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ANMCO POSITION PAPER: Prognostic and therapeutic relevance of non-obstructive coronary atherosclerosis

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Atherosclerosis often affects the coronary arterial tree. Frequently the disease does not translate in significant narrowing of the vessels, thus determining only a non-obstructive disease. This condition that is described as non-obstructive coronary artery disease (NobsCAD) should be distinguished from the absence of disease (i.e. smooth coronary arteries) as it carries a specific prognostic value. The detection and reporting of NobsCAD should prompt preventive measures that can be individualized upon the degree of the underlying burden of disease. The accompanying clinical condition, the other cardiovascular risk factors present, and the description of the severity and extent of NobsCAD should provide the framework for an individualized treatment that should also consider the best available scientific evidence and guidelines. The description of NobsCAD represents important information to be collected whenever a coronary angiogram (both invasive and non-invasive) is performed. Treating the patient according to the presence and extent of NobsCAD offers prognostic benefits well beyond those offered by considering only the traditional cardiovascular risk factors. In order to reach this goal, NobsCAD should not be confused

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with the absence of coronary atherosclerosis or even ignored when detected as if it was a trivial information to provide.

Introduction

Several studies have substantially described the history of coronary heart disease focusing on the detection of significant stenosis, their capacity to limit coronary flow, and their treatment. The treatment of coronary heart disease has therefore become equivalent of treating ischaemic heart disease, namely coronary artery stenosis. It is well-known that atherosclerotic disease begins and progresses with elementary lesions of the coronary walls and that only at an advanced stage does it determine clinical events. Seriate studies have shown how non-obstructive coronary artery disease (NobsCAD) is a precursor of more severe lesions and of the subsequent appearance of atherothrombotic complications and the relative clinical symptoms.[1] In the past, various observations have been made on the NobsCAD clinical and prognostic role.[2-4] However, it was only after the results of large prospective studies mainly conducted by using coronary computed tomography angiography (CCTA) that it became evident that NobsCAd negatively affects prognosis (in particular its severity and extent) albeit to a smaller extent compared to the obstructive disease[5,6] (*Figure 1 and 2*). Therefore, it is necessary to consider NobsCAD within the cardiovascular risk continuum. It reflects the atherosclerotic vessel damage and therefore identifies a 'local' risk, but it should also be considered as a sign of increased global cardiovascular risk.[7] The guidelines do not currently provide a specific therapy for NobsCAD. However, several findings identify this condition as a 'risk modifier' and therefore as a further indicator

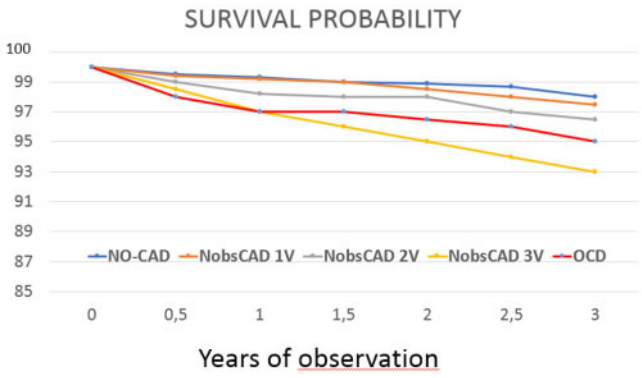

Figure 2 Survival probability of patients with obstructive coronary disease (OCD), non-obstructice coronary artery disease (NobsCAD) and with no atherosclerotic disease (NO-CAD). NobsCAD is further categorized based on the number of vessels diseased. The progressive burden of NobsCAD is associated with an increasingly worse outcome. 3VNobsCAD carries a worse outcome compared to OCD. Adapted from Min *et al.*[5] and Lin *et al.*[6]

