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EDITORIAL

Therapeutic inertia in the pharmacological management of heart failure with reduced ejection fraction

Nicolas Girerd[1]*, Jean-Jacques Von Hunolstein[2], Pierpaolo Pellicori[3], Antoni Bayés-Genís[4], Tiny Jaarsma[5], Lars H. Lund[6], Pascal Bilbault[7,8], Jean-Marc Boivin[1,9], Tahar Chouihed[10,11], Jérôme Costa[12], Jean-Christophe Eicher[13], Estelle Fall[14], David Kenizou[15], Bruno Maillier[16], Pierre Nazeyrollas[12], Gérald Roul[17], Noura Zannad[18], Patrick Rossignol[1], Marie-France Seronde[19,20] and EF-HF Group

[1]*Université de Lorraine, INSERM, Centre d'Investigations Cliniques-Plurithématique 1433, CHRU Nancy, and INSERM U1116, CHRU, F-CRIN INI-CRCT (Cardiovascular and Renal Clinical Trialists), 4 Rue du Morvan, 54500 Vandoeuvre lès, Nancy, France;* [2]*Division of Cardiovascular Medicine, Nouvel Hôpital Civil, Strasbourg University Hospital, Strasbourg, France;* [3]*Robertson Centre for Biostatistics, Institute of Health and Wellbeing, University of Glasgow, Glasgow, UK;* [4]*CIBERCV, Servicio de Cardiología, Hospital Germans Trias i Pujol, Universitat Autònoma de Barcelona, Barcelona, Spain;* [5]*Department of Health, Medicine and Caring, Linköping University, Linköping, Sweden;* [6]*Department of Medicine, Karolinska Institutet, and Department of Cardiology, Karolinska University Hospital, Stockholm, Sweden;* [7]*Emergency Department, Hôpitaux Universitaires de Strasbourg, Strasbourg, France;* [8]*INSERM (French National Institute of Health and Medical Research), UMR 1260, Regenerative NanoMedicine (RNM), Fédération de Médecine Translationnelle (FMTS), University of Strasbourg, Strasbourg, France;* [9]*Université de Lorraine, APEMAC, équipe MICS, Nancy, France;* [10]*Emergency Department, University Hospital of Nancy, Nancy, France;* [11]*INSERM, UMRS 1116, University Hospital of Nancy, Nancy, France;* [12]*Pôle vasculaire, service de cardiologie, centre hospitalo-universitaire de Reims, Reims, France;* [13]*Department of Cardiology, CHU Dijon, Dijon, France;* [14]*Université de Lorraine, APEMAC, Metz, France;* [15]*Department of Cardiology, Hôpital Emile Muller, Mulhouse, France;* [16]*Service de cardiologie, Centre hospitalier de Troyes, Troyes, France;* [17]*Unité Fonctionnelle Dédiée à L'insuffisance Cardiaque, Pôle Médical et Chirurgical des Maladies Cardio-vasculaires, Hôpitaux Universitaires de Strasbourg, Strasbourg, France;* [18]*Department of Cardiology, Regional Hospital, Mercy Hospital, Metz, France;* [19]*Department of Cardiology, University Hospital Besançon, Besançon, France; and* [20]*EA3920 University of Burgundy Franche-Comté Besançon, Besançon, France*

Introduction

Randomized controlled trials (RCTs) have established the efficacy of several therapies to improve both symptoms and outcomes for patients with heart failure and reduced left ventricular ejection fraction (HFrEF). It is now recommended to rapidly initiate all four pillars of life-saving HFrEF therapy [viz. angiotensin receptor–neprilysin inhibitor (ARNI), beta-blocker, mineralocorticoid receptor antagonist (MRA), and sodium glucose cotransporter 2 inhibitor (SGLT2i)] and subsequently uptitrate to the maximum tolerated dose.[1] Yet evidence suggests suboptimal use of HFrEF therapies, partly due to therapeutic inertia.[2]

Therapeutic inertia could be defined as the failure to modify therapy according to guidelines, when clinically indicated.[3] Multiple reasons can lead to therapeutic inertia: patient apparent stability (falsely suggesting no need for further optimization), physician lack of time, training, or experience, factors related to socioeconomical aspects, and poor awareness of recent therapeutic developments, reinforced by the absence of practice models focusing on achieving therapeutic goals.[4] Importantly, the term stable HF should be abandoned because it may perpetuate medical inertia, as recently stressed in an expert consensus document that defines HF.[5]

This viewpoint aims to generate greater awareness regarding the clinical consequences of therapeutic inertia in HFrEF and at proposing specific solutions. This debate is of uttermost importance in light of the arrival of SGLT2 inhibitors in the core treatment of HFrEF, even more so in the context of the COVID-19 pandemic, where access to specialist care has been substantially limited for patients with HFrEF.

