Mavacamten for hypertrophic obstructive cardiomyopathy

We read with enthusiasm the results of the EXPLORER-HCM trial reported by Iacopo Olivotto and colleagues.[1] These findings bring both hope and uncertainty to patients and will open debates on management in our heart teams.

We challenge the effectiveness of mavacamten from a vision of excellence in management of hypertrophic obstructive cardiomyopathy. The definition of responders is unambitious: gains in minimal peak oxygen consumption (pVO_2) and one New York Heart Association (NYHA) class decrease. However, only 45 (37%) of 123 patients receiving mavacamten were responders at 30 weeks, compared with 22 (17%) of 128 patients in the placebo group.[1] In the mavacamten group, unchanged functional class was seen in 43 (35%) of 123 patients; 26 (26%) of 101 patients presented a post-exercise gradient of more than 50 mm Hg (the usual threshold for surgery); and 49 (43%) of 113 patients showed gradients of more than 30 mm Hg, which are associated with suboptimal outcomes. Complete response was tepidly defined as NYHA functional class I and a gradient of less than 30 mm Hg; striving for no residual gradient now vanished.

With mavacamten, the persistence of obstruction was high, improvement in pVO_2 was suboptimal in a young study population (mean age 58 years), and its lifetime tolerance was unassessed. The risk of left ventricular dysfunction in the long term and further side-effects are yet to be clarified. We hope that mavacamten can enhance the quality of life for patients currently managed conservatively. We fear that unmeasured enthusiasm might lead to acceptance of inferior outcomes for surgical candidates with hypertrophic obstructive cardiomyopathy. Septal myectomy is a low-risk therapy proven to abolish obstruction, allow patients to return to typical lifestyle and lifespan, and reduce arrhythmias.[2] Freedom from medications is common after myectomy, which is another benefit of this therapy in terms of quality of life.

We declare no competing interests.

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1 Olivotto I, Oreziak A, Barriales-Villa R, et al. Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2020; **396:** 759–69.

2 Maron BJ, Yacoub M, Dearani JA. Controversies in cardiovascular medicine. Benefits of surgery in obstructive hypertrophic cardiomyopathy: bring septal myectomy back for European patients. *Eur Heart J* 2011; **32:** 1055–58.

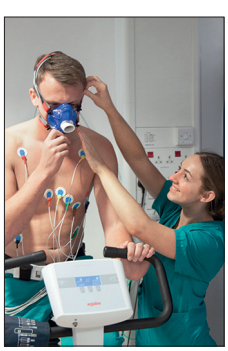
Authors' reply

We thank Eduard Quintana and colleagues for their Correspondence. The EXPLORER-HCM trial[1] is the largest prospective, double-blind, placebo-controlled study ever done in patients with symptomatic obstructive hypertrophic cardiomyopathy. Far from being "unambitious", the study included a vast array of endpoints ranging from objective measurements of performance to gradient reduction and key aspects of quality of life. The primary endpoint was developed following discussions with the US Food and Drug Administration, and was defined as either a 1·5 mL/kg per min or greater increase in peak oxygen consumption (pVO_2) with at least one New York Heart Association (NYHA) class improvement, or a 3·0 mL/kg per min or greater increase in pVO_2 with no worsening of NYHA class. The endpoint was met by 45 (37%) of 123 patients receiving mavacamten, with an absolute difference of 19·2% over placebo (p=0·0005). Quintana and colleagues' observation that "only 45 (37%) of 123 patients receiving mavacamten were responders at 30 weeks, compared with 22 (17%) of 128 patients in the placebo group", refers to those patients who had at least a 3·0 mL/kg per min improvement in pVO_2 and at least one class change in NYHA class, which was not the primary or alpha-controlled endpoint, although still clinically and statistically significant.

Of note, improvements in pVO_2 are notoriously challenging in hypertrophic cardiomyopathy, and several studies have not found such improvements. Even after surgical myectomy and alcohol septal ablation, improvements in pVO_2 remain uncertain to this day, despite the indisputable clinical benefits of both procedures.[2]

Overall, the effect of mavacamten in obstructive hypertrophic cardiomyopathy appeared considerable,[1] particularly because the primary endpoint was achieved in patients who were predominantly in functional NYHA class II (72% of patients) and would not have been candidates for septal reduction therapies. This finding is evident in crucial secondary and exploratory endpoints. Foremost among these endpoints is reduction in left ventricular outflow tract obstruction, which dropped by a mean of 47 mm Hg in the treatment group, and patient-reported outcomes, which showed substantial improvement. Furthermore, the profound and sustained reduction in circulating concentrations of N-terminal pro B-type natriuretic peptide and high-sensitivity cardiac troponin I suggest improved myocardial status, even when complete gradient abolition did not occur, indicating a potential for long-term benefit.

