Associations of myocardial bridging with adverse cardiac events: a meta-analysis of published observational cohort studies involving 4,556 individuals

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Contributions: (I) Conception and design: C Zhu, S Wang; (II) Administrative support: S Wang; (III) Provision of study materials or patients: C Zhu, S Wang, B Tang; (IV) Collection and assembly of data: C Zhu, S Wang, H Cui, B Tang; (V) Data analysis and interpretation: C Zhu, S Wang, H Cui; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Background: Data derived from small series have demonstrated an association of myocardial bridge (MB) with adverse cardiac events, while MB has been traditionally considered as a benign condition. Hence, the precise clinical implications of MB on prognosis remains inconsistent. Our purpose is to perform a meta-analysis to assess the clinical implications of MB on prognosis.

Methods: We performed an extensive search of PubMed and reference lists of relevant articles. Studies which compared prognosis between subjects with and without MB were identified from 1960 to 31 March 2018. Studies selection was limited to human data and restricted to English language.

Results: Six eligible studies were included in current meta-analysis. Of 4,556 subjects, 1,389 (30.5%) presented MB. MB was associated with an increased risk of adverse cardiac events [odds ratio (OR), 1.71; 95% confidence interval (CI): 1.29 to 2.26; P=0.0002], non-fatal myocardial infarction (OR: 3.17; 95% CI: 1.21 to 8.31; P=0.02), and angina requiring hospitalization (OR: 2.31; 95% CI: 1.55 to 3.45; P<0.0001), respectively, compared with subjects without MB.

Conclusions: This meta-analysis of currently available observational cohort studies suggests that MB has an association with adverse cardiac events. Further prospective multicenter studies with large sample size are needed to confirm current findings. Moreover, studies refining the impact of different types of MB on cardiac events, myocardial ischemia, and symptoms requiring therapy, may provide more insights to this issue.

Keywords: Myocardial bridging (MB); adverse cardiac events (ACEs); prognosis; meta-analysis

Submitted Oct 20, 2019. Accepted for publication Jan 10, 2020.
doi: 10.21037/atm.2020.02.24
View this article at: http://dx.doi.org/10.21037/atm.2020.02.24

Introduction

Myocardial bridging (MB) is a congenital variant of coronary artery anatomy which indicates the myocardium overlying an intramural segment of an epicardial coronary artery. MB mostly involves the middle segment of the left anterior descending artery (LAD), though its prevalence varies according to different imaging modalities and methods used (1-3). The data derived from small sample studies indicate MB may cause a variety of adverse cardiac events (ACEs) including myocardial infarction (MI), life-threatening arrhythmias, and sudden cardiac death (3-6). In this regard, the clinical relevance of MB is of crucial
importance. Actually, MB has long been considered as a benign condition given that the prevalence of MB is usually high in autopsy and blood flow runs through normal coronary artery mainly during diastolic phase, while MB compression occurs during systolic phase and only approximately in one third of subjects with MB (3,7-10). Therefore, the precise clinical implication of MB on prognosis remains controversial. We aimed to conduct a meta-analysis of currently available evidence to examine the clinical implication of MB on prognosis among general population.

**Methods**

The present meta-analysis was performed with a predefined protocol and complied with PRISMA and MOOSE guidelines (Table S1, S4).

**Search strategy**

An extensive search of PubMed with English language restriction was performed using the terms like “myocardial bridging”, “myocardial bridge”, “intramural coronary artery”, “mural coronary artery”, “coronary artery overbridging”, “tunneled artery” and “myocardial loop”. Additional reference lists of relevant articles were reviewed. Studies published between 1960 in which year MB was first reported angiographically and 31 March 2018 were identified (3,4,11). The detailed search strategy was presented in Table S2.

**Study selection**

We only included observational cohort studies either prospective or retrospective comparing the outcome of subjects with and without MB, which represent the best level of clinical evidence to date. Inclusion criteria were the followings: (I) population referred consecutively to hospital for imaging examination of coronary artery; (II) explicit description of inclusion or exclusion criteria; and (III) comparison of outcome during follow-up between subjects with and without MB. Exclusion criteria were the followings: (I) studies incapable of extracting specific data; (II) studies dealing with patient population with specific disease like hypertrophic cardiomyopathy. Potentially eligible studies were evaluated by two independent reviewers (C Zhu and S Wang) as well as data extraction and quality evaluation of the final included studies. Any discrepancies were resolved by consensus meeting of all authors of this meta-analysis subsequently.

