

Neuromodulation in heart failure

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This issue in the EHJ Supplement—the Heart of the Matter on neuromodulation in heart failure (HF) is very timely. Indeed, although most HF literature is busy with the latest results from the sodium/glucose cotransporter 2 inhibitors, and despite the remarkable recent major advances in HF drug therapy, across the spectrum of ejection fraction, the residual risk in this disease is still unacceptably excessively high. In the most recent drug trials, patients suffering from HF with reduced ejection fraction (HFrEF) receiving the best guideline-directed medical therapy (GDMT) have an annual rate of HF hospitalization and cardiovascular death around 18%, up to 25% in HF with EF below 25%.¹ The absolute risk of all-cause mortality after a worsening episode in patients with HFrEF is up to 17%.² Put in context, the risk of suffering from a disease-specific outcome is on average almost a 10-fold higher in HFrEF than in atherosclerotic cardiovascular disease.³ In an ideal world, if HFrEF patients receive all four foundational drugs, all-cause mortality as well as the risk of cardiovascular death and HF hospitalization may decrease by up to 60%.⁴ Unfortunately, in the less ideal real world, implementation of optimal drug therapy is extremely challenging. Although, admittedly, addition of SGLT2i therapy may be more straightforward, despite strong professional recommendations through guidelines, GDMT use among eligible HFrEF patients remains suboptimal.⁵ In this context, device therapy may be a most welcome addition in HF therapy. So far, only cardiac resynchronization therapy, with cardiac defibrillator therapy, has gained high level of evidence and strong recommendation in international guidelines. However, this therapy is effective only in patients with large QRS, ideally with a left bundle branch block. Other candidate HF device therapies are on high demand.

Developing novel HF therapies has proven extremely challenging. The experience so far is extremely humbling for clinical trialists. Failures are so common and successes mostly serendipitous. Many exciting and sound mechanistically driven developments failed desperately to pass the clinical trial test. This is true for drug therapy

as much as for device therapy. An important difference though, is that drug therapy may have multiple mechanisms of action, not all really known. The mechanism of action of device therapy is thought to be more straightforward and more predictable.

Rationale

The rationale for neuromodulation device HF therapy is very well explained by Gronda *et al.*⁶ in this EHJ issue. Sympathetic overactivation and vagal withdrawn in HFrEF have been extensively documented in pre-clinical as well as clinical work. Electroceuticals or bio-electronic medicine is a discipline aiming at developing treatments based on electrical neuromodulation.

Vagal nerve stimulation (VNS) with electrodes implanted around the vagal nerve, in the neck, is aimed at countering the long-term deleterious effects of vagal withdrawn. Baroreflex dysfunction results in autonomic dysregulation and has been related to the development and progression of HF. Baroreflex activation therapy (BAT) stimulates the carotid baroreceptor resulting in a centrally mediated decrease in sympathetic activity and an increase in the parasympathetic activity. In both therapies, electrodes deliver electrical impulses from an implanted pulse generator, implanted in the pectoral region. Spinal cord stimulation may have more complex mechanisms, blunting sympathetic reflex responses to cardiac stressors by modulation of both sympathetic and parasympathetic cardiac output. The focus of this EHJ Supplement issue is on these most studied device-based neuromodulation modalities in the setting of HFrEF: VNS, BAT, and SCS.

Regulatory framework, trial design issues, and the march to approval

The long march to regulatory approval and coverage of neuromodulation HF therapy has started years ago and is still ongoing. Similarly, to drug therapy development, this march is challenging, time-consuming, costly, and with uncertain outcome.

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The path to approval is less well harmonized among international regulatory agencies. The legal basis for the US Food and Drug Administration's (FDA) approval of a device is based on a 'least burdensome' approach, which ensures timely availability of devices. This is defined 'to be the minimum amount of information necessary to adequately address a relevant regulatory question or issue through the most efficient manner at the right time.' The FDA pathways for approval of medical devices are shorter and generally less costly than the pathways for drug approvals. As for drugs, 'Real-world' evidence can be used to support regulatory decisions for medical devices. Real-world data are often used for ongoing device safety using post-marketing surveillance programmes and may provide supportive evidence for effectiveness. In addition, the FDA has in place a Signal Management Program to address safety signals related to marketed devices. Because demonstrating improvements in cardiovascular mortality and HF hospitalization outcomes require more time and larger studies, the Breakthrough Devices Program may permit assessing effectiveness through patient-centred outcomes such as functional capacity, quality of life, and biomarkers in the initial expedited phase of premarket approval, as long as safety is demonstrated.

