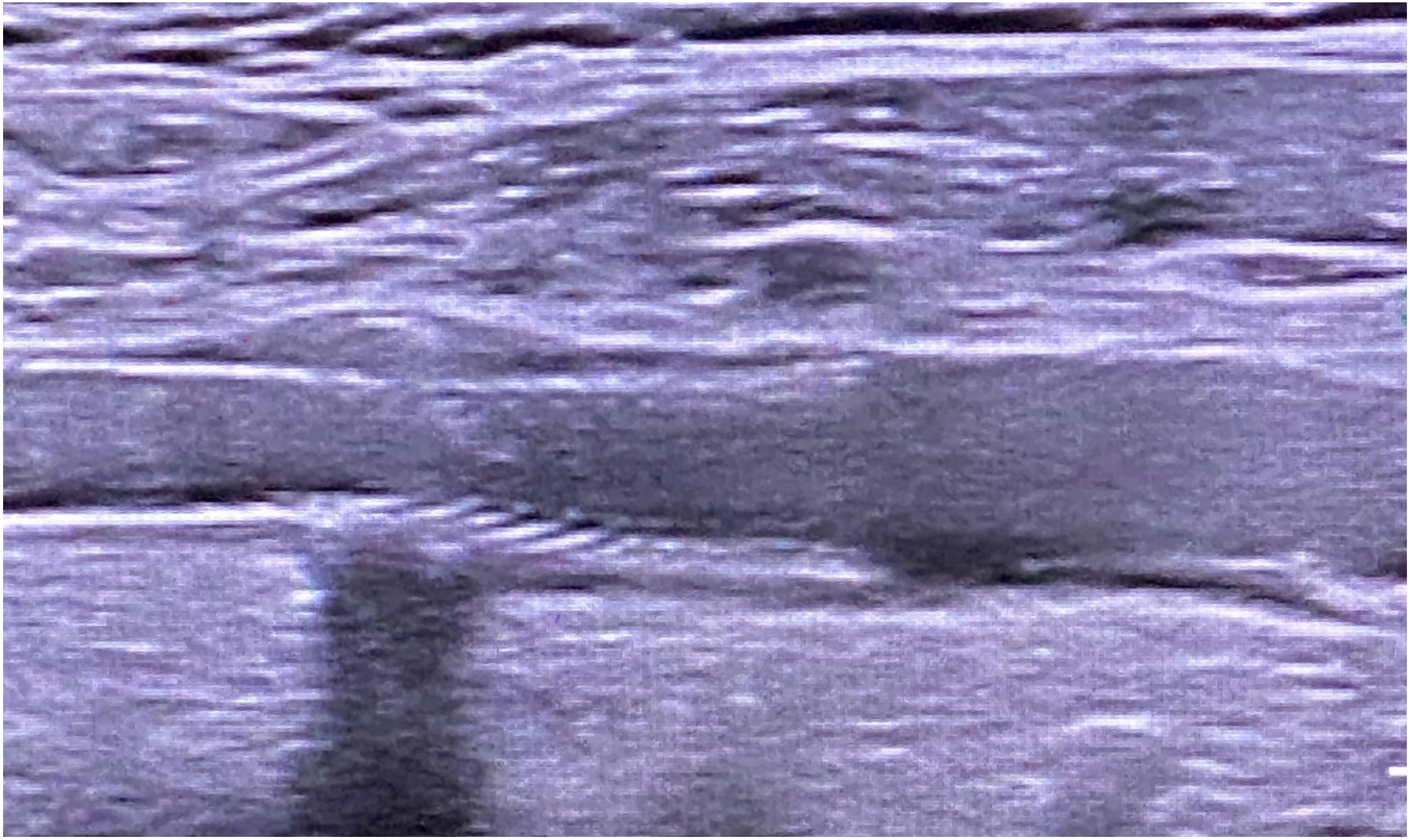

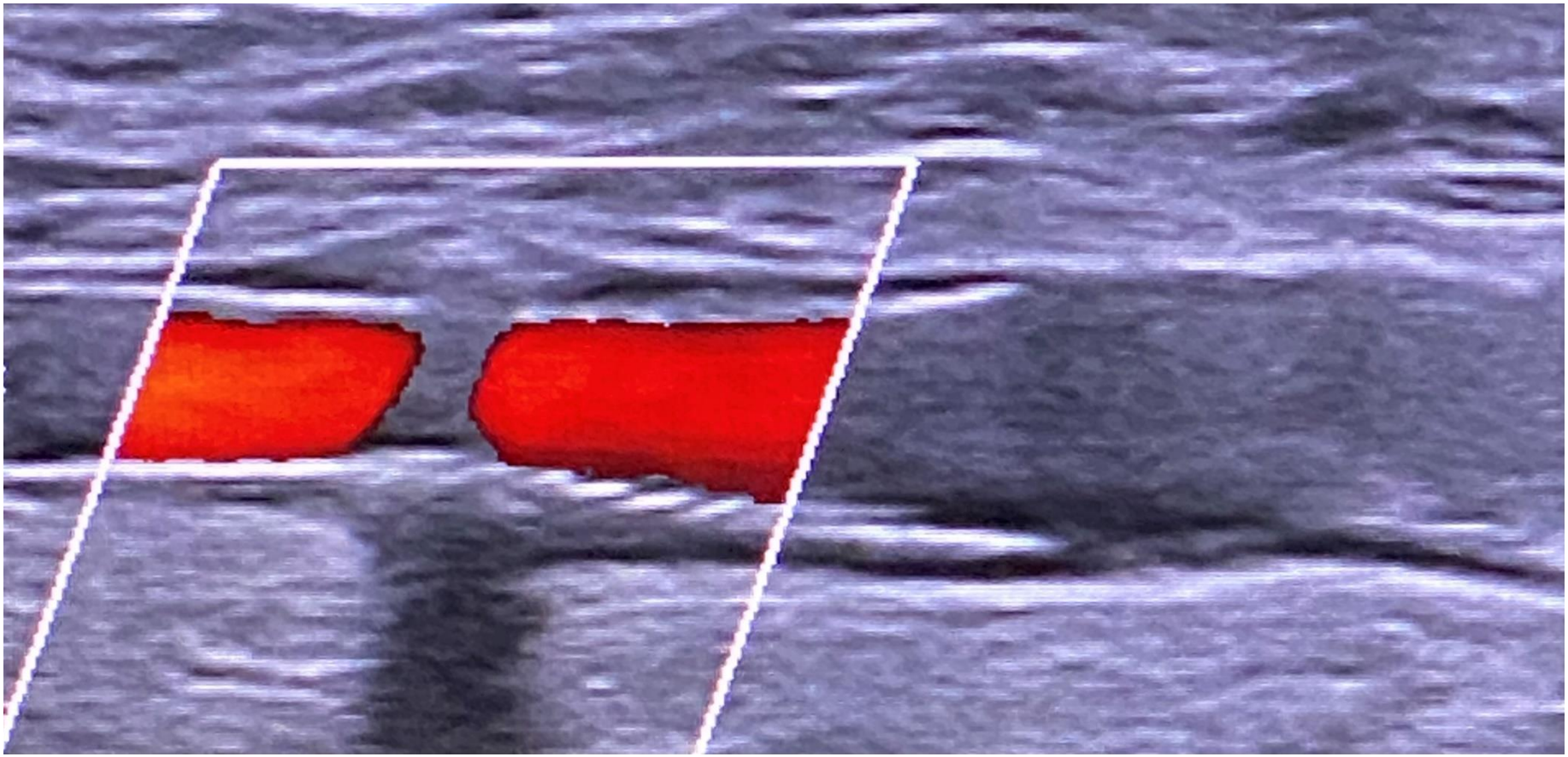

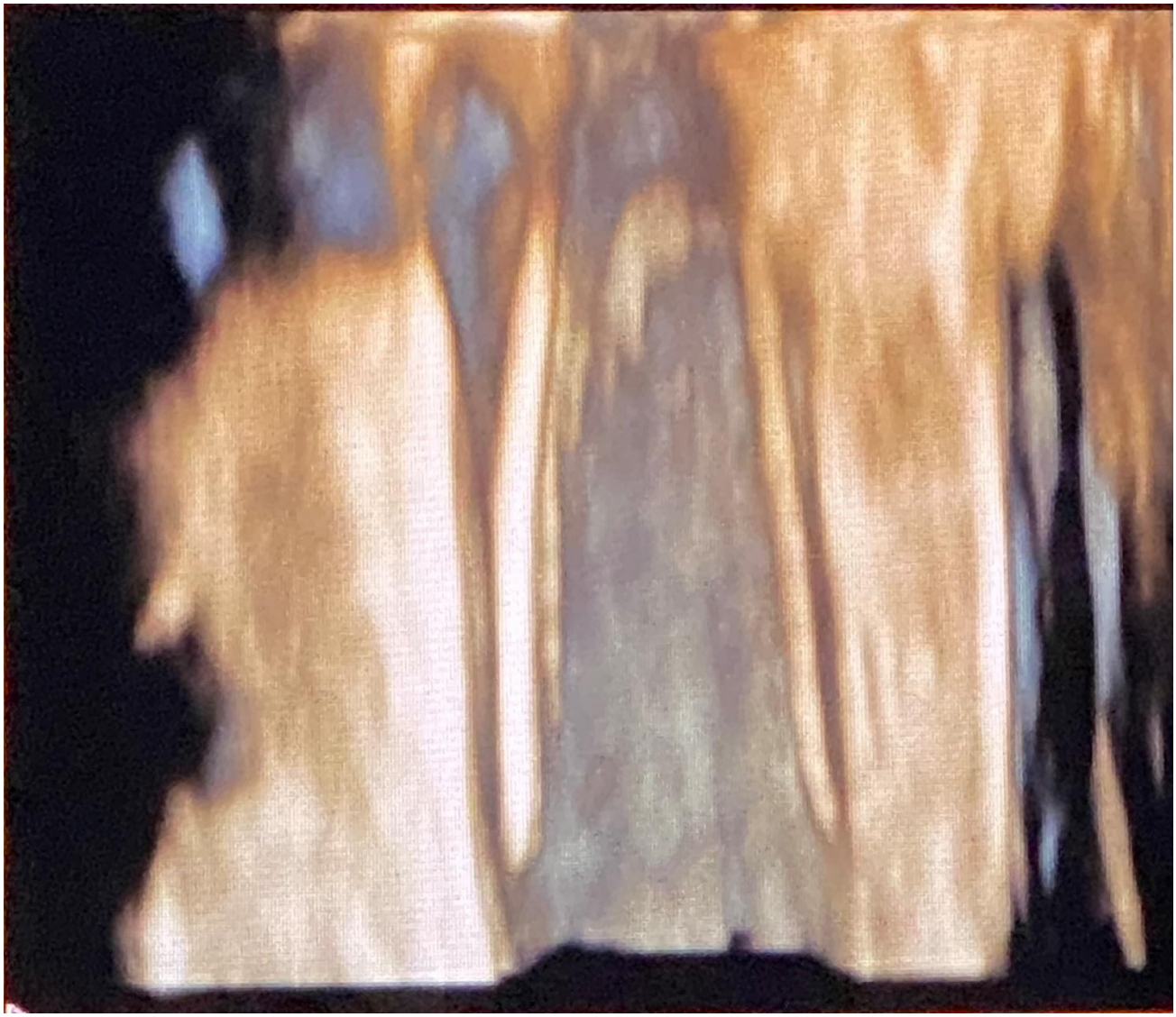

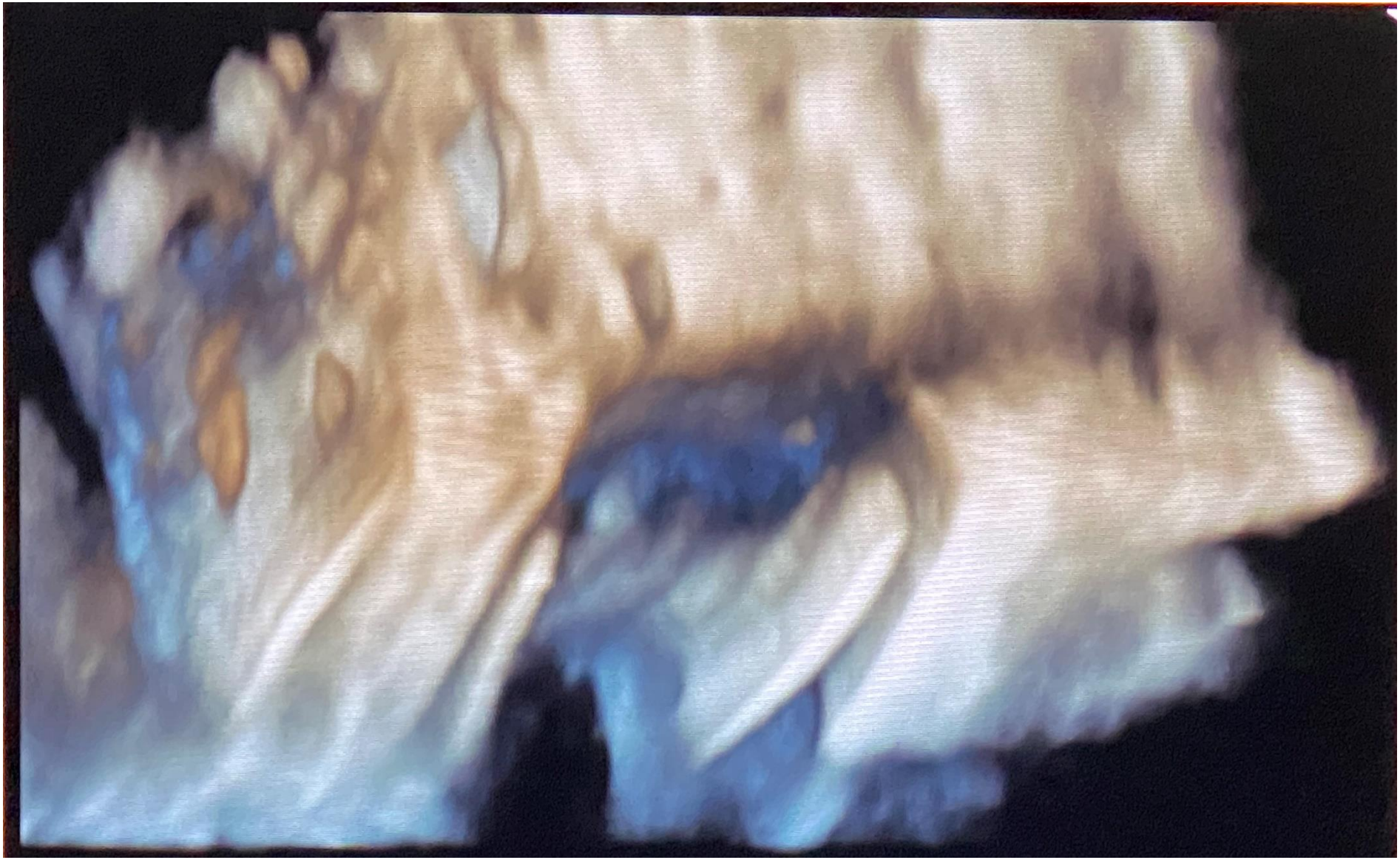

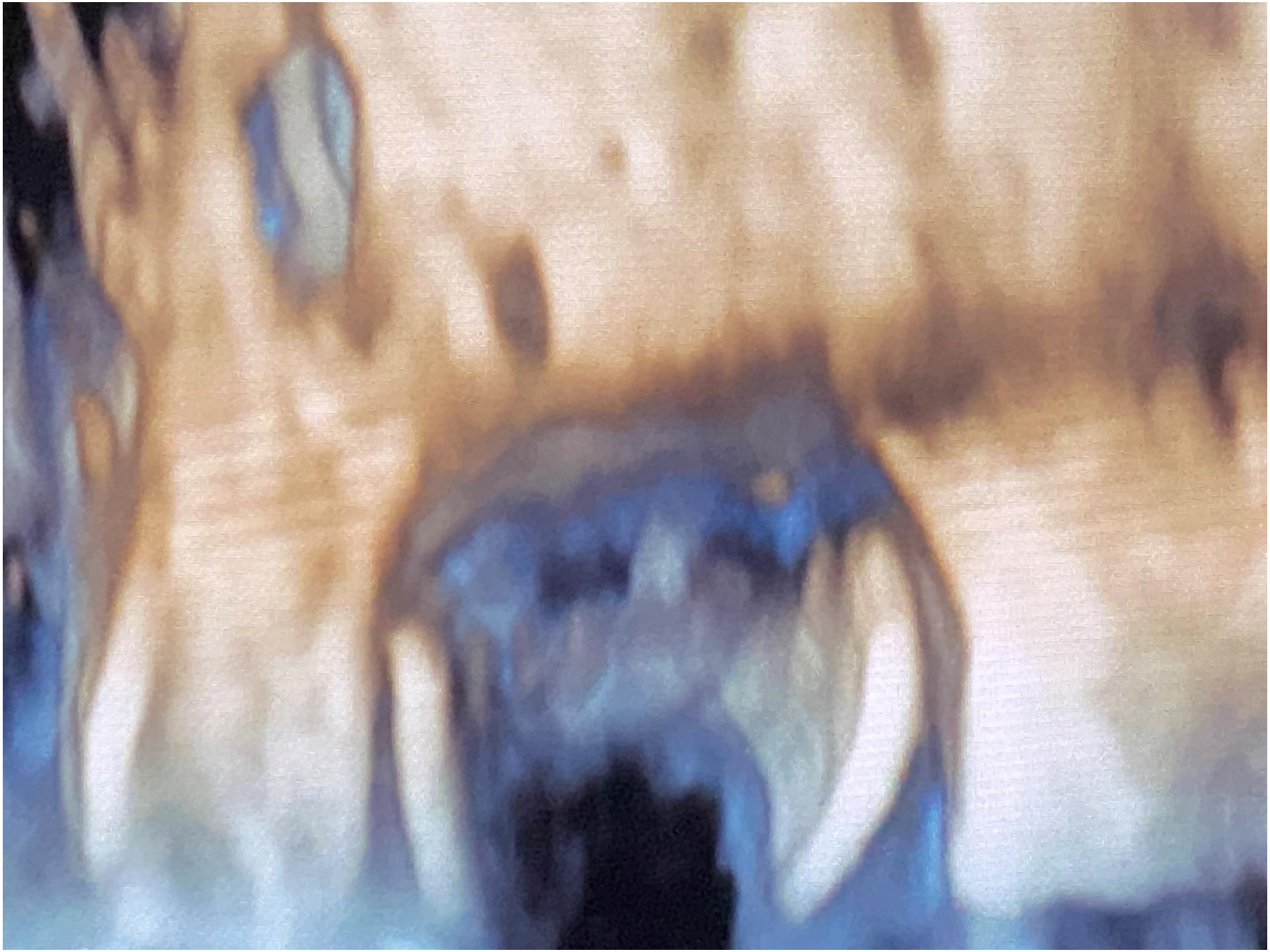

# Percutaneous Myocardial Revascularization in Late-Presenting Patients With STEMI

Journal of the American College of Cardiology



## TAKE-HOME MESSAGE

- The authors reviewed registry data for patients presenting with STEMI between 12 and 48 hours after symptom onset. Revascularization was completed within 48 hours after hospital admission in 67.6% of patients. At 30-day follow-up, the all-cause death rate was significantly lower among revascularized latecomers. In multivariate analysis, revascularization of latecomer STEMI patients was independently associated with a significant reduction in mortality during follow-up.
- Coronary revascularization of latecomer STEMI patients should be prioritized to optimize outcomes.

