

# World Journal of *Cardiology*

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## Retrospective Study

# Effectiveness and safety of antithrombotic strategies in elderly patients with acute myocardial infarction

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## Abstract

### BACKGROUND

Elderly patients represent a rapidly growing part of the population more susceptible to acute coronary syndromes and their complications. However, literature evidence is lacking in this clinical setting.

### AIM

To describe the clinical features, in-hospital management and outcomes of “elderly” patients with myocardial infarction treated with antiplatelet and/or anticoagulation therapy.

### METHODS

This study was a retrospective analysis of all consecutive patients older than 80 years admitted to the Division of Cardiology of St. Andrea Hospital of Vercelli from January 2018 to December 2018 due to ST-elevation myocardial infarction (STEMI) or non-ST elevation myocardial infarction (NSTEMI). Clinical and laboratory data were collected for each patient, as well as the prevalence of previous or in-hospital atrial fibrillation (AF). In-hospital management, consisting of an invasive or conservative strategy, and the anti-thrombotic therapy used are described. Outcomes evaluated at 1 year follow-up included an efficacy ischemic endpoint and a safety bleeding endpoint.

### RESULTS

Of the 105 patients enrolled (mean age  $83.9 \pm 3.6$  years, 52.3% males), 68 (64.8%) were admitted due to NSTEMI and 37 (35.2%) due to STEMI. Among the STEMI patients, 34 (91.9%) underwent coronary angiography and all of them were treated with percutaneous coronary intervention (PCI); among the NSTEMI patients, 42 (61.8%) were assigned to an invasive strategy and 16 (38.1%) of them underwent a PCI. No significant difference between the groups was found



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concerning the prevalence of previous or in-hospital de-novo AF. 10.5% of the whole population received triple antithrombotic therapy and 9.5% single antiplatelet therapy plus oral anticoagulation (OAC), with no significant difference between the subgroups, although a higher number of STEMI patients received dual antiplatelet therapy without OAC as compared with NSTEMI patients. A low rate of in-hospital death (5.7%) and 1-year cardiovascular death (3.3%) was registered. Seven (7.8%) patients experienced major adverse cardiovascular events, while the rate of minor and major bleeding at 1-year follow-up was 10% and 2.2%, respectively, with no difference between NSTEMI and STEMI patients.

## CONCLUSION

In this real-world study, a tailored evaluation of an invasive strategy and antithrombotic therapy resulted in a low rate of adverse events in elderly patients hospitalized with acute myocardial infarction.

**Key Words:** Antiplatelet therapy; Anticoagulant therapy; Elderly patients; Safety; Acute myocardial infarction

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**Core Tip:** This real-world study focuses on the difficult but common scenario of elderly patients admitted with acute myocardial infarction (AMI), for which literature evidence is lacking. We retrospectively identified 105 patients older than 80 years admitted for AMI. An invasive revascularization strategy was weighed considering the ischemic/hemorrhagic risk and was more common in ST-elevation myocardial infarction than in non-ST-elevation myocardial infarction patients. Despite the significant prevalence of atrial fibrillation and concomitant treatment with oral anticoagulation, the rates of in-hospital and 1-year cardiovascular death, ischemic and bleeding events were lower than those described previously, underlying the importance of a tailored therapeutic approach in this population.

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## INTRODUCTION

Elderly patients, with an increased average lifespan, represent a rapidly growing part of the population who are more susceptible both to acute coronary syndromes (ACS) and to their complications as well as complications related to antithrombotic treatment<sup>[1,2]</sup>. These patients are poorly represented in clinical studies and are more likely to have multiple comorbidities<sup>[3,4]</sup>.

There is no universally accepted definition of an “elderly” patient. The most commonly used cut-off in the literature is 75 years as a significant worsening of outcome after an acute coronary event has been shown by this age<sup>[5]</sup>, but a cut-off of 80 years might be more significant and correspond to clinical practice<sup>[6]</sup>. As these patients more frequently present with atypical symptoms, the diagnosis of myocardial infarction (MI) may be delayed or missed. Irrespective of age, an early invasive strategy should be considered in ACS, although increasing age is known to be an important predictor of worse outcomes<sup>[6-8]</sup>. Furthermore, the need to start antiplatelet therapy and eventually anticoagulant therapy, if atrial fibrillation (AF) is associated, increases the risk of morbidity and mortality in this frail population. For all these reasons and due to the paucity of specific evidence, the management of these patients still represents a challenge<sup>[9]</sup>.

In the present real-world study on a population of “elderly” patients hospitalized



due to an acute myocardial infarction, we aimed to investigate our practice during in-hospital time and outcomes during the first year of follow-up, including the safety of antithrombotic therapy<sup>[10]</sup>.

## MATERIALS AND METHODS

All consecutive patients older than 80 years admitted to the Division of Cardiology of St. Andrea Hospital of Vercelli from January 2018 to December 2018 for ST-elevation myocardial infarction (STEMI) or non-ST elevation myocardial infarction (NSTEMI) were retrospectively evaluated. The diagnosis was based on the European Society of Cardiology guidelines for the management of acute myocardial infarction in patients presenting with and without ST-segment elevation<sup>[3,4]</sup>.

For each patient, we evaluated cardiovascular risk factors (hypertension, hyperlipidemia, diabetes, overweight defined as body mass index > 25, smoking, family history of coronary artery disease), creatinine and hemoglobin levels at admission and discharge. An evaluation of the global hemorrhagic risk for each patient was performed a posteriori by calculating the PRECISE-DAPT score<sup>[11]</sup>. We also reported the prevalence of previous paroxysmal, persistent/permanent AF or its in-hospital de-novo incidence.

In-hospital management, consisting of coronary angiography and percutaneous coronary angioplasty or conservative strategy is described, as well as the following medical therapy for each patient, in particular treatment with single or dual antiplatelet therapy (DAPT) started during hospitalization and, when necessary, anticoagulant therapy [vitamin K inhibitors (VKAs) or direct oral anticoagulants (DOACs)].

The 1-year follow-up data were collected through ambulatory visits or telephone interviews and were focused on the efficacy endpoint consisting of major adverse cardiovascular events (MACEs, including CV death, stroke and myocardial infarction) and the safety endpoint including minor and major bleeding, classified according to the modified thrombolysis in myocardial infarction trial definitions<sup>[12]</sup>: A bleeding event was defined as major if it was intracranial or if red blood cell transfusion was clinically indicated in association with a significant drop in hemoglobin level. One-year global death is also reported.

A comparison between STEMI and NSTEMI patients was performed concerning clinical features, invasive and medical management and subsequent follow-up.

### Statistical analysis

Data are shown as median (interquartile range) for continuous variables, and number (percentage) for categorical data. Student's *t*-test, Mann-Whitney *U* test, Fisher's exact test, and  $\chi^2$  test were used, as appropriate. A *P* value < 0.05 was considered statistically significant. Survival curves including the log-rank test for STEMI and NSTEMI patients were built. Statistical analyses were performed with SPSS Statistics Version 23 (IBM, United States). The statistical methods used in this study were reviewed by our expert Biostatistician Eraldo Occhetta.

## RESULTS

Baseline patients' characteristics are shown in **Table 1**. Of the 105 patients enrolled, 68 (64.8%) were admitted for NSTEMI and 37 (35.2%) for STEMI (**Figure 1**). The mean age of these patients was  $83.9 \pm 3.6$  years.

Patients presenting with STEMI were more likely to receive an invasive treatment: 34 (91.9%) underwent coronary angiography and all of them were treated with percutaneous revascularization; among the NSTEMI patients, 42 (61.8%) underwent coronary angiography and 16 (38.1%) of them had a percutaneous angioplasty performed (**Table 2** and **Figure 2**). The most common reasons for revascularization not being performed in this subgroup of patients were non-obstructive coronary artery disease, small target vessels inappropriate for intervention, extensive three vessel disease without a "culprit lesion" identified and associated severe valvular disease. The most common reason for coronary angiography not being performed in 38.2% of patients, instead, was the perception of the absence of a net clinical benefit by the treating physicians considering the global risk/benefit ratio.

Twenty-five patients (23.8%) had AF either before or as new onset during the index

**Table 1** Baseline patients' characteristics, *n* (%)

Parameters	All ( <i>n</i> = 105)	Pathology		<i>P</i> value
		STEMI ( <i>n</i> = 37)	NSTEMI ( <i>n</i> = 68)	
Age (yr)	83.9 ± 3.6	83.6 ± 3.9	84.0 ± 3.5	0.592
Males	55 (52.3)	16 (43.2)	39 (57.3)	0.239
BMI (kg/m <sup>2</sup> )	25.9 ± 5.4	25.7 ± 3.8	26 ± 6.1	0.787
LVEF (%)	45 ± 11.1	43 ± 12.2	46 ± 10.5	0.190
History of AF	15 (14.3)	5 (13.5)	10 (14.7)	0.900
Paroxysmal	7 (7.7)	3 (8.1)	4 (5.9)	-
Persistent/Permanent	8 (7.6)	2 (5.4)	6 (8.8)	-
New onset AF	10 (9.5)	3 (8.1)	7 (10.2)	0.999
Hypertension	75 (71.4)	23 (62.2)	52 (76.5)	0.186
Dyslipidemia	36 (34.3)	10 (27)	26 (38.2)	0.347
Diabetes	34 (32.4)	13 (35.1)	21 (30.9)	0.821
Overweight	20 (19)	5 (13.5)	15 (22.1)	0.421
Smoking active or previous	21 (20)	5 (13.5)	16 (23.5)	0.332
Family history of CAD	9 (8.6)	4 (10.8)	5 (7.4)	0.789
Creatinine at admission (mg/dL)	1.15 ± 0.4	1.0 ± 0.4	1.2 ± 0.5	0.039
Creatinine at discharge (mg/dL)	1.31 ± 0.6	1.3 ± 0.5	1.3 ± 0.7	0.999
Hemoglobin at admission (g/dL)	12.6 ± 2.1	13.2 ± 2.0	12.3 ± 2.1	0.035
Hemoglobin at discharge (g/dL)	12.3 ± 1.9	12.4 ± 1.7	12.2 ± 1.9	0.594

Continuous variables are presented as mean value ± SD or median value (IQR). STEMI: ST-elevation myocardial infarction; NSTEMI: Non-ST-elevation myocardial infarction; BMI: Body mass index; LVEF: Left ventricular ejection fraction; AF: Atrial fibrillation; CAD: Coronary artery disease.

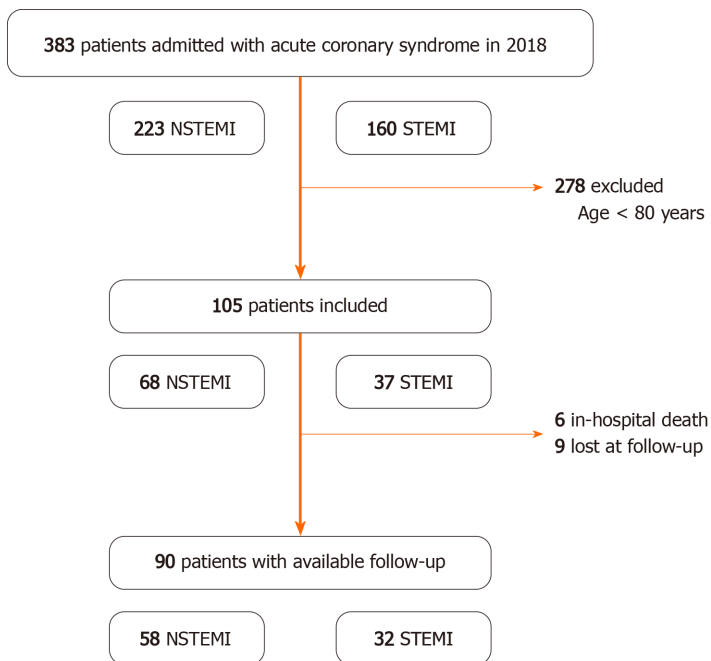
**Table 2** Acute management and antithrombotic therapy, *n* (%)

Treatment strategy	All ( <i>n</i> = 105)	Pathology		<i>P</i> value
		STEMI ( <i>n</i> = 37)	NSTEMI ( <i>n</i> = 68)	
Acute management				
Coronary angiography	76 (72.4)	34 (91.9)	42 (61.8)	0.001
Coronary revascularization	60 (57.1)	34 (91.9)	26 (38.2)	< 0.001
Elective medical therapy	29 (27.6)	3 (8.1)	26 (38.2)	0.001
Antithrombotic therapy				
SAPT	18 (17.1)	3 (8.1)	15 (22)	0.115
DAPT	66 (62.9)	28 (75.7)	38 (55.9)	0.072
SAPT + OAC	10 (9.5)	3 (8.1)	7 (10.3)	0.999
Triple therapy	11 (10.5)	3 (8.1)	8 (11.8)	0.823

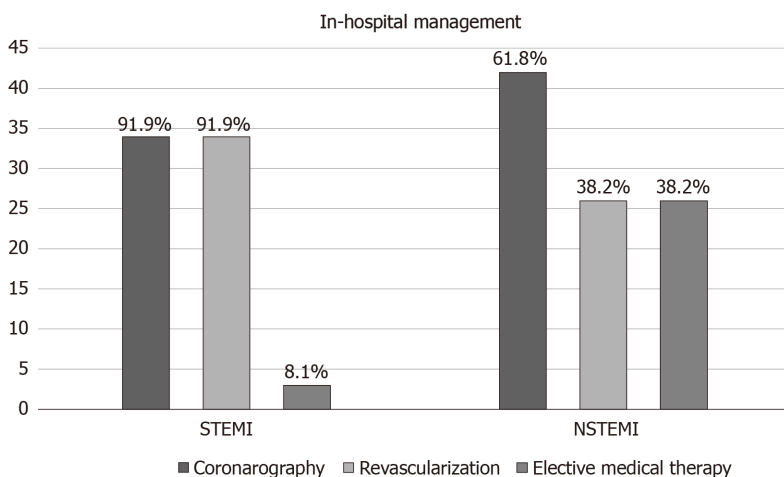
STEMI: ST-elevation myocardial infarction; NSTEMI: Non-ST-elevation myocardial infarction; SAPT: Single antiplatelet therapy; DAPT: Double antiplatelet therapy; OAC: Oral anticoagulation.

hospitalization that required specific treatment with oral anticoagulation. No significant difference was found between NSTEMI and STEMI patients concerning the history or new onset of AF.

