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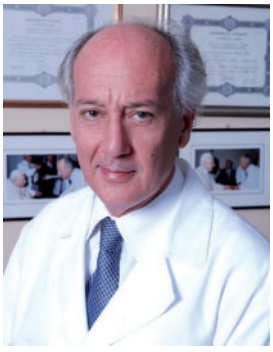
The first Debate and a focus on trials



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This Issue opens with the first of a new article category of the *European Heart Journal* (EHJ): the Debate. Each Debate is made up of three sections: an Introduction, which presents the topic to debate and why it has been selected, together with a Pro and a Contra. This article category reproduces the format of the Debate sessions seen at the Annual Meeting of the European Society of Cardiology. The current contribution is entitled '**Debate: Prasugrel rather than ticagrelor is the preferred treatment for NSTE-ACS patients who proceed to PCI, and pre-treatment should not be performed in patients planned for an early invasive strategy**'.[1] In this first Debate, a panel of distinguished colleagues led by Evangelos Giannitsis, the authors of the Contra section, raise their concern over some recommendations included in the Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation in regard to antithrombotic treatment in patients undergoing percutaneous coronary intervention (PCI).[2] The authors of the Guidelines led by Holger Thiele explain the reasons which led to their recommendations in the Pro section of the Debate. The EHJ offers this unique platform, the Debate, with the goal of helping readers to dissipate the grey in the difficult decisions they must take during their daily practice.

In a Viewpoint article entitled '**Interpreting myocardial infarction analyses in ISCHEMIA: separating facts from fallacy**', Raffaele De Caterina from the University of Pisa and David Brown from Washington University in St Louis[3] note that after a decade of planning and execution, the International Study of Comparative Health Effectiveness With Medical and Invasive Approaches (ISCHEMIA) trial was published in April 2020 and a flow of ancillary reports rapidly followed.[4] This landmark study found that in patients with chronic coronary syndromes (CCS), both the composite primary endpoint [cardiovascular (CV) death, myocardial infarction (MI), hospitalization for unstable angina or heart failure, or resuscitated cardiac arrest] and the secondary endpoint (CV death and MI) were not different between the two strategies, refuting the hypothesis and long-held belief of a prognostic benefit from an invasive strategy with revascularization by PCI or coronary artery bypass graft (CABG) surgery in CCS patients with moderate to severe inducible myocardial ischaemia. Not surprisingly, peri-procedural MI was more frequent in the invasive arm, whereas late, spontaneous MI was more frequent in the conservative arm. On this basis, some have concluded that revascularization should be offered to CCS patients to prevent 'prognostically important' infarctions, i.e. spontaneous (Type 1) MI. This commentary seeks to provide a rebuttal to this speculative conclusion also based on the results of some recent studies.[5,6]

In another Viewpoint entitled '**The importance of achieving sex- and gender-based equity in clinical trials: a call to action**', Jeske van Diemen from the Amsterdam Universitair Medische Centra in the Netherlands, and colleagues note that women are under-represented in clinical trials and the current guidelines are based on recommendations from clinical trials that predominantly included men to generate the evidence behind our therapies and interventions.[7] Additionally, there is a paucity of knowledge regarding the reasons for the under-representation of women. After an extensive literature search of CV clinical trials, the authors found only six articles that reported on challenges and barriers and the motivators behind the decisions to participate in clinical trials. In terms of barriers, both male and female participants reported time constraints, apprehension towards being in a clinical trial with an experimental design or therapy, or the potential of an unfavourable outcome and risk of harm. Women declined to participate more often than men because they perceived a higher risk of harm from trial participation as compared with men. Overall, women need extra reassurance of their significant value in order to participate in a clinical research setting. The challenges and facilitators are likely to differ based on country, regions, and across cultures and healthcare systems, and there is no 'one size fits all' solution. By implementing the right frameworks for the design of the trial, including more women leadership in clinical trial committees and inviting women patients to participate in the discussion of the design, researchers will be more likely to attain sex and gender parity.[8]