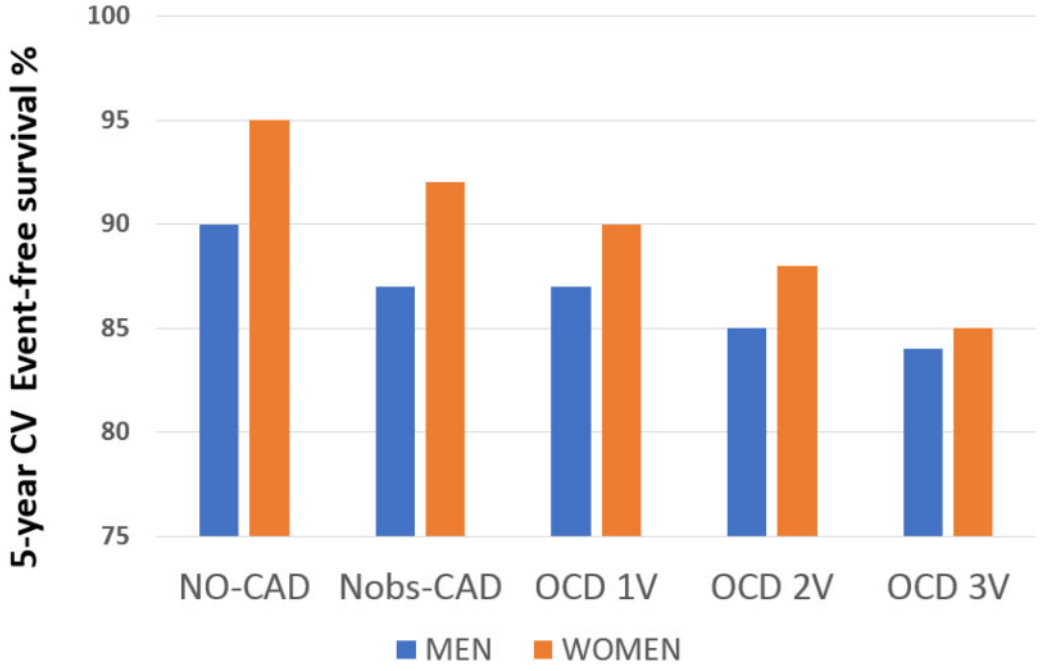

Figure 1 Even-free survival and age adjusted survival of 4711 women and 6512 men who performed an invasive coronary angiography for stable angina categorized according to the presence and severity of atherosclerosis. Obstructive coronary artery disease was defined as the presence of at least one stenosis >50%. Non-obstructive coronary artery disease was defined as the presence of 1-49% lesion of at least one epicardial artery. The observed events included cardiovascular death, hospitalization for myocardial infarction, heart failure and stroke. It can be noted how non-obstructive coronary atherosclerosis (NobsCAD) has a negative prognostic value, comparable to that observed for patients with a critical stenosis in men while it is even higher for women.

(NobsCAD = non-obstructive coronary artery disease, OCD = Obstructive coronary disease, 1-2-3V = 1-2-3 vessels (Adapted from Jespersen et al.).[32]

of increased cardiovascular risk.[8] This Position Paper aims at focusing the Italian scientific community's attention on NobsCAD, by recommending its accurate identification and description in order to grant specific measures able to reduce the risk of events, as suggested by a some recent clinical trials.[9,10]

Description and identification of non-obstructive coronary atherosclerosis

Non-obstructive coronary atherosclerosis description

Two recent Consensus documents—one of the American Heart Association (AHA)[11] and the other by European Society of Cardiology (ESC)[12] in addition to the ESC Guidelines on non-ST-elevation in acute coronary syndromes (ACS-NSTE)[13] have described and identified NobsCAD as detected at coronary angiography (*Table 1*). While both documents agree in considering the presence of NobsCAd only for those lesions determining <50% lumen reduction in at least one epicardial branch less unanimous appears the definition of no coronary heart disease. In fact, the Working Group on Cardiovascular Pharmacotherapy includes among those with no coronary disease those with lesions <30%.[12]

Identification of non-obstructive coronary atherosclerosis

NobsCAD can be detected through the use of various imaging techniques, such as conventional coronary angiography (CCA), CCTA, and coronary magnetic-resonance angiography (CMRA).

Conventional coronary angiography

It represents the main used technique in the detection of coronary disease. However, some limitation which affects its sensitivity and specificity in correctly examining the atherosclerotic disease and its effects. Conventional coronary angiography provides a two-dimensional luminography, which through multiple projections allows a three-dimensional image reconstruction and subsequently an indirect estimate of the lesion severity. A major limitation of CCA is the lack of information about the plaque composition of the lesions observed and the accurate detection of the overall atherosclerotic burden of the artery. The description of the severity of a lesion by CCA is affected by the subjective description of the Cardiologist performing the examination and also by technical issues such as the presence of curved lesions, overlapping vessels, possible non-optimal opacification, and biological events (i.e. variation in muscle tone, spasms). All the above-mentioned aspects may lead to a significant intra- and inter-observer variability and, finally to a potentially relevant inaccurate estimation of the disease severity.[14-16]

Finally, it is well-known that the sole CCA description of a coronary lesion does not allow to obtain adequate clinical information, especially in NobsCAD patients. Besides any concern about the accuracy of this tool, it is important to highlight that the relation between the stenosis lesion and ischaemia is affected by factors that go well beyond the stenosis severity of the epicardial vessel.[17]

Intravascular ultrasound/optical coherence tomography

Many intravascular ultrasound (IVUS) studies are reported in literature and have shown a significant coronary atherosclerotic burden even in subjects whose vessels have been defined as 'normal' by CCA.[18] Due to the insufficient adoption in clinical practice of intracoronary imaging techniques [IVUS and optical coherence tomography (OCT)], it is not always possible to evaluate the non-obstructive lesions and determine their true 'ischaemic' significance. There are reports using IVUS or OCT showing that in NobsCAD patients (between 30% and 40% stenosis), at least one out of five presented a vulnerable plaque, predictor of cardiovascular events.[19]

Coronary computed tomography angiography

A powerful method to identify NobsCAD is represented by CCTA. In consideration of the technological progress over the past few years, it is possible to accurately assess the presence and severity of coronary stenosis (sensitivity and negative predictive value to the detection/exclude stenosis >50%, both > 90%),[20] the atherosclerotic 'burden' and qualitative plaque characteristics, thus adding prognostic information of primary relevance.[21,22]

