European Society of Cardiology Congress 2018

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A total of 32,859 health care professionals gathered in Munich to hear breaking news on cardiovascular medicine presented at the European Society of Cardiology (ESC) Congress 2018, held August 25–29. Notable among the key sessions reviewed below are several major negative trials with findings that are important for clinical practice. Sessions on large-scale aspirin and anticoagulation trials, weight loss, fish oil, gout, endocarditis and cardiomyopathy are featured here.

The Aspirin to Reduce Risk of Initial Vascular Events (ARRIVE) Study

- J. Michael Gaziano, MD, Brigham and Women's Hospital, Boston, MA

In the ARRIVE (Aspirin to Reduce Risk of Initial Vascular Events) study, low-dose aspirin's effect on cardiovascular events was no different from that of placebo among subjects at moderate cardiovascular risk.

In acute treatment and in the secondary prevention of coronary and cerebrovascular disease, aspirin's role is firmly established. Its use in primary prevention, however, remains controversial. Many fewer primary prevention trials have been conducted, and most of those, Dr. Gaziano said, have included subjects at low cardiovascular risk.

ARRIVE was conducted in seven countries (Germany, Italy, Ireland, Poland, Spain, the United Kingdom, and the U.S.) among men ≥ 55 years of age with two or more cardiovascular risk factors and women ≥ 60 years of age with three or more cardiovascular risk factors. It included 12,546 subjects (mean age, 64 years, ~30% female) at moderate estimated risk for a first acute cardiovascular event (defined as 20–30% 10-year cardiovascular disease risk, 10–20% coronary heart disease risk). Subjects were randomized in a double-blind fashion to receive 100 mg of enteric-coated aspirin or placebo. The primary efficacy endpoint was time to first occurrence of a composite of cardiovascular death, myocardial infarction, unstable angina, stroke and transient ischemic attack.

Observed cardiovascular event rates were considerably lower than investigators anticipated. While they had based their estimates on a 10-year rate of > 17%, the observed rates corresponded to a population with a 10-year event rate of less than 9%. In the intention-to-treat population, after a median follow-up of 60 months, the primary outcome rate was 4.29% in the aspirin group versus 4.48% in the placebo group (hazard ratio [HR], 0.96; 95% confidence interval [CI], 0.81–1.13; $P = 0.60$). In the per-protocol analysis, the primary endpoint occurred in 3.40% of participants in the aspirin group versus 4.19% in the placebo group (HR, 0.81; 95% CI, 0.64–1.02; $P = 0.0756$).

Also in the per-protocol analysis, aspirin reduced the risk of total and nonfatal myocardial infarction (HR, 0.53; 95% CI, 0.36–0.79; $P=0.0014$; and HR, 0.55; 95% CI, 0.36–0.84; $P = 0.0056$, respectively). The relative risk reduction of myocardial infarction in the aspirin group was 82.1%, and 54.3% in the 50–59 and 59–69 age groups, respectively. Dr. Gaziano commented, "Participants who took aspirin tended to have fewer heart attacks, particularly those aged 50–59 years, but there was no effect on stroke."

Drug-related adverse events were more frequent with aspirin (16.75%) than placebo (13.54%) ($P < 0.0001$), with indigestion, nosebleeds, gastro-esophageal reflux disease, and upper abdominal pain being the most common. Gastrointestinal bleeding, mostly mild, was reported at a higher rate in the aspirin group (0.97% versus 0.46%, respectively; $P = 0.0007$). Fatal bleeding rates were similar, as were rates of death attributed to adverse events (1.24% for placebo; 1.26% for aspirin).

"The decision on whether to use aspirin for protection against cardiovascular disease should be made in consultation with a doctor, considering all the potential risks and benefits," Dr. Gaziano concluded. He noted further that effects on specific outcomes in ARRIVE, such as first heart attack, were generally consistent with other studies.

ASCEND (A Study of Cardiovascular Events iN Diabetes): Randomized Placebo-Controlled Trial of Aspirin 100 mg Daily in 15,480 Patients With Diabetes and No Baseline Cardiovascular Disease

- Jane Armitage, MD, Nuffield Department of Population Health, University of Oxford, U.K.

In patients with diabetes, benefits in absolute vascular events with low-dose aspirin were largely counterbalanced by increases in major bleeding. No subgroup, said Dr. Armitage, the lead investigator in the ASCEND (A Study of Cardiovascular Events iN Diabetes) trial, displayed benefits clearly outweighing the risks.

