Coronary calcified nodules versus nonnodular coronary calcifications: a systematic review and meta-analysis

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Original article

Coronary calcified nodules versus nonnodular coronary calcifications: a systematic review and meta-analysis

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Background Percutaneous coronary intervention (PCI) on severely calcified coronary lesions is challenging. Coronary calcified nodule (CN) refers to an eccentric and protruding coronary calcification associated with plaque vulnerability and adverse clinical events. This study aims to conduct an extensive review of CNs, focusing on its prognostic impact in comparison with nonnodular coronary calcification (N-CN).

Method A systematic literature review on PubMed, MEDLINE, and EMBASE databases was conducted for relevant articles. Observational studies or randomized controlled trials comparing CNs and N-CNs were included.

Results Five studies comparing CNs and N-CNs were pertinent for inclusion. The total number of individuals across these studies was 1456. There were no significant differences in the baseline demographic, clinical, and angiographic data between the CN and N-CN groups. Intracoronary imaging was always utilized. At follow-up, CNs were associated with significantly increased, target vessel revascularization [odds ratio (OR) 2.16; 95% confidence interval (CI): 1.39–3.36, *P*-value < 0.01, $I^2 = 0\%$] and stent thrombosis (OR 9.29; 95% CI: 1.67–51.79, *P*-value = 0.01, $I^2 = 0\%$) compared with N-CN. A trend for greater cardiac death was also assessed in the CN group (OR 1.75; 95% CI: 0.98–3.13, *P*-value = 0.06, $I^2 = 0\%$).

Conclusion CN has a significantly negative impact on outcomes when compared with N-CN.

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Keywords: coronary calcified nodule, coronary calcified nodule AND thrombosis, coronary calcified nodule AND acute coronary syndrome, coronary calcified nodules AND nonnodular coronary calcification

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Introduction

Performing percutaneous coronary intervention (PCI) on severely calcified coronary lesions poses significant challenges and is linked to unfavorable outcomes.[1–4] Stent deployment in heavily calcified lesions often results in stent underexpansion and incomplete stent apposition, which can increase the risk of in-stent restenosis (ISR) and thrombosis.[5,6] As atherosclerotic plaque progresses, calcification becomes more closely associated with cardiovascular events.[7,8] Different calcification patterns have been described, although their distribution and outcomes may vary.[9] Among these patterns, a calcified nodule (CN) refers to the presence of protruding calcium deposits within the walls of the coronary arteries. They have been linked to increased plaque vulnerability and adverse coronary events, including thrombosis and refractory ISR.[10–14] Notably, acute thrombosis at the CN site accounts for up to 7% of acute coronary syndromes (ACS).[11,15] Chronic kidney disease and diabetes mellitus are prominent risk factors associated with CN development.[16] However, the precise pathophysiology of CN needs to be fully understood, as multiple mechanisms might be involved. Intracoronary imaging provides valuable insights into calcific plaque morphology beyond angiographic findings. Among the imaging modalities, optical coherence tomography (OCT) is particularly useful as it can penetrate calcium, providing detailed information about the structure, morphology, and fibrous cap abnormalities of calcified lesions.[17] In this context, mounting evidence has focused on a specific CN subgroup: the eruptive CN (E-CN), which is believed to be associated with worse outcomes as compared with noneruptive CNs.[18]

Thus, the objective of our study is to conduct a comprehensive review of CNs, focusing on treatment strategies and prognosis in comparison with nonnodular coronary calcification (N-CN).

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Methods

Search strategy

A systematic literature review was conducted until June 2023, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[19] Pertinent articles were systematically searched for in the PubMed, MEDLINE, and EMBASE databases. The search terms used to identify the desired studies were 'coronary calcified nodule,' 'coronary calcified nodule AND acute coronary syndrome,' 'coronary calcified nodule AND thrombosis,' 'coronary calcified nodules AND nonnodular coronary calcification.' Only peer-reviewed studies on human patients published in English were included in the search. To ensure comprehensive coverage, two authors (F.O. and I.A.A.) independently reviewed the reference lists of the included relevant articles to identify any additional citations that were deemed relevant.

Study selection

Two reviewers (F.O. and I.A.A.) independently conducted the initial screening process to identify all potentially acceptable citations. The following inclusion criteria were applied:

(1) Studies comparing coronary CNs and N-CNs.
(2) Participants aged 18 years or older.
(3) Observational studies or randomized controlled trials published in peer-reviewed journals.
(4) Untranslated original studies that were written only in English.

Full-text papers corresponding to the identified abstracts and meeting the inclusion criteria were assessed for eligibility. The inter-rater reliability between the two reviewers was evaluated using the Kappa statistic.[20]

Data extraction

Two authors (F.O. and M.V.O.) independently collected relevant data using a standardized recording tool. The data recorded included details such as the study setting and design, year of publication, number of study participants, country of origin, clinical characteristics of the participants, and study outcomes.

Quality assessment

The quality assessment of the included observational studies was conducted using the Newcastle-Ottawa Scale (NOS). Two authors (F.O. and B.B.) independently evaluated the quality of each study by considering three main categories: selection, comparability, and outcomes. Each study could receive a maximum of nine stars, with four stars for selection, two stars for comparability, and three stars for outcomes.[21] To standardize the evaluation, we converted the NOS score of each study to match the standards applied by the Agency for Healthcare Research and Quality (AHRQ).[22] As a result, the studies were classified into three categories of quality:

(1) Poor quality: A study received $\leq$1 star for the selection domain, OR 0 stars for the comparability domain, OR $\leq$1 star for the outcome domain.
(2) Fair quality: A study received 2 stars for the selection domain, AND 1 or 2 stars for the comparability domain, AND 2 or 3 stars for the outcome domain.
(3) Good quality: A study received $\geq$3 stars for the selection domain, AND 1 or 2 stars for the comparability domain, AND 2 or 3 stars for the outcome domain.

These quality categories are summarized in Table S1, http://links.lww.com/JCM/A644.