**Quality evaluation of included studies**

The Newcastle-Ottawa Scale for cohort studies, which is a “star system” providing an easy and convenient quality assessment of nonrandomized studies in a systematic review, was used to evaluate the quality of included studies on three perspectives: selection of cohorts, comparability of cohorts, and ascertainment of outcome for cohorts (12,13). Nine stars represent the highest study quality. At least 5 stars were defined to be adequate quality for inclusion in the present meta-analysis. With regard to evaluation for publication bias of included studies, the visualized funnel plot was used if applicable.

**Outcomes**

The primary outcome was defined as ACEs including cardiovascular death and non-fatal MI. Secondary outcomes were non-fatal MI, angina requiring hospitalization, and all-cause mortality. Furthermore, a composite endpoint was defined as a combination of ACEs, non-cardiac death and angina requiring hospitalization.

**Statistical analysis**

Analysis was conducted using Review Manager Version 5.3 (The Cochrane Collaboration, Update Software, Copenhagen, The Nordic Cochrane Centre). Heterogeneity test was measured utilizing the $\chi^2$ test (Cochrane’s Q) and $I^2$ value. $I^2$ values less than 50%, 50% to 75%, and more than 75% represent a low, moderate, high degree of heterogeneity, respectively. If homogenous, fixed-effect model was used. Otherwise, a random-effects model was used. Odds ratio (OR) was calculated for dichotomous variables with 95% confidence interval (CI). An OR represents the ratio between odds of outcomes in the context of a particular exposure and odds of outcomes in absence of the exposure. A P value of less than 0.05 was considered statistically significant.

**Results**

**Selection of studies**

Six observational cohort studies were included in the
present meta-analysis for data extraction which yielded a total of 4,556 selected subjects (Figure 1) (11,14-18). Of these six included studies, only the study by Rubinshtein et al. was prospective, whereas the remaining 5 studies were retrospective. The study by Rubinshtein et al. included subjects with compromised left ventricular function or valvular heart disease who were referred to rule out obstructive coronary artery disease (11). In contrast, the study by Kim et al. excluded subjects with any risk factors of chest pain including valvular heart disease (18). The detailed inclusion and exclusion criteria and outcome measurements of selected studies were presented in Table 1. Besides, the study by Kim et al. assessed MB with coronary angiography. Table 2 demonstrates data extracted from all included studies in the present meta-analysis. All subjects were in absence of prior coronary heart disease or obstructive coronary artery disease which was defined as equal to or more than 50% coronary luminal stenosis of any coronary artery.

The quality evaluation of selected studies was demonstrated in Table S3. None of these six included studies provided information on losses to follow-up.

### Pooled prevalence and characteristics of MB

Of the 4,556 selected subjects included, 1,389 had MB. Thus, the pooled prevalence of MB in the present study is 30.5%. Most MB involved the LAD, which was consistent among included studies. Three studies reported MB with
### Table 1 (Continued)

| First author, year | Location | Source of participants | Total number of participants | Inclusion criteria | Exclusion criteria | Study endpoints | Risk of bias* |
|--------------------|----------|------------------------|----------------------------|-------------------|-------------------|----------------|--------------|
| Rubinshtein et al., 2013 (11) | Israel | Lady Davis Carmel Medical Center and the Ruth and Bruce Rappaport School of Medicine | 334 | Subjects with chest pain syndromes referred for coronary computed tomographic angiography | Prior history of obstructive coronary artery disease or coronary revascularization; obstructive coronary artery disease (≥50% stenosis); obstructive disease | Adverse cardiac events (cardiac death, nonfatal myocardial infarction) | Low |
| Sheu et al., 2011 (16) | China | Taipei Veterans General Hospital | 425 | Subjects undergoing coronary computed tomographic angiography for known or suspected coronary artery disease or for physical health check | A history of coronary artery disease; previous percutaneous coronary intervention/stenting, and coronary artery bypass graft; inadequate clinical information of cardiovascular illness; loss to follow-up | Cardiac death; Nonfatal myocardial infarction; Revascularization (CABG, PCI); Ventricular arrhythmia | Low |
| Marcos-Alberca et al., 2011 (17) | Spain | Hospital Clínico San Carlos | 74 | Subjects with stable chest pain and intermediate risk of coronary artery disease (30–70% stenosis) referred for coronary computed tomographic angiography | NR | Cardiac death; Nonfatal myocardial infarction; Revascularization (CABG, PCI); Recurrent ischemic symptoms requiring hospitalization | Low |
| Kim et al., 2010 (18) | Korea | Chonnam National University Hospital | 684 | Subjects with chest pain and without significant coronary artery disease (<50% stenosis) referred for coronary angiography | Obstructive coronary artery disease (≥50% stenosis) | Readmission during follow-up†; Cardiac death; Nonfatal myocardial infarction; Non-cardiac death; Recurrent angina refractory to medical therapy | Moderate |

