Sex and Cardiovascular Risk:
Are Women Advantaged Or Men Disadvantaged?

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There are more women than men living with cardiovascular disease, and the absolute annual number of cardiovascular deaths among women exceeds that in men.\(^1\) While sex differences in cardiovascular risk are recognized in the risk stratification tools (e.g. Framingham risk score, CHA2DS2-VASc score) and sex-specific risk management guidelines developed for clinical practice, it has to be recognized that women remain under-represented in clinical trials. Approximately half of individuals with hypertension, diabetes, or coronary artery disease are women, yet women make up only 25-44% of patients enrolled in trials studying these disorders.\(^2\)

Furthermore, less than a third of primary trial publications include sex-specific results.\(^2\)

The sex-specific analysis of the large ONTARGET and TRANSCEND trials by Kappert et al\(^3\) adds new data from 9,378 women and 22,168 men with, or at high risk of, cardiovascular disease. Despite the large number of women, they comprised less than 30% of the study population. The analysis was performed to assess sex difference in outcomes irrespective of treatment arm. Such an analysis, derived from large randomized controlled trials, provides the advantage of systematic follow-up and adjudication of outcomes in a controlled setting, but the potential disadvantage of selection bias. The baseline characteristics of the study population demonstrate important differences: women were more likely to qualify for entry into the trials with diabetes and stroke, whereas men were more likely to have coronary artery disease. Women were also older and more likely to be hypertensive and obese than men. Lifestyle factors differed, with women being less active, less likely to consume tobacco or alcohol, and having received less education than men. While adjustment for differences in baseline characteristics addressed the internal validity of the results, whether or not the trial populations were truly representative of the populations from which they were drawn is less certain. For example, the
inclusion of older women may suggest a survival bias contributing to the better outcomes in these elderly women who were well enough to participate in the trials.

What were the main findings? Among adults ≥ 55 years old with established cardiovascular disease or high risk diabetes mellitus, women had ~20% lower adjusted annual risk of combined endpoint of cardiovascular death, myocardial infarction, stroke, or heart failure hospitalization over a median of 56 months compared to men. This was driven primarily by a lower risk of myocardial infarction among women. Women also had a lower risk of cardiovascular death, but not stroke or heart failure admissions, compared to men. Women experienced the combined endpoint an average of 5.7 years later than men of similar risk profiles, with a particularly pronounced delay of 10.7 years for myocardial infarction. A history of prior myocardial infarction increased the risk of events in both men and women, with women remaining at lower risk except in the oldest age group (≥75 years). However, if a new myocardial infarction or stroke occurred during the course of the trials, the unadjusted risk of poor outcomes appeared higher in women than men, with no difference in risk following adjustment for potential confounders. Among risk factors for myocardial infarction, the presence of diabetes mellitus imparted a greater increased risk in women than men, while alcohol consumption appeared to protect women more than men.

The delayed onset of cardiovascular events, especially acute myocardial infarction, in women is consistent with epidemiologic data showing that the median age of women with myocardial infarctions is about a decade older than men,¹ and that the incidence of coronary disease increases dramatically after the menopause in women.⁵ The fact that this female advantage is observed globally, across populations of widely varying coronary risk profiles and lifestyles, points to an intrinsic female cardioprotective trait -- the obvious candidate being
estrogen. Indeed, potential beneficial mechanisms of estrogen include induction of mitochondrial biogenesis, upregulation of cardioprotective genes, and activation of the nitric oxide and natriuretic hormone pathways.\(^5\) However several lines of evidence argue against the simple “estrogen protects” explanation: The majority, if not all, the women in ONTARGET and TRANSCEND were likely to already be postmenopausal with low estrogen levels. Furthermore, older men may have higher estrogen levels than postmenopausal women of similar age.\(^7\) Epidemiologic data from the Framingham Heart Study showed that the negative impact of surgical menopause on coronary risk was independent of the removal or preservation of the ovaries.\(^5\) Most compellingly, clinical trials of estrogen therapy have failed to demonstrate cardiovascular protection, whether in women\(^8,9\) or men.\(^10\)