Data analysis and synthesis

We employed the Review Manager software (*RevMan-5.4.1*) to perform our statistical analyses. For each analyzed parameter, we used a random-effects model to combine the overall odds ratio (OR) or mean difference (MD) and their corresponding 95% confidence intervals (CIs). To visually assess the pooling results and identify potential publication biases and study power, we created forest plots and funnel plots. An OR $>$1 indicates an increased risk of the considered outcome, an OR value of 1 suggests no observed association, and an OR less than 1 indicates a decreased risk of the considered outcome. Statistical significance was determined by a two-sided *P*-value of $<$0.05. Additionally, we calculated the heterogeneity of the included studies using the Higgins I^2 statistic, which quantifies the percentage of total variation across the studies.[23] The I^2 values range from 0% to 100%. A value of 0% suggests no heterogeneity. We categorized heterogeneity as mild ($I^2 < 25\%$), moderate ($I^2 \leq 25\% < 50\%$), severe ($I^2 \leq 50\% < 75\%$) or very severe ($I^2 \geq 75\%$).[24]

Results

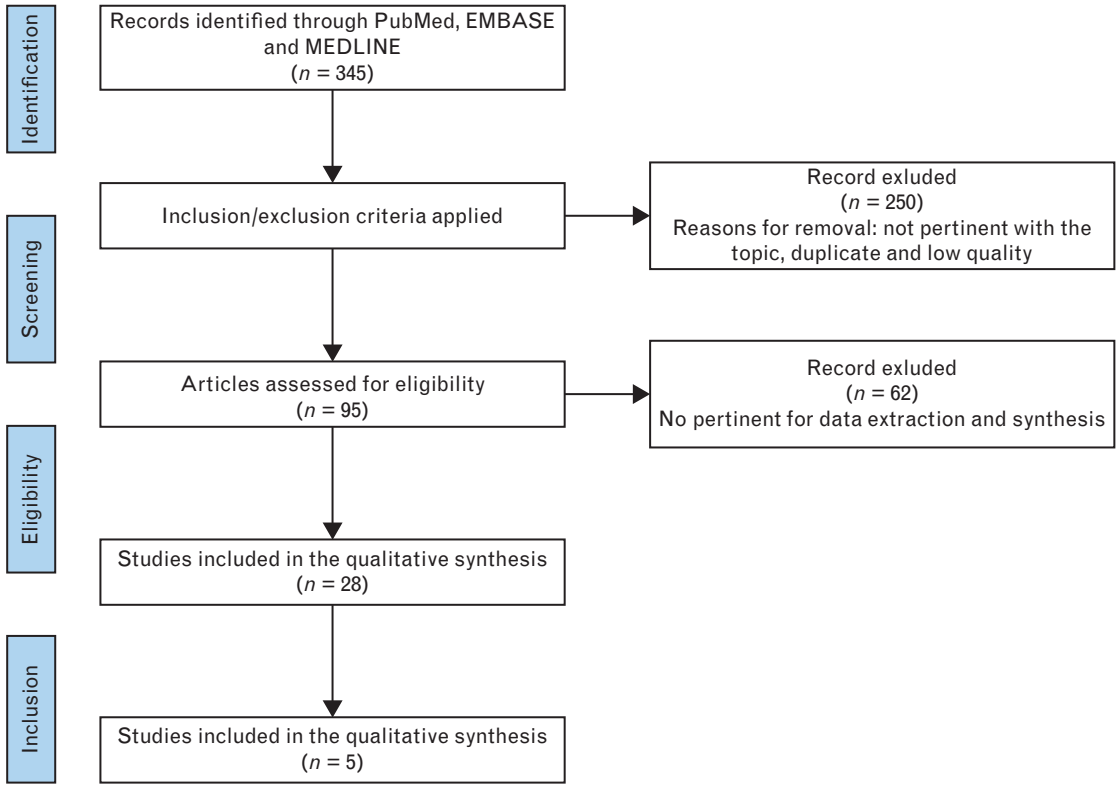
Literature search

Figure 1 shows the PRISMA flow diagram of studies identification. Altogether, a total of 345 records were identified in the preliminary search. Of these 312 did not meet the inclusion criteria and were therefore excluded. A total of 28 studies were used for data extraction and synthesis for our systematic review. Five articles comparing CNs versus N-CNs were finally included in our meta-analysis.[12,25–28]

Characteristics of the included studies

Characteristics of the included studies are listed in Table 1. All five included papers comparing CNs versus N-CNs

Fig. 1



PRISMA flow diagram checklist.

were observational in design.[12,25–28] The overall number of included individuals was 1456. No significant difference in female gender was assessed (36.1% versus 36.8%, OR 0.95; 95% CI: 0.71–1.26, *P*-value 0.71, $I^2 = 27\%$). Furthermore, hypertension (75.9% versus 77.3%, OR 0.96; 95% CI: 0.59–1.58, *P*-value 0.89, $I^2 = 27\%$), smoking habit (24.5% versus 27.1%, OR 0.80; 95% CI: 0.61–1.06, *P*-value 0.13, $I^2 = 0\%$), diabetes mellitus (43.7% versus 41.7%, OR 1.18; 95% CI: 0.74–1.87, *P*-value 0.49, $I^2 = 71\%$) and dyslipidemia (54.8% versus 57.7%, OR 0.99; 95% CI: 0.74–1.31, *P*-value 0.94, $I^2 = 0\%$) were comparable between the two included groups (Fig. 2). On angiography, both the reference vessel diameter (MD 0.04 mm; 95% CI: −0.12/0.19 mm, *P*-value 0.66, $I^2 = 73\%$) and the percentage of stenosis (MD 1.21%; 95% CI: −1.79/4.21 mm, *P*-value 0.43, $I^2 = 63\%$) of the target lesions were comparable among the two groups (Figure S1, Supplemental Digital Content, http://links.lww.com/JCM/A643).

Clinical outcomes

Although there was a nonsignificant trend for more cardiac deaths in the CN group (OR 1.75; 95% CI: 0.98–3.13, *P*-value = 0.06, $I^2 = 0\%$), target vessel revascularization (TVR) (OR 2.16; 95% CI: 1.39–3.36, *P*-value < 0.01, $I^2 = 0\%$) and stent thrombosis (OR 9.29; 95% CI: 1.67–51.79, *P*-value = 0.01, $I^2 = 0\%$) were significantly higher in the CN group compared with the N-CN group (Fig. 3).

