Prognostic implications of ischemia with nonobstructive coronary arteries (INOCA): Understanding risks for improving treatment

Myocardial ischemia commonly manifests as angina pectoris and is generally ascribed to atherosclerotic narrowing of epicardial coronary arteries [1,2]. Yet, ischemic heart disease does not necessarily mean obstructive coronary disease. A relevant proportion of patients (about 30%–40%) undergoing coronary catheterization because of angina and documented myocardial ischemia do not have "significant" coronary artery disease (i.e., no stenosis of $\geq 50\%$ in any major epicardial artery) [1,2]. This condition, often defined as "angina with nonobstructive coronary arteries" or "ischemia with nonobstructive coronary arteries" (INOCA), is more frequent in women and can be mainly attributed to two major clinical entities [1]. First, vasospastic angina (VSA), in which the myocardium is jeopardized by dynamic epicardial coronary obstruction or spasm due to vasomotor disorders [1,2]. Second, microvascular angina (MVA), in which myocardial ischemia is caused by coronary microvascular dysfunction related to structural abnormalities (i.e., fixed obstruction) or vasomotor disorders (i.e., dynamic obstruction) affecting the microvasculature. The two clinical scenarios of epicardial VSA and MVA can also coexist [1,2].

Despite interest and efforts to clarify the mechanisms and clinical implications of INOCA have increased in the last decades, the prognosis and management of these patients remain controversial. Some studies showed that INOCA is associated with unfavorable clinical outcomes compared with "healthy" subjects, reporting a higher incidence of cardiovascular events, repeated hospitalizations for coronary angiography, impaired quality of life, and increased healthcare costs [1,2]. However, these data have not been univocally confirmed such that the available evidence remains conflicting. In a recent aggregate-data meta-analysis of 35,039 participants from 54 observational studies, stable angina without obstructive coronary disease showed a relatively benign course, with an incidence of death or non-fatal myocardial infarction (MI) of approximately 1.0% person-years [3]. Yet, this pooled analysis suggested an extreme variability in patients' prognosis that was apparently worse in those presenting with a higher burden of coronary atherosclerosis and cardiovascular risk factors [3]. Although informative, this meta-analysis suffered from several limitations, including mixed patient populations and heterogeneous definitions of anginal symptoms, coronary artery disease severity (i.e., "entirely normal" vs. "less than obstructive" coronary arteries), and myocardial ischemia across studies [3]. More solid evidence is therefore well needed to further characterize this intriguing condition, better understand the prognostic implications of INOCA, and define the optimal management of these patients. The paper by Radico et al. in this issue of the *Journal of Internal Medicine* represents a step forward in this respect [4].

Radico and colleagues reported the results of a study exploring the long-term prognosis and main prognostic determinants of INOCA [4]. Using data from three large Italian datasets, the authors analyzed 956 consecutive patients with angina and objective evidence of myocardial ischemia who did not have obstructive coronary disease (i.e., luminal stenosis was less than 50% in all cases). The inclusion of a large cohort of patients receiving systematic and uniform cardiovascular evaluation over long-term follow-up is a strength of this study compared with previous reports. Coronary anatomy was assessed by invasive coronary angiography (87%) or coronary computed tomography angiography (13%). Myocardial ischemia was objectively documented with exercise ECG stress test in 44% of cases and with imaging pharmacological stress tests (i.e., single-photon emission computed emission tomography, positron emission tomography, cardiac magnetic resonance, and/or echocardiography) in 52% of cases. In the remaining 4%, the test for documenting ischemia was not

specified. Patients with unstable symptoms (i.e., acute coronary syndrome), prior MI or coronary revascularization, and other potentially confounding conditions (i.e., severe valve disease, anemia) were excluded. At a median follow-up of 6.6 years, the incidence of all-cause death or non-fatal MI in this large INOCA cohort was 0.92/100 person-years, which is comparable to previous estimates from meta-analyses (0.98/100 person-years) [3] and similar to that reported in general population datasets [5]. To put this information into context, we have to bear in mind that the incidence of death or non-fatal MI approximates 4/100 person-years in patients with stable angina and obstructive coronary artery disease [6,7] and 10/100 person-years in those with acute coronary syndrome [6–10], resulting therefore 4- to 10-fold higher than INOCA.

A key finding of the study is that the authors demonstrated that two features—namely, the presence of nonobstructive coronary atherosclerosis at angiography and the documentation of myocardial ischemia at stress imaging tests—were capable of effectively risk-stratifying patients by clearly separating survival curves at follow-up. Specifically, the coexistence of normal coronary arteries and ischemia at ECG stress test alone identified patients having the lowest risk of cardiovascular events. On the other hand, the presence of nonobstructive coronary atherosclerosis and myocardial ischemia at imaging stress tests (both verified) was associated with the highest risk of future events (about 10-fold higher than the absence of both factors). Finally, patients presenting only one of the two risk conditions showed an intermediate risk status [4]. These results highlight the prognostic relevance of these two easily available features to guide risk stratification and, ultimately, decision-making in patients with INOCA. Of note, the presence of typical versus atypical angina showed a neutral effect on the risk of adverse clinical events, suggesting that the "objective" demonstration of heart disease carries more reliable information than the "subjective" experience reported by patients.

