LATE-BREAKING CLINICAL TRIALS ON PRIMARY CARDIOVASCULAR PREVENTION

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Among the several exciting late-breaking clinical trials on prevention presented at the 2018 ESC congress, I will focus on ARRIVE, ASCEND, and CAMELLIA.

ARRIVE

The benefit of low-dose aspirin in patients with acute coronary syndromes or a previous myocardial infarction, stroke, or transient ischemic attack is supported by more than 200 studies involving more than 200 000 patients. In contrast, the role of aspirin in the primary prevention of myocardial infarction and stroke in groups with a moderate estimated risk of a first cardiovascular event has been controversial, despite 30 years of randomized trials. A major issue complicating the interpretation of these studies is a low, but well-described, risk of bleeding, ranging from more common episodes of easy bruising and epistaxis to less frequent, but life-endangering, gastrointestinal hemorrhage and hemorrhagic stroke.

ARRIVE was a randomized, double-blind, placebo-controlled, multicenter study conducted in seven countries.[1] Eligible patients were aged 55 years (men) or 60 years (women) and older and had an average cardiovascular risk, deemed to be moderate based on the number of specific risk factors. The primary efficacy end point was a composite outcome of time to first occurrence of cardiovascular death, myocardial infarction, unstable angina, stroke, or transient ischemic attack. Safety end points were hemorrhagic events and incidence of other adverse events. The trial enrolled 12 546 patients who were randomly assigned to receive aspirin (n=6 270) or placebo (n=6 276), with a median follow-up was 60 months. In the intention-to-treat analysis, the primary end point occurred in 269 (4.29%) patients in the aspirin group vs 281 (4.48%) patients in the placebo group (HR, 0.96; 95% CI, 0.81-1.13; *P*=0.6038). Gastrointestinal bleeding events (mostly mild) occurred in 61 (0.97%) patients in the aspirin group vs 29 (0.46%) in the placebo group (HR, 2.11; 95% CI, 1.36-3.28; *P*=0.0007). The overall incidence rate of serious adverse events was similar in both treatment groups (n=1266 [20.19%] in the aspirin group vs n=1311 [20.89%] in the placebo group).

Findings from ARRIVE are generally consistent with many other studies that tended to show aspirin's ability to lower the risk of a first nonfatal myocardial infarction without affecting the risk of total stroke. With respect to safety, as expected, the rates of gastrointestinal bleeding events and some other minor bleeding events were higher in the aspirin treatment group.

ASCEND AND ASPIRIN

Another controversial area is the role of aspirin in the primary prevention of cardiovascular events in patients with diabetes. ASCEND was a two by two factorial study that randomly assigned adults who had diabetes, but no evident cardiovascular disease to receive aspirin at a dose of 100 mg daily or matching placebo and to receive 1-g capsules containing either n–3 fatty acids (fatty acid group) or matching placebo (olive oil) daily. This section summarizes the effects of the randomization to aspirin or matching placebo.[2] The primary efficacy outcome was the first serious vascular event (ie, myocardial infarction, stroke, or transient ischemic attack, or death from any vascular cause, excluding any confirmed intracranial hemorrhage). The primary safety outcome was the first major bleeding event (ie, intracranial hemorrhage, sight-threatening bleeding event in the eye, gastrointestinal bleeding, or other serious bleeding). Secondary outcomes included gastrointestinal tract cancer. A total of 15 480 participants underwent randomization. During a mean follow-up of 7.4 years, serious vascular events occurred in a significantly lower percentage of participants in the aspirin group than in the placebo group (658 participants [8.5%] vs 743 [9.6%]; rate ratio, 0.88; 95% CI, 0.79-0.97; *P*=0.01). In contrast, major bleeding events occurred in 314 participants (4.1%) in the aspirin group vs 245 (3.2%) in the placebo group (rate ratio, 1.29; 95% CI, 1.09-1.52; *P*=0.003), with most of the excess being gastrointestinal bleeding and other extracranial bleeding. There was no significant difference between the aspirin group and the placebo group in the incidence of gastrointestinal tract cancer (157 participants [2.0%] vs 158 [2.0%], respectively) or all cancers (897 [11.6%] vs 887 [11.5%]). Thus, the absolute benefits were largely counterbalanced by the bleeding hazard. Indeed, aspirin use prevented serious vascular events in people who had diabetes and no evident cardiovascular disease at trial entry, but it also caused major bleeding events. The absolute benefits were largely counterbalanced by the bleeding hazard.

Taken together, ARRIVE and ASCEND clearly indicate that the main goal in primary prevention remains optimization of lifestyle and control of traditional risk factors, including diabetes, hypertension, and dyslipidemia. They also probably put an end to the controversial issue of aspirin in primary prevention.

