EDITORIAL COMMENT

End of the Road for Vagus Nerve Stimulation?*

John J.V. McMurray, MD,a Lars V. Køber, MD, DMSb

The need to further reduce morbidity and mortality in patients with heart failure is undisputed. Certain drug and device therapies have already been remarkably successful in attaining these goals, but more are needed (1,2). Vagus nerve stimulation is a rational, novel approach to treating heart failure that has experimental support (3–6). Of course, the efficacy of any new treatment must be demonstrated in an appropriately designed clinical trial. Designing and conducting trials using devices is more challenging than trials using drugs, and the investigators, Gold et al. (7), who led the INOVATE-HF (Increase Of Vagus TonE in Heart Failure) trial published in this issue of the Journal are to be congratulated. Unfortunately, INOVATE-HF did not show any benefit from vagus nerve stimulation in patients with heart failure and reduced ejection fraction, well treated with evidence-based drug and device therapy.

Whenever a trial fails to demonstrate benefit, it is inevitable that there is an intellectual autopsy. For example, was the trial design optimal? Was the trial conduct satisfactory? Did the patients receive the treatment, and was the dosage correct? Was there an unexpected “off-target” harmful effect of the treatment studied, offsetting any benefit? Or was it simply that the scientific hypothesis was wrong, after all?

Key to the success of any trial is accrual of a sufficient number of events likely to respond to the experimental therapy (and which, hopefully, reflect outcomes that are important to patients with the disease in question). Sufficient accrual of endpoints depends on the event rate among the patients included in the trial and the number enrolled. Completeness of follow-up and capture of suspected endpoints is obviously essential as well.

Of similar importance is whether an efficacious dose of treatment was chosen (the INOVATE-HF investigators tried to ensure an adequate “dose” of vagus nerve stimulation [6]), whether the treatment was actually taken (of course, with devices, adherence is less of an issue than with drugs) and, crucially, the treatment effect size anticipated. Provided the criteria mentioned previously are met, a trial will be successful. Whether the treatment is effective or ineffective will be definitively demonstrated by the trial.

HOW DOES INOVATE-HF MATCH UP TO THESE STANDARDS?

The patients enrolled in INOVATE-HF were appropriate, well-characterized, and well-treated and, consequently, at relatively low risk. The primary efficacy outcome varied somewhat from that most commonly used in recent heart failure trials (i.e., the composite of cardiovascular death or heart failure hospitalization) (8–11). One difference was use of all-cause mortality, which has the advantage of objectivity but the disadvantage of including events (i.e., noncardiovascular deaths) unlikely to be influenced by the treatment under investigation. The proportion of noncardiovascular deaths in patients with heart failure is increasing and was approximately 30% in INOVATE-HF (12). Inclusion of these events will attenuate the treatment effect size. This can be seen in the recent prospective comparison of ARNI with angiotensin-converting-enzyme inhibitors (ACE-I) to PARADIGM-HF (Determine Impact on Global Mortality and Morbidity in Heart Failure) trial, where the
reduction in cardiovascular mortality with sacubitril/valsartan therapy compared to that with enalapril was 20%, whereas the reduction in all-cause mortality was 16% (10). In a very large trial with ample power, this probably does not matter, but if the power is marginal it may. The other difference was the inclusion of nonhospitalized episodes of heart failure worsening. Although these episodes have been included in composite outcomes in some other trials and have been endorsed in recent guidance on endpoints in trials, we have limited information on whether such episodes are influenced by effective therapies as much as heart failure hospitalization (13,14). Thus, although both modifications of the conventional composite will inflate the event rate, they may dilute the treatment effect size. Also, nonhospitalized events may not inflate the event rate by much, as shown in INOVATE-HF and other studies (7,14).

The investigators do not report the expected event rate or anticipated treatment effect size. However, the relatively small sample size (n = 707) and modest target number of primary efficacy endpoints (n = 376 events) suggest a sizeable treatment effect was expected, perhaps one that was unrealistically large.

As it turned out, INOVATE-HF was terminated early for futility. Planning for such a scenario makes sense, especially in device trials, as it reduces patient exposure to therapies that are ineffective (and continued exposure to the harm associated with treatment) and financially costly. There may be nagging doubt that prematurely stopping a study for reasons of futility may mean a benefit has been missed. However, INOVATE-HF was stopped when only approximately 209 of the target number of events (n = 376) had accrued, suggesting there was probably a trend toward harm rather than benefit. The lack of effect on the only other objective outcome, left ventricular remodeling, is supportive of a lack of efficacy. In a nonblinded trial, it is hard to place any value on subjective endpoints such as walking distance and health-related quality of life (15).

Where does this leave us with respect to vagus nerve stimulation in heart failure? The one other blinded trial using vagus nerve stimulation was too small (n = 96) and too short (6 months) to show a definitive effect on any outcome. Although INOVATE-HF itself was also probably underpowered to give a definitive answer about efficacy, the clear trend toward harm is likely to discourage any further studies of this intervention in heart failure. This finding also raises the question of how safe the use of vagus nerve stimulation is in other disease areas.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. John J.V. McMurray, British Heart Foundation Cardiovascular Research Centre, University of Glasgow, 126 University Place, Glasgow G12 8TA, United Kingdom. E-mail: john.mcmurray@glasgow.ac.uk.

REFERENCES
2. McMurray JJ, Adamopoulos S, Anker SD, et al., ESC committee for practice guidelines. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012;33:1787–847.

KEY WORDS angiotensin-converting enzyme inhibitors, heart failure, sacubitril/valsartan, vagus nerve stimulation