For the purpose of the analysis, a control group of 1905 age- and risk-factors-matched subjects from the MOLI-SANI study, who were asymptomatic for angina and had no history of cardiovascular diseases, was included for comparison [4]. The incidence of death or non-fatal MI in this asymptomatic, real-world population was— somehow surprisingly—numerically higher than in the overall INOCA cohort, with an estimate of 1.31/100 person-years. Yet, these results can be at least partly explained by the less frequent use of preventive measures (i.e., healthy lifestyle, statins) in the control group compared with the symptomatic study population with angina, as well as possible selection bias, since controls had no information about the status of their myocardium and coronary arteries [4].

The study by Radico and colleagues [4] opens an interesting window to a better understanding of INOCA. Despite some limitations intrinsic to the study design, this rigorous and well-conducted investigation supports the concept that considerable prognostic heterogeneity exists across the entire spectrum of patients with INOCA. The course of this condition can therefore evidently vary, being severe in some individuals (i.e., those with higher atherosclerotic burden) while rather benign in others. The present work keenly warns clinicians that patients with angina and nonobstructive coronary disease should not be overlooked in daily practice. The recognition of high-risk features should prompt careful evaluation, strict follow-up, and aggressive risk factor management to timely tackle atherosclerotic disease progression and prevent life-threatening complications (Figure 1) [1,2]. The absence of coronary lesions necessitating coronary stent implantation should not be misinterpreted as the absence of a disease necessitating medical attention. INOCA is associated with a prognosis that is not benign in a non-negligible proportion of cases, and, at present, there is no uniform approach to this condition. The research agenda for the next decade should address the need to create risk assessment tools to risk-stratify INOCA patients and develop standardized care pathways to improve the quality of life and prognosis of this rapidly growing patient population.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

AUTHOR CONTRIBUTIONS

Conceiving and planning of the work: Paolo Calabrò and Felice Gragnano. Guarantor: Paolo Calabrò. Manuscript draft: Paolo Calabrò and Felice Gragnano.
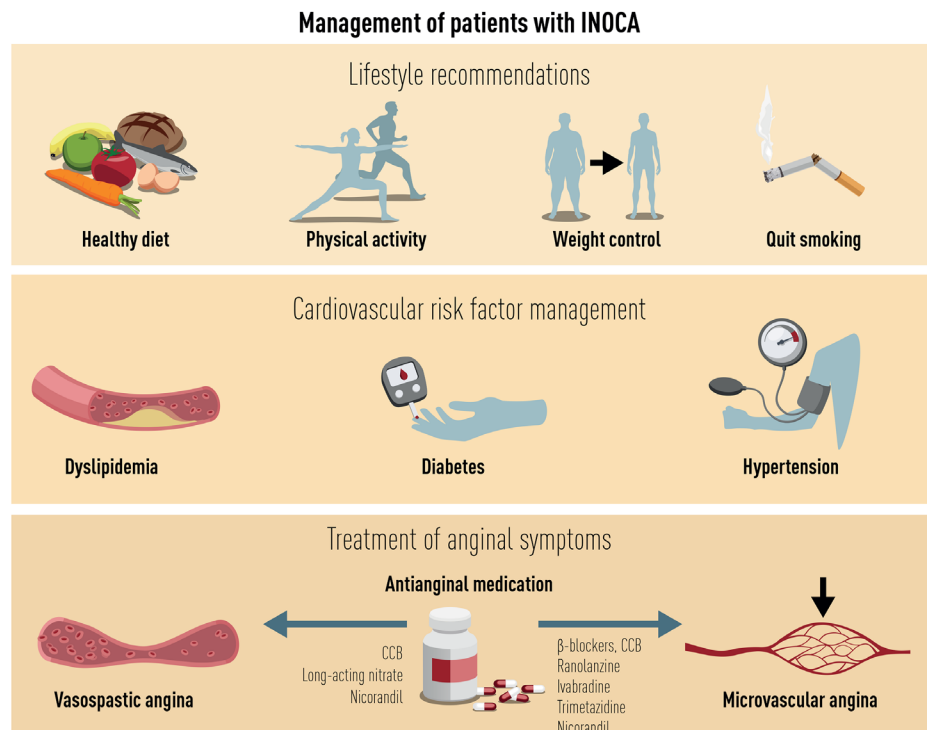
Management of patients with INOCA

Fig. 1 *Management of patients with INOCA. Abbreviations: CCB, calcium channel blockers; INOCA, ischemia with nonobstructive coronary arteries*

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