Therapeutic inertia in heart failure

The importance of therapeutic inertia in heart failure was emphasized by the European Society of Cardiology (ESC) in two European Surveys[6]: despite improvement in quality of care across Europe, 20% of patients hospitalized with HF in 2016 were still identified as not treated according to guidelines. More recently, the OFICA Study,[7] which included >1600 patients hospitalized with HF in 170 French centres on a single day, found that discharge medications were rarely at optimal dosage and remained largely unchanged following

discharge.[8] The result is that a large proportion of patients with HFrEF does not receive cardinal HF treatments or is prescribed suboptimal doses.[9–11] Recently, the CHAMP-HF registry showed that only 1% of patients with HFrEF was treated, simultaneously, with target dose of ACE-I/ARB/ARNI, beta-blocker, and MRA.[9] Reasons for not prescribing, or not up-titrating guideline-recommended medications might be many, but when audited, they are commonly not reported or clearly stated. One of these might be the fear to change the status quo or the risk to be blamed if an adverse event occurs after any treatment modification: in other words, because of therapeutic inertia.[12,13] However, these data need to be tempered, because considering therapeutic inertia as a failure of achieving optimal target doses accordingly to guidelines might be reductive. The maximum tolerated dose (i.e. higher doses are related to important adverse events—especially hypotension and severe worsening in renal function—that cannot be tolerated) is actually what matters from a clinical standpoint.

Determinants of and potential remedies against therapeutic inertia

'Risk treatment paradox'

A 'risk treatment paradox' concept has been proposed, meaning sicker patients receive fewer and lower doses of HF medications.[9] This may reflect fear of adverse events in frailer patients. The potential benefit of treatment initiation/up-titration might be underestimated and may reflect a misguided belief that symptoms are related to medication rather than to the illness itself.[14] Trial evidence suggests that relative risk reduction are similar regardless of severity, meaning that absolute risk reductions are greater in sicker patients. However, higher risk often parallels a higher burden of co-morbidities and authentic physiological limitation limiting the ability to optimize GDMT.[15]

Renal dysfunction and dyskalaemia

Hyperkalaemia and renal dysfunction are main drivers of RAASi underuse.[16,17] The fear of inducing these adverse events ('primum non nocere') may instead deprive patients of life-saving drugs. For instance, data from the ESC-HF long-term registry showed that hyperkalaemia was associated with a higher probability of discontinuing RAASi, which was associated with increased mortality.[18]

Pragmatic practical algorithms can be of assistance (as the recently proposed A2M algorithm[16]). Compared with ACE-I, the use of ARNI decreases the risk of renal dysfunction and severe hyperkalaemia in HFrEF.[19] Adding an SGLT2 inhibitors would also prevent deterioration of kidney function and decrease the risk of hyperkalaemia.[20] The use of novel potassium binders could normalize K levels; whether this will lead to higher prescription or RAASi and better outcomes is currently under evaluation.[21,22]

Hypotension

Low blood pressure is a marker of more advanced disease and associates with poor prognosis but does not diminish the efficacy of HF treatments.[23] Yet low BP is a common barrier to HFrEF medication use and up-titration.[24] Even with systolic BP $>$ 110 mmHg, a majority of patients do not receive target doses of GDMT,[25] suggesting that overemphasized fear of hypotension (or therapeutic inertia) may exist.

