

European Society of Cardiology Highlights: Late-breaking Science MINOCA/ANOCA

Peter Ong  and Andreas Seitz 

Department of Cardiology and Angiology, Robert-Bosch-Krankenhaus, Stuttgart, Germany

Keywords

MI with non-obstructed coronary arteries, angina and non-obstructed coronary arteries, comprehensive diagnostic assessments, coronary spasm, microvascular dysfunction

Disclosure: PO has received speaker honoraria from Abbott, Philips, Pfizer, BMS and Edwards, and is a regional editor of *European Cardiology Review*; this did not affect the decision to publish. AS has no conflict of interest to declare.

Funding: This work received funding from the Robert Bosch Foundation and the Berthold Leibinger Foundation.

Received: 13 May 2022 **Accepted:** 18 May 2022 **Citation:** *European Cardiology Review* 2022;17:e18. **DOI:** <https://doi.org/10.15420/ecr.2022.22>

Correspondence: Peter Ong, Department of Cardiology and Angiology, Robert-Bosch-Krankenhaus, Auerbachstrasse 110, 70376 Stuttgart, Germany. E: Peter.Ong@rbk.de

Open Access: This work is open access under the CC-BY-NC 4.0 License which allows users to copy, redistribute and make derivative works for non-commercial purposes, provided the original work is cited correctly.

Angina pectoris and ischaemic heart disease have fascinated physicians in general and cardiologists in particular for decades. In today's era of precision medicine, the challenge remains to correctly interpret the patient's symptoms and determine the underlying (cardiac) cause. This provides the basis for adequate and appropriate treatment strategies. It is why the traditional concept of ischaemic heart disease focusing on epicardial atherosclerotic stenoses only is now outdated.

The spectrum of ischaemic heart disease is broad and encompasses several epicardial pathologies such as atherosclerotic disease, spontaneous coronary dissection and coronary spasm as well as microvascular abnormalities, such as microvascular spasm, impaired microvascular vasodilatation and increased microvascular resistance. The complex interplay between epicardial vessels and microvessels under physiological and pathophysiological conditions (so-called coronary autoregulation) should be appreciated.

In this context, the aim of the present article was to summarise contributions to the ESC Congress 2021 in the field of MI with non-obstructive coronary arteries (MINOCA) and angina with non-obstructive coronary arteries (ANOCA). This may help in opening up new avenues of research and clinical care for our patients.

In recent years, the clinical scenario of patients with MINOCA has received increasing attention. A diagnostic algorithm for MINOCA patients was published in the 2020 European Society of Cardiology (ESC) guidelines on non-ST-elevation MI (NSTEMI) and the so-called traffic-light approach should be followed to reach a final diagnosis in these patients (*Figure 1*).¹

Several studies presented at the ESC Congress 2021 assessed the prognosis of patients with MINOCA. Hinrichs et al. assessed and compared the prognosis of 1,704 patients who had type 2 MI, patients with type 1 MI

(n=1,699) and those without MI (total n=14,883) from Germany.²

Type 2 MI was defined as a significant troponin increase without percutaneous coronary intervention. During a mean follow-up of 3.4 ± 3.6 years, 3,321 deaths occurred (18.2%). Compared to patients without MI (16.1%), patients with type 1 MI (25.2%) and type 2 MI (29.1%) had significantly higher mortality rates ($p < 0.001$). Kaplan–Meier analysis confirmed the lowest survival rates occurred in patients with type 2 MI.²

Moreover, Barrett et al. showed that 1,544 MINOCA patients from Israel had a favourable short-term outcome but their long-term outcome was comparable to that of patients with acute MI due to obstructive coronary artery disease.³