The value of low-dose aspirin for secondary prevention of cardiovascular events is well established. A primary prevention value for routine use in the higher-risk group of patients with diabetes remains unproven, however. Dr. Armitage noted that post-hoc analyses of selected randomized trials of aspirin have suggested that there is a lowered cancer risk, especially reduced gastrointestinal cancer risk. European guidelines, she observed, have been more cautious about recommending routine use of antiplatelet therapy than U.S. guidelines.

ASCEND investigators enrolled patients with any diabetes and no baseline cardiovascular disease who were 40 years of age and older. Mean age in the 15,480 subject U.K. population was 63 years (63% male). Patients were randomly assigned to 100 mg daily of aspirin or placebo. Patients in a third trial arm reported separately were randomized to omega-3 fatty acid supplements or placebo. The primary efficacy endpoint was the first serious vascular event (defined as non-fatal myocardial

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infarction, non-hemorrhagic stroke or transient ischemic attack or cardiovascular death excluding any intracranial hemorrhage).

Serious vascular event rates after a mean follow-up of 7.4 years were significantly lower among patients receiving aspirin (8.5% versus 9.6%; rate ratio, 0.88 [0.79–0.97]; $P = 0.01$). Adding in revascularization, the aspirin benefit persisted (10.8% for aspirin, 12.1% for placebo; [0.80–0.97]; P=0.01). Aspirin had no effect on any cancer (11.6% with aspirin; 11.5% with placebo) or on gastrointestinal cancer (2.0% for both), specifically.

In the aspirin group, bleeding risk was increased significantly, with a first major bleed occurring in 4.1% of participants allocated to aspirin and in 3.2% of participants receiving placebo. The increase (9 of every 1,000 participants) represented a 29% (95% CI, 9–52%; P=0.003) proportional increase in the risk of major bleeding. Dr. Armitage underscored that there was no group with benefits clearly outweighing bleeding risks, including the participants at the highest vascular risk of more than 2% annually.

"Most participants were taking proven safe treatments, such as statins and blood pressure–reducing medicines which will be protecting them from heart attacks and strokes. For them, we have shown that there is no added benefit of taking aspirin," Dr. Armitage concluded.

ASCEND: A Randomized Trial of Omega-3 Fatty Acids (Fish Oil) Versus Placebo For Primary Cardiovascular Prevention in 15,480 Patients With Diabetes

• Jane Armitage, MD, and Louise Bowman, MD, Nuffield Department of Population Health, University of Oxford, U.K.

The largest and longest duration placebo-controlled, randomized trial of omega-3 fatty acid supplementation showed no primary prevention effect on the primary outcome of serious vascular events in patients with diabetes. The trial analysis, ASCEND (A Study of Cardiovascular Events iN Diabetes), said Dr. Bowman, also revealed no effects of fish oil on cancer, total or cause-specific mortality.

The estimated global market for omega-3 products was about $31 billion in 2015. Their wide use was reflected, as well, in a large U.K. prospective study showing 31% of adults taking fish oils, and in an estimated 19 million taking them in the U.S. Beneficial effects are claimed for the heart and brain, on weight, vision, inflammation, skin, pregnancy, liver fat, depression, childhood behavior, mental decline, allergies, and bones. Dr. Bowman pointed out that higher fish intake is associated with lower cardiovascular risk. She noted, "Diabetes increases cardiovascular risk, so a safe dietary supplement that reduced risk would be of value." Recommendations for fish oil supplementation are based on secondary prevention trials conducted in the 1980s and 1990s. Recent meta-analyses of randomized trials, however, have not shown benefits of omega-3 fatty acids in primary or secondary prevention.

Patients enrolled in ASCEND met the criteria of having any diabetes, no baseline cardiovascular disease, and were 40 years of age and older (mean age, 63 years; 63% male). Mean diabetes duration was seven years and most (94%) had type-2 diabetes. Patients were randomly assigned to omega-3 fatty acids (1 g capsule/day) or placebo (olive oil). The primary efficacy endpoint was the first serious vascular event (defined as non-fatal myocardial infarction, non-hemorrhagic stroke or transient ischemic attack or cardiovascular death excluding any intracranial hemorrhage). Adherence to treatment was 77%.