Discussion

Definition

Making a comprehensive and pertinent definition of a CN is challenging. Historically, pathology describes a CN as an eccentric, protruding calcified mass with fragments disrupting the fibrous cap, surrounded by thrombi.[29] However, based on recent evidence, CNs may be further divided into two groups: the E-CN and NE-CN.[10] The disruption of the fibrous cap sets E-CNs apart from NE-CNs,[10] with the latter frequently recognized by pathologists as quiescent bystanders and unrelated to intraluminal thrombosis.[30]

Pathophysiology

CN formation in the coronary arteries requires several steps, even if the precise mechanisms are still not fully understood. In the coronary wall, microcalcification arises from the apoptosis of smooth muscle cells.[11,31,32] Over time, these regions of microcalcification merge, resulting

Table 1 Baseline patient characteristics and outcomes in studies comparing CNs versus N-CNs

Author	Year	Journal	Country	Design	Scenario	Imaging	Outcomes	Follow-up	Patients (*N*)
Ali *et al.*[27]	2023	JACC CVI	USA	Multicenter, retrospective observational study	NA	OCT	Intracoronary imaging	Before hospital discharge	54–194
Demuyakor *et al.*[26]	2022	BMC Cardiovascular Disorders	China	Single-center, retrospective observational study	ACS: 100% vs. 100%	OCT	Intracoronary imaging	Before hospital discharge	236–259
Jinnouchi *et al.*[25]	2022	J. Atheroscler. Thromb.	Japan	Single-center, retrospective observational study	CCS: 78% vs. 85.9% ACS: 22% vs. 14.1%	IVUS	Intracoronary imaging + clinical	780 (465–1102) days vs 590 (278–989) days	100–149
Morofuji *et al.*[12]	2020	Catheter Cardiovasc. Interv..	Japan	Single-center, retrospective observational study	CCS: 84.4% vs. 89.7% ACS: 15.6% vs. 10.3%	IVUS	Intracoronary imaging + clinical	5 year	128–136
Pengchata *et al.*[28]	2023	Journal of Interventional Cardiology	Thailand	Single-center retrospective, observational study	CCS: 73.6% vs. 79.6% ACS: 26.4% vs 20.4%	IVUS	Intracoronary imaging + clinical	26 (14–44) months	Outcome: 87–113 (IVUS: 54–71)

Age (years)	Female (*N*)	EF (%)	HTN (%)	Smoking (%)	Dyslipidemia (%)	DM (%)	CKD (%)	Anatomy (%)	Angio baseline: reference diameter (mm)	Angio baseline: minimum lumen diameter (mm)
NA	NA	NA	NA	NA	NA	NA	NA	NA	3.07 ± 0.45 vs 2.92 ± 0.51	NA
63.8 ± 10.1 vs 59.6 ± 10.0	90 (38.1%) VS 95 (36.7%)	57.3 ± 6.5 VS 58.5 ± 6.2	53.0 vs 52.5	44.1 vs 48.0	22.3 vs 22.0	25.0 vs 22.9	4.3 vs 2.7	RCA: 36.1 vs 34.0 LAD: 54.2 vs 52.7 CX: 9.7 vs 13.4	2.6 ± 0.5 vs 2.7 ± 0.5	2.1 ± 0.5 vs 2.2 ± 0.5
75 (70 - 81) vs 76 (70 - 81)	22 (22%) VS 48 (32.2%)	58 (46 – 66) VS 62 (50 – 68)	97.0 VS 98.7	13.0 vs 20.1	92.0 vs 94.0	66.0 vs 49.0	NA	RCA: 37.0 vs 10.7 LM/LAD: 58.0 vs 84.6 CX: 5.0 vs 4.7	2.6 (2.2 - 3.0) vs 2.2 (2.0 - 2.6)	NA
74 (67–80) vs 74 (68–78)	48 (37.5) vs 44 (32.4)	58 (45–65) vs 59 (49–66)	85.2 vs 87.5	13.3 vs 16.9	73.4 vs 70.6	49.2 vs 60.3	NA	RCA: 42.2 vs 17.6 LM/LAD: 43.7 vs 69.8 CX: 14.1 vs 12.5	2.51 (2.23–2.95) vs 2.44 (2.14–2.73)	0.70 (0.45–0.92) vs 0.64 (0.42–0.88)
72.7 ± 10.1 vs 72.4 ± 8.8	39 (44.8%) vs 55 (48.7%)	62 (47–70) vs 61 (46–67)	100.0 vs 93.8	5.7 vs 3.5	73.6 vs 76.1	60.9 vs 53.1	41.4 vs 45.1	RCA: 20.7 vs 18.6 LM/LAD: 73.6 vs 78.7 CX: 5.7 vs 2.7	2.65 ± 0.64 vs 2.58 ± 0.53	0.50 ± 0.37 vs 0.47 ± 0.30

Angio baseline: stenosis (%)	Angio post: acute gain (mm)	IC imaging baseline: lesion length (mm)	IC imaging baseline: reference diameter (mm)	IC imaging baseline: mean lumen area (mm_2)	IC imaging baseline: minimum lumen area (mm_2)	IC imaging post: calcium fracture (%)
66 ± 14 vs 61 ± 10	1.75 (1.51–2.20) vs 1.54 (1.32–1.85)	26.4 (18.6–36.8) vs 32.1 (24.0–37.8)	NA	4.9 (4.2–6.6) vs 4.4 (3.4–5.7)	NA	78.7 vs 65.2
20.3 ± 8.3 vs 20.4 ± 9.9	NA	31.0 (25.2–38.5) vs 29.0 (22.8–34.1)	NA	NA	0.9 (0.8–1.2) vs 0.9 (0.7–1.2)	NA
NA	NA	20.0 (8–28) VS 14.0 (8–23)	NA	4.0 (3.2–5.2) vs 3.3 (2.7–3.9)	2.0 (1.6–2.8) VS 2.0 (1.6–2.5)	NA
16.1 (10.5–21.1) vs 17.0 (13.0–23.0)	1.71 (1.25–2.01) vs 1.44 (1.24–1.77)	25.6 (17.2–46.5) vs 35.5 (23.5–50.0)	2.5 (2.2–3.0) vs 2.4 (2.1–2.7)	NA	2.0 (1.6–2.6) vs 1.8 (1.4–2.1)	NA
81.13 ± 12.51 vs 81.52 ± 12.66	1.95 ± 0.42 vs 1.94 ± 0.47	35.5 ± 17.2 vs 38.8 ± 16.9	2.7 ± 0.6 vs 2.6 ± 0.5	NA	NA	86.2 vs 78.8

IC imaging POST: Minimum stent area (mm2)	IC imaging post: stent expansion (%)	IC imaging post: stent expansion <80% (%)	IC imaging post: stent strut malapposition (%)	IC imaging post: major edge dissection (%)	Cardiac death (%)	TVR (%)	ST (%)	MACE (%)
NA	NA	NA	NA	NA	NA	NA	NA	NA
5.0 (3.9–6.3)	70.0 (62.7–81.8)	72.3	41.1	2.9	NA	NA	NA	NA
vs	vs	vs	vs	vs				
5.4 (4.2–6.7)	75.0 (65.2–86.6)	59.5	39.7	3.1				
5.0 (3.9–6.3)	69.7 (57.5–83.7)	NA	NA	NA	NA	29.0	2.0	NA
VS	VS					vs	vs	
4.5 (3.7–5.5)	76.5 (66.1–87.4)					14.1	0.0	
5.5 (4.1–7.4)	NA	NA	NA	NA	18.9	18.9	7.0	35.4
vs					vs.	vs.	vs.	vs.
4.3 (3.5–5.2)					11.9	11.9	0.9	18.8
6.7 ± 2.6	NA	NA	NA	NA	9.2	6.9	0.0	20.7
vs					vs	vs	vs	vs
6.5 ± 2.2					5.3	2.7	0.0	8.8

