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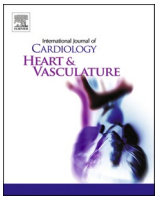

Editorial

The hasty generalization fallacy: not all coronary artery disease is the same

Hypertension, hypercholesterolemia, diabetes mellitus, and smoking are well-known factors contributing to coronary artery disease (CAD) and have been effectively targeted by primary and secondary prevention strategies. However, there has been an increasing proportion of patients with acute (ACS) or chronic coronary syndrome (CCS) who do not exhibit any of these standard modifiable cardiovascular risk factors (SMuRFs) [1]. Despite recent evidence suggesting that SMuRF-less patients may have an elevated risk of adverse events following ACS [2], the clinical outcomes of this population undergoing percutaneous coronary intervention (PCI) have never been evaluated.

In this issue of IJC Heart & Vasculature, Kobo et al [3] evaluated the clinical outcomes of patients undergoing PCI for either ACS or CCS within the prospective and multicentric e-Ultimaster registry, categorizing them into four groups based on the presence of SMuRFs - none, 1, 2, 3 or 4 -. The study's primary endpoint was target lesion failure (TLF), a composite of cardiac death, target vessel-related myocardial infarction or clinically driven target lesion revascularization at 1-year. At the 1-year follow-up, the occurrence of TLF increased along with the number of SMuRFs (2.65 %, 2.75 %, 3.23 %, and 4.24 % for 0, 1, 2, and 3–4 SMuRFs, respectively; p for trend < 0.0001), as well as for the other predefined clinical endpoints. After inverse propensity score weighted (IWPS) adjustment, SMuRF-less patients maintained a favorable risk profile compared to those with 3–4 SMuRFs, without significant differences between SMuRF-less patients and those with 1 or 2 SMuRFs. This trend persisted among patients with CCS, but not in ACS patients following IWPS adjustment.

The investigators should be commended for conducting this large analysis of the impact of SMuRFs in patients undergoing PCI, providing valuable insights into this complex and debated topic.

Therefore, several questions remain unanswered: 1) Is the pathogenesis of CAD the same in these patients? 2) Where do patients with myocardial infarction and non-obstructive coronary arteries (MINOCA) with confirmed underlying ischemic cause (through intravascular imaging or other multimodal imaging techniques) fit in, and how should they be approached? 3) Is the evidence-based and recommended therapeutic management equally valid in this heterogeneous population and addresses the same pathophysiological needs? 4) Is the disparity in the clinical outcomes among these patients solely due to variation in guideline-based therapy, or are there other significant factors involved?

First of all, it's essential to consider that we are dealing with two distinct patient populations. Patients with more SMuRFs often present with CCS or unstable angina (UA), are typically older [4], with more comorbidities, and have a more complex CAD (proximal lesions, total occlusions, calcified lesions, or bifurcations); in such cases, revascularization procedures are complex, sometimes incomplete, with a need for tailored antiplatelet therapy in terms of regimen and duration, due to the specific patient's coexisting increased ischemic and hemorrhagic risk [5]. In contrast, patients with fewer SMuRFs tend to be younger, often present with ACS, have less complex CAD, and require a standard post-PCI antiplatelet regimen (Fig. 1). In SMuRF-less patients, there are likely undiscovered disease mechanisms that contribute to CAD. These pathways encompass multifactorial causes such as polygenic and epigenetic backgrounds, biomechanical factors, inflammatory states, sleep disorders, and others, which are not fully understood. The specific weight of each factor and their interaction in promoting CAD remains unknown, and they are not routinely incorporated into primary prevention strategies or represented in clinical trials and current international guidelines. It's crucial for the scientific community to identify SMuRF-less patients and develop dedicated clinical pathways to provide guidance for clinicians [6].

Secondly, some evidences suggest that MINOCA patients exhibit a lower prevalence of SMuRFs compared with patients with myocardial infarction (MI) and obstructive CAD [7], but a higher prevalence of unconventional risk factors, such as inflammatory and autoimmune diseases, hypercoagulable states, cancer, anxiety, and depression [8].

Regarding medical therapy, international guidelines recommend the same approach for all ischemic patients, irrespective of the presence and number of SMuRFs. However, it remains unclear whether SMuRF-less patients directly benefit from traditional pharmacologic strategies or their pleiotropic effects, such as plaque stabilization and anti-inflammatory properties.