With regard to antithrombotic medications: 8.1% of STEMI patients and 22% of NSTEMI patients received a single antiplatelet therapy; 75.7% of STEMI patients and



**Figure 1 Study flow-chart.** This figure shows the patients selected and followed-up in our study. NSTEMI: Non-ST-elevation myocardial infarction; STEMI: ST-elevation myocardial infarction.



**Figure 2 In-hospital patient management.** This figure shows the in-hospital management of patients. Percentages refer to the single non-ST-elevation myocardial infarction and ST-elevation myocardial infarction population, respectively. NSTEMI: Non-ST-elevation myocardial infarction; STEMI: ST-elevation myocardial infarction.

55.9% of NSTEMI patients were treated with DAPT; 8.1% of STEMI and 10.3% of NSTEMI were treated with single antiplatelet therapy plus antithrombotic therapy (VKAs or DOACs); 8.1% of the STEMI group and 11.8% of the NSTEMI group were treated with DAPT plus anticoagulant therapy (VKAs or DOACs) (Table 2). Following statistical analyses, STEMI patients, as compared with NSTEMI patients, showed a trend towards a higher rate of DAPT administration.

Values of serum creatinine varied significantly from admission to discharge, in STEMI but not in NSTEMI patients, while a trend towards significance was found for hemoglobin; these differences may likely reflect the higher percentage of the invasive strategy in the former group.

During hospitalization, 6 (5.7%) patients (3 in the NSTEMI and 3 in the STEMI group) died, all due to cardiovascular causes. One major bleeding complication (hematoma at the femoral access site) and 2 minor bleeding complications occurred.

After hospital discharge, 9 patients were lost to follow-up. For the remaining 90 patients, the mean follow-up was  $11.1 \pm 7.2$  mo. Table 3 summarizes the main outcomes.



**Table 3 Clinical outcomes, *n* (%)**

Clinical outcomes	All	Pathology		P value
		STEMI	NSTEMI	
Efficacy endpoint				
In-hospital mortality	6/105 (5.7)	3/37 (8.1)	3/68 (4.4)	0.702
1-year MACEs <sup>1</sup>	7/90 (7.8)	4/32 (12.5)	3/58 (5.2)	0.457
Ischemic stroke	1/90 (1.1)	0/32	1/58 (1.7)	-
Cardiovascular death	3/90 (3.3)	2/32 (6.3)	1/58 (1.7)	-
Myocardial infarction	3/90 (3.3)	2/32 (6.3)	1/58 (1.7)	-
1-year non-cardiovascular death	11/90 (12.2)	6/32 (18.8)	5/58 (8.6)	0.369
Safety endpoint				
In-hospital minor bleeding	2/105 (1.9)	0/37	2/68 (2.9)	0.834
In-hospital major bleeding	1/105 (1.0)	0/37	1/68 (1.5)	0.999
Minor bleeding after discharge <sup>1</sup>	9/90 (10)	3/32 (9.4)	6/58 (10.3)	0.999
Major bleeding after discharge <sup>1</sup>	2/90 (2.2)	0/32	2/58 (3.4)	0.846

<sup>1</sup>1-year MACE and after-discharge bleeding events percentages refer to 90 patients (9 patients were lost to follow-up and 6 patients died during hospitalization). STEMI: ST-elevation myocardial infarction; NSTEMI: Non-ST-elevation myocardial infarction; MACEs: Major adverse cardiovascular events.

MACEs were recorded in 7 patients (7.8%). Only 3 patients (3.3%) experienced cardiovascular death, while 11 patients (12.2%) died of non-cardiovascular causes, mainly due to malignancy, pneumonia or sepsis. No deaths attributable to bleeding complications were recorded.

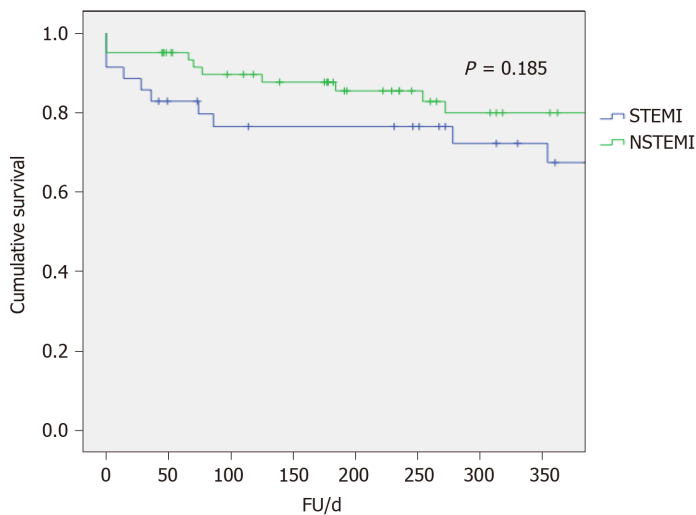
No significant difference was found between NSTEMI and STEMI patients concerning the incidence of all-cause death or any event during hospitalization or follow-up (Figure 3 and Table 3).

Concerning the safety endpoint, 2 patients experienced a major non-fatal spontaneous bleeding event at follow-up: One of them was on DAPT, the other was on triple antithrombotic therapy. Minor bleeding was reported in 9 patients (10%). Even if no specific antithrombotic strategy significantly correlated with the safety endpoints, all patients who experienced bleeding were taking DAPT or dual/triple antithrombotic therapy. The hemorrhagic risk estimated through the PRECISE-DAPT score [median value 35 (IQR 29-40)] did not correlate with the incidence of minor or major bleeding events ( $P = 0.602$ ); however, as specified, this score was retrospectively calculated and was not used to determine the duration of DAPT.

## DISCUSSION

In this retrospective registry of elderly patients admitted to our division due to myocardial infarction, we describe our in-hospital management of this population, and report a low incidence of complications in the short and medium-term follow-up.

Available data to guide the management of elderly patients are limited, both because they are underrepresented in Acute Coronary Syndrome registries (27%–34%) and randomized controlled trials (RCTs) (13%–15%)<sup>[13–15]</sup>, and because, due to a selection bias, RCTs may not be representative of the population treated in everyday clinical practice<sup>[1,2]</sup>. It is known that the atypical clinical and ECG presentation and the lower specificity of troponin assays may delay the diagnosis<sup>[16,17]</sup>. In registries, elderly patients are less likely to receive evidence-based therapies and undergo an invasive strategy compared with younger patients<sup>[13]</sup>. Therefore, focusing on this subgroup is of particular interest for two main reasons. Firstly, with the aging of the population, the elderly represent a growing number of patients presenting with myocardial infarction. Moreover, age is a very important prognostic factor: Patients over 75 years account for 60% of the entire mortality due to cardiovascular diseases and they are often more subject to infarct-related complications such as heart failure and pulmonary edema,



**Figure 3 Kaplan-Meier curves of all-cause death.** This figure shows the 1-year survival curves. *P* value refers to the Log-rank test. NSTEMI: Non-ST elevation myocardial infarction; STEMI: ST elevation myocardial infarction; FU: Follow-up.

which occur in more than half of patients over 75 years and in 65% of patients over the age of 85; shock occurs in more than 10% of patients over 75 years and is mainly due to rupture of the left ventricular free wall or papillary muscles or to advanced ventricular dysfunction<sup>[2,18]</sup>.

In our real-world cohort, the mean age was 83 years, higher than that reported in previous studies<sup>[19,20]</sup>. A tailored therapeutic approach based on a comprehensive evaluation of the patient's status and comorbidities proved successful as we report a rate of adverse events at follow-up lower than previous studies<sup>[21,22]</sup> (Table 4). Since the available evidence differs between NSTEMI and STEMI elderly patients, we differentiated these populations, reporting data for each subgroup.

### Revascularization in NSTEMI

European clinical practice guidelines on non-ST elevation acute coronary syndrome (NSTEMI-ACS) state that elderly patients should be considered for an invasive strategy and emphasize the need for a detailed clinical evaluation including comorbidities, life expectancy, quality of life, frailty and patient preferences, in order to individualize the risks and benefits<sup>[3]</sup>. However, no specific recommendation is available to guide therapeutic decisions based on these parameters.

With regard to NSTEMI in the GRACE registry, coronary angiography was performed in 67% of patients < 70 years of age compared with 33% in patients over 80 years<sup>[21,22]</sup>. Similar percentages were observed in the CRUSADE experience (coronary revascularization performed in 40.1% of patients 75–89 years of age *vs* 12.6% in those ≥ 90 years)<sup>[23,24]</sup>, in the SWEDEHEART experience<sup>[25]</sup> and in the Euroheart ACS survey<sup>[13]</sup>. In our experience, the percentages were higher than those reported in previous studies. In fact, 61.8% of NSTEMI patients greater than 80 years underwent coronary angiography and of these 61.9% underwent percutaneous revascularization. Nagata *et al*<sup>[19]</sup> adopted an invasive strategy in 94% of NSTEMI but reported high rates of in-hospital mortality (8.5%) in patients > 80 years of age.

Whether acute revascularization is the best strategy for these patients is still a matter of debate. In the FRISC II-ICTUS-RITA-3 study, the invasive therapeutic strategy performed better in elderly NSTEMI-ACS patients than in younger patients<sup>[26]</sup>. On the contrary, Sanchis *et al*<sup>[27]</sup> and García-Blas *et al*<sup>[28]</sup> showed that invasive management did not modify long-term outcome in comorbid elderly patients with NSTEMI. The Italian-ACS trial included 313 NSTEMI-ACS patients over 75 years and found no significant benefit of the routine invasive strategy in a composite primary endpoint including ischemic and bleeding events, when compared to selective invasive strategy<sup>[6]</sup>. On the other hand, the After Eighty trial (457 NSTEMI-ACS patients ≥ 80 years) showed a significant benefit of the routine invasive strategy in the composite primary ischemic endpoint compared to the conservative strategy<sup>[29]</sup>, although only 457 patients were included out of 4187 screened and the included population may not reflect the whole spectrum of elderly patients. In a meta-analysis of four RCTs comparing routine invasive strategy with a selective invasive strategy, including 1887 patients (mean age 79 years) no significant difference in all-cause death, cardiovascular

**Table 4 Comparison of observational studies including elderly patients with acute coronary syndrome**

Ref.	Cohort	Mean age (yr)	Invasive strategy (%)	In-hospital mortality (%)	Major bleeding (%)	MACEs (%)
Rosengren <i>et al</i> <sup>[13]</sup> , 2006	NSTE-ACS, STE-ACS	N/A; 25% of patients > 75 yr	34.6	4.7; 9.7 in patients > 75 yr	N/A	N/A
Devlin <i>et al</i> <sup>[22]</sup> , 2008	NSTE-ACS	66	38	5.8	2.4	9.2
Nagata <i>et al</i> <sup>[19]</sup> , 2017	NSTE-ACS (Elderly group > 80 yr)	73	79	8.5	0	9.9
Toleva <i>et al</i> <sup>[32]</sup> , 2015	STE-ACS (Elderly group > 75 yr)	82.2	70.1	14.2	13	27.6

NSTE-ACS: Non ST-elevation acute coronary syndrome; STE-ACS: ST-elevation acute coronary syndrome; MACEs: Major adverse cardiovascular events; N/A: Not available.

death or major bleeding was found between both strategies at a median 36-mo follow-up<sup>[30]</sup>.

The prognostic impact of revascularization in our patients would be difficult to assess due to the retrospective nature of the study design. Within this context, evidence from the literature and clinical practice shows that a routine early invasive strategy is not always the most favorable, because similar results may be obtained with a medical conservative strategy.

### Revascularization in STEMI

Despite the lower rate of revascularization in the elderly, its benefit appears to be maintained at an older age in this context<sup>[7]</sup>. There is no upper age limit with respect to reperfusion, especially with primary percutaneous coronary intervention (PCI)<sup>[31]</sup>. Observational studies have shown that coronary reperfusion therapy (thrombolysis or PCI) also during STEMI is little used in older age, with a trend directly correlated to age (64.8% between 65 and 69 years, 60.1% between 70 and 74 years, 50.4% between 75 and 79 years, 35.4% between 80 and 84 years, 20.4% > 85 years)<sup>[32]</sup>. A possible explanation for this is the paucity of data on reperfusion in the elderly with STEMI, the presence of atypical symptoms and the related diagnostic and therapeutic delay and comorbidities<sup>[18]</sup>. In our hospital 91.9% of STEMI patients underwent coronary angiography and primary PCI.

### Antithrombotic therapy

The optimal therapy after STEMI and NSTEMI acute treatment is well codified by the actual ESC guidelines<sup>[33]</sup>. In addition, anticoagulant therapy association in AF patients (triple therapy) has recently been confirmed in a Joint European Consensus<sup>[34]</sup>. One of the reasons for suboptimal administration of evidence-based medications in the elderly is that patients may more frequently have contraindications to medications or pharmacodynamic characteristics (absorption, metabolism, distribution and excretion of drugs) that make them prone to medication side effects<sup>[1,2]</sup>. In particular, they have an augmented bleeding risk due to aging, impaired renal function and comorbidities. Observational studies have shown frequent excess dosing of antithrombotic therapies in elderly patients: In this context, lower doses of DOACs could avoid these risks<sup>[35,36]</sup>. Moreover, personalized therapeutic choices between dual and triple antithrombotic therapy for concomitant AF may improve benefits and reduce risks in frail and elderly patients<sup>[37,38]</sup>. Our population presented a high hemorrhagic risk as shown by the median values of the PRECISE-DAPT score; however, with a tailored therapeutic approach we found a low rate of significant bleeding even in those treated invasively.

