The Ability of Near-Infrared Spectroscopy to Identify Vulnerable Patients and Plaques: A Systematic Review and Meta-Analysis

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KEYWORDS

• NIRS • Vulnerable plaque • ACS • LRP

KEY POINTS

- A near-infrared spectroscopy (NIRS) meta-analysis provides a more precise estimate of the efficacy of NIRS.
- NIRS-derived lipid core burden index (LCBI) is an effective method for quantifying and identifying high-risk plaques and patients at increased risk of future MACE/MACCE.
- A max$LCBI_{4mm}$ of 400 or greater seems to be an effective threshold for classifying at-risk plaques.

INTRODUCTION

Coronary artery disease continues to be a major cause of global morbidity and mortality despite medical advancements and effective preventive measures.[1] Acute coronary syndromes (ACS) are most often caused by rupture or fissure of a lipid-rich core-containing plaque and a large plaque burden, termed a vulnerable plaque.[2,3] Autopsy findings determined that these atheromas have a large plaque size, cholesterol-rich lipid core, and thin fibrous cap.[4] Atheromas tend to occur at multiple sites resulting in high atherosclerotic burden, which confers to a patient at high-risk of adverse cardiac events.[2] More recently, research has focused on preemptively identifying at-risk plaques and patients in a more proactive strategy of targeted secondary prevention.

Currently, the only imaging modality validated to identify lipid-rich plaques is near-infrared spectroscopy (NIRS).[5] NIRS uses unique technology via an add-on optic fiber as part of an imaging system attached to an intravascular ultrasound (IVUS) catheter that can easily identify lipid-rich plaque.[5] NIRS is able to deliver quantitative data regarding lipid composition within coronary artery walls, providing a more precise identification of vulnerable plaques than previously available,[6] which may provide clinicians with improved patient-level risk estimation for more targeted interventions.

Although NIRS has been evaluated in the context of many different clinical scenarios, for

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the purposes of this study, we chose to focus on the association of NIRS and cardiovascular (CV) outcomes. Emerging evidence suggest that NIRS-derived lipid core burden index (LCBI) provides prognostic data at the patient level as well as the plaque level. Individual studies evaluating the role of NIRS are characterized by the inclusion of a small number of patients and may not provide adequately powered analysis, thus prompting the need for a systematic appraisal of treatment effects and quality of evidence. Therefore, this systematic review and meta-analysis aims to compile the currently available data regarding the prognostic value of NIRS-derived LCBI on adverse cardiac outcomes to provide more precise effect estimates.

METHODS

Protocol

This systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines.[7] The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication. The data supporting the findings in this study are available from the corresponding author on reasonable request.

Search Strategy

We performed a comprehensive literature search of all published studies—retrospective, prospective, observational—available through PubMed and Ovid (inception through December 31, 2021), without language restrictions. Case reports, letters to the editor, reviews, and book chapters were not included in this meta-analysis. Key search terms used were, "NIRS," "IVUS," "LCBI," "MACE," "MACCE," "coronary artery disease," "coronary heart disease," "angina," "myocardial infarction," "acute myocardial infarct," "myocardial ischemia," "acute coronary syndrome," "ischemic heart disease" including their subheadings, MeSH terms, and all synonyms. References for each of the studies selected were also screened. The PRISMA guidelines were applied for this search process.

Selection Criteria

Studies were eligible if they met the following criteria: (1) investigated the diagnostic performance of NIRS in predicting adverse cardiac outcomes; (2) in a patient population undergoing an invasive catheterization laboratory procedure, regardless of indication; (3) involving a unique patient population not included in another study; and (4) reported at least 1 of the following CV outcomes: all-cause mortality, CV mortality, myocardial infarction, stroke, or urgent coronary revascularization. Study selection was performed by 2 independent reviewers (R.B. and J.P.), first by screening of titles and abstracts, followed by review of full texts and their corresponding references. In cases in which there was a disagreement over eligibility, a third reviewer (H.G.) assessed the discrepancy, and decisions were reached by consensus. Quality of the data was analyzed using the Downs and Black Checklist or the Cochrane Risk of Bias tools, as applicable, by study type. An overview of referenced studies is provided in **Table 1**.

Data Extraction

Data on study characteristics, patient characteristics, and endpoint event rates were independently extracted and organized into a structured data set by 2 reviewers (R.B. and J.P.), compared, and reported in **Table 2**. Any discrepancy resulted in reevaluation of the primary data and involvement of a third reviewer (H.G.), with disagreements resolved by consensus.

