# Systematic Review and Meta-Analysis of Cardiovascular Consequences of Myocardial Bridging in Hypertrophic Cardiomyopathy

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**Myocardial bridging (MB) is a congenital variant in which a segment of a coronary artery follows an atypical intramural course under a "bridge" of myocardium and is notably common in hypertrophic cardiomyopathy (HCM). This systematic review and meta-analysis explored the clinical consequences of MB in patients with HCM. A total of 3 outcome domains were investigated: cardiovascular mortality, nonfatal adverse cardiac events, and investigative indicators of myocardial ischemia. A meta-analysis was performed on 10 observational studies comparing outcomes in patients with HCM with and without MB. Studies were identified through a systematic search of 4 databases (PubMed, Scopus, Medline Complete, and Web of Science). The quality of the studies was assessed using a modified version of the Downs and Black tool, from which studies could score a maximum of 23 points. The mean score was 17.5 ± 1.3 (good). The meta-analysis showed that MB was not associated with cardiovascular mortality (odds ratio [OR] 1.70, 95% confidence interval [CI] 0.56 to 5.15, p = 0.35) or nonfatal adverse cardiac events (OR 1.80, 95% CI 0.98 to 3.28, p = 0.06) but was associated with myocardial ischemia (OR 1.89, 95% CI 1.03 to 3.44, p = 0.04). In conclusion, the potential prognostic implications of MB in HCM, especially in those with hemodynamically significant bridges and/or severe underlying disease, should not be ignored. The focus of future studies should be to establish functional and morphologic thresholds, by which MB may adversely influence prognosis by corroborating imaging findings with clinical outcome data.**  **(Am J Cardiol 2023;188:110−119)**

Myocardial bridging (MB) is an anatomic variant in which a segment of a usually epicardial coronary artery follows a "tunneled" intramural path under a "bridge" of myocardium for a length of its course,[1] leaving it vulnerable to systolic compression with subsequent flow disturbance and possible myocardial ischemia. Although it has traditionally been thought to be largely benign among the general population, its potential for adverse outcomes is supported by observational studies and meta-analyses which demonstrate increases in the incidence of major adverse cardiac events, myocardial ischemia, myocardial infarction, and angina requiring hospitalization.[2,3] Hypertrophic cardiomyopathy (HCM) is a hereditary cardiac disease characterized by abnormal structural morphology, including left ventricular hypertrophy, which may adversely affect diastolic function, potentially leading to progressive heart failure.[4] MB holds particular significance in those with HCM because of its high prevalence in this group. A meta-analysis found a prevalence of 36.8% compared with a general pooled prevalence of 17.5%.[5] This gains increased significance in consideration of the fact that myocardial perfusion abnormalities are independently predictive of progressive heart failure and arrhythmias leading to cardiac death in HCM.[6] This systematic review and meta-analysis investigated the prognostic implications of MB in HCM through the combining of data from existing observational studies comparing outcomes in patients with HCM with versus without MB. Data were combined across studies on 3 outcome domains: cardiovascular mortality, nonfatal adverse cardiac events, and investigative indicators of myocardial ischemia.

## Methods

In identifying studies for inclusion in the review, a systematic search strategy involving abstract screening, followed by full-text screening was used within 4 databases: PubMed, Scopus, Medline Complete, and Web of Science. The search strategy including search terms, inclusion and exclusion criteria, and data extraction process have been explained in detail in Supplementary Methods.

All studies eligible after full-text screening underwent methodologic quality assessment using the Downs and Black tool.[7] This tool assessed the study methods across 5 areas: reporting, external validity, bias, confounding, and power. To adapt the tool to the studies in the review, modifications were made, which involved removing irrelevant questions or replacing them with questions that were more suitable to the design and objectives of the studies. The

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modified tool was a 22-item checklist from which studies could score a maximum of 23 points, as shown in Supplementary Table 1. A maximum of 2 points were available for 1 question relating to confounding. The confounding variables that were considered are shown in Supplementary Table 2 and included general cardiovascular risk factors, co-morbidities, and HCM-specific confounders. Studies were arranged into quality categories based on their checklist score as follows: excellent, good, moderate, poor. Any studies falling into the "poor" category would not be included in the qualitative or quantitative syntheses. Quality assessment was carried out by 2 independent reviewers (CB, NU). Discrepancies in scores were addressed through discussion, leading to a consensus.

Outcome measures were organized into 3 domains: cardiovascular mortality, nonfatal adverse cardiac events, and investigative indicators of myocardial ischemia. Cardiovascular mortality was defined as any death with a known cardiovascular cause or no known noncardiac cause. Nonfatal adverse cardiac events were defined as adverse events with a cardiac cause not resulting in death. Aborted sudden cardiac death and heart transplantation were included as cardiovascular mortality end points, with the expectation that the lack of intervention would have resulted in mortality. Investigative modalities in the investigative indicators of myocardial ischemia domain were chosen because they were widely represented in previous studies. Events classified into each of the domains are given in Table 1.

The pooled results for each of the 3 outcome domains were calculated as summary odds ratios (ORs) with their 95% confidence intervals (CIs) using random-effects models. The generic inverse variance method of meta-analysis was used for the investigative indicators of myocardial ischemia and nonfatal adverse cardiac events domains because this allowed entry of adjusted ORs that were presented in studies where regression analysis was carried out. The Mantel-Haenszel method was used for the cardiovascular mortality domain because this allowed calculation of ORs where the number of events falling into each of these domains in patients with and without MB was presented. Heterogeneity between studies was assessed quantitatively using the $I^2$ statistic. $I^2$ values of <50%, between 50% and 75%, and >75% were taken to represent low, moderate, and high degrees of heterogeneity, respectively. All statistical procedures were performed with Review Manager version 5.4 (The Cochrane Collaboration, Copenhagen, Denmark).