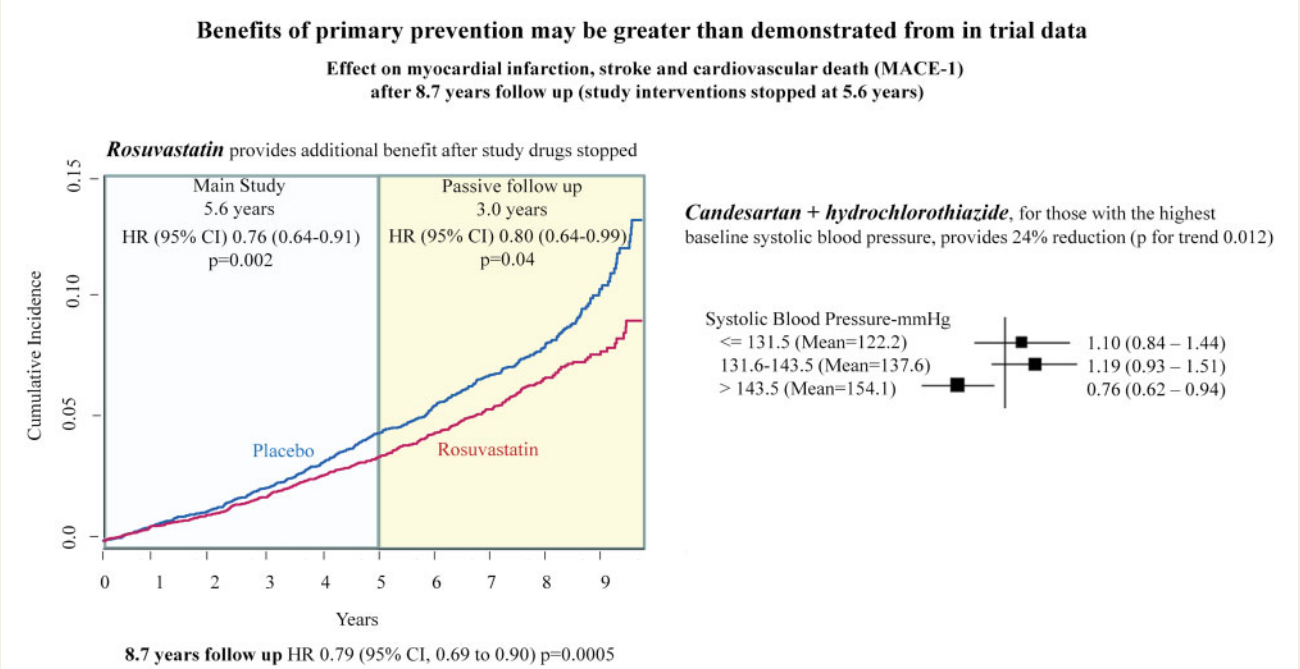

Figure 1 Graphical Abstract (from Bosch J, Lonn EM, Jung H, Zhu J, Liu L, Lopez-Jaramillo P, Pais P, Xavier D, Diaz R, Dagenais G, Dans A, Avezum A, Piegas LS, Parkhomenko A, Keltai K, Keltai M, Sliwa K, Held C, Peters RJG, Lewis BS, Jansky P, Yusoff K, Khunti K, Toff WD, Reid CM, Varigos J, Joseph P, Leiter LA, Yusuf S; On behalf of the Heart Outcomes Prevention Evaluation (HOPE)-3 Investigators. Lowering cholesterol, blood pressure, or both to prevent cardiovascular events: results of 8.7 years of follow-up of Heart Outcomes Evaluation Prevention (HOPE)-3 study participants. See pages 2995–3007).

The foundations for prevention of CV diseases are lifestyle modification, including smoking cessation, moderate alcohol intake, healthy diet, and regular exercise. However, these strategies are not fully implemented and, even when implemented, do not eliminate the risk of CV diseases. Therefore, added interventions with drugs are often required.[9,10] The Heart Outcomes Prevention Evaluation (HOPE)-3 study was designed to determine if a reduction in LDL cholesterol (LDL-C) or blood pressure (BP), either alone or in combination, would reduce CV events in patients at intermediate risk with no prior overt clinical CV events. After 5.6 years of treatment, rosuvastatin 10 mg daily compared with placebo reduced MACE (including MI, stroke, or death from CV causes) by 24%. Despite reducing systolic BP by 6 mmHg, the combination of candesartan (16 mg daily) and hydrochlorothiazide (12.5 mg daily) compared with placebo did not reduce MACE significantly in the overall trial population. In a Clinical Research article entitled '**Lowering cholesterol, blood pressure, or both to prevent cardiovascular events: results of 8.7 years of follow-up of Heart Outcomes Evaluation Prevention (HOPE)-3 study participants**', Jackie Bosch from McMaster University in Hamilton, Canada, and colleagues examined whether the benefits observed during the active treatment phase in the HOPE-3 trial were sustained, enhanced, or attenuated 3.1 years after cessation of all the trial medications.[11] The first co-primary outcome for the entire duration of follow-up was the composite of MI, stroke, or CV death (MACE-1), and the second was MACE-1 plus resuscitated cardiac arrest, heart failure, or coronary revascularization (MACE-2); 78% of 11 994 surviving HOPE-3 subjects consented to participate in this extended follow-up. During 3.1 years of post-trial observation, participants originally randomized to rosuvastatin compared with placebo had a significant 20% additional reduction in MACE-1 and a 17% additional reduction in MACE-2 of borderline statistical significance. In sharp contrast, there was no significant benefit of BP lowering in the overall study, during either the active or the post-trial observation period, although a 24% reduction in MACE-1 was observed over 8.7 years in those with the highest blood pressure values at baseline (*Figure 1*).