ACS, acute coronary syndrome; CCS, chronic coronary syndrome; CKD, chronic kidney disease; CN, calcified nodule; DM, diabetes mellitus; EF, ejection fraction; HTN, hypertension; IC, intracoronary; IVL, intracoronary lithotripsy; IVUS, intracoronary ultrasound; MACE, major adverse cardiac events; N-CN, nonnodular coronary calcification; OCT, Optical Coherence Tomography; RA, rotational atherectomy; ST, stent thrombosis; TVR, target vessel revascularization.

in the formation of larger areas of fragmented calcification (diameter $\geq$1 mm).[11,31,32] If at least a quadrant of the circumference or >3 mm in the diameter of the artery is involved by diffuse areas of fragmented calcification, they will be classified as sheet calcifications.[9,16,31,33] Notably, mechanical stress applied on these calcified sheets might lead to sheet calcification fracture, eventually forming a CN.[10,17] In a recent OCT study, CNs were most frequently found in the mid-segment of the right coronary artery (RCA), a region associated with more significant hinge movement on the angiogram.[17] Continuous cyclic mechanical forces exerted on the segment of hinge movement over a prolonged period may cause the weakening of calcified plaque, leading to fracture.[17,34] Even with proper stent implantation, the continuous hinge movement may induce the underlying CN to project into the lumen through the stent struts, increasing the chance of target lesion revascularization.[25]

Microscopically speaking, some studies highlighted that in the apoptotic areas of the smooth muscle cells, the increase in serum calcium-phosphorus product induces a switch toward an osteoblast-like phenotype.[35,36] Subsequently, osteogenic primed vascular smooth muscle cells express alkaline phosphatase and secrete bone-associated proteins by releasing mineralization-competent matrix vesicles.[36] Other factors like diabetes mellitus and aging might induce hormonal and physiological abnormalities associated with intimal calcification, including endothelial dysfunction, oxidative stress, increased inflammatory cytokine production, alterations in mineral metabolism, and the release of osteoprogenitor cells from the marrow into the circulation.[37]

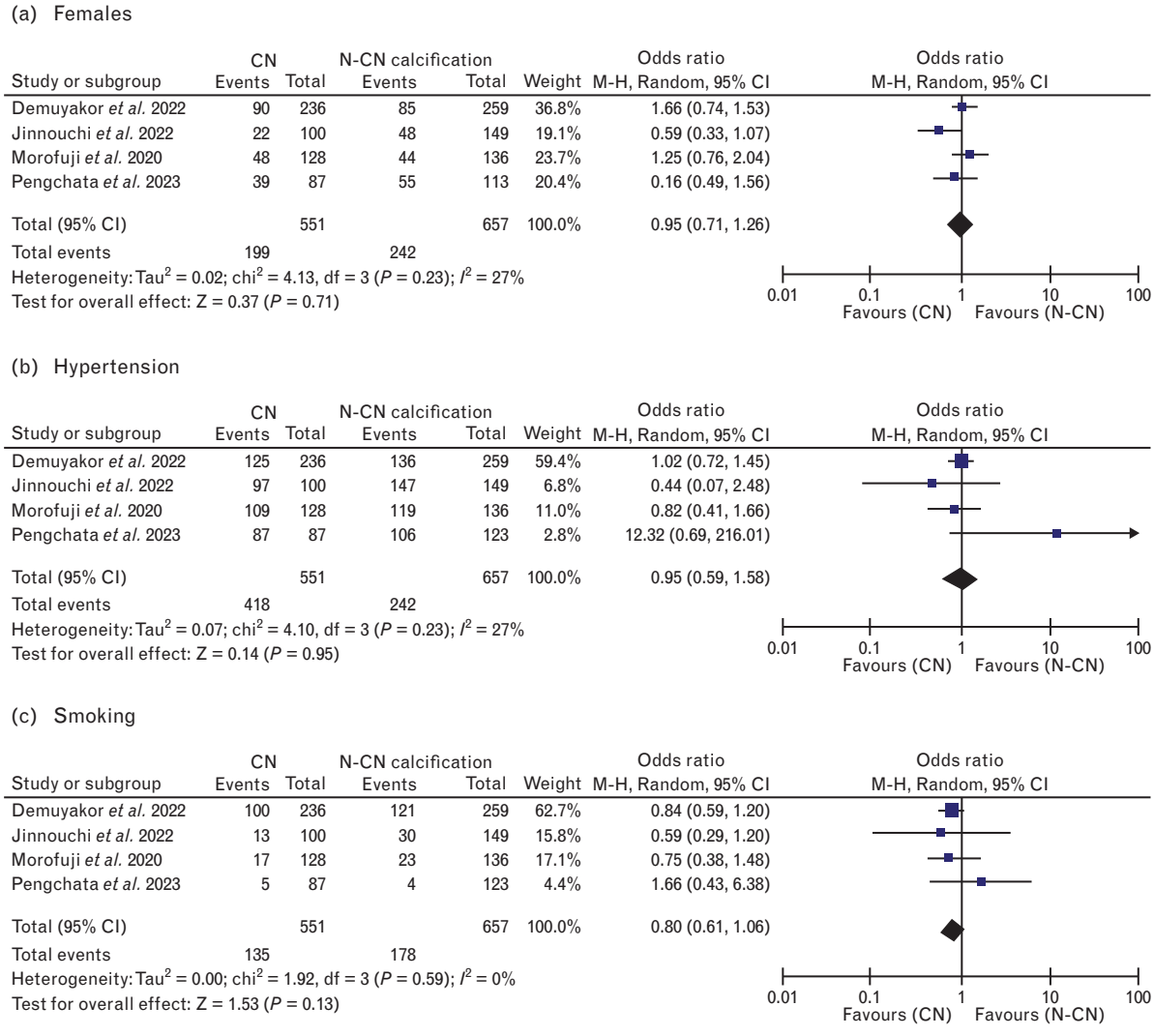
Although the disruption of the fibrous cap distinguishes E-CNs from NE-CNs, it is believed that both E-CNs and NE-CNs share similar structures and origins.[10,38] Even if a potential hypothesis is that any NE-CN may present as an E-CN if granted enough mechanical stress and time;[38] whether the E-CNs are an evolution (or complication) of NE-CNs is still to be thoroughly demonstrated.

