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**INVITED EDITORIAL**

# Beware of early drug intolerance in secondary prevention of cardiovascular disease

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**This editorial refers to 'Early occurrence of drug intolerance as risk factor during follow-up in patients with acute coronary syndrome or coronary revascularization', by S. Albani *et al.*, on page 195.**

In addition to smoking cessation and physical activity, pharmacological therapy with anti-platelet, LDL-cholesterol (LDL-C) and blood pressure-lowering medications [e.g. beta-blockers and angiotensin-converting enzyme (ACE) inhibitors especially after a myocardial infarction with reduced ventricular function] has significantly reduced the risk of recurrence of major atherosclerotic cardiovascular events (MACE) and mortality in individuals with previous coronary heart disease (CHD).[1] In stable CHD patients, intensive pharmacological therapy can be as efficacious as percutaneous coronary interventions (PCIs) in reducing MACE recurrence.[2] Moreover, after an acute coronary event, pharmacological therapy exerts a complementary and important role to PCI of severely obstructed complicated atherosclerotic plaques.[3]

Unfortunately, despite the indisputable grade IA guideline evidence of beneficial effects of these pharmacological treatments in secondary prevention of CHD, a significant number of high-risk individuals simply do not use these medications in the long term.[4–6] This contributinges to recurrence of MACE and even mortality.[5,7,8] The problem may grow with polypharmacy, [9] and increasing numbers of novel medications that may further reduce MACE risk on top of traditional ones, such as proprotein convertase kexin type 9 (PCSK9) inhibitors, [10] rivaroxaban, [11] sodium–glucose co-transporter 2 (SGLT2) inhibitors, [12,13] and glucagon-like peptide 1 (GLP-1) analogues[14] (the last two medications in diabetics) bring a new challenge for medication adherence.

Low adherence to pharmacological treatment is a complex and multifactorial problem where socio-economic, health literacy, and communication aspects play independent roles.[5] In addition, and not totally independent from these latter reasons, drug intolerance (DI) play an important role.

Among many aspects of cardiovascular prevention, rehabilitation programmes are necessary to educate patients not only about the benefits of a healthy lifestyle but also on the use of evidence-based medicine-proven pharmacological therapies with the goal of reducing MACE recurrence and their ominous consequences. Additionally, these programmes must include information on possible adverse events of pharmacological treatment aiming at reduction of patient's concerns and maintenance of treatment adherence. Indeed, these programmes may increase adherence to preventive pharmacological therapy, as recently demonstrated in the European Action on Secondary and Primary Prevention by Intervention to Reduce Events (EUROASPIRE) IV survey.[15] However, what happens with patients that despite attending rehabilitation programmes do not adhere adequately to preventive pharmacological treatments due to DI?

In this issue of the journal, Stefano Albani and colleagues[16] add interesting real-world evidence to the already frustrating field of non-adherence to pharmacological therapy in cardiovascular medicine. In this single-centre study performed in Italy, the authors followed 891 consecutive patients (age 68 ± 11 years, 24% females, 18.5% diabetics, 74.7% hypertensive, 59.4% dyslipidaemics) with either acute coronary syndromes (52%) or elective coronary revascularization (48%) referred to a cardiac rehabilitation programme lasting 5.5 ± 2.5 months and followed for a median of 18 (interquartile range 11–24) months. DI was defined as the occurrence of a pharmacological adverse event leading to either drug discontinuation or reduction of recommended dosages. Resolution or significant improvements of adverse symptoms upon a dose decrease or discontinuation of the suspected drug were necessary to meet the authors' DI criteria. DI occurred therefore in roughly one in every three patients (34.7%) during follow-up. ACE inhibitors (13.1%) and statins (12.8%) were the most frequent drugs associated with DI, followed by beta-blockers (7.5%) and calcium channel blockers (5.5%). Of note, only 2.9% ($n = 26$) were intolerant to aspirin. Of intolerant patients, 70% ($n = 218$), 21% ($n = 66$), 5% ($n = 16$), and 3% ($n = 9$) were intolerant to one, two, three, and four or more drugs, respectively. The authors tested the association of intolerance not only to a single drug but also to multiple medications with both intermediate endpoints of blood pressure and lipids at the end of the rehabilitation programme and MACE occurrence during follow-up.