The primary endpoint rates were 8.9% in the fish-oil arm and 9.2% in the placebo arm (rate ratio, 0.97 [0.87–1.08]; $P = 0.55$) after a mean follow-up of 7.4 years. When revascularization rates were added to serious vascular events, the outcomes were again similar, at 11.4% for fish oil and 11.5% for placebo (rate ratio, 1.00 [0.91–1.09]; $P = 0.92$). Analysis of subgroups based on sex, body mass index and five-year vascular risk revealed no differences, as did analysis of cause-specific mortality. Similarly, fish oil supplementation had no effect on total cancer rates (11.6% with fish oil; 11.5% with placebo; rate ratio, 1.00 [0.91–1.10]) or site-specific rates. No safety concerns were reported.

Dr. Bowman noted that findings of ongoing trials of omega-3 fatty acids using much higher doses (2–4 g) will be of interest. She commented: "It's hard to put much emphasis now on using fish oil supplements even in secondary prevention when you add these data in with all the other data from the last few years showing no benefit." Dr. Bowman concluded, "Guideline recommendations should be reconsidered."

Cardiovascular Safety and Efficacy of Lorcaserin in Overweight and Obese Patients: Primary Results From the CAMELLIA-TIMI 61 Trial

• Erin Bohula, MD, Brigham and Women's Hospital, Boston, MA

Lorcaserin administered on top of a background of lifestyle interventions led to sustained weight loss and modest improvements in cardiovascular risk factors in overweight and obese patients with high cardiovascular risk. Results from the CAMELLIA-TIMI 61 trial also showed that risk of major adverse cardiovascular events (MACE) was not increased in patients receiving lorcaserin.

Lorcaserin, an appetite suppressant, was approved in the U.S. in 2012 for weight loss in overweight adults with a body mass index (BMI) of 30 kg/m^2 or greater, or with a BMI of 27 kg/m^2 or greater and at least one weight-related health condition such as high blood pressure, type-2 diabetes, or high cholesterol. It is a selective agonist of the serotonin (5HT)-2C receptor. With several weight loss agents having been shown to precipitate cardiovascular or psychiatric side effects, Dr. Bohula noted, uptake has been slow, despite the fact that guidelines recommend them as adjuncts to lifestyle modification. Also, none have yet convincingly demonstrated cardiovascular safety in a rigorous clinical outcomes study. The FDA, she added, mandates that cardiovascular safety be demonstrated for all weight loss agents. The CAMELLIA-TIMI 61 trial, which examined the safety and efficacy of lorcaserin with regard to MACE and progression to diabetes, was conducted in response to the FDA's postmarketing requirement.

CAMELLIA-TIMI 61 entry criterion included a BMI of at least 27 kg/m^2 and either established cardiovascular disease (with or without diabetes) or diabetes and at least one other cardiovas-

cular risk factor. Investigators enrolled 12,000 adults (median age, 64 years; 64% male) at 473 centers in eight countries, and randomized them 1:1 (double-blind) to lorcaserin 10 mg twice daily or placebo. All received advice on diet and exercise. The primary safety endpoint was non-inferiority for MACE; the efficacy endpoint was MACE superiority.

Serious adverse events occurred in 31% of patients receiving lorcaserin and in 32% of patients receiving placebo. No new adverse events or increases in malignancy rates were observed. A non-significant increase in asymptomatic valvular heart disease was reported in the lorcaserin group (1.8% versus 1.3%).

Patients receiving lorcaserin, after a median follow-up of 3.3 years, lost 4.2 kg and those receiving placebo lost 1.4 kg (net difference, -2.8 kg, $P < 0.001$). At one year, weight loss of 5% or more was reported in 39% of patients receiving lorcaserin and in 17% of placebo patients (OR, 3.01 [2.74, 3.30]; $P < 0.001$). Weight loss of 10% or more at one year was reported in 15% and 5% of lorcaserin and placebo-group patients, respectively (OR, 3.40 [2.92, 3.95]). MACE (cardiovascular death, myocardial infarction or stroke) per year was similar for both groups, at 2.0% for lorcaserin and 2.1% for placebo (non-inferiority $P < 0.001$). The superiority efficacy outcome of combined cardiovascular death, myocardial infarction, stroke, heart failure, hospitalization for unstable angina or coronary revascularization was not met (12.8% with lorcaserin, 13.3% with placebo; $P = 0.55$).

Among secondary endpoints compared to placebo, lorcaserin showed less conversion to diabetes among those with prediabetes at baseline and small improvements in triglycerides, serum glucose, heart rate, and blood pressure.