Epidemiology

In-vivo studies have shown that CNs are more commonly observed in the RCA.[12,17,25] However, evidence from pathology studies has highlighted that the majority of CNs were found in the left anterior descending artery.[39] This observation might be attributed to the design of autopsy-based studies and the inclusion of cases with ACS, suggesting that CNs involving the left anterior descending artery could be potentially more lethal and, therefore, more prevalent in pathology registries.

Approximately 7–8% of ACS cases are attributed to acute thrombosis at the site of the CN.[11,15,40] It is noteworthy that patients with CN as a fatal culprit tend to be older than

Fig. 2



Forest plots for baseline clinical characteristics in CN versus N-CN. (a) Female gender; (b) hypertension; (c) smoking; (d) diabetes mellitus; (e) dyslipidemia; (f) chronic kidney disease.

those with plaque rupture or erosion,[41] further emphasizing the progressive nature of CNs. Consistently with these findings, a registry of postmortem radiographs of hearts from sudden-death cases demonstrated a progressive increase in the percentage of coronary artery calcification relative to plaque burden over several decades.[37]

Although CN lesions are often associated with diabetes mellitus and chronic kidney disease,[16,25,37] our pooled analysis did not reveal any significant differences between CN and N-CN calcifications.

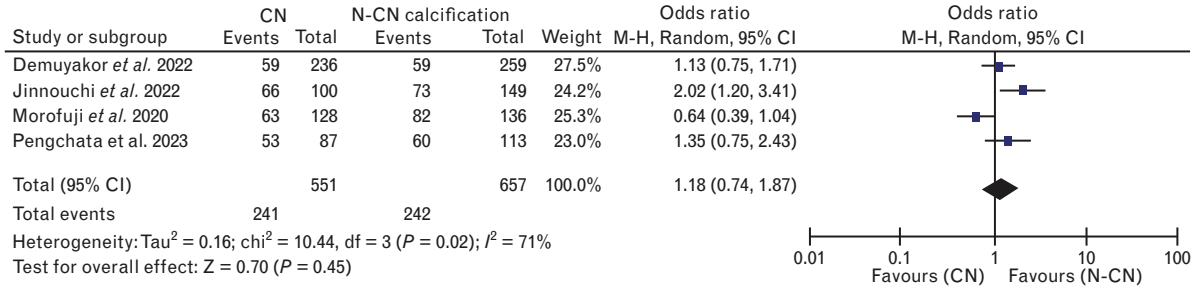
Diagnosis

Pathology represents the gold standard for making a diagnosis of CN. *In vivo*, the accuracy of angiography in detecting CNs is far from being as accurate as pathology.

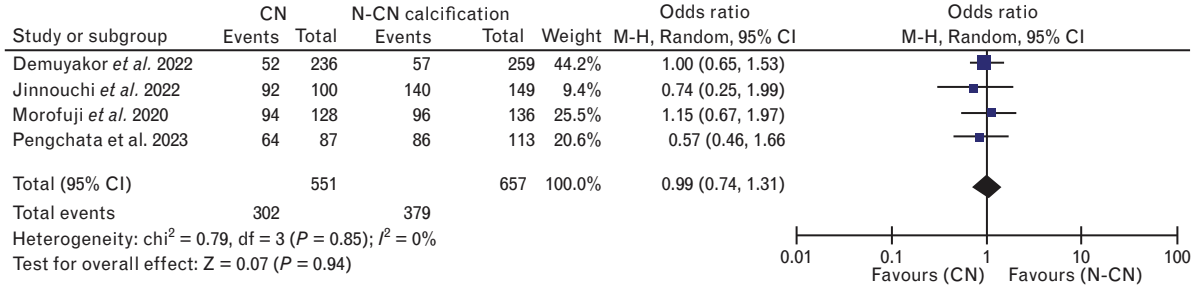
Compared with angiography, intravascular ultrasound (IVUS) offers greater sensitivity for detecting coronary calcification.[30,42] Nevertheless, IVUS provides valuable information about the calcification pattern, including its arc, length, and location.[30,42] Furthermore, IVUS can provide essential data after stent implantation, such as minimal stent area, malposition, or underexpansion.[12,25,28] However, IVUS presents limitations. First, calcified plaques create a significant shadow that hampers accurately measuring their thickness. Second, the resolution is frequently insufficient to appreciate microscopic differences such as fibrous cap thickness or disruption.

Fig. 2 (Continued)