Table 1
Events falling under the 3 main outcome domains

| Cardiovascular mortality |
|---|
| • Sudden cardiac death – unexpected nocturnal death in a previously stable patient or unexpected death within 1 h of a witnessed collapse. |
| • Aborted sudden cardiac death – resuscitated cardiac arrest or appropriate termination of a lethal arrhythmia by ICD. |
| • Heart failure-related death – death in heart failure patients with progressively declining cardiac function for at least 1 y before death. |
| • Stroke-related death – stroke causing death. |
| • Fatal myocardial infarction – myocardial infarction causing death. |
| • Heart transplantation – patients undergoing heart transplant for progressive cardiac decompensation. |
| • Other death for which there is no known non-cardiac cause and a cardiac cause is suspected. |
| **Nonfatal adverse cardiac events** |
| • Heart failure progression – progressive heart failure requiring hospital admission, or progression of heart failure by at least 1 NYHA class. |
| • Nonfatal myocardial infarction – documented myocardial infarction without a fatal outcome. |
| • Nonfatal arrhythmia – recorded episodes of arrhythmia. |
| • Unexplained syncope – episodes of syncope with no explainable noncardiac cause. |
| • Angina requiring hospitalization. |
| • Nonfatal stroke or transient ischemic attack. |
| **Investigative indicators of myocardial ischemia** |
| • Abnormal thallium scintigraphy suggestive of ischemia. |
| • ECG signs suggestive of ischemia (ST-segment changes, flattened or inverted T-waves, pathological Q waves), which may be provoked through exercise stress testing. |

## Results

After a systematic search of the literature and application of inclusion and exclusion criteria, data from 10 observational studies were included in the review. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram is shown in Figure 1. In total, 7 cohort studies (4 prospective, 3 retrospective)[8–14] and 3 case-control studies[15–17] were included. A total of 1,504 patients with HCM were included, 353 with MB and 1,151 without MB. Participant numbers in the included studies ranged from 36 to 420 (mean 120, SD 86). A total of 2 studies investigated only pediatric populations,[10,11] whereas the remaining 8 studies investigated adult populations generally within the 40 to 60 years age range. In identifying MB, 2 studies used coronary computed tomography angiography (CCTA),[15,16] whereas the remaining 8 used conventional angiography (CAG). Zhai et al[14] only included patients with a relatively rare morphologic subtype of HCM, whereas Kitazume et al[8] and Nie et al[17] only included patients with obstructive HCM. The remainder of the studies did not specify any 1 form of HCM for inclusion. The details of the characteristics and findings for each of the studies, including the outcome domains they investigated, are seen in Table 2.