Outcomes of Interest

The central illustration (**Fig. 1**) shows an example of a NIRS-derived chemogram and the value of NIRS in identifying high-risk patients and plaques. The prespecified primary endpoint in this study was major adverse cardiovascular and cerebrovascular events (MACCE). For trials not reporting MACCE, MACE was chosen as primary endpoint.[8–14] Note that max$LCBI_{4mm}$ was used in all studies except Danek and colleagues, which did not have the data available, and therefore used the LCBI of the vessel with highest lipid burden.[10] Thus, the authors of this article use the term LCBI to refer to all the NIRS-derived measurements for purposes of the primary analysis. Note that the max$LCBI_{4mm}$ refers to the 4 mm long segment with the maximum LCBI. The authors of this study then investigated their own secondary endpoint using a threshold max$LCBI_{4mm}$ at or around 400 as suggested by prior studies including Waksman and colleagues.[13] Each endpoint was assessed according to the definitions reported in the original study protocols. The list of endpoints for each study is listed in **Table 3** along with the definitions of each endpoint.

Risk of Bias

Methodological quality of included studies was assessed using the Risk of Bias In Non-randomized Studies of Interventions assessment

Table 1
Study overviews

Trial/Author Year	Study Design	Multicenter	Population	Follow-Up
Oemrawsingh, et al,[8] 2014	Observational (prospective) Primary endpoint: MACCE	No	Patients with clinical indication for diagnostic coronary angiography and/or PCI due to ACS or stable CAD	1 y
Madder, et al,[9] 2016	Observational (prospective) Primary endpoint: MACCE	No	Patients with clinical indication for invasive coronary angiography and/or PCI due to ACS or stable CAD	1.7 y ± 0.4 y
Danek, et al,[10] 2017	Observational (prospective) Primary endpoint: MACE	No	Patients with clinically indicated cardiac catheterization and NIRS imaging due to ACS or stable CAD	Median 5.3 y
Schuurman, et al,[11] 2017	Observational (prospective) Primary endpoint: MACE	No	Patients undergoing diagnostic coronary angiography or PCI due to ACS or stable CAD	Median 4.1 y
Karlsson, et al,[12] 2019	Observational (retrospective enrollment, prospective follow-up) Primary endpoint: MACCE	Yes	Patients with clinical indication for coronary catheterization due to ACS or stable CAD	Mean 2.9 ± 1.3 y
LRP Study Waksman, et al,[13] 2019	Prospective, cohort Primary endpoint: MACE	Yes	Patients with indication for cardiac catheterization with possible ad hoc PCI due to known or suspected ACS or stable CAD	2 y
PROSPECT II Erlinge, et al,[14] 2021	Prospective, observational Primary endpoint: MACE	Yes	Patients intended for coronary angiography ± PCI due to recent STEMI or NSTEMI enrolled after successful intervention of all flow-limiting culprit lesions	Median 3.7 y

Abbreviations: CAD, coronary artery disease; NSTEMI, non-ST segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST segment elevation myocardial infarction.

Table 2
Background characteristics

Trial/Author	Age[b] (y)	Men (%)	HTN (%)	DM2 (%)	HLD (%)	Prior MI (%)	Prior PCI (%)	Prior CABG (%)	Prior Stroke (%)	Index Presentation (%)
Oemrawsingh, et al,[8] 2014	63.4	72.9	56.2	20.2	56.7	38.9	38.4	3.0	3.0	Composite ACS 46.8 Stable Symptoms 53.2
Madder, et al,[9] 2016	62.5	68.6	57.9	19.8	57.9	14.0	18.2	NR	5.0	Composite ACS 85.1 Stable Symptoms 14.9
Danek, et al,[10] 2017[a]	63.5	99	95	50	93	36	11	23	11.0	Composite ACS 39 Stable Symptoms 61
Schuurman, et al,[11] 2017	62.5	76.7	60.0	21.5	57.5	34.2	35.6	2.2	5.8	Composite ACS 42.5 Stable Symptoms 57.5
Karlsson, et al,[12] 2019	66.5	70.8	53.5	19.4	NR	29.2	NR	NR	9.7	Composite ACS 81.9 Stable Symptoms 18.1
LRP Study (Waksman, et al,[13] 2019)	64.0	69.5	80.4	36.7	80.3	23.5	44.9	NR	NR	Composite ACS 53.7 Stable Symptoms 46.3
PROSPECT II (Erlinge, et al,[14] 2021)	63.0	83.0	37.2[c]	12.1	25.2[d]	9.9	11.9	0.0	5.2	Composite ACS 100.0

Included background characteristics refer to the full study populations as defined in Table 1 of the individual studies.

Abbreviations: CABG, coronary artery bypass graft; CAD, coronary artery disease; DM2, diabetes mellitus type 2; HLD, hyperlipidemia; HTN, hypertension; MI, myocardial infarction; NSTEMI, non-ST segment elevation MI; PCI, percutaneous coronary intervention; SAP, stable angina pectoris; STEMI, ST segment elevation MI; Sx, symptoms; UAP, unstable angina pectoris.