Table 1 Meta-analysis on the prevalence and prognosis of non-obstructive coronary atherosclerosis

	MACE[a] Incidence	Annual MACE incidence in-stable angina	Annual MACE incidence In ACS-NSTE
No coronary disease (stenosis 0-≤20%)	Moderate vs. no coronary disease: Risk ratio 1.85 (95% CI 1.52-2.26)	0.3% (95% CI 0.1-0.4%)	1.2% (95% CI 0.02-2.3%)
Moderate coronary disease (stenosis ≥20-≤50%)	Moderate vs. obstructive (95% CI 0.20-0.38)	0.7% (95% CI 0.5-1.0%)	4.1% (95% CI 3.3-4.9%)
Obstructive coronary disease (stenosis >50%)		2.7% (95% CI 1.7-3.7%)	17.0% (95% CI 8.4-25.7%)

ACS-NSTE, non-ST segment elevation acute coronary syndromes; CI, confidence interval; MACE, major adverse cardiovascular events.
[a]Cardiac death and myocardial infarction.
Adapted from Wang *et al.*[33]

Hystopathological studies have shown the characteristics associated with a major vulnerability of the coronary plaques: presence of a thin-cap fibro-atheroma, a necrotic core, an elevated plaque 'burden', and a positive remodelling of the arterial wall. Many of these characteristics can be detected by CCTA. The presence of high-risk plaque characteristics allow to identify patients that at a later stage more frequently will suffer major adverse cardiovascular events (MACE). Despite the capability of identifying the characteristics associated to plaque vulnerability, the predictive value of these findings as well as a definite clinical intervention strategy has not yet been well established.[23] More information and data are instead available about the atherosclerotic plaque 'burden'.

Coronary computed tomography angiography suffers from some limitations. Compared to CCA, CCTA has a lower spatial resolution,[24] and also there is a significant inter-observer variability in the definition of the plaque characteristics.[25] Atrial fibrillation and high heart rates significantly and negatively affect image. The latest generation of scanners is less affected by these limitations. Radiation exposure can now even be lower compared to CCA.[26]

Coronary magnetic resonance angiography

Another non-invasive method used to detect NobsCAD is CMRA. Unfortunately, this tool possesses a significantly lower spatial resolution compared to CCTA. So far CMRA allows only an accurate evaluation of the anatomy of the proximal coronary segments; therefore, it cannot be considered an elective method to diagnose NobsCAD. By using a multiparametric approach CMRA may allow an accurate evaluation of the atherosclerotic plaque components. However, this potentiality can only be considered something clinically useful when a sufficient spatial resolution will be possible.

The prevalence of non-obstructive coronary atherosclerosis in different clinical conditions

Atherosclerosis is the most common disease involving the coronary arteries and is usually detected through the study of the coronary tree in patients with signs or symptoms of myocardial ischaemia. In the last few decades, the increased use of diagnostic methods for the study of the coronary arteries in patients with suspected myocardial ischaemia has led to the detection of a NobsCAD in a large proportion of patients. Similarly, NobsCAD has been observed in both acute and chronic coronary syndromes. Furthermore, not rarely, NobsCAD is described in patients occasionally evaluated by coronary artery imaging studies performed for other conditions.

To date there is no agreement regarding the definition of obstructive/non-obstructive coronary disease, therefore, the available epidemiological data in scientific literature are very heterogeneous.[7] Although the standard angiographic value for the definition of obstructive coronary disease applies to stenosis =≡ or >50% of the epicardial coronary vessel, several clinical studies include in the non-obstructive stenosis group all the coronary lesions that do not exceed a >70% lumen obstruction. In other studies, the cut-off to distinguish a critical obstruction from a non-critical one is equal to 50% for the common trunk and 70% for the remaining epicardial branches. Furthermore, sometimes a minimum value >20% allows to consider NobsCAD as present, while in other studies no precise value is indicated to determine the presence of atherosclerotic disease. Indeed, the use of imaging methods, such as IVUS, has allowed to detect the presence of coronary atherosclerotic lesions even in patients with CCA described as free of lesions or 'normal'.[18] In addition, the increasingly common use of CCTA has made the description of NobsCAD less accurate. In fact, when using CCTA the coronary lesions can be considered obstructive with a good confidence only when >90%. For those lesions, 50–90% it is suggested to perform other tests[27] to determine their clinical meaning.