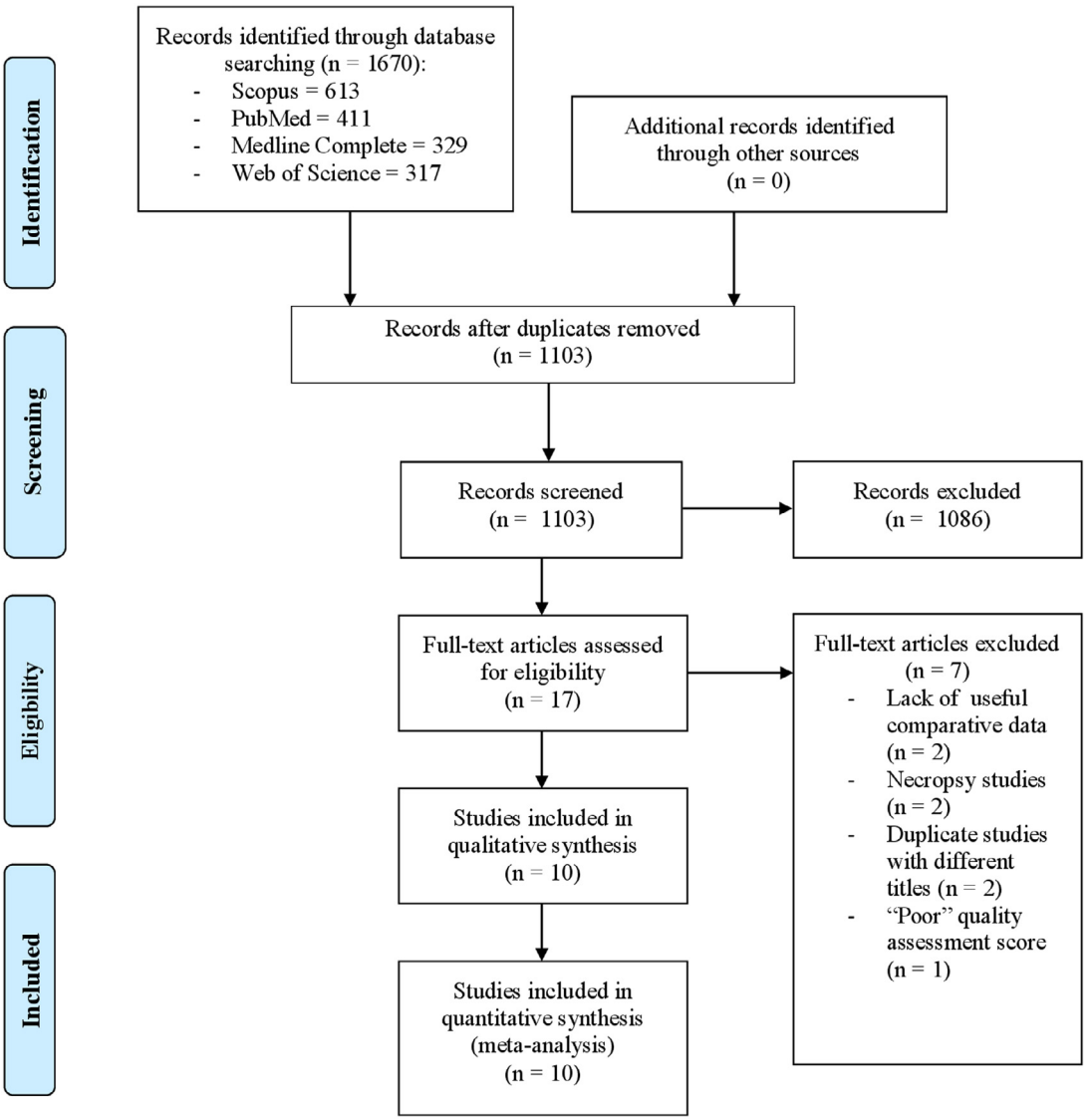


Figure 1. PRISMA flow chart summarizing the results of the literature search and screening process. After literature screening, 10 studies were appropriate for inclusion in the meta-analysis. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Differences in the definitions of MB existed across studies, as shown in Table 2. A total of 4 studies defined MB as transient systolic compression of an epicardial coronary artery by 50% of its diameter.[10–13] Nie et al[17] set this value at >30%, whereas Navarro-Lopez et al[9] set an even lower threshold for MB of 25% systolic compression. Kitazume et al[8] defined 2 groups for MB; 1 group with systolic compression of 25% and another group with systolic compression of 50%. Nassar et al[15] defined MB when an intramural segment was surrounded by at least 1 mm of myocardium, whereas the requirement in Van der Velde et al's study[16] was that the intramural segment had to be fully enveloped by myocardium, with no further requirements for length and depth. Zhai et al[14] defined MB crudely as "a segment of a coronary artery that courses through the myocardium."

Quality assessment scores for included studies ranged from 15 to 19 (mean 17.5, SD). In the highest scoring studies, confounding was minimized, clear functional thresholds for what constitutes MB were given, and blinding of at least 1 of either the outcome data collectors to bridging status or imaging reviewers to patient clinical histories was carried out. The quality assessment scoring for each study is shown in Supplementary Table 1.

The pooled analyses found no statistically significant associations between MB and cardiovascular mortality (OR 1.70, 95% CI 0.56 to 5.15, p = 0.35), as shown in Figure 2, or nonfatal adverse cardiac events (OR 1.80, 95% CI 0.98 to 3.28, p = 0.06), as shown in Figure 3. However, there was a statistically significant association between MB and myocardial ischemia (OR 1.89, 95% CI 1.03 to 3.44, p = 0.04), as shown in Figure 4. The domains of cardiovascular mortality, nonfatal adverse cardiac events, and myocardial ischemia were comprised of 8, 5, and 4 studies, respectively. There was moderate statistical heterogeneity between studies within the domains of cardiovascular

Table 2
Summary of the characteristics of the studies included in the review and the findings for each of the three domains

| Study | Study design and follow-up period | Imaging method | Patients excluded | Participant characteristics | MB definitions | CV mortality findings | Nonfatal ACE findings | Myocardial ischemia findings | Quality score |
|---|---|---|---|---|---|---|---|---|---|
| Kitazume (1983) | Prospective cohort<br>Follow-up: 5.7 years (median) for MB, 4.2 years (median) for no MB. | CAG | Co-existing coronary artery disease, aortic valvular disease, or open-heart surgery with myectomy, valve replacement or bypass grafting. | 20 patients with MB (30.3%), 46 patients without MB (69.7%).<br>Mean participant age: 48.8 ± 22.8 | Group I (46 patients): No bridging<br>Group II (10 patients): Systolic compression of left anterior descending artery < 50%<br>Group III (10 patients): Systolic compression of left anterior descending artery ≥ 50% | 0 events in MB group<br>3 sudden cardiac deaths in non-MB group.<br>($p = 0.07$). | - | - | 16 (good) |

| Study | Study design and follow-up period | Imaging method | Patients excluded | Participant characteristics | MB Definitions | CV mortality findings | Nonfatal ACE findings | Myocardial ischemia findings | Quality score |
|---|---|---|---|---|---|---|---|---|---|
| Navarro-Lopez (1986) | Retrospective cohort<br>Follow-up of 5 patients with severe systolic compression for evaluation of mortality but not the remainder. | CAG | Patients with significant atherosclerotic coronary artery disease (greater than 50% stenosis) (n = 3) excluded from analysis. | 12 patients with MB (23.5%), 39 patients without MB (76.5%).<br>Mean participant age: 50 ± 10 years. | Systolic transient compression of left anterior descending artery ≥ 25% | - | - | Exercise-induced myocardial ischemia on thallium scintigraphy in 6/9 MB patients and 2/31 non-MB patients with relevant recorded data.<br>**($p < 0.05$)** | 15 (moderate) |

| Study | Study design and follow-up period | Imaging method | Patients excluded | Participant characteristics | MB definitions | CV mortality findings | Nonfatal ACE findings | Myocardial ischemia findings | Quality score |
|---|---|---|---|---|---|---|---|---|---|
| Yetman (1998) | Retrospective cohort<br>Follow-up: 7.1 ± 5.4 years | CAG | - | 10 patients with MB (27.8%), 26 patients without MB (72.2%).<br>Mean participant age: 7.1 ± 5.8 years. | Systolic compression of left anterior descending artery ≥ 50% | 7 events in MB group (sudden cardiac death [n=3], aborted cardiac arrest [n=4])<br>2 events (sudden cardiac death [n=2]) in group without MB<br>**($p = 0.004$)** | - | ST-segment changes suggestive of myocardial ischemia in 7/10 MB and 9/26 non-MB patients with relevant recorded data<br>($p = 0.08$). | 18 (good) |