In conclusion, the authors of this article acknowledge that specific guidelines on the management of elderly patients with ACS are lacking, yet these patients tend to present with various comorbidities, often associated, and exploring every specific scenario in order to standardize clinical management would be impractical.

Trials necessarily restrict enrollment criteria and tend to exclude extreme ages or patients with comorbidities due to the heterogeneity of their clinical presentation.

We therefore present a small cohort of patients showing what is likely to be a common scenario in a cardiology ward. We do believe that, in such a complex context, the approach to treatment should be tailored to the patient: Even if a thorough knowledge of the scientific evidence is essential, physicians need to draw on

experience and common sense.

### **Limitations of the study**

Our study has some limitations. First of all, due to the limited sample size studied, our comparison between STEMI and NSTEMI patients does not have adequate statistical power (90%) for all the results reported (though keeping in mind the limits of a post-hoc power analysis), which therefore need to be interpreted with caution.

Moreover, the retrospective design of the study did not allow a more comprehensive evaluation of patients through a “frailty” assessment that may be useful in the context studied. Moreover, as the PRECISE-DAPT score values were retrospectively calculated, we could not assess its impact in guiding DAPT duration in order to reduce bleeding events. Observational studies, despite their methodological limitations, may reflect evidence closer to the real-life population. Indeed, our study was conceived to describe our real-world practice in elderly patients with acute myocardial infarction and provide information on the management and outcome of this disease in the aging society.

## **CONCLUSION**

In this observational study, we describe data from a real-world setting of elderly patients hospitalized with acute myocardial infarction, and report low in-hospital mortality and a low rate of medium-term ischemic and hemorrhagic complications.

Although the available evidence does not allow us to establish firm recommendations in this subgroup of patients, we report that an invasive strategy in selected cases and an adequate antithrombotic therapy, even in this critical context, can be safely performed. Measures to reduce complication rates in this population include an accurate selection of patients suitable for an invasive strategy, evaluating the presence of comorbidities, a radial access whenever possible and correct dosing of antithrombotic drugs.

Larger registry cohorts with a higher number of patients enrolled are mandatory to study the setting of elderly patients with acute coronary syndromes.

## **ARTICLE HIGHLIGHTS**

### **Research background**

Despite the aging of the population, which makes the clinical presentation of elderly patients with acute myocardial infarction more common, there are no specific guidelines on the management of this subgroup and data are generally extrapolated from trials in which elderly patients represent a minority of the cohort studied. Indeed, controversy exists both on the need for an invasive strategy, especially in frailer patients, and on the optimal medical management.

### **Research motivation**

Exploring and describing the setting of elderly patients with myocardial infarction is particularly useful to identify aspects that need to be improved and sources of mistakes in everyday clinical practice.

### **Research objectives**

In the present real-world study on a population of elderly patients hospitalized due to an acute myocardial infarction, we aimed to investigate our practice during in-hospital time and outcomes during the first year of follow-up.

### **Research methods**

We retrospectively analyzed all consecutive patients older than 80 years admitted to the Division of Cardiology of our center in 2018 for acute myocardial infarction. Clinical and laboratory data were collected. In-hospital management, consisting of an invasive or conservative strategy, and the anti-thrombotic therapy used were described. Outcomes evaluated at 1 year follow-up included an efficacy ischemic endpoint and a safety bleeding endpoint.



### Research results

We enrolled a total of 105 patients with a mean age was  $83.9 \pm 3.6$  years. Patients presenting with ST-elevation myocardial infarction (STEMI) (35%) received an invasive treatment in more than 90% of cases, while the number of patients with non-ST-elevation myocardial infarction (NSTEMI) (65%), who underwent coronary angiography and percutaneous angioplasty was lower (38%). Coronary angiography was not performed when the absence of a net clinical benefit was perceived by the treating physicians considering the global risk/benefit ratio, while coronary angioplasty was not performed mainly due to the absence of an obstructive coronary artery disease or technical reasons. Atrial fibrillation, either before or as new onset during the index hospitalization, was found in 24% of patients. With regard to antithrombotic medications, 10.5% of the whole population received triple antithrombotic therapy and 9.5% single antiplatelet therapy plus oral anticoagulation (OAC), with no significant difference between the subgroups, although a higher number of STEMI patients received dual antiplatelet therapy without OAC as compared with NSTEMI patients. A low rate of in-hospital death (5.7%) and 1-year cardiovascular death (3.3%) was registered. Major adverse cardiovascular events were recorded in 7 patients (7.8%). Interestingly, 11 of 14 deaths at one-year follow-up were the result of non-cardiovascular causes, mainly due to malignancy, pneumonia or sepsis. No deaths attributable to bleeding complications were recorded, while only 2 patients experienced a major non-fatal spontaneous bleeding event at follow-up.

### Research conclusions

The authors of this article acknowledge that specific guidelines on the management of elderly patients with acute coronary syndrome are lacking, yet these patients tend to present with various comorbidities, often associated, and exploring every specific scenario in order to standardize clinical management would be impractical. Trials necessarily restrict enrollment criteria and tend to exclude extreme ages or patients with comorbidities due to the heterogeneity of their clinical presentation. We therefore present a small cohort of patients showing what is likely to be a common scenario in a cardiology ward. We do believe that, in such a complex context, the approach to treatment should be tailored to the patient: Even if a thorough knowledge of the scientific evidence is essential, physicians need to draw on experience and common sense. Through this approach, the rate of complications and death was relatively low in our population. The main limitation of this study, namely its retrospective nature, is somehow a point of strength, as it avoids selection biases which characterize previous studies.

### Research perspectives

Future studies on the elderly population should be based on a registry design. Larger studies with a higher number of patients enrolled are mandatory.

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## Clinical Trials Study

## Endothelial progenitor cells mobilization after maximal exercise according to heart failure severity

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## Abstract

## BACKGROUND

Vascular endothelial dysfunction is an underlying pathophysiological feature of chronic heart failure (CHF). Patients with CHF are characterized by impaired vasodilation and inflammation of the vascular endothelium. They also have low levels of endothelial progenitor cells (EPCs). EPCs are bone marrow derived cells involved in endothelium regeneration, homeostasis, and neovascularization. Exercise has been shown to improve vasodilation and stimulate the mobilization of EPCs in healthy people and patients with cardiovascular comorbidities. However, the effects of exercise on EPCs in different stages of CHF remain under investigation.

## AIM

To evaluate the effect of a symptom-limited maximal cardiopulmonary exercise

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testing (CPET) on EPCs in CHF patients of different severity.

## METHODS

Forty-nine consecutive patients (41 males) with stable CHF [mean age (years):  $56 \pm 10$ , ejection fraction (EF, %):  $32 \pm 8$ , peak oxygen uptake ( $\text{VO}_2$ , mL/kg/min):  $18.1 \pm 4.4$ ] underwent a CPET on a cycle ergometer. Venous blood was sampled before and after CPET. Five circulating endothelial populations were quantified by flow cytometry: Three subgroups of EPCs [ $\text{CD34}^+/\text{CD45}^-/\text{CD133}^+$ ,  $\text{CD34}^+/\text{CD45}^-/\text{CD133}^+/\text{VEGFR}_2$  and  $\text{CD34}^+/\text{CD133}^+/\text{vascular endothelial growth factor receptor 2 (VEGFR}_2)$ ] and two subgroups of circulating endothelial cells ( $\text{CD34}^+/\text{CD45}^-/\text{CD133}^-$  and  $\text{CD34}^+/\text{CD45}^-/\text{CD133}^-/\text{VEGFR}_2$ ). Patients were divided in two groups of severity according to the median value of peak  $\text{VO}_2$  (18.0 mL/kg/min), predicted peak  $\text{VO}_2$  (65.5%), ventilation/carbon dioxide output slope (32.5) and EF (reduced and mid-ranged EF). EPCs values are expressed as median (25th-75th percentiles) in cells/ $10^6$  enucleated cells.

## RESULTS

Patients with lower peak  $\text{VO}_2$  increased the mobilization of  $\text{CD34}^+/\text{CD45}^-/\text{CD133}^+$  [pre CPET: 60 (25-76) *vs* post CPET: 90 (70-103) cells/ $10^6$  enucleated cells,  $P < 0.001$ ],  $\text{CD34}^+/\text{CD45}^-/\text{CD133}^+/\text{VEGFR}_2$  [pre CPET: 1 (1-4) *vs* post CPET: 5 (3-8) cells/ $10^6$  enucleated cells,  $P < 0.001$ ],  $\text{CD34}^+/\text{CD45}^-/\text{CD133}^-$  [pre CPET: 186 (141-361) *vs* post CPET: 488 (247-658) cells/ $10^6$  enucleated cells,  $P < 0.001$ ] and  $\text{CD34}^+/\text{CD45}^-/\text{CD133}^-/\text{VEGFR}_2$  [pre CPET: 2 (1-2) *vs* post CPET: 3 (2-5) cells/ $10^6$  enucleated cells,  $P < 0.001$ ], while patients with higher  $\text{VO}_2$  increased the mobilization of  $\text{CD34}^+/\text{CD45}^-/\text{CD133}^+$  [pre CPET: 42 (19-73) *vs* post CPET: 90 (39-118) cells/ $10^6$  enucleated cells,  $P < 0.001$ ],  $\text{CD34}^+/\text{CD45}^-/\text{CD133}^+/\text{VEGFR}_2$  [pre CPET: 2 (1-3) *vs* post CPET: 6 (3-9) cells/ $10^6$  enucleated cells,  $P < 0.001$ ],  $\text{CD34}^+/\text{CD133}^+/\text{VEGFR}_2$  [pre CPET: 10 (7-18) *vs* post CPET: 14 (10-19) cells/ $10^6$  enucleated cells,  $P < 0.01$ ],  $\text{CD34}^+/\text{CD45}^-/\text{CD133}^-$  [pre CPET: 218 (158-247) *vs* post CPET: 311 (254-569) cells/ $10^6$  enucleated cells,  $P < 0.001$ ] and  $\text{CD34}^+/\text{CD45}^-/\text{CD133}^-/\text{VEGFR}_2$  [pre CPET: 1 (1-2) *vs* post CPET: 4 (2-6) cells/ $10^6$  enucleated cells,  $P < 0.001$ ]. A similar increase in the mobilization of at least four out of five cellular populations was observed after maximal exercise within each severity group regarding predicted peak, ventilation/carbon dioxide output slope and EF as well ( $P < 0.05$ ). However, there were no statistically significant differences in the mobilization of endothelial cellular populations between severity groups in each comparison ( $P > 0.05$ ).

## CONCLUSION

Our study has shown an increased EPCs and circulating endothelial cells mobilization after maximal exercise in CHF patients, but this increase was not associated with syndrome severity. Further investigation, however, is needed.

**Key Words:** Chronic heart failure; Endothelial progenitor cells; Circulating endothelial cells; Maximal exercise; Cardiopulmonary exercise testing; Severity

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**Core Tip:** Vascular endothelial dysfunction is an underlying pathophysiological feature of chronic heart failure (CHF). Exercise has been proven to increase the mobilization of endothelial progenitor cells (EPCs), which are involved in vascular endothelial restoration and neo-vascularization, in healthy people and patients with co-morbidities. However, the effect of exercise on EPCs in patients with CHF of different severity remains unknown. In the present study, we compared the mobilization of EPCs in CHF patients of different severity, according to functional markers, after a symptom-limited cardiopulmonary exercise testing. No differences were found between severity groups, indicating thus the beneficial effect of exercise in these patients.

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## INTRODUCTION

Chronic heart failure (CHF) is a multifactorial clinical syndrome with an incidence between 1% and 2% per year in developed countries in all age categories, while increasing to > 10% in the age category > 70 years<sup>[1]</sup>. Prognosis of patients with CHF is poor as the survival rates do not exceed 50% within 4 years and 26.7% within 10 years from the diagnosis<sup>[2,3]</sup>.

A characteristic pathophysiological feature of CHF is vascular endothelial dysfunction<sup>[4]</sup> and microcirculation abnormalities associated with CHF severity<sup>[5]</sup>. Systemic inflammation caused by secretion of cytokines leads to disruption of the vascular endothelial barrier and causes acute endothelitis<sup>[6]</sup>. Vessels show impaired vasodilation due to increased degradation and reduced bioavailability of the nitric oxide (NO)<sup>[6,7]</sup>.

Exercise has a beneficial impact in the function of the vascular endothelium. It has been shown that it suppresses the generation of free radicals and oxidative stress, increases the bioavailability of NO and induces vasodilation, thereby improving the aerobic capacity<sup>[8,9]</sup>. Endothelial progenitor cells (EPCs) have been proven to be involved in the shielding of vascular protection, the restoring of dysfunctional and injured endothelium, the promotion of angiogenesis and the regulation of vascular homeostasis<sup>[10,11]</sup>. The level of EPCs seem to predict the occurrence of cardiovascular events and death from cardiovascular causes and may help to identify patients at increased cardiovascular risk<sup>[12]</sup>. Low counts of EPCs have been shown to be strongly and independently predictive of mortality in patients with cardiovascular comorbidities<sup>[13]</sup>.

Regular aerobic exercise induces the mobilization of EPCs from the bone marrow, not only in the healthy population but also in populations with comorbidities and increased risk factors<sup>[14,15]</sup>. However, the effect of maximal exercise on EPCs in patients with CHF, and especially in patients of different severity, remains under investigation.

We hypothesized that maximal exercise has a beneficial effect on vascular endothelial function in patients with CHF irrespectively of their severity. The aim of the study was to assess, quantify and compare the acute mobilization of EPCs after maximal exercise in patients with CHF of both lower and higher severity.

