doi:10.1002/ejhf.3015
Online publish-ahead-of-print 6 September 2023

Effects of tafamidis on heart failure hospitalization: The tale of the dog that did not bark. Letter regarding the article 'Improved long-term survival with tafamidis treatment in patients with transthyretin amyloid cardiomyopathy and severe heart failure symptoms'

- *Detective: 'Is there any other point to which you would wish to draw my attention?'*
- *Holmes: 'To the curious incident of the dog in the night-time'.*
- *Detective: 'The dog did nothing in the night-time'.*
- *Holmes: 'That was the curious incident'.*

Arthur Conan Doyle, 'Silver Blaze' (1892), cited by Coats.[1]

The expression 'a dog that doesn't bark' designates the instance when something expected does not happen, representing a clue to the truth (in the original story, the guard dog did not bark because he had recognized the intruder). This expression was used by Coats to comment on the lack of any information about the VICTORIA trial several months after the announcement of its positive results: 'there has been no reverberation, no resonance, and very little speculation [...] I speculate the result may be [...] positive for one aspect (such as hospitalization), but not another such as mortality'.[1]

This brilliant metaphor came us to mind when reading the recent publication of the long-term extension (LTE) study of ATTR-ACT.[2] This analysis focused on patients with amyloid transthyretin cardiomyopathy (ATTR-CM) and New York Heart Association (NYHA) class III at baseline.[2] These patients have come under scrutiny following a subgroup analysis of ATTR-ACT showing an increase in the rate of heart failure (HF) hospitalizations compared to patients in NYHA class I or II ($p < 0.001$).[3] This subgroup analysis was necessarily underpowered to reliably detect a difference between NYHA class I–II ($n = 186$ in the tafamidis arm and 114 in the placebo arm) and NYHA class III ($n = 78$ and $n = 63$, respectively),[3] and this difference could be just a play of chance. An alternative explanation was that patients with NYHA class III on tafamidis had to be hospitalized more often than those on placebo simply because they had a longer survival. Indeed, no subgroup difference was noted in terms of all-cause death, which means that patients with NYHA class III had a survival benefit from tafamidis that did not differ significantly from patients with NYHA class I–II.[3] A simple competing risk analysis would have easily solved this problem, but was not performed in the original publication[3] nor in a following *post-hoc* analysis. Afterwards, Elliott *et al.*[4] published the results of an interim analysis from the LTE study, which focused on all-cause mortality without mentioning cause-specific mortality, HF hospitalizations or the primary endpoint of the ATTR-ACT. The new analysis by Elliott *et al.* reports again a 'reduced all-cause mortality with continuous tafamidis treatment compared with delayed tafamidis treatment (placebo then tafamidis) in patients with NYHA class III symptoms at baseline' over a longer follow-up.[2] The reader is again left to wonder which are the effects of tafamidis on cardiovascular versus non-cardiovascular mortality and HF hospitalizations. Reporting even negative results would be important to allow a thorough understanding of the effects of tafamidis, especially now that alternative options to tafamidis are emerging, such as acoramidis[5] and patisiran.[6] Data about HF hospitalization would be particularly important for policy makers assessing the reimbursability of tafamidis in patients with NYHA class III as HF hospitalizations account for up to 90% of the costs of HF care.[7] For these reasons, we would encourage ATTR-ACT investigators to consider a publication focused on the effects of tafamidis on cardiovascular mortality and HF hospitalization.

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