# Medication Titration in Heart Failure: Too High or Too Complex?

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The prevalence of heart failure (HF) continues to rise, driven by an ageing population, increasing rates of obesity , diabetes, and better survival in patients with cardiovascular disease [1]. While HF is associated with substantial morbidity and mortality, large-scale randomized controlled trials (RCTs) have demonstrated that angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs) , beta-blockers and mineralocorticoid receptor antagonists all improve clinical outcomes in patients with HF associated with a reduced left ventricular ejection fraction (HFrEF) [2-9]. Indeed, such studies suggest that the combination of an ACEI/ARBs and beta-blockers may translate to a 60–70 % relative risk reduction in all-cause mortality [10]. The large HF RCTs evaluating the efficacy of ACEIs, ARBs and beta-blockers used forced up-titration at pre-specified intervals, unless there were adverse events or intolerance, aiming for target doses largely guided by those used to treat hypertension.

As a result, HFrEF prescription rates for both ACEIs/ARBs and beta-blockers have increased substantially over the past two decades [11-13] ,such that 92 % of patients were on ACEI or ARBs therapy and 93% were on beta-blockers in the recent European Society of Cardiology Heart Failure Long-term Registry, with most of those patients not on treatment having a documented contraindication or previous medication intolerance [13]. Nevertheless, recent reports suggested that only 10-30% of patients were on target doses of ACEI/ARBs and 18 % were on target doses of beta-blockers, with approximately one-third having no reason documented for the failure to up-titrate.

This contrasts with the RCTs, where at least 50-60% of patients achieved target doses.[2,3,7-9].One reason for the low titration rates achieved in clinical practice may be that the patients are not selected in the same way as those enrolled in clinical trials; in practice, patients are generally over a decade older with numerous co-morbidities. Other Barriers to medication titration include health-provider knowledge, self-efficacy and attitudes; patient-related factors, including age, body mass index, co-morbidities and polypharmacy; and limited time and support structures to facilitate regular monitoring.[14,15] Patients also frequently demonstrate transition between the acute and community healthcare sectors which further complicates care coordination.

In the July 2020 issue of the *Israeli Medical Association Journal* (*IMAJ*) Itzhaki Ben Zadok and colleagues [16] determined the baseline characteristics associated with attaining upper-range recommended doses of ACEI/ARBs and beta blockers in an up-titration program of HFrEF patients treated in a community-based, dedicated HF clinic. Upper-range recommended doses were defined as ≥ 75% of target recommended doses by heart failure society guidelines and were achieved in 41% and 35% of patients receiving ACEI/ARBs and beta blockers, respectively. Achievement of upper-range ACEI/ARBs doses was associated with elevated body mass index (BMI) even after adjusting for other co-morbidities (at the range of BMI < 40 kg/m2).In addition, presence of diabetes and male gender were independently associated with upper-range doses. The authors concluded that these findings may serve as benchmarks for up-titration programs.

The most important point evolving from the study is the importance of dedicated outpatient heart failure programs to facilitate the treatment in this patient group while identifying markers for higher success. Indeed, past clinical studies demonstrated the efficacy of multidisciplinary HF disease management [17]. These include the availability of dedicated physicians, nursing and pharmacists' staff that undertake regular follow-up and monitoring of their patients and also provide a convenient point of contact.

In a study of specially trained nurses working in a dedicated HF clinic, the percentage of patients receiving the goal dose of β-blocker therapy increased from 10–43% as a result of more frequent interaction between nurses and patients and adherence to standardized practices [18]. In another study of a nurse-managed, structured remote telephonic titration protocol, 71% of patients reached the target daily dose of beta blockers in approximately 8 weeks without safety problems [19]. No HF hospitalizations occurred during remote titration. These observations suggest that more focused interventions addressing dose titration may be required to improve the portion

of patients treated at target doses. This may include enhanced systems of care to better educate patients to expect dose up-titration even if their HF symptoms have improved or resolved, to provide more prominent point-of-care physician decision support for up-titration, and to ensure outpatient follow-up visits at set intervals until target doses are achieved.

## LIMITATIONS

A few limitations of the present study require mention. Some unmeasured variables may have impacted the results. As a single-centered study the results may not apply to other up-titration programs in inpatient or outpatient clinics. Exclusion criteria made patient selection bias prominent, as patients with good compliance were more likely to adhere to visits in the clinic. Furthermore, there was a potential inaccuracy of attaining information on medication doses from the electronic drug prescription fill, which may not represent the actual dose taken by patients.

## CONCLUSIONS

We should congratulate Itzhaki and colleagues for pointing an important, yet often forgotten, issue. The challenge for future physicians will be to address the need for strategies that engage primary care with timely communication, clear role delineation and point-of-care decision support may have wider applicability to allow the impressive gains demonstrated in the clinical trials to be applied to the broader HF population.

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**Capsule**

## Promising antiviral protease inhibitors

With no vaccine or proven effective drug against the virus that causes coronavirus disease-2019 (COVID-19), scientists are racing to find clinical antiviral treatments. A promising drug target is the viral main protease Mpro, which plays a key role in viral replication and transcription. **Dai** et al. designed two inhibitors, 11a and 11b, based on analysis of the structure of the Mpro active site. Both strongly inhibited the activity of Mpro and showed good antiviral activity in cell culture. Compound 11a had better pharmacokinetic properties and low toxicity when tested in mice and dogs, suggesting that this compound is a promising drug candidate.

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