[a] Authors did not present any decimals.
[b] All ages are reported as means except Erlinge et al. is a median.
[c] HTN in PROSPECT-II defined as hypertension requiring medication.
[d] HLD in PROSPECT-II defined as hyperlipidemia requiring medication.

Tool from Cochrane handbook (ROBINS-I). Two investigators (R.B. and J.P) independently assessed 7 domains of bias: (1) confounding, (2) selection of participants, (3) classification of interventions, (4) deviations from intended interventions, (5) missing outcome data, (6) measurement of the outcome, and (7) selection of the reported results.

Statistical Analysis

Odds ratios (OR) and 95% confidence intervals (CI) were calculated using the DerSimonian and Laird random-effects model, with the estimate of heterogeneity being taken from the Mantel-Haenszel method. When the required numbers to pool the data were not available in the text or tables, we used an online semiautomated software to extract underlying numerical data from applicable Kaplan-Meier curves provided to determine the number of events above and below the relevant LCBI threshold in each study (WebPlotDigitizer 4.5, Ankit Rohatgi, Pacifica, California, USA). The presence of heterogeneity among studies was evaluated with the Cochran Q chi-square test, with $P \leq .10$ considered of statistical significance, and using the I^2 test to evaluate inconsistency. A value of 0% indicates no observed heterogeneity, and larger values indicate increasing heterogeneity. I^2 values of 25% or lesser, 50% or lesser, and greater than 50% indicated low, moderate, and high heterogeneity, respectively. A prespecified sensitivity analyses was performed by removing the studies not using a threshold $\text{maxLCBI}_{4\text{mm}}$ at or around 400.

Analyses were performed according to the intention-to-treat principle. The statistical level of significance was 2-tailed $P < .05$. Statistical analyses were performed with the Stata software version 13.1 (StataCorp LP, College Station, Texas, USA).

RESULTS

Search Results

A total of 7 studies involving 2948 patients were identified for this study as shown in Table 1. Each study was published within the last 10 years. All were observational studies with prospective follow-up.

Two of the studies, Schuurman and colleagues and Oemrawsingh and colleagues, included the same study population with results reported at different periods of follow-up.[8,11] Because