†, including death (cardiac death, non-cardiac death), nonfatal myocardial infarction, and recurrent angina refractory to medical therapy; *, the risk of bias was evaluated by two reviewers independently. Based on the comprehensive analysis of selection bias, multiple publication biases, measurement bias, statistical reporting bias, studies were classified into three levels: high, moderate and low. CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; NR, not reported.
Table 2 Extracted data of included studies in the present meta-analysis

| Variable                                      | Liu et al., 2017 (14) | Dimitriu-Leen et al., 2017 (15) | Rubinshtein et al., 2013 (11) | Sheu et al., 2011 (16) | Marcos-Alberca et al., 2011 (17) | Kim et al., 2010 (18) |
|-----------------------------------------------|-----------------------|---------------------------------|-----------------------------|------------------------|-------------------------------|-----------------------|
|                                               | Total MB | MB− | Total MB | MB− | Total MB | MB− | Total MB | MB− | Total MB | MB− | Total MB | MB− | Total MB | MB− |
| Study design                                  | Retrospective cohort study | Retrospective cohort study | Prospective cohort study | Retrospective cohort study | Retrospective cohort study | Retrospective cohort study |
| N                                             | 2,092 | 634 | 1,458 | 947 | 210 | 737 | 425 | 89 | 336 | 74 | 31 | 43 | 684 | 308 | 376 |
| Modality                                      | CTG | CTG | CTG | CTG | CTG | CTG | CTG | CAG | |
| Definition of MB                              | At least half encasement | >1 mm of myocardium surrounding | Covered by a bridge of myocardium | Full encasement | Myocardium surrounding | Systolic compression |
| Age, years                                    | 58.9±8.9 | 59.3±9.2 | 58.7±9.2 | 54.0±12.0 | 54.0±11.0 | 53.0±12.0 | 57±13 | 57±13 | 57±13 | 57±13 | 57±13 | 57±13 | 57±13 | 57±13 |
| Female, %                                      | 43.1 | 44.6 | 42.4 | 56 | 60 | 55 | 43 | 48 | NR | 23.7 | NR | 61 | 74 | 49.9 | 53.9 | 47.1 |
| BMI, kg/m²                                     | 24.7±3.7 | 24.6±3.7 | 24.7±3.7 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| Hypertension, %                                | 75.8 | 78.2 | 74.8 | 56 | 60 | 55 | 36 | 39 | NR | 59.5 | NR | 48 | 33 | NR | 37.7 | 43.9 |
| Hyperlipidemia, %                              | 69.7 | 72.2 | 74.8 | 40 | 40 | 39 | 36 | 39 | NR | 44.9 | NR | 48 | 33 | NR | 37.7 | 43.9 |
| Hypercholesterolemia, %                        | NR | NR | NR | 35 | 35 | 35 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| Diabetes mellitus, %                           | 21.7 | 19.2 | 22.8 | 27 | 29 | 26 | 12 | 11 | NR | 17.9 | NR | 26 | 12 | NR | 16.2 | 16.0 |
| Smoking, %                                     | 42.3 | 39.7 | 43.4 | 15 | 16 | 15 | 20 | 19 | NR | 13.4 | NR | 3 | 11 | NR | 26.9 | 21.5 |
| Clinical symptom, %                            | 53.8 | 59.6 | 51.3 | 57 | 53 | 58 | 100 | 100 | 100 | NR | 66.2 | NR | 100 | 100 | 100 | 100 | 100 |
| Non-obstructive CAD, %                         | 47.8 | 56.6 | 43.9 | 58 | 62 | 57 | 52 | 63 | 45 | NR | NR | NR | NR | NR | 22.7 | 23.7 | 21.8 |
| Prevalence of MB, %                            | 30.3 | 22 | 35 | 20.9 | 41.9 | 45 |
| MB of LAD, %                                   | 79.4 | 39 | 71 | 49.9 | 87 | 98.7 |
| Complete MB, %                                 | NR | NR | 73 | 100 | NR | NR |
| Deep MB, %                                     | 70.6 | 40 | NR | 10.7 | NR | NR |
| MB length, mm                                  | 20.5±7.5 | NR | 27±14 | 21.4±9.6 | NR | NR |
| MB depth, mm                                   | 2.8±0.9 | 1.9 | 2.6±1.4 | 2.55±9.6 | NR | NR |
| Follow-up time, years                          | 4.3±0.7 | 4.9 | 6.1±1 | 1.8±0.3 | 0.5 | 3.1±1.2 |
| Angina requiring hospitalization               | NR | NR | NR | 13 | 2 | 11 | NR | NR | NR | 3 | 0 | 3 | 33 | 19 | 14 | 79 | 52 | 27 |
| Revascularization                              | NR | NR | NR | NR | NR | NR | NR | NR | NR | 9 | NR | 2 | 2 | 0 | NR | NR | NR |
| Adverse heart events                           | 202 | 81 | 121 | NR | NR | NR | 13 | 6 | 7 | 0 | 0 | 0 | 2 | 1 | 1 | 8 | 7 | 1 |
| Cardiac death                                  | NR | NR | NR | NR | NR | NR | 10 | 4 | 6 | 0 | 0 | 0 | 0 | 0 | 0 | NR | NR |
| Non-fatal MI                                   | NR | NR | NR | 7 | 2 | 5 | 3 | 2 | 1 | 0 | 0 | 0 | 2 | 1 | 1 | 8 | 7 | 1 |
| All-cause mortality                            | NR | NR | NR | 23 | 4 | 19 | 19 | 7 | 12 | NR | NR | NR | NR | NR | NR | NR | 4 | 0 | 4 |

