LATE-BREAKING TRIAL HIGHLIGHTS FROM THE 2018 ESC CONGRESS

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Keywords: *anticoagulation; cardiac amyloidosis; rivaroxaban; tafamidis*

A number of interesting studies were presented in this very large international congress, which hosted more than 33 000 delegates from five continents.

HEART FAILURE

Low-dose rivaroxaban does not improve outcomes in patients with HFREF in sinus rhythm

The COMMANDER HF trial[1] addressed the issue of anticoagulation in patients with chronic heart failure with reduced ejection fraction (<40%) and in sinus rhythm. It is well established that heart failure is associated with a prothrombotic state through inflammation and endothelial dysfunction, and it is a key component of the CHA_2DS_2-VASc score in patients with atrial fibrillation in order to define the risk of stroke and embolic events. However, the benefit of anticoagulation in patients with heart failure and in sinus rhythm is not well established and several trials have failed to demonstrate any benefit with warfarin, with an increased risk of bleeding compared with antiplatelet agents or no therapy.

The purpose of COMMANDER HF was to evaluate the potential benefit of the new oral anticoagulant rivaroxaban administered at a low dose (2.5 mg twice daily) compared with placebo on top of the standard of care in a population of 5022 patients who had chronic heart failure, coronary artery disease, a reduced ejection fraction, and evidence of elevated plasma natriuretic peptides after an episode of decompensated heart failure within 21 days. After a median 21-month follow-up, there was no between-group difference in either the occurrence of the primary composite end point of death of any cause, myocardial infarction, or stroke (HR, 0.94; 95% CI, 0.84-1.05; *P*=0.27) or in all-cause mortality. There was a numeric trend for reducing stroke events. There was also no difference in the major safety end point of fatal or serious bleeding with potential permanent disability.

This trial has limitations, including the absence of a central adjudication of events so that one cannot exclude misclassification of events and of electrocardiographic monitoring with possible underdiagnosis of asymptomatic atrial fibrillation.

However, these negative results have important clinical implications:

- They confirm the fact that nonfatal thrombotic events, particularly deep venous thrombosis and pulmonary embolism, are rather uncommon during the course of heart failure.
- They lead to the conclusion that new oral anticoagulants are not routinely indicated in patients with heart failure of ischemic origin with low ejection fraction in sinus rhythm.

Remote patient monitoring is associated with improved clinical outcomes

Inconsistent results have been reported with remote distance monitoring of patients with heart failure: a few studies are positive, whereas others negative. The TIM-HF2 trial[2] was a randomized, prospective trial conducted in 1538 patients with heart failure in NYHA class II or III with an ejection fraction <45% or >45% provided that they were treated with diuretics. Patients were recruited in German cardiology centers and among general practitioners; they were assessed by a specific score in order to rule out significant depression. The rationale for excluding depression derived from a post hoc analysis from a previous telemonitoring study, TIM-HF1, which suggested that patients without depression might benefit from this approach. A previous heart failure hospitalization within 12 months was also required as an inclusion criterion. The median time from the index hospitalization was approximately 3 months and patients were well treated by modern standards.

Several biomarkers and vital signs or urgent calls were transferred online 24/7 to a telemonitoring center, allowing, if needed, immediate action by contact of the general practitioner, the cardiologist, or of an emergency unit. All data were reviewed on a daily basis. The primary end point was a composite of all-cause mortality and percentage of days lost due to unplanned cardiovascular hospitalization. There was a significant reduction in favor of the patients receiving telemonitoring vs patients receiving usual care with a 20% relative risk reduction (P=0.046). All-cause mortality was also significantly reduced by 30% (P=0.028) and there was a nonsignificant trend for a reduction in cardiovascular mortality. The number of days lost due to unplanned heart failure hospitalization was also significantly reduced by 20% (3.8 vs 5.6 days/year; P=0.007).

This positive study highlights the fact that, in order to be successful, remote monitoring in patients with heart failure must include transmission of data, patient education, and a good cooperation between the monitoring center and the downstream professionals. One key for the success of TIM-HF2 is undoubtedly the fact that the monitoring center was active 24/7 in order to manage the flow of information.

Tafamidis: first medication to show benefit in cardiac amyloidosis

Transthyretin amyloid cardiomyopathy is caused by the deposition of transthyretin amyloid fibrils, composed of misfolded transthyretin proteins, in the myocardium. These deposits result in abnormally stiff ventricles, restrictive cardiomyopathy, and conduction defects, but no treatment so far has shown any benefit in this disabling, late-onset condition that is associated with a very poor prognosis. The condition can be an autosomal dominant trait caused by mutations in the transthyretin gene or by the wild-type transthyretin protein. Although the prevalence of the disease is not well known, some studies suggest that it could account for 10% to 15% of the cases of heart failure with preserved ejection, particularly in older patients.

Tafamidis is a drug that binds to the thyroxine binding sites of transthyretin, thus inhibiting the dissociation of tetramers into monomers, limiting intramyocardial deposits. The ATTR-ACT trial[3] assessed the efficacy and safety of tafamidis in 441 patients with transthyretin amyloid cardiomyopathy in a double-blind, placebo-controlled design. Two doses of tafamidis, 20 and 80 mg, were tested against placebo for 30 months. In the primary analysis, all-cause mortality followed by cardiovascular hospitalizations was hierarchically assessed. Secondary analyses included 6-minute walking distance and quality of life as assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ).