Dr. Bohula observed that CAMELLIA TIMI-61 results support lorcaserin's role as an adjunct to lifestyle modification for long-term weight management even in patients at high cardiovascular risk. She concluded, "The CAMELLIA-TIMI 61 study is notable as it provides the first demonstration of cardiovascular safety of any weight loss agent in a dedicated cardiovascular outcomes trial."

Febuxostat for Cerebral and CaRdiorenovascular Events PrEvEntion StuDy (FREED)

- Sunao Kojima, MD, Kawasaki Medical School, Okayama, Japan

FREED (Febuxostat for Cerebral and CaRdiorenovascular Events PrEvEntion StuDy) results showed that febuxostat significantly reduced the levels and effects of serum uric acid in patients 65 years of age and older with hyperuricemia (gout) as compared with allopurinol, the standard treatment, with lifestyle modification. Febuxostat is a non-purine-selective inhibitor of xanthine oxidase, which is needed for uric acid production. It is a more potent reducer of uric acid levels than allopurinol, Dr. Kojima said.

Hyperuricemia may lead to the development and progression of chronic kidney disease and renal failure, along with coronary artery disease, hypertension, stroke, and death. Recurrence of urate deposition-related disease, Dr. Kojima said, can be prevented with the use of anti-hyperuricemic drugs. In gout patients with cardiovascular disease in the CARES (Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities) trial, all-cause mortality and cardiovascular mortality were higher with febuxostat than with allopurinol. With the cause of the higher event rates remaining unclear, the FREED study was conducted to further compare events with febuxostat and conventional treatment in this population.

FREED, a multicenter Japanese, prospective, randomized, open-label, blinded endpoint study, included 1,070 elderly patients (mean age, 69 years) with hyperuricemia who were at risk for cardiorenovascular disease. They were randomized to 36 months of febuxostat or conventional therapy. In both groups, the dose of febuxostat or allopurinol was adjusted to avoid a serum uric acid level of less than 2 mg/dL. In the non-febuxostat group, the use of allopurinol 100 mg was considered if serum uric acid was elevated. Hyperuricemia was defined by serum uric acid levels > 7.0 to ≤ 9.0 mg/dL. All participants had one or more cerebral, cardiovascular or renal disease risk factors, which included active hypertension, type-2 diabetes, renal disorder (eGFR ≥ 30 to < 60 mL/min/1.73 m^2) or a history of cerebrocardiovascular disease occurring > 3 months prior to enrollment. The primary composite endpoint was comprised of cerebral or cardiorenal vascular disease death, new or recurring cerebrovascular disease, new or recurring non-fatal coronary artery disease, cardiac failure requiring hospitalization, arteriosclerotic disease requiring treatment, renal impairment, new atrial fibrillation, or death due to other causes.

The average dose of febuxostat at the end of the study was 29 mg daily. In the standard therapy arm, 27% of patients received allopurinol 100 mg. Average serum uric acid levels reached 4.4 mg/dL in the febuxostat group and 6.7 mg/dL in the group not receiving febuxostat.

The primary outcome was significantly reduced in the febuxostat group at 23% versus 29% (HR, 0.75; 95% CI, 0.59–0.95; P=0.017). Renal impairment, the most frequent event, occurred at rates of 16.2% and 20.5% in the febuxostat and standard treatment arms, respectively ($P = 0.041$). Analysis also showed direct correlations between rising serum uric acid levels and risk for primary outcome events. A composite of hard endpoints (death due to any cause, cerebrovascular disease, or non-fatal coronary artery disease) was not significantly reduced with febuxostat, however (HR, 0.861; $P = 0.6$).

At 24.6% and 25% in the febuxostat and non-febuxostat arms, respectively, adverse event rates were similar between groups.

"Uric acid level lowering by febuxostat provides clinical benefit for prevention of cerebral, cardiovascular, and renal events in elderly patients with hyperuricemia," Dr. Kojima concluded.

Speaking about FREED results at an ESC press briefing, Kunihiko Matsui, MD, of Kumamoto University, Japan, stated: "Febuxostat has greater renoprotective effect, however, cardiovascular protection may not be expected compared with renal protection."

Partial Oral Treatment of Left-Sided Infectious Endocarditis: The POET Trial

- Henning Bundgaard, MD

In POET (Partial Oral Treatment of Endocarditis Trial), shifting to oral antibiotic treatment was non-inferior to con-

tinued intravenous antibiotic treatment in stabilized patients with left-sided endocarditis. The finding is important, said lead investigator Henning Bundgaard of the Copenhagen University Hospital in Denmark. "It is a huge challenge for patients to stay in hospital for up to six weeks receiving intravenous treatment."

