STORY OF THE WEEK

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Identifying Optimal Doses of Heart Failure Medications in Men Compared With Women

The Lancet

1 Expert Comment

TAKE-HOME MESSAGE

- This post hoc analysis of data from the prospective European BIOSTAT-CHF study examined the effects of gender on optimal doses of ACE inhibitors, ARBs, and beta blockers in patients (1308 men and 402 women) with heart failure with reduced ejection fraction (HFrEF). Eligible patients had a left ventricular ejection fraction (LVEF) <40% and survived at least 3 months after initiation or up-titration of ACE inhibitors, ARBs, or beta blockers. Women were significantly older than men (74 vs 70 years). Although there was no significant difference in BMI by gender, women were shorter and weighed less than men. Guideline-recommended target doses of ACE inhibitors, ARBs, and beta blockers were reached in similar numbers of men and women. Although men taking 100% of the recommended dose of these medications had lower hazards of hospitalization for heart failure or death, women had a 30% lower risk of these outcomes at 50% of the guideline-recommended target dose and did not show further benefits with increased doses.
- Although guideline-recommended doses of ACE inhibitors, ARBs, and beta blockers are currently the same for men and women, these results suggest that the optimal therapy for women may require lower doses.

Cardiology

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A major theme in the care of patients with heart failure is optimizing the benefit of guideline-directed medical therapy (GDMT) for heart failure with reduced ejection fraction. Multiple recent reports have highlighted the consistent shortcomings in the attainment of optimal doses of life-enhancing therapies. It is important to note, however, that optimal doses of current GDMT are based less on drug effect or pharmacology and more on agreed-upon targets, some empirically derived, in randomized controlled trials. Age, race, sex, and comorbidities have all been implicated as circumstances impacting the pharmacokinetics of evidence-based therapy, but careful study of how these important patient cohorts with heart failure affect target dosing of GDMT has not yielded a verified and actionable database. Understanding pharmacogenomics and implementing a precision medicine approach are the ideal goals, but we are not yet there for any of the proven effective therapies for heart failure. Now, however, we have new data evaluating the influence of sex on optimal doses of GDMT for heart failure.

Voors et al performed a post hoc analysis of BIOSTAT-CHF, a study in heart failure in which the doses of ACE inhibitors, ARBs, and beta blockers were up-titrated by protocol. A primary outcome of all-cause mortality or hospitalization for heart failure was evaluated after accounting for at least a 3-month survival. The data were evaluated according to sex for 1308 men and 402 women. Findings confirmed the lowest hazard of death or hospitalization at 100% of recommended doses in men. At only 50% of recommended doses, women

manifested a 30% reduction in risk with no further benefit at higher doses. A validation dataset within ASIAN-HF interestingly confirmed the same finding. These findings would argue that our approach to heart failure should vary significantly as a function of sex. Is that a correct approach and should we change our treatment strategies? For a US-based population, these data were derived in European cohorts and validated in Asian cohorts. To the extent that genetic diversity varies according to geographic locations, these data may not be relevant for North American populations. As well, post hoc analyses are always subject to confounding and should be interpreted as worthy ideas to pursue, but not as definitive evidence.

These data, when carefully interpreted, are important and do make clear that a singular approach in the titration of GDMT is not ideal. But recognizing differences in drug therapy as a function of sex is only the first step and is clearly not sufficient. This kind of reductionist logic will undoubtedly lead to under-treatment in some women and over-treatment in others. Moreover, it would subject all men with reduced ejection fraction heart failure to substantial doses of GDMT that may expose harm rather than lead to additional benefit. The concerns of age, race, and genetic influences on drug metabolism, polypharmacy, and comorbidities still remain, and therapeutic misadventures are an ever-present risk. In an era with multiple effective medical therapies and a growing portfolio of informative biomarkers as well as surrogate indices of ventricular function, we can do better than this. The current data are important when we consider populations affected by heart failure; but, for the practitioner, *the key consideration is what dose and which agents are most effective for a given patient?* While we await true precision medicine, dosing targets for GDMT in the setting of heart failure with reduced ejection fraction should be considered guides not edicts. Finesse should prevail over hammers and good clinical judgement remains the immutable standard of care.

Abstract

BACKGROUND

Guideline-recommended doses of angiotensin-converting-enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs), and β blockers are similar for men and women with heart failure with reduced ejection fraction (HFrEF), even though there are known sex differences in pharmacokinetics of these drugs. We hypothesised that there might be sex differences in the optimal dose of ACE inhibitors or ARBs and β blockers in patients with HFrEF.

METHODS

We did a post-hoc analysis of BIOSTAT-CHF, a prospective study in 11 European countries of patients with heart failure in whom initiation and up-titration of ACE inhibitors or ARBs and β blockers was encouraged by protocol. We included only patients with left ventricular ejection fraction less than 40%, and excluded those who died within the first 3 months. Primary outcome was a composite of time to all-cause mortality or hospitalisation for heart failure. Findings were validated in ASIAN-HF, an independent cohort of 3539 men and 961 women with HFrEF.

FINDINGS

Among 1308 men and 402 women with HFrEF from BIOSTAT-CHF, women were older (74 [12] years vs 70 [12] years, p<0·0001) and had lower bodyweights (72 [16] kg vs 85 [18] kg, p<0·0001) and heights (162 [7] cm vs 174 [8] cm, p<0·0001) than did men, although body-mass index did not differ significantly. A similar number of men and women reached guideline-recommended target doses of ACE inhibitors or ARBs (99 [25%] vs 304 [23%], p=0·61) and β blockers (57 [14%] vs 168 [13%], p=0·54). In men, the lowest hazards of death or hospitalisation for heart failure occurred at 100% of the recommended dose of ACE inhibitors or ARBs and β blockers, but women showed approximately 30% lower risk at only 50% of the recommended doses, with no further decrease in risk at higher dose levels. These sex differences were still present after adjusting for clinical covariates, including age and body surface area. In the ASIAN-HF registry, similar patterns were observed for both ACE inhibitors or ARBs and β blockers, with women having approximately 30% lower risk at 50% of the recommended doses, with no further benefit at higher dose levels.

INTERPRETATION

This study suggests that women with HFrEF might need lower doses of ACE inhibitors or ARBs and β blockers than men, and brings into question what the true optimal medical therapy is for women versus men.

Additional Info

Disclosures | Article Citation

Disclosure statements are available on the authors' profiles:

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We Recommend

Importance of ACE-Inhibitor and Beta-Blocker Dosing for Outcomes in Patients With Heart Failure
PracticeUpdate, 2017

Medical Therapy for HFrEF
PracticeUpdate, 2018

Impact of ACE Inhibitor and ARB Dose on Outcomes in Heart Failure
PracticeUpdate, 2017

Check the findings of the observational GIOTAG study — sequential afatinib and osimertinib in patients with EGFR mutation-positive non-small-cell lung cancer
Future Oncology

Medical Therapy for Heart Failure With Reduced Ejection Fraction: The CHAMP-HF Registry
Stephen J. Greene et al., Journal of the American College of Cardiology, 2018

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