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The prognostic value of a new left bundle branch block in patients with acute myocardial infarction: A systematic review and meta-analysis

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ABSTRACT

Objective: To assess the prognostic value of new left bundle branch block (LBBB) in patients with acute myocardial infarction (AMI).
Background: LBBB develops in many cardiac conditions, including AMI. The empirical evidence for the contribution of LBBB to mortality in AMI is not consistent.
Methods: Medline, PubMed, CINAHL, and EMBASE were searched. Inverse variance meta-analysis was performed with odds ratios as the effect estimates. The I^2 statistic and risk of bias were assessed.
Results: Eight studies involving 105,861 participants were eligible. New LBBB was associated with higher mortality at 30 days (OR: 2.10, 95% CI 1.27 to 3.48) and 1-year follow up (OR: 2.81, 95% CI 1.64 to 4.80), and increased heart failure risk (OR: 2.64, 95% CI 1.84 to 3.77).
Conclusions: AMI patients with new LBBB are a high risk group and must be treated accordingly. Yet, more research is needed given the limitations of studies.

Introduction

Many studies have shown that patients with acute myocardial infarction (AMI) who present with bundle branch block (BBB) may have a worse prognosis than AMI patients who have normal conduction.[1–5] Yet investigators of these studies did not compare the effects of right versus left BBB. A recent systematic review[6] showed that patients with right BBB and AMI were at more than 2-fold higher risk of all-cause mortality at 30 days of follow up compared to those with no block. On the other hand, the literature on left bundle branch block (LBBB) is not consistent. Indeed, a number of investigators of cohort studies found that LBBB is associated with, and may be an independent predictor of higher mortality among patients with AMI.[7–14] However, other investigators did not find LBBB to be an independent predictor of mortality; they attributed the higher mortality in this population to other risk factors and co-morbidities.[15–18]

The American Heart Association (AHA) and European Society of Cardiology (ESC) in their guidelines consider AMI patients with new LBBB a high risk group and recommend for their treatment early reperfusion therapy with percutaneous coronary intervention (PCI) or fibrinolytic therapy.[22,23] Yet both organizations acknowledge that it is difficult to diagnose ST elevation MI in the setting of LBBB and ascertain whether the LBBB is old or new, considering that oftentimes no prior ECG is available for comparison.[19,20] Wong et al[21] found significantly higher mortality rates in AMI patients with definite new LBBB compared to those with no LBBB, but no difference when LBBB was present at baseline versus no LBBB; this suggests that the time of onset of LBBB is significant in estimating associated mortality. In light of the above, and in an attempt at quantifying the independent contribution of new LBBB to patient outcomes in AMI patients, we conducted a systematic review and

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meta-analysis in order to assess the prognostic value of new LBBB in patients hospitalized with AMI, in terms of risk for 30-day and one-year mortality, and risk of heart failure.

Methods

We published the protocol of this study in PROSPERO (Registration number: CRD42014015286). The eligibility criteria of the included studies were:

- Design: Observational studies, including cohort and case – control studies.
- Population: Patients with acute myocardial infarction.
- Exposure: New LBBB compared to no new LBBB.
- Outcomes: The primary outcomes were in-hospital mortality (or mortality within 30 days) and one-year mortality. Secondary outcomes were heart failure, atrio-ventricular block (AV block) that developed after LBBB, and placement of a pacemaker. We included studies that reported adjusted or unadjusted risk estimates.

This systematic review followed the PRISMA guidelines. We decided to exclude from the analysis studies conducted prior to 1980 because the introduction of revascularization therapy, which started in the 1980s, have led to significant reduction in mortality rates in AMI patients.[22] Only 2 studies conducted prior to 1980 fit our inclusion criteria.

The first author (B.A.) and a medical librarian searched PubMed, Medline, EMBASE, and CINAHL starting the date of their inception. The search terms for Medline were: myocardial infarction, bundle branch block, prognosis, survival analysis, and related synonyms. The full search strategy is provided in the online supplement. In addition, the references cited in the included studies were screened for relevance. No restrictions were made by language.

