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Pathological Findings at Invasive Assessment in MINOCA: a Systematic Review and a Meta-Analysis

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ABSTRACT

Background. Pathological mechanisms of myocardial infarction with non-obstructive coronary arteries (MINOCA) are heterogeneous, with an unknown impact on prognosis, and often remain unrecognised in clinical practice. This study aimed to evaluate the prevalence and prognostic impact of pathological findings by invasive coronary angiography (ICA), optical coherence tomography (OCT), and coronary function testing in MINOCA.

Methods. Studies published until August 2023 were searched on PubMed and SCOPUS and included if reporting the prevalence of patients with non-obstructive coronary arteries (NObs-CA; 1-49% coronary stenosis) versus normal coronary arteries (NCA; 0% coronary stenosis) by ICA, pathological findings by OCT, and/or coronary vasomotor tests in MINOCA. Newcastle-Ottawa Scale was used for quality assessment. The pooled prevalence of pathological findings was estimated with random-effects models. Pooled risk ratios (RR) with 95% confidence intervals (CI) of all-cause death, MI, and the composite of both in patients with NObs-CA versus NCA, were calculated at short-term (<1 month), 1-year, and long-term follow-up (> 1 year).

Results. Forty-five studies including 17539 patients were analysed. The pooled prevalence of NObs-CA at ICA was 53% [95% CI 0.47-0.60]. OCT showed acute pathological findings in 62% [95% CI 0.44-0.78] of patients and coronary vasomotor tests were positive in 49% [95% CI 0.31-0.67]. NObs-CA compared to NCA was associated with an increased 1-year risk of all-cause death or MI (RR = 1.49 [95% CI 1.17-1.90]) and MI alone (RR = 1.80 [95% CI 1.26-2.59]), whereas the risk of all-cause death was comparable. Similar results were seen at long-term, but not at short-term follow-up.

Conclusions. Stratification of MINOCA into NObs-CA versus NCA has prognostic value. OCT and vasospasm testing, often informative about the pathological mechanism of MINOCA, should be part of an invasive diagnostic algorithm.

Keywords: MINOCA, invasive coronary angiography, optical coherence tomography, acetylcholine, vasospasm.

ABBREVIATIONS

ACh = acetylcholine

CMD = coronary microvascular dysfunction

ICA = invasive coronary angiography

IVUS = intravascular ultrasound

MI = myocardial infarction

MINOCA = myocardial infarction with non-obstructive coronary arteries

NCA = normal coronary arteries (0% coronary arteries stenosis)

NObs-CA = non-obstructive coronary arteries (1-49% coronary arteries stenosis)

OCT = optical coherence tomography

INTRODUCTION

Myocardial infarction with non-obstructive coronary arteries (MINOCA) represents approximately 10% of all acute myocardial infarctions (MI). [1] The diagnosis can be considered when the criteria for acute MI according to the 4th Universal definition are met, in the absence of coronary stenosis ≥50% and other causes of non-ischemic myocardial injury. [2,3] The best treatment for MINOCA has not been clearly established as several pathophysiological mechanisms may be responsible for myocardial injury, including plaque disruption, spontaneous coronary artery dissection (SCAD), coronary vasospasm, and microvascular dysfunction. [4–6] In the early phase of an acute coronary syndrome (ACS), intravascular imaging (including intravascular ultrasound [IVUS] and optical coherence tomography [OCT]) and coronary function testing help to identify the pathophysiological mechanisms, especially when invasive coronary angiography (ICA) is inconclusive. [7] The current European Society of Cardiology Guidelines regarding ACS recommend a diagnostic algorithm that includes intravascular imaging and assessment of coronary physiology as a first-line approach to identify the aetiology of MINOCA. [8] However, the prognostic impact of the pathological findings detected at ICA and other invasive assessment tools in this setting is currently poorly understood. The primary objective of this systematic review was to evaluate the prevalence and relative prognostic impact of pathological findings by ICA, intracoronary imaging, and coronary function testing in MINOCA.