— Samer Ajam, MD

# Angiography After Out-of-Hospital Cardiac Arrest Without ST-Segment Elevation - TOMAHAWK

**Aug 29, 2021**



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|---|---|
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| **Summary Reviewer:** | Deepak L. Bhatt, MD, MPH, FACC |
| **Trial Sponsor:** | German Center for Cardiovascular Research |
| **Date Presented:** | 08/29/2021 |
| **Date Published:** | 08/29/2021 |
| **Date Updated:** | 08/29/2021 |
| **Original Posted Date:** | 08/29/2021 |

References

## Contribution To Literature:

The TOMAHAWK trial failed to show that early coronary angiography was beneficial to initial intensive care management among patients with out-of-hospital cardiac arrest.

## Description:

The goal of the trial was to evaluate early coronary angiography compared with initial intensive care management with delayed/selective coronary angiography among patients who suffered an out-of-hospital cardiac arrest of possible coronary origin.

## Study Design

- Randomization
- Parallel

Participants with out-of-hospital cardiac arrest of possible coronary origin were randomized to early coronary angiography (n = 265) versus initial intensive care management with delayed/selective coronary angiography (n = 265).

- Total number of enrollees: 530
- Duration of follow-up: 30 days
- Median patient age: 70 years
- Percentage female: 30.4%
- Percentage with diabetes: 29%

Inclusion criteria:

- Out-of-hospital cardiac arrest
- No ST-segment elevation on post-resuscitation electrocardiography

## Principal Findings:

The primary outcome, all-cause mortality at 30 days, was 54.0% in the early coronary angiography group compared with 46.0% in the initial intensive care management group (p = 0.06).

Secondary outcomes:

- Death or severe neurologic deficit: 64.3% in the early coronary angiography group compared with 55.6% in the initial intensive care management group