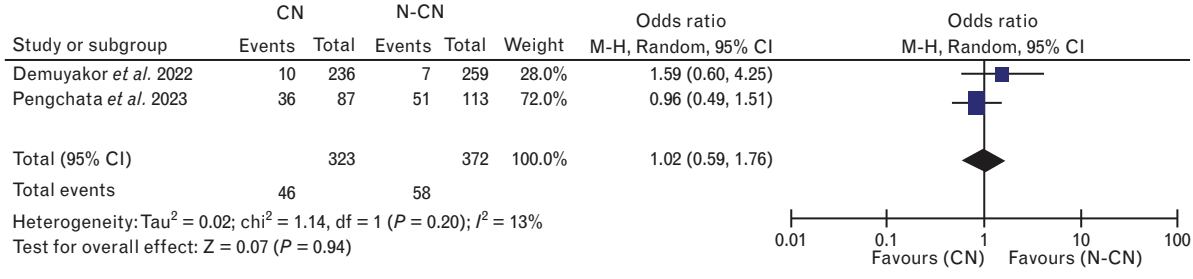
(d) Diabetes mellitus



(e) Dyslipidemia



(f) Chronic kidney disease



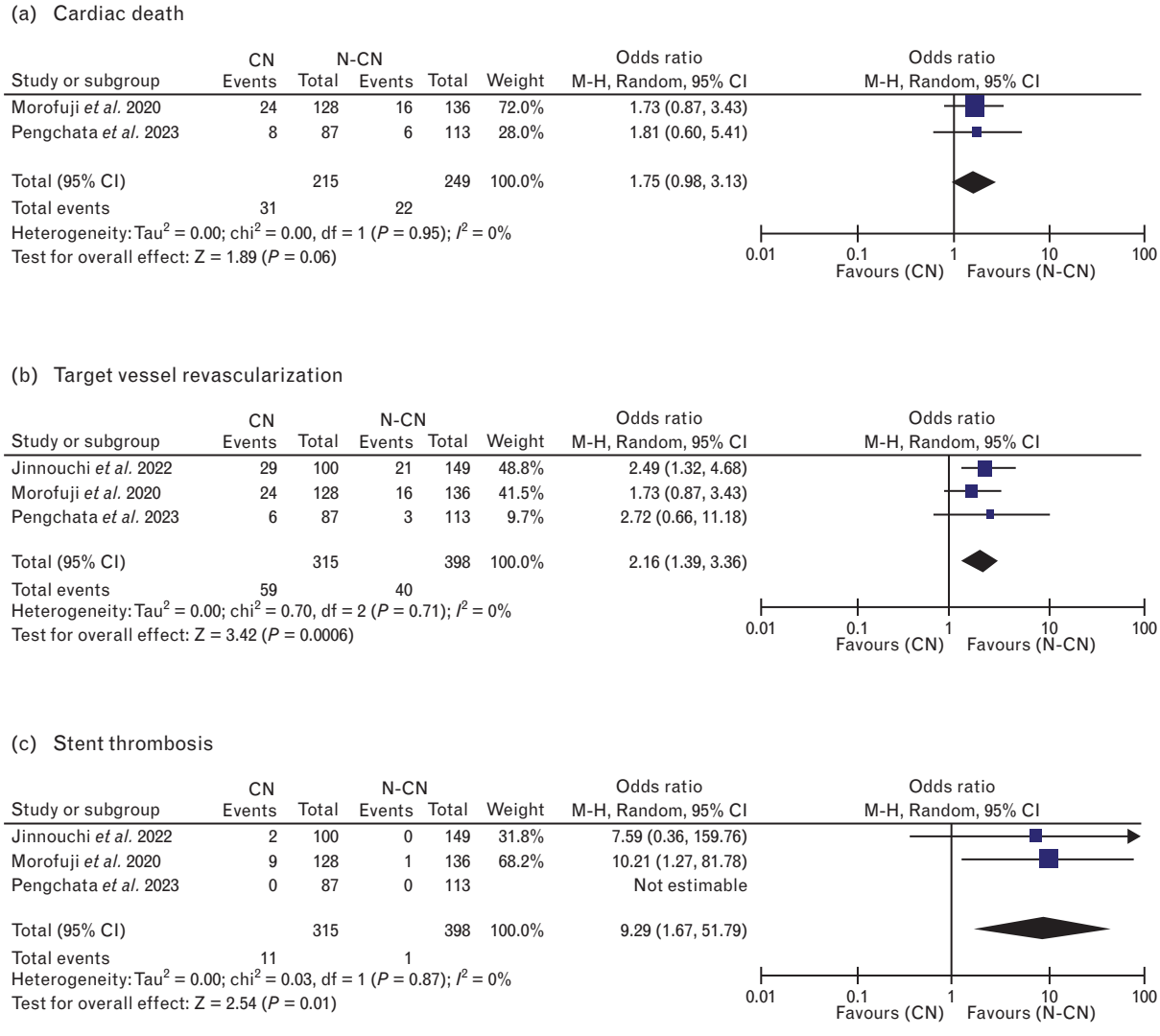
Thus, a correct distinction between E-CN and NE-CN is frequently not reliable with this method. Yet, the upgraded high-definition IVUS could help us to overcome these technical limitations.

OCT, with its tenfold higher spatial resolution, presents a valuable tool to analyze calcium deposits on the coronary wall further (Fig. 4). The OCT leads to the distinction between E-CNs and NE-CNs, identifying the eruptive morphology of the former, which includes a disrupted surface and intraluminal thrombosis appositions.[17,30,43] Additionally, OCT is also applicable in acute settings with a CN as a culprit.[9] However, the limitations of OCT should also be considered, including the need for a significant amount of contrast and the necessity to obtain accurate images of aspirating occlusive thrombus before imaging, which itself could disrupt plaque architecture. Indeed, it is likely that the manipulation required to obtain accurate images could potentially introduce changes in plaque characteristics, which may result in reduced accuracy (compared with pathology) in distinguishing NE-CNs from E-CNs. However, our statement is purely exploratory and additional studies are necessary. Noninvasive methods for the diagnosis of CNs are still not available. In a retrospective study, Sugiura *et al.* explored the possibility of introducing coronary computed tomography angiography for CN detection.[44] Although the results were promising, more data are necessary.

Clinical outcomes

Calcific lesions represent a difficult target for PCI. The focal, eccentric, and hard nature of CNs is frequently the

Fig. 3



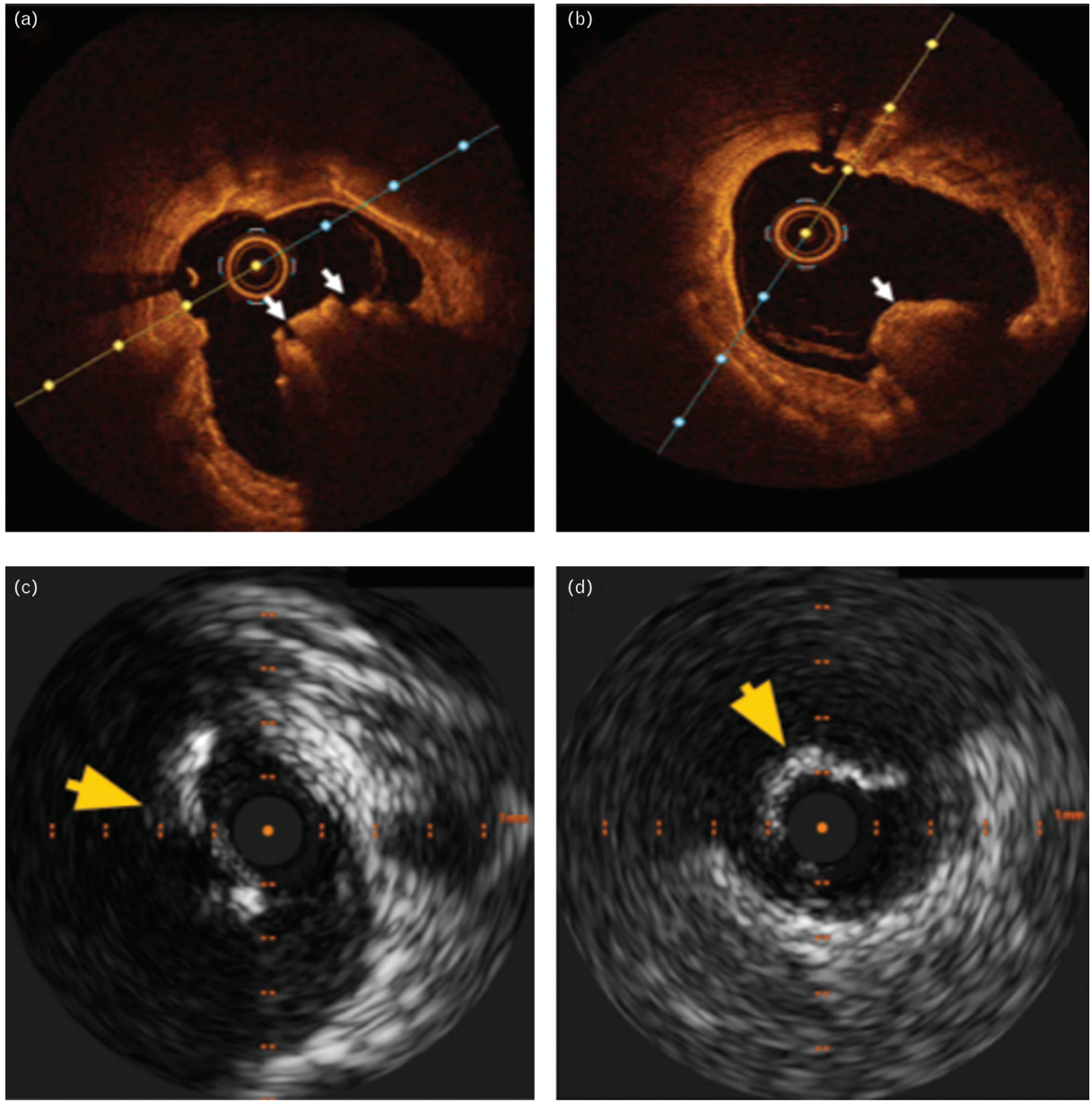
Forest plots for clinical outcomes in CN versus N-CN. (a) Cardiac death; (b) target vessel revascularization (TVR); (c) stent thrombosis.