METHODS

The protocol of this meta-analysis was registered in the International Prospective Register of Systematic Reviews (PROSPERO), registration number CRD42023468183. The results are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (**Supplementary Table 1**). [9]

Search strategy and selection criteria

Studies for potential inclusion were searched in PubMed and SCOPUS using "myocardial infarction" and "no coronary artery stenosis ≥50%" as key concepts (complete search strings in **Supplementary Table 2**). The references of included studies and the key systematic reviews were screened to identify additional studies. Observational studies and randomized trials published in English up to August 2023 were considered for inclusion. Case reports, comments, editorials, duplicate publications, and abstracts were excluded. Two reviewers (D.F. and D.C.) screened the studies according to the following inclusion criteria:

1) Studies including patients admitted for acute MI without coronary artery stenosis ≥50% at ICA.
2) Reporting at least one outcome of interest among:
    a) The prevalence of patients with non-obstructive coronary arteries (NObs-CA), defined as the presence of at least one stenosis between 1-49%, compared to patients with normal coronary arteries (NCA; 0% coronary stenosis) at ICA.
    b) The prevalence of pathological findings by OCT. IVUS was not included in the quantitative analysis because less than 3 studies concerning this technique were found.
    c) The results of vasospasm testing.

Studies with cut-offs other than 50% to define obstructive coronary arteries or only focusing on specific alternative diagnoses to explain myocardial damage were excluded. The study with the larger sample size was considered if more studies with overlapping populations were found. A third reviewer (C.P.) solved disagreements. The quality of the included studies was assessed independently by two reviewers (F.B. and N.S.) using the Newcastle-Ottawa Scale.

Endpoints

The endpoints with effect measures investigated in this meta-analysis including patients with MINOCA are shown in **Table 1**. The prognostic impact of OCT and vasospasm tests findings was not analysed by quantitative meta-analysis as less than three studies reporting prognostic data were found.

Statistical analysis

The pooled prevalence of NObs-CA on ICA, pathological findings on OCT, and positive vasospasm tests was estimated with 95% confidence intervals (CI). Pooled risk ratios (RR) with 95% CI comparing NObs-CA with NCA was estimated for the short-term, 1-year, and long-term outcomes. A DerSimonian-Laird random-effects model was used for all analyses. Funnel plots and Egger test were used to assess possible publication bias or small study effect for the analysis of prognostic outcomes. A leave-one-out meta-analysis was performed to test statistical robustness. The data are presented using forest plots. Heterogeneity was assessed using I^2. In the case relevant heterogeneity (I^2>50%), subgroup analyses were performed, adjusting for time of publication, study design, and geographical context. Meta-regression including the most relevant clinical and instrumental characteristics was used to estimate the effect of these characteristics on heterogeneity. Bubble plots were constructed to show the relationships between outcomes and statistically significant characteristics. Further information on quality assessment, definitions used as synonyms during data extraction, subgroup analysis, and characteristics included in meta-regression is provided in the **Supplementary material – Extended methods**. All analyses were performed using Stata 18.0 (Stata Corp LLC, College Station, TX). Statistical significance was defined as $p<0.05$.

RESULTS

After a thorough literature search, 374 articles underwent full-text evaluation, with 45 studies eventually included in the meta-analysis (**Figure 1**). The quality assessment showed an overall low risk of biases. Only 5 studies had potential selection bias or comparability concerns scoring 7/9 points at the Newcastle-Ottawa Scale (**Supplementary Table 3**). Sensitivity analyses excluding these studies have been performed and are discussed below.

Prevalence of non-obstructive versus normal coronary arteries

Thirty-five studies reported the prevalence of NObs-CA versus NCA in MINOCA, including 17281 patients. The characteristics of the patients in these studies are shown in **Supplementary Table 4**. The pooled prevalence of NObs-CA was estimated to be 53% [95%CI: 0.47-0.60] (**Figure 2**). The leave-one-out analysis and the sensitivity analyses excluding studies with a sample size of <100 patients or with 7/9 points at Newcastle-Ottawa Scale confirmed this result (**Supplementary Figure 1**). Heterogeneity was high (I^2=98.0%), but none of the clinical-instrumental characteristics tested in meta-regression analyses had a significant impact on the I^2, except for a minimal influence of the age (residual I^2=97.2%, p=0.014). Subgroup analysis showed no significant differences when studies were stratified by geographical context or by the inclusion of myocarditis, takotsubo syndrome, and cardiomyopathies (**Supplementary Figure 2**). Finally, variability in MINOCA definition and use of CMR across studies might partially account for the heterogeneity (**Supplementary Table 5**).

