

Association of CHA₂DS₂-VASc Score with No-Reflow Phenomenon after PCI: A Systematic Review and Meta-Analysis

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Abstract

Background: The no-reflow (NR) phenomenon is a serious complication of percutaneous coronary intervention (PCI), associated with poor clinical outcomes. The CHA₂DS₂-VASc score, originally developed to assess thromboembolic risk in atrial fibrillation, has shown potential in being associated with adverse cardiovascular events, but its predictive value for NR remains uncertain.

Objective: To evaluate the association between the CHA₂DS₂-VASc score and the occurrence of NR in patients undergoing PCI through a systematic review and meta-analysis.

Methods: A systematic review of the literature was performed across Cochrane, EMBASE, and PubMed databases to identify studies examining the relationship between the CHA₂DS₂-VASc score and the occurrence of NR following PCI. A random-effects meta-analysis was conducted, using odds ratios (ORs) and 95% confidence intervals (CIs) as the measures of effect size. Heterogeneity was calculated by using Cochran's Q test and Higgins' I² statistics.

Results: A total of 10 studies including 6,557 patients (1,068 NR cases and 5,489 non-NR cases) were analyzed. An elevated CHA₂DS₂-VASc score was strongly associated with a higher risk of NR occurrence after PCI (OR, 1.86; 95% CI, 1.51–2.29; $p < .00001$; $I^2 = 85\%$).

Conclusion: This meta-analysis supports that the CHA₂DS₂-VASc score may be a useful tool for identifying patients at increased risk of NR during PCI. Further prospective studies are required to validate these findings and optimize risk stratification approaches.

Keywords: Percutaneous Coronary Intervention; Meta-Analysis.

Introduction

After percutaneous coronary intervention (PCI), a critical issue known as the no-reflow (NR) phenomenon may occur, potentially resulting in severe complications such as increased hospital stay, myocardial infarction, and death.¹ Its multifactorial mechanisms include distal embolization, microvascular dysfunction, and reperfusion injury, highlighting the need for reliable predictors.²

The CHA₂DS₂-VASc score, originally designed to assess the likelihood of thromboembolic events in individuals with atrial fibrillation (AF), has been explored for its broader

cardiovascular predictive value.³ Given its components, hypertension, diabetes, and vascular disease, its potential association with NR in PCI patients is gaining attention.⁴

Studies on this association have yielded inconsistent results. This meta-analysis synthesizes available data to determine whether the CHA₂DS₂-VASc score is reliably associated with NR, potentially aiding risk stratification and clinical decision-making.

Methods

Search strategy

This meta-analysis was conducted in compliance with the PRISMA 2020 checklist for systematic reviews and meta-analyses, as well as the MOOSE guidelines for meta-analyses of observational studies.^{5,6} We registered our protocol in the International Prospective Register of Systematic Reviews (PROSPERO) database under the registration ID “CRD42025640659”. A systematic literature review was performed by screening the Cochrane, EMBASE, and PubMed

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Central Illustration: Association of CHA₂DS₂-VASc Score with No-Reflow Phenomenon after PCI: A Systematic Review and Meta-AnalysisABC Cardiol
Arquivos Brasileiros de Cardiologia**Question:** Can CHA₂DS₂-VASc score predict the no-reflow (NR) phenomenon following percutaneous coronary intervention (PCI)?**Answer:** The CHA₂DS₂-VASc score may be useful predictor of no-reflow in PCI patients. It could support risk stratification before intervention.**POOLED POPULATION**

- Patients undergoing PCI
- 6,557 total (1,068 NR cases, 5,489 non-NR cases)

METHODS

- **Design:** Systematic review & meta-analysis.
- **Databases:** PubMed, EMBASE, Cochrane
- **Studies included:** 10 observational studies
- **Outcome:** Odds ratio (OR) per 1-unit increase CHA₂DS₂-VASc

PRIMARY OUTCOME

- NR phenomenon
- **Higher CHA₂DS₂-VASc scores** were significantly associated with **increased NR risk**

LIMITATIONS

- Observational studies only
- Heterogeneity present (I² = 85%)
- Potential publication bias

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databases (Central Illustration). The reference lists of eligible studies and systematic reviews were reviewed to detect further relevant research. Detailed search strategies for each database are provided in the Supplemental Material. The database search was performed up to February 15, 2025.