## MATERIALS AND METHODS

### Study design

This interventional clinical study was conducted in accordance with the Declaration of Helsinki and approved by the Administration Board and the Ethics Committee of "Evangelismos General Hospital" in Athens, Greece (Approval No. 117/3-7-2017). All of the patients signed an informed consent form in order to participate in the study. This is a post-hoc analysis study of a previous conducted research study published recently aiming to assess EPCs mobilization after exercise in patients with CHF<sup>[16]</sup>. Patients were referred for assessment to the "Clinical Ergospirometry, Exercise and Rehabilitation Laboratory" of "Evangelismos General Hospital" by heart failure outpatient clinics of Athens. The diagnosis of CHF was based on personal history forms, clinical evaluation and laboratory testing of every patient.

### Patients

The population of the study consisted of 49 consecutive patients with stable CHF and a reduced or mid-ranged ejection fraction (EF) who underwent a single session of symptom limited maximal cardiopulmonary exercise testing (CPET) on an electromagnetically braked cycle ergometer (Ergoline 800; SensorMedics Corporation, Anaheim, CA, United States). Inclusion criteria were stable CHF at maximum tolerated medication and EF ≤ 49%. Exclusion criteria were severe valvulopathy, uncontrolled arterial hypertension, severe chronic obstructive pulmonary disease, severe peripheral angiopathy, neuromuscular diseases and contraindications for

maximum cardiopulmonary stress testing<sup>[17]</sup>.

Patients were divided in groups according to syndrome severity. CPET indices [peak oxygen uptake ( $\text{VO}_2$ ), predicted peak  $\text{VO}_2$  and ventilation (VE)/carbon dioxide output ( $\text{VCO}_2$ )] were used in order to divide these patients in two groups for each parameter. Cut off values (medians) were set for each of these parameters; a value of 18.0 mL/kg/min was set for peak  $\text{VO}_2$ , a value of 65.5% for predicted peak  $\text{VO}_2$  and a value of 32.5 for VE/ $\text{VCO}_2$ . The demographic and exercise characteristics between severity groups divided by peak  $\text{VO}_2$  are shown in Table 1 and for the other parameters in Supplementary Tables 1-3).

Patients were also divided in two groups according to their EF. The first group consisted of patients with CHF with a reduced EF (< 40%), while the second group included patients with CHF with a mid-ranged EF (40%-49%).

### CPET

Patient performed a ramp-incremental exercise test, using the Hansen *et al*<sup>[18]</sup> equation for individual work rate increments, so as to aim for a test of 8-12 min duration. The nose of the patients was clamped, and they breathed through a special mask with a low resistance valve and a known gas mixture. Breathing parameters such as  $\text{VO}_2$ ,  $\text{VCO}_2$  and VE were measured in each breath by the software, and their values were recorded at the monitor of the computer system (Vmax 229, Sensor Medics). The gas exchanges of each patient were also recorded in order to calculate more specific values such as resting  $\text{VO}_2$ ,  $\text{VO}_2$  at peak exercise (peak  $\text{VO}_2$ ), predicted  $\text{VO}_2$  at peak exercise (predicted peak  $\text{VO}_2$ ) and VE/ $\text{VCO}_2$  slope.

All of the measurements were usually recorded in four time points; the first was for 2 min at rest (baseline values), the second for 2 min of unloaded pedaling before the beginning of the exercise, the third during exercise and the last for 5 min during the recovery point. A 12-lead electrocardiogram system was also attached on the patient's body in order to monitor the heart rate and the heart rhythm, a pulse oximeter on the patient's finger measured the saturation and blood pressure was measured every 2 min. The end point of the session was due to electrocardiogram abnormal rhythm at the monitor, dyspnea or leg fatigue of the patient.

The peak values for  $\text{VO}_2$ ,  $\text{VCO}_2$  and VE were calculated as the average of measurements made during the 20-s period before the end of exercise<sup>[19]</sup>. Peak work rate was defined as the highest work rate reached and maintained at a pedaling frequency of no less than 65 revolutions per min. The ventilatory response to exercise was calculated as the slope by linear regression of VE *vs*  $\text{VCO}_2$  from the beginning of exercise to anaerobic threshold, where the relationship was linear<sup>[19]</sup>.

### Flow cytometry analyses

For evaluation of EPCs, blood samples were drawn from a peripheral vein of each patient, once before the CPET at rest and once just after the CPET. Venous blood was collected in ethylenediaminetetraacetic acid tubes. Blood samples were taken to the immunology laboratory within the first hour after the collection where they were measured with the use of flow cytometry. The protocol that we implemented was the Duda *et al*<sup>[20]</sup> protocol, where four types of monoclonal antibodies were used; CD45, CD34, CD133 and vascular endothelial growth factor receptor 2 (VEGFR<sub>2</sub>, CD309). In the meantime, five different cellular populations, three subgroups of EPCs and two subgroups of circulating endothelial cells (CECs) were defined; these were CD34<sup>+</sup>/CD45<sup>-</sup>/CD133<sup>+</sup>, CD34<sup>+</sup>/CD45<sup>-</sup>/CD133<sup>+</sup>/VEGFR<sub>2</sub>, CD34<sup>+</sup>/CD133<sup>+</sup>/VEGFR<sub>2</sub> (EPCs subgroups), CD34<sup>+</sup>/CD45<sup>-</sup>/CD133<sup>-</sup> and CD34<sup>+</sup>/CD45<sup>-</sup>/CD133<sup>-</sup>/VEGFR<sub>2</sub> (CECs subgroups).

Four-color flow cytometry was performed in the Flow Cytometry Core Laboratory with BD FACSCantoII (Becton-Dickinson, Franklin Lakes, NJ, United States) flow cytometer. Each analysis on the flow cytometer included  $1 \times 10^6$  events. The number of EPCs was expressed as absolute number of cells/ $10^6$  enucleated cells (Figure 1).

### Statistical analyses

Patients were divided according to CHF severity based on CPET assessment, and results are presented according to severity groups. Descriptive characteristics are expressed as mean  $\pm$  standard deviation while values of cellular populations belong to non-normal distribution, and they are expressed in median (25<sup>th</sup>-75<sup>th</sup> percentiles). All categorical variables are presented as absolute and percentage values. Normality of distribution was checked with the Shapiro-Wilk test. We used the Spearman's correlation coefficient to assess the direction and the magnitude of the association between the absolute and percentage differences of each endothelial cellular



**Table 1 Demographic characteristics and maximal cardiopulmonary exercise testing indices of patients with chronic heart failure of different severity based on peak oxygen uptake**

Demographic characteristics	Group 1	Group 2
Patients, <i>n</i>	25	24
Gender, males/females	21/4	20/4
Age in yr <sup>1</sup>	57 ± 10	55 ± 9
Height in cm <sup>1</sup>	174 ± 11	175 ± 9
Weight in kg <sup>1</sup>	92 ± 25	87 ± 21
NYHA stage, class II/III	16/9	18/6
EF, % <sup>1</sup>	32 ± 9	32 ± 8
<b>Type of CHF</b>		
Dilated cardiomyopathy, <i>n</i> (%)	7 (28)	5 (21)
Ischemic, <i>n</i> (%)	14 (56)	15 (63)
Other, <i>i.e.</i> valvulopathy, <i>etc.</i> , <i>n</i> (%)	4 (16)	4 (17)
<b>Medication</b>		
Diuretics, <i>n</i> (%)	19 (76)	13 (54)
ACE inhibitors, <i>n</i> (%)	11 (44)	13 (54)
ARBs, <i>n</i> (%)	5 (20)	2 (8)
β-Blockers, <i>n</i> (%)	25 (100)	23 (96)
Aldosterone antagonists, <i>n</i> (%)	19 (76)	18 (75)
<b>Cardiopulmonary exercise testing parameters</b>		
Peak VO <sub>2</sub> in mL/kg/min <sup>1</sup>	14.5 ± 2.5	21.8 ± 2.4 <sup>a</sup>
Predicted peak VO <sub>2</sub> , % <sup>1</sup>	52 ± 13	74 ± 11 <sup>a</sup>
VE/VCO <sub>2</sub> slope <sup>1</sup>	34 ± 5	33 ± 4
Peak WR in watts <sup>1</sup>	75 ± 34	118 ± 34 <sup>a</sup>

Group 1: Peak VO<sub>2</sub> < 18.0 mL/kg/min, Group 2: Peak VO<sub>2</sub> ≥ 18.0 mL/kg/min.

<sup>1</sup>Values are expressed as mean ± SD; Difference between the 2 severity groups for demographic characteristics and cardiopulmonary exercise testing parameters (<sup>a</sup>*P* < 0.05). ACE: Angiotensin-converting-enzyme; ARB: Angiotensin II receptor blockers; CPET: Cardiopulmonary exercise testing; CHF: Chronic heart failure; EF: Ejection fraction; NYHA: New York Heart Association; VCO<sub>2</sub>: Carbon dioxide output; VO<sub>2</sub>: Oxygen uptake; WR: Work rate.

population and the values of CPET parameters and EF. Unpaired two sample Student's *t* test analyzed differences in demographics and CPET parameters between severity groups. Wilcoxon signed-rank test for non-parametric data analyzed differences between cellular populations within severity groups. Differences between severity groups were assessed with factorial analysis of variance (ANOVA) 2 × 2 (time × group). Dependent variables were transformed with the natural logarithm when deviating from normality prior to entering the ANOVA models. All tests were two-tailed, and level of observed statistical significance was adjusted to 0.05. No adjustment for multiple comparisons was performed as ANOVA analyses assessed independent outcomes. Statistical analyses were performed with IBM SPSS 25 Statistics software (Armonk, NY, United States).

## RESULTS

Both severity groups, which were divided according to the median value of peak VO<sub>2</sub>, increased the mobilization of their endothelial cellular populations after a symptom-limited CPET (Table 2). In group 1 (peak VO<sub>2</sub> < 18.0 mL/kg/min), all endothelial cellular populations increased except for the CD34<sup>+</sup>/CD133<sup>+</sup>/VEGFR<sub>2</sub> EPCs population, while in group 2 (peak VO<sub>2</sub> ≥ 18.0 mL/kg/min) all endothelial cellular populations increased (Table 2). No differences in the mobilization of endothelial

**Table 2** Acute mobilization of endothelial cellular populations after a symptom-limited cardiopulmonary exercise testing of two different severity groups according to the median value of peak oxygen uptake

Endothelial cellular populations	Group 1 of $n = 25$ , peak $\text{VO}_2 < 18.0$ mL/kg/min		Group 2 of $n = 24$ , peak $\text{VO}_2 \geq 18.0$ mL/kg/min		P value between groups
	Before CPET	After CPET	Before CPET	After CPET	
CD34 <sup>+</sup> /CD45 <sup>+</sup> /CD133 <sup>+</sup>	60 (25-76)	90 (70-103) <sup>e</sup>	42 (19-73)	90 (39-118) <sup>e</sup>	0.329
CD34 <sup>+</sup> /CD45 <sup>+</sup> /CD133 <sup>+</sup> /VEGFR <sub>2</sub>	1 (1-4)	5 (3-8) <sup>e</sup>	2 (1-3)	6 (3-9) <sup>e</sup>	0.075
CD34 <sup>+</sup> /CD133 <sup>+</sup> /VEGFR <sub>2</sub>	13 (9-17)	13 (9-26)	10 (7-18)	14 (10-19) <sup>b</sup>	0.257
CD34 <sup>+</sup> /CD45 <sup>+</sup> /CD133 <sup>+</sup>	186 (141-361)	488 (247-658) <sup>e</sup>	218 (158-247)	311 (254-569) <sup>e</sup>	0.101
CD34 <sup>+</sup> /CD45 <sup>+</sup> /CD133 <sup>+</sup> /VEGFR <sub>2</sub>	2 (1-2)	3 (2-5) <sup>e</sup>	1 (1-2)	4 (2-6) <sup>e</sup>	0.471

Difference within each severity group.

<sup>b</sup> $P < 0.01$ .<sup>e</sup> $P < 0.001$ . CPET: Cardiopulmonary exercise testing;  $\text{VO}_2$ : Oxygen uptake.

cellular populations between the two severity groups were observed (Table 2 and Supplementary Figure 1). Figure 2 shows the difference between the two groups.

Regarding severity groups divided according to the median value of predicted peak  $\text{VO}_2$ , they both increased the mobilization of their endothelial cellular populations after maximal CPET (Supplementary Table 4). In group 1 (predicted peak  $\text{VO}_2 < 65.5\%$ ), all endothelial cellular populations increased, while in group 2 (predicted peak  $\text{VO}_2 \geq 65.5\%$ ) all endothelial cellular populations increased except for the CD34<sup>+</sup>/CD133<sup>+</sup>/VEGFR<sub>2</sub> EPCs population (Supplementary Table 4). No differences in the mobilization of endothelial cellular populations between the two severity groups were observed (Supplementary Table 4).

As far as severity groups divided according to the median value of VE/ $\text{VCO}_2$  slope are concerned, they both increased the mobilization of their endothelial cellular populations after maximal CPET (Table 3). In group 1 (VE/ $\text{VCO}_2 < 32.5$ ), all endothelial cellular populations increased except for the CD34<sup>+</sup>/CD133<sup>+</sup>/VEGFR<sub>2</sub> EPCs population, while in group 2 (VE/ $\text{VCO}_2 \geq 32.5$ ) all endothelial cellular populations increased (Table 3). No differences in the mobilization of endothelial cellular populations between the two severity groups were observed (Table 3).

Finally, for severity groups divided according to their EF, they both increased the mobilization of their endothelial cellular populations after maximal CPET (Table 4). In group 1 (EF < 40%), all endothelial cellular populations increased, while in group 2 (EF  $\geq 40\%$ ) all endothelial cellular populations increased except for the CD34<sup>+</sup>/CD133<sup>+</sup>/VEGFR<sub>2</sub> EPCs population (Table 4). No differences in the mobilization of endothelial cellular populations between the two severity groups were observed (Table 4).