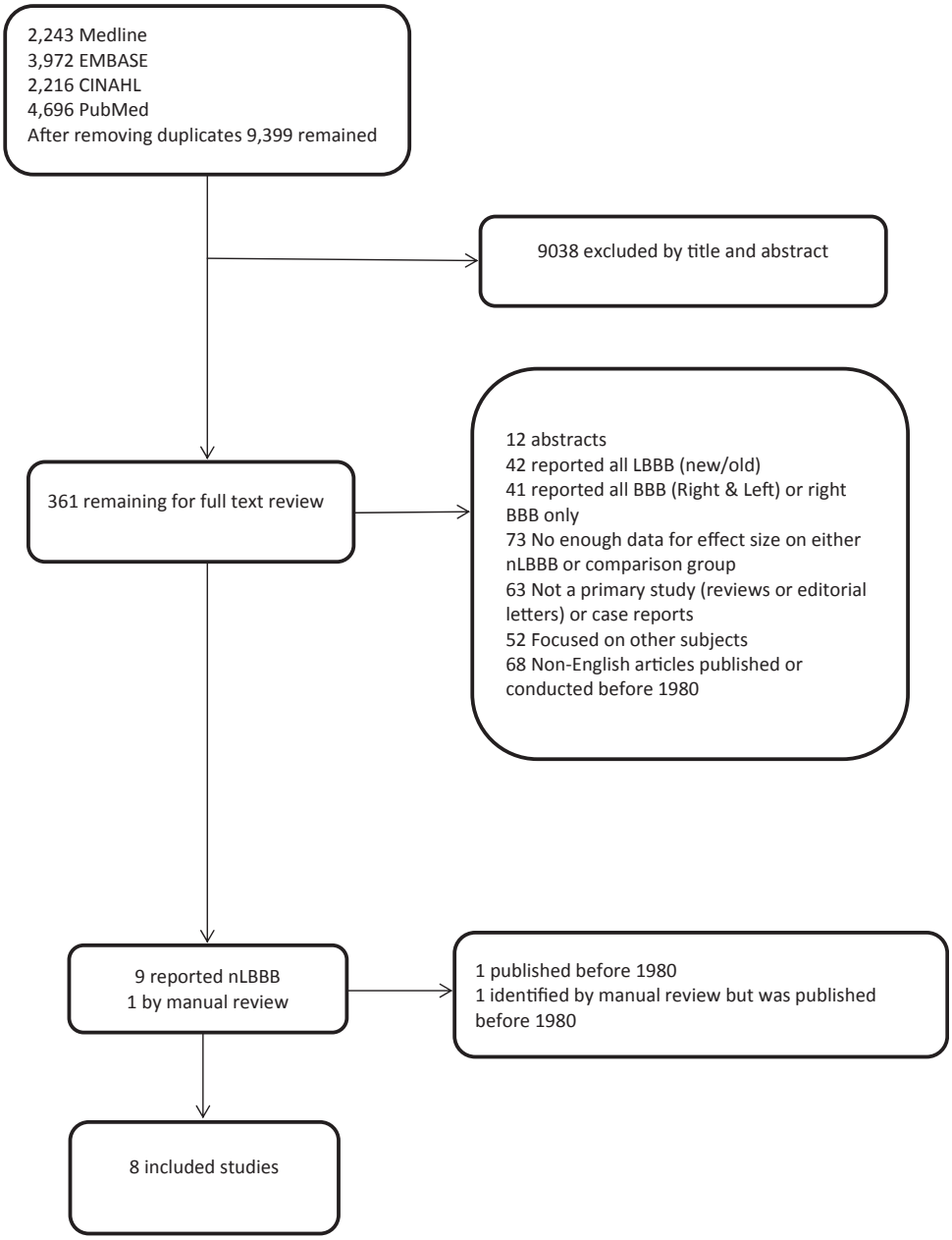

Fig. 1. Study flow.

Table 1
Characteristics of included studies.