While guidelines recommend up to six weeks of intravenous antibiotics for left-sided infectious endocarditis, Dr. Bundgaard said, 15–30% of patients die in the hospital, and up to half of patients require surgery to remove infected tissue and repair or replace infected heart valves. Events occur, however, mostly in the early phase, and the long hospital stays are associated with increased complications. In other diseases, Dr. Bundgaard noted, reducing them has improved outcomes. "Oral antibiotics could be a safe way to achieve this."

The randomized, unblinded, non-inferiority POET trial included data from all Danish heart centers. It tested the feasibility and safety of a strategy of reduced intravenous antibiotic duration through shifting to oral administration. POET investigators enrolled 400 clinically stable patients (mean age, ~67 years; ~23% female) with endocarditis. After at least 10 days of intravenous antibiotics, they were randomly assigned to continued intravenous antibiotics or to oral antibiotics. Patients assigned to oral treatment were given the option of outpatient treatment. Investigators assessed the combined endpoint of all-cause death, unplanned cardiac surgery, embolic events, and reinfection at six months after completion of antibiotic treatment.

Left-sided endocarditis infecting agents included Streptococcus spp, Enterococcus faecalis, Staphylococcus aureus, or coagulase-negative staphylococci. After the mandatory intravenous treatment period, intravenous or oral antibiotics were taken for a median of 18 days. During the follow-up period, the primary endpoint rates were reported at 12.1% in the intravenous treatment group and 9.% in the oral treatment group (odds ratio, 0.72 [95% CI, 0.31–1.36; $P = 0.34$).

Side effect rates were similar at 6% for intravenous treatment and 5% for oral treatment.

Efficacy and safety among patients shifted to oral anti biotic treatment were non-inferior to that in patients receiving continued intravenous antibiotics, Dr. Bundgaard concluded.

GLOBAL LEADERS: Ticagrelor Monotherapy Beyond One Month Versus Standard Dual Antiplatelet Therapy Following Drug-Eluting Stent Implantation: A Randomised Multicenter Superiority Trial

- Patrick W. Serruys MD, PhD, Erasmus University, Rotterdam, The Netherlands

Patients receiving ticagrelor monotherapy beyond one month versus standard dual antiplatelet therapy following drug-eluting stent implantation, failed to demonstrate statistically superior two-year all-cause mortality and non–Q-wave myocardial infarction rates in the GLOBAL LEADERS trial. Standard therapy, Dr. Serruys said, consisted of dual antiplatelet therapy (aspirin plus a P2Y12 inhibitor) for 12 months and aspirin monotherapy for 12 months.

Dual antiplatelet therapy for one month after percutaneous coronary interventions (PCIs) offers protection during the period of high stent thrombosis risk, Dr. Serruys said. Ticagrelor, a potent and consistent antiplatelet agent, he added, may be a better foundation as a monotherapy for long-term antiplatelet therapy compared to aspirin in at-risk patients because the strategy may obviate the potentially higher bleeding risks of adding even low-dose aspirin.

GLOBAL LEADERS entry criteria allowed patients scheduled to undergo PCI and to receive a drug-eluting stent for stable coronary artery disease or acute coronary syndromes. Investigators enrolled 15,991 patients (mean age, ~64.6 years; ~23% female) from 130 centers in 18 countries in Europe, North and South America, and Asia Pacific. All received the direct thrombin inhibitor bivalirudin, and then were randomly assigned in a 1:1 ratio to the experimental arm (one month of dual antiplatelet therapy with aspirin plus the P2Y12 inhibitor ticagrelor, followed by ticagrelor monotherapy for 23 months) or the standard treatment arm (12 months of dual antiplatelet therapy with aspirin plus a P2Y12 inhibitor [clopidogrel for patients with stable coronary artery disease, ticagrelor for those with acute coronary syndromes], followed by aspirin monotherapy for 12 months). The primary endpoint was all-cause death or nonfatal myocardial infarction at two years.

The primary endpoint rates at two years were 3.8% in the monotherapy group and 4.% in the standard treatment group (rate ratio, 0.87; 95% CI, 0.75–1.01, $P = 0.073$). The all-cause mortality rate was 2.8% in the monotherapy group and 3.2% in the standard treatment group (rate ratio, 0.88; 95% CI, 0.74–1.06; $P = 0.186$). The incidence of nonfatal myocardial infarction was 1.0% versus 1.3%, respectively (rate ratio, 0.80; 95% CI, 0.60–1.07; $P = 0.142$). Rates of moderate or severe bleeding were also similar between groups at 2.0% for monotherapy versus 2.1% for standard treatment (rate ratio, 0.97; 95% CI, 0.78–1.20; $P = 0.766$).