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The drug-intolerant and tolerant groups were similar regarding their baseline characteristics. At the end of the rehabilitation programme, those with DI differed only from those without DI when LDL-cholesterol and the percentage of patients with LDL-cholesterol <70 mg/dL (1.8 mmol/L) as recommended by European guidelines[1] were taken into account; 86 ± 31 vs. 79 ± 26 mg/dL ($P = 0.005$) and 20.4% vs. 29.2% ($P = 0.01$) respectively. No differences were seen in other biomarkers such as blood pressure or left ventricular ejection fraction. Most importantly, MACE defined as hospital admission for acute coronary syndromes, elective percutaneous coronary angioplasty, heart failure, or stroke occurred in 14.1% ($n = 43$) of patients classified as drug intolerant and in 8% ($n = 47$) in those without DI ($P = 0.007$). Drug-intolerant patients had significant increases in acute coronary syndromes, 5.2% ($n = 16$) vs. 1.2% ($n = 7$), $P = 0.001$, and coronary angioplasty, 6.6% ($n = 20$) vs. 1.2% ($n = 13$), $P = 0.002$. After multivariate analysis, DI to one drug [odds ratio (OR) 1.8, 95% confidence interval (CI) 1.01–3.18, $P = 0.043$] or to two drugs (OR 2.56, 95% CI 1.27–5.17, $P = 0.008$) was independently associated with MACE. Regarding the association of a specific class of prognostic drugs, only DI to ACE inhibitors was independently associated with MACE (OR 2.31, 95% CI 1.14–4.65, $P = 0.019$).

The main messages of this study are clear: (i) non-adherence to pharmacological treatment is associated with greater recurrence of MACE even in the short term; indeed if we refer to figure 3 of the study of Albani *et al.*, the Kaplan–Meier survival curves start to diverge before 6 months of follow-up ($P = 0.005$); [16] and (ii) the greater the number of non-tolerated drugs the greater the risk of MACE recurrence. However, the authors were not able to explain why intolerance to ACE inhibitors and not to other more robust disease-modifying drugs in the setting of atherosclerosis prevention such as statins[17] and aspirin[18] occurred; in particular, since most of those intolerant to ACE inhibitor were treated with angiotensin receptor blockers (ARBs), medications that do not differ from the former regarding their putative anti-atherosclerotic effects.[1]. Possible explanations for that are the short time of follow-up, lack of adjustment for angiographic characteristics in a study where revascularization was one of the endpoints, a relatively small number of events, and the presence of residual confounding.

As usually happens in real-life studies, intolerance to statins and ACE inhibitors is greater than encountered in randomized studies.[20] Indeed, even considering run-in periods to select more adherent individuals to participate in clinical trials, these rates are much greater than expected. Also, probably that was the case in the current study. Statin intolerance is a serious problem that may increase the risk of cardiovascular events[8] and mortality, [7] and efforts must be made to reduce LDL-cholesterol with changing statin dose or type, associating ezetimibe with the lowest tolerated dosages, or using PCSK9 inhibitors.[21] ACE inhibitors and aspirin intolerance should be treated with ARBs[19] and $P_2Y_{12}$ inhibitors such as clopidogrel, respectively.[1]

The most important message of the study of Albani *et al.*[16] is that regardless of the cause, DI must be detected early, and other medications need to be used in order to provide lipid, blood pressure, and anti-platelet therapy in secondary prevention. Patient literacy about benefits and harms of evidence-based medicine-proven preventive medications, and easy access to health professionals to detect and correct DI are essential to circumvent this serious problem.

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