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Critical Appraisal of the 2018 ACC Scientific Sessions Late-Breaking Trials From a Statistician's Perspective

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ABSTRACT

The late-breaking clinical trials presentations at the American College of Cardiology Scientific Sessions in March 2018 are an important contribution to the field of cardiology. This paper presents a constructive critical appraisal of 7 key studies: ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab), VEST (Vest Prevention of Early Sudden Death Trial), SECURE-PCI (Statins Evaluation in Coronary Procedures and Revascularization), TREAT (Ticagrelor in Patients with ST-Elevation Myocardial Infarction treated with Pharmacological Thrombolysis), POISE (PeriOperative ISchemic Evaluation), SMART-DATE (Safety of 6-Month Duration of Dual Antiplatelet Therapy After Percutaneous Coronary Intervention in Patients With Acute Coronary Syndrome), and CVD-REAL 2 (Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors). For each study, our aim is to document and interpret the main findings, noting particularly when "positive spin" appears to occur, and to provide a balanced account of each study, paying attention to both constructive new findings and study limitations. These topical examples also provide useful general insights on what to look for when critiquing clinical trial presentations and publications. (J Am Coll Cardiol 2018;■:■–■)

Each year, the American College of Cardiology (ACC) Scientific Sessions are a major forum for presentations of original findings across a broad spectrum of research activities in cardiology. Of particular interest are the late-breaking clinical trials sessions, because they provide the latest pivotal evidence on both new and established treatment practices in cardiology.

This year, from March 10 to 12, 2018, there were 8 such sessions in which 37 studies were presented. To review all of these studies would be an immense task; hence, we chose to provide a constructive critical appraisal of 7 key presentations (**Central Illustration**). These studies were chosen as they were: 1) of major clinical importance; and 2) within our sphere of expertise.

For each study, our aim is to place it in context, summarize the design, present the main findings, and then provide a critical interpretation. We paid particular attention to the multiplicity of data available for presentation and the consequent problems that arise (e.g., in having multiple secondary endpoints or multiple subgroup analyses). Potential biases (e.g., in the 1 nonrandomized study we review) are assessed.

There is a natural desire for trialists to wish to emphasize the more positive aspects of their study findings. This "positive spin" carries the risk that presentations may not provide a balanced account of the totality of evidence (1). We point out instances when this appears to occur.

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ABBREVIATIONS AND ACRONYMS

CHD = coronary heart disease

DAPT = dual antiplatelet therapy

MACE = major adverse cardiovascular events

MI = myocardial infarction

NSTEMI = non-ST-segment elevation myocardial infarction

oGLD = other glucose-lowering drugs

PCI = percutaneous coronary intervention

SGLT2i = sodium-glucose cotransporter-2 inhibitors

STEMI = ST-segment elevation myocardial infarction

WCD = wearable cardioverter-defibrillator

Overall, we hope this paper provides a meaningful commentary on some of the most topical (and sometimes controversial) presentations at ACC 2018.

THE ODYSSEY OUTCOMES TRIAL

ALIROCUMAB IN ACUTE CORONARY SYNDROME. The ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) trial (2) recruited 18,924 patients who: 1) had an acute coronary syndrome (ACS) event in the past 1 to 12 months; 2) were on high-intensity statin therapy; and 3) had inadequate control of lipids (e.g., low-density lipoprotein [LDL] cholesterol ≥70 mg/dl). Patients were randomized to alirocumab (a PCSK9 inhibitor) or placebo. The primary composite efficacy endpoint was coronary heart disease (CHD) death, nonfatal myocardial infarction (MI), fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization. As is common practice, we will refer to these as major adverse cardiovascular events (MACE). Median follow-up was 2.8 years. As expected, patients on alirocumab had a marked reduction in LDL cholesterol compared with placebo: −62.7% at 4 months, which attenuated slightly to −54.7% at 4 years.

Results for the primary efficacy endpoint and its components are shown in the top half of Table 1. MACE had a highly significant 15% relative reduction (hazard ratio [HR]: 0.85) with 95% confidence interval (CI): 7% to 22%; p = 0.0003. All 4 components of MACE had fewer events on alirocumab compared with placebo, although this was not significant for CHD death.

It is relevant to express this primary result on an absolute scale. There were 149 fewer patients with a MACE event on alirocumab of 9,462 patients per arm followed for a median 2.8 years. This translates into a reduction of 5.62 first MACE events per 1,000 years of treatment, with 95% CI: 2.35 to 8.89 per 1,000 patient-years. This can be converted to a number needed to treat: to prevent 1 MACE event, one needs to treat 63 patients for a median of 2.8 years (95% CI: 41 to 141 patients). This is helpful in elucidating whether an overall strategy of prescribing alirocumab to all eligible patients is sufficiently effective and in turn cost-effective.

There are several important considerations here:

1. We are confined to the trial's inevitably limited follow-up, so we cannot generalize to the effects of longer-term treatment.
2. The plot of cumulative MACE events over time by treatment group (Figure 1) reveals no separation of the curves out to 1 year. This significant treatment-time interaction (p = 0.03) means that all the benefit appears to kick in after 1 year of treatment. This departure from proportional hazards calls into question whether an HR is the best overall summary of the treatment effect.
3. This absolute benefit will vary from patient to patient: that is, higher-risk patients are liable to have a higher absolute benefit. For instance, the 27% of patients who were >65 years of age had a MACE rate around 55% higher than the rest. We would encourage the authors to undertake appropriate multivariable analysis so patients can be stratified according to their risk status (3). This will help refine which patients benefit the most from alirocumab treatment.

Now, we turn to the main secondary endpoints (bottom half of Table 1), which are listed in a predefined order for hierarchical statistical testing (4). This is to keep the overall type 1 error at 0.05. The first 4 on the list were all highly significant, but CHD death and cardiovascular (CV) death were not (p = 0.38 and p = 0.15, respectively).

For all-cause death, there is an observed 15% relative risk reduction (HR: 0.85) with a 95% CI: 2% to 27% reduction; p = 0.026. However, because this sits lower in the hierarchy of statistical testing, it does not fit in the formal list of claims for treatment efficacy within the bounds of strict type 1 error control. A counter-argument is that overall survival is clearly the most important matter for patients and, hence, merits special attention beyond statistical formalities. A weakness in this statement is that the all-cause death finding rests on combining nonsignificant reductions in both CV and non-CV deaths (31 and 27 fewer deaths, respectively), and the latter has no obvious rationale.

The next concern is over the interpretation of subgroup analyses for the primary MACE outcome. For the 5 main pre-specified subgroups, there were no statistically significant interactions with treatment. This would normally be the end of the matter: insufficient evidence that there are any identifiable effect-modifiers. But, in this case, the idea is pursued that alirocumab may be more effective in the 30% of patients who had baseline LDL cholesterol ≥100 mg/dl: the observed relative risk reduction becomes 24% (95% CI: 13% to 35%), but it is questionable whether a post hoc emphasis on this finding is justifiable (5,6).

Even more doubtful is the claim that all-cause mortality is reduced by 29% (95% CI: 10% to 44%) in