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Editorial

Microvascular angina: Are all women created equal?☆

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Contrary to popular wisdom, stable ischemic heart disease (SIHD) is not a "male-only" condition, as women are affected by stable angina pectoris similarly to, or even more often than, men. In a recent survey conducted in four large European countries, women reported more severe angina, a higher number of angina attacks per month, and more frequently accompanying symptoms (dyspnea, arrhythmias/tachycardia), than men [1]. On the other hand, compared to men women more often refer atypical symptoms [2], while angina is more frequently evoked by episodes of mental stress, and relatively less by exercise [3]. Differences in clinical characteristics are mirrored by differences in pathophysiology, as among symptomatic women undergoing coronary angiography about a half shows non-significant coronary artery disease [4–6], and functional assessment indicates that coronary microvascular alterations are instead quite common [6,7].

As a consequence, in women angina episodes may not always follow the paradigm of ischemia being the consequence of increased oxygen demand not matched by adequate flow supply because of coronary artery stenosis. Instead, maldistribution of coronary flow at the level of coronary microvasculature, is now considered a major contributing mechanism [8]. The "microvascular" mechanism also helps explaining why treatment based on classical anti-anginal drugs may be less effective in women suffering of angina in the absence of significant coronary artery stenosis, who also frequently continue to complain symptoms with consequent poor quality of life, which also impact prognosis [1,9].

The quest for therapeutic options for SIHD has put ranolazine under the spotlight. Ranolazine acts through a non-hemodynamic mechanism. By inhibiting myocyte late-inward Na + current, ranolazine is thought to reduce calcium overload during ischemia; this is expected to diminish ischemia-related myocardial stiffening and vascular compression during diastole, thus improving subendocardium perfusion. Randomized clinical trials have established ranolazine's efficacy in patients with stable angina [10,11].

With respect to microvascular angina, ranolazine has been shown to reduce symptoms in small studies [12–14]; more recently, a larger trial randomized patients with angina symptoms, no obstructive CAD (<50% epicardial coronary stenosis), and preserved LV ejection fraction, to ranolazine or placebo for two weeks in a cross-over design; ranolazine was effective in the subgroup in whom impaired coronary flow reserve (CFR) -and hence microvascular dysfunction- was documented [15].

In this issue of the Journal, Rambarat et al. [16] expand on that latter trial, reporting the results of a subanalysis aimed at further defining the correlation between the effects of ranolazine and CFR, having divided patients (n = 128; 96% women) in 2 groups: impaired (<2.5) CFR, or normal (≥2.5) CFR. On ranolazine treatment, patients with CFR <2.5 showed significant improvement of both subjective symptoms (as assessed through Seattle Angina Questionnaire and Seattle Angina Questionnaire-7) and objective index of myocardial perfusion (midventricular perfusion reserve index, MRPI) by cardiac magnetic resonance. These findings are quite relevant, as they reinforce the notion that ranolazine can be of benefit also in selected patients with microvascular angina, and that microvascular dysfunction is both a contributor to symptoms and a potential target of treatment.

However, Rambarat's data also potentially unveil an as yet unreported "phenotypic" difference among women with microvascular angina. In fact, in the group with normal CFR ≥2.5 no benefits, but actually a trend in worsening of Seattle Angina Questionnaire-7 (increased angina frequency, more physical limitation, less treatment satisfaction) were seen during ranolazine treatment; furthermore, this was associated with a significant reduction in MPRI.

Why was ranolazine not effective in women with normal CFR? This cannot be dismissed as just the result of a play of chance. Data were carefully gathered, by investigators who have much contributed to this field, in a relatively large population (for this type of investigations). More importantly, lack of benefit (or even trend to worsening) was seen not only on subjective parameters, but also objectively documented by MRPI. Finally, in a previous study in 13 women with typical angina and documentation of myocardial ischemia (>10% at MPRI), these investigators had similarly observed that women with CFR <3 showed MPRI