Dealing with acute coronary syndromes (ACS), the prevalence of myocardial infarction with non-obstructive coronary artery disease (MINOCA) (absence of stenosis >50%) ranges between 5% and 15%, depending on the population studied.[11] The use of intra-coronary imaging techniques has allowed the detection of ruptured atherosclerosis plaques in over a third of patients with MINOCA.[28] Furthermore, it has been observed that in the majority of MINOCA patients those plaques that undergo a rupture are not the among the most severe.[29]

As above mentioned, coronary plaques can be observed in ~50% of patients with unstable angina in absence of critical coronary stenosis.[2]

Large-scale US observational studies of patients who underwent elective coronary angiography have reported the presence of a NobsCAD (non-critical lesion but >20%) in 18–22% of the whole population examined.[30,31] In particular, NobsCAD involving only one coronary artery was reported in 12% of patients while was detected in two vessels in 7%. In the same study, a three-vessel NobsCAD was observed in 3%. In a large study conducted in Denmark, which enrolled patients with suspect stable angina, with the exclusion of those with a previous diagnosis of cardiac disease, 17% males and 14% females showed evidence for a widespread NobsCAD, defined as a presence of stenosis, involving any coronary artery,[32] between 1% and 49%.

A meta-analysis of clinical studies, using CCA or CCTA, assessed the coronary tree of patients with chest pain. The study reported an 18% prevalence of moderate obstructive coronary disease in patients who underwent CCA and 35% in those who underwent CCTA.[33] Compared to patients with obstructive coronary disease, patients with non-obstructive disease are generally younger (median age 60 vs. 64 years), more frequently are female (41% vs. 28%), and have a minor prevalence of comorbidities such as arterial hypertension (60% vs. 78%), diabetes mellitus (16% vs. 26%), and dyslipidaemia (61% vs. 81%).[34]

Atherosclerotic burden and coronary stenosis

Coronary atherosclerosis is the main cause of both acute and chronic ischaemic heart disease and its basic lesion is

the atherosclerotic plaque, which could account for a variety of clinical syndromes.[35–42] In the majority of subjects, the disease can be documented already at the age of 20 albeit silent or sub-critical,[43,44] it may affects the intimal layer of the vessel wall in a variable manner and therefore diffused and also at a local or even focal level. During its natural history, the plaque could increase in size and should it exceed the critical stenosis threshold, may cause ischaemia limit the hyperaemic flow. The atherosclerosis plaque can also become unstable and undergo an abrupt atherothrombotic complication causing acute clinical conditions (unstable angina, myocardial infarction, sudden death). The atherosclerotic plaques are classified as stable, vulnerable, and unstable. The stable plaque is 'dormant', and slow-growing—it becomes symptomatic when its volume causes a critical stenosis. The stenosis is generally fixed as the plaque represents a mechanical obstacle to the blood flow without any functional contribution (vasospasm).[35,41,42] It is important to remember that the vulnerable plaques (i.e. those that are prone to complications), are generally non-obstructive (<75% stenosis) due to a positive vessel wall remodelling or expansion (so they can be appear as angiographically not severe), they are silent and do not promote the development of a collateral circulation. The severity of the stenosis is not a reliable marker of risk of acute events.

Clinical implications of non-obstructive coronary atherosclerosis

A growing series of evidence shows how an association exists between the presence of coronary disease and the risk, over time, of cardiovascular events. Also, it is now well established that the severity of a stenosis is not necessarily associated to a critical event which could occur over time, namely ACS. In patients with angina, who underwent both coronary angiography and CCTA, it has been shown that the presence of a non-critical coronary disease (stenosis <50%) is related to the same risk of infarction and death as that of patients with one-vessel critical disease (stenosis >70%).[30,32,34,45]

A large registry study on 37 674 patients with NobsCAD but no obstructive disease in any of the three diseased vessels, had a 3% annual risk of infarction, similar to the risk of patients with one-vessel significant coronary disease. Likewise, it was noted how the extension and the number of vessels with NobsCAD was related to a progressive increase of the MACE.[6,33] In a meta-analysis of 32 studies, including 41 960 patients who underwent CCTA, with a median follow-up of 2 years, the incidence of cardiac death or myocardial infarction was 0.04% in the absence of coronary artery disease, 1.29% in patients with NobsCAD, and 6.53% in patients with obstructive coronary artery disease. This latter group showed a much higher risk compared to those without any coronary disease [odds ratio 6.41%, 95% confidence interval (CI) 2.44–16.84].[46] A recent meta-analysis which included 1 395 190 patients, assessed the prevalence and prognosis of NobsCAD patients (stenosis ≤50%), who underwent coronary angiography or CCTA for established or suspected coronary disease.[33] The NobsCAD patients were further divided in patients without coronary disease (coronary stenosis between 0% and ≤20%) and in those with moderate coronary disease (coronary stenosis between ≥20% and ≤50%). The prevalence of patients with non-obstructive coronary disease with stable angina was 67% (95% CI 6.3–7.1%) while was 13% (95% CI 11–16%) in ACS-NSTE patients. The incidence of MACE (cardiac death and infarction) was lower in patients with moderate coronary disease compared to those with obstructive coronary disease (risk ratio 0.28, 95% CI 0.20–0.38), but higher compared to those without, coronary artery disease (risk ratio 1.85, 95% CI 1.52–2.26).