Eligibility criteria, data extraction, and outcome of interest

For this meta-analysis, only studies that met the following eligibility criteria were included: (1) observational studies, either prospective or retrospective, that (2) compared patients with NR after PCI with those who did not develop NR, and (3) conducted multivariate regression analyses to determine if the CHA₂DS₂-VASc score is associated with NR. We excluded studies with overlapping patient populations, conference abstracts, case reports, or case series, and studies not published in English.

Three investigators independently conducted the data search, selected the studies, and extracted relevant data from the included studies. Conflicts were addressed through consensus among the authors, following a review of the full article and eligibility criteria in consultation with the senior author.

Quality assessment

The Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tool was employed to assess potential biases for observational studies.⁷ Two independent investigators

performed risk of bias assessment for the included studies. Conflicts were settled in consultation with the senior author.

Data analysis

We conducted the data analysis following the recommendations outlined by Cochrane.⁸ We analyzed binary endpoints utilizing the Mantel-Haenszel test with a random-effects model, reporting the odds ratio (OR) and 95% confidence interval (CI) as measures of effect size. All studies analyzed the CHA₂DS₂-VASc score as a continuous variable in the multivariate analysis, and ORs were extracted to reflect the change in outcomes per 1-unit increase in the CHA₂DS₂-VASc score (Central Illustration). Heterogeneity was calculated by using Cochrane's Q statistic and the I² statistic by Higgins and Thompson. P values below 0.10 and I² values exceeding 25% were deemed indicative of substantial heterogeneity. We performed sensitivity analyses using the "leave-one-out" approach. We assessed for publication bias using funnel plot analysis. Statistical analyses were conducted using R Software version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria) and Review Manager 5.4 (The Nordic Cochrane Centre, The Cochrane Collaboration, Denmark).

Results

As shown in Figure 1, our initial search identified 43 records. After the removal of duplicate reports, 29

studies were reviewed in full text. Ten studies met our inclusion criteria,⁹⁻¹⁸ comprising 6,557 patients, of whom 1,068 (16.3%) were in the NR group, and 5,489 (83.7%) were in the no-NR group, as summarized in the Central Illustration. All studies were within the last ten years. Seven studies included patients with acute ST-segment elevation myocardial infarction (STEMI),^{9,11-16} one study included patients with non-ST-segment elevation myocardial infarction (NSTEMI),¹⁷ and two studies focused on patients undergoing PCI of saphenous vein graft (SVG).^{10,18} Kanal et al. examined elective PCI cases for SVG,¹⁸ while Gurbak et al. investigated NSTEMI patients undergoing PCI for SVG.¹⁰ Additional details about the included studies are provided in Table 1.

A pooled analysis of 1,068 patients with NR and 5,489 without NR showed a significantly higher rate association of NR with higher CHA₂DS₂-VASC score in patients undergoing PCI (OR, 1.86; 95% CI, 1.51 to 2.29; $p < 0.00001$; $I^2 = 85\%$; Figure 2) (Central Illustration). We performed subgroup analysis for patients with acute STEMI, which also demonstrated a significantly higher rate association of NR with higher CHA₂DS₂-VASC score in patients undergoing PCI (OR, 1.82; 95% CI, 1.40 to 2.36; $p < 0.00001$; $I^2 = 89\%$; Figure 3). Three studies had a considerably higher effect size compared to the others, with ORs of 6.52, 6.32, and 3.06.^{12,13,17} Subgroup analysis, after removing those studies, also showed a significantly higher association of NR with a higher CHA₂DS₂-VASC score. (OR, 1.50; 95% CI, 1.34 to 1.67; $p < 0.00001$; $I^2 = 43\%$; Figure 4). A subgroup analysis was conducted following the exclusion of studies involving patients undergoing SVG PCI.^{10,18} This analysis continued to demonstrate a significant association between a higher CHA₂DS₂-VASC score and the occurrence of the NR phenomenon (OR, 2.02; 95% CI, 1.57 to 2.61; $p < 0.00001$; $I^2 = 65\%$; Figure 5).

The overall risk of bias in observational studies was classified as moderate (Table S4). The funnel plot analysis indicated the presence of a small-study effect due to publication bias, as studies with comparable weights were asymmetrically distributed relative to their standard errors, and outliers were observed in the funnel plot (Figure S1). In the leave-one-out analysis, the CHA₂DS₂-VASC score showed a consistent risk effect (Supplementary Figure S2).