cause of adverse events.[10–14] Moreover, the surrounding area frequently presents severe calcifications and tortuosity, which may prevent intracoronary material delivery.[10,17] As for all calcified lesions, aggressive lesion preparation and postdilation are mandatory. However, if excessive, it might significantly increase the risk of complications. Indeed, since the balloon dilation works mainly through the eccentric expansion of the healthy vessel wall opposite the nodule, high-pressure inflation dramatically increases the risk of dissection and perforation and has only marginal effects on the nodule itself.

In our pooled analysis, compared with N-CN calcifications, CNs negatively affect outcomes. Although the baseline clinical and angiographic characteristics were comparable between CN and N-CN calcifications, the long-term relevant clinical events occurred more frequently in the first group. Specifically, CN patients have more than double the risk of experiencing TVR and stent thrombosis.

Data from the literature have widely highlighted that stent underexpansion is frequently associated with ISR and stent thrombosis.[5,6] In this contest, Demuyakor *et al.* demonstrated that, even if the mean reference lumen areas were comparable between CN and N-CN calcifications, the post-PCI minimum stent area was significantly smaller in the first group compared with the latter ($P = 0.011$), and stent underexpansion was most frequent ($P = 0.003$) in the CNs.[26] Although a pooled analysis could not be performed due to lack of data, stent underexpansion might be reasonably considered as a potential cause of the increased TVR and stent thrombosis highlighted by our analysis.

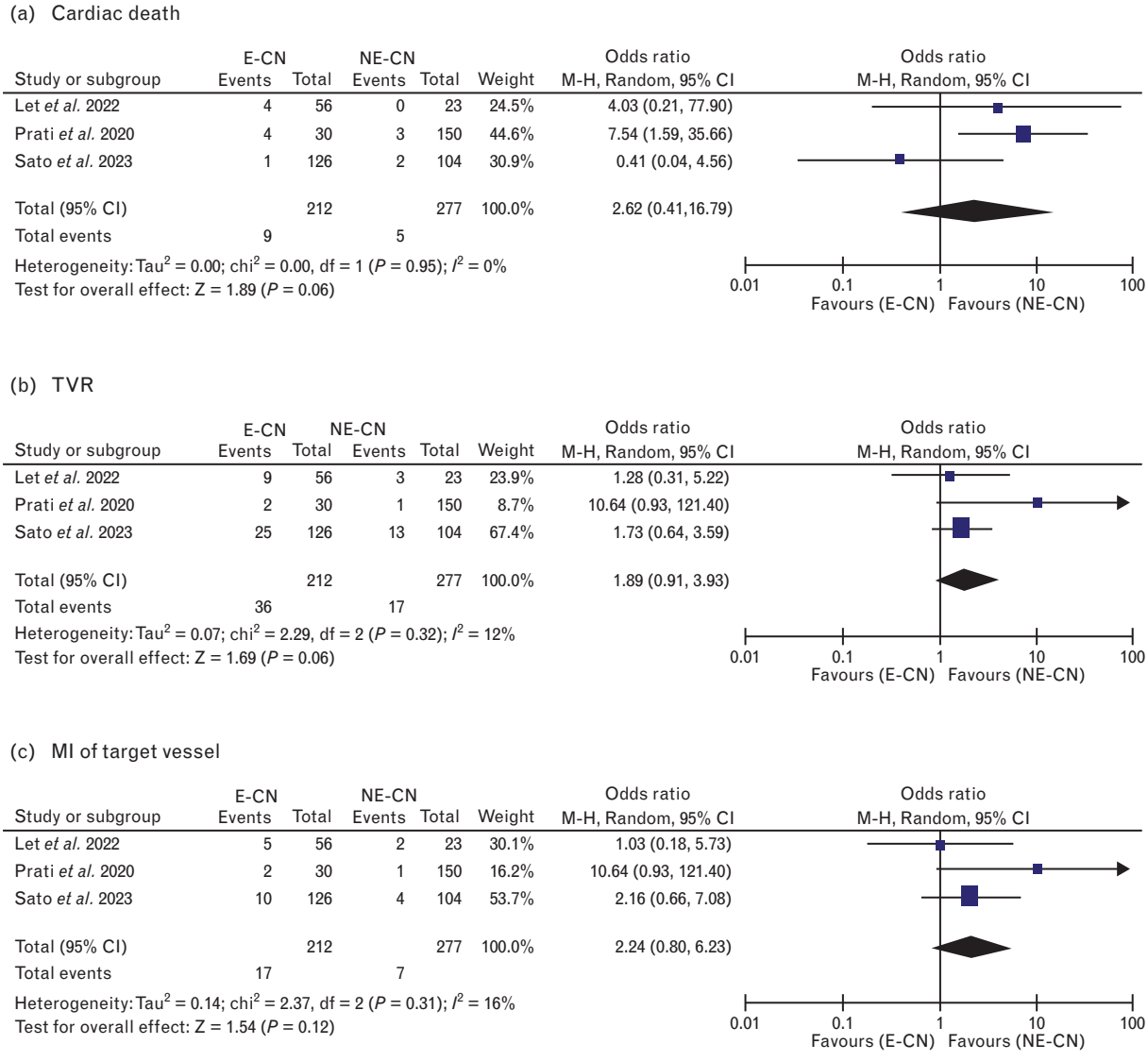
Fig. 4



Optical coherence tomography of an eruptive calcified nodule (E-CN, Panel a) and a noneruptive calcified nodule (NE-CN, Panel b). The E-CN is defined as an accumulation of calcium fragments protruding and disrupting the fibrous cap (arrow), frequently presenting small amounts of thrombus. NE-CN is characterized by an accumulation of calcium fragments with a smooth intact fibrous cap (arrow) without concomitant thrombus. (Panels c and d) Intravascular ultrasound imaging examples of calcified nodules, showing the typical aspect of protruding, convex-shaped calcification with irregular surface, generating an acoustic shadow.