ESC guidelines recommend that a heart-failure specialist advice should be sought rather than simply discontinuing or decreasing drugs with Class I indication in HFrEF in patients with persistent low BP or symptoms of hypotension. A pharmacological management algorithm, based on a comprehensive review of available evidence aimed at helping physicians treat HFrEF patients with low BP, has been recently proposed.[24] Reducing diuretic dose or stopping unnecessary medications (i.e. calcium-antagonists) should be considered to improve their management in this situation.[24]

Difficulties related to health care systems

Limited access to HF expertise is a major driver of both therapeutic inertia and poor implementation more generally.[26,27] The number of patients with HF is increasing in Europe and USA (mostly in the context of rising number of HF with preserved ejection fraction), and current healthcare systems are not well developed to provide optimal care for everyone, fuelling inertia. Many patients with HFrEF do not receive cardiology input whilst in hospital, and many others are not followed-up early after discharge or are only managed by primary care physicians.[26]

Disease management programmes remain underdeveloped and/or inadequately implemented, even though they offer specialized follow-up, improve HF prognosis, and are cost-saving.[28]

Finally, aside from healthcare systems, awareness of HF burden is limited in the general population and underrepresented in the media. This may favour the absence of incentive from healthcare systems to optimize HFrEF treatment. Those incentives are needed as treatment optimization is by

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nature time/resource-consuming in comparison with therapeutic inertia.

How to develop a global response to fight therapeutic inertia

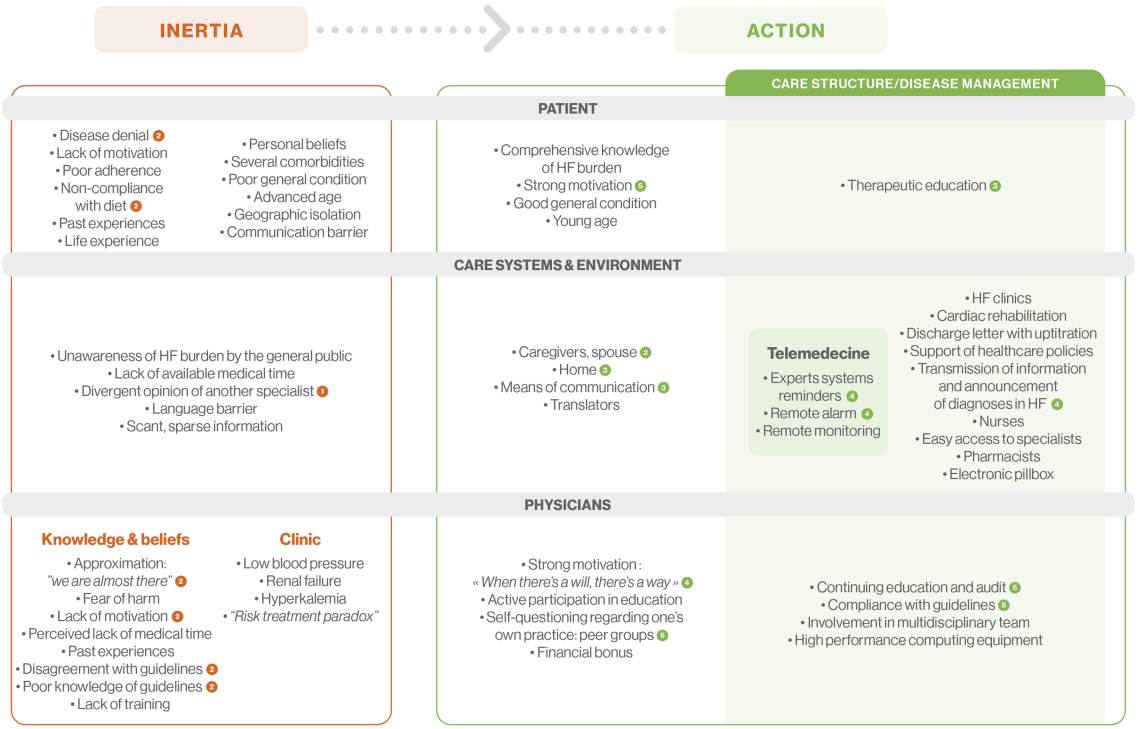
The determinants and possible solutions to inertia are shown in *Figure 1*.