MB, myocardial bridging; CTG, coronary computed tomographic angiography; CAG, coronary angiography; BMI, body mass index; CAD, coronary artery disease; LAD, left ascending artery; MI, myocardial infarction; NR, not reported.
Primary outcome

ACEs were reported in five included studies comprising a total of 225 events among 3,609 subjects (11,14,16-18). The pooled incidences of ACEs were 8.1% and 5.3% in subjects with MB and without MB, respectively. On pooled analysis, subjects with MB had an increased risk of ACEs compared with subjects without MB (OR: 1.71; 95% CI: 1.29 to 2.26, \( P=0.0002 \)) (Figure 2A). There was no statistical significance of heterogeneity test between included studies (Cochrane Q = 2.46, \( P=0.48 \), \( I^2=0\% \)). Besides, the corresponding funnel plot indicated that no publication bias existed (Figure 2B).

Sensitivity analysis was performed by only including five studies which used coronary computed tomographic angiography for detection of MB. Results were unchanged for ACEs in subjects with MB compared to that in subjects without MB (OR: 1.62; 95% CI: 1.21 to 2.15, \( P=0.001 \)) (Figure S1).

Secondary outcomes

Non-fatal MI was reported in five studies comprising a total of 20 events among 2,464 subjects (11,15-18). The pooled incidences of non-fatal MI were 1.6% and 0.5% in subjects with MB and without MB, respectively. Subjects with MB had an increased risk of experiencing non-fatal MI compared with subjects without MB (OR: 3.17; 95% CI: 1.21 to 8.31, \( P=0.02 \)) (Figure 3). There was no statistical heterogeneity for the outcome of non-fatal MI between included studies (Cochrane Q = 2.17, \( P=0.54 \), \( I^2=0\% \)).

Angina requiring hospitalization was reported in 4 studies comprising a total of 128 events among 2,130 subjects (15-18). The pooled incidences of angina requiring hospitalization were 11.4% and 3.7% in subjects with MB and without MB, respectively. Subjects with MB had an increased risk of angina requiring hospitalization compared with subjects without MB (OR: 2.31; 95% CI: 1.55 to 3.45,
Figure 4 Pooled risk of angina requiring hospitalization. (A) Forest plot of included studies describing angina requiring hospitalization during follow-up. Subjects with myocardial bridging had higher risk of experiencing angina requiring hospitalization; (B) corresponding funnel plot of included studies. MB, myocardial bridge; CI, confidence interval; OR, odds ratio; SE, standard error.

