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INVITED EDITORIAL

Rapid uptitration: what's the evidence?

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This article refers to 'Sequencing and titrating approach of therapy in heart failure with reduced ejection fraction following the 2021 European Society of Cardiology guidelines: an international cardiology survey' by C. Fauvel *et al.*, published in this issue on pages 213–222.

In the recent 2021 European Society of Cardiology (ESC) guidelines, the 'foundational four' therapies, including angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor–neprilysin inhibitors (ARNI), mineralocorticoid receptor antagonists (MRA), and sodium–glucose cotransporter 2 inhibitors (SGLT2i), are recommended for patients with heart failure (HF) with reduced ejection fraction (HFrEF).[1] In contrast to the earlier 2016 ESC HF guidelines, which followed the 'traditional' uptitration sequence according to the chronological order of trials,[2] the new guidelines focus on co-initiation and faster uptitration.

However, adequate uptake of guideline-directed medical therapy (GDMT) remains challenging, even though therapies are proven to improve outcome and quality of life in patients with HF. Several treatment barriers, such as health insurance-, provider- and patient-related barriers, prevent optimization of GDMT. Provider-related barriers consist of understaffing in outpatient cardiology clinics and lead to increased likelihood of patients not being on GDMT.[3] Furthermore, physician or clinical inertia, defined as the failure to initiate, intensify or change effective, well-tolerated therapies despite their availability, has been proposed as an explanation.[4] Some inertia is the result of (perceived) risk of worsening renal function and hyperkalaemia, in particular in patients with a recent hospital admission for HF.[5] However, no data are available on the perception on implementation of the HF guidelines in physicians, and cardiologists in particular as they might struggle with decision-making. Moreover, as there is no randomized clinical trial performed to evaluate the effect of simultaneous initiation of low doses of quadruple therapy versus sequential use of the four classes of HF drugs in patients with HFrEF, clinical practice differs in the cardiology community (including cardiologists, HF specialists, and other physicians).

Therefore, Fauvel *et al.*[6] investigated the opinion of cardiologists on sequencing, titration and optimal timing of all the recommended HFrEF drugs in their work published in this issue of the Journal. The authors present results from a large international survey, with data collected among more than 600 practicing cardiologists from 55 countries. Interestingly, although the majority of physicians ($n = 358$, 58%) stated that adding another HFrEF drug class is more important than uptitrating those already started, the sequential 'historical approach' remained the preferred strategy. The order of preferred sequence appeared to be starting with ACEi or ARNI, beta-blocker next, MRA after, and lastly, adding an SGLT2i. However, most participants (84%) agreed it is feasible to start the four foundation therapies together.

Notably, there were differences in prescribing habits, with HF specialists considering optimizing treatment more frequently when compared to non-specialists ($p = 0.002$), and reaching full uptitration in more than 50% of cases by 56% of specialists, versus 37% in non-specialists ($p < 0.001$). In patients with an estimated glomerular filtration rate (eGFR) <30 ml/min, 65% of the total participants choose to introduce an MRA, increasing to 69% in HF specialists. Furthermore, the main side effects observed by participants were cough in patients receiving ACEi ($n = 231$, 38%), symptomatic hypotension with ARNI ($n = 456$, 75%), hyperkalaemia with MRA ($n = 507$, 83%), bradycardia with beta-blocker ($n = 369$, 59%), and urinary tract infection with SGLT2i ($n = 318$, 52%). However, whether these adverse events had any effect on their subsequent medical decision-making to not start, decrease, or discontinue any of these life-saving HFrEF therapies was not investigated. The real question therefore still remains, what type of evidence is needed to fill the continuing implementation gap?