As a comparison with HF, management of cancer has evolved towards integrated pathways of care, involving dedicated/specialized clinical structures. HFrEF morbidity and mortality is similar to many of the most severe cancers, but such effort has been scarcely undertaken in HFrEF. We believe that dedicated units/systems, providing specialist knowledge and experience for early HF diagnosis and treatment optimization, could reduce therapeutic inertia and improve outcomes. Importantly, the level of inertia and the most prominent cause for inertia are likely largely varying across geographical regions, either across countries or within different regions of a given country. The most appropriate approach to fight inertia is consequently to individualized to the context/geographical aspects.

Management of hospitalized patients

Multidisciplinary HF team management is recommended to improve guideline adherence, reduce hospitalizations, and costs.[28] Mobile HF units are particularly suited to manage HF in hospitals. These multidisciplinary teams typically include HF cardiologists and specialist HF nurses, able to assess and provide therapeutic counselling in non-HF units. HFrEF patients are frequently hospitalized in non-cardiovascular wards (e.g. internal medicine and geriatrics)[26] for issues related or unrelated to HFrEF. As the core of these HF units is more focused on HF, it is likely that their interventions will improve quality of care and limit therapeutic inertia (e.g. aiming to discharge patients on the four pillars of HFrEF pharmacological therapy).

Figure 1 Determinants and solutions to therapeutic inertia.



Transition of care

An early follow-up visit after discharge is a crucial feature of transition of care to decrease risk of premature re-hospitalization or death.[29] Current HF guidelines recommend a follow-up visit 7–14 days after hospital discharge and the inclusion of patients in DMP. Transition of care based on home-visiting programmes and multidisciplinary HF clinic interventions have been shown to reduce all-cause readmission[30] and mortality.[31] These early follow-ups are an opportunity to maximize the four pillars of HFrEF treatment and identify their side-effects earlier, while some of the barriers to treatment optimization faced during the hospital stay fade away.