In Europe, the EU Medical Devices Directive was replaced recently by the Medical Device Regulations, which is now being applied, after a long delay. This regulation repeals the CE mark pathway judged by many as inappropriately lenient. The new regulations introduced stricter requirements for clinical evaluation and increased scrutiny through the use of annual periodic safety update reports. Although conceived to help drive innovation while preserving a high level of safety and performance of devices, these regulations are generally found as very complex, and an adaptation period is needed. There is concern that this new legislation, with its long transition period, is delaying the introduction of new devices in Europe, imposing barriers to innovation of new devices.

As a result of the divergent evolutions of the FDA and the EU regulatory framework, after a long period of supremacy of device trials in Europe in the late 2000s and early 2010s, there is a dramatic shift of device development from Europe to the USA. In the USA, overall, while device approval may be perceived as more lenient than in Europe and compared with drug approval, it remains stringent and evidence based.

The FDA 'Expedited Access for Premarket Approval and De Novo Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Diseases or Conditions' document was issued as a guidance for industry. The Expedited Access Pathway was designed as a new programme for medical devices that demonstrated the potential to address unmet medical needs for life threatening or irreversibly debilitating conditions. The FDA accepts assessments of a device's effect on intermediate endpoints that, when improving in a congruent fashion, are reasonably likely to predict clinical benefit. Such endpoints are natriuretic peptides, such as N-terminal pro-B-type natriuretic peptide/

B-type natriuretic peptide, the 6-min walk test distance, and health-related quality of life in HF.⁷ Consequently, these initial trials tend to be smaller and not powered for 'hard' clinical outcomes. Approval may be granted, at least at the FDA, based on such trials, with the understanding that the very trial based on surrogates will continue recruitment and follow-up until completion based on hard outcomes. Until event-driven conclusion is reached, the manufacturer may market the device and potentially get it reimbursed by Medicare (CMS), for a period of 4 years, according to a specific US FDA-CMS agreement.

Trial design issues

Trial design issues are important to understand. As a result of the 'least burdensome' approach, some statistical subtleties are allowed by the FDA, such as using the win-ratio approach allowing for prioritization of clinical outcomes, testing of hierarchical outcomes, and incorporation of patient-centred endpoints. Statistical Bayesian analysis, in contrast to the more classical frequentist approach can integrate new study data with previous data, thus making better use of the totality of evidence. Blinding is challenging in device trials. Sham-control is more complex, is not always feasible, and is not without ethical issues. Reliance on a blinded evaluation of endpoints may mitigate some issues relative to open or single-blinded trials, but do not protect entirely from biases.

Even though drug-response relationships are not necessarily well understood before embarking in large outcome drug trials, doses used in these trials are selected on some dose-finding considerations in earlier phases' trials. In contrast, dosing of electrical stimulation in neuromodulation trials (a balance of intensity and frequency of stimulations), are applied uniformly, such as in BAT, based on experimental data and technical considerations, or optimized in each patient, based on local tolerance to nerve stimulation, such as in VNS. Indeed, there is no validated and easy to measure readout of effective neuromodulation, which may serve for individual 'dose' selection.

Finally, because of the lack of simple measures of the state of the vagal tone and/or baroreflex sensitivity, neuromodulation therapy is applied to patients independent of the status of their autonomic nervous dysfunction. At least conceptually, therapy might be more effective in 'responders', if only there is a simple way to define responder profile. For example, cardiac resynchronization therapy has proven to be most effective in patients with large QRS or LBBB, where asynchrony is likely to be most important. Admittedly, no responder profile is validated for any GDMT drug.

Conclusion

In this issue of EHG Supplements, De Ferrari *et al.*'s⁷ and Duncker and Bauersachs's⁸ and Dusi *et al.*'s⁹ excellent overviews examine the available clinical evidence with

the neuromodulation therapies under development in HF. While more data are being accrued, the best available totality of evidence allows for applying BAT, the single neuromodulation therapy approved so far, in patients with HFrEF, symptomatic despite optimal guideline-directed medication, and non-eligible for cardiac resynchronisation therapy. The ongoing BEAT-HF outcome trial may provide further and more definitive evidence of efficacy. Meanwhile and until the results on cardiovascular mortality and HF hospitalization become available, the Barostim device may be used, as an FDA approved device through the Breakthrough Devices Program, in the USA, based on improvement of patient-centred outcomes such as functional capacity, quality of life, and no safety concern. These patient-centred outcomes are relevant and important to patients suffering from chronic HF.

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