First author	Study design/funding	Sample size	Patients	Exposure	Comparison	Outcome	Country
Miller et al.[29]	Cohort. Funding N.R.	907	Patients admitted to CCU with AMI	Patients with AMI and new LBBB	Patients with AMI and normal conduction	In-hospital mortality	USA
Widimsky et al.[28]	Cohort. Partially supported by the Charles University Prague research project.	6742	Consecutive patients with AMI who underwent coronary angiography	Patients with AMI and new LBBB	Patients with AMI and normal conduction.	In-hospital mortality	Czech Republic
Wong et al.[21]	Cohort. The author H.D.W. received partial support from the Green Lane Research and Educational Fund Board.	15,365	Secondary analysis of HERO- 2 trial data	Patients with AMI and new LBBB	Patients with AMI and normal conduction	In-hospital mortality	46 countries
Yeo et al.[18]	Cohort. Multiple funding sources for different authors.	46,006	Data from the ACTION-GWTG registry	Patients with AMI and new LBBB	Patients with STEMI without LBBB	In-hospital mortality HF	USA
Mijailovic et al.[26]	Cohort. Funding N.R	577	Consecutive patients admitted to CCU with AMI	Patients with AMI and new LBBB	Patients with AMI and normal conduction	In-hospital mortality	Serbia
Brown et al.[25]	Cohort. Funding N.R.	1445	Patients presenting for PPCI at one Tertiary referral center	Patients with AMI and new LBBB	Patients with STEMI without LBBB	One-year mortality	UK
Al-Faleh et al.[27]	Cohort. Funding N.R.	22,839	Data from 2 trials (ASSENT 2 and 3 trials)	Patients with AMI and new LBBB	Patients with AMI and normal conduction	In-hospital and one-year mortality, HF	29 countries
Juarez-Herrera et al.[30]	Cohort. Funding N.R.	4237	Data from registry of the Mexican Cardiology Society	Subgroup of patients with AMI and new LBBB	Patients with AMI and normal conduction	In-hospital mortality	Mexico
		Total: 105,861					

Legend: N.R.: Not reported. ACTION-GWTG: National Cardiovascular Data Registry Acute Coronary Treatment and Intervention Outcomes Network Registry—Get With the Guidelines; AMI: Acute Myocardial Infarction. CCU: Coronary Care Unit; LBBB: Left Bundle Branch Block. STEMI: ST Elevation Myocardial Infarction. HF: Heart Failure. UK: United Kingdom.

In the first round, we screened the titles and abstracts of all the citations identified in the search. The primary investigator screened all references, and five other team members screened the same references in duplicate and independently. We obtained the full text articles for the citations that were judged as potentially eligible by at least one reviewer. Then, we screened these full text articles for eligibility in duplicate and independently, using a standardized screening form. Results were compared and disagreements were resolved by discussion and in consultation with a senior author (E. A.).

Two of the authors (B. A. and S. N.) abstracted the data independently using a standardized form. Disagreements were resolved with the help of a third author (E. A.). For each study, the following data were extracted: surname of the first author, year of publication; study design, source of funding, country of origin, description of the sample, exposure group, comparison group, outcome measures and reported effect sizes. We extracted both adjusted and unadjusted estimates when available.

We also assessed the risk of bias in each study based on the appropriateness of the determination of inclusion and exclusion criteria, validity of the exposure measure, validity of the outcome measure, control for confounding variables and completeness of data using the GRADE guidelines.[23]

We present the effect sizes as odds ratios (OR) with corresponding confidence intervals (CI) because most of the included studies either reported effect sizes as odds ratios, or reported data from which it was possible to calculate OR and CI. We pooled the effect sizes across studies using an inverse variance meta-analysis and the random effect model. We generated for each outcome a forest plot to display the individual study OR and 95% CI, as well as

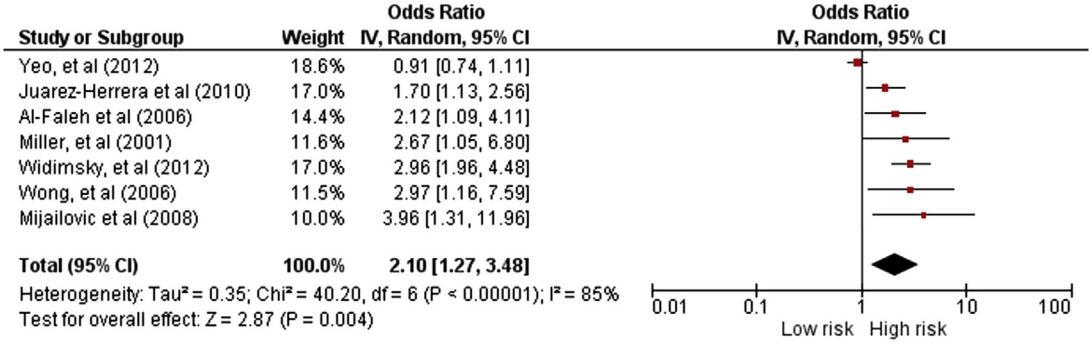

Fig. 2. Mortality at 30 days.

