EDITORIAL

Long-term management of patients with chronic obstructive pulmonary disease who undergo percutaneous coronary intervention still needs to be dramatically improved

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There is good evidence that chronic obstructive pulmonary disease (COPD) is associated with increased risk of cardiovascular disease.[1] In particular, an Italian population-based retrospective cross-sectional study documented that the prevalence of angina and coronary disease was 2.69% in the general population and 9.20% in patients with COPD, whereas that of acute or old myocardial infarction (MI) was 1.63% in the general population and 4.81% in patients with COPD.[2] Reduced forced expiratory volume in 1 second is associated with a history of acute coronary syndrome in patients with coronary arterial stenosis irrespective of any coronary risk factors.[3] Furthermore, airflow limitation is more prevalent in patients with coronary stenosis than in the general population.[3]

The mechanism responsible for the increased risk of cardiovascular disease in patients with COPD is not known; however, several hypotheses have been proposed. Individuals with moderate to very severe COPD have increased arterial stiffness compared with controls without COPD because of several factors: increased blood pressure (systolic and diastolic), severity of inflammation, increased coronary artery calcification, older age, imbalance between proteases and antiproteases, severity of hypoxia, and chronic hyperglycemia.[4] Moreover, the levels of matrix metalloproteinases (MMP)-2, MMP-9, and neutrophil elastase are increased in patients with COPD.[4] These proteases are implicated in numerous pathological processes, such as atherosclerotic plaque formation, destabilization and rupture, thrombus formation, and a change in the arrangement of elastic fibers in the vessel wall.[4] A further increase in arterial stiffness seems to be related to airway inflammation during COPD exacerbations, particularly in patients with underlying ischemic heart disease.[5]

A recent systematic review and meta-analysis has confirmed the high risk of MI in people with COPD and provided evidence for an increased risk of death in long-term follow-up after MI for patients with COPD.[6] However, it is still unclear if this increased risk is due to COPD itself or due to potentially modifiable factors, such as a less aggressive treatment after MI. However, the evidence for an increased risk of MI during episodes of acute exacerbation of COPD compared with stable periods seems to be poor.[6]

It is not surprising, therefore, that Januszek et al,[7] who prospectively analyzed collected national data from all patients who underwent percutaneous coronary intervention (PCI) in Poland between January 2015 and December 2016, found that patients with COPD have multiple risk factors for cardiovascular disease, consequently, are characterized by a frequent occurrence of disseminated coronary atherosclerosis. In our opinion, the documentation that restenosis and in-stent thrombosis were more common, whereas de novo lesions were less common, in patients with COPD referred for PCI compared with those without COPD seems to be a more interesting finding, although it cannot be considered a truly new one.

COPD has been long documented to significantly reduce long-term survival in patients with predominantly 1- and 2-vessel coronary artery disease (CAD) after PCI.[8] A large Italian observational multicenter study reported that patients with ST-segment elevation MI (STEMI) and concomitant COPD are at greater risk for death and hospital readmissions due to cardiovascular

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causes (eg, recurrent MI, heart failure, coronary revascularization bleedings) than patients without COPD.[9] Recently, the analysis of data from the BASKET-PROVE trials I and II[10] showed that patients with COPD and concomitant CAD presented higher rates of not only all-cause death but also cardiac death and stent thrombosis after PCI at 2 years, even after adjustment for potential confounders. It is likely that it was the first study to report an association between COPD and stent thrombosis. The authors suggested that increased platelet activation, higher fibrinogen levels, and polycythemia in patients with COPD could be the Virchow triad conditions that predispose these patients to this potentially fatal complication after PCI.[10]

In the analysis of Januszek et al,[7] non–ST-segment elevation MI (NSTEMI) was a more common clinical presentation of CAD in the COPD group, while STEMI occurred more frequently in the group without COPD. It has already been documented that patients with COPD presenting with NSTEMI have higher adjusted risks for in-hospital and 6-month mortality, not only because they are more likely to have an initial diagnosis other than acute coronary syndrome and less likely to undergo angiography, but also because they are less likely to receive recommended medications at discharge.[11]