## Interpretation:

Among patients with out-of-hospital cardiac arrest of possible coronary origin, a strategy of early coronary angiography was not beneficial compared to initial intensive care management with delayed/selective coronary angiography. Early coronary angiography did not improve 30-day survival, or death or severe neurologic deficit.

# Edoxaban vs. Standard of Care and Their Effects on Clinical Outcomes in Patients Having Undergone Transcatheter Aortic Valve Implantation–Atrial Fibrillation - ENVISAGE-TAVI AF

Aug 28, 2021



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|---|---|
| **Author/Summarized by Author:** | Dharam J. Kumbhani, MD, SM, FACC |
| **Summary Reviewer:** | Kim A. Eagle, MD, MACC |
| **Trial Sponsor:** | Daiichi Sankyo |
| **Date Presented:** | 08/28/2021 |
| **Date Published:** | 08/28/2021 |
| **Date Updated:** | 08/28/2021 |
| **Original Posted Date:** | 08/28/2021 |

References

## Contribution To Literature:

The ENVISAGE-TAVI AF trial showed that edoxaban is noninferior to VKAs for efficacy but did not meet criteria for noninferiority for bleeding among patients undergoing TAVR with either incident or prevalent AF.

## Description:

The goal of the trial was to assess the efficacy and safety of edoxaban compared with vitamin K antagonists (VKAs) among patients undergoing transcatheter aortic valve replacement (TAVR) with either incident or prevalent atrial fibrillation (AF).

## Study Design

Eligible patients were randomized in an open-label 1:1 fashion to either edoxaban 60 mg daily (n = 713) or VKA with an international normalized ratio (INR) goal of 2-3 (n = 713). Specified antiplatelet therapy in either trial group was allowed at the treating physician's discretion, including dual antiplatelet therapy for up to 3 months after TAVR or single antiplatelet therapy indefinitely.