Although the survey by Fauvel and colleagues is very timely, we need to acknowledge its limitations. No random sampling strategy was used, and therefore the representativeness and generalization of the results are limited. The scope of respondents differs from real-world cardiologists, as HF specialists were likely overrepresented. Therefore, the results of Fauvel *et al.* possibly reflect a 'best-case' scenario. Moreover, the questions were rather general,

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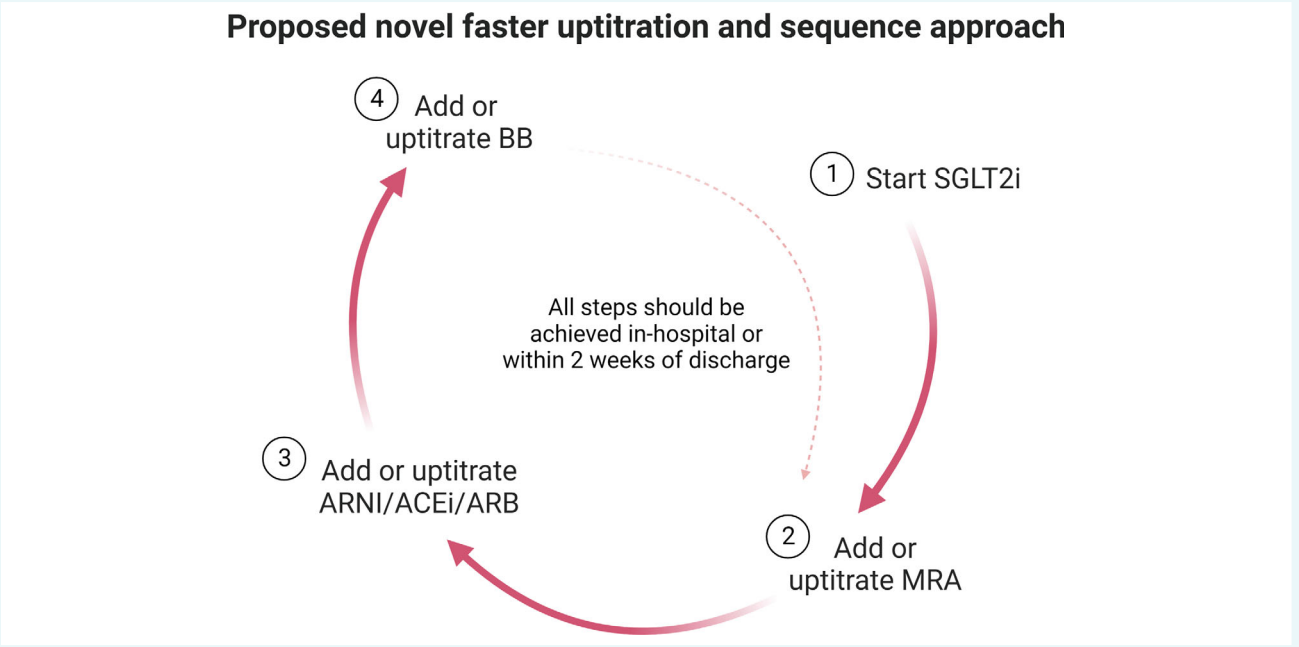

Figure 1 Proposed faster uptitration sequencing approach. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BB, beta-blocker; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

with no follow-up questions investigating possible causes or consequences of treatment discontinuation, nor the underlying rationale of their decision-making. However, their findings emphasize the importance of awareness and can serve as a starting point for future studies.

Recently the Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-proBNP Testing, of Heart Failure Therapies (STRONG-HF) trial demonstrated the effectiveness of fast uptitration to 100% of recommended dose of ACEi or angiotensin receptor blockers (ARB) or ARNI, beta-blockers and MRAs within 2 weeks of discharge versus usual care in patients admitted for HF.[7] The trial was stopped early due to overwhelming benefit in the intensive treatment strategy group compared to usual care. This suggests that patients admitted for HF benefit the most when treatment is started and quickly uptitrated in-hospital, and that this benefit is not limited to patients with HFrEF but also includes patients with HF with mildly reduced and preserved ejection fraction.