A positive correlation between percentage difference in CD34<sup>+</sup>/CD45<sup>+</sup>/CD133<sup>+</sup>/VEGFR<sub>2</sub> population and peak  $\text{VO}_2$  was observed ( $r = 0.341$ ,  $P = 0.017$ ), while the numeric difference in the same population tended also to correlate positively ( $r = 0.252$ ,  $P = 0.081$ , Supplementary Table 5). We defined new groups of patients according to the median value of the percentage increase of each endothelial cellular population's mobilization. It was revealed that demographics and CPET indices did not differ between the two groups for all endothelial cellular populations except for CD34<sup>+</sup>/CD45<sup>+</sup>/CD133<sup>+</sup>/VEGFR<sub>2</sub> EPCs. Patients with greater increase of this latter EPC population after exercise were younger, had higher peak  $\text{VO}_2$  and work rate peak and lower VE/ $\text{VCO}_2$  slope (Supplementary Table 6).

## DISCUSSION

Our present study demonstrated that a symptom-limited maximal CPET exercise stimulates the mobilization of EPCs and CECs in patients with CHF. However, the results of our study did not show any clear association of EPCs and CECs mobilization and CHF severity.

Attenuated endothelial function has been previously associated with decreased EPCs<sup>[21]</sup>, and EPCs have been linked to the repair mechanism of endothelial damage<sup>[10,11]</sup>.

**Table 3 Acute mobilization of endothelial cellular populations after a symptom-limited cardiopulmonary exercise testing of different severity groups according to the median value of ventilation/carbon dioxide output slope**

Endothelial cellular populations	Group 1 of $n = 27$ , VE/VCO <sub>2</sub> slope < 32.5		Group 2 of $n = 22$ , VE/VCO <sub>2</sub> slope $\geq$ 32.5		P value between groups
	Before CPET	After CPET	Before CPET	After CPET	
CD34 <sup>+</sup> /CD45 <sup>-</sup> /CD133 <sup>+</sup>	62 (41-81)	95 (81-118) <sup>e</sup>	31 (18-66)	70 (33-99) <sup>e</sup>	0.711
CD34 <sup>+</sup> /CD45 <sup>-</sup> /CD133 <sup>+</sup> /VEGFR <sub>2</sub>	1 (1-3)	5 (3-8) <sup>e</sup>	2 (1-4)	5 (3-8) <sup>e</sup>	0.311
CD34 <sup>+</sup> /CD133 <sup>+</sup> /VEGFR <sub>2</sub>	10 (7-16)	13 (10-18)	12 (8-18)	16 (9-29) <sup>b</sup>	0.134
CD34 <sup>+</sup> /CD45 <sup>-</sup> /CD133 <sup>-</sup>	222 (147-287)	419 (267-576) <sup>e</sup>	198 (152-376)	382 (249-794) <sup>e</sup>	0.540
CD34 <sup>+</sup> /CD45 <sup>-</sup> /CD133 <sup>-</sup> /VEGFR <sub>2</sub>	1 (1-2)	3 (2-5) <sup>e</sup>	1 (1-2)	4 (3-6) <sup>e</sup>	0.464

Differences within each severity group.

<sup>b</sup> $P < 0.01$ .<sup>e</sup> $P < 0.001$ . CPET: Cardiopulmonary exercise testing.**Table 4 Acute mobilization of endothelial cellular populations after a symptom-limited cardiopulmonary exercise testing of two different severity groups according to reduced or mid-ranged ejection fraction**

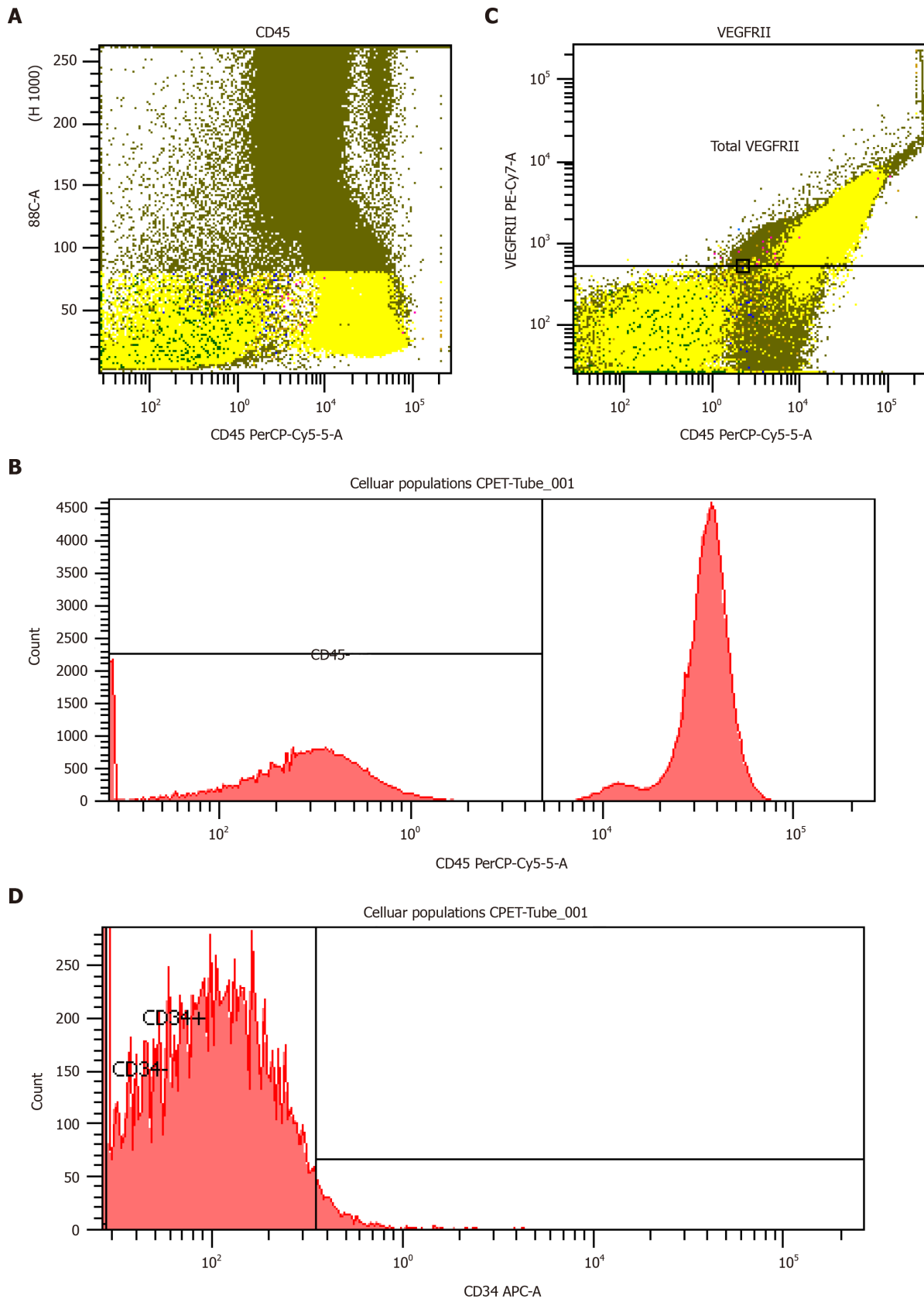
Endothelial cellular populations	Group 1 of $n = 37$ , EF < 40%		Group 2 of $n = 12$ , EF $\geq$ 40%		P value between groups
	Before CPET	After CPET	Before CPET	After CPET	
CD34 <sup>+</sup> /CD45 <sup>-</sup> /CD133 <sup>+</sup>	42 (22-75)	90 (37-106) <sup>e</sup>	63 (40-76)	90 (65-103) <sup>b</sup>	0.888
CD34 <sup>+</sup> /CD45 <sup>-</sup> /CD133 <sup>+</sup> /VEGFR <sub>2</sub>	2 (1-3)	5 (3-8) <sup>e</sup>	2 (1-4)	8(4-8) <sup>b</sup>	0.507
CD34 <sup>+</sup> /CD133 <sup>+</sup> /VEGFR <sub>2</sub>	11 (7-17)	14 (10-23) <sup>b</sup>	15 (9-20)	13 (9-22)	0.473
CD34 <sup>+</sup> /CD45 <sup>-</sup> /CD133 <sup>-</sup>	200 (152-279)	427 (260-626) <sup>e</sup>	227 (135-372)	336 (214-624) <sup>b</sup>	0.702
CD34 <sup>+</sup> /CD45 <sup>-</sup> /CD133 <sup>-</sup> /VEGFR <sub>2</sub>	1 (1-2)	3 (2-6) <sup>e</sup>	1 (1-2)	3 (2-5) <sup>b</sup>	0.828

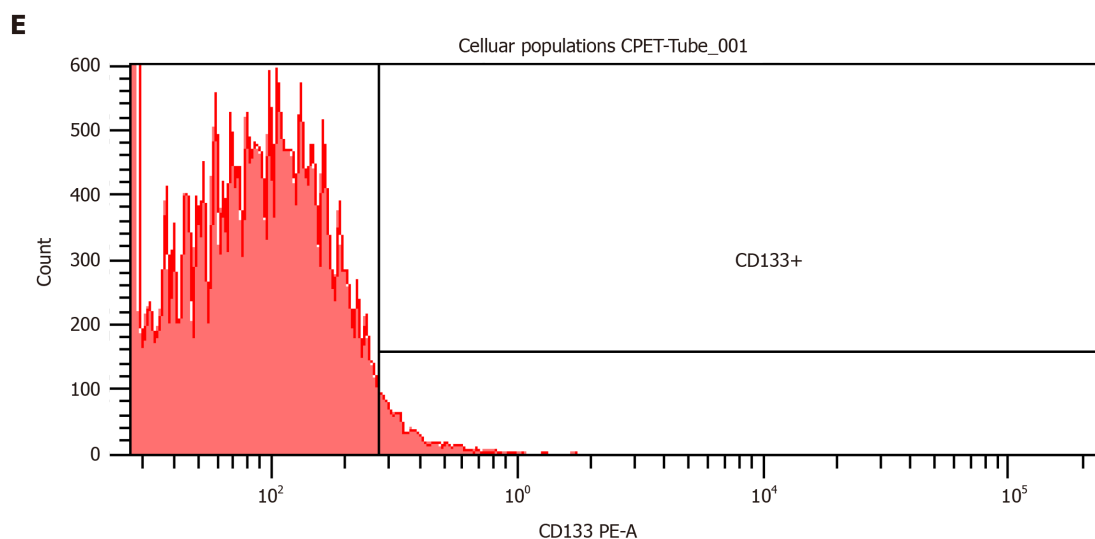
Differences within each severity group.

<sup>b</sup> $P < 0.01$ .<sup>e</sup> $P < 0.001$ . CPET: Cardiopulmonary exercise testing; EF: Ejection fraction.

To our knowledge only one single study has been conducted so far investigating the acute effect of maximal exercise on vascular endothelial function in patients with CHF and most specifically on the EPC populations<sup>[22]</sup>. This was the study of Van Craenenbroeck *et al*<sup>[22]</sup>, who has investigated the effect of a single exercise bout in reversing endothelial dysfunction in CHF patients. Although Van Craenenbroeck *et al*<sup>[22]</sup> have shown a significant improvement in circulating angiogenic cell migratory capacity after exercise, they did not notice a significant increase in EPCs. In the present study, we extend previous findings showing that there is a significant EPCs mobilization after a symptom-limited maximal CPET in patients with CHF, but there was no significant difference between CHF severity groups. An explanation of these differences between the two studies may be the fact that we used different inclusion criteria and parameters for patient severity. In contrast with Van Craenenbroeck *et al*<sup>[22]</sup>, who divided patients according to N-terminal pro-brain natriuretic peptide levels, in our study, we divided patients according to strong prognostic indicators such as peak VO<sub>2</sub>, predicted peak VO<sub>2</sub>, VE/VCO<sub>2</sub> slope and EF. Another possible explanation of the differences might be the methodology used in our study for the EPC quantification. In our study, we have used a more analytic EPC quantification with five endothelial populations defined with the use of four monoclonal antibodies, whereas Van Craenenbroeck *et al*<sup>[22]</sup> used two populations of endothelial cells for their determination (defined as CD34<sup>+</sup>/KDR<sup>+</sup>/CD3<sup>-</sup> and CD34<sup>+</sup>/CD3<sup>-</sup> progenitor cells).