Is there still a potential role for estrogen in explaining the risk delay in women? Important considerations may include the duration of estrogen exposure, the time course of life time exposure, levels and bioavailability of the active hormone, potential threshold for effect, modifications at the receptor level, or endogenous levels relative to androgens. While androgens have been studied less extensively with regard to cardiovascular effects, available evidence suggests that they might mediate sex differences in cardiovascular disease. In rodent models of myocardial infarction, administering supra-physiological levels of testosterone in ovariectomized females worsened cardiac function, while castrated males had reduced mortality and improved cardiac function.\(^11\) Both animal and human data suggest that testosterone may exert a suppressive effect on the natriuretic peptide system.\(^12\) The delayed onset of coronary events in women may be more appropriately explained by a slowing of the acceleration of events in middle-aged men (with declining androgen levels), rather than an acceleration of coronary deaths among postmenopausal women.\(^13\) Thus, instead of women enjoying a delay advantage, it is possible that
men suffer the disadvantage of “premature” disease. Regardless of mechanism, the ONTARGET/TRANSCEND population showed that any advantage or disadvantage was lost following an event in the study, and subsequent risk was equally high in men and women. While sex hormones offer an attractive explanation for the common sex trends in cardiovascular risk, the differences between coronary death rates between countries are greater than the differences between the sexes. This suggests a significant role for cardiovascular risk factors and/or inter-ethnic genetic differences. Indeed, the multinational INTERHEART study showed that >90% of myocardial infarctions could be explained by modifiable risk factors, and that the earlier onset in men was largely explained by higher levels of dyslipidemia and smoking. Kappert et al concluded that “diabetic females were characterized by a higher risk for acute myocardial infarction compared to diabetic males”. In fact, their results showed that the ratio of risk of myocardial infarction in diabetic women compared to non-diabetic women was significantly greater than that in diabetic compared to non-diabetic men (HR 1.98 in women versus 1.36 in men; p for interaction=0.002). What were the absolute risks for diabetic and non-diabetic men and women? The reader is left uninformed on this point. In the Rancho Bernardo Study, the survival in diabetic women approached that of diabetic men over more than a decade follow-up, while non-diabetic women had a survival advantage over non-diabetic men. The higher hazard associated with diabetes in women was therefore a function of their superior survival in the absence of diabetes, rather than higher event rates in diabetic women compared to diabetic men. Thus, diabetes has a serious impact on women that negates their innate risk advantage.

An insulin-androgen association may provide an explanation for the increased cardiovascular risk in men and diabetic women, while sparing non-diabetic women. There is an
association between hyperinsulinemia (insulin resistance, central obesity) and hyperandrogenemia, a typical example being the polycystic ovarian syndrome. Other potential explanations include sex disparities in care among diabetic women, or greater risk factor clustering among diabetic women versus men.

Alcohol consumption was another risk factor that appeared to differentially impact women and men. Of note, this variable was crudely measured as a binary response to regular alcohol consumption (at least once/week), thus limiting any inferences regarding quantity of alcohol consumed and any divergent effects of high versus low levels of consumption, drinking patterns or beverage choice. Whether alcohol consumption was a surrogate for other lifestyle or socioeconomic factors (physical activity, smoking, education) was not fully explored. Hence, the authors appropriately caution that their results should not be used to promote alcohol consumption as a cardiovascular preventive strategy.

In contrast to the large sex differences in myocardial infarction, there was no sex difference in the adjusted annual risk of stroke, and the mean time delay for strokes in women was only 3.9 years, less than half that of myocardial infarction (10.7 years). Data were not available regarding the prevalence of atrial fibrillation -- a known risk factor for stroke that impacts women more than men. Similarly, the degree of blood pressure control achieved in hypertensive women versus men was unknown. Are there sex differences in the way cardiovascular disease may differentially affect various vascular beds? This was examined in the Rotterdam Study, where there was a striking sex difference in the involvement of the coronary vasculature, which was much larger than the difference in the carotids, and there were no differences in the aorta and the lower extremity vessels. These sex differences in vascular sites were not explained by differences in cardiovascular risk factors. Potential explanations include...
differences in vascular anatomy, regional hemodynamic disturbances or local changes in the arterial wall that impact thrombotic tendency.

The study by Kappert et al is an encouraging sign that the gender gap of representation in cardiovascular trials is narrowing. The results reflect the comparison between older metabolically challenged women and younger male smokers with coronary artery disease, and raise some important questions. Are women at an advantage or men at a disadvantage for myocardial infarction? Why is there a sex interaction with diabetes and risk? Is any advantage or disadvantage specific to a particular vascular bed? How do these findings relate to the general population? Since women generally live longer than men, women constitute a larger proportion of the elderly population in which the prevalence of cardiovascular disease is greatest. Globally, cardiovascular disease remains the leading cause of death in both men and women. Thus regardless of whether it’s a delay advantage in women or acceleration disadvantage in men, these sobering statistics indicate that preventive measures are of critical importance in both women and men.

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**References:**


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