Discussion

This meta-analysis, comprising 10 studies and 6,557 patients, compared those who developed NR following PCI to those who did not. The main finding from our pooled analyses was that a higher CHA₂DS₂-VASC score was associated with a significantly higher rate of NR development in patients undergoing PCI. This association was also observed in a subgroup analysis with only acute STEMI patients. Furthermore, even after excluding studies with larger effect sizes, the CHA₂DS₂-VASC score continued to be significantly associated with an increased probability of NR occurrence. As depicted in the Central Illustration, this consistent association reinforces the potential utility of the CHA₂DS₂-VASC score in PCI-related NR risk.

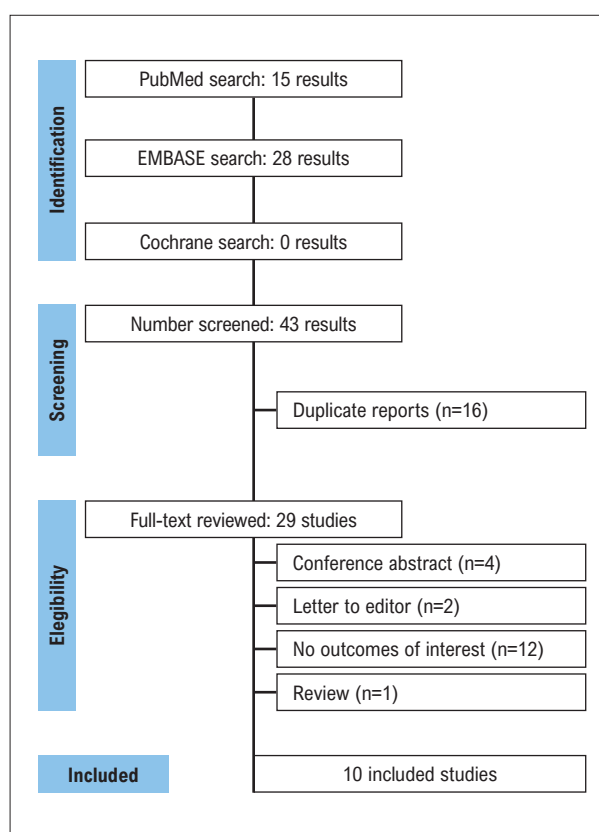


Figure 1 – PRISMA flow diagram of study screening and selection.

The CHA₂DS₂-VASC scoring system, widely utilized in contemporary clinical practice, serves as a simple yet clinically significant tool for assessing thromboembolic risk in patients with AF.³ This scoring system incorporates multiple clinical parameters, including congestive heart failure (HF), hypertension (HT), age, diabetes mellitus (DM), stroke, gender, and vascular disease, all of which are closely linked to the pathophysiological mechanisms underlying atherosclerosis. Consequently, recent research has explored the utility of the CHA₂DS₂-VASC score in risk stratification for various cardiovascular conditions and its role as a marker associated with adverse clinical outcomes, independent of AF.⁴ Several studies have revealed a significant association between the CHA₂DS₂-VASC score and cardiovascular prognosis in HF, Takotsubo syndrome, and acute coronary syndrome (ACS) patients.¹⁹⁻²²

NR development is multifactorial, with its exact etiology yet to be fully elucidated.² The pathophysiology of NR involves several factors, including distal plaque and thrombus embolization, reperfusion injury due to the reactive oxygen species, microvascular damage, myocardial necrosis, vasoconstriction resulting from elevated alpha-adrenergic activity, and activated tissue factor from disrupted plaque.²³⁻²⁵ The NR is associated with HF, myocardial necrosis, and poor cardiac prognosis, characterized by recurrent myocardial infarction, arrhythmias, and increased mortality, irrespective of infarct size.¹⁴ Therefore, it is crucial to identify risk factors for NR.