Prognosis of non-obstructive versus normal coronary arteries

Thirteen studies, including 7925 patients, reported at least one outcome of interest. None of the funnel plots nor the Egger test showed a possible publication bias or small study effect for any of the outcomes (**Supplementary Figure 3D-F, Figure 3D-F, Figure 4D-F**). No differences in patients with NObs-CA compared to NCA at ICA were found regarding short-term outcomes (**Supplementary Figure 3A-C**). Considering 1-year events (**Figure 3A-C**), NObs-CA patients had a higher risk of the composite of all-cause death or MI (RR=1.49; 95%CI 1.17-1.90) and MI alone (RR=1.80; 95%CI 1.26-2.59), but not of all-cause death alone (RR=1.12; 95%CI 0.77-1.60) compared to patients with NCA. Similar results were confirmed for follow-up periods longer than 1 year (range 2-10 years; **Figure 4A-C**), with NObs-CA being associated with a higher risk than NCA of the composite of all-cause death or MI (RR=1.54; 95%CI 1.11-2.14), driven by a higher risk of MI (RR=2.16; 95%CI 1.26-3.71). Sensitivity analyses excluding studies with 7/9 points on the Newcastle-Ottawa Scale confirmed all the results obtained, except for the outcome of all-cause death at long-term follow-up (**Table 2**). Indeed, the trend seen for a higher risk of all-cause death at a longer follow-up period (>1 year) in NObs-CA compared with NCA became statistically significant (RR=1.62; 95%CI 1.32-1.97). Heterogeneity was very low for all the considered short-term and 1-year follow-up events. The low-to-moderate heterogeneity found for long-term events may be due to the wide variability in the follow-up periods, so no further analyses were performed. Four studies reported the medications at discharge stratified by the presence or absence of NObs-CA (**Supplementary Table 6**). NObs-CA compared to NCA patients received more often aspirin (89% vs 69%), P2Y12-inhibitors (52% vs 29%), renin-angiotensin-system antagonists (53% vs 40%), beta-blockers (70% vs 57%), and statins (86% vs 60%; p<0.01 for all).

Prevalence of acute pathological findings detected by OCT

Five studies reporting acute OCT findings (i.e., plaque disruption, lone thrombus, calcified nodules, and SCAD) in MINOCA were identified. The definitions used in the studies and the characteristics of participants are summarized in **Supplementary Tables 7-8**. In these 5 studies, the pooled prevalence of acute OCT findings was 50% [95%CI 0.23-0.77] with high heterogeneity (I^2=95.1%). The leave-one-out analysis showed no significant difference (**Supplementary Figure 4**), but a trend towards a higher prevalence of acute OCT findings with a reduction in heterogeneity was observed, when the study by Reynolds et al. was excluded. [10] Importantly, when extracting data from this study, we did not count some of the findings that the Authors considered as "culprit lesion", such as layered plaque and intraplaque cavity. As later highlighted, the first entity does not play a certain role in the acute phase of an ACS and the second is not clearly defined. [11,12] In addition, the study by Reynolds and colleagues [10] might have introduced a selection bias because the population entirely consisted of females and performing a meta-regression model including this study indicated a significant effect of female sex on heterogeneity (residual I^2=84.1%; p=0.007). For all these concerns, we excluded the latter study from the final analysis. In the remaining 4 studies, we obtained a prevalence of 62% [95%CI 0.44-0.78] of acute OCT findings in MINOCA (**Figure 5A**). The subgroup analysis showed similar results when stratifying for the inclusion of myocarditis, takotsubo syndrome, and cardiomyopathies (**Supplementary Figure 5**). Meta-regression highlighted the significant impact of age (residual I^2=12.8%, p<0.001), smoking status (residual I^2=45.8%, p=0.007), diabetes mellitus (residual I^2=61.0%, p=0.034), and dyslipidaemia (residual I^2=44.4%, p=0.007) on heterogeneity (**Supplementary Figure 6**). The pooled prevalence of each component of "acute OCT findings" is shown in **Supplementary Figure 7**. Specifically, plaque disruption was the most frequent with a prevalence of 47% [95%CI 0.33-0.62].

Prevalence of vasospasm as a pathological mechanism in MINOCA

Seven studies reported the prevalence of vasospasm in MINOCA. The definitions used in the studies and the characteristics of participants are summarised in **Supplementary Tables 9-10**. The pooled prevalence of positive vasospasm tests was 49% [95%CI 0.31-0.67] with high heterogeneity (I^2=94.5%), as shown in **Figure 5B**. The leave-one-out analysis showed no significant difference. Left ventricular ejection fraction was the only clinical-instrumental characteristic tested in the meta-regression accounting for some of the heterogeneity (residual I^2=71.3%, $p<0.001$). Stratification according to the protocol used for vasospasm testing, but not geographical context, seems to partially explain heterogeneity (**Supplementary Figure 8**). Indeed, studies using acetylcholine (ACh) as a stressor, rather than ergonovine, had a higher prevalence of positive results (57% vs 44%) and lower heterogeneity, even though not reaching significance.