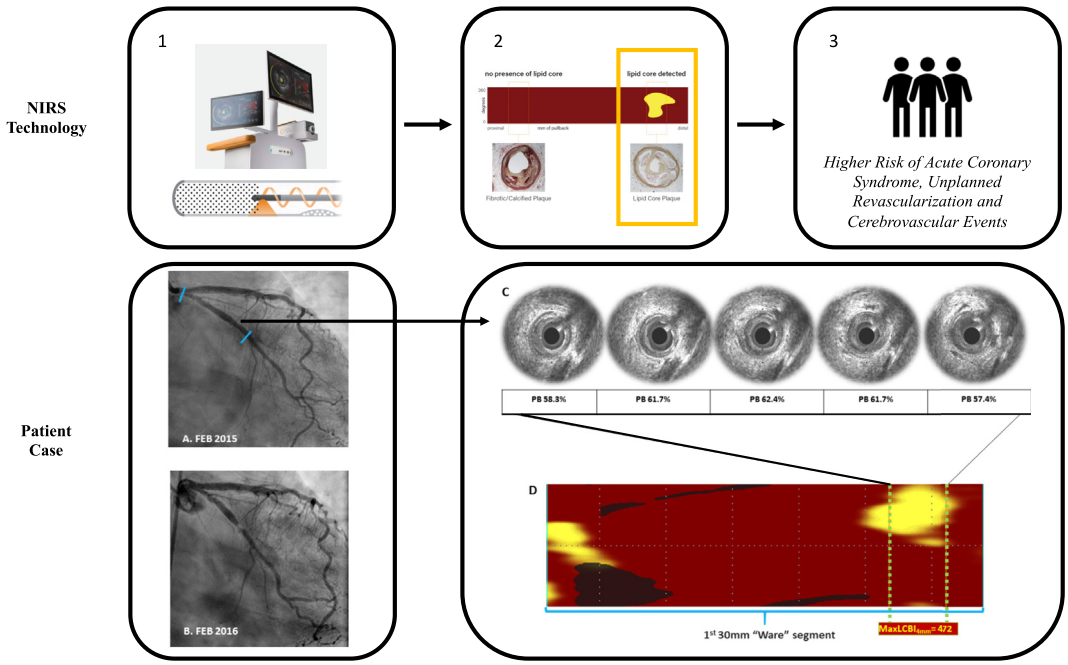

Fig. 1. The near-infrared spectroscopy instrument and example patient case. The top half of the image contains 3 panels, labeled 1 to 3 and outlined with black boxes, to introduce the near-infrared spectroscopy technology. The top image in panel 1 shows the NIRS machine while the bottom image in panel 1 shows the Dualpro catheter that delivers light to the vessel wall. Panel 2 is an example chemogram derived from the machine in panel 1. The red and yellow colors differentiate plaque characteristics. Yellow color on the chemogram as shown represents lipid core plaque. There is a yellow box around the identified lipid core plaque. Panel 3 emphasizes the association of this type of lipid core plaque with patient morbidity and mortality, particularly events defined in MACE/MACCE such as acute coronary syndrome, unplanned coronary revascularization, and cerebrovascular events. The bottom half of the figure shows a patient case representing the utility of NIRS.[13] There are 2 parts outlined with black boxes, each with 2 panels, labeled (*A*–*D*). Panel A shows the baseline coronary angiography of the left circumflex artery with no stenosis at the time of study enrollment. The light blue lines correspond to the 30 mm Ware segment as defined in the study protocol. Panel B shows the follow-up coronary angiography 1 year later, this time with a new significant lesion on the left circumflex. The intravascular ultrasound grayscale images in Panel C correspond to the $maxLCBI_{4mm}$ at baseline. The plaque burden of each 1-mm interval frame is found underneath each intravascular ultrasound image. In each interval, the plaque burden is moderate, between 57.4% and 62.4%. (*A*) NIRS-derived chemogram of the 30 mm Ware segment at baseline is seen in Panel D, indicating a $maxLCBI_{4mm}$ of 472. This patient case emphasizes the importance of NIRS-identification of lipid-rich plaque. Even though the angiography at baseline showed no stenosis, the area with $maxLCBI_{4mm}$ as discovered by NIRS was the culprit of a new lesion 1 year later. NIRS can predict potential areas of complication and provide an opportunity for prevention at the patient and plaque level.

Schuurman and colleagues published results with a greater duration of follow-up and larger sample size the authors chose to include those results and exclude Oemrawsingh and colleagues from the statistical analysis. Furthermore, although the total study population in Danek and colleagues was 239 patients, available data for nontarget vessel LCBI was only available for 39 patients.

Baseline Characteristics

Main baseline characteristics of included patients for each individual study are summarized in **Table 2**. Most patients were men with a mean age ranging from 62.5 to 66.5 years. The percentage of patients with hypertension ranged between 37.2% and 95%, whereas those with type 2 diabetes ranged from 12.1% to 50%. The presence of hyperlipidemia was between 25.2% and 93%. A subset of patients in each study experienced prior myocardial infarction, ranging from 9.9% to 38.9% of the populations. ACS was the index presentation in between 39% and 100% of patients.

Clinical Outcomes

The primary analysis and individual OR are shown in **Fig. 2**. The 6 included studies used different LCBI thresholds, ranging from LCBI of 77 or

Table 3
Outcome definitions

Trial/Author	MACCE	MACE	ACS	Cerebrovascular Events	MI	Unstable Angina	Unplanned Coronary Revascularization	Cardiac Death
Oemrawsingh, et al,[8] 2014	All-cause mortality Nonfatal ACS Stroke Unplanned coronary revascularization	NR	Per guidelines of the European Society of Cardiology	Per guidelines of the European Stroke Organization	NR	NR	PCI or CABG which initially was not planned after index angiography and study enrollment	NR
Madder, et al,[9] 2016	All-cause mortality Nonfatal ACS Acute cerebrovascular events	NR	MI or UA arising from a de novo culprit lesion and requiring revascularization	TIA or stroke	Universal definition	ACS presentations in the absence of cardiac biomarker elevations	NR	NR
Danek, et al,[10] 2017	NR	Cardiac death ACS Unplanned coronary revascularization Stroke after discharge from index hospitalization	Third Universal Definition of Myocardial Infarction	NR	Third Universal Definition	Third Universal Definition	PCI or CABG that was not planned after the index coronary angiography and NIRS imaging procedure	NR
Schuurman, et al,[11] 2017	NR	All-cause death Non-fatal ACS Unplanned coronary revascularization	Per guidelines of the European Society of Cardiology	NR	ESC Guidelines	ESC Guidelines	Any PCI or CABG that was not planned after the index angiography and enrollment in the study	Any death due to proximate cardiac cause, unwitnessed death or death of unknown cause
Karlsson, et al,[12] 2019	All-cause mortality Recurrent ACS requiring revascularization Cerebrovascular events	NR	Event requiring revascularization	TIA or stroke	NR	NR	NR	NR