Bosch *et al.* conclude that the cardiovascular benefits of rosuvastatin, and BP lowering in those with elevated systolic BP, compared with placebo, continue to accrue for at least 3 years after cessation of randomized treatment in individuals without CV disease, indicating a legacy effect. Indeed, both statins and BP lowering may cause structural changes in the vasculature, such as alterations of plaque morphology and composition that may lead to continued or enhanced benefits during further observation. The contribution is accompanied by an **Editorial** by Eric Boersma and Isabella Kardys from Erasmus MC in Rotterdam, the Netherlands.[12] The authors conclude that the initial beneficial effect of rosuvastatin treatment that was observed in the HOPE-3 trial persisted for at least 3 years after termination of the study. For now, the effective use of such agents by individuals without clinically established disease, and at low to moderate CV risk, seems

to remain a matter of shared decision-making by these individuals and their physicians, which includes a well-informed weighing up of the pros and cons.

Iron deficiency is a potential therapeutic target in patients with heart failure.[13] In a clinical research article entitled '**The effect of intravenous ferric carboxymaltose on health-related quality of life in iron-deficient patients with acute heart failure: the results of the AFFIRM-AHF study**', Ewa Jankowska from Wrocław Medical University in Poland, and colleagues evaluated the impact of i.v. ferric carboxymaltose (FCM) vs. placebo on health-related quality of life (HRQoL) for the AFFIRM-AHF population.[14] The baseline 12-item Kansas City Cardiomyopathy Questionnaire (KCCQ-12), which was completed for 1058 patients, was administered prior to randomization and at weeks 2, 4, 6, 12, 24, 36, and 52. The baseline KCCQ-12 overall summary score (OSS) mean ± SE error was 38.7 ± 0.9 (FCM group) and 37.1 ± 0.8 (placebo group); corresponding values for the clinical summary score (CSS) were 40.9 ± 0.9 and 40.1 ± 0.9. At week 2, changes in OSS and CSS were similar for FCM and placebo. From week 4 to week 24, patients assigned to FCM had significantly greater improvements in OSS and CSS scores vs. placebo. The adjusted mean difference at week 4 was: 2.9 ($P = 0.018$) for OSS and 2.8 ($P = 0.029$) for CSS; and at week 24: 3.0 ($P = 0.028$) for OSS and 2.9 ($P = 0.035$) for CSS. At week 52, the treatment effect had attenuated but remained in favour of FCM.

The authors conclude that in iron-deficient patients with heart failure and left ventricular ejection faction ≤50% stabilized after an episode of acute heart failure, treatment with i.v. FCM, compared with placebo, results in clinically meaningful beneficial effects on HRQoL as early as 4 weeks after treatment initiation, lasting up to week 24. The manuscript is accompanied by an **Editorial** by Tibor Kempf from the Hannover Medical School in Germany.[15] Kempf concludes that AFFIRM-AHF identifies iron deficiency as a treatment target in patients stabilized after an episode of acute heart failure. The in-hospital setting provides an excellent opportunity to administer FCM prior to discharge, thereby enhancing clinical uptake of this safe, simple, and effective treatment. Heart failure networks need to ensure that a second dose is infused after 6 weeks, if necessary, and that iron status is re-assessed every 3–4 months. Future studies should explore the regulation and functional implications of cardiac and skeletal muscle iron deficiency in heart failure patients to design individualized iron supplementation strategies.

The issue is also complemented by two Discussion Forum contributions. In a commentary entitled '**Underlying mechanisms involved in the icosapent ethyl reduction of cardiovascular events still cannot be attributed to an anti-atherosclerotic effect**', Gaston Rodriguez-Granillo from the Clinica La Sagrada Familia in Buenos Aires, Argentina and colleagues comment on the recent publication '**Effect of icosapent ethyl on progression of coronary atherosclerosis in patients with elevated triglycerides on statin therapy: final results of the EVAPORATE trial**' by Matthew J Budoff from the Lundquist Institute at Harbor-UCLA Medical Center in Torrance, CA, USA.[16,17] Budoff *et al.* respond in a separate comment.[18]

The editors hope that readers of this issue of the *European Heart Journal* will find it of interest.

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