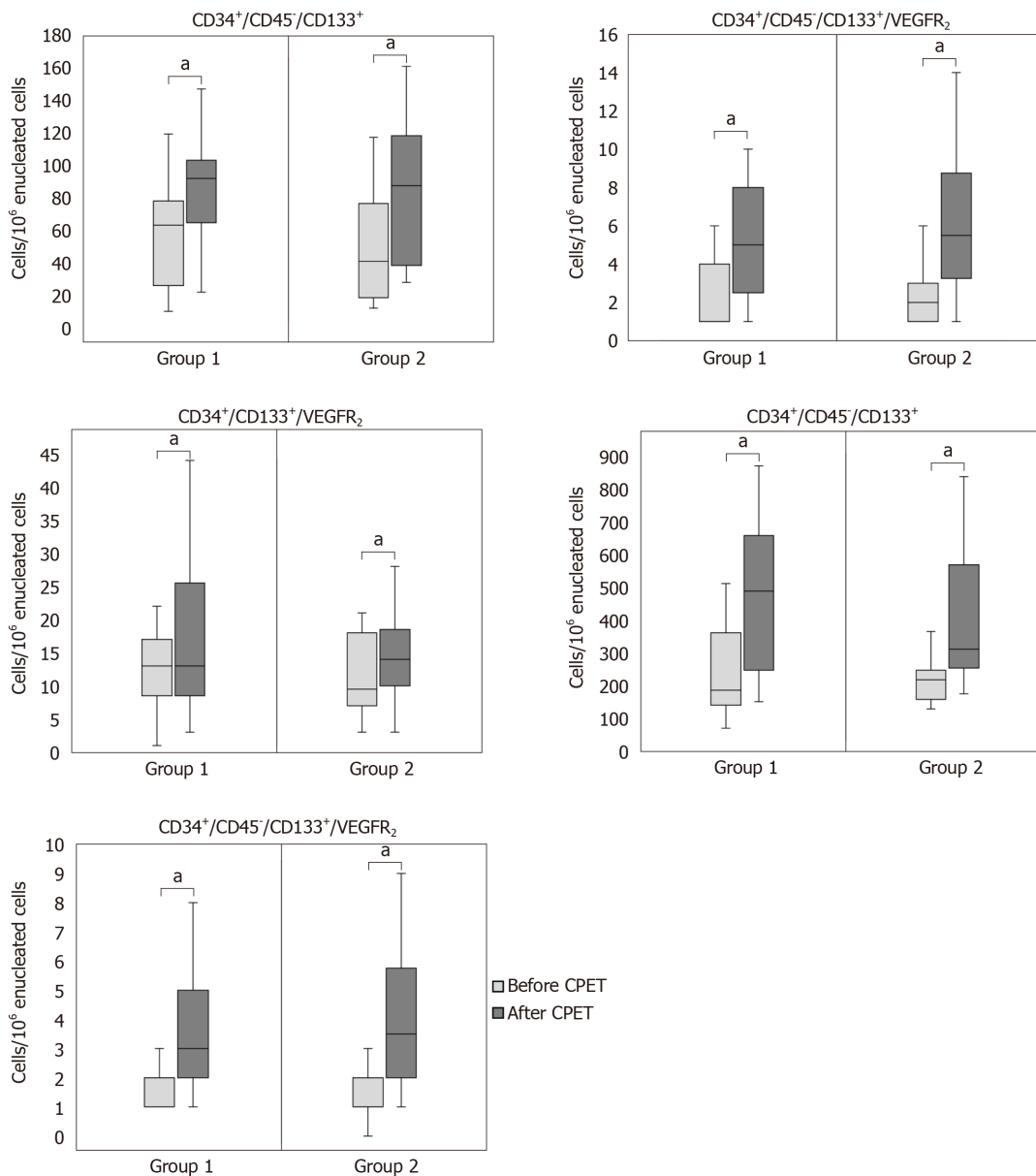
In a previous study from our institute, Stefanou *et al*<sup>[23]</sup> quantified three populations of EPCs in critically ill patients with sepsis including CD34<sup>+</sup>/CD45<sup>-</sup>/CD133<sup>+</sup>, CD34<sup>+</sup>/CD45<sup>-</sup>/CD133<sup>+</sup>/VEGFR<sub>2</sub> and CD34<sup>+</sup>/CD45<sup>-</sup>/VEGFR<sub>2</sub>. In that study, neuromuscular electrical stimulation, considered as an alternative method of exercise, was applied to these patients showing that it could stimulate the mobilization of EPCs in all of the





**Figure 1 Boolean analysis.** A and B: Flow cytometry analysis for the identification of cellular populations using monoclonal antibodies CD45; C: VEGFR<sub>2</sub>; D: CD34; E: CD133. In all samples, the CD34 expression was weak. CPET: Cardiopulmonary exercise testing; VEGFR<sub>2</sub>: Vascular endothelial growth factor receptor 2.





**Figure 2** Boxplots representing the acute mobilization of each endothelial cellular population before and after a symptom limited maximal cardiopulmonary exercise testing between two severity groups according to the median value of peak oxygen uptake. Group 1: Peak oxygen uptake ( $\text{VO}_2$ ) < 18.0 mL/kg/min; Group 2: Peak  $\text{VO}_2 \geq 18.0$  mL/kg/min. <sup>a</sup> $P < 0.05$  indicates statistically significantly increase.

cellular populations mentioned. The findings of the Stefanou *et al*<sup>[23]</sup> study is in agreement with our findings as we also observed a mobilization of EPCs in all cellular populations after a single session of exercise training.

The novel insight of our study, in comparison with previous studies, is the assessment of the acute mobilization of EPCs after maximal exercise according to CHF severity by using strong prognostic CPET parameters such as peak  $\text{VO}_2$  and  $\text{VE}/\text{VCO}_2$  slope. An interesting finding from our study was that those patients who had a greater increase in a single EPCs population (*i.e.*  $\text{CD34}^+/\text{CD45}^-/\text{CD133}^-/\text{VEGFR}_2$  cells population) were younger and had better CPET performance. The underlying mechanism of this finding cannot be discerned from the present study; secreting cytokines such as VEGF might interact more with this particular EPC population, and its secretion might be related with the degree of endothelium damage and the exercise stimuli. However, further study is needed to investigate this finding.

The present study has also introduced a more analytic methodology to quantify and define EPCs and CECs compared to previous studies. EPCs and CECs are being used as an index of the endothelium restoration potential and to reflect vascular endothelial function<sup>[10]</sup>. In our study, a large number of endothelial cellular populations was defined and quantified: Three groups of EPCs ( $\text{CD34}^+/\text{CD45}^-/\text{CD133}^+$ ,  $\text{CD34}^+/\text{CD45}^-/\text{CD133}^+/\text{VEGFR}_2$  and  $\text{CD34}^+/\text{CD133}^+/\text{VEGFR}_2$ ) and two groups of CECs ( $\text{CD34}^+/\text{CD45}^-/\text{CD133}^-$  and  $\text{CD34}^+/\text{CD45}^-/\text{CD133}^-/\text{VEGFR}_2$ ) broadened our knowledge of the phenotype of endothelial cellular populations. Monoclonal antibodies such as CD45, CD34, CD133 and VEGFR<sub>2</sub> (CD309) are the most widely used for the definition of EPC and CEC phenotypes<sup>[20,24,25]</sup>. Other monoclonal antibodies such as CD146, CD105 and CD144 have been previously used, however, without providing more information or specialization in EPC or CEC phenotypes<sup>[24,26]</sup>.

CHF is characterized by increased inflammatory status, endothelial dysfunction and impaired microcirculation, which are crucially involved in development and progression of the disease<sup>[27]</sup>. Impaired endothelium dependent vasodilatation, in addition to impaired cardiac function, is a main determinant of exercise intolerance in patients with CHF, limiting physical exercise capacity and deteriorating peak aerobic capacity<sup>[6,7,27]</sup>. Exercise has been reported to increase blood flow and shear stress, therefore increasing endothelial NOS activity and NO production and reducing inflammation<sup>[28]</sup>. Patients with CHF usually have a different level of deterioration of their vascular endothelium. However, through the present study, exercise was shown to enhance the acute mobilization of EPCs and CECs in these patients in a similar beneficial way, irrespectively of their severity. Targeting endothelial dysfunction could be a breakthrough therapy as endothelial function is recognized as a crucial component underlying HF.

Regarding the potential mechanisms of the mobilization of EPCs, shear stress could be suggested as a triggering factor for their release after a symptom limited maximal CPET. Shear stress seems to upregulate the activity of endothelial NO synthase and increase the production of NO<sup>[29,30]</sup>. Moreover, the activation of ion, cation and stretch sensitive channels and a transient increase in intracellular  $\text{Ca}^{2+}$  have been observed in endothelial cells immediately after exposure to shear stress<sup>[29,30]</sup>. All these endothelial functions contribute to the amplified number and activity of circulating EPCs, and they could play a role in signaling to the cell that it is under shear and eliciting a response<sup>[29,30]</sup>.

Another possible mechanism that may be suggested is the ischemic/hypoxic stimulus. Ischemic/hypoxic stimulus has been shown to increase EPCs count in short-term studies enrolling patients with cardiovascular disease<sup>[31]</sup> and in patients with peripheral arterial occlusive disease<sup>[32]</sup>. Exercise has the potential to induce hypoxic stimuli, as suggested by alterations in microcirculation indices during exercise sessions in healthy populations and patients with cardiovascular comorbidities<sup>[33,34]</sup>. These mechanisms may relate to up-regulation of transcriptional factors, such as matrix metalloproteinases, stromal cell-derived factor 1 and vascular endothelial growth factor, which mediate processes to promote proliferative and migratory capacities of circulating EPCs<sup>[22,32,34]</sup>.

Our study had certain limitations. This was a post-hoc analysis study not designed to compare CHF groups, making our analysis underpowered for group comparison. However, this is the larger sample size tested and analyzed to date and provides significant results according to CHF severity. Our results cannot be generalized to all CHF populations. We excluded patients with unstable and/or decompensated heart failure due to the inability to perform maximal CPET, and for this reason our findings cannot be applied in such cohort of patients.

On the other hand, our study broadens horizons for future fields of research. The function and role of each cellular population in the vascular endothelium, the

relationship between cellular populations, local and systemic neurohumoral factors and cytokines or other vascular endothelium factors and exercise modalities (type, intensity, duration, volume) merits further investigation. Furthermore, other non-invasive methodologies reflecting endothelium function and microcirculation such as flow mediated dilation and near-infrared spectroscopy should be tested and investigated in relationship to EPC measurements to provide potential indirect evaluation of bone marrow response.

## CONCLUSION

In conclusion, a single symptom-limited maximal CPET induces a significant mobilization of EPCs and CECs in CHF patients, but there was no significant association with disease severity.

## ARTICLE HIGHLIGHTS

### Research background

Vascular endothelial dysfunction is an underlying pathophysiological feature of chronic heart failure (CHF). Patients with CHF are characterized by impaired vasodilation and inflammation of the vascular endothelium. They also have low levels of endothelial progenitor cells (EPCs). EPCs have been used as an index of the endothelium restoration potential, therefore reflecting the vascular endothelial function. Exercise has a beneficial impact in the function of the vascular endothelium and EPCs.

### Research motivation

Despite the proven beneficial effect of exercise training in patients with cardiovascular comorbidities, the effect of maximal exercise on EPCs in patients with CHF, and especially in patients of different severity, remains under investigation.

### Research objectives

This study was conducted to assess, quantify and compare the acute mobilization of EPCs after maximal exercise in patients with CHF of both lower and higher severity.

### Research methods

Forty-nine consecutive patients with stable CHF underwent a cardiopulmonary exercise testing (CPET) on a cycle ergometer. Venous blood was sampled before and after CPET. Five circulating endothelial populations were quantified by flow cytometry. Patients were divided in two groups of severity according to the median value of peak oxygen uptake ( $\text{VO}_2$ ), predicted peak  $\text{VO}_2$  ventilation (VE)/carbon dioxide output ( $\text{VCO}_2$ ) slope and ejection fraction (EF).

### Research results

Patients with lower peak  $\text{VO}_2$  increased the mobilization of  $\text{CD34}^+/\text{CD45}^-/\text{CD133}^+$ ,  $\text{CD34}^+/\text{CD45}^-/\text{CD133}^+/\text{VEGFR}_2$ ,  $\text{CD34}^+/\text{CD45}^-/\text{CD133}^-$  and  $\text{CD34}^+/\text{CD45}^-/\text{CD133}^-/\text{VEGFR}_2$ , while patients with higher  $\text{VO}_2$  increased the mobilization of  $\text{CD34}^+/\text{CD45}^-/\text{CD133}^+$ ,  $\text{CD34}^+/\text{CD45}^-/\text{CD133}^+/\text{VEGFR}_2$ ,  $\text{CD34}^+/\text{CD133}^+/\text{VEGFR}_2$ ,  $\text{CD34}^+/\text{CD45}^-/\text{CD133}^-$  and  $\text{CD34}^+/\text{CD45}^-/\text{CD133}^-/\text{VEGFR}_2$ . A similar increase in the mobilization of at least four out of five cellular populations was observed after maximal exercise within each severity group regarding predicted peak,  $\text{VE}/\text{VCO}_2$  slope and EF, as well ( $P < 0.05$ ). However, there were no statistically significant differences in the mobilization of endothelial cellular populations between severity groups in each comparison ( $P > 0.05$ ).

### Research conclusions

Our study has shown an increased EPC and CEC mobilization after maximal exercise in CHF patients, but this increase was not associated with syndrome severity.

### Research perspectives

EPCs could be the cornerstone to the treatment of CHF. Understanding their possible mechanisms of action on vascular endothelial function through exercise would create

innovative ideas regarding their distribution and proliferation in these patients in order to take advantage of their beneficial effects on the endothelium and reverse cardiac remodeling.

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## Rapid right ventricular pacing for balloon valvuloplasty in congenital aortic stenosis: A systematic review

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**Conflict-of-interest statement:** The authors have no conflict of interest and no financial ties to declare.

**PRISMA 2009 Checklist statement:** We conducted the present systematic review according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines.

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### Abstract

#### BACKGROUND

Balloon aortic valvuloplasty (BAV) is a well-established treatment modality for congenital aortic valve stenosis.

#### AIM

To evaluate the role of rapid right ventricular pacing (RRVP) in balloon stabilization during BAV on aortic regurgitation (AR) in pediatric patients.

#### METHODS

A systematic review of the MEDLINE, Cochrane Library, and Scopus databases was conducted according to the PRISMA guidelines (end-of-search date: July 8, 2020). The National Heart, Lung, and Blood Institute and Newcastle-Ottawa scales was utilized for quality assessment.

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## RESULTS

Five studies reporting on 72 patients were included. The studies investigated the use of RRVP-assisted BAV in infants (> 1 mo) and older children, but not in neonates. Ten (13.9%) patients had a history of some type of aortic valve surgical or catheterization procedure. Before BAV, 58 (84.0%), 7 (10.1%), 4 (5.9%) patients had AR grade 0 (none), 1 (trivial), 2 (mild), respectively. After BAV, 34 (49.3%), 6 (8.7%), 26 (37.7%), 3 (4.3%), patients had AR grade 0, 1, 2, and 3 (moderate), respectively. No patient developed severe AR after RRVP. One (1.4%) developed ventricular fibrillation and was defibrillated successfully. No additional arrhythmias or complications occurred during RRVP.

## CONCLUSION

RRVP can be safely used to achieve balloon stability during pediatric BAV, which could potentially decrease AR rates.