- Total screened: 1,451
- Total number of enrollees: 1,426
- Median duration of follow-up: 540 days
- Mean patient age: 82.1 years
- Percentage female: 47.5%

Inclusion criteria:

- Age ≥18 years
- Successful TAVR without unresolved periprocedural complications
- Prevalent or incident AF

Exclusion criteria:

- Coexisting conditions conferring high risk of bleeding

Other salient features/characteristics:

- Mean Society of Thoracic Surgeons risk score (predicted 30-day mortality): 4.9%
- Prior stroke: 17%
- Mean $CHA_2DS_2$-VASc score: 4.5
- Supra-annular self-expanding valve: 46%; balloon-expandable valve: 48%
- Median time within the therapeutic range in VKA arm: 68.2%

## Principal Findings:

The primary efficacy outcome, all-cause mortality, myocardial infarction, ischemic stroke, systemic thromboembolic event, valve thrombosis, or major bleeding, for edoxaban vs. VKA, was 17.3/100 person-years (PY) vs. 16.5/100 PY (hazard ratio [HR] 1.05, 95% confidence interval [CI] 0.85-1.31, p = 0.01 for noninferiority).

- Primary safety endpoint, major bleeding: 9.7/100 PY vs. 7/100 PY (HR 1.40, 95% CI 1.03-1.91, p = 0.93 for noninferiority)

Secondary outcomes for edoxaban vs. VKA:

- All-cause mortality: 7.8/100 PY vs. 9.1/100 PY
- Ischemic stroke: 2.1/100 PY vs. 2.8/100 PY
- Valve thrombosis: 0 vs. 0
- Intracranial hemorrhage: 1.5/100 PY vs. 2.1/100 PY

## Interpretation:

The results of this trial indicate that edoxaban is noninferior to VKA for efficacy but did not meet criteria for noninferiority for bleeding among patients undergoing TAVR with AF (bleeding events, primarily gastrointestinal bleeding events, were higher). There were no clinical valve thrombosis events. These results are overall similar to data with edoxaban among patients with AF but not undergoing TAVR; the higher bleeding rates are likely a reflection of the population enrolled: elderly and frail with multiple comorbidities.

In the GALILEO trial, low-dose rivaroxaban had worse outcomes compared with antiplatelet therapy among patients undergoing TAVR and who did not have an indication for oral anticoagulation (OAC). In the ATLANTIS trial, apixaban was superior to VKA in reducing valve thrombosis on 4D computed tomography among TAVR patients who had an indication for OAC, but had similar clinical outcomes. Among patients who did not have an indication for OAC, noncardiovascular mortality was higher with apixaban compared with antiplatelet therapy use.

# Empagliflozin Outcome Trial in Patients With Chronic Heart Failure and a Reduced Ejection Fraction - EMPEROR-Reduced

**Aug 27, 2021**



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|---|---|
| **Author/Summarized by Author:** | Dharam J. Kumbhani, MD, SM, FACC |
| **Summary Reviewer:** | Deepak L. Bhatt, MD, MPH, FACC |
| **Trial Sponsor:** | Boehringer Ingelheim and Eli Lilly |
| **Date Presented:** | 08/27/2021 |
| **Date Published:** | 08/27/2021 |
| **Date Updated:** | 08/27/2021 |
| **Original Posted Date:** | 08/29/2020 |

References

## Contribution To Literature:

Highlighted text has been updated as of August 27, 2021.

The EMPEROR-Reduced trial showed that empagliflozin is superior to placebo in improving HF outcomes among patients with symptomatic stable HFrEF (EF ≤40%) on excellent baseline GDMT, irrespective of diabetes status.

## Description:

The goal of the trial was to assess the safety and efficacy of empagliflozin in patients with symptomatic heart failure with reduced ejection fraction (HFrEF), irrespective of diabetes status.

## Study Design

Patients were randomized in a 1:1 fashion to either empagliflozin 10 mg (n = 1,863) or matching placebo (n = 1,867). All the patients were receiving appropriate treatments for heart failure.

- Total screened: 7,220
- Total number of enrollees: 3730
- Duration of follow-up: 16 months (median)
- Mean patient age: 67 years
- Percentage female: 24%

Inclusion criteria:

- Age ≥18 years
- Chronic HF, New York Heart Association (NYHA) functional class II/III/IV
- Left ventricular EF (LVEF) ≤40%
- HF hospitalization within 12 months
- N-terminal pro–B-type natriuretic peptide (NT-proBNP) ≥600 pg/ml if EF ≤30%; ≥1000 pg/ml if EF 31-35%; ≥2500 pg/ml if EF >35%
- If concomitant atrial fibrillation, then above thresholds were doubled)

Exclusion criteria:

- Acute coronary syndrome, stroke, or transient ischemic attack (TIA) within 90 days
- Listed for orthotopic heart transplantation, currently implanted LV assist device (LVAD)
- Cardiomyopathy based on infiltrative/accumulation diseases, muscular dystrophies, reversible causes, hypertrophic cardiomyopathy, pericardial restriction, peripartum, cardiomyopathy caused by chemotherapy within 12 months
- Severe valvular heart disease
- Acute decompensated HF
- Implantable cardioverter-defibrillator (ICD) or cardiac resynchronization therapy (CRT) within 3 months

Other salient features/characteristics:

