Prevention of congestive heart failure in high risk patients

Kristian Wachtell*

Department of Cardiology, The Heart Center B2142, Righospitalet, 9 Blegdamsvej, 2100 Copenhagen, Denmark

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This editorial refers to ‘Blood pressure reduction and renin–angiotensin system inhibition for prevention of congestive heart failure: a meta-analysis†, by P. Verdecchia et al., on page 679

Congestive heart failure, in particular with preserved left ventricular ejection fraction, is increasing in incidence. Hypertensive disease is also increasing, and data suggest that this is a major contributor to the increasing incidence of congestive heart failure. In addition, there are data suggesting that patients with hypertension not only have a high prevalence of impaired left ventricular diastolic function, but in particular when left ventricular hypertrophy is present also have a high prevalence of impaired left ventricular myocardial function that in turn can lead to congestive heart failure. Furthermore, there are also data suggesting even more complex relationships between left ventricular systolic and diastolic function and that these conditions are in fact inter-related.3

We and others have shown that blood pressure reduction does in fact improve measures of left ventricular diastolic4 and systolic5 function. Furthermore, it has also been shown that improvement of the electrocardiographic strain pattern during antihypertensive treatment does reduce the risk of new-onset heart failure.6 It seems logical that if reduction in blood pressure can improve myocardial load by improving left ventricular systolic and diastolic function, this in turn would be associated with a reduced risk of subsequent heart failure. However, the data from the Blood Pressure Lowering Treatment Trialists’ Collaboration did not show any clear association between blood pressure reduction and reduced risk of congestive heart failure.7

Another question is whether the same pharmacological treatment used in congestive heart failure with depressed left ventricular ejection fraction is useful for the prevention of heart failure in patients with preserved left ventricular ejection fraction. The study of Verdecchia et al.8 is an interesting meta-analysis evaluating all relevant antihypertensive trials with the goal of estimating how much blood pressure reduction per se reduces risk of subsequent congestive heart failure. The analysis shows that greater blood pressure reduction leads to more prevention of congestive heart failure. For every 5 mmHg reduction in systolic blood pressure, the risk of congestive heart failure decreased by 24%. Furthermore, at any given level of blood pressure reduction, blockade of the renin–angiotensin system was superior to calcium channel blockade for prevention of congestive heart failure that is over and above the blood pressure reduction achieved. Furthermore, treatment with angiotensin-converting enzyme inhibitors (ACEIs) reduced the risk of congestive heart failure by 21% compared with placebo, while calcium channel blockers had no effect, but did on the other hand not increase the risk of congestive heart failure. ACEIs did not reduce the risk of congestive heart failure compared with β-blocker/diuretic combination therapy, while calcium channel blocker therapy was associated with an 18% increased risk of congestive heart failure compared with β-blocker/diuretic combination therapy.

One major concern of the meta-analysis as a modus to derive additional information is that the input equals the output, and the information derived can be flawed by one large study with poor design outweighing smaller studies with proper design. This meta-analysis actually includes data from the large ALLHAT study, a study flawed by the inclusion of blacks with poor blood pressure response to treatment with renin–angiotensin-inhibiting therapy.9 It is reassuring that the authors have performed additional sensitivity analyses, estimating that ALLHAT did not exert significant influence on the overall estimates on the effect of ACEIs and angiotensin receptor blockers (ARBs) or calcium channel blockers vs. other active drugs.

Another concern regards the assessments of congestive heart failure as an endpoint. The different studies are quite heterogeneous, with regard to independent adjudication, need for hospitalization, symptoms, echocardiography, X-ray, etc. Although all systematic reviews of current data on congestive heart failure share the same caveat, this introduces uncontrolled bias of a larger degree than when evaluating cardiovascular mortality.
myocardial infarction, or stroke. This issue is touched upon by the authors, discussing the need for consensus of diagnostic criteria for heart failure as an endpoint in clinical trials, and has been discussed in this journal previously.17 Another issue concerning reporting of congestive heart failure as an endpoint that deserves mentioning is the obvious, especially when evaluating the effect of calcium channel blockers and congestive heart failure; that there is a direct association between peripheral oedema, a side effect of calcium channel blockers, and the endpoint congestive heart failure. That is, peripheral oedema could be misinterpreted by some investigators as the endpoint congestive heart failure. The lack of consensus regarding reporting congestive heart failure as the endpoint is aggravated when investigating calcium channel blocker therapy because of frequent peripheral oedema side effects. The results do support the hypothesis that reduction in blood pressure with calcium channel blockers is associated with a reduction in incident congestive heart failure although weaker than seen with ACEIs or ARBs, and it is entirely possible that this weaker association could be a result of a systematic association between calcium channel blocker side effects and endpoint reporting for congestive heart failure.

Another bias is the ‘competing risk’ phenomenon applied to the single studies selected for the meta-analysis (i.e. the possibility that a patient may experience an event other than congestive heart failure, which alters the probability of experiencing the event of interest). In this way, censoring would not be ‘non-informative’ (i.e. independent of mechanisms that would cause the patient to be censored), but actually dependent by the other case-specific event. However, the current study only deals with the actual absolute number of events without reference to the time to event. So, the competing risk phenomenon is unlikely but may still affect the estimates.

That said, the current study emphasizes the importance of blood pressure reduction in reducing risk of congestive heart failure in high risk patients. Treatment with ACEIs or ARBs seem to be the treatment of first choice, while it is likely that a combination of ACEI, β-blockade, and diuretic treatment, a logical antihypertensive combination regimen for moderate to severe hypertension, may be associated with the most effective treatment for prevention of congestive heart failure, although the combination therapy has not been formally tested.

Furthermore, this is also a reminder to the clinician that congestive heart failure per se is considered as ‘established cardiovascular disease’ with ‘very high added risk’ and, as such, a given patient with systolic blood pressure >120 mmHg should by definition be considered as hypertensive and treatment should be initiated. The current European Society of Cardiology/European Society of Hypertension Guidelines on treating Hypertension12 have already taken these considerations into account, as patients with an associated clinical condition (i.e. acute myocardial infarction, stroke, renal impairment, or congestive heart failure) should have antihypertensive treatment initiated if systolic blood pressure exceeds 120 mmHg.

Conflict of interest: none declared.

References