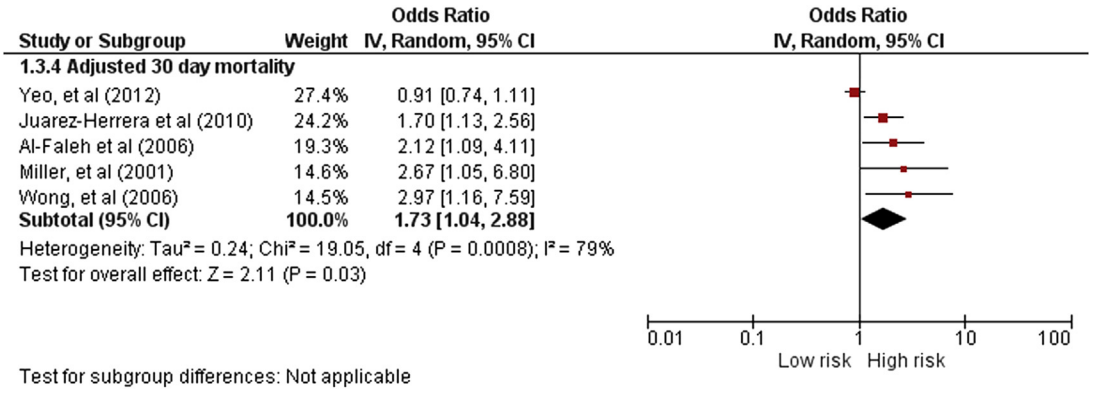

Fig. 3. Adjusted 30 days mortality.

the summary OR and 95% CI. In addition, we conducted a sensitivity meta-analysis for the 30-day mortality outcome restricted to studies that reported adjusted effect estimates.

Wong et al[21] presented effect size data for one group of 300 patients with LBBB at baseline that was classified as presumed new LBBB, and another group of 25 patients who developed LBBB within 60 min of receipt of therapy and were considered definite new LBBB. We used the effect estimate of the definite new LBBB[21] group for that study in the main analysis. We also did a sensitivity analysis using the effect estimate for the group with LBBB at baseline[21]; that summary effect size was not statistically significant (OR: 1.28; 95% CI: 0.84 to 1.97).

We assessed heterogeneity among the included studies using the I-squared statistic. We considered an I^2 value greater than 50% as indicative of substantial heterogeneity.[24] We conducted the analyses using RevMan Analyses version 5.3 (Nordic Cochrane Center, Ringshopitalet 2014).

Results

Fig. 1 shows the study flow, including the number of excluded studies and reasons for exclusion. Of the 9399 citations identified by the search strategy, 8 articles reporting observational cohort studies met the inclusion criteria.[18,21,25–30] One of the studies was published in the Serbian language, whereas the remaining ones were in English. Among the studies published before 1980 that were excluded, only 2 reported about new LBBB.

Table 1 summarizes the characteristics of the 8 included studies. The studies were conducted in the following countries: the USA ($n = 2$), Czech Republic ($n = 1$), Serbia ($n = 1$), the UK ($n = 1$), Mexico ($n = 1$), and in more than 1 country ($n = 2$). The sample size ranged from 577[31] to 46,006.[21] The total number of participants in all the studies combined was 105,861. All the studies used the cohort design, including 2 that used registry data, 2 that were secondary analyses of data from clinical trials registries, and 4 that included consecutive patients admitted to referral centers for angiography or to coronary care unit. Seven studies reported in-hospital mortality, 2 reported one-year mortality, and 2 reported on heart failure. None of the studies reported on the occurrence of AV block or placement of a pacemaker as outcomes.