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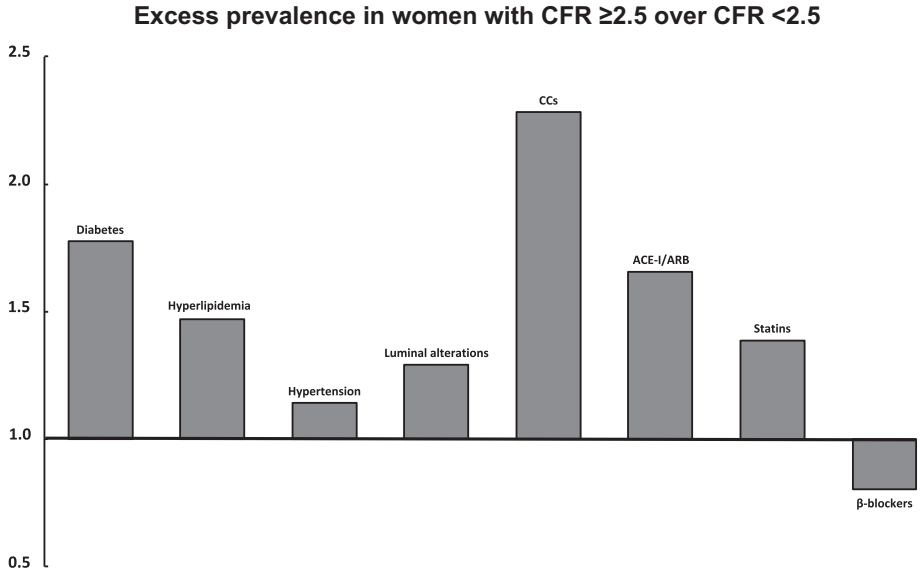

Fig. 1. Different prevalence of selected clinical characteristics in the cohort of patients with CRF ≥2.5 compared to patients with CFR <2.5. Bar represent prevalence in patients with CRF ≥2.5 divided by prevalence in patients CFR <2.5, for each variable, i.e., ratio of excess prevalence. Line set at 1.0 marks identical prevalence in the 2 groups. Note that characteristics suggestive of high cardiovascular risk profile are paradoxically more prevalent in the subgroup with CFR ≥2.5.

improvement with ranolazine, while women with CFR >3 showed worsening in MPRI compared to placebo [12].

A tempting explanation for these findings is that women with angina and normal coronary flow reserve may represent a different population, who have no microvascular dysfunction (as we currently define it, i.e., CFR >2.5), and in whom mechanisms for ischemia are distinct and definitely not amenable to response to ranolazine's mode of action. At the same time, these findings cannot be easily explained by invoking non-cardiac angina-like pain, or altered pain perception, to justify symptoms unrelated to myocardial ischemia, as these "non-responder" women seem instead to fit a true "cardiovascular disease-prone" description.

In fact, closer scrutiny of Rambarat's data reveals that women enrolled with CFR ≥2.5 actually were at a relatively high atherosclerotic risk, as indicated by: a) high prevalence of hyperlipidemia (63.9%), hypertension (52.2%), diabetes (26.1%); b) presence of atherosclerotic coronary lumen alterations, albeit non-obstructive, in almost all of them (93%); c) background cardiovascular therapy with one or more drugs (67.4% on statins; 47.3% on ACE-inhibitors/angiotensin-receptor blockers; 41.3% on beta-blockers; 32.6% on calcium-channel blockers). This finding is somewhat unexpected, as if CFR ≥2.5 were to define no or minimal coronary atherosclerotic disease, one would have predicted it to go along with a "milder" risk profile.

However, of even greater potential interest is the observation that if one compares prevalence of those clinical characteristics in patients with CFR ≥2.5 vs <2.5, major differences emerge, and risk profile of women whose CFR is "normal" actually seems to be paradoxically higher than what observed in women with CFR <2.5 (Fig. 1). Although not reaching statistical significance, likely because of small cohort size, parameters consistently went in the same direction, again pointing to a high(er) risk profile in the CFR ≥2.5 group, who did not respond to ranolazine.

So, we are apparently confronted with the possible existence of another phenotype of women with angina and non-significant coronary artery disease, in whom typical angina pain tends to occur in the setting of a risk profile suggestive of atherosclerotic risk, yet this is not reflective of (major) impairment of coronary flow reserve, and it is not responsive to ranolazine, nor to classical anti-anginal drugs. It is now appreciated that microvascular angina underscores pathophysiological mechanisms that are not only complex but also heterogeneous [7]. Occurrence of alterations in microvascular remodeling [17,18], and/or diffuse microvascular spasm 6), are additional mechanisms that on the one hand might explain lack of CFR impairment, and poor response to certain anti-anginal drugs, and on the other hand suggest that different therapeutical approaches might be more effective [17,18]. At the same time, newer techniques to investigate coronary microcirculation, such as the index of microcirculatory resistance (IMR), might prove more suitable to further characterize such patients [7].

Thus, the observations by Rambarat et al., while puzzling at first glance, may spur further interest in the complex pathophysiology of microvascular angina in women.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

Abbreviations

CFR coronary flow reserve
CCs use of calcium-channel blockers
ACE-I/ARB use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers

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