The annual incidence of MACE of patients with stable angina without coronary disease, with moderate or with severe coronary artery disease was respectively 0.3% (95% CI 0.1–0.4%), 0.7% (95% CI 0.5–1.0%), and 2.7% (95% CI 1.7–3.7%). In ACS-NSTE patients, the result was 1.2% (95% CI 0.02–2.3%), 4.1% (95% CI 3.3–4.9%), and 17.0% (95% CI 8.4–25.7%). NobsCAD was therefore associated to a more favourable prognosis compared to the obstructive disease, but was not benign; hence, NobsCAD patients deserve a specific risk stratification, to identify the best therapeutic strategy.

Histopathological studies have shown how some morphological characteristics represents factors linked to plaque instability and therefore precursors of ACS. Investigations performed using CCTA have demonstrated the possibility of exploring *in vivo* the coronary plaque characteristics and particularly some of the alterations which characterize the vulnerable plaques, such as a large lipid core, the remodelling of the vessel wall and plaque, the presence of 'spotty' calcification and the extension of the atherosclerotic disease.[47–50]

In a recent study, 25 251 patients who underwent CCTA were followed 3.4 ± 2.1 years to evaluate the incidence of new coronary events. Among those who developed an ACS, only 34.6% had a >50% stenosis and only 12.50% had >70%. The most interesting result was that among patients with >50% stenosis and >70%, only 2.4% and 4.7%, respectively, had an acute coronary event. In this study, the qualitative characteristics of the plaques also demonstrated a relevant predictive value.[49] The opportunity to identify and characterize qualitatively NobsCAD can therefore provide further elements that can help to treat selectively those patients at increased risk in order to avoid the development of MACE over time.

From coronary vessel stenosis to the plaque 'burden'

An accurate evaluation of the coronary atherosclerotic lesions, regardless of the entity of the stenosis, represents an important diagnostic target, because as previously reported, the number and the extent of the atherosclerotic lesions significantly influence the prognosis. Recent studies indeed indicate that the atherosclerotic load, from a prognostic point of view, is currently to be considered more relevant, than the demonstration of inducible ischaemia.[30,51] The prevalence and prognostic value of NobsCAD in-stable angina and NSTE-ACS have been evaluated in the already cited meta-analysis of Wang *et al.*[33] which included over a million patients. The results are summarized in *Table 1*.

In the PROSPECT study, 697 ACS patients who underwent CCA and IVUS after coronary angioplasty were followed for a mean 3.4 years. The cumulative incidence of MACE (cardiac death, cardiac arrest, myocardial infarction, or unstable angina re-hospitalization) was 20.4%. The new event was related to the original culprit lesion in 12.9%, while it was related to an original non-culprit lesion in 11.6% of cases. The events related to 'non-culprit' lesions were mainly attributed to mild degree stenosis detected during CCA, vulnerable plaques, with a significant atherosclerotic burden.[52] Another registry, with over 20 000 symptomatic patients, showed a risk of events strictly correlated to the atherosclerotic burden.[46] In the COURAGE Study, 60% of the 2287 enrolled patients underwent functional tests of ischaemic and angioplasty. At follow-up, 7.9 years later, the number of diseased vessels was significantly associated to a worse prognosis [hazard ratio (HR) 1.25, 95% CI 1.09–1.43), while the demonstration of ischaemia did not (HR 0.99, 95% CI 0.80–1.22).[53]

The prognostic role of coronary calcium (CAC) was evaluated and compared to that of obstructive coronary artery disease as shown by CCTA[54] in the Western Denmark Heart Registry on 23 759 symptomatic patients. The cardiovascular events observed at 4.3 years of follow-up were more common in patients with obstructive CAD and higher CAC score. However, when the stenosis was stratified by the CAC score quintiles, the presence of the obstructive disease did no longer result linked to a higher risk of events compared to those observed in patients with NobsCAD. This study shows that atherosclerosis and its severity is the major determinants of worse prognosis, while the simple detection of an obstructive lesion *per se* does not offer relevant prognostic information.[54]

Clinical significance of non-obstructive coronary artery atherosclerosis

Several clinical entities share the presence of NobsCAD. It can be found occasionally in totally asymptomatic subjects during tests performed for screening of disease but also in patients with evidence of myocardial ischaemia or myocardial infarction. The clinical entity of NobsCAD and myocardial ischaemia is known as INOCA (ischaemia with non-obstructive coronary artery disease),[55] while myocardial infarction without obstructive coronary artery diseases as MINOCA.[56]

The clinical and prognostic meaning of NobsCAD varies according to the clinical context in which it is detected. It has been demonstrated how the presence of NobsCAD, although variable in the studies, appears frequently.[5,32] The benign NobsCAD paradigm changed in 2015 when Park *et al.*[57] demonstrated that 17% of patients with a coronary stenosis <50% presented an inducible ischaemia. The database of the American College of Cardiology-National Cardiovascular Data Registry and of the WISE (Women's Ischaemic Syndrome Evaluation) of the National Heart, Lung and Blood Institute reports that 3–4 million women and men with symptoms suggestive for myocardial ischaemia do not have a significant coronary artery disease.[58,59]