ASCEND AND n–3 FATTY ACID SUPPLEMENTS

This section summarizes the effects of the randomization to n-3 (also known as omega-3) fatty acid supplements or matching placebo.[3] The primary outcome was a first serious vascular event (ie, nonfatal myocardial infarction or stroke, transient ischemic attack, or vascular death, excluding confirmed intracranial hemorrhage). The secondary outcome was a first serious vascular event or any arterial revascularization. The trial randomly assigned 15480 patients with diabetes, but without evidence of atherosclerotic cardiovascular disease to receive 1-g capsules either containing n-3 fatty acids (fatty acid group) or matching placebo (olive oil) daily. During a mean follow-up of 7.4 years (adherence rate, 76%), a serious vascular event occurred in 689 patients (8.9%) in the fatty acid group and in 712 (9.2%) in the placebo group (rate ratio, 0.97; 95% CI, 0.87-1.08; *P*=0.55). The composite outcome of a serious vascular event or revascularization occurred in patients (11.4%) and 887 patients (11.5%), respectively (rate ratio, 1.00; 95% CI, 0.91-1.09). Death from any cause occurred in 752 patients (9.7%) in the fatty acid group and in 788 (10.2%) in the placebo group (rate ratio, 0.95; 95% CI, 0.86-1.05). In subgroup analyses of serious vascular events or revascularization, there was no evidence that the proportional effects of n-3 fatty acids varied according to aspirin or placebo assignment.

Observational studies in different populations have suggested that fish consumption once or twice a week is associated with a reduced risk of heart disease; these observations were confirmed in a meta-analysis. However, randomized trials of supplementation with n-3 fatty acids have shown conflicting results regarding the effects on fatal or nonfatal outcomes; meta-analyses of these trials have generally not identified significant beneficial effects of n-3 fatty acid supplementation on major vascular events.

These findings, together with results from earlier randomized trials involving patients with and without diabetes, do not support the current recommendations for routine dietary supplementation with n-3 fatty acids to prevent vascular events. Taken together, the totality of evidence suggests again that, in primary prevention, the main goal remains traditional risk factor control, while no room is left for antithrombotic drugs or dietary supplements.

CAMELLIA

The prevalence of obesity has nearly tripled during the past 40 years worldwide. As of 2016, 13% of adults globally were obese, with rates as high as 40% in several countries, including the United States. An additional 39% of adults worldwide are overweight. Obesity is associated with the development and progression of multiple coexisting complications, including hypertension, dyslipidemia, type 2

diabetes, coronary artery disease, stroke, and heart failure, as well as a risk of death from any cause. Yet, no pharmacologic strategy has shown cardiovascular safety or benefit. Indeed, several agents have precipitated various cardiovascular or neuropsychiatric complications, which has led to their removal from the markets by regulatory agencies and left clinicians without a pharmacologic weight-loss agent with proven cardiovascular safety.

Lorcaserin is a selective serotonin 2C receptor agonist that modulates appetite that has proven efficacy for weight management in overweight or obese patients. In CAMELLIA, 12 000 overweight or obese patients with atherosclerotic cardiovascular disease or multiple cardiovascular risk factors were randomly assigned to receive either lorcaserin (10 mg twice daily) or placebo.[4] The primary safety outcome of major cardiovascular events (a composite of cardiovascular death, myocardial infarction, or stroke) was assessed at an interim analysis to exclude a noninferiority boundary of 1.4. If noninferiority was met, the primary cardiovascular efficacy outcome (a composite of major cardiovascular events, heart failure, hospitalization for unstable angina, or coronary revascularization [extended major cardiovascular events]) was assessed for superiority at the end of the trial. At 1 year, weight loss of at least 5% had occurred in 1986 of the 5135 patients (38.7%) in the lorcaserin group and in 883 of the 5083 patients (17.4%) in the placebo group (odds ratio, 3.01; 95% CI, 2.74-3.30; $P<0.001$). During a median follow-up of 3.3 years, the rate of the primary safety outcome was 2.0% per year in the lorcaserin group and 2.1% per year in the placebo group (HR, 0.99; 95% CI, 0.85-1.14; $P<0.001$ for noninferiority); the rate of extended major cardiovascular events was 4.1% per year and 4.2% per year, respectively (HR, 0.97; 95% CI, 0.87-1.07; $P=0.55$).

Thus, the results of this trial are encouraging because they show that this new drug is safe and that it can reduce weight. On the other hand, at the end of the follow-up period, the difference in weight was about 2 kg and therefore probably inadequate to translate into a reduction in clinical end points, as confirmed by lack of efficacy in this trial, suggesting that the mainstay of treatment for obesity remains counseling and bariatric surgery in patients with morbid obesity. ■

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