Gender and the response to blood pressure-lowering treatment

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This editorial refers to 'Do men and women respond differently to blood pressure-lowering treatment? Results of prospectively designed overviews of randomized trials'† by F. Turnbull et al., on page 2669

Hypertension is a global public health problem, making it one of the leading causes of cardiovascular morbidity and mortality.1,2 The management of hypertension can broadly be divided into the appropriate identification and cardiovascular risk stratification and, secondly, a holistic therapeutic strategy. Given the marked benefits of treating hypertension on complications such as stroke and myocardial infarction, it is no longer a question of ‘do we treat hypertension?’ but the more important questions in relation to hypertension treatment are ‘who to treat…’ and ‘how to treat?’

We know that the prevalence of hypertension is extremely variable in various epidemiological regions of the world. Indeed, ethnic differences in the prevalence of hypertension and its complications are evident, and may influence the approach to cardiovascular prevention.2,3 Furthermore, understanding of genetic, environmental, and biological factors contributing to the development of high blood pressure—as well as responses to drug therapies—could assist in the formulation of primary and secondary prevention programmes. Also, many clinical trials, especially those performed in the last decade, have been conducted to assess the clinical response to various individual and combined antihypertensive regimens.

Is gender a major consideration when we choose antihypertensive drugs? The influence of gender differences on cardiovascular disease prevalence, expression, and long-term outcomes has long been the subject of intense research. Nonetheless, females have tended to be under-represented in many large clinical trials of hypertension. The reasons for this gender difference in some cardiovascular diseases and its risk factors remain unknown, and, for some conditions, biological plausibility has even been debated. Also, some studies have demonstrated important differences in prevalence of cardiovascular event rates between men and women, for various cardiovascular disorders. For example, atrial fibrillation is more common in men compared with women,4 but some studies—such as the ATRIA cohort study5 and an ancillary analysis from the SPORTIF trial6—have reported that women with atrial fibrillation were much more prone to develop ischaemic stroke and systemic thromboembolism.

Whilst large-scale observational studies have shown that lower blood pressure is associated with lower cardiovascular risk in both men and women, a variable prevalence of hypertension and other cardiovascular diseases between women and men raises the question about whether there are gender-based differences in the responses and efficacy of antihypertensive management that may influence different outcomes between the sexes.

The meta-analysis by Turnbull et al.7 quantifies the gender effects of blood pressure-lowering treatment, to determine if differences in benefits of antihypertensive treatment between men and women are really present. In their analysis of 31 randomized trials that included 103 268 men and 87 349 women, the achieved blood pressure reductions were comparable for both men and women. For the primary outcome of total major cardiovascular events, there was no convincing evidence that men and women obtained different levels of protection from blood pressure lowering or from drug regimens based on different antihypertensive drug classes. Although some noteworthy and recent large trials have been excluded from their analysis, individual and combined antihypertensive regimens provided equivalent protection in both male and female subjects, and differences in cardiovascular risks between sexes are unlikely to reflect differences in response to blood pressure-lowering treatments.

These observations are broadly similar to a meta-analysis of individual patient data from randomized, controlled trials, provided by the INDANA (INdividual Data ANalysis of Antihypertensive inter-vention trials) Investigators.6 The latter analysis was based on seven trials that included 20 802 women and 19 975 men recruited...
between 1972 and 1990. These investigators found that in terms of relative risk, treatment benefit did not differ between women and men, although—unsurprisingly—the absolute risk reduction attributable to treatment depended upon untreated risk. The meta-analysis by Turnbull et al.7 has the similar advantage of very large numbers, but also relies on studies in relatively diverse trial populations, with different inclusion/exclusion criteria, being conducted over different time periods.

Nonetheless, it is possible that medical care could have significantly changed over the study periods of the individual trials. The latter point is relevant as in the last few years, the approach to the management of hypertension has taken a much more holistic approach, and assessment of the cardiovascular risk of an individual person would help rationalize and individualize antihypertensive treatment.8 Thus, any management strategy should include proactive treatment for co-existing risk factors or diseases associated with hypertension, e.g. lipid-lowering therapy with statins markedly improved outcomes in hypertensive patients.9

Do the benefits of gender differences in responses to anti-hypertensive therapy—if real—extend to the other disorders/risk factors associated with high blood pressure? The current evidence does not entirely support this notion. In heart failure and coronary artery disease, gender differences are clearly manifest in causation, presentation, prognosis, and therapeutic response. However, age-adjusted systolic heart failure incidence rate, hospitalization, and mortality are much less in females compared with men of the same ethnic group;10 conversely, a poorer prognosis in females has been demonstrated in subjects with diastolic heart failure.11 Furthermore, women have worse outcome associated with coronary artery disease compared with men, which has been attributed to underutilization of pharmacological therapies, such as β-blockers, angiotensin-converting enzyme (ACE) inhibitors, and/or statins. Indeed, gender is an independent risk factor for poor outcomes after coronary artery bypass graft surgery and percutaneous coronary interventions.12 However, there remain the sceptics who believe that poor outcomes in female subjects with coronary artery disease actually represent a true phenomenon.13 Perhaps we need much greater efforts to understand the unique aspects of hypertension associated with female subjects. Hormonal changes (including oral contraceptive and hormone replacement therapy use), pregnancy-related hypertension, and obesity are some of the many factors involved in the understanding of the pathogenesis of cardiovascular disease—including hypertension—amongst female subjects. Hypertension in pregnancy (including pre-eclampsia) may lead to a greater propensity of women to develop essential hypertension in later life. There is also the suggestion of different pathogenic mechanisms being involved, e.g. in the relationship between obesity and hypertension in men and women,14 as well as differences in sympathetic activity, with hypertension in women being associated with a lower level of central sympathetic hyperactivity than in men.15 For now, we can have some reassurance from the study by Turnbull et al. that we should treat according to target blood pressures, and all antihypertensive drug classes would essentially do the job.

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References