The meta-analysis of all 7 studies that reported effect estimates (adjusted and unadjusted) on 30-day mortality found an OR of 2.10 (95% CI 1.27 to 3.48) for the association between new LBBB and all-cause mortality at 30 days of follow up (Fig. 2).

We performed sensitivity analysis by conducting a meta-analysis for the 5 studies that reported adjusted effect sizes; here also, new LBBB was significantly associated with increased risk of all-cause mortality within 30 days (OR: 1.73, 95% CI: 1.04 to 2.88), as shown in Fig. 3. The I^2 statistic showed substantial heterogeneity among the studies that reported 30-day mortality. The I^2 was 79% and 85% for studies that reported adjusted effect estimates and those that reported adjusted and unadjusted effect estimates, respectively.

The meta-analysis of the 2 studies that reported effect estimates on one-year mortality found an OR of 2.81 (95% CI: 1.64 to 4.80) for the association between new LBBB and all-cause mortality (Fig. 4). The test of heterogeneity showed no significant heterogeneity ($I^2 = 4\%$).

Only 2 studies reported data on heart failure (Fig. 5). The summary effect estimate derived from these 2 studies showed an increased risk of developing heart failure in patients who present with AMI and new LBBB (OR: 2.64; 95% CI: 1.84 to 3.77). There was a substantial heterogeneity between those two studies ($I^2 = 79\%$).

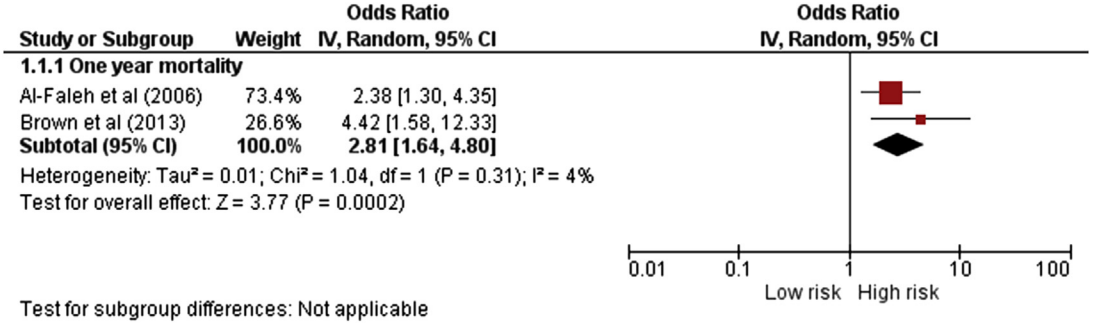

Fig. 4. One-year mortality.

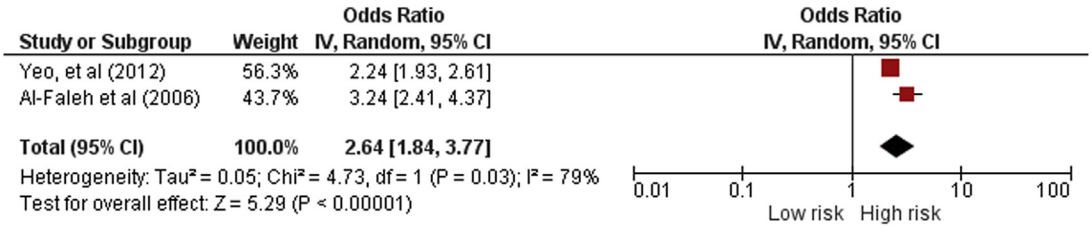

Fig. 5. Heart failure.

Two authors (B.A. and S.N.) assessed the risk of bias independently using the GRADE guidelines[23] and discrepancies were resolved by discussion. The results of the assessment of the risk of bias for each study and the overall risk of bias in all studies are shown in Figs. 6 and 7, respectively. The main biases were in the sample eligibility in half of the studies and the lack of adjustment for confounding variables in three studies. For example, Al-Faleh et al[27] included a select group of participants who were enrolled in 2 trials that tested different thrombolytic agents but the odds ratio calculated were adjusted for many confounders. On the other hand, Brown et al[25] included consecutive patients referred for primary PCI at a single tertiary referral center, but the authors failed to adjust for confounders. Moreover, the exposure measure was unclear in 2 studies.[18,26]

Discussion

In summary, we identified 8 studies with a total of 105,861 patients that evaluated the prognostic value of a new LBBB in patients with AMI. The results show that new LBBB is associated with increased risk of 30-day mortality, 1-year mortality and development of heart failure in patients with AMI.