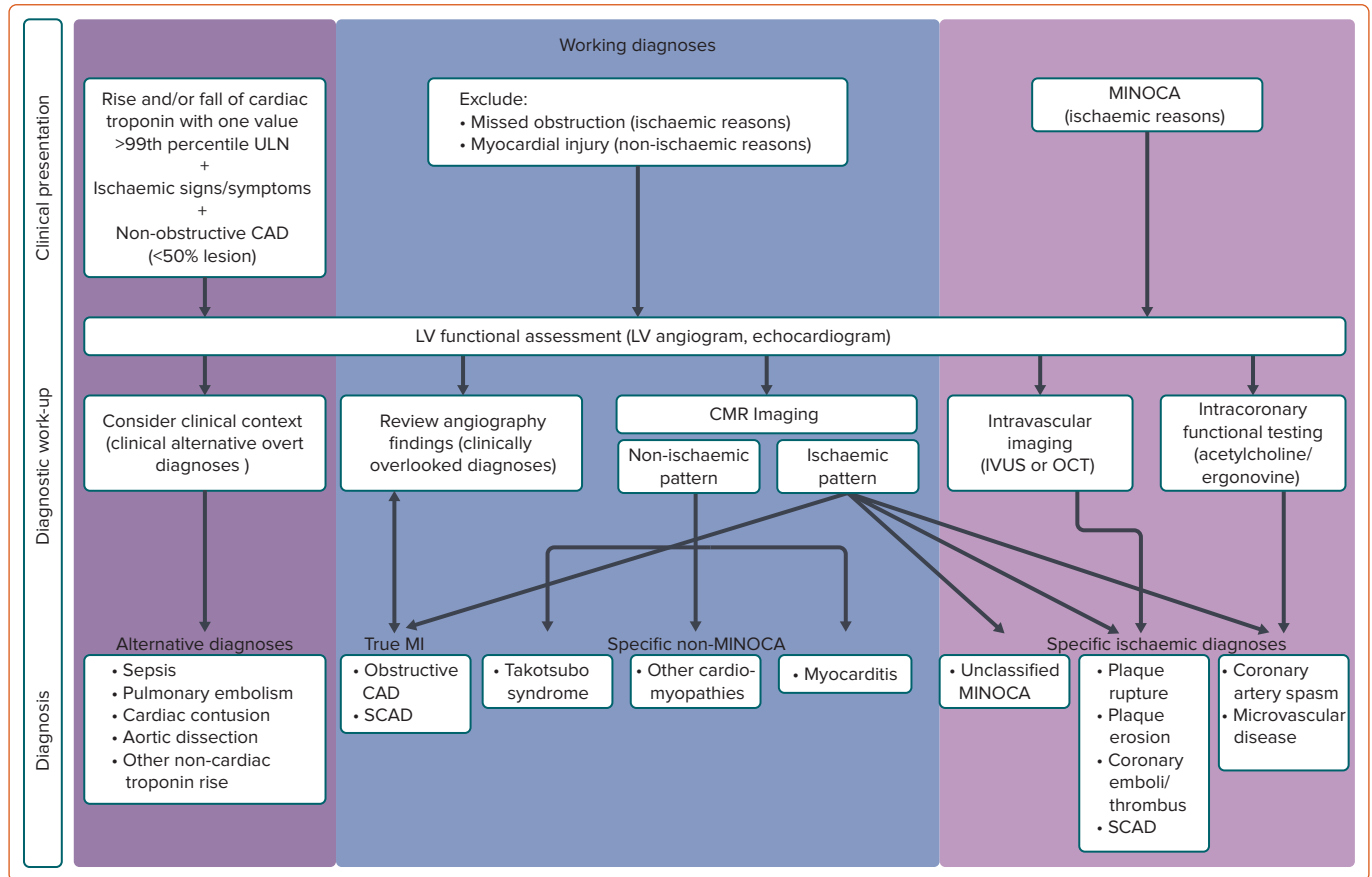
In addition, in a study including 712 Spanish patients with acute coronary syndrome (ACS), Espinosa Pascual et al. highlighted that pro-inflammatory states such as autoimmune pathologies, connective tissue disease, active cancer and infections should be regarded as risk factors for the occurrence of MINOCA.⁴

Therefore, the prognosis of MINOCA patients is not as good as previously thought and establishing a final diagnosis as the cause for the event should be pursued to initiate the most appropriate treatment.

One important MINOCA subtype is that arising from coronary spasm. Pirozzolo et al. showed that patients with MINOCA due to coronary spasm (determined by acetylcholine provocation testing) had a worse prognosis than MINOCA patients with an uneventful spasm test.⁵ Ninety-six patients with MINOCA were followed up for a median of 5 years. Patients with coronary spasm on acetylcholine testing (n=51) had a significantly worse prognosis regarding death from any cause and MI during follow-up than those with an uneventful spasm test (n=45).

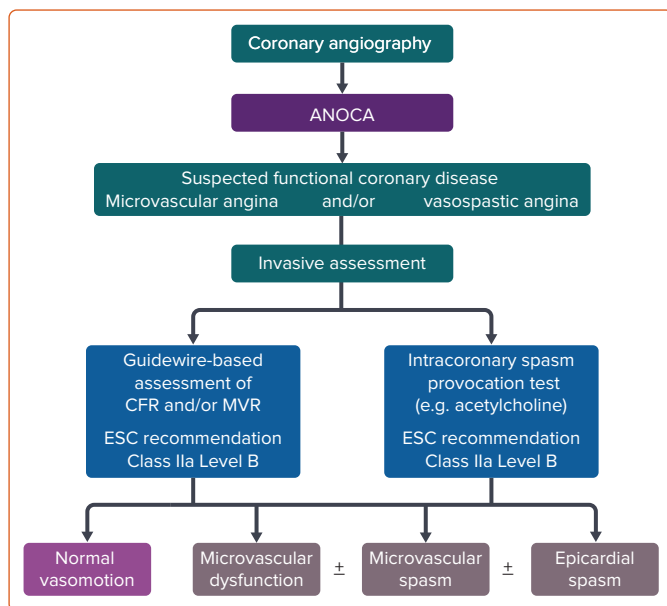
Montone et al. showed that acetylcholine provocation testing in patients

