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CORRESPONDENCE

Pharmacogenetic testing to broaden patient eligibility for mavacamten

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The European Medicines Agency (EMA) approved mavacamten in June 2023 for the treatment of symptomatic obstructive hypertrophic cardiomyopathy (oHCM).[1,2] Clinical trials have demonstrated its efficacy in improving exercise capacity, reducing the left ventricular outflow tract (LVOT) gradient, and alleviating symptoms, and decreases the need for invasive septal reduction therapies.[3,4]

Given that pharmacists may lack access to patients' full medication lists, it falls on cardiologists to ensure mavacamten's appropriate use. Pharmacogenetics affects both dosing of mavacamten and its interaction with other medications, a critical consideration that cardiologists should be aware of. We have hence summarized key pharmacokinetic (PK) information to guide prescribers on EMA-recommended dosing, particularly concerning comedications (*Figure 1*).[2]

Mavacamten has high oral bioavailability (90–100%) and undergoes first-pass metabolism (CYP3A4/5), resulting in an exposure of ∼85% with peak concentration at 1 h.[5] It exhibits a large volume of distribution (114–206 L) with high protein binding (93%). The drug's elimination half-life (t½) ranges from 3 to 23 days, with significant accumulation during initiation (up to 7.5-fold). It is primarily metabolized by CYP2C19 (74%), CYP3A4 (18%), and CYP2C9 (8%) contribute minimally. Inactive metabolites are cleared renally.[6,7] Due to its long t½ and substantial interindividual PK/pharmacodynamic variability, slow uptitration, and regular follow-up are recommended, including the monitoring of left ventricular ejection fraction (LVEF) for safety and LVOT gradient for efficacy.[1,6]

Different dosing approaches have been evaluated. PIONEER-HCM ($n = 21$) identified a concentration-dependent effect on LVOT obstruction, with a proposed target range of 350–700 ng/mL. Plasma concentrations of ≥1000 ng/mL were associated with LVEF reductions ($n = 4$), which recovered after discontinuing mavacamten.[8] In EXPLORER-HCM ($n = 251$), a stepped dosing approach was applied. There were no instances where mavacamten therapy was halted due to concentrations of ≥1000 ng/mL. VALOR-HCM ($n = 108$) omitted plasma monitoring altogether, focusing instead on clinical and echocardiographic follow-up.[4] This has been adopted by the US Food and Drug Agency (FDA) as part of their Risk Evaluation and Mitigation Strategies (REMS) program for mavacamten.[9] Conversely, the EMA mandates determining CYP2C19 status as part of a pharmacogenetic dosing strategy.[2]

CYP2C19 metabolizing status is a critical determinant of mavacamten dosing and exposure, guiding both starting and maximum doses, as well as how to manage drug-drug interactions.[5,7] Poor metabolizers (PMs), who have two loss-of-function alleles (*2/*2, *2/*3, *3/*3), have a significantly longer t½ of mavacamten (533 h) compared to extensive metabolizers (72 h) and intermediate metabolizers (150 h).[5,7] Compared to non-PMs, PMs exhibit a 241% increase in total plasma exposure of mavacamten. Hence, according to EMA, PMs will achieve similar exposure with 5 mg once daily at a steady state compared to non-PMs who receive 15 mg.[5]

CYP2C19 status also guides drug-drug interaction management (*Figure 1*). Mavacamten is metabolized by both CYP3A4/5 and CYP2C19, the degree of which is determined by CYP2C19 status.[1,7] Strong inhibitors can significantly increase mavacamten levels, potentially causing adverse effects such as a reduced LVEF or heart failure symptoms. Regulatory agencies classify this strength based on its impact on the exposure of selected probes, e.g. midazolam for CYP3A4.[10] For mavacamten, we should be mostly concerned with CYP2C19 and/or CYP3A4/5 inhibitors that can raise mavacamten exposure by more than five-fold (=strong) or two- to five-fold (=moderate).[10] In CYP2C19 PMs, the focus should be on drug-drug interactions with CYP3A4/5 inhibitors and inducers, as CYP2C19 does not play a major role in these patients. Among non-PMs, interactions with both CYP2C19 and CYP3A4/5 inhibitors need consideration. If CYP2C19 status is unknown, dosing defaults to the most conservative scneario.[2] Since PM status is rare in Europe, most clinically relevant interactions involve CYP2C19 inhibitors, which are less common and can be summarized in concise lists (*Figure 1*).[5]

Mavacamten presents an interesting case study for the role of pharmacogenetics. While FDA and EMA differ on dosing recommendations, pharmacogenetic testing does broaden patient eligibility for mavacamten in terms of allowed comedications. EMA offers specific guidance on co-administering mavacamten with CYP2C19 and CYP3A4 inhibitors/inducers, depending on CYP2C19 status, facilitating a more tailored and potentially safer treatment approach.[2] Conversely, the FDA's REMS program currently contraindicates the use of certain CYP2C19 and CYP3A4 inhibitors and inducers.[9]

In the future, if real-world data robustly confirm the favourable safety profile of mavacamten in oHCM, systematic CYP2C19 testing might still be waived given the low prevalence of PM status in Europe and the growing clinical trial and modelling data supporting the clinical and imaging-guided approach.[4,7]

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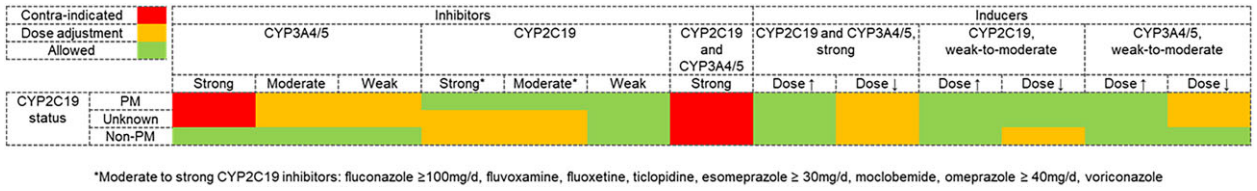

Figure 1 Management of drug-drug interactions with mavacamten. Abbreviations: PM, poor metabolizer; non-PM, non-poor metabolizer.

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Data availability

No data were generated or analysed for this article.

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