DISCUSSION

To our knowledge, this is the first large-scale meta-analysis evaluating the integration of anatomical and functional invasive assessment in identifying the aetiology of MINOCA and its prognostic implications. Our key findings are: i) the prevalence of NObs-CA as assessed by ICA was 53%; ii) NObs-CA emerged as a relevant predictor of adverse outcomes at both 1-year and longer follow-up, despite medical therapy being prescribed more often in these patients compared to those with NCA; iii) OCT detected a pathological finding in 62% of MINOCA, mainly consisting of plaque disruption; iv) coronary vasomotor testing led to the diagnosis of coronary vasospasm in 49% of MINOCA.

Non-obstructive versus normal coronary arteries in MINOCA

We estimated a 53% prevalence of NObs-CA in MINOCA, in agreement with previous studies. [13,14] Prior meta-analyses compared the prognosis of MINOCA to MI with obstructive CAD. [15] Conversely, the evolving concept emphasising the importance of atherosclerotic burden rather than stenosis has not been extensively analysed in MINOCA. Only two studies demonstrated a worse long-term prognosis in the case of 3-vessel or left main NObs-CA. [16,17] A meta-analysis by Pasupathy et al. including 4 studies showed no differences in the prognosis of patients with NObs-CA versus NCA. [1] A more recent analysis suggested an association between NObs-CA and higher mortality. [5] However, it was affected by a high risk of bias and high heterogeneity due to a wide variability in follow-up time. Therefore, this is the first meta-analysis to show that MINOCA patients with NObs-CA have a higher risk of all-cause death or MI compared to NCA, mainly driven by a higher risk of MI, probably due to the risk of the atherosclerotic plaque-related acute events. Indeed, a progression of atherosclerosis has been recently shown in MINOCA patients with a recurrent MI. [18] In our analysis, there was also a trend towards an increased risk of 1-year and long-term all-cause death in patients with NObs-CA, especially in the sensitivity analysis. However, given the inclusion of fewer studies and the variability in the length of follow-up, this finding should be interpreted with caution. Our results support the need to stratify MINOCA patients into those with NCA and those with coronary artery stenosis of 1-49%, as this is prognostically relevant and may guide treatment. Compared to NCA patients, NObs-CA patients are more likely to receive medical therapy at discharge but appear to be undertreated compared to patients with obstructive MI [19,20], probably due to the limited evidence favouring secondary prevention in MINOCA. [21–24] Specific studies should aim to determine whether patients with NObs-CA may benefit from a more aggressive treatment.

The role of intravascular imaging

The worse prognosis in NObs-CA prompts to better characterize atherosclerosis in MINOCA. Our results confirm the potential role of OCT, showing pathological findings in 62% of cases, similar to previous estimates, ranging between 42% and 75%. [25] Conversely, Pelliccia et al. reported a lower overall prevalence of plaque disruption of 38% [26]. This might be explained by the stricter criteria for studies selection in our analysis, according to the current definition of MINOCA, and the inclusion of up-to-date literature. Moreover, Pelliccia and colleagues included studies using both OCT and IVUS. However, IVUS has a lower resolution in detecting superficial plaque features. [27] Over time, there has been increasing interest in the use of OCT over IVUS in MINOCA. Only two independent studies evaluated IVUS in MINOCA, showing a 38-45% prevalence of atherosclerotic plaque disruption. [28,29] Additionally, OCT can also identify vulnerable plaque features (e.g. thin-cap fibroatheromas) and signs of previous plaque disruption (e.g. layered plaque), with an estimated rate in MINOCA of 27-30% and 13-21%, respectively. [10,30,31] In our study, the pooled prevalence of SCAD was 6%, lower than the 12% estimate by Pelliccia et al., which was driven by the inclusion of studies focusing only on SCAD. The prognostic impact of each pathological finding at OCT in MINOCA is still debated, but there is some evidence that the prognosis is worse when OCT detects plaque disruption, SCAD, or thin-cap fibroatheromas. [31,32]