| Study | Study design and follow-up period | Imaging method | Patients excluded | Participant characteristics | MB definitions | CV mortality findings | Nonfatal ACE findings | Myocardial ischemia findings | Quality score |
|---|---|---|---|---|---|---|---|---|---|
| Mohiddin (2000) | Retrospective cohort<br>Follow-up: 8 ± 6 years. | CAG | - | 23 patients with MB (40.4%), 34 patients without MB (59.6%).<br>Mean participant age: 10 ± 6 years. | All coronary segments showing evidence of bridging were assessed. MB defined as maximum systolic compression ≥ 50% | Cardiovascular mortality events (sudden death [n=2], cardiac arrest [n=4], heart transplant [n=2]) occurred in 3 patients with MB and 5 patients without MB<br>($p = 0.9$). | - | Abnormal thallium scintigraphy in 17/18 MB patients and 14/30 non-MB patients with relevant recorded data.<br>(Adjusted $p = 0.14$). | 17 (good) |

| Study | Study design and follow-up period | Imaging method | Patients excluded | Participant characteristics | MB definitions | CV mortality findings | Nonfatal ACE findings | Myocardial ischemia findings | Quality score |
|---|---|---|---|---|---|---|---|---|---|
| Sorajja (2003) | Prospective cohort<br>Follow-up: 6.8 ± 5.4 years. | CAG | Patients who had previous MB resection or concomitant coronary artery disease (n = 98) excluded from survival analysis. | 54 patients with MB (16.5%), 274 patients without MB (83.5%).<br>Mean participant age: 60 ± 15 years | Change in luminal compression of an epicardial coronary artery ≥ 50% during systole | 4 events (2 sudden cardiac death [n=2], heart failure death [n=2]) in MB group<br>34 events (sudden cardiac death [n=10], heart failure death [n=14], myocardial infarction [n=3], heart transplant [n=1], cardiac arrest [n=1]) in non-MB group.<br>($p = 0.78$) | - | - | 19 (good) |

| Study | Study design and follow-up period | Imaging method | Patients excluded | Participant characteristics | MB definitions | CV mortality findings | Nonfatal ACE findings | Myocardial ischemia findings | Quality score |
|---|---|---|---|---|---|---|---|---|---|
| Tian (2014) | Prospective cohort<br>Follow-up: 4.2 ± 2.3 years. | CAG | Patients with concomitant coronary artery disease (n=88) excluded from survival analysis. | 32 patients with MB (15.2%), 178 patients without MB (84.8%).<br>Mean participant age: 53 ± 12 years. | Maximal systole compression of an epicardial coronary artery ≥ 50% | 1 event in MB group (sudden cardiac death [n=1])<br>8 events in non-MB group (sudden cardiac death [n=2], heart failure death [n=4], stroke-death [n=2]),<br>($p = 0.60$) | Deterioration of heart failure in 4/28 patients with MB and in 21/158 without MB<br>($p = 0.84$)<br>(Excludes severe pre-existing heart failure) | ST depression suggestive of myocardial ischemia in 192/264 non-MB patients and 26/34 MB patients with relevant recorded data<br>($p = 0.64$). | 18 (good) |

(*continued on next page*)

Table 2 (***Continued***)

| Study | Study design and follow-up period | Imaging method | Patients excluded | Participant characteristics | MB definitions | CV mortality findings | Nonfatal ACE findings | Myocardial ischemia findings | Quality score |
|---|---|---|---|---|---|---|---|---|---|
| Zhai (2018) | Prospective cohort<br>Follow-up: 5.5 ± 4.2 years. | CAG | Patients with obstruction or coronary artery disease (n = 52) excluded from survival analysis. | 60 patients with MB (37.5%), 100 patients with MB (62.5%).<br>Mean participant age: 52 ± 10 years. | Segment of a coronary artery that courses through the myocardium | 2 events in MB group (aborted cardiac arrest [n=2]),<br>1 event in non-MB group (aborted cardiac arrest [n=1])<br>($p = 0.29$) | 23 events in MB group (unexplained syncope [n=5], non-sustained ventricular tachycardia [n=2], atrial fibrillation [n=6] progressive heart failure [n=6] stroke [n=4])<br>12 events in non-MB group (unexplained syncope [n=1], non-sustained ventricular tachycardia [n=1], atrial fibrillation [n=9], progressive heart failure [n=1])<br>**($p = 0.009$)** | - | 18 (good) |
| Study | Study design and follow-up period | Imaging method | Patients excluded | Participant characteristics | MB definitions | CV mortality findings | Nonfatal ACE findings | Myocardial ischemia findings | Quality score |
| Nassar (2019) | Case-control with a follow-up arm for HCM patients<br>Follow-up: 5.5 ± 3.5 years. | CCTA | History of coronary artery disease or a finding of obstructive coronary disease on coronary CT angiogram. | 57 patients with MB (62.0%), 35 patients without MB (38.0%).<br>Mean participant age: 57.0 ± 12.6 years. | Any epicardial coronary artery segment that runs intramurally, surrounded by ≥ 1mm myocardium | No deaths in MB or non-MB groups. | 17 events in MB group (angina requiring hospitalization [n=16], myocardial infarction [n=1]<br>11 events in non-MB group (angina requiring hospitalization [n=8], myocardial infarction [n=3])<br>($p = 0.89$). | - | 19 (good) |
| Study | Study design and follow-up period | Imaging method | Patients excluded | Participant characteristics | MB definitions | CV mortality findings | Nonfatal ACE findings | Myocardial ischemia findings | Quality score |
| Van der Velde (2020) | Case-control but with a follow-up arm for HCM patients<br>Follow-up: 3.7 years (1.8-6.1 years range). | CCTA | Patients with HCM caused by Anderson-Fabry disease, Danon disease, Noonan syndrome, amyloidosis, or other metabolic, mitochondrial or malformation disorders. | 42 patients with MB (50.0%), 42 patients without MB (50.0%).<br>Mean participant age: 54 ± 11 years. | A segmental intramyocardial course of any epicardial coronary artery, only when fully enveloped by the myocardium without further requirements for length and depth. | 7 events in MB group (Aborted sudden cardiac death [n=2], heart transplant [n=3], unspecified CV mortality [n=2])<br>2 events in non-MB group (heart transplant [n=1], unspecified CV mortality [n=1])<br>($p = 0.08$) | 11 events in MB group (heart failure [n=11])<br>9 events in non-MB group (heart failure [n=9])<br>($p = 0.61$). | - | 16 (good) |
| Study | Study design and follow-up period | Imaging method | Patients excluded | Participant characteristics | MB definitions | CV mortality findings | Nonfatal ACE findings | Myocardial ischemia findings | Quality score |
| Nie (2021) | Case-control<br>No follow-up period due to case-control design | CAG | Patients with coronary artery disease, who had undergone heart surgery or who had no angiography records. | 43 patients with MB (10.2%), 377 patients without MB (89.8%).<br>Mean participant age 50.7± 11.3 with AF and 50.4±11.2 without AF | Reduction of >30% in the diameter of the mural artery during systole without any significant atherosclerosis | - | 20/105 patients with AF had MB, 23/315 patients without AF had MB<br>($p = 0.001$) | - | 17 (good) |