Table 1 – Baseline characteristics of included studies

Study	Population	No. of patients, NR/no NR	Female, % NR/no NR	Age ^a , y NR/no NR	DM, % NR/no NR	HTN, % NR/no NR	Previous MI, % NR/no NR	Previous CABG, % NR/no NR	HF, % NR/no NR	Stent length ^a mm NR/no NR	Stent diameter ^a , mm NR/no NR
Ashoori et al. 2019 ¹¹	acute STEMI	295/1036	57.3/9.4	71.1/56.1	NA	NA	NA	3.7/1.2	NA	28.1/27.5	2.8/3.0
Mirbolouk et al. 2018 ¹²	acute STEMI	102/294	37.2/22.4	63/57	51/18	72/31.3	43.1/8.8	2.3/1.7	22.5/1.3	26/27	2.95/3.0
Ippek et al. 2016 ⁹	acute STEMI	111/1670	27.9/18.4	62/57	43.2/32.3	47.7/34.7	15.3/12.0	6.3/2.0	25.2/8.4	24/20	2.75/3.0
Gürbük et al. 2020 ¹⁰	PCI of SVG ^b	78/190	25.6/15.8	66.2/62.6	53.8/38.4	84.6/76.3	61.5/45.3	100/100	55.1/17.9	26.6/23.5	3.44/3.2
Eldessouki et al. 2022 ¹³	acute STEMI	30/78	13.3/7.7	66.4/52.6	86.7/20.5	80/28.2	NA	NA	20/2.6	33.0/33.4	3.35/3.31
Avci et al. 2018 ¹⁴	acute STEMI	194/303	34/27	63.6/61.6	27/28	45/36	0/0	0/0	NA	NA	NA
Zorlu et al. 2020 ¹⁵	acute STEMI	75/1138	28/18.3	65/60	42.6/32	41.3/34.2	16.1/12.8	6.5/2.3	NA	26/22	2.75/3.0
Zhang et al. 2020 ¹⁶	acute STEMI	80/374	22.5/26.2	63.2/59.1	31.3/23.4	55.0/42.0	NA	NA	1.3/0.8	43.7/39.6	3.20/3.23
Barman et al. 2020 ¹⁷	NSTEMI	84/307	30/27	56.7/55.5	36/22	54/38	NA	NA	20/10	23.8/22.6	2.96/2.96
Kanal et al. 2023 ¹⁸	PCI of SVG ^c	19/99	15.7/27.2	56.7/55.5	36/22	68.4/65.6	NA	100/100	31.5/21.2	24.0/20.0	3.5/3.0

^a mean or median; ^b NSTEMI patients; ^c elective cases. CABG: coronary artery bypass graft; DM: diabetes mellitus; HF: heart failure; HTN: hypertension; MI: myocardial infarction; NA: not available; NR: no-reflow; NSTEMI: non-ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction; SVG: saphenous vein graft.

Original Article

All the studies we included similarly report that the CHA₂DS₂-VASC score may be a useful scoring tool for identifying patients at increased risk of the NR phenomenon in patients undergoing PCI, except for Kanak et al.¹⁸ They did not find any association between the CHA₂DS₂-VASC score and NR, likely due to a small sample size with lower

statistical power. Additionally, there was no independent predictor of NR, including stent length and diameter, after multivariate analysis, likely for the same reason.¹⁸ Otherwise, reduced left ventricular ejection fraction (LVEF), triple vessel disease, longer lesion length, lower stent diameter, reference luminal diameter with smaller size, lower thrombolysis in

