Stable or not, woman or man: is there a difference?

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This editorial refers to ‘Women and men with stable coronary artery disease have similar clinical outcomes: insights from the international prospective CLARIFY registry’, by P.G. Steg et al., on page 2831

In 2010 a dedicated group of researchers interested in women’s hearts, gathered in Brussels for a workshop discussing gender differences in cardiovascular disease (CVD). The workshop was undertaken as a result of an earlier report the same year from the European Heart Health Strategy (Euro-Heart) project showing that women are still under-represented in many cardiovascular clinical trials.

Fewer women than men have been included in cardiovascular trials and, consequently, the evidence base is less firm for women regarding several treatments. The mean percentage of women enrolled in cardiovascular clinical trials since 2006 was 30%, while only 50% of trials reported results by gender analysis. Fewer evidence-based preventive, diagnostic, and therapeutic options for women with CVD may lead to undertreatment and a lower quality of care in comparison with men.

Prospective studies to elucidate whether there are true differences in the effects of different treatment strategies according to gender and outcome are greatly needed to identify the most appropriate treatment for men and women, respectively (Table 1).

The CLARIFY population has now been analysed from a gender perspective. The CLARIFY, being a prospective, observational, longitudinal registry of patients with stable coronary artery disease consisting of >33 000 patients in 45 countries worldwide, has the potential to fill in some of the gaps called for in the Red Alert for Women’s Heart, workshop. Indeed this is a very good attempt to straighten out some unclarified fields in the cardiovascular area.

What is the new knowledge from this analysis? It is a well-known fact that co-morbidities, risk factors, medication, management, and sometimes, but not always, outcome differ. The authors claim that this as a large contemporary cohort of outpatients with stable coronary artery disease (CAD), and broad geographic representation provides new information. It may well be so, but some issues have to be taken into consideration and merit some further attention.

(i) What is really the difference between this ‘stable’ population that mostly consists of post-myocardial infarction (MI) or post-revascularization patients from other acute coronary syndrome (ACS) registry populations? Who is a stable CAD patient? Is it the one who has only stable angina and has never had any event such as revascularization or MI? Or is it the one (as in CLARIFY) who did not have any event for 3 months after a first event? Thus the definition of stable CAD is not clear cut and gives us in CLARIFY a case mix of patients, leading to difficulties in interpreting the results. Does it matter and should we divide CAD patients into stable–unstable and acute? Is it not the same disease?

(ii) The patients seem to be highly selected, as only 22.6% were women and, according to epidemiological investigations, the prevalence usually is the same and in fact even slightly higher in women with angina. As the physicians involved were requested to recruit 10–15 stable CAD outpatients, this selection bias could have been avoided by requesting them to recruit 50% women and 50% men. This selection significantly limits the representativeness and generalizability of the results.

(iii) As in all registries on clinical practice, one limitation is the handling of missing data. This is also the case in CLARIFY. At 1-year follow-up, 6.8% of the patients either withdrew their consent, had no follow-up, or the follow-up was still ongoing. This is a high drop-out rate, whatever the reason. The investigators could have waited for the results of the 1202 patients who had not completed 1-year follow-up, which would have decreased the drop-out rate considerably. Furthermore, as in all observational data sets, the adjustment might be influenced by the lack of registration of some possible confounding factors, e.g. non-cardiac co-
Table 1  Strategies to improve perspectives of cardiovascular disease in women

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<th>Strategy</th>
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<td>Governmental support to encourage more cardiovascular research in women</td>
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<td>Public health efforts to increase awareness of cardiovascular disease risk in women</td>
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<td>Development of educational programmes on gender differences in cardiovascular diseases</td>
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<td>Standardized registration of gender differences in cardiovascular care</td>
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<td>More interaction among various medical disciplines involved in women’s health</td>
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<td>More gender-specific analysis and higher enrolment of women in clinical trials</td>
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<td>Use of appropriate study designs and statistical tools to detect gender effects</td>
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<td>Improve sensitivity and specificity for symptom evaluation of cardiovascular disease in women</td>
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<td>Provide gender-specific data in all guidelines on cardiovascular disease</td>
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<td>Implementation of gender-specific strategies in clinical practice</td>
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From Maas et al.1

morbidity, contraindications to specific treatment, and reduced kidney function. A glomerular filtration rate <60 mL/min has recently been shown to be far more common in CAD women than men and could have been included in the adjustment.11,12

(iv) To be sure of the trustworthiness of the given data in any clinical trial, it is of the utmost necessity for the results to be monitored by an independent monitor. In CLARIFY, this was done in only 5% of centres—events were accepted as reported by physicians and were not adjudicated.

Given these limitations the CLARIFY study adds value to the CAD gender knowledge as it included a large amount of patients from a wide geographical area. The results do, however, have to be interpreted with caution.

As the authors discuss that ‘Concerted efforts are needed to modify both physician and patient behaviours by increasing awareness of the prevalence of coronary artery disease in women’, I would like to add that concerted efforts are also needed to plan such a large study, involving so many physicians and patients, in such a way that more gender-specific analysis and enrolment of a higher number of women could have been done.

Conclusion

Gender is associated with differences between women and men regarding behaviour and disease, as well as with inequality of life conditions. Thus gender is, and should be, an important variable at the level of the individual physician, especially as it relates to interpersonal interactions with patients. It is also known that men and women have well-documented differences in how they communicate, and, not surprisingly, these differences also extend to how male and female physicians interact with their patients and each other. This must always be taken into consideration, even when planning a clinical trial, randomized controlled trial, or an observational study.

Conflict of interests: none declared.

References