Vasospasm testing and microvascular dysfunction in MINOCA

Coronary vasomotor disorders can cause MINOCA. [33] Prior studies reported a prevalence of coronary vasospasm in MINOCA ranging from 3% to 95%. [14,26] We estimated a rate of 49% of positive coronary vasospasm testing in MINOCA. The use of ACh was associated with more homogeneous results and a higher likelihood of positive tests compared with ergonovine, possibly due to a more standardized ACh protocol and its ability to detect microvascular spasm. Thus, ACh should be preferred also in MINOCA, as recommended by the COVADIS group for the chronic setting. [34] The prognostic role of vasospasm in MINOCA remains uncertain, with a possible increased risk of hospitalizations for UA in patients with positive functional tests. [35–37] Some safety concerns regarding the administration of stressors during acute events may have limited the use of vasospasm testing in MINOCA. However, a low complication rate has been reported in MINOCA. [35,38] Coronary microvascular spasm may indicate coronary microvascular dysfunction (CMD). [39] Assessment of CMD is poorly studied in MINOCA [40–42] but CMD was identified in one third of patients by a pilot study. [43] Additionally, the coronary angiography-derived index of microvascular resistance (IMR) appears to predict major adverse cardiac events. [44,45] Hence, the invasive measurement of IMR and coronary flow reserve in

MINOCA is an interesting area for further investigation. [46]

Clinical impact of invasive assessment of MINOCA: the need for a diagnostic algorithm

Our meta-analysis highlights the importance of a comprehensive invasive assessment in the diagnostic work-up of patients with MINOCA (**Figure 6**). While invasive assessment might unmask the cause, CMR reveals the effects of MINOCA on the myocardium. [47] OCT could detect high-risk plaque features and aid in identifying the culprit lesion. As vasospasm could be provoked by the plaque disruption itself rather than an intrinsic predisposition of the coronary artery to spasm, OCT should be prioritized. [48] In the absence of acute findings by OCT, vasomotor testing should follow, given the high prevalence of vasospasm detection in this population and the potential therapeutic implications. Coronary physiology could then be assessed to investigate CMD. Definite conclusions on the timing and the clinical benefit of each invasive test require further investigations. The ongoing PROMISE trial (NCT05122780) will evaluate the efficacy of a structured diagnostic algorithm versus a standard prescription of secondary prevention drugs. [49]

Limitations of the study

Differences in baseline clinical characteristics and treatment between groups may have influenced prognosis. The high heterogeneity in the prevalence analysis was probably due to changes in MINOCA definition, in the availability of advanced diagnostic techniques, and in the criteria for defining a positive vasospasm testing across studies spanning a wide publication period. To estimate the pooled effect sizes across different populations with high variability, we used a random-effects model in which the weights of each study to the overall findings depend not only on the within-study variance (and therefore on the sample size), but also on the between-study variance. Additionally, subgroup and meta-regression analyses considering the key differences in study characteristics were performed to assess heterogeneity. In observational studies, the decision to perform OCT may have been favoured by the presence of some degree of coronary artery stenosis, which may alter the estimate of the true prevalence of pathological findings by OCT in MINOCA. Visual assessment of coronary artery stenosis is operator-dependent, altering the estimation of the relative prevalence of NObs-CA and NCA. Few studies have evaluated the predictive value of OCT and vasospasm testing, preventing to infer robust conclusions.

CONCLUSIONS

About one half of MINOCA patients have non-significant coronary artery stenosis, with an increased risk of all-cause death or MI at 1-year and long-term follow-up compared to patients with NCA, mainly due to a higher risk of MI. OCT identifies a possible explanation for ACS in 62% of patients and vasospasm tests are positive in 49% of them. Therefore, a comprehensive invasive assessment of MINOCA should be pursued to determine the aetiology of ACS, stratify prognosis, and possibly guide management.

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TABLES

Table 1. Effect measures, outcomes, and definitions used in this meta-analysis including patients with myocardial infarction with non-obstructive coronary arteries.

Effect measure and outcome		Follow-up length
1)	Prevalence of NObs-CA (1-49% coronary artery stenosis) versus NCA (0% coronary artery stenosis) as assed by ICA	N/A
2)	Relative risk in patients with NObs-CA compered to NCA of: • All-cause death or MI • All-cause death • MI	• Short-term (in-hospital to 1 months after discharge) • 1-year • Long-term (>1 year)
3)	Prevalence of acute OCT findings, including plaque disruption (rupture or erosion), calcified nodule, lone thrombus, and SCAD*	N/A
4)	Prevalence of positive vasospasm testing (epicardial or microvascular spasm)*	N/A

*: The definition of acute findings by OCT and positive vasospasm testing was based on the criteria outlined in individual studies.