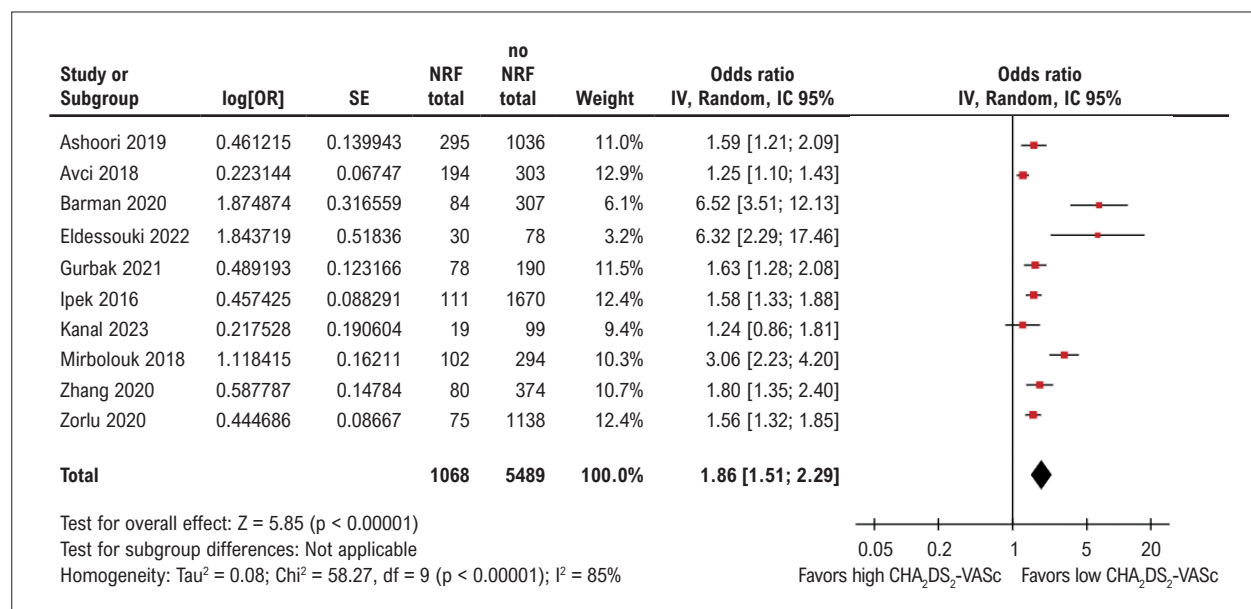


Figure 2 – A higher CHA₂DS₂-VASC score had a significantly higher rate association of no-reflow in patients undergoing percutaneous coronary intervention.

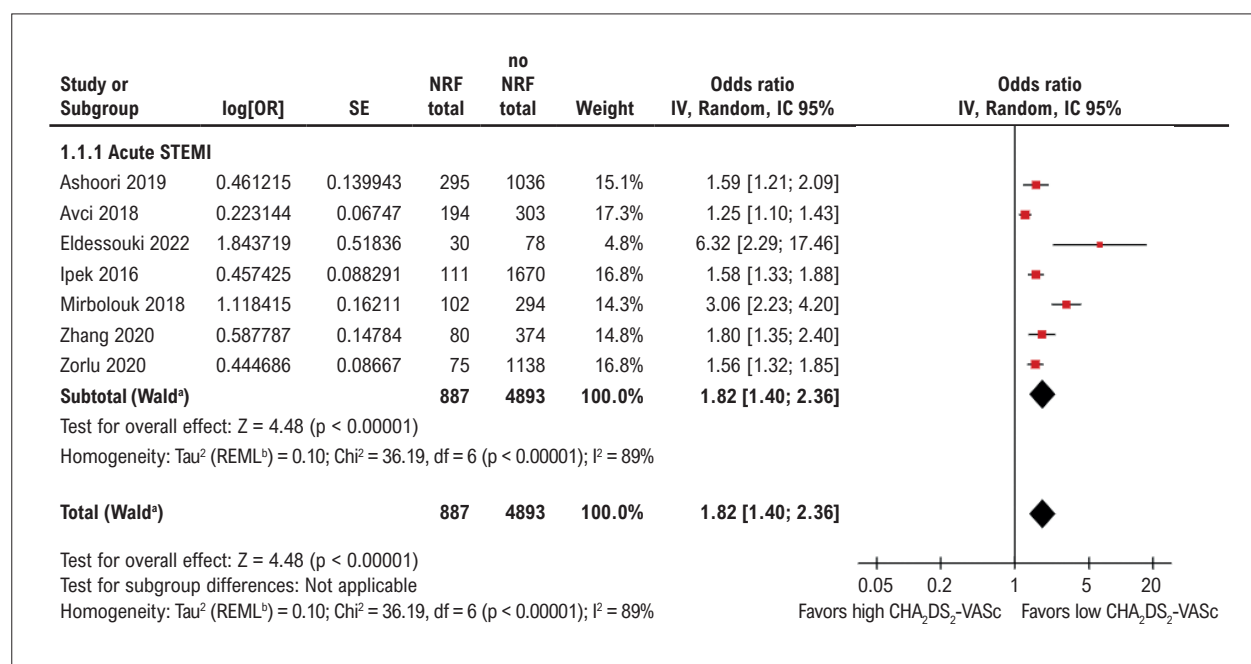


Figure 3 – Subgroup analysis of acute STEMI patients demonstrated a significantly higher rate of association of NR with higher CHA₂DS₂-VASC score in patients undergoing percutaneous coronary intervention. a: indicates the confidence interval (CI) calculated using the Wald-type method; b: indicates τ^2 calculated using the restricted maximum-likelihood (REML) method.