- White 70%, Asian 18%
- North America: 11%, Europe: 36%, Asia: 13%, Latin America: 34%
- NYHA functional class II: 75%
- Mean LVEF: 27%
- Type 2 diabetes: 50%
- Estimated glomerular filtration rate (eGFR) <60: 48%
- Medications: angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker: 70%, angiotensin receptor-neprilysin inhibitor: 19%, mineralocorticoid receptor antagonist (MRA): 71%, beta-blocker: 94%
- ICD: 31%, CRT 12%

## Principal Findings:

The primary outcome, cardiovascular death or HF hospitalization, for empagliflozin vs. placebo, was 19.4% vs. 24.7% (hazard ratio [HR] 0.75, 95% confidence interval [CI] 0.65-0.86, $p < 0.001$)

- Cardiovascular death: 10% vs. 10.8% (HR 0.92, 95% CI 0.75-1.12)
- HF hospitalization: 13.2% vs. 18.3% (HR 0.69, 95% CI 0.59-0.81)

Secondary outcomes:

- Total hospitalizations: 388 vs. 553 ($p < 0.001$)
- Composite renal outcome (chronic hemodialysis, renal transplantation, profound sustained reduction in eGFR): 1.6 vs. 3.1 (HR 0.50, 95% CI 0.32-0.77, $p < 0.01$)
- All-cause mortality: 13.4% vs. 14.2% (HR 0.92, 95% CI 0.77-1.10, $p > 0.05$)
- New-onset type 2 diabetes among patients with prediabetes: 11.2% vs. 12.6% ($p > 0.05$)
- Change in hemoglobin A1c between baseline and week 52 (patients with diabetes): -0.28 vs. -0.12% ($p < 0.05$)
- Systolic blood pressure -2.4 vs. -1.7 mm Hg ($p > 0.05$)
- Confirmed hypoglycemic event: 1.4% vs. 1.5%

- Death/HF hospitalization/emergent or urgent HF visit requiring intravenous treatment or diuretic intensification/deterioration of NYHA class: 32.7% vs. 43% ($p < 0.0001$)
- Intensification of diuretics: 15.9% vs. 22.2% ($p < 0.0001$)
- Emergent or urgent HF visit requiring intravenous treatment: 6.8% vs. 9.9% ($p = 0.0004$)
- Hospitalization for HF requiring cardiac care unit/intensive care unit care: 4.8% vs. 5.7% ($p = 0.002$)

Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score (KCCQ-CSS): Benefit of empagliflozin vs. placebo was maintained across tertiles of baseline KCCQ-CSS for the primary endpoint, total HF hospitalizations and eGFR slope. In addition, benefit of empagliflozin vs. placebo for mean KCCQ-CSS was noted as early as 3 months, and noted to be sustained over 12 months.

Patients with volume overload within 4 weeks of enrollment: Primary endpoint for empagliflozin vs. placebo among patients with recent volume overload: 28.4% vs. 24.8% (p = 0.035); without volume overload: 16.0% vs. 22.2% (p = 0.0004; p for interaction = 0.34). Similarly, no difference was noted for the endpoint of total HF hospitalizations by volume overload status (p for interaction = 0.09). Intensification of diuretics was also similar between the two subgroups of patients (p for interaction = 0.88). Similarly, there was no difference in NT-proBNP, systolic blood pressure, or body weight for empagliflozin vs. placebo between patients with and without recent volume overload.

Influence of MRAs: 71% on MRAs in this trial. Composite endpoint for empagliflozin vs. placebo among MRA users: 18.6% vs. 24.4%; among nonusers: 21.2% vs. 25.8% (p for interaction = 0.83). Similarly, no interaction was observed for secondary endpoints and adverse events (including hyperkalemia) by MRA use as well.

Influence of region and race/ethnicity: Regional distribution: 36.3% Europe, 34.5% Latin America, 11.4% in North America, and 13.2% in Asia; 70.5% were White, 6.9% Black, and 18.0% Asian. Important differences were noted in baseline characteristics. Placebo arm event rate (per 100 person-years) for the primary outcome of cardiovascular death or HF hospitalization was highest in Asia (27.7) and North America (26.4) and lowest in Europe (17.5). Event rate (per 100 person-years) for the primary composite outcome of cardiovascular death or HF hospitalization in the placebo group was highest among Black patients (34.4) and lowest in White patients (18.7). The magnitude of the effect of empagliflozin on the primary composite outcome and total hospitalizations for HF was most pronounced in Asia (hazard ratios of 0.55 and 0.41, respectively); intermediate in North America (hazard ratios of 0.69 and 0.71, respectively) and Latin America (hazard ratios of 0.73 and 0.65, respectively); and least pronounced in Europe (hazard ratios of 0.94 and 0.96, respectively) (p for interaction = 0.1). The magnitude of the effect of empagliflozin on the primary composite outcome and on total hospitalizations for HF was most pronounced in Black patients (hazard ratios of 0.46 and 0.39, respectively) and Asian patients (hazard ratios of 0.57 and 0.45, respectively) and least pronounced in White patients (hazard ratios of 0.88 and 0.90, respectively) (p for interaction = 0.008).