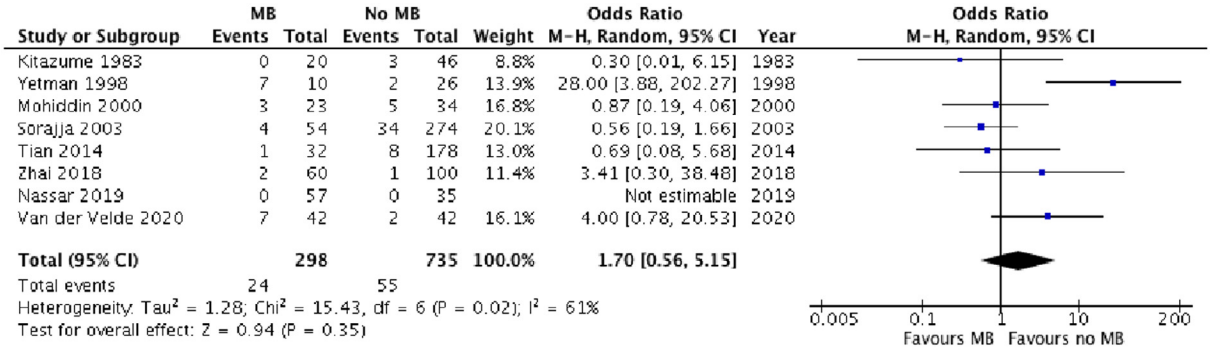


Figure 2. Forest plot showing the pooled effect of all studies investigating cardiovascular mortality. The meta-analysis found no statistically significant association (p = 0.35) between presence of MB and cardiovascular mortality. M-H = Mantel-Haenszel.

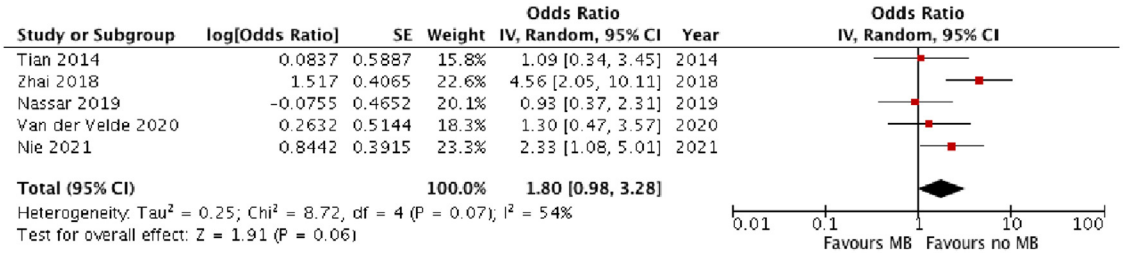


Figure 3. Forest plot showing the pooled effect of all studies investigating nonfatal adverse cardiac events. The meta-analysis found no statistically significant association (p = 0.07) between presence of MB and nonfatal adverse cardiac events. IV = inverse variance.

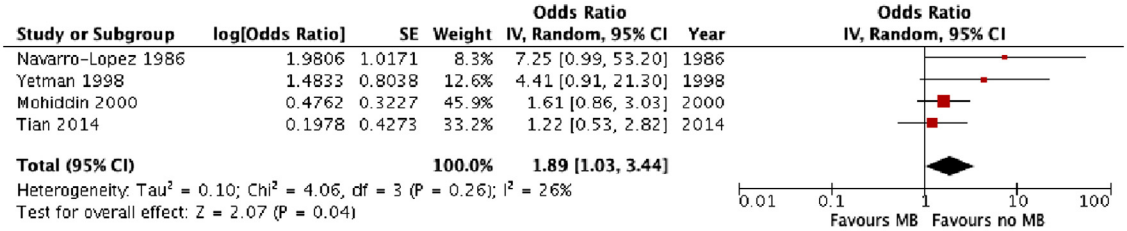


Figure 4. Forest plot showing the pooled effect of all studies presenting data on investigative indicators of myocardial ischemia. The meta-analysis detected a statistically significant association between MB and myocardial ischemia (p = 0.04). IV = inverse variance.

mortality ($I^2$ = 61%) and nonfatal adverse cardiac events ($I^2$ = 54%), whereas low heterogeneity was found for investigative indicators of myocardial ischemia ($I^2$ = 26%). The funnel plots for each of the 3 domains were visually symmetrical, indicating low probabilities of publication bias. These can be viewed in the Supplementary Figures 1 to 3.