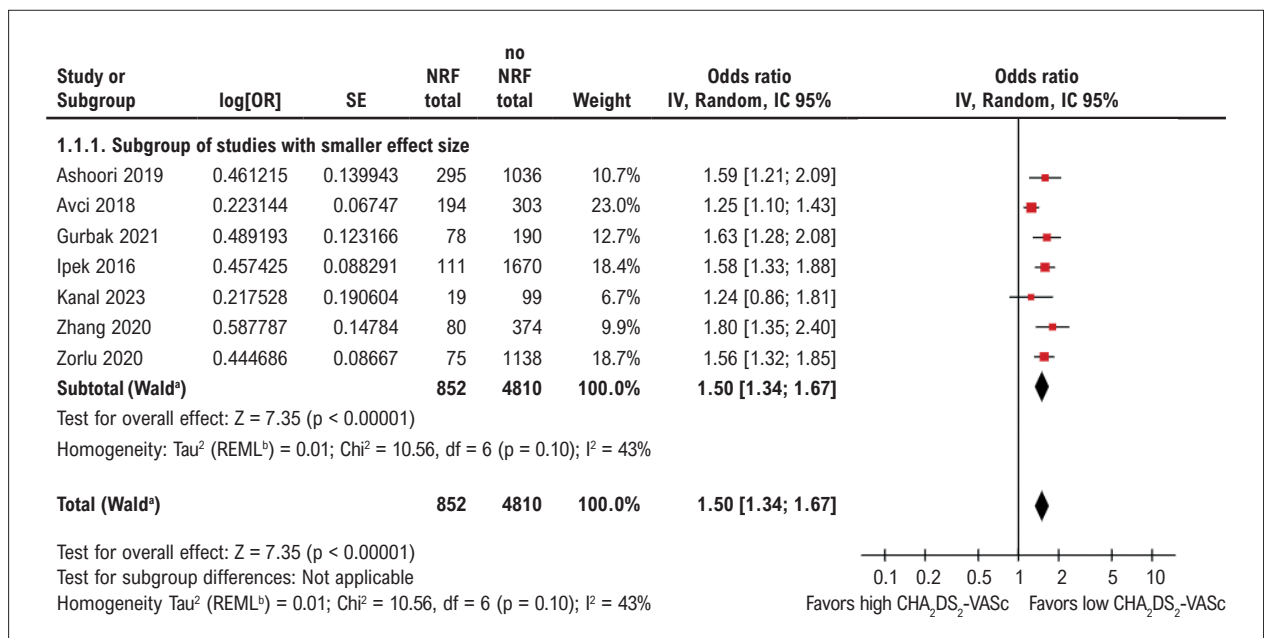


Figure 4 – Subgroup analysis, after excluding the studies with higher effect sizes, showed a significantly higher association of NR with a higher CHA₂DS₂-VASc score. a: shows the confidence interval CI calculated using the Wald-type method; b: indicates Tau² calculated using the restricted maximum-likelihood (REML) method.