However, data from the STRONG-HF trial do not provide evidence for the best treatment sequencing strategy. A recent modelling study by Shen *et al.*[8] suggests that an uptitration sequence starting with an SGLT2i or MRA was associated with the greatest potential benefit. The potential additional benefits of starting with an SGLT2i or MRA was a consequence of the speed of getting to target dose: SGLT2i is a single fixed dose and MRAs only require two dose steps.[8] In contrast, beta-blockers require multiple steps and are often started at between one-sixteenth and one-eighth of the intended target dose.[8] Combined with data from STRONG-HF, this suggests that sequences starting with medications with the fewest dose steps might be most beneficial. The fact that SGLT2i might reduce the risk of hyperkalaemia and have renal protective effects might tip the scale to choosing SGLT2i, perhaps together with an MRA, as the first medication of choice (*Figure 1*). One might even argue that for patients with HF, starting SGLT2i and MRA in-hospital could have additional beneficial diuretic effects and reduce residual congestion.[9–11]

Within this context, the survey by Fauvel *et al.* provide an important baseline assessment of contemporary cardiologists' thinking.[6] Their results show that most cardiologists and physicians still prefer the conventional uptitration sequence, which largely follows the chronology of clinical trials. However, most participants felt that rapid uptitration within 1 month was feasible, demonstrating physicians' openness to change. The results of STRONG-HF support rapid uptitration. However, the likelihood that therapy sequence strategy trials will be implemented and funded is low, especially given the large number of sequencing combinations and limited industry incentives. Instead, to start with recommended medications with the fewest dose steps seems a logical starting point. As Fauvel *et al.* suggest, a shift to better implementation strategies of existing therapies, through for example nurse-led HF clinics or electronic decision support tools, is warranted.[3,6] Therefore, future studies are required focusing on implementing strategies to optimize HF therapy.

In conclusion, data from the survey by Fauvel and colleagues provide important new evidence on the understanding of physicians of uptitration strategies. Their results demonstrate the awareness of physicians of the importance of uptitration and openness to change, highlighting an opportunity to optimize therapy.

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References

1. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail*. 2022;**24**:4–131.
2. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail*. 2016;**18**:891–975.
3. Tromp J, Voors AA. Heart failure medication: moving from evidence generation to implementation. *Eur Heart J*. 2022;**43**:2588–90.
4. Greene SJ, Butler J, Albert NM, DeVore AD, Sharma PP, Duffy CI, et al. Medical therapy for heart failure with reduced ejection fraction: the CHAMP-HF registry. *J Am Coll Cardiol*. 2018;**72**:351–66.
5. Beldhuis IE, Lam CSP, Testani JM, Voors AA, Van Spall HGC, Ter Maaten JM, et al. Evidence-based medical therapy in patients with heart failure with reduced ejection fraction and chronic kidney disease. *Circulation*. 2022;**145**:693–712.
6. Fauvel C, Bonnet G, Mullens W, Giraldo CIS, Mežnar AZ, Barasa A, et al. Sequencing and titrating approach of therapy in heart failure with reduced ejection fraction following the 2021 European Society of Cardiology guidelines: an international cardiology survey. *Eur J Heart Fail*. 2023;**25**:213–22.
7. Mebazaa A, Davison B, Chioncel O, Cohen-Solal A, Diaz R, Filippatos G, et al. Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF): a multinational, open-label, randomised, trial. *Lancet*. 2022;**400**:1938–52.
8. Shen L, Jhund PS, Docherty KF, Vaduganathan M, Petrie MC, Desai AS, et al. Accelerated and personalized therapy for heart failure with reduced ejection fraction. *Eur Heart J*. 2022;**43**:2573–87.
9. Heerspink HJL, Jongs N, Chertow GM, Langkilde AM, McMurray JJV, Correa-Rotter R, et al.; DAPA-CKD Trial Committees and Investigators. Effect of dapagliflozin on the rate of decline in kidney function in patients with chronic kidney disease with and without type 2 diabetes: a prespecified analysis from the DAPA-CKD trial. *Lancet Diabetes Endocrinol*. 2021;**9**:743–54.
10. Adamson C, Docherty KF, Heerspink HJL, de Boer RA, Damman K, Inzucchi SE, et al. Initial decline (dip) in estimated glomerular filtration rate following initiation of dapagliflozin in patients with heart failure and reduced ejection fraction: insights from DAPA-HF. *Circulation*. 2022;**146**:438–49.
11. Lin DSH, Lee JK, Chen WJ. Clinical adverse events associated with sodium-glucose cotransporter 2 inhibitors: a meta-analysis involving 10 randomized clinical trials and 71 553 individuals. *J Clin Endocrinol Metab*. 2021;**106**:2133–45.