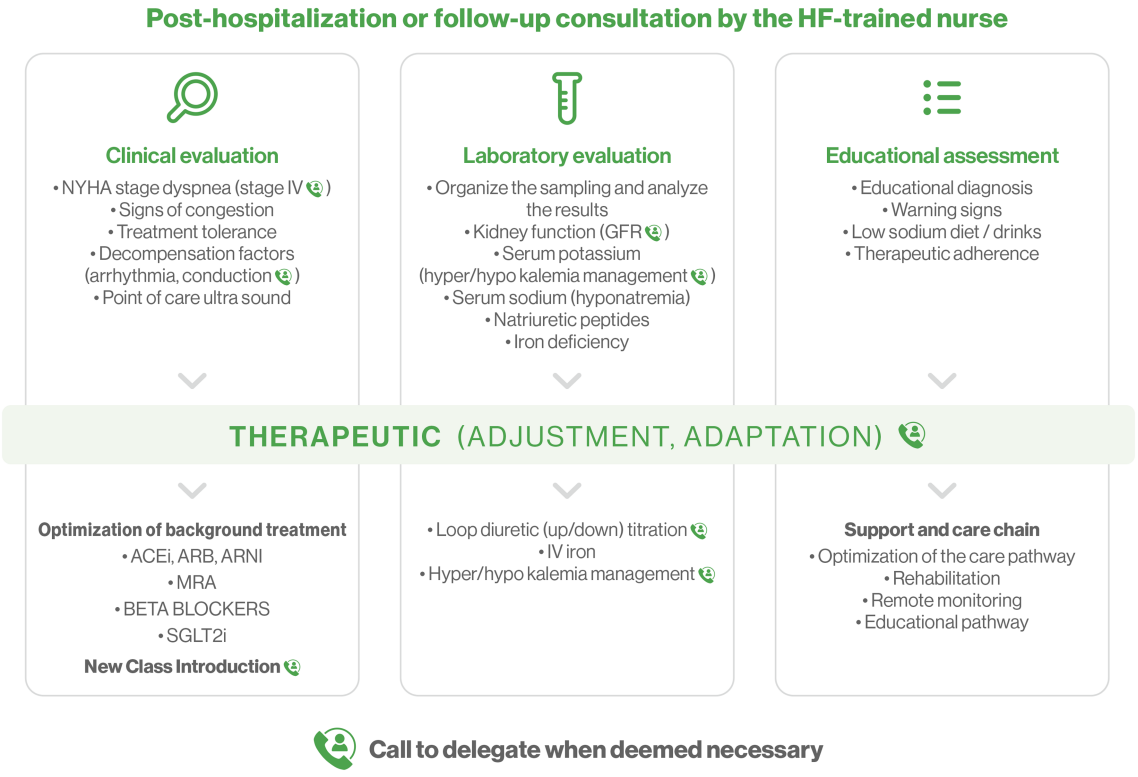
Heart failure clinics

Dedicated HF clinics (which can be highly involved in transition of care) improve management of HF and possibly outcomes (p.e. in Swedish and Canadian HF centres experience[32,33]). These HF clinics can operate in hospitals through medical and nurses' consultations, day hospitalization, and telemedicine bundles. Importantly, these facilities should be able to rapidly see patients with suspected worsening HF in order to identify factors triggering decompensation and tailor investigations and therapies. They may furthermore operate through ambulatory IV diuretics infusion.[34] Despite their usefulness, the use of HF clinics is suboptimal, possibly due to lack of capacity, geographical considerations, and funding issues.[35]

Ambulatory disease management programmes

DMP, usually providing care outside of hospitals, have been shown to reduce the risk of both all-cause mortality and HF-related hospital readmission by approximately 30%[36] and are now formally recommended in 2021 ESC guidelines on HF. The implementation of these DMPs now often relies on telemonitoring (and e-tools) and telemedicine solutions[37] (including remote monitoring of pulmonary artery pressure). These e-Health approaches are even more cardinal following the advent of the COVID-19 pandemic (which highlighted the limitations of our healthcare organizations in HFrEF). Telemedicine has the major advantage of being relatively unaffected by lockdowns or periods of quarantine, decreases risks of infection, and, therefore, ensures continuity of care even during a pandemic.[38]

Figure 2 Tasks that could be delegated to HF-trained nurses.



The role of heart failure nurses to tackle therapeutic inertia

Specialist HF nurses are usually the cornerstone of DMPs and HF clinics. Over the years, a number of countries have developed programmes certifying specialized HF nurses. The tasks that can be delegated to HF nurses are illustrated in *Figure 2*. The benefit of nurse-lead HF management covers the initiation and up-titration of live-saving HF drugs and results in reduced risk of hospitalization.[39] Importantly, the access of such nurse led management is not currently available all across Europe.

Patients (and their families) empowerment

Healthcare providers can have powerful interactions with their patients and thus influence their decisions. In addition, as emphasized in *Figure* 1, a patient's close circle of friends, family, and caregivers creates a physician–patient–caregiver team that reduces the risk of therapeutic inertia. The efficacy of patient empowerment has been emphasized recently by the EPIC-HF trial.[40] Patient education can reinforce the partnership between health professionals and patients (i.e. patient-care partner approach).

Fast-track approach to medication up-titration

How to best achieve an optimal dose of the four pharmacological pillars in HF is a matter of debate (and likely practice progress).[22,41] A plea for a near-simultaneous initiation of all four HF drugs have been promoted by Green *et al*.[22] These faster approaches to treatment initiation/up-titration may facilitate reaching optimal pharmacological treatment, especially if implemented in the aforementioned systemic tools (HF clinics, DMPs) dedicated to HFrEF treatment optimization. These fast-track strategies, given the very rapid effect of drug following initiation,[22] may have a sizable short-term prognostic effect. Importantly, given the rapidity of their action, the absence of treatment optimization should actually be perceived as an accountable risk to the patient, something that could actually tackle therapeutic inertia.

Conclusions

Therapeutic inertia appears as a major barrier to achieving optimal HF care. A number of tools can be used to combat therapeutic inertia (as emphasized in *Figure* 1), most of which rely on dedicated HF healthcare models of care. We propose that multidisciplinary management, the rising availability/empowerment of dedicated HF nurses, patient/public awareness/empowerment, the increasing use of telemedicine and e-tools embedded in modern models of care, and recognition of HF care specificity can reduce therapeutic inertia in HFrEF. Notwithstanding the latter, we need healthcare policies and support from both payers and decision-makers that will hasten this change and support progress towards a zero-tolerance to therapeutic inertia.

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