Pooled analysis of EMPEROR-Reduced and EMPEROR-Preserved on renal outcomes (profound and sustained decreases in eGFR or renal replacement therapy), total n = 9,718: 2.8% vs. 3.5% for empagliflozin vs. placebo, with significant heterogeneity between both trials (p = 0.016 for

Interpretation:

The results of this trial indicate that empagliflozin is superior to placebo in improving HF outcomes among patients with symptomatic stable HFrEF (EF ≤40%) on excellent baseline guideline-directed medical therapy (GDMT), irrespective of diabetes status. Benefit is primarily driven by a reduction in HF hospitalizations, not mortality. There was an early and sustained benefit on KCCQ-CSS. There was also a benefit in renal outcomes. The use of MRAs did not influence the effect of empagliflozin on clinical outcomes. Some regional and racial differences in efficacy were noted. This is a very important trial, and mirrors similar findings from the DAPA-HF trial for dapagliflozin. Even patients with severe LV dysfunction appeared to benefit. Of note, the DAPA-HF trial was larger, and did show a benefit in cardiovascular and all-cause mortality with dapagliflozin use.

Even though the sodium-glucose cotransporter 2 (SGLT2) inhibitors were introduced as type 2 diabetes management drugs, the results of the EMPA-REG OUTCOME trial and others indicated a clear benefit in HF management. This trial enrolled a dedicated HF population, and conclusively shows a benefit in this patient population, irrespective of diabetes status. These drugs will likely have a prominent role in future HF management guidelines. The mechanism of benefit is unclear. The subgroup analysis of this trial suggests that this benefit may not necessarily be driven by a diuretic effect alone (as noted among patients with and without recent volume overload), but further studies are needed to clarify this and other potential mechanisms of benefit. The pooled analysis of EMPEROR-Reduced and EMPEROR-Preserved suggests that the renal benefit is primarily among patients with HFrEF, and eGFR slope analysis may not be predictive of renal outcomes among patients with HF.

Written by  Eugene Braunwald MD

Heart failure with preserved ejection fraction (HFpEF), described near the end of the 20th century, has rapidly risen in incidence and prevalence and has become responsible for at least one half of all patients with heart failure in North America and other industrially-developed regions. It is now a relatively common cause of hospitalization and death. In a large majority of patients with HFpEF the specific cause is unknown but it usually occurs in the elderly and is frequently accompanied by one or more co-morbidities including hypertension, Type 2 diabetes mellitus, obesity, and chronic kidney disease. The management of HFpEF has been difficult, and for many years was limited to the treatment of the comorbidities, e.g. reduction of elevated blood pressure, intensification of diabetes control, weight loss, as well as diuretics and a low sodium diet. These measures were inadequate and the search for a definitive treatment of HFpEF has become of critical importance.

During the last few years, a number of tantalizing studies have suggested that sodium-glucose cotransporter 2 (SGLT2) inhibitors could be effective in this condition, but none of them were definitive. The EMPEROR-Preserved trial is the first large, placebo-controlled double-blinded trial that tested explicitly the efficacy of empagliflozin, a drug in this class. Anker et al showed that empagliflozin significantly reduced the primary prespecified endpoint – cardiovascular death or heart failure hospitalization. (1) This result was triggered by a marked reduction of heart failure hospitalization; cardiovascular death, a trailing indicator, decreased numerically, but not statistically. Given the marked reduction in heart failure hospitalization, it is expected that reduction of cardiovascular death would also become significant if patients were followed for a longer period.

In a companion paper describing the results of EMPEROR-Preserved, published in *Circulation*, Packer et al reported that empagliflozin also reduced the need for positive inotropic therapy, vasopressor drugs, as well as intensive care. In addition, outpatient worsening of heart failure events such as the need for unplanned urgent care visits and intensification of administration of diuretics were also reduced. (2) EMPEROR-Preserved appeared to be equally effective in patients with ejection fractions between 40 and 60% and to decline in patients with fractions exceeding 60%. The precise mechanism(s) of action of this SGLT2 inhibitor in HFpEF remain to be defined.

The favorable responses to empagliflozin in EMPEROR-Preserved are similar to those reported last year by Packer et al in the EMPEROR-Reduced trial in patients with heart failure and reduced ejection fraction (HFrEF). (3)

EMPEROR-Preserved is truly a landmark trial. The Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure trial (DELIVER), a similar placebo-controlled trial of patients with HFpEF studying a different SGLT2 inhibitor, will be reported shortly. (4) If it confirms the results of EMPEROR-Preserved (which I consider to be likely), the management of a huge population of patients will be substantially improved.