Unfortunately, the registry at disposal of Januszek et al[7] did not include this kind of data; thus, they were unable to establish if patients received β-blockers, aspirin, and statins at discharge after PCI. However, it must be admitted that the available evidence is not sufficient to come to conclusions regarding the beneficial effects of statins on the reduction of the restenosis rate, although statins not only lower the levels of low-density lipoprotein cholesterol, but they likely have significant beneficial pleiotropic effects on various inflammatory mechanisms in atherosclerotic disease, from reducing endothelial dysfunction to decreasing the serum levels of C-reactive protein.[12]

It is our opinion that factors intrinsic to the patient with COPD, such as hypoxemia or systemic inflammation, could in any case increase the risk of restenosis and in-stent thrombosis. Unfortunately, the analysis of Januszek et al[7] did not consider patients according to their COPD phenotype, and this does not allow us to clarify which patient with COPD is at greater risk of restenosis and in-stent thrombosis. It would be important to know if these events are more common in patients suffering from frequent exacerbations. These patients are characterized by a malignant clinical course, that is, progressive impairment of pulmonary function, additionally increased risk of cardiovascular disease, as well as a significantly higher total mortality rate as compared with other patients with COPD.[13]

Actually, during the COPD exacerbation, next to other changes, a significant impairment of endothelial function also occurs. Hypoxia and a more intense oxidative stress induce local inflammation in respiratory airways, in addition to the systemic inflammatory response, which could be in connection with the development or an intensification of endothelial dysfunction, being specific for CAD but also described in COPD.[13]

This is a huge problem because endothelial injury or denudation is a frequent occurrence during the delivery and deployment of vascular medical devices. Endothelial cell trauma results in a loss of or decline in the production of critical cellular factors, giving rise to inflammation and prothrombotic conditions.[14] However, the clinical relevance of endothelial dysfunction for late events following stent implantation is not completely proven, neither is the role of therapies directed against endothelial dysfunction.

Since the importance of inflammation and inflammatory pathways in atherosclerosis, CAD, and COPD is well established, there is an interest in developing therapeutics that target inflammatory pathways to mitigate the onset of complications after acute coronary syndromes.[12] Over the last decades, several novel therapies able to target inflammatory pathways involved in these diseases have shown promising results in early animal models and preclinical studies. However, they have failed to demonstrate a significant improvement in clinical outcomes when tested in large randomized trials.[12]

Given the high risk of restenosis and in-stent thrombosis in patients suffering from COPD and undergoing PCI, it becomes imperative to identify what is currently the best therapeutic approach for these patients. Our opinion is that, first of all, it is essential to guarantee the optimization of the treatment of COPD, ensuring that the patient is adherent to the prescribed therapy. The type of an implanted stent may have significant implications with respect to a reduction in the risk of in-stent restenosis in this high-risk population. However, Januszek et al[7] did not find significant differences in the rates of restenosis after implantation of drug-eluting stents, bare metal stents, bioresorbable scaffolds, drug-eluting balloons, or plain old balloon angioplasty between the subgroups of patients with stable angina and those with acute coronary syndrome in the COPD group on admission. Obviously, antiplatelet and antithrombotic therapies must be systematically considered to prevent restenosis following coronary stent implantation. Moreover, the recommended duration of antiplatelet and antithrombotic therapies after elective PCI depends on the stent type, bleeding risk, and ischemic risk, but there is no specific recommendation for patients with COPD. Therefore, specifically designed trials in these patients should provide more data about these therapies in the future.

In any case, we strongly believe that when a patient with COPD has disseminated coronary atherosclerosis, as evidenced by Januszek et al,[7] multidisciplinary teams, which must include

also a specialist in respiratory medicine, should be aware when considering treatment options that coronary artery bypass grafting is associated with significantly lower rates of repeat revascularization.[15] Clearly, we should continue research on the modulation of inflammation to improve cardiovascular and pulmonary outcomes.

NOTE The opinions expressed by the author are not necessarily those of the journal editors, Polish Society of Internal Medicine, or publisher.

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