LRP Study (Waksman, et al,[13] 2019)	NR	Nonculprit cardiac death, cardiac arrest, nonfatal MI, ACS, revascularization by CABG or PCI, and readmission to hospital for angina with more than 20% diameter stenosis progression	UA or MI requiring revascularization as defined in PROSPECT I[19]	2014 ACC/AHA Definition (TIA or Stroke)	2014 ACC/AHA and PROSPECT I[19] Definition	NR	All interventional cardiology methods for treatment of coronary artery disease and 2014 ACC/AHA Definition	2014 ACC/AHA Definition: Any death due to immediate cardiac cause (MI, low-output failure, fatal arrhythmia)
PROSPECT II (Erlinge, et al,[14] 2021)	NR	Cardiac death MI Unstable angina Progressive angina either requiring revascularization or with rapid lesion progression (defined in the appendix) arising from untreated, nonculprit lesions during follow-up	NR	Intracranial hemorrhage or nonhemorrhagic stroke that led to death	Third Universal Definition and SCAI criteria	Ischemic chest pain (or equivalent) at rest considered to be myocardial ischemia on final diagnosis and without elevation in cardiac biomarkers of necrosis	NR	The composite of sudden cardiac death, death due to acute myocardial infarction, death due to heart failure, death due to arrhythmia, or death not due to known vascular or non-CV causes

Abbreviations: NR, not reported.

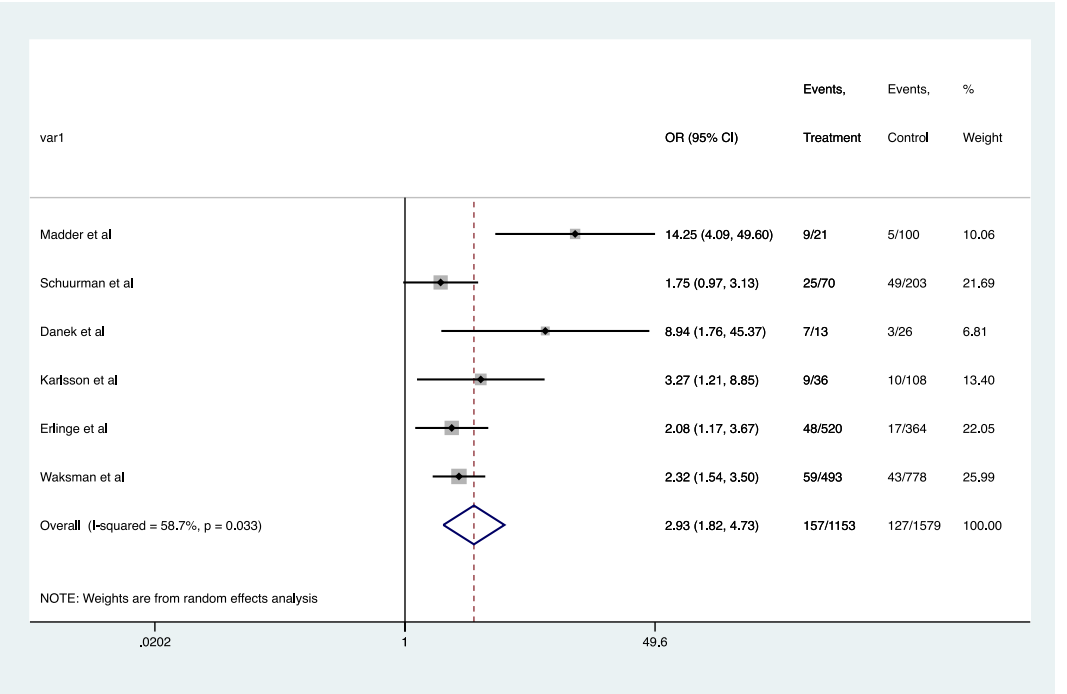

Fig. 2. Odds ratios and 95% confidence intervals for the occurrence of MACE/MACCE during follow-up after index presentation associated with all LCBI thresholds. The forest plot shows the results from the 6 included studies in the meta-analysis, listed by first author, along with the overall pooled summary estimate. The x-axis represents odds ratio values. The odds ratios and associated 95% confidence intervals are reported as a dot and line segment, respectively. The size of square data markers is proportional to the study weight in the meta-analysis. The summary measure point estimate and 95% confidence interval is represented as a diamond at the bottom of the plot. Number of events in the treatment group, defined as LCBI above threshold, and control group, defined as LCBI below threshold, used in the odds ratio calculations are provided on the right side of the table. All included study results suggest that LCBI values above the prespecified threshold was significantly associated with an increased odds of MACE/MACCE during follow-up. The thresholds used are as follows: $maxLCBI_{4mm} \geq 400$, $maxLCBI_{4mm} \geq 360$ (fourth quartile), LCBI $\geq$ 77 (determined using receiver-operator characteristic analysis), $maxLCBI_{4mm} \geq 400$, $maxLCBI_{4mm} \geq 324.7$, and $maxLCBI_{4mm} > 400$ for Madder, Schuurman, Danek, Karlsson, Erlinge, and Waksman and colleagues, respectively.

greater to LCBI of 400 or greater (specifically, $maxLCBI_{4mm}$). Overall, identification of vulnerable plaques with NIRS is associated with 2.93 times increased odds of MACE/MACCE (95% CI 1.82–4.73, I^2 = 58.7%) in the pooled meta-analysis. Waksman and colleagues was weighted the most at 25.99%. Erlinge and colleagues was weighted the second highest at 22.05%.