The global clinic and economic impact of NobsCAd are not very different to that of obstructive coronary artery disease. This is due to the similarity of clinical symptoms, hospitalizations, and need of diagnostic evaluation including CCA for the two entities.[58-60] The results of a recent meta-analysis conducted by Radico *et al.*[61] are in line with the aforementioned observations. This meta-analysis in fact not only confirms the higher risk of adverse events associated to the identification of NobsCAD during CCTA in symptomatic angina patients and also highlights the additional risk of patients who present inducible ischemia documented by the results of the provocative tests of ischaemia. Furthermore, analysing the studies for which data relating to the hospitalizations during the follow-up (24 out of 54 in total) was available, it was noted how NobsCAD patients had a higher incidence of hospitalizations, of relapse of angina, and of repeated coronary angiographies, with a clear evidence for a worsened quality of life.[61]

The available data as a whole not only confirm the far from benign outcome of patients with NobsCAD but how their prognosis is also influenced by the clinical context in which atherosclerosis is detected (effort induced angina vs. ACS-NSTE; presence or absence of inducible ischaemia). In the evaluation of the clinical impact of NobsCAD, it is necessary to consider not only the prognostic impact in terms of major clinical events but also in terms of symptoms and quality of life. The CIAO-ISCHEMIA study,[62] a subproject of the ISCHEMIA Trial evaluated 221 patients excluded from the main investigation because of NobsCAD at enrolment. They had nonetheless the demonstration of myocardial ischaemia at a functional test of ischaemia. Their outcome was compared to that of the 1079 patients of the main study. The patients of both groups did not differ in terms of ischaemic severity but it is interesting to note how women were more represented in the CIAO-ISCHEMIA (66%) in comparison to the main study (26%). With respect to the patients of the ISCHEMIA the CIAO-ISCHEMIA patients experienced angina more frequently and more severe symptoms (17% vs. 4%).

How to navigate among guidelines, recommendations, and therapeutic strategies. The challenge of the everyday practice

Clinical trials

In the absence of controlled randomized trials, it is not always clear, which are the therapeutic choices for patients with a coronary tree void of significant stenosis. In the MINOCA, the aggressive measures of secondary prevention should be applied only in case of NobsCad. In the SWEDEHEART Registry significant beneficial effects were observed on MACE by using statins (HR 0.77, 95% CI 0.68–0.87) and ACE-inhibitors/angiotensin II receptor blockers (HR 0.82, 95% CI 0.73–0.93), basically positive for beta-blockers (HR 0.86, 95% CI 0.74–1.01), while the dual antiplatelet therapy (DAPT) had a neutral effect (HR 0.90, 95% CI 0.74–1.01).[63] However, the registry did not differentiate patients with NobsCad from those with coronary arteries

free from lesions. In a study with 13 104 patients who underwent CCA, the lack of use of renin–angiotensin–system inhibitors (RAASi) (HR 2.63; $P = 0.033$) and of statins (HR 2.17; $P = 0.039$) was a significant predictor of total mortality[64] in those with a diagnosis of MINOCA.

Besides the ACS clinical framework, the NobsCAD therapy without evidence of inducible ischaemia appears quite controversial, and it is uncertain whether to treat these patients as high-risk cardiovascular patients. A specific risk stratification is therefore deemed necessary to identify a 'personalized' prevention. Through CCTA the plaque characteristics identify high-risk patients. A risk prediction model of the MACE has been developed (age, gender, hypertension, diabetes, anaemia, C-reactive protein, and the entity of the atherosclerotic burden): patients with the highest score received a significant benefit from statin therapy (HR 0.62; $P = 0.033$) while in those with a lower score, aspirin was associated with a higher risk of cardiovascular events (HR 2.57; $P = 0.004$).[65] In NobsCAD patients, cardiac rehabilitation improves, the ability to exercise, the quality of life, symptoms, and myocardial perfusion.[66]

By using IVUS and during an aggressive statin therapy a continuous inverse relationship has been observed between the volume of atheroma and the LDL cholesterol levels; similar results have been reported by using PCSK9 inhibitors.[67] In the CONFIRM study (Coronary CT Angiography EvaluatioN For Clinical Outcomes: an International Multicenter Registry), statins demonstrated to reduce mortality in NobsCAD patients (HR 0.32; $P < 0.001$).[68] In the same study, an increase in mortality or MACE with the increase of CAC or of the atherosclerotic burden was not noted[69] in patients on basal statin therapy. In 8372 NobsCAD patients documented by CCTA, and who received a statin therapy regardless of the other parameters, there was a 60% reduction in the mortality rate (HR 0.397; $P < 0.0001$) and 57% in MACE incidence (HR 0.43; $P < 0.0001$).[63]

RAASi significantly reduce MACE and mortality. In the Korean AMI registry, the MACE incidence resulted the same in the MINOCA patients treated with ACE-inhibitors or angiotensin II receptor blockers (10.4% vs. 15.6%, HR 0.65; $P = 0.301$), but the incidence of re-infarction was inferior among those treated with ACE-inhibitors (2.1% vs. 10.4%, HR 0.18; $P = 0.031$).[70]

In the CONFIRM Study, aspirin did not show any significant effect on mortality,[68] while in another study it reduced the total mortality rate but only in high-risk patients, without any significant reduction of MACE (0.841; $P = 0.1577$).[71] In the SWEDEHEART Registry, the use of DAPT did not confer any benefit.[63]

In the real world, it has been reported[63] that NobsCAD patients have a low probability of receiving secondary prevention therapy at discharge.