Figure 5 Pooled risk of the composite endpoint. (A) Forest plot of included studies describing the composite endpoint during follow-up. Subjects with myocardial bridging had higher risk of experiencing the composite endpoint. (B) Corresponding funnel plot of included studies. MB, myocardial bridge; CI, confidence interval; OR, odds ratio; SE, standard error.

There was no statistical heterogeneity between included studies (Cochrane Q =4.50, P=0.21, I² =33%).

All-cause mortality was reported in three studies comprising a total of 46 events among 1,965 subjects (11,15,18). The pooled incidences of all-cause mortality were 1.7% and 2.6% in subjects with MB and without MB, respectively. Subjects with MB had no significant increase in the risk of all-cause mortality compared with subjects without MB (OR: 0.75; 95% CI: 0.38 to 1.49, P=0.41) (Figure S2). There was no statistical heterogeneity between included studies (Cochrane Q =1.36, P=0.51, I² =0%).

Discussion

The present meta-analysis aims to examine the impact of MB on clinical prognosis in the general population which includes the latest cohort studies to date as far as we know. Our results indicate that MB is associated with an increased risk of ACEs and non-fatal MI in the present study. Thus, our findings may have important implications with regard to clinical practice and may alter our previous conceptions and strategies to provide more attention and optimal management of MB.

The pooled prevalence of MB with 30.5% in the present study is similar to that in the prospective study by Rubinshtein et al. and the average prevalence of 25% detected in autopsy which is usually regarded as a reference
standard (7,11,16). Generally, according to previous studies, depiction rate of MB in coronary angiography, coronary computed tomographic angiography and autopsy is increased in ascending order (4,5,7,11). The prevalence of MB on coronary computed tomographic angiography in more recent studies is in accordance with autopsy series, which may be attributed to the increasingly high spatial resolution of newer generation computed tomography capable of refining MB (4,19).

Our key findings suggest that MB confers an increased risk of ACEs (OR: 1.71; 95% CI: 1.29 to 2.26, P=0.0002) and non-fatal MI (OR: 3.17; 95% CI: 1.21 to 8.31, P=0.02) in subjects with MB compared with subjects without MB, respectively. Thus, our findings are contrary to previous studies and traditional consideration that MB is a normal variant or a benign coronary anomaly (11,15). Regarding clinical symptom, subjects with MB had an increased risk of angina requiring hospitalization (OR: 2.31; 95% CI: 1.55 to 3.45, P<0.0001) compared with subjects without MB.

There are several potential mechanisms that may attribute to the association of MB with ACEs or myocardial ischemia. First, MB itself mostly involves the LAD which is one of the most important coronary arteries and whose lesion commonly contributes to most MI or myocardial ischemia in obstructive coronary artery disease. Hemodynamic relevance of MB differs significantly with regard to its anatomy especially depth (1,20). Second, multiple studies on MB using intracoronary ultrasound, Doppler and quantitative coronary angiography have revealed that systolic compression of MB persists into diastolic phase of cardiac cycle rather than that MB is just a systolic event (21-25). This finding is deemed highly unique as it can only be detected in the segment of MB with systolic compression (1,26). Moreover, findings by intracoronary Doppler demonstrate that MB compression delays luminal recovery in early diastole which may impair diastolic hemodynamics, which is left unidentified before (21). Additionally, the degree of the systolic compression of MB is positively associated with reduction of luminal diameter and corresponding decrease in flow and flow reserve during diastole (27). Third, previous studies reveal endothelial dysfunction of the tunneled coronary artery beneath MB (28,29). Furthermore, reduced expression of some vasoactive agents like endothelial nitric oxide synthase, endothelin-1, and angiotensin-converting enzyme at the MB site were ascertained to attribute to endothelial dysfunction of the tunneled coronary artery, which may predispose tunneled coronary artery to spasm at the same time (4,28,29). Fourth, several studies demonstrated a higher incidence of cardiac death and nonfatal MI in subsets of patients with coronary artery spasm and without obstructive coronary artery disease (30,31). Fifth, it has been found that vessel segment proximal to MB predisposes to development of atherosclerosis or formation of plaques, though vessel segment within MB is protected from development of atherosclerotic lesions (6,32). Disturbed retrograde flow produced by systolic compression of MB alters significantly shear stress on the coronary artery wall proximal to MB leading to atherosclerosis of corresponding part of the coronary artery (6,32). This finding has been thought to increase the risk of ACEs or myocardial ischemia.