The secondary outcome is shown in Fig. 3, which provides a forest plot depicting pooled results from studies using a max 4 mm LCBI threshold at or around 400. Studies included for the secondary endpoint were Madder and colleagues, Schuurman and colleagues, Karlsson and colleagues, Erlinge and colleagues, and Waksman and colleagues. Madder and colleagues, Karlsson and colleagues, and Waksman and colleagues used 400 as the threshold $maxLCBI_{4mm}$. Schuurman and colleagues used $maxLCBI_{4mm}$ of 360 or greater and Erlinge and colleagues used $maxLCBI_{4mm}$ of 324.7 or greater as the primary analysis, both representing the upper quartile. The pooled odds ratio was 2.67 (95% CI 1.67–4.25, I^2 = 58.4%). Waksman and colleagues and Erlinge and colleagues again were weighted the most at 28.79% and 23.85%, respectively.

Risk of Bias Assessment

All included studies were considered at high overall risk of bias.

DISCUSSION

Meta-Analysis Findings

This quantitative analysis showed that the detection of large lipid-rich plaque by NIRS is a powerful tool to predict major adverse CV events in patients with coronary artery disease. The main

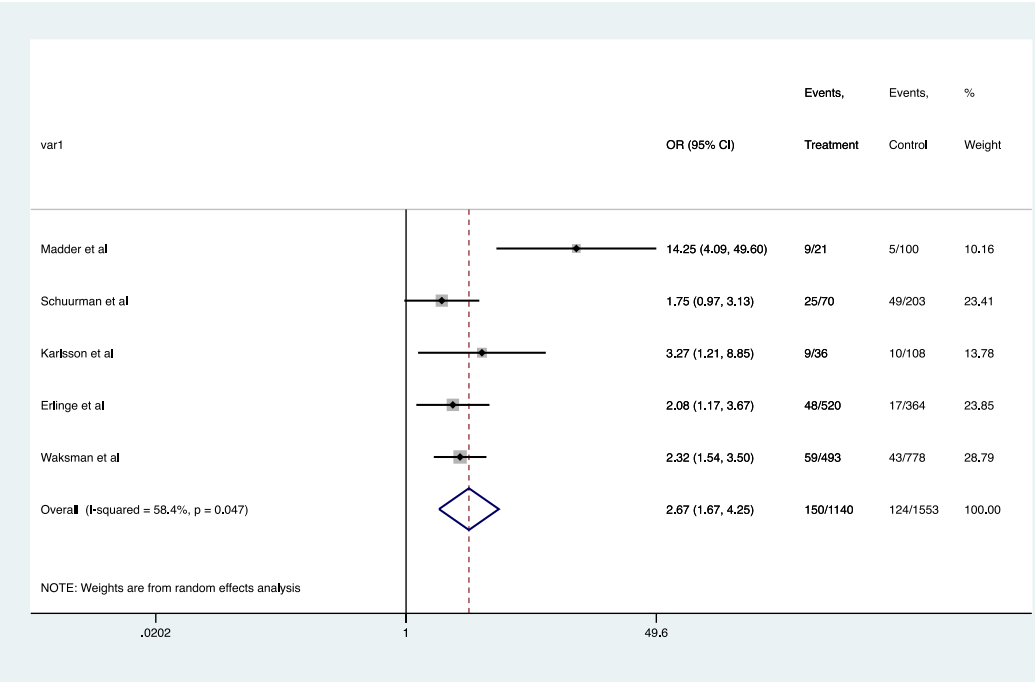

Fig. 3. Odds ratios and 95% confidence intervals for the occurrence of MACE/MACCE during follow-up after index presentation associated with $maxLCBI_{4mm}$ thresholds at or around 400. The forest plot shows the results from the 5 included studies in the meta-analysis, listed by first author, along with the overall pooled summary estimate. The x-axis represents odds ratio values. The odds ratios and associated 95% confidence intervals are reported as a dot and line segment, respectively. The size of square data markers is proportional to the study weight in the meta-analysis. The summary measure point estimate and 95% confidence interval is represented as a diamond at the bottom of the plot. Number of events in the treatment group, defined as $maxLCBI_{4mm}$ above threshold, and control group, defined as $maxLCBI_{4mm}$ below threshold, used in the odds ratio calculations are provided on the right side of the table. All included study results suggest that $maxLCBI_{4mm}$ values above the prespecified threshold was significantly associated with an increased odds of MACE/MACCE during follow-up. The thresholds used are as follows: $maxLCBI_{4mm} \geq 400$, $maxLCBI_{4mm} \geq 360$ (fourth quartile), $maxLCBI_{4mm} \geq 400$, $maxLCBI_{4mm} \geq 324.7$, and $maxLCBI_{4mm} > 400$ for Madder, Schuurman, Karlsson, Erlinge, and Waksman and colleagues, respectively.