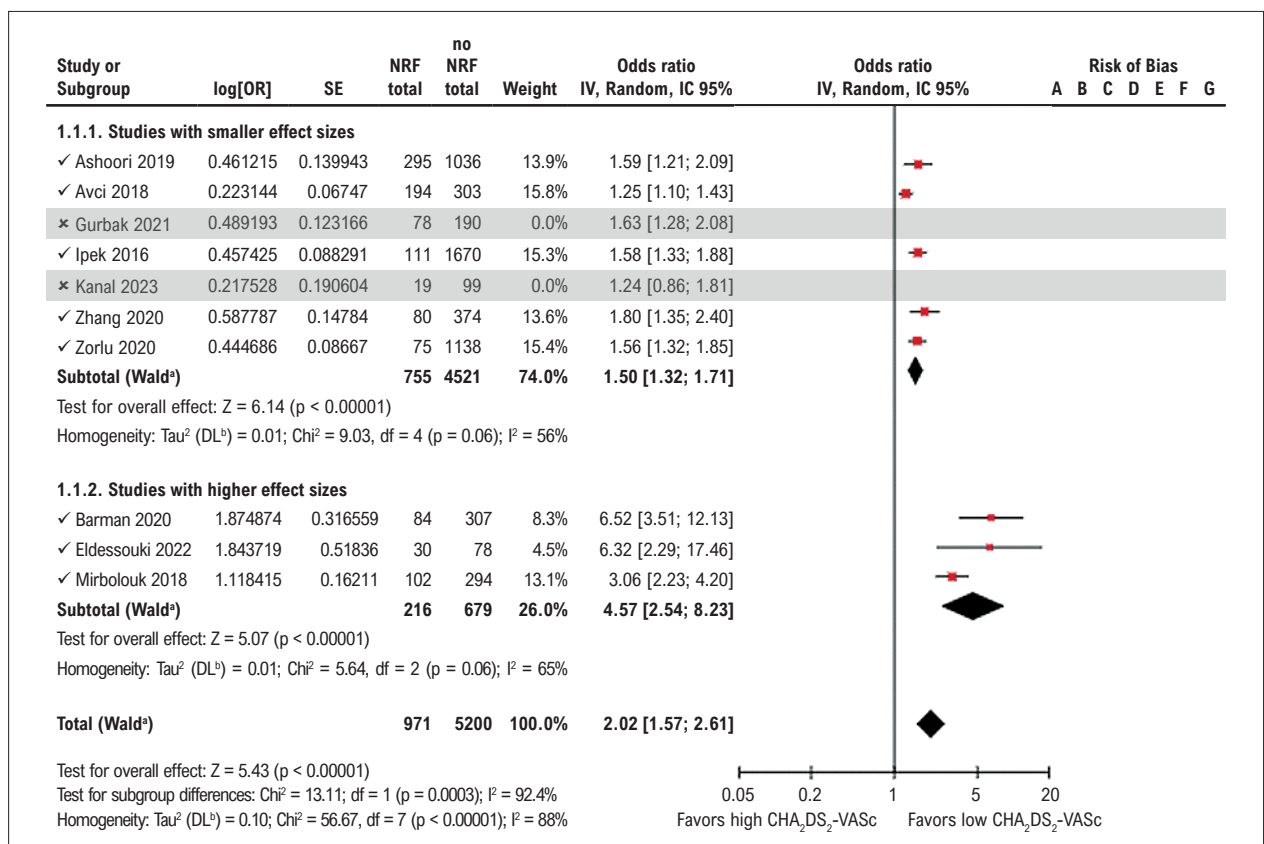


Figure 5 – Subgroup analysis, after excluding the studies including patients undergoing SVG PCI, showed a significantly higher association of NR with a higher CHA₂DS₂-VASc score. a: shows the confidence interval CI calculated using the Wald-type method; b: indicates Tau² calculated using the DerSimonian and Laird (DL) method.

myocardial infarction (TIMI) flow, and high thrombus burden on presentation have been demonstrated as predictors of NR in PCI patients.^{2,26-28} Ipek and Zorlu et al also found stent length and diameter as independent predictors of NR, as in the previous studies.^{9,15} Kanak et al. was the only study that excluded ACS patients.¹⁸

To assess the strength of our findings, a sensitivity analysis using the leave-one-out method was conducted. The results demonstrated that removing any of the studies did not significantly change the pooled OR, which consistently remained between 1.70 and 2.09, even when Barman et al study was omitted, the OR decreased to 1.70 [1.40, 2.07], and I² reduced to 78.8%. We also performed subgroup analysis for the studies that only included acute STEMI patients. However, the I² value for this subgroup remained high at 89%. Furthermore, to address the high heterogeneity in the pooled analysis, we performed a subgroup analysis after removing those studies by Barman, Eldessouki, and Mirbolouk et al., as they reported considerably higher ORs compared to the other studies.^{12,13,17} As a result, heterogeneity significantly dropped from 85% to 43%. One caveat about those studies is that they have a relatively smaller study population compared to the other included studies. In addition, Barman et al. did not include TIMI flow or reference luminal diameter in their multivariate analysis, which may have resulted in relatively higher ORs compared to other studies. Furthermore, Mirbolouk et al. did not include reference luminal diameter and stent length in their multivariate analysis, which may have also contributed to the relatively increased ORs. However, even after excluding those studies with higher effect sizes,^{12,13,17} a higher CHA₂DS₂-VAsC score remained associated with NR development.

