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EDITORIAL COMMENT

Residual Inflammatory Risk After Percutaneous Coronary Intervention

Underappreciated But Modifiable*

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Since its introduction in 1977, the field of percutaneous coronary intervention (PCI) has evolved considerably. Nonetheless, the cumulative risk for major adverse cardiovascular events (MACE) during the 10 years after PCI with implantation of state-of-the-art drug-eluting stents and additional pharmacological and lifestyle interventions still remains around 45%.[1] During the first year after PCI, these repeat events are mostly related to the original target lesion, whereas after the first year, most events arise from coronary segments other than the previously stented lesion.[2] This underscores the importance, not only of achieving an optimal technical result of the PCI procedure of the target lesion, but also of optimal secondary prevention tailored to a patient's individual cardiovascular risk profile.

Ongoing efforts are made into the identification of patients vulnerable for future cardiovascular events. The understanding of mechanisms that make certain atherosclerotic plaques more at risk to cause MACE than others has led to a universal definition of the high-risk vulnerable plaque and vulnerable patient.[3] One of the hallmarks of these vulnerable plaques is the presence of a large lipid-rich necrotic core that is covered with a thin fibrous cap.[3] The formation of this lipid-rich plaque depends on the influx of low-density lipoprotein cholesterol (LDL-C) and inflammatory cells, including macrophages, T lymphocytes, and mast cells, into the vessel wall.[4] Therefore, aggressive pharmacologic LDL-C reduction is one of the backbones of the prevention of coronary artery disease.[5] Although LDL-C reduction is highly effective in reducing the cardiovascular risk in many patients, still a sizeable proportion remains at increased cardiovascular risk despite achieving low serum LDL-C while on an extensive lipid-lowering regime.[6] This suggests an important role for interventions beyond lowering LDL-C to target progression of atherosclerosis. Biological studies have shown that the LDL-C influx is accompanied by an extensive inflammatory response.[7] Almost 20 years ago, it was demonstrated that elevated C-reactive protein (CRP) before elective PCI was predictive for adverse cardiac events during 2-year follow-up,[8] suggesting a role of CRP as biomarker for the residual inflammatory risk (RIR). A large, retrospective analysis of 7,026 patients included in a North American PCI registry demonstrated that elevated high-sensitivity CRP (hs-CRP) ≥2 mg/L, the definition of high RIR, was persistent in 38% of patients undergoing elective PCI.[9] These patients with persistent high RIR were at higher risk for adverse cardiovascular outcome than patients with normal CRP levels. Additionally, in patients with controlled cholesterol levels, defined as LDL-C level ≤70 mg/dL (ie, 1.8 mmol/L), a similar prevalence of persistent high RIR was observed, that is, 34%, which was again strongly associated with adverse clinical outcome.[10] Thus, a persistent high RIR is an important predictor for clinical outcome, regardless of LDL-C management, based on these studies conducted in European and North American populations. However, data on the RIR among patients of East Asian descent are limited. Because different risk profiles exist among different ethnicities, study outcomes of non-East Asian patients

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cannot simply be translated to the East Asian population. With respect to the inflammatory biomarkers, significant differences in CRP levels have been observed among patients of East Asian descent. Generally, CRP levels among East Asian patients are one-half to two-thirds lower than in Caucasians.[11]

Indeed, in the study by Ahn et al,[12] published in this issue of *JACC: Asia*, the prevalence of high RIR among East Asian patients was 18%, which is much lower than the previously reported 34% to 38% in North American patients.[9] In this study, 4,562 East Asian patients from a South Korean PCI registry with serial hs-CRP measurements (>4 weeks apart) were included and divided into 4 groups depending on their hs-CRP levels at baseline and at 1-month follow-up based on the Western cutoff ≥2.0 mg/L. The primary endpoint, all-cause death at 1 year after PCI, occurred in 5.2% of patients, and the secondary endpoint MACE, consisting of cardiovascular death, myocardial infarction, stroke, and major bleeding, occurred in 11.4% of patients at 1 year after PCI. Elevated hs-CRP was predictive for all-cause death and MACE, and the strongest association was found for the 1-month hs-CRP (HR: 2.82 for all-cause mortality and HR: 1.60 for MACE). Patients most at risk for all-cause death and MACE were those with persistent high RIR (both elevated hs-CRP at baseline and 1 month). These findings correspond with the previous studies conducted in non-East Asian patients. Although the frequency of persistent high RIR in the East Asian population is lower than in non-East Asian patients, it still appears to be a strong predictor for future adverse cardiovascular events in this population.

The design of the study by Ahn et al[12] comes with certain limitations. The investigators retrospectively selected all patients with hs-CRP measurement at baseline and 1-month follow-up. This resulted in the exclusion of about one-fifth of patients because of unavailable hs-CRP at 1 month. One-month CRP measurement was not a predefined requirement for the registry and could therefore in theory only be performed upon indication. Moreover, the cutoff value used in the study for hs-CRP of ≥2.0 mg/L is based on previous studies in Western patient populations, whereas studies demonstrated that CRP levels are generally a factor of 0.36 to 0.52 lower in East Asian patients than in Western patients.[11] This could partly explain the lower rates of persistent high RIR compared with the North American studies.[9] Introduction of an adjusted cutoff value for hs-CRP might result in a more representative prevalence of high RIR among this population. Despite these limitations, the study demonstrates that hs-CRP is an important clinical parameter, also in the East Asian population, which could be used to further define the vulnerable patient at risk for adverse cardiovascular events after PCI.

Taking these findings into account, reducing the inflammatory risk is an interesting therapeutic strategy to mitigate the atherosclerotic process. Several large placebo-controlled randomized trials investigated the effect of anti-inflammatory agents for the reduction of the cardiovascular risk, such as the interleukin-1β antagonist canakinumab (CANTOS [Cardiovascular Risk Reduction Study (Reduction in Recurrent Major CV Disease Events)]), colchicine (COLCOT [Colchicine Cardiovascular Outcomes Trial] and LoDoCo2 [Low Dose Colchicine for Secondary Prevention of Cardiovascular Disease]), and methotrexate (CIRT [Cardiovascular Inflammation Reduction Trial]).[13-16] Both colchicine and canakinumab obtained considerable cardiovascular risk reductions; however, further implementation of canakinumab was stopped because of high costs and increased risk of fatal infections. Contrarily, low-dose methotrexate was unable to reduce CRP levels or cardiovascular events.[16] Given the low cost, proven efficacy, favorable safety profile and wide availability of colchicine, it was recently implemented in the updated 2021 European Society of Cardiology guidelines on cardiovascular disease prevention in clinical practice (Class IIb, Level of Evidence: A).[5]

In conclusion, high RIR should be considered a sensitive, strong, and modifiable risk factor for atherosclerotic cardiovascular disease, both in East Asian and Western patients. This analysis once again underscores the importance of identification and treatment of RIR after PCI.

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