Figure 1: European Society of Cardiology Traffic Light Approach for Diagnosis in Patients with MINOCA



CAD = coronary artery disease; CMR = cardiac magnetic resonance; IVUS = intravascular ultrasound; LV = left ventricular; MINOCA = MI with non-obstructive coronary arteries; OCT = optical coherence tomography; SCAD = spontaneous coronary artery dissection; ULN = upper limit of normal. Source: Collet et al. 2021.¹ Reproduced with permission from Oxford University Press.

Figure 2: Recommended Comprehensive Assessment of Coronary Function in Patients with ANOCA



ANOCA = angina with non-obstructive coronary arteries; CFR = coronary flow reserve; ESC = European Society of Cardiology; MVR = microvascular resistance.

with either chronic coronary syndrome or acute coronary syndrome is safe and that the test itself does not affect long-term prognosis.⁶ This should reassure clinicians and interventionists that they can proceed with such tests to establish a clear diagnosis followed by targeted

treatment.

Another MINOCA subtype are patients with spontaneous coronary artery dissection (SCAD). These are often younger, female patients and they are frequently undiagnosed. However, Elkaryoni et al. showed that in-hospital mortality of 338 patients with SCAD was comparable to that of 17,218 non-SCAD ST-elevation MI (STEMI) patients.⁷

Furthermore, Mori Junco et al. showed that a specific angiotype of SCAD – a circumscribed contained intramural haematoma – was associated with an increased risk of short-term adverse clinical events that persisted during follow-up.⁸ This underlines that interventionists should be familiar with the angiographic classification of SCAD, and additional intravascular imaging may be needed in cases with diagnostic uncertainty.⁹

A working diagnosis of MINOCA is also frequently given to patients who are finally diagnosed with takotsubo syndrome. Although this syndrome has been classified as non-*ischaemic* in the traffic-light approach, debate is ongoing over whether this is correct. Studies have shown that coronary spasm and microvascular dysfunction are, indeed, present in patients with takotsubo syndrome, suggesting that a vascular dysfunction leading to myocardial *ischaemia* may be involved in the syndrome.^{10–12}

At ESC 2021, a study by Bonanni et al. shed new light on the molecular profile of patients with takotsubo syndrome. This showed that these patients (in comparison to those with STEMI due to obstructive coronary disease) had significantly higher gene expressions for nitric oxide

synthase 3, superoxide dismutase 1 and transferrin receptor, all of which are involved in oxidative stress pathways.¹³

Patients with ANOCA are equally heterogeneous as those with MINOCA and several endotypes have been defined.¹⁴ A study by Toya et al., assessing coronary flow reserve and hyperaemic microvascular resistance using adenosine in patients with ANOCA, showed that coronary flow reserve was predictive of outcomes in men whereas hyperaemic microvascular resistance was predictive of outcomes in women.¹⁵ This study highlights the importance of comprehensive diagnostic assessments in patients with ANOCA as recommended by the ESC 2019 guideline on chronic coronary syndromes.¹⁶

Invasive assessments for coronary spasm using provocation testing have a Class IIa recommendation as invasive measurements of coronary flow reserve and microvascular resistance (Figure 2).

Although coronary spasm is much more frequent in ANOCA patients than impaired microvascular vasodilatation (i.e. diminished coronary flow reserve or increased microvascular resistance), the latter is a strong prognostic marker, as recently shown by Kelshiker et al.^{17,18}

Ejupi et al. investigated proteomics in patients with ANOCA and found that several biomarkers were associated with vascular dysfunction in these patients, with little overlap between different endotypes.¹⁹ This underscores the need for more multidisciplinary research in this area in search of new pharmacological targets and the potential application for diagnostic purposes.

In summary, the field of MINOCA and ANOCA is evolving and, apart from comprehensive diagnostic assessments in clinical routine, randomised studies on pharmacological treatments in patient subtypes are eagerly awaited. □

