NEWS ON ISCHEMIC HEART DISEASE AT THE ESC 2018 CONGRESS

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Keywords: *angina; cardiac troponin; CT coronary angiography; prevention*

Traditionally, the studies presented in Munich will influence practice and may lead to guideline updates in the future. However, if the "bright side" of the trials is highlighted during the ESC congress, it is now time to identify the "take-home messages"!

HIGH-STEACS TRIAL

The High-STEACS trial,[1] a cluster-randomized controlled trial that compared the high-sensitivity troponin assay with the contemporary assay, enrolled consecutive patients with suspected acute coronary syndrome. The trial included 2 phases: (i) a 6-month validation phase during which the contemporary cardiac troponin assay was used to guide clinical decisions; and (ii) a 6- to 24-month implementation phase during which only the results from the high-sensitivity assays were disclosed. Both assays were measured throughout the trial, and hs-TnI sex-specific cutoffs were used to reclassify patients with troponin levels below the diagnostic threshold as having myocardial injury.

A total of 48 282 consecutive patients were enrolled with 1771 (17%) patients being reclassified as having a myocardial injury or infarction by hs-TnI who were not identified with the contemporary assay. Reclassified patients had a hospital stay that was twice as long and they were more likely to undergo coronary angiography (11% vs 4%). However, 1-year outcomes showed no differences between the two groups (adjusted odds ratio for implementation vs validation phase, 1.10; 95% CI, 0.75-1.61; *P*=0.620). These results were surprising and disappointing, suggesting that the selection of an appropriate population needs to be rethought in order to give the best possible care.

ASCEND TRIAL

With the ASCEND trial,[2] another established concept has been challenged. The ASCEND trial included 15 480 participants, with no previous cardiovascular disease, who were randomized to aspirin at a dose of 100 mg daily or matching placebo. 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. 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%]). 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).

Again, there was no net benefit in taking aspirin since the reduction in vascular events was counterbalanced by an increase in bleeding. The ASCEND trial was also a good test of the overall hypothesis of aspirin for total cancer prevention, and, in this setting, the results were disappointing since no suggestion of benefit was noted.

GLOBAL LEADERS TRIAL

GLOBAL LEADERS[3] was an open-label superiority trial that randomized patients undergoing percutaneous coronary intervention for stable coronary artery disease or acute coronary syndrome to receive (1:1) either 75–100 mg aspirin daily plus 90 mg ticagrelor twice daily for 1 month, which was followed by 23 months of ticagrelor monotherapy, or standard dual antiplatelet therapy with 75–100 mg aspirin daily plus either 75 mg clopidogrel daily (for patients with stable coronary artery disease) or 90 mg ticagrelor twice daily (for patients with acute coronary syndromes) for 12 months, which was followed by aspirin monotherapy for 12 months. A total of 15 968 participants were randomized (7980 to the experimental group and 7988 to the control group). After the 2-year follow-up, 304 (3.81%) participants in the experimental group died or had a nonfatal MI vs 349 (4.37%) participants in the control group (rate ratio, 0.87; 95% CI, 0.75-1.01; *P*=0.073). Again, the results [the overall results] did not show that ticagrelor alone was better than the traditional approach.

VERDICT TRIAL

In the VERDICT trial,[4] 2147 patients with clinical suspicion of NSTE-ACS were randomized to receive (1:1) very early invasive coronary angiography (within 12 hours) or standard invasive care (within 48 to 72 hours). The primary end point was a combination of all-cause death, nonfatal recurrent myocardial infarction, hospital admission for refractory myocardial ischemia or hospital admission for heart failure. Of the patients randomized to the very early invasive care arm, 1075 had invasive coronary angiography performed at a median of 4.7 hours after

randomization, whereas 1072 patients assigned to standard invasive care had invasive coronary angiography performed 61.6 hours after randomization. The primary end point occurred in 296 (27.5%) of the participants in the very early invasive coronary angiography group vs 316 (29.5%) in the standard care group (HR, 0.92; 95% CI, 0.78-1.08). In conclusion, a very early invasive strategy did not improve clinical outcomes vs an invasive strategy conducted within 2 to 3 days in patients with NSTE-ACS. Of note, one-third of patients enrolled with a diagnosis of NSTE-ACS had no significant coronary stenosis.