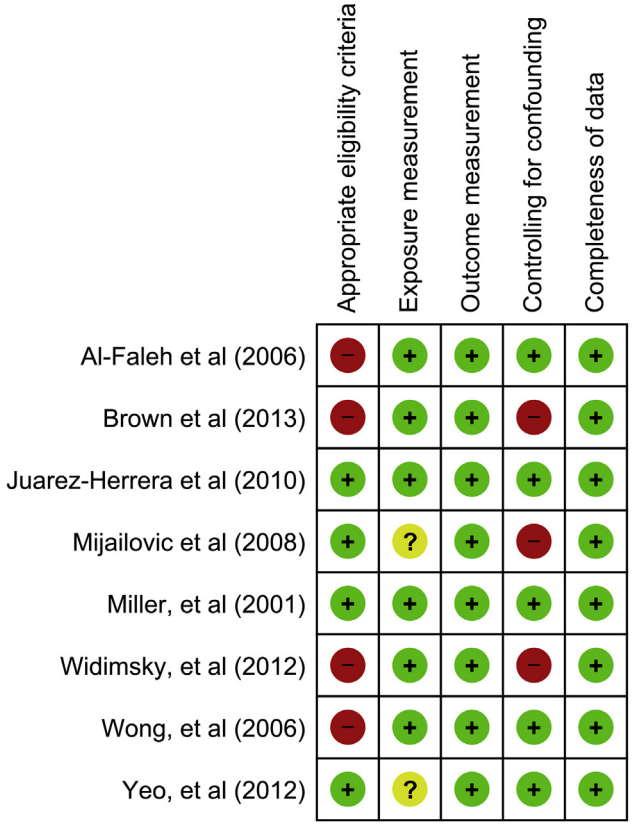

Fig. 6. Risk of bias of individual studies.

This study has a number of strengths. First, and to the best of our knowledge, this is the first meta-analysis of observational studies on the prognostic value of new LBBB in the context of AMI. Second, we followed a systematic methodology with a very comprehensive search, using duplicate study selection and data extraction, and a formal assessment of the risk of bias of all the included studies. Our findings reflect the gap of knowledge in this area, as only 8 studies were found.

The findings related to mortality suggest a higher risk in AMI patients with new LBBB, thus lending support to the continued application of the treatment guidelines for this population,[19,20] although these recommendations were based on earlier studies.[31] LBBB may progress to complete atrio-ventricular block, bradyarrhythmias, torsades de pointes and sudden cardiac death, which could explain the findings.[32] It is worth noting that heterogeneity for the studies that reported 30-day mortality was high, which can be the result of many factors. The included studies involved patients from different settings, including select groups of patients in two studies. In addition, variation in the treatment modalities may have a substantial impact on the outcomes. Some studies involved patients who underwent PCI whereas others had patients who received thrombolytic medications that included Streptokinase, Tenecteplase, and Alteplase. In some of the included studies the treatment used in those patients was not even described. Moreover, the time from the onset of symptoms to receipt of the treatment may have a substantial impact as well.[32]

In few cases, the determination or criteria for LBBB were not clearly described. Some authors reported using the criteria by Sgarbossa et al,[33] whereas others mentioned wide QRS and the shape of LBBB as diagnostic criteria. The Sgarbossa diagnostic criteria are limited by their lack of sensitivity.[34] Moreover, diagnosing AMI in the presence of LBBB is challenging because ST elevation may not be present. Still LBBB, in case of troponin elevation but no ST segment elevation, may represent a marker of illness severity and these patients must be considered for angiography and possible PCI. In case Troponin is negative, the ESC guidelines recommend repeating Troponin 1–2 h following symptom onset when BBB is of uncertain origin, in order to help decide whether or not to do coronary angiography and PCI.[19] In case the initial ECG is negative, it must be repeated or ST segmented monitored.[19]