Abbreviations: ICA = invasive coronary angiography; MI = myocardial infarction; N/A = not applicable; NCA = normal coronary arteries; NObs-CA = non-obstructive coronary arteries; OCT = optical coherence tomography; RR = relative risk; SCAD = spontaneous coronary artery dissection.

Table 2. Sensitivity analyses evaluating the prognostic impact of NObs-CA in MINOCA at short-term (<1 month), 1-year, and long-term (>1 year) follow-up, excluding the 5 studies with 7/9 points in the Newcastle-Ottawa Quality Assessment scale. The relative risk with 95% confidence intervals of each outcome comparing patients with non-obstructive coronary arteries with normal coronary arteries is shown. I^2 represents the estimated heterogeneity.

Outcome	Included studies, n	RR [95% CI]	I2
Short-term all-cause death or MI	2	1.90 [0.82 – 4.39]	0%
Short-term all-cause death	5	1.73 [0.87 – 3.46]	0%
Short-term all-cause MI	2	1.25 [0.23 – 6.67]	1%
1-year all-cause death or MI	3	1.62 [1.22 – 2.14]	0%
1-year all-cause death	4	1.42 [0.99 – 2.03]	0%
1-year all-cause MI	3	1.95 [1.25 – 3.07]	0%
Long-term all-cause death or MI	3	1.84 [1.42 – 2.39]	45%
Long-term all-cause death	4	1.62 [1.32 – 1.97]	0%
Long-term all-cause MI	3	2.83 [1.17 – 6.82]	73%

Abbreviations: CI = confidence intervals; MI = myocardial infarction; n = number; RR = relative risk.

FIGURE LEGENDS

Figure 1. Flowchart of the meta-analysis. Studies utilizing cut-off other than 0% versus 1-49% in the stratification of the myocardial infarction were excluded. NObs-CA = Non-Obstructive Coronary Arteries (coronary artery stenosis 1-49%); OCT = optical coherence tomography.

Figure 2. Forest plot of studies evaluating the prevalence of non-obstructive coronary arteries in MINOCA. NObs-CA = non-obstructive coronary arteries.

Figure 3. 1-year outcomes comparison between non-obstructive coronary arteries versus normal coronary arteries in MINOCA. On the left, forest plots illustrating the risk ratio of 1-year all-cause death or myocardial infarction (A), all-cause death (B), and myocardial infarction (C) with heterogeneity. On the right, funnel plots of the studies evaluating the 1-year risk of all-cause death or myocardial infarction (D), all-cause death (E), and myocardial infarction (F) with Egger tests. NCA = normal coronary arteries; NObs-CA = non-obstructive coronary arteries.

Figure 4. Long-term outcomes comparison between non-obstructive coronary arteries versus normal coronary arteries in MINOCA. On the left, forest plots illustrating the risk-ratio of long-term (2 years through 10 years) all-cause death or myocardial infarction (A), all-cause death (B), and myocardial infarction (C) with heterogeneity. On the right, funnel plots of the studies evaluating the long-term risk of all-cause death or myocardial infarction (D), all-cause death (E), and myocardial infarction (F) with Egger tests. NCA = normal coronary arteries; NObs-CA = non-obstructive coronary arteries.

Figure 5. The pooled prevalence of pathological findings by invasive assessment tools. Forest plot illustrating the pooled prevalence of acute findings by optical coherence tomography (A) and vasospasm testing (B). OCT = optical coherence tomography.

Figure 6. A proposal for a comprehensive invasive assessment of MINOCA. The usefulness of each diagnostic tool in establishing the diagnosis and stratifying prognosis is represented in green or red boxes according to the certainty of the evidence assessed by this systematic review. Blue borders are used in the case of entities that were not assessed in our work, representing areas that require further investigation. BBs = beta-blockers; CAD = coronary artery disease; CCBs = calcium-channel blockers; CMD = coronary microvascular dysfunction; DAPT = dual antiplatelet therapy; MINOCA = myocardial infarction with non-obstructive coronary arteries; NObs-CA = non-obstructive coronary arteries; PE = pulmonary embolism; SCAD = spontaneous coronary artery dissection; UDMI = universal definition of myocardial infarction.