We agree with Quintana and colleagues that early enthusiasm should not derail our attention with regard to the unknown long-term safety of mavacamten (currently investigated in the long-term extension study MAVA-LTE, NCT03723655), nor to the risk of inappropriately delaying



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septal reduction therapies in surgical candidates. In fact, this issue is the objective of the ongoing VALOR-HCM trial (NCT04349072). However, in a broad perspective, surgical myectomy and alcohol septal ablation should not be considered a panacea for patients with hypertrophic cardiomyopathy, and ideal results are far from guaranteed outside a limited number of centres that have experienced high patient volumes.[3,4] Therefore, effective medical therapies such as mavacamten might be particularly important as an alternative in many settings.

From the patients' perspective, the possibility to have surgical results without surgery is highly desirable. It is no surprise that there is enthusiasm for a first-in-class disease-targeted therapy supported by robust evidence in this pivotal trial. Further studies are now ongoing to establish how to best position this novel treatment among available options for our patients.

DJ has received personal fees from MyoKardia. CYH has received payments as a consultant from MyoKardia and Ambry Genetics. SJL has received payments as a consultant from MyoKardia. AW has received grants from MyoKardia; personal fees from Cytokinetics; and payments as a consultant from MyoKardia. IO has received grants from MyoKardia, Sanofi-Genzyme, Shire, and Bayer; personal fees from Sanofi-Genzyme, Shire, and Bayer; and payments as a consultant from MyoKardia.

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1 Olivotto I, Oreziak A, Barriales-Villa R, et al. Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2020; **396:** 759–69.

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Managing NSTEMI in older patients

In the SENIOR-NSTEMI study, Amit Kaura and colleagues[1] exploit state-of-the-art statistical approaches including target trial design, propensity score-adjusted regression, and inverse probability of treatment weighting, with the results clearly favouring an invasive management strategy in older patients (≥80 years old) with NSTEMI. However, some additional details should be provided by the investigators, to avoid any suspicion of residual confounding factors and strengthen the evidence that the invasive strategy is actually and mechanistically beneficial. Invasive management entails an invasive coronary angiography early on during treatment, and only the accurate reporting and analysis of diagnostic findings and ensuing treatments can confirm that there has not been a so-called black-box effect.[2]

In particular, focusing on diagnostic features, no details were provided on the extent and severity of coronary artery disease (eg, location and number of coronary stenoses), despite their notable prognostic effect and influence on the management strategy.[3] Although revascularisation was done in 74% of patients undergoing invasive management, no additional details on the type of revascularisation are provided. Moreover, no details on subsequent ancillary medical therapy (including, but not limited to, antithrombotic therapy) are given. On a potentially smaler note, 4% of patients were excluded because of missing data. This approach risks creating systematic bias, and we would also recommend a sensitivity analysis based on missing data imputation and subsequent pooling, according to the Rubin rule.[4]

Although we find the SENIOR-NSTEMI trial and its findings useful, their effect and credibility would definitely be strengthened by providing additional details and analyses.

GB-Z has consulted for Cardionovum, InnovHeart, Meditrial, and Replycare. All other authors declare no competing interests.

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3 Stepien K, Nowak K, Skorek P, et al. Baseline indicators of coronary artery disease burden in patients with non-ST-segment elevation acute coronary syndrome. *Minerva Cardioangiol* 2019; **67:** 181–90.

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With the results of the SENIOR-NSTEMI study, Amit Kaura and colleagues[1] conclude that invasive management reduced 3-year mortality by 36% and hospital admissions for heart failure by 33%. These are illustrative results, but some aspects need further discussion.

First, Kaura and colleagues did not analyse or adjust for heart failure incidence during the index acute coronary syndrome, which we have shown to have a crucial effect on mortality and post-discharge heart failure.[2]

Second, Kaura and colleagues did not do a competing event regression analysis, and their analyses might overestimate the effect. The competing risk regression was developed for situations when the