Controlled randomized studies are currently ongoing exploring the incidence of MACE in NobsCAD patients treated with RAASi and beta-blockers (MINOCA BAT NCT03686696), or statins and RAASi (Warrior, NCT03417388).

The guidelines

The International guidelines do not provide specific recommendations about the follow-up of patients in whom a NobsCAD had been identified.[13,14,19,56] The recommendations are quite scarce even in regard to the therapeutic choices.

A pharmacological therapy with aspirin, statin, ACE-inhibitors, angiotensin, and calcium antagonist receptor inhibitors (in case of suspected vasospasm) is suggested as a routine in non-ST-segment elevation myocardial infarction MINOCA[13] (CI recommendation). The ESC guidelines suggest to apply to this condition the same treatments recommended for the secondary prevention of other atherosclerotic acute events; however, this recommendation is not supported by solid evidence (IIb C recommendation). The ESC Guidelines for the management of ST-segment elevation myocardial infarction do not provide any specific recommendation for these patients.[5]

An ESC position paper suggests that the DAPT could be taken into consideration in MINOCA patients, based on pathophysiological considerations, but the evidence is scarce.[12] The European Guidelines on chronic coronary syndromes[28] do not provide any specific recommendations. There are some recommendations about the management of clinical symptoms or demonstration of myocardial ischaemia, both of which can occur even in the absence of NobsCAD.

Finally, the guidelines on cardiovascular prevention identify as high risk only patients with significant coronary plaques.[8]

The operative approach

The diagnostic and therapeutic approach to NobsCAD patients is quite complex due to the multifaceted anatomical and functional alterations responsible for the different associated clinical conditions. The therapeutic choices should be personalized although there is no clear evidence of efficacy for many suggested measures due to the lack of specific randomized studies in such an heterogeneous population (*Figure 3*).

From the operative point of view, it is essential to distinguish the symptomatic forms (both in the MINOCA and in the angina pectoris framework) from the asymptomatic ones.

In the first case, as reported in the Consensus Document of the European Association of Percutaneous Cardiovascular Interventions (EAPCI),[72] the different causes of ischaemia require diversified diagnostic goals and personalized therapies. Coronary angiography and coronary computerized tomography are not sufficient to identify the cause of ischaemia. The functional tests exploring the vascular reactivity (i.e. adenosine test for the detection of microvascular dysfunction and acetylcholine test for the diagnosis of vasospastic angina) become very useful.[28-72]

It has also been suggested to use RAASi[73] in patients with MINOCA and platelet aggregation inhibitors, especially in those patients in whom the intravascular imaging techniques show a rupture/erosion of the plaque.[74]

Even more controversial is the treatment of NobsCAD in asymptomatic patients. It may be particularly difficult to start a secondary prevention pharmacological therapy in such patients in the absence of strong recommendations. However, it is important to distinguish NobsCAD from the