contribution of this meta-analysis is the significantly improved precision of the pooled estimate odds ratio of 2.93 (95% CI 1.82–4.73) as seen in Fig. 2. The 95% CIs of the individual OR from each study were generally wider and more varied, with the narrowest interval of OR 1.54 to 3.50 in Waksman and colleagues and the widest interval of OR 1.76 to 45.37 in Danek and colleagues. The pooled estimate provides a narrow CI of OR 1.82 to 4.73. This more precise odds ratio with a narrow standard deviation of the relationship between lipid-rich plaques identified by NIRS and subsequent adverse events can be used in future studies to guide sample size calculations.

Furthermore, this meta-analysis confirms $maxLCBI_{4mm}$ of 400 or greater as an appropriate cutoff for identifying high-risk lipid rich plaques at the patient and individual plaque level. Similarly, it improves the precision of this cutoff in predicting adverse events. The narrowest 95% CI of the 4 included studies was Waksman and colleagues from 1.54 to 3.50 while the widest interval was Madder and colleagues from 4.09 to 49.60. The pooled estimate from the meta-analysis provided an OR of 2.67 with a 95% CI of 1.67 to 4.25. This suggests that this is a reasonable binary cutoff to use in future studies.

Literature Review

Relationship between increasing lipid core burden index and adverse events

NIRS is a catheter-based intracoronary imaging technique that uses diffuse reflectance spectroscopy to measure the chemical signature of cholesterol within the coronary vessel wall. The specific molecular features of cholesterol lie within the near-infrared light wavelength region and can

thus be distinguished from collagen to identify lipid-rich plaques from normal vessel or fibrotic and calcified plaques.[8] The technology has been previously validated to detect lipid-rich plaque.[6,15] The studies included in this meta-analysis evaluate the effectiveness of NIRS as a tool to identify plaques and/or patients likely to experience future adverse events. It is hypothesized that detecting at-risk patients and prospectively treating vulnerable plaques could prevent future coronary events.

The predictive ability of NIRS has evolved from identification of vulnerable patients based on global lipid burden to identification of individual vulnerable plaques with the potential for secondary intervention. The earliest studies explored the prognostic value of identifying vulnerable patients based on findings of lipid-rich plaques without addressing the potential for plaque-level prognostic identification. However, these studies were relatively small and used different LCBI thresholds. Oemrawsingh and colleagues with a sample size of 203 patients was the first to identify the long-term prognostic value of NIRS as assessed in nonculprit vessels using an LCBI threshold of 43.0, representing the median.[8] The study reported a 1-year cumulative incidence of MACCE to be 16.7% in patients with an LCBI of 43 or greater versus 4.0% in those with an LCBI less than the threshold.

Schuurman and colleagues expanded on the findings of Oemrawsingh and colleagues, increasing the sample size to 275 by adding the IBIS-3-NIRS cohort to the original ATHEROREMO-NIRS cohort and increasing follow-up from 1-year to 4-year. The authors reported a statistically significant and independent continuous relationship between higher $maxLCBI_{4mm}$ values and a higher risk of MACE in a nontarget vessel using hazard ratios (HR). Each additional 100 units of $maxLCBI_{4mm}$ value was associated with a 19% increase in MACE (HR 1.19, 95% CI 1.07–1.32). This is similar to the findings from later studies such as Waksman and colleagues, which reported that there is an 18% increase in risk at the patient level for each 100-unit increase in $maxLCBI_{4mm}$ (HR 1.18, 95% CI 1.05–1.32) using a much larger sample size of 1271.

Waksman and colleagues further determined that NIRS can predict adverse outcomes at the individual plaque level by testing the association between $maxLCBI_{4mm}$ in a Ware segment, as defined in the study protocol, and occurrence of MACE within that same segment during the 24-month follow-up period. Waksman and colleagues showed each additional 100 units of $maxLCBI_{4mm}$ value at the plaque level was associated with a 45% increase in MACE (unadjusted HR 1.45, 95% CI 1.3–1.60). Erlinge and colleagues similarly corroborated this relationship with a 4-year Kaplan-Meier estimated rate of events that showed an increase in nonculprit lesion-related MACE according to baseline $maxLCBI_{4mm}$ in increments of 100. Erlinge and colleagues showed a 3.7% increased site-specific risk of MACE during a 4-year period from index presentation in patients with $maxLCBI_{4mm}$ between 400 and 500, a 5.7% increase in patients with $maxLCBI_{4mm}$ between 500 and 600, and a 10.4% increased risk in patients with $maxLCBI_{4mm}$ more than 600. The ability to prospectively identify risk of particular lipid-rich plaques makes for more robust risk prediction. An example patient case emphasizing the role of NIRS in risk prediction, modified from Waksman and colleagues, is described in **Fig. 1**. Further research may explore opportunities for intervention and treatment at the plaque-level to prevent future coronary events.