- Collet JP, Thiele H, Barbato E, et al. ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2021;42:1289–367. <https://doi.org/10.1093/eurheartj/ehaa575>; PMID: 32860058.
- Hinrichs L, Hendricks S, Dykun I, et al. Increased long-term mortality in patients with type 2 myocardial infarction, data from the ECAD registry. *Eur Heart J* 2021;42:1270. <https://doi.org/10.1093/eurheartj/ehab724.1270>
- Barrett O, Edry Nadv O, Peles I, et al. Long-term outcome of patients with myocardial infarction with nonobstructive coronary arteries. *Eur Heart J* 2021;42:1351. <https://doi.org/10.1093/eurheartj/ehab724.1351>.
- Espinosa Pascual MJ, Lopez Pais J, Izquierdo Coronel B, et al. Role of inflammation in myocardial infarction with non-obstructive coronary arteries. *Eur Heart J* 2021;42:1296. <https://doi.org/10.1093/eurheartj/ehab724.1296>.
- Pirozzolo G, Seitz A, Sechtem U, et al. Long-term follow-up of patients with MINOCA (myocardial infarction with unobstructed coronary arteries) undergoing intracoronary spasm provocation testing. *Eur Heart J* 2021;42:1490. <https://doi.org/10.1093/eurheartj/ehab724.1490>.
- Montone RA, Rinaldi R, Del Buono MG, et al. Safety and prognostic relevance of acetylcholine testing in patients with stable myocardial ischaemia or myocardial infarction and non-obstructive coronary arteries. *EurIntervention* 2022. <https://doi.org/10.4244/EIJ-D-21-00971>; PMID: 35377315.
- Elkanyoni A, Klappa A, Doukas D, et al. Outcomes of ST-elevation myocardial infarction due to spontaneous coronary artery dissection: a nationwide cohort sample. *Eur Heart J* 2021;42:1471. <https://doi.org/10.1093/eurheartj/ehab724.1471>.
- Mori Junco R, Macaya FM, Cerrato EC, Escaned JE. Clinical outcomes by angiographic type of spontaneous coronary artery dissection. *Eur Heart J* 2021;42:1305. <https://doi.org/10.1093/eurheartj/ehab724.1305>; PMID: 33650491.
- Adlam D, Alfonso F, Maas A, et al. European Society of Cardiology, acute cardiovascular care association, SCAD study group: a position paper on spontaneous coronary artery dissection. *Eur Heart J* 2018;39:3353–68. <https://doi.org/10.1093/eurheartj/ehy080>; PMID: 29481627.
- Galiuto L, De Caterina AR, Porfidia A, et al. Reversible coronary microvascular dysfunction: a common pathogenetic mechanism in apical ballooning or tako-tsubo syndrome. *Eur Heart J* 2010;31:1319–27. <https://doi.org/10.1093/eurheartj/ehq039>; PMID: 20215125.
- Verna E, Provasoli S, Ghiringhelli S, et al. Abnormal coronary vasoreactivity in transient left ventricular apical ballooning (tako-tsubo) syndrome. *Int J Cardiol* 2018;250:4–10. <https://doi.org/10.1016/j.ijcard.2017.07.032>; PMID: 29169759.
- Patel SM, Lerman A, Lennon RJ, Prasad A. Impaired coronary microvascular reactivity in women with apical ballooning syndrome (takotsubo/stress cardiomyopathy). *Eur Heart J Acute Cardiovasc Care* 2013;2:147–52. <https://doi.org/10.1177/2048872613475891>; PMID: 24222824.
- Bonanni A, Pedicino D, Vinci R, et al. Takotsubo syndrome: a way to reach a straightforward diagnosis. *Eur Heart J* 2021;42:1392. <https://doi.org/10.1093/eurheartj/ehab724.1392>.
- Kunadian V, Chieffo A, Camici PG, et al. An EAPCI expert consensus document on ischaemia with non-obstructive coronary arteries in collaboration with European Society of Cardiology working group on coronary pathophysiology and microcirculation endorsed by coronary vasomotor disorders international study group. *EurIntervention* 2021;16:1049–69. https://doi.org/10.4244/EIJY20M07_01; PMID: 32624456.
- Toya T, Ahmad A, Corban MT, et al. Sex-dependent impact of coronary microvascular dysfunction on long-term clinical outcomes in patients with non-obstructive coronary artery disease. *Eur Heart J* 2021;42:1079. <https://doi.org/10.1093/eurheartj/ehab724.1079>.
- Knuuti J, Wijns W, Saraste A, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 2020;41:407–77. <https://doi.org/10.1093/eurheartj/ehz425>; PMID: 31504439.
- Konst RE, Damman P, Pellegrini D, et al. Vasomotor dysfunction in patients with angina and nonobstructive coronary artery disease is dominated by vasospasm. *Int J Cardiol* 2021;333:14–20. <https://doi.org/10.1016/j.ijcard.2021.02.079>; PMID: 33711394.
- Kelshiker MA, Seligman H, Howard JP, et al. Coronary flow reserve and cardiovascular outcomes: a systematic review and meta-analysis. *Eur Heart J* 2022;43:1582–93. <https://doi.org/10.1093/eurheartj/ehab775>; PMID: 34849697.
- Ejupi A, Aziz A, Ong P, et al. Proteomic biomarker profiles and vascular dysfunction in angina with no obstructive coronary artery disease. *Eur Heart J* 2021;42:1081. <https://doi.org/10.1093/eurheartj/ehab724.1081>.