



EDITORIAL COMMENT

Clinical inertia in heart failure care – Should we worry? Insights from “real-world” practice

Inércia clínica no tratamento da insuficiência cardíaca – motivo de preocupação? Percepções da prática clínica

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“The future depends on what we do in the present” – Mahatma Gandhi

There is a broad recognition that heart failure (HF) is one of the epidemics of the 21st century. Temporal trends on disease burden have been steadily growing, as shown by its metrics (incidence, prevalence, lifetime risk, and the number of hospitalizations). Importantly, it is the leading cause of hospitalization among elderly persons in developed economies. In contrast, survival rates have leveled off or slightly improved over time, but, still, mortality reduction has been modest in the past two decades. Noticeably, as much as 50% of HF patients die within five years after their first hospitalization.^{1,2} Accordingly, HF profoundly impacts overall burden of diseases and healthcare expenses, both of which are expected to continue escalating in the coming years, not only globally but also in Portugal.^{3,4}

Despite substantial progress in HF management (pharmacological, devices, and organizational), it is still a severe, costly condition with high morbidity and mortality regard-

less of its clinical phenotypes.^{1,2,5} Several underlying causes are instrumental to this burdensome societal effect, ranging from patient-based factors to reasons related to healthcare systems. Clinical inertia is likewise a prominent feature of this intricate interplay of outcome determinants. Clinical inertia in HF care, as in other medical fields, is broadly described as the lack of therapeutic intensification in a patient who is not at evidence-based targets. Its impact is most striking in HF with reduced ejection fraction (HFrEF) given the robust and extensive evidence on outcome-impacting treatment options in this setting. However, adopting, optimizing, and tackling the management subtleties of the recommended multi-drug guideline-directed medical treatment (GDMT) regimen can be a demanding undertaking. While reliant on multiple other aspects, a sizable share of clinical inertia stems from the physicians' misperception of disease control, as pioneeringly expressed by Phillips et al.⁶

In the study by Maltês et al.,⁷ presented in this issue of the journal, investigators explored the thesis that clinical stability in HFrEF, alongside good functional capacity, might not be synonymous with an uneventful clinical course, a good outcome, or an interruption in disease progression.

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In keeping with this assumption, they sought hard clinical events. There is a related, unstated, yet untested, intertwined goal of using their results as an argument to exalt the importance of pursuing GDMT, even in seemingly stable patients, to halt future clinical deterioration.

This research is valuable for its real-world perspective. The authors conducted a single-center retrospective cohort investigation including low risk HFrEF patients referred to cardiopulmonary exercise testing (CPET) over a sixteen-year span (2003–2018). Patients were selected based on their functional status as determined by Weber class adjudication, and 72 (mean age 52 ± 10 years; 83% males) qualifying as Weber class A (good functional capacity, defined by a peak O_2 uptake >20 ml/kg/min), were enrolled. HF risk stratification by CPET is well-established, and Weber's classification is standard for this purpose, thus validating the investigators' methodology.⁸ Despite most patients (93%) displaying proof of ongoing neurohormonal activation, their N-terminal proBNP median baseline levels were low (388 pg/ml; interquartile range: 201–684 pg/ml) compared to similar series. Their overall low risk was further reinforced by a predominance of New York Heart Association (NYHA) classes I/II (90%) and a low rate of loop diuretics use (50%). Except for sodium-glucose co-transporter 2 inhibitors, which were not yet approved at the time, the cohort mirrored and even outperformed contemporary clinical practice regarding prognosis-modifying therapies (94%, 90%, and 42% of patients were on renin-angiotensin-aldosterone system inhibitors (RAASi), beta blockers (BB), and mineralocorticoid receptor antagonists (MRA), respectively; 44% had an implantable cardioverter-defibrillator and/or a cardiac resynchronization therapy device).⁵

