47-0.94), and major adverse cardiac events (MACE) and CV-related mortality, which each had a 28% risk reduction (MACE: 95% CI, 0.56-0.93; CV-related mortality: 95% CI, 0.39-1.32).²

At the 1-year mark, the mean SBP for the intensive-treatment group was 127.5 mm Hg, compared with 135.3 mm Hg for the standard-treatment group. These did not differ greatly from the means seen over the entire 3.34-year follow-up, which were 126.7 and 135.9 mm Hg, respectively. However, the overall decrease from baseline was almost twice as great for the intensive-treatment vs the standard-treatment group: 19.4 vs 10.1 mm Hg. Close to 78% of the intensive-treatment group had reached the goal range

at 3 years of follow-up, and 3.5% vs 4.6% of the standard-treatment group had any of the primary outcome events during the 3.34-year follow-up.²

Between the groups, there were no significant differences in risk reduction for coronary revascularization and atrial fibrillation, or in renal and safety outcomes. Incidence of hypotension was higher in the intensive-treatment group.²

In the news conference announcing the findings, senior author Jun Cai, MD, PhD, director of the Hypertension Center at FuWai Hospital in Beijing, stated, “These data underscore the importance of a lower SBP target in older patients with hypertension. We recommend that in older patients treated for hypertension, systolic blood pressure should be lowered to < 130 mm Hg.”³

However, an editorial in the *New England Journal of Medicine* accompanying the published study results raised some questions about the research: Why, for instance, were patients with a history of stroke excluded from analysis? And why was quality of life not evaluated?⁴

Noting that not only were STEP and the earlier SPRINT about BP control in persons with hypertension, but that they also focused on treating elevated BP in the context of CV risk, editorial author Mark R. Nelson, MB, BS, MFM, PhD, from Menzies Institute for Medical Research, University of Tasmania, Hobart, Australia, wrote, “We continue to manage blood pressure as an isolated risk factor rather than as an integrated part of a patient’s risk profile because we adhere to the rusted-on clinical concept of hypertension. The approach of focusing on the absolute risk of adverse cardiovascular events has been promoted for decades from the Antipodes. Perhaps the STEP trial is another impetus for broader adoption of this approach.”⁴

The STEP authors appear to agree with that approach. They did note that a principal limitation of their findings, potentially limiting generalizability, was not including patients with a stroke history.² ♦

REFERENCES

1. SPRINT Research Group; Wright JT Jr, Williamson JD, Whelton PK, et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med*. 2015;373(22):2103-2116. doi:10.1056/NEJMoa1511939
2. Zhang W, Zhang S, Deng Y, et al; STEP Study Group. Trial of intensive blood-pressure control in older patients with hypertension. Published online August 30, 2021. *N Engl J Med*. doi:10.1056/NEJMoa2111437
3. Cai J. STEP study: intensive vs standard blood pressure control among older hypertensive patients. Presented at: ESC Congress 2021; August 27-30, 2021; virtual. Accessed September 2, 2021. <https://escardio.app.box.com/s/umpd65eagtpci89j1yuy7lqwt5w9i9/file/852949292511>
4. Nelson MR. Moving the goalposts for blood pressure — time to act. *N Engl J Med*. Published online August 30, 2021. doi:10.1056/NEJMe2112992