To further enhance the robustness of our findings and minimize heterogeneity related to graft interventions, we conducted a subgroup analysis excluding studies that focused on patients undergoing SVG PCI.^{10,18} This exclusion was based on the fact that SVG lesions typically exhibit a greater atherosclerotic burden, friable plaque morphology, and an increased risk of distal embolization, all of which may independently predispose patients to the NR phenomenon.^{29,30} After excluding these studies, the association between a higher CHA₂DS₂-VAsC score and NR remained statistically significant, with an OR of 2.02 (95% CI, 1.57–2.61; *p* < 0.00001; I² = 65%). This finding reinforces the association of the CHA₂DS₂-VAsC score in native coronary artery PCI populations and suggests that its prognostic utility extends beyond specific procedural contexts.

Our meta-analysis revealed that a higher CHA₂DS₂-VAsC score was associated with an increased likelihood of NR development in patients following PCI. One potential explanation is the association of microvascular dysfunction with each component of the CHA₂DS₂-VAsC score. Microvascular dysfunction is also a key factor in the underlying mechanisms of the NR phenomenon. Thus, as components of the CHA₂DS₂-VAsC score, hypertension, diabetes mellitus, and female sex have been shown to be associated with impaired microcirculatory perfusion after PCI.^{23,31} In most studies, diabetes was found to be significantly more prevalent in the NR group.^{9,12,15,17,18}

Despite the various methodological approaches and the use of multivariate adjustments in the included studies, it is important to acknowledge that all were observational in nature. As such, these studies are inherently susceptible to residual and unmeasured confounding. Factors such as procedural technique, operator experience, use of adjunctive pharmacotherapies, and lesion or stent length were not uniformly reported or adjusted for across studies and may have influenced the observed associations. Moreover, the CHA₂DS₂-VAsC score incorporates multiple clinical components associated with adverse cardiovascular outcomes, which could introduce confounding. Therefore, the association between a higher CHA₂DS₂-VAsC score and the NR phenomenon should be interpreted with caution. Ultimately, prospective validation in well-designed, adequately powered studies is essential before considering the CHA₂DS₂-VAsC score for routine clinical use in risk stratification of PCI-related NR.

Conclusion

This meta-analysis found a strong relationship between higher CHA₂DS₂-VAsC scores and the risk of NR in patients undergoing PCI. Our results suggest that a higher CHA₂DS₂-VAsC score is associated with an increased likelihood of NR after PCI. Since NR has multiple causes and serious effects, the CHA₂DS₂-VAsC score could help identify high-risk patients. This is visually summarized in the Central Illustration. Additional research is necessary to validate these findings and evaluate their impact on clinical decision-making.

Limitations

Our meta-analysis has some limitations. First, all included studies were observational, which introduces the possibility of residual confounding despite multivariate adjustments. Second, significant heterogeneity was observed across studies, which may reflect variations in study populations. Third, funnel plot analysis suggested publication bias, indicating a potential small-study effect. Fourth, the included studies did not consistently adjust for all known predictors of NR, such as stent length, stent diameter, and thrombus burden, which could influence the observed association. Fifth, the retrospective nature of most included studies may introduce selection bias. Lastly, none of the studies included in this meta-analysis investigated the impact of the CHA₂DS₂-VAsC score on clinical outcomes such as mortality, heart failure, or long-term major adverse cardiovascular events, limiting the scope of our findings to the association with the NR phenomenon alone. Thus, large-scale prospective studies are required to corroborate our results and improve risk stratification models incorporating CHA₂DS₂-VAsC in PCI patients.

Author Contributions

Conception and design of the research: Ozbay MB, Nriagu BN, Ozen Y, Yayla C; Acquisition of data: Ozbay MB, Gullu A, Degirmen S; Analysis and interpretation of the data: Ozbay MB, Gullu A, Degirmen S, Nriagu BN; Statistical analysis: Ozbay MB, Degirmen S, Nriagu BN; Writing of the manuscript: Ozbay MB, Gullu A, Degirmen S, Ozen Y, Yayla C; Critical

revision of the manuscript for content: Ozbay MB, Gullu A, Ozen Y, Yayla C.

Potential conflict of interest

No potential conflict of interest relevant to this article was reported.

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Study association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Use of Artificial Intelligence

The authors did not use any artificial intelligence tools in the development of this work.

Data Availability Statement

The underlying content of the research text is contained within the manuscript.

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*Supplemental Materials

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