For investigating the differences between adult and pediatric populations, subgroup analyses were completed for the domains of cardiovascular mortality and myocardial ischemia because these domains were investigated in both pediatric and adult studies. For investigating the possible differences in the effects between studies using different imaging techniques (CCTA and CAG), a subgroup analysis was completed for the domain of nonfatal adverse cardiac events but not cardiovascular mortality nor myocardial ischemia. Only 1 study would form the CCTA subgroup in the cardiovascular mortality domain, meaning the subgroup analysis would not be informative. As for the myocardial ischemia domain, all studies used CAG.

Figures 5 and 6, respectively, show that subgroup analyses did not detect a statistically significant subgroup effect between pediatric and adult studies within the domain of cardiovascular mortality (p = 0.43) or investigative indicators of myocardial ischemia (p = 0.88). It could therefore not be concluded that the odds of cardiovascular mortality nor myocardial ischemia were significantly modified in either of these 2 age categories. However, it is worth noting the small number of pediatric studies, which may have limited the power of the test to detect a statistically significant result. Likewise, Figure 7 shows that the subgroup analysis within the domain of nonfatal adverse cardiac events did not detect a statistically significant subgroup effect between studies using CCTA versus CAG (p = 0.11).

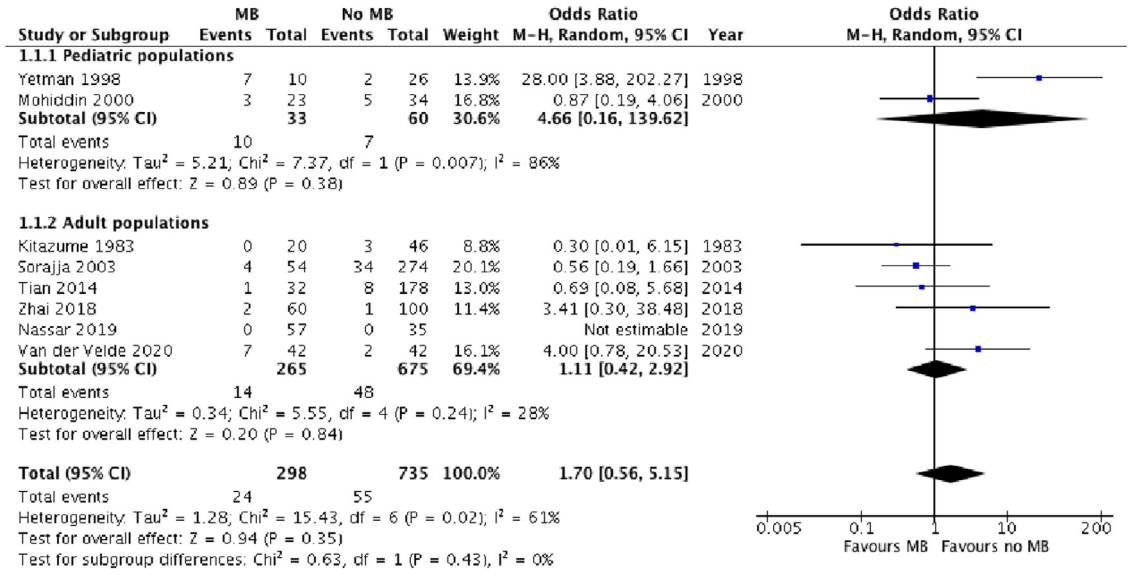


Figure 5. Subgroup analysis within the domain of cardiovascular mortality for studies investigating pediatric populations and studies investigating adult populations. Subgroup analysis did not detect a statistically significant subgroup difference (p = 0.43) between adult and pediatric studies. M-H = Mantel-Haenszel.

## Discussion

This is the first systematic review and meta-analysis to investigate the prognostic implications of MB solely within the HCM population. This review of 10 studies found no statistically significant associations between MB and cardiovascular mortality (p = 0.35) or nonfatal adverse cardiac events (p = 0.06) but did so for myocardial ischemia (p = 0.04).

The results of this review show some consistencies with previous meta-analyses investigating the consequences of MB in more general populations. Hostiuc et al[2] found no statistically significant association between MB and cardiac death but did find such an association between MB and myocardial ischemia, and major adverse cardiac events (a composite of cardiovascular death, myocardial infarction, target vessel revascularization, and stent thrombosis). A total of 4 studies of patients with HCM were included in their review. Zhu et al[3] excluded all studies of patients with HCM in their meta-analysis and found statistically significant associations between MB and cardiac events (cardiovascular death or nonfatal myocardial infarction) and angina requiring hospitalization. It is clear that the effect MB has on prognosis remains especially controversial in patients with HCM, for which no previous meta-analyses exist.