There was a significant reduction in the primary end point ($P<0.001$) in the pooled tafamidis arms related to a reduction in all-cause mortality (HR, 0.70; 95% CI, 0.51-0.96) and in cardiovascular hospitalizations, which were reduced by 32%. Tafamidis treatment was also associated with a lower rate of decline in exercise capacity and quality of life. The effect on functional capacity was observed at 6 months, whereas the effect on mortality was only apparent at 18 months. The benefit was similarly observed in inherited and wild-type transthyretin amyloidosis. There was no differential effect across prespecified subgroups except the rate of cardiovascular hospitalizations, which was higher in tafamidis-treated patients in NYHA class III. Finally, there were no specific safety concerns and the rate of adverse events was similar in the intervention and the placebo groups, as well as with the two doses of tafamidis.

This trial, which enrolled a growing proportion of elderly patients with heart failure, has important clinical implications, as it shows, for the first time, benefit of an intervention in a deadly condition, where only palliative treatments have been provided so far.

PREVENTION

Secondary prevention

The EUROASPIRE program is a survey that has been conducted across European countries since 1996. The survey assesses, at regular intervals, the quality of secondary prevention measures in patients with documented coronary artery disease. The results of EUROASPIRE V, which was conducted in 2016–2018 in 21 European countries, were presented in Munich. The results from this survey are appalling: if medical therapy in general is in line with the recommendations, lifestyle and preventive measures do not show any progress compared with EUROASPIRE IV, which was conducted in 2012–2015.

Patients included in the latest survey had a history of acute coronary syndrome or myocardial revascularization 6 months to 3 years before enrollment. The rate of smoking increased from 48% to 53%, patients exercising regularly declined from 44% to 34%, the rate of patients who were overweight remained stable and concerned 81%, and increased blood pressure was reported in 46% vs 45%. The proportion of patients having a diet based on a sufficient proportion of fruits and vegetables declined from 80% to 68%. The only matter of satisfaction was the decline in patients with raised LDL cholesterol, which dropped from 43% to 36%.

Overall, these results highlight the need for a better cooperation between professionals and a better education of patients regarding lifestyle and prevention measures in the large population of European citizens with coronary artery disease.

Primary prevention in patients with diabetes mellitus

Low-dose aspirin is not beneficial

Patients with diabetes mellitus have an increased risk of cardiovascular events compared with patients without diabetes mellitus. Aspirin is beneficial in secondary prevention, but the benefits in primary prevention have not been well established in the general population or in patients with diabetes mellitus. Moreover, excess bleeding has been reported, thus counterbalancing the potential benefit observed in patients treated in primary prevention.

The ASCEND trial[4] was a randomized trial that compared the efficacy and safety of enteric-coated aspirin 100 mg/day with placebo in patients with diabetes and without manifest cardiovascular disorder. A factorial design was used to assign patients to a regimen of n–3-fatty acid or placebo. A total of 15 480 patients with diabetes of any type were randomized and followed-up for an average of 7.4 years. The primary efficacy end point was the first serious vascular event, ie, myocardial infarction, stroke, transient ischemic attack, or cardiovascular death, and the primary safety end point was the first major bleeding event, ie, intracranial hem-

orrhage, a sight-threatening bleeding event in the eye, gastrointestinal bleeding, or other serious bleedings.

Aspirin was associated with a significant reduction in the occurrence of the primary end point (HR, 0.88; 95% CI, 0.79-0.97; *P*=0.01), but the benefit was offset by a significant increase in serious bleeding events (HR, 1.29; 95% CI, 1.09-1.52; *P*=0.003), with most of the excess being gastrointestinal bleeding. There was no difference in the incidence of gastrointestinal tract cancers or in any cancer between groups. The randomization to the n–3-fatty acid arm did not yield any benefit in this population.

The ASCEND trial confirms that low-dose aspirin in patients with diabetes without documented cardiovascular disease confers a mild benefit on cardiovascular events, but that this benefit is counterbalanced by an excess in major bleeding events. Therefore, these results should lead the guidelines on prevention not to recommend aspirin in primary prevention in patients with diabetes in the absence of manifest cardiovascular disease.

Primary prevention in moderate-risk patients

Low-dose aspirin fails

The absence of benefit of low-dose aspirin in primary prevention has been confirmed by another study, ARRIVE,[5] which was conducted in 7 countries in patients without known cardiovascular disease or diabetes and with an estimated moderate risk of cardiovascular events (20% to 30% at 10 years). Male patients had to be at least 55 years old with at least 2 risk factors and female patients had to be at least 60 years old with 3 risk factors. A total of 12546 patients were randomized to either enteric-coated aspirin 100 mg or to placebo. Due to a low event rate, the study moved from an event-driven design to a fixed-termination date.

The primary composite end point was cardiovascular death, myocardial infarction, stroke/unstable angina, or transient ischemic attack. Aspirin did not confer benefit (HR, 0.96; 95% CI, 0.81-1.10; *P*=0.60) and the only positive effect was observed in a per-protocol analysis in patients who were at least 60% treatment compliant, where a significant reduction in fatal or nonfatal myocardial infarction was observed (HR, 0.53; 95% CI, 0.36-0.79; *P*=0.0014). Prespecified subgroup analyses did not show any difference between the different subgroups. There was a significant 2-fold increase in the risk of gastrointestinal bleeding (HR, 2.11; 95% CI, 1.36-3.28; *P*=0.0007), with most of these events being mild or moderate.

This second primary prevention study in patients at moderate cardiovascular risk without diabetes mellitus suggests that aspirin should not be given routinely in the absence of documented cardiovascular disease and that it is associated with a substantial increase in the risk of bleeding. ■

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