For the secondary composite endpoint of all-cause mortality, stroke or new Q-wave MI, rates were 4.54% and 5.21% for the experimental and standard arms, respectively (rate ratio, 0.87; 95% CI, 0.76–1.00; $P = 0.056$).

"The GLOBAL LEADERS trial," Dr. Serruys concluded, "failed to demonstrate statistically ($P = 0.073$) the superiority of an antiplatelet regimen consisting of one month of ticagrelor in combination with low-dose aspirin followed by 23 months of ticagrelor alone in reducing the two-year rate of all-cause mortality and nonfatal new Q-wave MI when compared with the reference treatment."

Adherence to assigned therapy at longer-term follow-up, Dr. Serruys pointed out, was higher in the reference arm at 92% and 93% at 18 and 24 months, respectively, versus 79% and 78% in the experimental arm. "Further per-protocol analysis will be performed to adjust for the difference in treatment adherence between the reference arm and the experimental arm," Dr. Serruys said. The main cause of ticagrelor discontinuation was dyspnea in 26% (the dyspnea discontinuation rate with aspirin was 3%).

Efficacy and Safety of Tafamidis in Transthyretin Amyloid Cardiomyopathy: Results of the ATTR-ACT Trial

• Claudio Rapezzi, MD, University of Bologna, Italy

In Transthyretin Amyloid Cardiomyopathy Clinical Trial (ATTR-ACT) findings, patients with transthyretin amyloid cardiomyopathy receiving tafamidis as compared with placebo had significantly reduced all-cause mortality and cardiovascular-related hospitalizations. Tafamidis has orphan- drug designation from the European Medicines Agency (EMA) and fast-track designation from the FDA.

Cardiomyopathy caused by transthyretin amyloidosis (ATTR-CM), a life-threatening disease, is characterized by accumulation of amyloid fibrils composed of misfolded transthyretin protein in the heart, leading to restrictive cardiomyopathy and progressive heart failure. The underlying cause, Dr. Rapezzi said in an ESC press briefing, is pathogenic mutations in transthyretin protein (ATTRm), or by deposition of wild-type protein (ATTRwt). Treatments for ATTR-CM have been limited to supportive care, and median survival after diagnosis in untreated patients is ~2.5 years for ATTRm and 3.6 years for ATTRwt. There are no guideline-recommended treatments.

Tafamidis, a novel non-NSAID benzoxazole derivative, binds to both variant and wild-type transthyretin and inhibits formation of transthyretin amyloid. ATTR-ACT assessed the efficacy, safety, and tolerability of an oral dose of tafamidis meglumine 80 mg or 20 mg soft-gel capsules (once daily) in comparison with placebo, in addition to standard of care, for 30 months in patients with hereditary or wild-type transthyretin amyloid cardiomyopathy. ATTR-ACT investigators enrolled 441 patients (mean age, ~74.3 years; ~90% male) at 48 sites in 13 countries. They were randomized in a 2:1:2 ratio to either tafamidis 80 mg, tafamidis 20 mg, or placebo. The primary endpoint was the hierarchical combination of all-cause death and cardiovascular-related hospitalizations from baseline to 30 months. The two tafamidis groups were combined and compared with the placebo group.

Compared with placebo, tafamidis significantly reduced death and cardiovascular-related hospitalization ($P = 0.0006$). The mortality rate was 29.5% in the tafamidis group and 42.9% in the placebo group, a 33% reduction. For this analysis, Dr. Rapezzi noted, patients undergoing heart transplant or receiving cardiac assist devices were counted as mortalities. Cardiovascular-related hospitalization rates were 52.3% and 60.5% in the tafamidis and placebo groups, respectively ($P < 0.0001$), a 32% reduction.

Patients receiving tafamidis had smaller declines in the secondary endpoints of six-minute walk distance and quality of life (as assessed by KCCQ-OS) than with placebo during follow-up.

Treatment-related discontinuations were fewer with tafadimis than with placebo, and its safety profile and that of placebo were comparable, with both being well tolerated.

Dr. Rapezzi concluded, "Tafamidis significantly reduced all-cause mortality and cardiovascular-related hospitalizations compared with placebo. These findings provide strong evidence that tafamidis is an effective therapy for patients with ATTR-CM." ■