The finding of a statistically significant association between MB and myocardial ischemia is important. The mechanisms behind ischemia in both MB and HCM have been investigated in previous studies. Consideration of how these mechanisms interact may offer insight into the findings of this review. The effects of MB in patients with HCM take on particular significance with consideration of

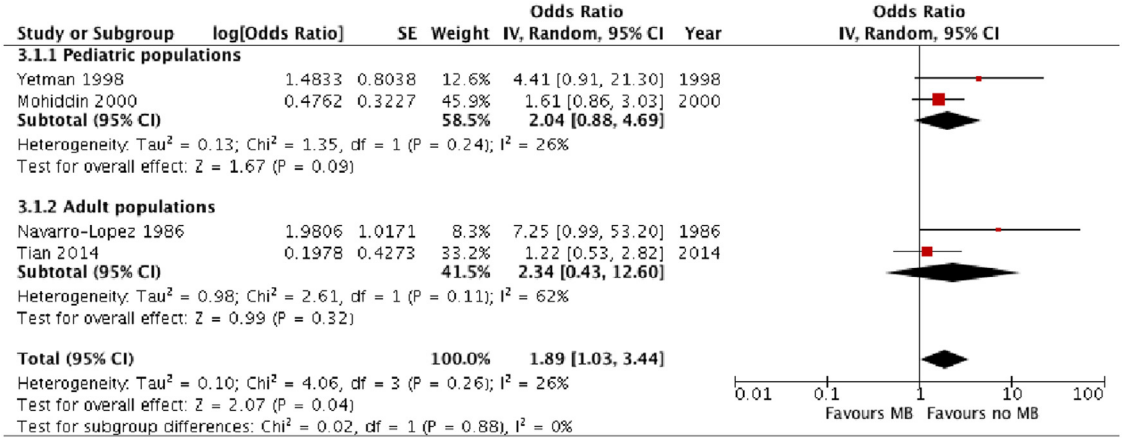


Figure 6. Subgroup analysis within the domain of investigative indicators of myocardial ischemia for studies investigating pediatric populations and adult populations. No statistically significant subgroup difference was detected between these 2 groups (p = 0.88). IV = inverse variance.

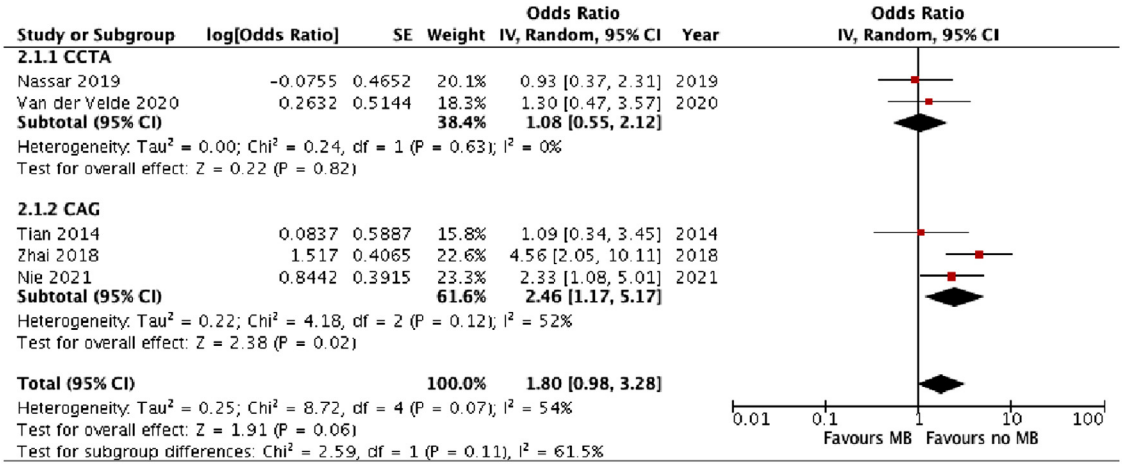


Figure 7. Subgroup analysis within the domain of nonfatal adverse cardiac events for studies utilizing CCTA and CAG. Subgroup analysis detected no statistically significant subgroup difference (p = 0.11) between studies utilizing CCTA and studies utilizing CAG. IV = inverse variance.

the fact that any ischemic process brought about by MB may be additive to the underlying ischemic processes characteristic of HCM.

Myocardial ischemia is an established process in HCM, even in the presence of what appear to be structurally normal coronary arteries[18] and may result from left ventricular outflow tract obstruction, leading to high intracavitary pressure during systole, elevated left ventricular end-diastolic pressure, compression of the coronary microvasculature because of hypertrophy, and microvascular dysfunction.[6,18] The functional consequences of these is impaired myocardial perfusion with a reduction of the coronary flow reserve (CFR).[18]

As for MB, the pathologic processes include hemodynamic impairment, and endothelial dysfunction in the form of accelerated proximal atherosclerosis[19] and coronary vasospasm resulting from vessel hyper-reactivity.[20] Hemodynamic changes have been observed as a "milking effect" on coronary angiography caused by systolic coronary compression. Although compression occurs during systole, it is widely acknowledged that both cardiac phases may be affected because of a persistent diastolic diameter reduction enduring to mid-diastole, with diastole being the principal stage of coronary filling. This is particularly exacerbated in tachycardia.[21] Klues et al[22] found a mean persistent diastolic diameter reduction of 35.3 ± 11% and a mean CFR of 2.5 ± 0.5 in their study of 12 symptomatic patients with MB. In healthy subjects, the CFR is usually >3.[23] Stent placement in 4 patients abolished the diastolic flow abnormalities and CFR improved to 3.8 ± 0.3 in these patients, therefore demonstrating flow disturbances amenable to treatment.

Although the ischemic mechanisms behind HCM and MB have been researched individually, their interactions in concomitant disease have rarely been investigated. The study by Sharzehee et al,[24] albeit small, presents valuable data in filling this evidence gap by aiming to define the additional hemodynamic impact of MB in patients with HCM. They enrolled 15 patients with MB, 7 with HCM and 8 without. Transient computational fluid dynamics simulations were constructed from their coronary angiograms, and simulated removal of the bridged segment was used to assess the hemodynamic changes resulting from the presence of MB. The persistence of systolic compression into diastole by MB was significantly greater in HCM hearts than controls (p <0.05), and this was accompanied by a significantly higher pressure decrease coefficient across the bridge in patients with HCM (p <0.05). A significant improvement in coronary blood flow (up to 40%) was observed on simulated removal of the bridged segment in those with an MB compression ratio >65%, and the authors recommended surgical intervention in these patients.