Notwithstanding the authors' resourceful approach to the question of therapy optimization in this group, we are unaware of whether each patient was receiving optimal therapy or whether there was a margin for it. The methodological subterfuges used to replace these missing data failed to support robust evidence for the benefits of therapy up-titration, so this was a far-fetched attempt. However, since this is not a minor issue, their intention ends up being well-justified. Given the prognostic implications, stepping up treatment to target doses should be one of the top priorities and concerns in HF care. McCullough et al. analyzed 14 880 HFrEF patients, of whom 69.8% were on GDMT, leniently defined as the combined use of BB and RAASi during the six-month period post diagnosis. They found that the non-GDMT subgroup had an excess mortality risk of 29% over two years (16% vs. 19%, respectively; hazard ratio (HR) 1.29; $p < 0.0001$). Apart from this, this study also confirms that in real-world practice, around 30% of patients fail to attain the best-proven treatment, which negatively affects survival.⁹ Aligned with these findings, the BIOSTAT-CHF registry, a European project, studied 2100 HFrEF patients (mean age 68 ± 12 years; 76% male), of whom only 22% achieved the target dose for angiotensin-converting enzyme inhibitor (ACE-i)/angiotensin II receptor blockers (ARBs) and 12% for BB. Moreover, reaching less than 50% of the recommended doses of both ACE-i/ARBs and BB resulted in significantly poorer survival (HR 1.50, 95% CI 1.33–1.67; HR 1.91, 95% CI 1.74–2.08, respectively).¹⁰ The Champ-HF registry's findings were similarly worrisome when they revealed that a substantial number of eligible patients were either not hav-

ing the appropriate drug combinations (RAASi-27%, BB-33%, MRA-67%) or optimal tolerable doses. In effect, less than 20% of the patients received target doses of RAASi, whereas only 28% were given maximal BB therapy. In contrast, most patients (77%) on MRA therapy received adequate dosing; additionally, only 22.1% of those qualifying for all components of triple therapy had them all at once, and barely 1% were simultaneously having each target dose.¹¹ Another report using health care electronic data from 2016 to 2019 from Sweden, the United Kingdom, and the United States have shown undertreatment, underdosing, and high discontinuation rate of GDMT among new users with a recent HF hospitalization (HFH). The target dose attainment in this incident medication analysis was limited (10–30%), and drug discontinuation was common (24–55%) over one year from initiation of therapy.¹² Age was an important determinant of up-titration, except for angiotensin receptor–neprilysin inhibitors. Patients with chronic kidney disease presented the highest discontinuation rates for all the pharmacological groups.¹²

The barriers to successful GDMT implementation involve patient-related (comorbidities, advanced age, physical and social frailty, cognitive impairment, poor adherence, reluctance to medication escalation, low-income status, health illiteracy), treatment-related (intolerance, side effects, polypharmacy), and healthcare-related aspects (costs, availability, accessibility, medical expertise). The physicians' attitude toward disease control further influences the whole process but conversely represents one of the most amenable to change. Importantly, in most studies addressing this subject, side effects and contraindications stand out as the leading obstacles to achieving GDMT.

The most prominent result from Maltês et al.'s research⁷ pertains to the significance of clinical stability for HFrEF patient outcomes. Over the two years of prespecified follow-up after CPET, 10% of the sample (seven patients) met the primary clinical endpoint, a composite of HFH or all-cause death (five HFH, three deaths). HF hospitalization preceded death in only one case. In light of the highly selective profile of this population (young age, overall low NYHA class, good functional capacity, modest neurohormonal activation, high rate of prognosis-modifying drugs and device use), this resonates as a meaningful, powerful message.

One of the best indicators of clinical stability in HF is the number of and time elapsed from a previous HFH. In the landmark trial PARADIGM-HF, 20% of the most stable patients, defined as those who had not ever been hospitalized for HF, had a primary event (a composite of death from cardiovascular causes or HFH), and 17% died throughout the trial.¹³ It is worth noting that cardiovascular death occurred in 51% of the first events. Moreover, there was no evidence of differential treatment effects across the whole risk spectrum, even if employing other metrics such as the MAGGIC and EMPHASIS-HF risk scores.¹⁴ Similarly, in DAPA-HF, in which two-thirds of the cohort was in NYHA class II, 11.8% of these mildly symptomatic patients on the treatment arm experienced clinical worsening or cardiovascular death over a median follow-up of 18.2 months compared to 18.1% in the placebo counterparts.¹⁵ Recurrently, clinical stability in HF emerges as a delusive prognostic indicator.

Borrowed from natural laws principles, clinical inertia can unfold as complex as the physics concept. Considering

the synergistic, additive benefits of optimized foundational therapies, these should form the bedrock of HFrEF management, to the greatest extent feasible, following a customized approach. This framework should apply to the entire risk continuum of HFrEF patients and, given their dismal prognosis, even those at the lower end of the risk range, as elegantly upheld by Maltês et al.⁷ As a corollary, it is unacceptable to miss out on the opportunity to put this into practice grounded on the misleading impression of clinical stability. This reasoning holds particularly true knowing that death can be the presenting feature of instability in approximately half of the cases.

Therefore, engaging with the maximization of all at-hand therapeutic resources in HF care, irrespective of the perception of clinical stability, is imperative from an outcome perspective.

Conflicts of interest

The author has no conflicts of interest to declare.

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