Lipid core burden index as a marker for therapy efficacy and response to therapy

NIRS has also demonstrated an ability to assess plaque modification by new pharmacologic therapies. In the PACMAN-AMI randomized clinical trial recently published by Räber and colleagues,[16] NIRS-derived $maxLCBI_{4mm}$ was used to show the superiority of alirocumab in reducing lipid core burden when given in addition to high-intensity statin versus high-intensity statin therapy alone. Mean change in $maxLCBI_{4mm}$ was −79.42 with alirocumab plus rosuvastatin and −37.60 with rosuvastatin alone after 52 weeks of therapy in patients with acute myocardial infarction (difference, −41.24, $P = .006$).[16] Particularly when used in conjunction with other imaging modalities such as IVUS and optical coherence tomography, NIRS allowed for valuable plaque level characterization that can be used in future studies to help evaluate the efficacy of novel treatments that may minimize complications at follow-up. As options for secondary prevention become more robust and efficacious, NIRS will have increasing importance as a strategy for both identifying high-risk patients and quantifying their response to treatment.

Lipid core burden index best cutoff associated with cardiovascular events

There have been different values defining elevated LCBI. Oemrawsingh and colleagues defined values above that of the median (LCBI > 43 in their study) as an elevated LCBI, which is relatively

similar to the definition used by Danek and colleagues (LCBI $\geq$ 77). Madder and colleagues, Karlsson and colleagues, and Waksman and colleagues define elevated LCBI as a $maxLCBI_{4mm}$ greater than 400 with Schuurman and colleagues choosing a similar value of any LCBI at or above the fourth quartile ($maxLCBI_{4mm} \geq 360$). Erlinge and colleagues used the upper quartile $maxLCBI_{4mm}$ of 324.7 as the prespecified definition of lipid-rich plaque. Erlinge and colleagues furthermore explored a different definition to define vulnerable plaques as any plaque with $maxLCBI_{4mm}$ in the highest quartile plus plaque burden greater than 70% or small luminal area (defined as ≤ 4 mm^2). We recommend to always use the LCBI value as a marker of continuum risk and $maxLCBI_{4mm}$ greater than 400 to categorize patients/plaques as a high risk.

Limitations

There are several limitations that must be acknowledged: First, reliability and validity of the WebPlotDigitizer program has been questioned in prior studies at an aggregate level.[17] However, results in a 2016 study indicated high levels of intercoder reliability and validity.[18] To minimize this limitation, we relied on reported numbers for odds ratio calculations whenever possible. Second, the primary outcomes for each study include a range of LCBI value thresholds to determine the OR. We conducted the secondary analysis including studies with $maxLCBI_{4mm}$ thresholds around 400 to optimize the comparison. Although the NIRS binary cutoff of 400 $maxLCBI_{4mm}$ was confirmed as a reasonable predictor for subsequent events at the patient and plaque level in Waksman and colleagues, a definitive optimal threshold has yet to be determined. Third, the longest length of follow-up was a median of 5.3 years, with the majority of the identified studies with less than 4 years of follow-up. Many of the studies might have missed important LCBI-related adverse events due to short follow-up. More research is needed to determine the incidence of adverse events over time. Finally, we recognize that there exists a moderate level of heterogeneity between studies, as delineated with the I^2 statistical (58.7%).

SUMMARY

NIRS-derived LCBI is an effective measurement for identifying vulnerable patients and plaques at risk of future MACE/MACCE. Patients with an elevated LCBI have 2.93 times higher odds of enduring a future adverse event. The precision of the pooled OR provides a more precise estimate that can be used in future studies. A $maxLCBI_{4mm}$ of 400 or greater seems to be a useful threshold for classifying at-risk plaques.

CLINICS CARE POINTS

- NIRS can identify particular patients at risk for future MACE/MACCE and provide an opportunity for risk stratification.
- NIRS-derived $maxLCBI_{4mm} > 400$ can locate high-risk lipid-rich plaques and predict potential areas of future complication.
- NIRS has demonstrated an ability to assess plaque modification by new pharmacologic therapies and quantify patient responsiveness to treatment.

DISCLOSURE

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