**Key Words:** Congenital aortic stenosis; Rapid right ventricular pacing; Balloon aortic valvuloplasty; Congenital heart disease; Systematic review; Aortic regurgitation

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**Core Tip:** Balloon aortic valvuloplasty (BAV) for congenital aortic valve stenosis is well established. Rapid right ventricular pacing (RRVP) is helpful in achieving balloon stability in children undergoing aortic valve dilatation. Our findings demonstrate that RRVP is an effective and safe procedure that helps stabilize the balloon during BAV and decreases the rate of aortic regurgitation in the pediatric population. No reports of severe aortic regurgitation after RRVP-assisted BAV have been published to date.

**Citation:** Mylonas KS, Ziogas IA, Mylona CS, Avgerinos DV, Bakoyiannis C, Mitropoulos F, Tzifa A. Rapid right ventricular pacing for balloon valvuloplasty in congenital aortic stenosis: A systematic review. *World J Cardiol* 2020; 12(11): 540-549

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## INTRODUCTION

Congenital aortic valve stenosis (AS) is the most frequent type of left ventricular outflow tract obstruction in the pediatric population and accounts for more than three-fourths of the left ventricular outflow tract obstruction cases in children<sup>[1,2]</sup>. The severity of obstruction and symptoms typically guide the management of valvar AS, while a peak-to-peak systolic gradient > 50 mmHg is associated with an increased likelihood of ventricular arrhythmias and sudden death mandating immediate intervention<sup>[3]</sup>. Treatment modalities focus on adequately relieving the obstruction, while simultaneously avoiding valvular damage and regurgitation. The two most commonly implemented modalities include balloon aortic valvuloplasty (BAV) and surgical aortic valvotomy (SAV), which have demonstrated an equivalent incidence of aortic regurgitation (AR), gradient reduction, and survival outcomes<sup>[4]</sup>. However, the invasiveness and long recovery period associated with SAV render BAV a more appealing first-line treatment option. On the other hand, BAV is also not a risk-free intervention because cardiac contractions and pulsatile blood flow can lead to balloon displacement during aortic valve dilation. Additionally, damage to vessels or intraluminal structures may also result from increased wall stress during cardiac contraction against an inflated balloon<sup>[5-12]</sup>. Overall, moderate to severe AR develops in about 15% post-BAV even if the balloon diameter does not oversize the aortic valve annulus<sup>[13-16]</sup>.

To increase stability during balloon placement and to minimize the risk of AR, several techniques have been implemented, including extra-stiff wires, long balloons, long sheaths, compliant balloons in the inferior and superior vena cavae or in the main pulmonary artery<sup>[17,18]</sup>. Bolus adenosine is a considerably safe and effective method to achieve transient, pharmacologic cardiac standstill; however, periods of asystole may

occur, which are variable and cannot be easily controlled or predicted<sup>[19]</sup>. Moreover, adenosine does not prevent ventricular contractions, which may occur spontaneously or be triggered by the balloon itself during inflation<sup>[20]</sup>.

Another mode of balloon stabilization during BAV includes rapid ventricular pacing, which decreases stroke volume, pulse pressure, and blood pressure without causing cardiac standstill and without the limitations associated with other techniques. Rapid right ventricular pacing (RRVP) was initially reported in 2002 and has since been broadly implemented throughout the world<sup>[5-12]</sup>. Rapid left ventricular pacing has also been reported but is less widely implemented<sup>[21,22]</sup>. RRVP is commonly utilized during BAV in older children and adults, but there is a scarcity of data regarding neonates and infants. We aimed to systematically review the literature and assess the safety and efficacy of RRVP-assisted BAV in children.

## MATERIALS AND METHODS

### **Study design and inclusion/exclusion criteria**

We conducted the present systematic review according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines (Supplementary Table 1)<sup>[23]</sup>. Since this study utilized only already published data, no patient written consent or Institutional Review Board approval was required.

The study selection criteria were defined by applying the PICO (Population/Participants, Intervention, Comparison, and Outcome) framework: Participants: Children (< 18 years) of any sex or race with congenital aortic stenosis; Intervention: RRVP-assisted balloon aortic valvuloplasty; Comparison: Not applicable; Outcomes: Aortic valve gradient reduction, incidence of AR, freedom from re-intervention, arrhythmias, and other procedure-related complications; Study design: Original randomized clinical trials, non-randomized prospective or retrospective clinical studies (*i.e.*, cohort, case-control, case series, case reports).

Exclusion criteria for the present systematic review were: (1) Non-English articles and (2) Narrative or systematic reviews and meta-analyses, animal and in-vitro studies, errata, comments, perspectives, letters to the editor, and editorials that did not provide any primary patient data. No publication date, sample size restrictions or any other search filters were applied.

### **Literature search strategy**

Two independent researchers (Mylonas KS, Ziogas IA) identified eligible studies through a systematic search of MEDLINE (through PubMed), the Cochrane Library, and Scopus (end-of-search date: July 8<sup>th</sup>, 2020). The search was executed using the following algorithm: (rapid ventricular pacing OR cardiac stimulation) AND aortic valvuloplasty AND (balloon OR transcatheter OR percutaneous) AND (pedi\* OR child\* OR adolescent OR neonat\*). The reference lists of eligible articles were hand-searched for potentially missed studies<sup>[24]</sup>. All eligibility concerns were addressed *via* consensus with the senior author (Tzifa A).

### **Data tabulation and extraction**

A pre-specified spreadsheet was utilized to perform data tabulation and extraction for evidence synthesis and assessment of study quality. Two reviewers (Mylonas KS, Ziogas IA) extracted the data independently, and any disagreements were addressed *via* consensus with the senior author (Tzifa A). We extracted the following data from the eligible articles: Study characteristics (PubMed identification number, first author, publication year, country, study design, study sample), patient demographics (sex, age in years, weight in kg, length in cm), cardiac pathology, past cardiac intervention history, timing of RRVP, pacing mode, pacing rate in beats/minute, pacing time in seconds, balloon length and diameter in mm, balloon displacement, pre-/post-BAV peak systolic gradient in mmHg, pre-BAV AR, aortic valve gradient post-BAV, incidence of AR after dilatation, freedom from re-intervention sustained arrhythmias, and other procedure-related complications.

### **Assessment of study quality**

The quality of the included case series was assessed using the National Heart, Lung, and Blood Institute (NHLBI) scale<sup>[25]</sup>. The NHLBI scale ranges from 1 to 9; with a score of 1-3 denoting poor quality, 4-6 fair quality and 7-9 suggesting good quality. In the item assessing whether the follow-up period was long enough for outcomes to occur,

the cut-off value was a priori set at one year after BAV. The mean and standard deviation for the NHLBI score of the entire review were calculated.

The Newcastle-Ottawa scale was utilized to evaluate the quality of case-control studies<sup>[26]</sup>. In the item assessing whether the follow-up period was long enough for outcomes to occur, the cut-off value was a priori set at 1 year after BAV. In line with standard practice, adequacy of follow-up was set at the 90% rate.

### Statistical analysis

Continuous variables were reported as medians and ranges or as means and standard deviations, while categorical variables as frequencies and percentages. All relative rates were estimated according to the available data for each variable of interest, and all data were handled based on the Cochrane Handbook principles<sup>[27]</sup>.

## RESULTS

### Study selection and characteristics

Five publications reporting on RRVP-assisted BAV for congenital aortic stenosis fulfilled our predetermined literature search criteria (Figure 1)<sup>[5-9]</sup>. All included eligible studies enrolled a total of 72 patients from September 1999<sup>[5]</sup> until August 2009<sup>[9]</sup>. Median patient age ranged from 10 to 13.4 years (1 mo-32 years) and median weight at the time of the intervention ranged from 14 to 48.5 kg (range: 4.4-79 kg). No neonates were treated with RRVP-assisted BAV in any of the published studies. Only 10 (13.9%) patients had a history of some type of aortic valve surgical or catheter-based procedure (Table 1).

### Assessment of study quality

According to the NHLBI scale, all published case series<sup>[5-8]</sup> were studies of good quality, and the mean NHLBI score of the review was  $7.5 \pm 1.0$ . The case-control study by Gupta *et al*<sup>[9]</sup> comparing RRVP alone to RRVP plus controlled transient respiratory arrest also showed high quality according to the Newcastle-Ottawa scale (score: 6). Detailed quality assessment for each study is provided in Supplementary Tables 2 and 3.

### RRVP-assisted BAV outcomes

Published studies have evaluated the use of rapid pacing for transcatheter valvuloplasty in infants (over 1 mo of age) and older children, but not in neonates. Daehenert *et al*<sup>[6]</sup> used RRVP after the failure of an initial non-paced balloon placement attempt. All other teams utilized rapid pacing from the outset of the procedure. Although initial pacing rates varied, most protocols employed RRVP until a 50% reduction in systolic aortic blood pressure was achieved.

Median pacing rates ranged between 209-240 (200-260) beats per minute. On average, pre-BAV peak systolic gradient was in the upper 60 s (mmHg), whereas after the procedure, it typically dropped below 20 mmHg (three-fold reduction). To accurately quantify the impact of RRPV on post-BAV AR rates, we had to exclude 3 patients from the Mehta *et al*<sup>[8]</sup> series since they had “mixed aortic valve disease” of unknown severity.

Prior to BAV, 58 (84.0%), 7 (10.1%), and 4 (5.9%) patients respectively had AR grade 0 (none), 1 (trivial), 2 (mild). After BAV, 34 (49.3%), 6 (8.7%), 26 (37.7%), 3 (4.3%), patients respectively had AR grade 0, 1, 2, and 3 (moderate). No patient developed severe aortic insufficiency after BAV with RRVP.

Gupta *et al*<sup>[9]</sup> compared RRVP alone to RRVP plus controlled transient cessation of positive-pressure ventilation and found no statistically significant difference in terms of peak systolic gradient reduction ( $P = 0.25$ ) and post-BAV aortic insufficiency rates ( $P > 0.05$ ). Lastly, among 72 reviewed patients, only one (1.4%) developed ventricular fibrillation and was cardioverted successfully<sup>[9]</sup>. No additional arrhythmias or other complications occurred after RRVP (Table 2).

## DISCUSSION

BAV constitutes the treatment of choice for severe congenital AS in several centers worldwide, as there is no requirement for cardiopulmonary bypass, the length of hospital stay is shorter, and its outcomes are comparable to that of SAV. However,

Table 1 Study and patient characteristics

PMID	Ref. (year of Publication)	Country	Study type	Study period	Patient sample	Male:female	Patient age (years)	Age groups			Weight (kg)	Length (cm)	Cardiac pathology	Past cardiac intervention history	
								Neonates	Infants	Children				BAV	SAV
20826965	Gupta <i>et al</i> <sup>[9]</sup> (2010)	India	Retrospective case series	June 2006-August 2009	A: 5 B: 5	A: 5:0 B: 4:1	A: 5.0 <sup>4</sup> B: 5.0 <sup>4</sup>	0	0	10	A: 20.0 <sup>4</sup> B: 14.0 <sup>4</sup>	NR	AS NYHA II & III	0	0
20465717	Mehta <i>et al</i> <sup>[8]</sup> (2010)	United Kingdom	Retrospective case series	NR	25	NR	11.6 <sup>1,4</sup> (1.0 mo-32.0) <sup>5</sup>	NR	NR	NR	38.8 <sup>1,4</sup> (4.4-67.1) <sup>5</sup>	NR	Isolated AS: 18/25 (72%) Mixed aortic valve disease: 3/25 (12%) Other associated lesions: 4/25 (16%)	7/25 (28%) <sup>2</sup>	
16889846	David <i>et al</i> <sup>[7]</sup> (2007)	Mexico	Non-randomized, prospective	September 2004-July 2005	10	6: 4	10.0 <sup>4</sup> (3.0-16.0) <sup>5</sup>	0	0	10	NR	NR	Untreated AS with gradient ≥ 50 mm Hg or less, with obstructive and AR grades I- II or without insufficiency.	0	0
15310698	Daehnert <i>et al</i> <sup>[6]</sup> (2004)	Germany	Prospective pilot	September 2001-August 2003	14	9: 5	13.4 <sup>4</sup> (0.3-20.2) <sup>5</sup>	0	1	13	48.5 <sup>4</sup> (7.0-79.0) <sup>5</sup>	158.0 <sup>4</sup> (65.0-180.0) <sup>5</sup>	AS: 14/14 (100%)	1 (7.6%)	2/14 (14.3%)
N/A <sup>3</sup>	Ing <i>et al</i> <sup>[5]</sup> (2002)	United States	Retrospective case series	September 1999-June 2001	13	NR	9.9 <sup>6</sup>	NR	NR	NR	31.7 <sup>6</sup>	NR	AS: 13/13 (100%)	0	0

<sup>1</sup>David *et al*<sup>[7]</sup> reported on 25 patients who underwent balloon aortic valvuloplasty and 4 patients who had stenting of coarctation (these demographics were not grouped according to type of cardiac pathology).

<sup>2</sup>Seven patients had previous interventions either in the form of surgery or catheterization.

<sup>3</sup>Ing *et al*<sup>[5]</sup> was the first group to describe rapid right ventricular pacing for balloon aortic valvuloplasty in an abstract at the Journal of the American College of Cardiology.

<sup>4</sup>Median.

<sup>5</sup>Range.

