Incremental efficacy of medical therapy for chronic heart failure with a reduced ejection fraction: a systematic review and network meta-analysis

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Topic(s):
Pharmacotherapy

Background
Over the last three decades, the step-wise addition of new drugs, including beta-blockers (BB), angiotensin-converting enzyme inhibitor (ACEi)/angiotensin receptor blockers (ARB), mineralocorticoid receptor antagonists (MRA), ivabradine (IVA), and angiotensin receptor neprilysin inhibitor (ARNI), has improved the outcomes of heart failure with reduced ejection fraction (HFrEF). Additional medications have been tested in recent randomized controlled trials (RCTs), individually showing benefit as compared with placebo.

Purpose
We performed a network meta-analysis (NMA, PROSPERO ID CRD42021228040) of all published evidence regarding the effects of pharmacological treatments for chronic HFrEF on all-cause death, cardiovascular (CV) death, and hospitalization for HF (HHF).

Methods
We systematically searched the major biomedical databases from inception to November 30th, 2020, and selected the phase 2 and 3 RCTs that compared investigational drugs vs. placebo or other drugs in HF populations with ≥90% subjects with a left ventricular EF <45%, and did not limit the enrollment to specific patient subgroups (e.g. with diabetes). NMA was based on a conservative random-effects model within a Bayesian framework using R software. The log follow-up time was used to transform the probability of an event into a constant rate for each trial arm by assuming an underlying Poisson process, and a log link was used to model the event rates. Non-informative priors were used.

Results
We included 70 RCTs comprising 92,661 patients, 149,533 patient/years and 16 different combinations of drugs, constituting a quasi-chronological progression-network of medications for HFrEF (Figure 1).

The random-effects NMA confirmed that the combination of BB, ACEi, ARB, and MRA reduced the risk of the tested outcomes as compared with single- or two-drug treatment approaches (Figure 2).

ARNI+BB+MRA and SGLT2 inhibitors (SGLT2i)+BB+ACEi+MRA were the most effective therapeutic strategies in decreasing all-cause death (HR 0.36, 95%CrI 0.20-0.59; and 0.37, 95%CrI 0.22-0.59, respectively), CV death (HR 0.33, 95%CrI 0.15-0.60, and HR 0.36, 95%CrI 0.18-0.63), and HHF (HR 0.24, 95%CrI: 0.11-0.43; and HR 0.23, 95%CrI 0.12-0.37) vs. placebo.

The risk of the adverse outcomes was also lower with IVA or vericiguat (VERI) on top of BB+ACEi+MRA than with triple neurohormonal inhibition alone, while it was comparable with nesiritide or ivermectin micarbil (OM) in addition to BB+ACEi+MRA vs. BB+ACEi+MRA (Figure 2).

Conclusions
The reduction in mortality and hospitalization in HFrEF attained by medical therapy is incremental and further enhanced by at least some of the most recent drugs. According to RCTs, state-of-the-art pharmacotherapy diminishes by about 60% the risk of death and by about 75% the one of HHF in HFrEF patients.
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The reduction in mortality and hospitalization in HFrEF attained by medical therapy is incremental and further enhance by at least some of the most recent drugs. According to RCTs, state-of-the-art pharmacotherapy diminishes by about 65% the risk of death and by about 75% the one of HHF in HFrEF patients.