**Limitations**

This meta-analysis has some limitations. First, our study itself is prone to inherent limitations of this kind of analysis like publication bias. Our data are confined to rely on published studies. Second, most included studies are retrospective except the study by Rubinshtein and colleagues (11). Therefore, our study may have limitations, potential confounding and biases of all retrospective studies. However, prospectively observational study examining the impact of MB on prognosis is relatively lacking, especially with a comparison group of subjects without MB, and has relatively small sample size. Third, of six included studies, the study by Kim et al. uses coronary angiography to detect MB, which differs from the other five included studies with coronary computed tomographic angiography used and is usually thought to has a lower detection rate of MB. However, Kim et al. administered intracoronary nitroglycerin in order to well define MB once suspecting MB during coronary angiography (18). Besides, six included studies only provided limited information about functional effects of MB or clinical symptoms in participants. Fourth, tools employed for diagnosis of MB may be different among included studies in different periods. However, the time span is relatively short, so differences in terms of anatomical definition and functional relapse are slight. Fifth, follow-up duration in two included studies was relatively short and none of included studies provided information on loss to follow-up, which may add some bias to our study (16,17). Sixth, our study could not respectively refine association of different MB types with presence/magnitude of coronary mal-perfusion and prognosis basing on current evidences due to a lack of source data.
Conclusions

MB is not uncommon especially assessed on coronary computed tomographic angiography. Subjects with MB and without obstructive coronary artery disease have increased risk of experiencing ACEs including cardiac death and non-fatal MI, as well as angina requiring hospitalization. These findings may have substantially important implication which may alter our traditional conception of MB as well as clinical practice. However, the present finding needs further prospectively longitudinal multicenter study with large sample size to validate.

Acknowledgments

Funding: This work was supported by National Natural Science Foundation of China (No. 81570276) and Beijing Science and Technology Program of China (No. Z161100000516154).

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Zhu C, Wang S, Cui H, Tang B, Wang S. Associations of myocardial bridging with adverse cardiac events: a meta-analysis of published observational cohort studies involving 4,556 individuals. Ann Transl Med 2020;8(6):369. doi: 10.21037/atm.2020.02.24
Summary of evidence: Identify the report as a systematic review, meta-analysis, or both

Abstract:

Structured summary:

Introduction:

Rationale:

Objectives:

Methods:

Protocol and registration:

Eligibility criteria:

Information sources:

Search:

Study selection:

Data collection process:

Data items:

Risk of bias in individual studies:

Summary measures:

Synthesis of results:

Risk of bias across studies:

Additional analyses:

Results:

Study selection:

Study characteristics:

Risk of bias within studies:

Results of individual studies:

Synthesis of results:

Risk of bias across studies:

Additional analysis:

Discussion:

Summary of evidence: Synthesize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers)

Limitations:

Conclusions:

Funding:

Funding: Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review

* Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.
### Table S2 Search strategy used in the PubMed database from 1960 to 31 March 2018

| Number | Search items                                                                 |
|--------|------------------------------------------------------------------------------|
| 1      | Myocardial bridging                                                          |
| 2      | Myocardial bridge                                                            |
| 3      | Intramural coronary artery                                                   |
| 4      | Mural coronary artery                                                        |
| 5      | Coronary artery overbridging                                                 |
| 6      | Myocardial loop                                                              |
| 7      | Intramural course of coronary artery                                         |
| 8      | 1 or 2 or 3 or 4 or 5 or 6 or 7                                              |
| 9      | Limit 8 to "1960/01/01"[PDAT] : "2018/03/31"[PDAT]                          |
| 10     | Limit 9 to English [LA]                                                      |
| 11     | 10 not Review [PT]                                                           |
| 12     | 11 not "Case reports" [PT]                                                   |
| 13     | 12 not Editorial [PT]                                                        |
| 14     | 13 not Comment [PT]                                                          |