Previous studies and registries have demonstrated an elevated cardiovascular risk in SMuRF-less patients presenting with ACS [9]. We can speculate that the lower prescription and adherence to guideline-based medical therapy in SMuRF-less patients significantly contribute to their heightened early mortality [10]. However, it's also conceivable that non-traditional risk factors, insufficiently recognized and consequently inadequately treated, may promote coronary atherosclerosis more than their counterparts with atherosclerosis explained by SMuRFs. In Kobo's study, the authors report no disparity in cardiovascular medication at discharge between different groups, which could explain the superior cardiovascular outcomes at 1 year among patients with fewer SMuRFs. Additionally, patients with 3 or 4 SMuRFs likely represent a more globally compromised population, potentially contributing to the observed outcome.

Finally, we must consider that cardiovascular risk factors are

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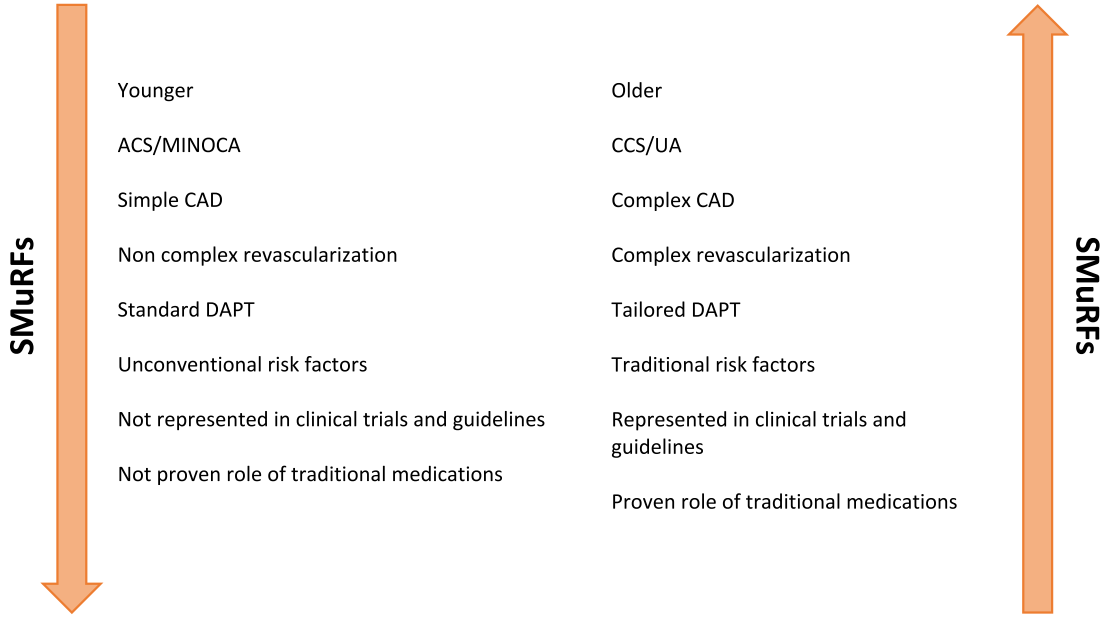

Fig. 1. Characteristics of ischemic patients according to the presence and number of SMuRFs. ACS, acute coronary syndrome, CAD, coronary artery disease, CCS, chronic coronary syndrome, DAPT, dual antiplatelet therapy, MINOCA, myocardial infarction with non-obstructive coronary arteries, SMuRFs, standard modifiable cardiovascular risk factors, UA, unstable angina.

assessed at baseline (upon hospital admission) and the authors evaluated the 1-year outcome. If these risk factors are then treated, given the availability of drugs such as PCSK9 inhibitors and SGLT2 inhibitors/GLP1 agonists, does the increased relative risk for the endpoint persist? Could it be that in the near future, with the extensive and early use of these drugs in patients with SMuRFs, we will observe a reverse trend?

Given this evidence, it's crucial to clarify the pathophysiological and clinical aspects defining the subset of patients with none or few SMuRFs, ensuring they receive a personalized approach. Furthermore, long-term prognostic data are needed to clearly define the impact of SMuRFs and their optimized treatment on cardiovascular outcomes in CAD.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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