Effect estimates of the risk of developing heart failure were provided in only 2 studies.[18,26] There was a statistically significant increase in the risk of heart failure in patients with new LBBB; however there was substantial heterogeneity between these studies (OR: 2.64 95% CI 1.84 to 3.77; $I^2 = 79\%$). Thus this summary effect should be interpreted with caution because the investigators of both studies did not report the criteria used to diagnose heart failure. In addition, they did not account for other risk factors that

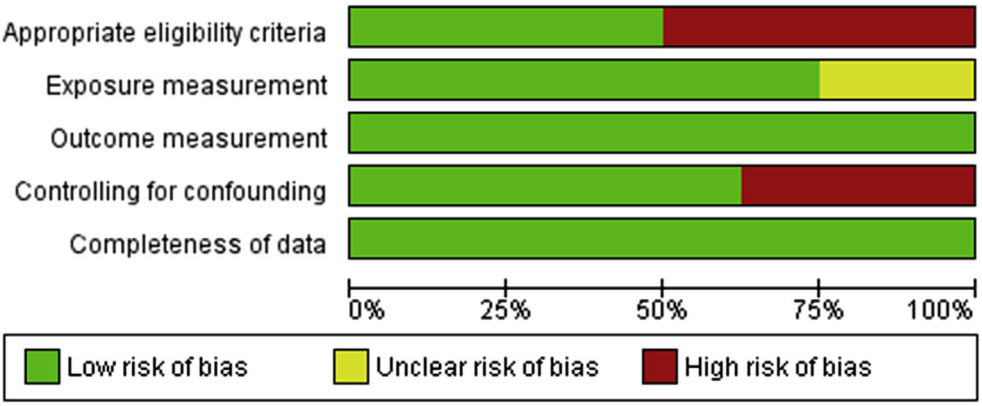

Fig. 7. Overall risk of bias.

may lead to the development of heart failure, such as congenital heart defects, infections, some diabetes medications and alcohol consumption.

Limitations

This analysis has a number of limitations. The number of studies[21,25–30] that met the inclusion criteria was small. In addition, the studies were heterogeneous in terms of the included participants and the treatments used, which could have influenced the outcomes. One important consideration in this area of study is the time of onset of LBBB, whether old or new, in relation to the AMI in order to isolate the prognostic impact of the LBBB. Unfortunately, the majority of the published studies on LBBB did not differentiate between old and new onset LBBB, which led to our small sample size. Another point worth considering is the definition of AMI, which has been modified since 1980, adding to the heterogeneity among studies. Moreover, a number of the included studies were prone to a high risk of bias, thus influencing the results. The relative prognostic value of new LBBB compared to old LBBB or RBBB, which could have enriched the findings, could not be addressed due to the lack of such data. Alternative outcomes such as cardiac mortality or major adverse cardiac events (MACE) were not measured in the reviewed studies; this gap can be addressed in future studies.

Future research in this area would benefit from rigorous studies with representative samples of patients with AMI and more consistent control over confounders. The variability in treatment modalities and time to treatment initiation must be accounted for in the study design and data analysis. Future research should also focus more on the actual onset of LBBB (old or new) and compare outcomes of AMI patients by time of onset of LBBB. Other complications that may follow this kind of conduction abnormality, such as AV block and heart failure must be studied as these have significant implications on the patients' quality of life and clinical outcome. Additional outcomes that investigators of the impact of new LBBB in patients with AMI ought to address include MACE and cardiac mortality.

In terms of clinical practice, one recommendation would be to monitor patients admitted with AMI for LBBB, as is done with ST segment monitoring, then report and document the onset of new LBBB in the medical record so that treatment is revised accordingly. Moreover, clinicians need to revisit the diagnostic criteria for LBBB in order to enhance its diagnostic accuracy and subsequent treatment adequacy of AMI patients.

In conclusion, although the findings of this meta-analysis support the current guidelines by the ACC/AHA and the ESC[19,20] in recommending treatment with early reperfusion therapy (PCI or thrombolytic therapy) of patients who present with new LBBB in the context of AMI, continued monitoring for new LBBB and future studies with stronger designs can substantiate the body of empirical evidence for the prognostic value of new onset LBBB.

Appendix. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.hrtlng.2016.11.002.

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