healthy volunteers (9), but there have been no studies focusing on the effect of CYP2D6 and CYP2C19 on TCAs in treatment of functional gastrointestinal disorders. In our study, we elected to use imipramine based on its profile to increase disorders. In our study, we elected to use of CYP2D6 and CYP2C19 on TCAs in
have been no studies focusing on the effect
democratizes the positive effects on symptoms improvement. Nonetheless, the current study was limited by lack of CYP2D6 and CYP2C19 genotype assessment and imipramine drug level measurement; thus, the benefit of dose increment is yet to be determined. Future research with genotypic/phenotypic polymorphism assessment and drug level monitoring in various ethnic backgrounds should provide an opportunity to optimize the use of TCAs in treatment of esophageal functional disorder. We also agree that other TCAs with better pharmacokinetic profiles and documented benefits in other functional gastrointestinal disorders such as amitriptyline and nortriptyline should be further studied (10).

CONFLICT OF INTEREST
The authors declare no conflict of interest.

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Tryclic Antidepressants in Refractory GERD: Poorly Effective Drugs or Wrong Patients?

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To the Editor: We read with great interest the paper by Limsrivilai et al. (1) carried out to assess the benefit of low dosage imipramine (25 mg daily) compared with placebo for 8 weeks in patients with esophageal hypersensitivity (EH) and functional heartburn (FH). The authors enrolled non-erusive reflux disease patients with no or partial response to once-daily proton pump inhibitors (PPIs) and classified them as EH or FH by impedance-pH monitoring, which includes the use of modern impedance variables, such as baseline impedance and post-reflux swallow-induced peristaltic wave (6), which were found to be more accurate in distinguishing the various forms of GERD (7). This new diagnostic approach has been recently supported by data on the positive correlation between mucosal integrity abnormalities and histological reflux-related changes with BI levels (8).

In conclusion, we believe that studies aiming to evaluate the effectiveness of novel therapeutic approaches in refractory GERD should be performed in better selected populations.

CONFLICT OF INTEREST
Guarantor of the article: Vincenzo Savarino, MD, PhD.
Specific authors contributions: Design of the study, writing of the manuscript, approving final version: Eedoardo Savarino, Manuele Furnari, Giorgia Bodini and Vincenzo Savarino.
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Response to Savarino et al.

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To the Editor: We sincerely thank Dr Savarino for his letter (1) regarding our recent study using imipramine in treatment of esophageal hypersensitivity (EH) and functional heartburn (FH) (2). Dr Savarino’s notion on proper patient selection for tricyclic antidepressant (TCA) treatment in our study is very well taken.

First, Fass et al. (3,4) have demonstrated that patients with gastroesophageal reflux disease (GERD) who did not respond to once daily dosing of proton pump inhibitors (PPI) had an improvement in heartburn symptoms after doubling the dose to twice daily. However, the impedance-pH monitoring to stratify patient population was not performed, and thus patients with true acid reflux may have been responsible for the treatment response in their studies. It should also be noted that the clinical response to double-dose PPI among patients failing standard dose who have negative reflux monitoring has not been reported, but we expect the response rate is theoretically low. Therefore, we only enrolled those who failed once daily dosing PPI as all of our study participants were documented to have no acid reflux. Nonetheless, we do agree that recruiting patients who failed double-dose PPI may better represent true PPI refractory population noting that the definition of refractory GERD is still not well established.

Second, we concur that the accuracy of either symptom-associated probability index or symptom index alone to identify EH and FH is imperfect especially when there are low reflux rates (5). Esophageal baseline impedance (BI) and post-reflux swallow-induced peristaltic wave (PSPW) have been shown to have better diagnostic accuracy than esophageal acid exposure time in the diagnosis of erosive reflux disease and nonerosive reflux disease. Moreover, recently published data from Frazzoni et al. (6) demonstrated that the PSPW index and the mean nocturnal BI increased the diagnostic yield of impedance-pH monitoring of patients with reflux disease. Thus, the combination of traditional indices of symptom-associated analysis and the new diagnostic tools should permit future studies to better identify proper patient population for each treatment strategy.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

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Hepatocellular Carcinoma With Peliosis-Like Change-Mimicking Hemangioma: A LI-RADS Exception

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