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EDITORIAL COMMENT

Defining Outcomes in East Asian Elderly STEMI Patients Without Standard Modifiable Risk Factors*

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The 4 standard modifiable cardiovascular risk factors (SMuRFs) of hypertension, dyslipidemia, diabetes mellitus, and smoking have for decades been central to the quantification of risk and focus of prevention efforts, especially after acute coronary syndrome (ACS) events. In the last few years, a distinct subset of patients presenting with their first ACS event who have none of these standard risk factors (ie, SMuRFless patients) have been described with the possible trend of this proportion rising over the last 2 decades. The initial SWEDEHEART (Swedish Web-system for Enhancement and Development of Evidence-based Care in Heart Disease Evaluated According to Recommended Therapies) Swedish registry found the proportion of SMuRFless patients with ST-segment elevation myocardial infarction (STEMI) to be 14.9%[1] and patients with non-STEMI to be 11.2%.[2] This has been subsequently confirmed in a meta-analysis of 15 international SMuRFless ACS studies to date including 1,285,722 patients, in which 12.9% of patients with STEMI and 7.4% of patients with non-STEMI were SMuRFless.[3] These patients were more likely to present with cardiac arrest (relative risk [RR]: 1.45; $P = 0.012$), and the culprit vessel tended to more frequently involve the left main and left anterior descending arteries (RR: 1.12; $P < 0.001$). The differences also seem in aggregate to extend to outcomes with a higher risk of in-hospital mortality (RR: 1.57; $P < 0.001$), cardiogenic shock (RR: 1.39; $P < 0.001$), and in-hospital cardiac death (RR: 1.76; $P < 0.001$). No differences were noted in revascularization strategies used between SMuRFless patients and patients with risk factors. However, SMuRFless patients seem to consistently receive reduced rates of guideline-directed secondary prevention therapy such as statins, antiplatelets, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and beta-blockers after their ACS events, which may in part account for their excess early mortality.

In this issue of *JACC: Asia*, Zhao et al[4] present an important addition to the growing field of knowledge surrounding SMuRFless patients, reporting on the characteristics, treatment, and in-hospital outcomes specifically of older (age ≥75 years) SMuRFless STEMI patients in China.

These patients were enrolled in the CCC-ACS (Improving Care for Cardiovascular Disease in China-ACS) Project, which is a Chinese nationwide registry and quality improvement collaborative initiative of the American Heart Association and Chinese Society of Cardiology over 5 years. A total of 10,775 elderly patients with no history of coronary artery disease presented with their first STEMI. Consistent with previously published cohorts, 15.2% of patients were SMuRFless, with a higher likelihood of cardiac arrest than patients with risk factors. Compared with patients with traditional risk factors, SmuRFless patients received less evidence-based inpatient and discharge treatment across all drug categories. Overall unadjusted in-patient mortality did not differ (5.4% vs 5.1%). Unlike prior studies, SMuRFless patients had a significantly lower rate of in-hospital mortality after adjustment for both baseline clinical characteristics and evidence-based treatment. It is worth noting, however, that increasing use of in-hospital treatment drug classes

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was still clearly associated with improved outcomes, lending support to the consistent observation that SMuRFless patients are undertreated compared with their counterparts. This discrepancy in outcomes compared with previously reported cohorts may in part be explained by survival bias: the cumulative impact of lifetime exposure to cardiovascular risk factors, especially for an elderly cohort, will likely result in a variance in prognosis between elderly SMuRFless patients and those with risk factors, as opposed to younger SMuRFless patients in whom disease may be driven by aggressive, nontraditional pro-atherosclerotic risk factors and STEMI outcomes additionally influenced by a lack of ischemic preconditioning.

It is important to emphasize, however, that the trends observed in this elderly Chinese East Asian cohort[4] may not be generalizable to other contemporary cohorts. Geographical differences in outcome were seen in the global meta-analysis, with the lowest overall rate of adverse outcomes noted in patients from Asia (7.5%) and higher rates in Australia (21.3%), Europe (10.1%), and North America (11.7%). Importantly, elderly Chinese patients from this cohort also had low rates of standard acute revascularization therapies, with 63% of patients from this cohort undergoing primary percutaneous coronary intervention (PCI) and only 4% of those who did not undergo primary PCI receiving thrombolysis. This low rate of reperfusion for STEMI in China was also seen in a large, recently published registry of patients with STEMI, the China Acute Myocardial Infarction registry, coalescing data from Chinese hospitals from all provinces and municipalities throughout China, with many patients experiencing significant delays to care.[5] The rate of primary PCI was 44% among all patients and 58% among patients admitted to hospitals within 12 hours of symptom onset. These revascularization rates are significantly lower compared with other well-developed systems of care such as the European SWEDEHEART statistics in which revascularization or thrombolysis was performed in 80.8% of patients overall, a difference that must affect outcomes in both groups.

SMuRFless patients who present with ACS are currently not recognized as a distinct group within contemporary guidelines, and clinical trials specific to these patients have yet to be completed. Progress has been made, however, with the proposal of a consensus clinical pathway in these patients, which was developed by an international, multidisciplinary team using a modified Delphi method.[6] The pathway essentially begins by ruling out non-atherosclerotic etiologies of acute myocardial infarction presentation and confirming atherosclerotic disease, after which SMuRFless status is confirmed by careful review and re-testing. This is followed by confirming the appropriate use of evidenced-based secondary prevention given the strong suggestion that SMuRFless patients are undertreated, and that even in this cohort, the increasing utilization of appropriate treatment is increasingly associated with improved outcomes. Finally, a systematic, non-hierarchical expanded screening of nontraditional potentially modifiable risk factors is applied. This includes testing for inflammatory disorders, prothrombotic predispositions, endocrinopathies, hormonal or sex-specific-factors, obstructive sleep apnea, inherited risk, cardio-oncology history, and finally psychological, social, and environmental factors.

To facilitate further understanding and begin improving the utility of the proposed SMuRFless coronary artery disease pathway, a multicenter, prospective, observational patient registry has been established with international data solicited. Ultimately, it will be important to design and test clinical interventions specific to the needs of this not-insignificant subset of patients while we work to further identify specific cohorts within this subset. New anti-inflammatory therapeutic secondary prevention strategies such as colchicine may be the focus of initial efforts, as possible nontraditional drivers of atherosclerotic disease.

In conclusion, much remains to be elucidated in SMuRFless patients presenting with ACS, and careful attention is needed to understand regional and ethnic differences in outcomes from international cohorts, with attempts to clarify the factors driving these differences. The Chinese study[4] in this issue of *JACC: Asia* adds to an expanding global literature with prior SMuRFless cohorts reported from Japan,[7] India,[8] Pakistan,[9] Singapore,[10] Australia,[11] the United Kingdom,[12] Sweden,[1] and the United States,[13] and emphasizes the importance of recognizing the potential difference in outcome in SMuRFless patients of different age groups.

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