Notably, all patients in our pooled analysis of clinical outcomes received RA as standard therapy. Thus it seems that, independently from more aggressive debulking treatment, CNs per se may be associated with worse clinical outcomes than other calcification types. To support our hypothesis, in a retrospective study confronting CNs treated with and without RA, RA failed to significantly improve acute lumen gain (final minimum lesion diameter–initial minimum lesion diameter), in-stent malposition, and calcium fracture.[45] More importantly, RA failed to significantly decrease the rate of TVR in patients with CNs.[45] These results are consistent with the ROTAXUS and PREPARE-CALC trials, where, although RA was associated with promising predischarge outcomes, no differences in late lumen loss or TVR were assessed in severely calcified lesions.[3,4] We retain that the eccentric nature of CNs may

Fig. 5



Forest plots for clinical outcomes in E-CN versus NE-CN. (a) cardiac death; (b) target vessel revascularization (TVR); (c) MI of target vessel.

explain the difficulty in obtaining consistent results with RA. Indeed, we do not support the routine use of RA for lesions with CNs, especially in primary PCI, since RA was significantly associated with adverse events in this clinical setting.[46]

Intravascular lithotripsy (IVL) has recently emerged as a valuable tool for effectively treating calcified coronary lesions.[47] Ali *et al.* have recently evaluated the efficacy of IVL in patients with CN or N-CN calcifications.[27] After IVL, the acute gain was significantly more prevalent in the CN group.[27] The post-PCI OCT highlighted a number of fractures per lesion significantly higher in the CN group.[27] However, no data regarding clinical outcomes were available. Thus, whether the previous findings positively influence outcomes has yet to be demonstrated.[27]

A specific subtype of CN, known as an eruptive calcified nodule (E-CN), has been recently examined for its potential to lead to worse clinical outcomes compared with other calcification types, despite the presence of conflicting data.[18,48,49] Specifically, Prati *et al.* highlighted that E-CNs were linked to a high 1-year incidence of cardiac death.[18] Conversely, Sato *et al.* did not observe similar outcomes over a longer-term follow-up.[48] We thus undertook an exploratory analysis by pooling data to compare E-CNs with NE-CNs.[18,48,49] Interestingly, E-CNs and NE-CNs were associated with a similar rate of cardiac death

(OR 2.62; 95% CI: 0.41–16.79, *P*-value 0.31, $I^2 = 51\%$), TVR (OR 1.89; 95% CI: 0.91–3.93, *P*-value 0.09, $I^2 = 12\%$) and target vessel myocardial infarction (OR 2.24; 95% CI: 0.80–6.23, *P*-value = 0.31, $I^2 = 16\%$) (Fig. 5). Nevertheless, potential limitations cannot be overlooked. Primarily, the analysis suffered from low statistical power due to the small sample size. Furthermore, potential confounding factors cannot be disregarded: the substantial flow of contrast employed during OCT assessments might disrupt the fibrous cap or displace a thrombus, potentially resulting in overlapping diagnoses. Moreover, the fact that mechanical thrombectomy was performed in approximately one-tenth of the patients prior to the OCT evaluation could have influenced the findings observed for OCT.

Potential eligible treatments

Although with intrinsic limitations, case report-based strategies provide further potential therapeutic options. Ikemura *et al.* proposed a stent-less combined strategy with RA and drug-coated balloon (DCB) in a patient with high bleeding risk for a CN involving the RCA. After 6 years, the patient was free from cardiovascular or hemorrhage events.[50] Again, Matsuda *et al.* described a case of an ostial left circumflex artery CN successfully treated with excimer laser coronary atherectomy (ELCA) and scoring balloon dilatation followed by DCB.[51] Stenting was avoided to prevent potential plaque shift in the acute phase. OCT at the 3-year follow-up revealed consistent results. Thus, ELCA followed by DCB dilatation might offer an alternative treatment for ostial CN lesions instead of stenting.[52] Compared with RA, ELCA allows the delivery of two guidewires with resultant protection of the bifurcation vessels during the debulking procedure, which implies other debulking devices (e.g. rotational atherectomy). Finally, Adachi *et al.* proposed a more aggressive escalation strategy to treat CNs. With the aid of optical frequency domain imaging, they used an Orbital Atherectomy System and RA to treat a CN in the RCA.[50] The imaging revealed a more profound groove inside the CN and the resultant luminal enlargement.

Limitations

While our study represents the first meta-analysis on this subject, it is not without limitations. Firstly, the observational nature of the included studies constrains the extent to which our results can be generalized. Secondly, the inclusion of various clinical scenarios, encompassing both acute and chronic coronary syndromes and different follow-ups, could have introduced considerable heterogeneity. Thirdly, there was variability in the use of intravascular imaging modalities, such as IVUS or OCT, which may have affected the consistency of our findings.

Conclusion

CNs is linked to poorer outcomes compared with other calcification subtypes. It is imperative for operators to quickly recognize the risks and challenges associated with PCI in these complex scenarios. Additional efforts are warranted to address the difficulties presented by this challenging type of coronary lesion.

Conflicts of interest

The Department of Cardiology of the Leiden University Medical Center received unrestricted research grants from Abbott Vascular, Bayer, Biotronik, Boston Scientific, Edwards Lifesciences, GE Healthcare and Medtronic. F. van der Kley received consultancy fees from Edwards Lifesciences and Abbott Vascular. JM. Montero received a research grant from Shockwave Medical and speaker fees from Abiomed, Boston Scientific and Penumbra Inc. The remaining authors have no conflicts of interest to declare. Alfonso Jurado: proctor Boston Scientific, Philips/Biomenco and Medtronic and speaker fees from Shockwave, Boston, Abbott, World Medica.

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