The autopsy study by Basso et al[25] also contributes valuable data, specifically in defining the morphologic characteristics of MB in 115 HCM hearts compared with MB in 140 non-HCM controls hearts. MB was more common in those with HCM (p = 0.002) and deep MBs (submerged 2 mm in the myocardium) were more common in HCM hearts than controls either with (p = 0.004) or without (p <0.001) hypertrophy. In addition, greater MB depth was associated with greater MB length (p <0.001). The study could not conclude that there was a systemic association between MB and sudden cardiac death because the MB prevalence did not differ significantly in those dying from sudden cardiac death as opposed to progressive heart failure; however, the finding of deeper bridges in HCM hearts takes on particular significance when considered alongside the results of previous autopsy studies investigating the pathologic consequences of differing MB severity.

Morales et al[26] examined 39 autopsy cases in hearts with MB of the left anterior descending artery and separated cases into 2 groups based on the presence (22 cases) or absence (17 cases) of myocardial lesions secondary to chronic ischemic injury. Sudden cardiac death only occurred in hearts with lesions, and MB depth was significantly greater in this group (3.8 ± 1.8 mm vs 1.9 ± 0.9 mm, p = 0.002). Hostiuc et al[27] (a separate study from the previously mentioned meta-analysis) also found that hemodynamically significant MB, characterized by increased bridge depth, was associated with a greater degree of fibrosis and interstitial edema in subjects who experienced sudden cardiac death. These findings are significant, given the powerful prognostic implications of fibrosis in HCM, with the extent of myocardial fibrosis being associated with adverse cardiac

remodeling and arrhythmogenesis, the potential consequences of which being sudden cardiac death.[28]

Although this meta-analysis found no associations between MB in HCM and the occurrence of cardiovascular mortality or nonfatal adverse cardiac events, its potential significance is reaffirmed by the finding of an association with myocardial ischemia. Numerous case reports have documented patients with HCM with MB with adverse outcomes, including chest pain, ventricular dysrhythmia, and syncope, in whom surgical and pharmacologic strategies for MB have resulted in improvement or even resolution of symptoms.[29–34] There may therefore exist select patients with HCM in whom MB may adversely affect prognosis. The existing challenge is identifying such patients and developing a more well-defined management protocol for them, with the aim of guiding decision making around surgery and appropriate follow-up.

In identifying those most vulnerable to adverse outcomes, consideration should be given to MB severity and the extent to which it leads to hemodynamic compromise and endothelial dysfunction, as determined by anatomic and functional features, including bridge depth, length, and contractile force, and individual patient factors, including symptoms and the severity of HCM phenotype. In the determination of what constitutes a clinically significant MB in any patient with HCM, the goals of future research should be to determine what degree of hemodynamic compromise (i.e., % luminal diameter reduction, % diastolic time compression persists) is a risk for poor outcomes and to correlate this with anatomic features of bridges. Modern imaging techniques, including high-definition computed tomographyand magnetic resonance imaging, which provide detailed anatomic and functional assessment of the coronary vasculature, offer ample opportunity to undertake such research. In corroborating these findings with real clinical outcomes, prospective follow-up in which these functional and anatomic parameters have been assessed would provide useful further data.

More pediatric cohort studies would be particularly useful in exploring any potential prognostic difference between adults and children because this meta-analysis only found 2 published pediatric cohort studies with a total of 93 participants, meaning that the necessary statistical power to detect any prognostic differences through subgroup analysis was limited.

This review has a few limitations. First, and the most important, is the broad range of definitions/parameters for MB among the included studies, owing to the lack of a universal definition. The potential implications of this are important because this may, in part, account for potential differences in conclusions across studies. Although we observed no pattern in which studies with more stringent definitions veered toward favoring MB or no MB, this heterogeneity in definitions must be noted. Second, this review could not correlate the presence of MB with severity of HCM phenotype using multiple linear regression because of the heterogenous nature of data reporting across studies. This meant that no clear conclusion could be confidently arrived at about the potential causal association between MB and myocardial ischemia in patients with HCM because those with MB may experience a worse HCM phenotype. Further prospective studies correlating the presence and severity of MB with the severity of HCM phenotype, and clinical outcomes, would be useful in addressing this. Third, a small number of studies with generally small numbers of participants have been included, therefore limiting the statistical power of the meta-analysis. Fourth, heterogeneity existed between included studies, resulting from the differences in imaging modalities used, population characteristics, outcomes assessed, and modalities for measuring myocardial ischemia. This necessitated the use of a random-effects model. Fifth, the nonfatal adverse cardiac events domain introduced difficulty in that any 1 patient may have experienced more than 1 event, therefore leading to the potential problem of overestimation of the total number of patients affected by events in this domain. However, this limitation only applied when compiling results from the study of Zhai et al.[14]

Overall, this review demonstrated an association between the presence of MB in HCM and myocardial ischemia but found no associations with clinical outcomes, including cardiovascular mortality and nonfatal adverse cardiac events. Future research should focus on identifying any specific populations that may be more vulnerable to adverse outcomes by corroborating morphologic and functional features of bridges with HCM phenotype and clinical outcomes using modern imaging techniques. Building this evidence base will be a step toward developing a management protocol, therefore improving patient outcomes. In limiting heterogeneity across studies, adaption of a standard or commonly used definition of MB based on the degree of systolic compression (e.g., 50%) or depth of the coronary bridge (e.g., ≥1 mm) would be an important step.

## Disclosures

The authors have no conflicts of interest to declare.

## Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2022.10.059.

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