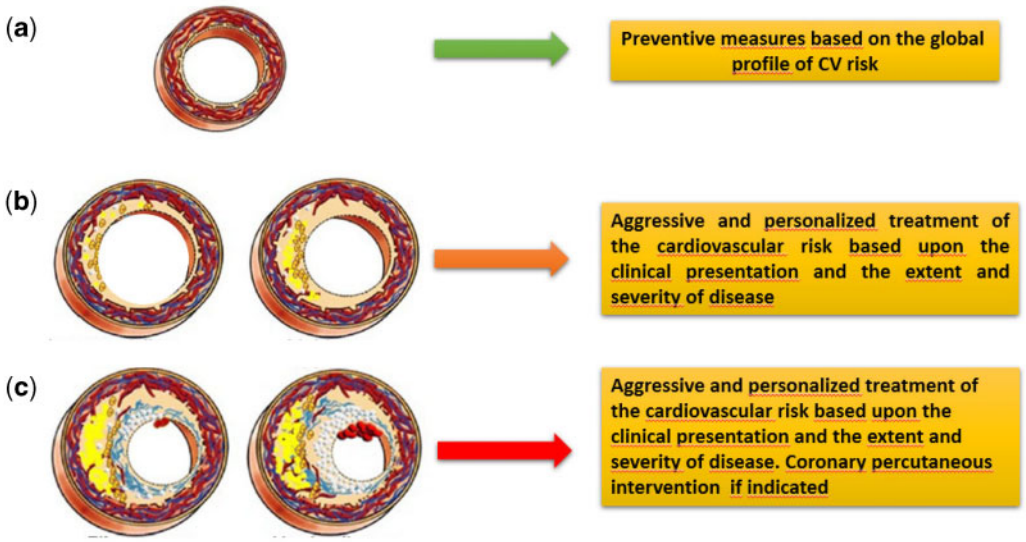

Figure 3 Summary of recommendations guided by the presence or absence of signs of coronary atherosclerosis. When there is no coronary atherosclerosis (a) the therapeutic choices are guided by the global cardiovascular risk of the patient. When atherosclerosis is detected the choice of treatment should be directed to halt the progression of disease and prevent acute events either for non-obstructive (b) or obstructive (c) disease. If only a NobsCAD is found (b) a preventive therapy should be started and personalized based upon both the clinical presentation and the severity of the atherosclerotic burden. When an obstructive disease is found (c) patients should receive a similar therapeutic approach to those with NobsCAD and eventually undergo a percutaneous interventional therapy if indicated.

absence of CAD. It is, therefore, essential in NobsCAD patients to implement the recommended healthy life-style measures (suitable diet, physical activity, stop smoking, stress-control) and start a personalized drug regimen when other risk factors are detected (hypertension, diabetes, dyslipidaemia).

Conclusions

The available data from literature indicate how the total atherosclerotic burden and a number of morphological characteristics of the coronary artery plaques have an important prognostic value. The presence and extension of the atherosclerotic disease constitutes a prognostic element independent from ischaemia and in some cases even superior to the ischaemia itself. NobsCAD represents a disease marker, and can, if its presence and severity are described, constitute a useful prognostic information that may help to promote a pharmacological intervention.

NobsCAD is a common finding both as an isolated finding and in association with obstructive stenosis. Its definition differs in the published studies. Sometimes incorporated in the broader definition of non-obstructive disease are included the absence of disease or diseased vessels with $<$50–70% stenosis. The opportunity of recognizing NobsCAD depends on the accuracy of the coronary anatomy evaluation after a morphological exam and also and especially, by the technique used. Commonly and more easily identified when CCT and IVUS are used, less precisely detected with conventional angiography. The clinical meaning of NobsCAD is linked to both its possible importance in the coronary circulation, and to that as a precursor of obstructive/complicated lesions able to determine symptoms or coronary events. Finally, NobsCAD by highlighting the presence of a vascular disease is entitled to be qualified as a vascular disease and become a cardiovascular risk modifier. The non-obstructive coronary disease is associated to a more favourable prognosis than that of an obstructive disease but it is definitely worse to that of subjects without any sign of coronary artery disease. The high prevalence for this condition warrants a specific risk stratification to establish the best therapeutic strategy in these patients whose prognosis is influenced by the clinical context as well as by the plaque burden. For this reason, the risk stratification in NobsCAD patients must be based on the presence of traditional risk factors but also on the possible presence of angina and/or inducible ischaemia, and the integration of these elements with the plaque characteristics.

The presence of NobsCAD identifies patients at risk of cardiovascular events and there is evidence that indicates the possibility to obtain prognostic benefits by intervening with a suitable pharmacological therapy. The existing guidelines that aim at treating ischaemic events based on atherosclerosis provide clear guidance should NobsCAD be correlated to MINOCA. When NobsCAD is found occasionally or in patients with angina the therapeutic choices are less obvious.

The guidelines on cardiovascular prevention identify as high-risk patients those who show a clinically relevant atherosclerotic disease not equivocal at imaging. Included in this definition are a peripheral arterial disease, an important coronary disease ($>$50% stenosis of at least two epicardial vessels at CCTA) or carotid plaques. CAC is also included in the guidelines as a risk modifier. Instead, no mention exists for the presence of NobsCAD. It is difficult

to understand why in spite of the huge demonstration of its negative prognostic weight NobsCAD has not yet received until now any specific attention.

In a hypothetic treatment scheme, assuming NobsCAD is a sign of coronary artery disease, it is necessary to consider three aspects: (i) the risk linked to the clinical condition (to one end ACS-NSTE, to the other end no clinical manifestation); (ii) the cardiovascular risk calculated on the basis of the presence of risk factors and on the use of the SCORE cards; (iii) presence and severity of NobsCAD ('atherosclerotic burden').

A NobsCAD with only one lesion on a single vessel, without other risk factors is clearly very different to a NobsCAD with multiple risk factors possibly documented in the occasion of an ACS-NSTE.

In conclusion, the ANMCO Position Paper supports the following recommendations:

a. emphasize the fundamental importance of an accurate description of NobsCAD if present, when performing, for any reason, a morphological examination of the coronary arteries;
b. consider the clinical context in which NobsCAD has been documented (i.e. ACS vs. non-ACS);
c. underline the need of considering NobsCAD in the context of the patient's individual cardiovascular risk;
d. treat the patient with NobsCAD in accordance with the existing guidelines (pending data from the randomized ad-hoc studies) and consider NobsCAD as an additional cardiovascular risk factor, taking into consideration its burden and therefore its physiopathological meaning; and
e. never confuse NobsCAD with the absence of coronary artery disease.

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