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Sex differences in hypertension and other cardiovascular diseases

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In the years following the publication of major clinical trials we commonly see additional papers related to the original study. These provide data on subgroup analyses, specific secondary outcomes, extended follow-up, analyses that were available at the time of publication of the original paper but not included in the manuscript, and data generated in the years after the original publication such as genetic and biomarker studies in stored samples. Although such papers often provide important information they are also often underpowered and only of subspecialist interest. Apart from their scientific value, they offer investigators who played less prominent roles in the original article the opportunity to publish first-author papers, and a wider range of journals the opportunity to get their piece of the cake where the original study has been published in a higher ranking journal.

The Systolic Blood Pressure Intervention Trial (SPRINT) [1] is clearly a landmark trial that has already reshaped contemporary blood pressure guidelines [2,3]. Not surprisingly we have read over the last couple of years a large number of additional analyses deriving from SPRINT which addressed important issues including outcomes by race and ethnicity; outcomes by baseline diastolic blood pressure; visit-to-visit blood pressure variability; outcomes in people with and without chronic kidney disease; and comparisons with other landmark studies into intensive blood pressure lowering strategies or treatment of patients at high cardiovascular risk. In the current issue of *Journal of Hypertension* we find a particularly important analysis of SPRINT in a paper by Capri Foy and colleagues [4].

Foy et al. [4] have studied whether the benefits of intensive systolic blood pressure lowering extends to both men and women by separately analysing data from male and female SPRINT participants. The authors have shown that the primary composite endpoint was reduced by 16% in women and by 27% in men with no interaction between treatment and sex. The lack of statistical interaction indeed suggests that the overall SPRINT data are not grossly different between men and women.

One may argue that a sex-specific subgroup analysis in SPRINT is not necessary. Even if SPRINT did not stratify treatment by sex men and women were equally represented in the two treatment groups, and the analyses were statistically adjusted for sex. The randomisation process and a sufficiently large sample size should indeed guarantee that there are no

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significant baseline differences between treatment arms. Following this line of argument, however, one would then not only query the importance of the present sex-specific analysis by Foy et al. [4] but also the need for adjustment for sex in the first place.

Clearly, adjustment by statistical means cannot take biological variability fully into account. This is particularly true with regard to biological and other differences between men and women that cannot be represented by a binary "sex" variable in statistical analysis. There are biological processes that are specific to women at different stages of their lives that are far more complex than a simple binary variable and include menarche, the contraceptive pill, pregnancy and menopause. Of course there are also male-specific biological conditions, and features in both sexes that extend beyond the simplistic binary variable and include societal expectations, interaction with peers and other aspects covered by the wider term of gender. There is a growing body of evidence that all of these affect cardiovascular health [5].

In the field of hypertension numerous differences between men and women have been recognised. These range from different prevalence of hypertension (more prevalent in men until the fifth decade; more prevalent in women at higher age [6]) to higher prevalence of white coat hypertension in women [7] whereas these are less evident when we consider how blood pressure translates to organ damage such as stroke [8]. Despite the immediately plausible notion that men and women are different, contemporary hypertension guidelines do not recommend sex-specific treatment strategies. In fact, the most recently released Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines states: "Other than special recommendations for management of hypertension during pregnancy, there is no evidence that the [blood pressure] threshold for initiating drug treatment, the treatment target, the choice of initial antihypertensive medication, or the combination of medications for lowering [blood pressure] differs for women versus men" [3].

Where this and other reports refer to "no evidence" it means to some extent "lack of evidence". Or to say it more bluntly, "absence of evidence" does not mean "evidence of absence". It is well known that women have traditionally been underrepresented in cardiovascular trials that form the basis for evidence-led guidelines. Foy et al. [4] refer to the paper by Westerman and Wenger [9] that nicely summarises this clinical problem. In fact, this extends to other conditions such as diabetic nephropathy where women are also underrepresented. Extreme examples such as the VA-NEPHRON D study [10] that included only 1% women can be explained by its recruitment strategy from the Veterans Affairs system – a source that also fed into SPRINT and explains in part why there also were fewer women (36%) than men (64%) in this trial.

The SPRINT study, like many other well designed randomised clinical trials, benefits from a large sample size that to some extent removes male and female specific factors across the treatment groups. It is therefore not surprising that the subgroup analysis by Foy et al. [4] does not change the overall message of SPRINT. Yet again, this subgroup analysis painfully reminds us of the underrepresentation of women in a landmark cardiovascular trial. Despite the absence of a significant interaction between men and women in the present analysis it should be noted that the hazard ratio for the primary endpoint in intensively treated women

(0.84 [95% confidence interval, 0.61 to 1.13]) did not reach statistical significance. Clearly the early termination of SPRINT for benefit has posed challenges on the statistical workup of the data and the study has a priori not been powered for sex-specific analyses. However, the fact that only approximately a third of the study participants were female did not help in this context.

The paper by Foy et al. [4] comes with bad news for the busy reader. Those who simply glance over the abstract will not be surprised by the results. However, to fully appreciate the value of this paper one has to take some time and dig deeper into the data. It cannot be a task for this editorial commentary to guide the reader through the paper but we would still like to highlight one particular aspect within the data by Foy et al. The reader will notice in Table 1 of the paper that baseline characteristics were overall similar in the standard vs intensive treatment groups in both men and women. This is expected if randomisation has been performed well. However, the same table (column I) highlights striking differences in baseline characteristics between all men and women. As it is always the case in large sample sizes, the P-values for significant differences are very low (<0.001) but more importantly there are quite substantial numerical differences in factors such as smoking (7.8 packyears in women vs 14.9 in men) and physical activity (35.3% of women report "rarely or never" vs 22.5% of men). As a community of physicians with an interest in hypertension and cardiovascular risk we must be alarmed by the underuse of ACE inhibitors (31.4% vs 40.0% in men) and of statins in women (43.9% vs 54.6% in men). It is this level of detail that is provided in the paper by Foy et al. [4] and that explains why such complex differences cannot always be reliably addressed by statistical adjustment for sex. Much more detailed analysis of sex differences as exemplified in a study by Huxley et al. [11] where age and regional differences have been taken into account is required to ultimately provide the data that can then inform clinical guidelines.

As clinicians we should still be proud that we have at least recognised the importance of sex and gender in our studies. A recent analysis of National Heart, Lung, and Blood Institute (NHLBI) funded research shows an increase in spending from $0.5 million in 1991 to $18.3 million in 2014 in research into sex differences in hypertension [12]. In contrast, in basic science research which provides us with so important data on underlying mechanisms of clinical observations, it has been "very rare that male and female animals are studied side by side" [13]. This notion has only recently translated into a new American Heart Association recommendation on design, execution and reporting of animal atherosclerosis studies, stating that "it is advisable to include sufficient mice of both sexes to permit sex-specific analysis of atherosclerosis. It is strongly recommended that reported data be segregated by sex" [14].

At this point we do not want the interested reader to spend more time on this editorial commentary but would rather encourage them to study the paper by Foy et al. [4] in this issue of the journal. We hope that the data will be explored in depth by many in the hypertension community and that this paper will influence future design of clinical trials and, ultimately, clinical practice.

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