### Table S3 Quality evaluation of included studies

| Study (published year) | Selection | Comparability | Outcome |
|------------------------|-----------|---------------|---------|
| Liu et al., 2017 (14)  | ★         | ★             | ★       |
| Dimitriu-Leen et al., 2017 (15) | ★         | ★             | ★       |
| Rubinshtein et al., 2013 (11) | ★         | ★             | ★       |
| Sheu et al., 2011 (16) | ★         | ★             | ★       |
| Marcos-Alberca et al., 2011 (17) | ★         | ★             | ★       |
| Kim et al., 2010 (18)  | ★         | ★             | ★       |
### Table S4 MOOSE checklist*

| Checklist item | Brief description |
|----------------|-------------------|
| Reporting of background | |
| Problem definition | Data derived from small series have demonstrated an association of myocardial bridge (MB) with adverse cardiac events, while MB has been traditionally considered as a benign condition. Hence, the precise clinical implications of MB on prognosis remains inconsistent. |
| Hypothesis statement | MB may have an association with adverse cardiac events (ACEs). |
| Description of study outcomes | ACEs including cardiovascular death and non-fatal myocardial infarction (MI); secondary outcomes like non-fatal MI, angina requiring hospitalization, and all-cause mortality; composite endpoint defined as a combination of ACEs, non-cardiac death and angina requiring hospitalization. |
| Type of exposure | With MB |
| Type of study designs used | Population-based cohort studies |
| Study population | Populations referred for computed tomographic coronary angiography or coronary angiography in hospital |
| Reporting of search strategy should include | |
| Qualifications of searchers | Changsheng Zhu, MD; Shuiyun Wang, MD |
| Search strategy, including time period included in the synthesis and keywords | Time period: from inception of PubMed to March 31, 2018 |
| Databases and registries searched | PubMed |
| Search software used, name and version, including special features | Endnote X 8.2 was used to manage references |
| Use of hand searching | Additional reference lists of relevant articles were searched |
| List of citations located and those excluded, including justifications | Details of the literature search process are presented in the flow chart (Figure 1). List of excluded citations is available on request. |
| Method of addressing articles published in languages other than English | The search was restricted to the English language |
| Method of handling abstracts and unpublished studies | None |
| Description of any contact with authors | Not applicable |
| Reporting of methods should include | |
| Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested | Methods section |
| Rationale for the selection and coding of data | Extracted data from included studies were related to population characteristics, study design, exposure and outcome measurements |
| Assessment of confounding | Not applicable |
| Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results | Study quality was assessed with the nine-star Newcastle-Ottawa Scale (NOS) which is pre-defined criteria including population representativeness, comparability, ascertainment of outcome (Table S3). |
| Assessment of heterogeneity | Heterogeneity of the studies was evaluated with I² statistic |
| Description of statistical methods in sufficient detail to be replicated | Details of statistical methods were described in the Methods section |
| Provision of appropriate tables and graphics | Tables 1, 2, Figures 1-5 |
| Reporting of results should include | |
| Graph summarizing individual study estimates and overall estimate | Figures 2-5 |
| Table giving descriptive information for each study included | Tables 1, 2 |
| Results of sensitivity testing | Not applicable |
| Indication of statistical uncertainty of findings | 95% confidence intervals were calculated for all summary estimates |
| Reporting of discussion should include | |
| Quantitative assessment of bias | Publication bias was assessed with funnel plot |
| Justification for exclusion | All studies were excluded based on the pre-defined inclusion and exclusion criteria in the Methods section |
| Assessment of quality of included studies | Quality assessment of included studies was described in Methods section |
| Reporting of conclusions should include | |
| Consideration of alternative explanations for observed results | Discussion section |
| Generalization of the conclusions | Results section |
| Guidelines for future research | Further prospective multicentre studies with large sample size are needed to confirm current findings |
| Disclosure of funding source | Dr. Shuiyun Wang has received grants from National Natural Science Foundation of China |

* Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;283:2008-12.
Figure S1 Sensitivity analysis only including five studies which used coronary computed tomographic angiography for detection of myocardial bridging. Subjects with myocardial bridging had higher risk of experiencing adverse cardiac events. MB, myocardial bridge; CI, confidence interval.

Figure S2 Forest plot of included studies describing all-cause mortality during follow-up. Subjects with myocardial bridging had higher risk of experiencing all-cause mortality. MB, myocardial bridge; CI, confidence interval.