SCOT HEART TRIAL

Now we come to the only trial, the SCOT HEART trial,[5] that was presented at the 2018 ESC congress as clearly positive. According to the authors, CT coronary angiography in addition to standard care in patients with stable chest pain resulted in a significantly lower rate of death from coronary heart disease or nonfatal myocardial infarction at 5 years. Please consider that, in the previously published shorter follow-up, only 25% of the patients in the SCOT HEART trial had obstructive coronary artery disease, and, at 6 weeks, only 12% had a diagnosis of angina due to coronary artery disease, and CT coronary angiography use was associated with more invasive procedures. These differences seem to disappear at the 5-year follow-up in favor of CT coronary angiography.

Several points challenge the credibility of the conclusions of this study. Patients were included because of "chest pain," which is not a diagnosis of angina and even less of myocardial ischemia. Actually, only 35% of included patients had possible angina and 61% atypical chest pain. Moreover, half of the trial population presented with normal or near-normal coronary arteries. At the 5-year follow up, the event rate was higher in patients with possible angina and, in this subgroup, there was no difference between CT coronary angiography and standard care, suggesting that clinical presentation and risk assessment should drive the therapeutic approach.

Given that the number of invasive procedures was similar in the two groups, the authors attributed the advantage of the CT coronary angiography arm to more preventive measures. However, the reduction in events in the CT coronary angiography group exceeds even the most optimistic expectations from aspirin/statin therapy. Relative to the observed reduction of 33 fewer events in 97 patients, only 3 could be attributed to aspirin/statin, assuming a NNT of 50. The effect size is much lower than expected: 3.1% vs a predicted 13.1%. The small number of events makes the trial susceptible to the play of chance. In addition, bias is always a major concern in open-label trials.

Once again, an implausible conclusion reached the highest level of medical communication, along with the results of the previously published PROMISE trial,[6] namely:

1. Almost 50% more invasive coronary angiographies were performed in the CT coronary angiography group, without any benefit in clinical outcome.
2. Most revascularizations in the CT coronary angiography group were performed in patients who had no objective evidence of myocardial ischemia.
3. Most importantly, in the CT coronary angiography group, about 400 patients had no obstructive coronary artery disease despite overt symptoms.

They all hold true!

THE DIAMOND APPROACH

An encouraging signal from the Munich ESC congress comes from the high interest and active participation in events proposing a new approach to diagnose and treat ischemic heart disease.[7,8] This major cultural change began several years ago, when a "Copernican Revolution" proposing a multifactorial nature of myocardial ischemia was launched. No longer was it a one-to-one association with obstructive coronary atherosclerosis, but a complex array of precipitating mechanisms, including severe stenosis, microvascular dysfunction, coronary vasospasm, etc. The notion was also popularized that these mechanisms may act in combination or alternate in time, leading to a much more complex and dynamic pathogenesis of myocardial ischemia.

A direct implication of this new understanding of ischemic heart disease is that both diagnostic and therapeutic algorithms must consider the complexity of the pathogenesis of myocardial ischemia. Moreover, drug selection for the optimal treatment of ischemic heart disease must also consider associated cardiac conditions and systemic comorbidities.

So, the diamond approach[7] suggests abandoning the traditional distinction between first-line and second-line agents, which is not supported by any evidence, and making an effort to match the agent with the precipitating mechanism(s) of ischemia in the individual patient and with the associated cardiac and systemic conditions (eg, heart rate, left ventricular function, blood pressure, diabetes, CKD, COPD, etc, etc).

TAKE-HOME MESSAGES

- High-STEACS: hs-TnI does not identify the correct patients to deliver the best possible care in the setting of ACS.

- VERDICT: In patients with NSTE-ACS, an early invasive strategy does not improve outcomes.
- ASCEND: There is no net benefit in taking aspirin in primary prevention.
- GLOBAL LEADERS: Ticagrelor alone is not better than the traditional approach.
- SCOT HEART: CT coronary angiography does not add any benefit in terms of outcomes in patients with angina. ■

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