<sup>6</sup>Mean. A: Rapid right ventricular pacing (RRVP); B: RRVP + controlled transient respiratory arrest. PMID: PubMed identification number; BAV: Balloon aortic valvuloplasty; SAV: Surgical aortic valvotomy; AS: Congenital aortic valve stenosis; AR: Aortic regurgitation; CTRA: Controlled transient respiratory arrest; NYHA: New York Heart Association.

patients treated with BAV are at risk of developing AR, which can be moderate to severe in about 15%<sup>[13-16]</sup> and may progress over time<sup>[14]</sup>. Several approaches have been implemented to stabilize the balloon and decrease the risk of post-BAV AR, including the use of special equipment (extra-stiff guidewires and double balloons)<sup>[5,28]</sup> or bolus intravenous adenosine. The latter is generally considered to be safe and effective in decreasing cardiac output and generating a transient state of asystole by inducing sinoatrial and atrioventricular block<sup>[19,20,29]</sup>. Nevertheless, adenosine needs to be titrated on a patient-by-patient basis, and the onset and duration of pharmacologic the transient cardiac standstill is dose-dependent and variable among patients. As RRVP can decrease stroke volume, blood pressure, and transvalvular flow without causing



Table 2 Outcomes of rapid right ventricular pacing-assisted balloon aortic valvuloplasty

PMID	Ref. (year of Publication)	Timing of RRVP	Pacing mode	Pacing rate (bpm)	Pacing time (sec)	Balloon length (mm)	Balloon diameter (mm)	Balloon displacement	Pre-BAV PS gradient (mmHg)	Post-BAV PS gradient (mmHg)	Pre-BAVAR	Post-BAVAR	Sustained arrhythmias	Other procedure-related complications
20826965	Gupta <i>et al</i> <sup>[9]</sup> (2010)	Pacing until SBP dropped by 50%	NR	NR	NR	Balloon:aortic annulus size = 1:1		A: 1/5 (20%) B: 0%	Gradient reduction (%): A: 52.2% B: 70.1%; <i>P</i> = 0.25		G0: 10/10 (100%)	A G0 0% B 2/5 (40%) G1 0% 0% G2 4/5 (80%) 3/5 (60%) G3 1/5 (20%) 0% G4 0% 0%	None	None
20465717 <sup>4</sup>	Mehta <i>et al</i> <sup>[8]</sup> (2010)	Initially 180 bpm. Pacing rate was increased by 20 bpm until SBP dropped by 50% ± pulse pressure by 25%	AAI/AO	240 <sup>5</sup> (200-260) <sup>6</sup>	NR	NR	NR	1/25 (4%)	Gradient reduction: 20 <sup>5</sup> (0-60) <sup>6</sup>		G0: 22 (88%) G1:0% G2:0% G3:0% G4:0%	G0: 16/22 (72.7%) G1:0% G2: 6/22 (27.8%) G3:0% G4: 0%	1/25 (4%) VFib which was successfully cardioverted	None
16889846	David <i>et al</i> <sup>[7]</sup> (2007)	Initially at a frequency slightly higher than the spontaneous patient's frequency. Pacing rate was increased until SBP dropped by 50%	NR	209 <sup>7</sup> (170-250) <sup>6</sup>	NR	40 (40-40)	18 <sup>5</sup> (14-22) <sup>6</sup>	NR	68.5 <sup>7</sup> ± 20 <sup>8</sup>	19.7 <sup>7</sup> ± 8.3 <sup>8</sup>	G0: 6/10 (60%) G1: 4/10 (40%) G3: 0% G4: 0%	G0: 5/10 (50%) G1: 5/10 (50%) G3: 0% G4: 0%	None	None
15310698	Daehnert <i>et al</i> <sup>[6]</sup> (2004)	After failure of first non-paced dilatation attempt	VVI	220 <sup>2</sup>	12.7 <sup>7</sup> (7-16) <sup>6</sup>	60 <sup>5</sup> (30-60) <sup>6</sup>	20 <sup>5</sup> (10-25) <sup>6</sup>	3/14 (21.4%) <sup>1</sup>	82.5 <sup>5</sup> (60-110) <sup>6</sup>	28.6 <sup>5</sup> (10-50) <sup>6</sup>	G0: 7/14 (50%) G1: 3/14 (21.4%)	G0: 1/14 (7.1%) G1: 0	None	None

											G2: 4/14 (28.6%)	G2: 11/14 (78.6%)		
											G3: 0%	G3: 2/14 (14.3%)		
											G4: 0%	G4: 0%		
N/A <sup>3</sup>	Ing <i>et al</i> <sup>[5]</sup> (2002)	Pacing just prior to balloon inflation. HR increased by an average of 80 ± 29% & LV systolic pressure decreased by 36 ± 12%.	NR	NR	NR	NR	NR	1/13 (20.1%)	67.8 <sup>7</sup> ± 18.6 <sup>8</sup>	19.4 <sup>7</sup> ± 9.1 <sup>8</sup>	G0: 13/13 (100%)	G0: 10/13 (76.9%) G1: 1/13 (7.7%) G2: 2/13 (18.4%) G3: 0% G4: 0%	None	None

<sup>1</sup>Two in the aorta and 1 in the left ventricle.

<sup>2</sup>In 2 patients the balloon continued to move and rapid right ventricular pacing (RRVP) was increased to 240 bpm.

<sup>3</sup>Ing *et al*<sup>[5]</sup> was the first group to describe rapid right ventricular pacing for balloon aortic valvuloplasty in an abstract at the Journal of the American College of Cardiology.

<sup>4</sup>To accurately quantify the impact of RRPV on post-balloon aortic valvuloplasty (BAV) aortic regurgitation (AR) rates, we had to exclude 3 patients since pre-BAV they had “mixed aortic valve disease” of unknown severity.

<sup>5</sup>Median.

<sup>6</sup>Range.

<sup>7</sup>Mean.

<sup>8</sup>Standard deviation. G0: No AR; G1: Grade 1 AR (trivial); G2: Grade 2 AR (mild); G3: Grade 3 AR (moderate); G4: Grade 4 AR (severe); A: RRVP; B: RRVP + controlled transient respiratory arrest; NR: not reported; PMID: PubMed identification number; RRVP: Rapid right ventricular pacing; PS: Peak systolic; AR: Aortic regurgitation; SBP: Aortic systolic blood pressure; VFib: Ventricular fibrillation; CTRA: Controlled transient respiratory arrest.

asystole and can be modified according to the needs of the procedure, a growing number of centers began using this approach as the method of choice for balloon stabilization in children and adults<sup>[5-9]</sup>. In the present systematic review, we sought to summarize all published literature assessing the safety and efficacy of RRVP-assisted BAV for congenital aortic valve stenosis.

Our findings suggest that the maximum aortic valvular gradient after aortic dilatation with pacing decreases significantly<sup>[5-9]</sup>. In children, RRVP is typically implemented from the beginning of the intervention, since even a single balloon displacement event can be enough to damage the aortic valve<sup>[7,8]</sup>. However, it should be emphasized that according to our systematic review, no cases of severe AR after rapid pacing have ever been reported. Despite its well-known benefits, RRVP has not been broadly employed in neonates and infants, and thus the outcomes of RRVP-assisted BAV in congenital AS patients < 1 year are largely unknown. The absence of a unified pacing approach during BAV in this population is based on the hypothesis that the low stroke volumes (1.0-1.5 mL/kg), higher heart rates, and low ejection fractions are unable to cause uncontrolled balloon movement and valvar damage. However, this theory cannot explain the need for a surgical bailout for severe AR post-BAV, which has been repeatedly reported for neonates and infants subjected to BAV without

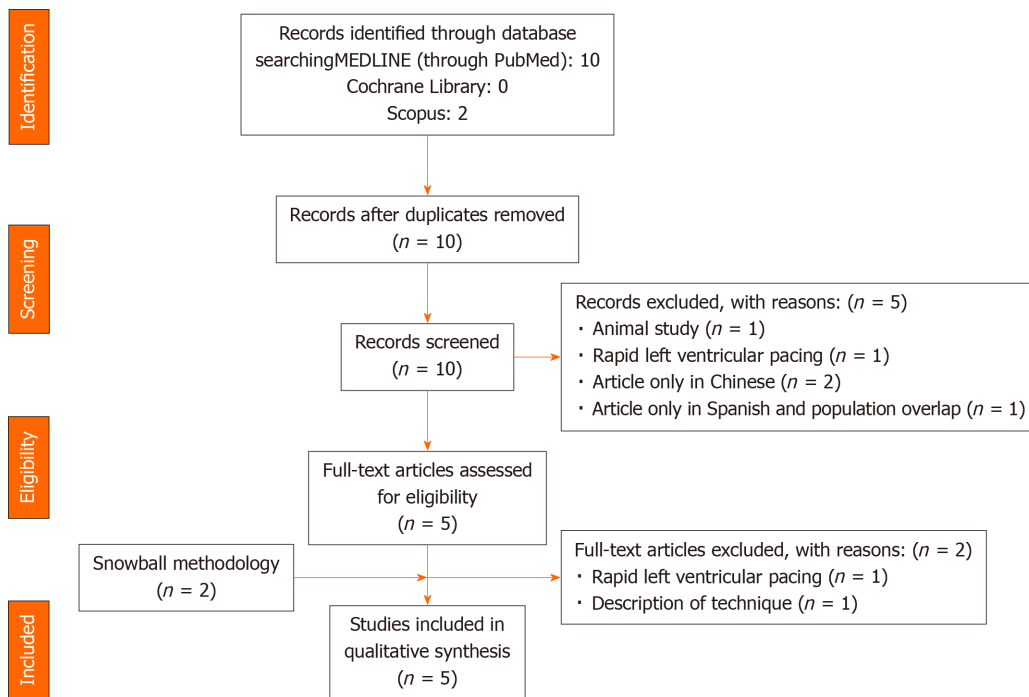


Figure 1 PRISMA flow diagram of the search strategy and study selection.

rapid pacing. Decreasing the risk and extent of post-BAV AR is vital in this population, in whom the performance of bailout Ross (with or without Konno) has been associated with poor prognosis<sup>[30]</sup>. Therefore, future studies should explore the role of RRVP-assisted BAV in neonates and infants. Nonetheless, RRVP does have certain pitfalls, including a prolongation in operative time and a potentially higher risk of cardiac perforation and pneumothorax (if performed *via* the jugular/subclavian vein)<sup>[18]</sup>. It has also been suggested that rapid ventricular pacing may increase the risk of sustained ventricular arrhythmias compared to the baseline risk of cardiac catheterization (< 1%)<sup>[31]</sup>. According to our findings, only one (1.4%) case of ventricular fibrillation has been described, which was still successfully defibrillated<sup>[8]</sup>.

Nonetheless, certain limitations inherent to the nature of the included studies should be considered when interpreting the results of the present systematic review. Three of the five included studies were retrospective in nature, and thus may impart a degree of selection bias; albeit, upon rigorous quality assessment, all studies were deemed to be of high-quality. Additionally, to accurately quantify the impact of RRVP on post-BAV AR rates, in the study by Mehta *et al*<sup>[8]</sup> we excluded three patients from the pooled analysis since their pre-BAV pathology was “mixed aortic valve disease” of unknown severity. Lastly, as with all systematic reviews, some of the eligible studies did not report on all characteristics or outcomes of interest, and thus the relative rates were estimated accordingly based on the availability of data.

## CONCLUSION

In conclusion, RRVP is an effective and safe procedure that can help stabilize the balloon during BAV and decrease subsequent AR rates. No reports of severe AR after RRVP-assisted BAV in children have been published to date.

## ARTICLE HIGHLIGHTS

### Research background

Congenital aortic valve stenosis is the most frequent type of left ventricular outflow tract obstruction in the pediatric population and accounts for more than three-fourths of the left ventricular outflow tract obstruction cases in children. The two most commonly implemented modalities include balloon aortic valvuloplasty (BAV) and

surgical aortic valvotomy, which have demonstrated an equivalent incidence of aortic regurgitation (AR), gradient reduction, and survival outcomes.

### Research motivation

Another mode of balloon stabilization during BAV includes rapid ventricular pacing, which decreases stroke volume, pulse pressure, and blood pressure without causing cardiac standstill and without the limitations associated with other techniques. Rapid right ventricular pacing (RRVP) was initially reported in 2002 and has since been broadly implemented throughout the world. Rapid left ventricular pacing has also been reported but is less widely implemented. RRVP is commonly utilized during BAV in older children and adults, but there is a scarcity of data regarding neonates and infants.

### Research objectives

RRVP is commonly utilized during BAV in older children and adults, but there is a scarcity of data regarding neonates and infants. We aimed to systematically review the literature and assess the safety and efficacy of RRVP-assisted BAV in children.

### Research methods

A systematic review of the MEDLINE, Cochrane Library, and Scopus databases was conducted according to the PRISMA guidelines (end-of-search date: July 8, 2020). The National Heart, Lung, and Blood Institute and Newcastle-Ottawa scales was utilized for quality assessment.

### Research results

Five studies reporting on 72 patients were included. The studies investigated the use of RRVP-assisted BAV in infants (> 1 mo) and older children, but not in neonates. Ten (13.9%) patients had a history of some type of aortic valve surgical or catheterization procedure. Before BAV, 58 (84.0%), 7 (10.1%), 4 (5.9%) patients had aortic regurgitation (AR) grade 0 (none), 1 (trivial), 2 (mild), respectively. After BAV, 34 (49.3%), 6 (8.7%), 26 (37.7%), 3 (4.3%), patients had AR grade 0, 1, 2, and 3 (moderate), respectively. No patient developed severe AR after RRVP. One (1.4%) developed ventricular fibrillation and was defibrillated successfully. No additional arrhythmias or complications occurred during RRVP.

### Research conclusions

RRVP is an effective and safe procedure that can help stabilize the balloon during BAV and decrease subsequent AR rates. No reports of severe AR after RRVP-assisted BAV in children have been published to date.

### Research perspectives

Future studies should explore the role of RRVP-assisted BAV in neonates and infants.

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## Effects of left ventricular assist device on pulmonary functions and pulmonary hemodynamics: A meta-analysis

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### Abstract

#### BACKGROUND

Given current evidence, the effect of left ventricular assist device (LVAD) implantation on pulmonary function tests remains controversial.

#### AIM

To better understand the factors contributing to the changes seen on pulmonary function testing and the correlation with pulmonary hemodynamics after LVAD implantation.

#### METHODS

Electronic databases were queried to identify relevant articles. The summary effect size was estimated as a difference of overall means and standard deviation on a random-effects model.

#### RESULTS

A total of four studies comprising 219 patients were included. The overall mean forced expiratory volume in one second (FEV1), forced vital capacity (FVC) and diffusion lung capacity of carbon monoxide (DLCO) after LVAD implantation were significantly lower by 0.23 L (95%CI: 0.11-0.34,  $P = 0.0002$ ), 0.18 L (95%CI: 0.03-0.34,  $P = 0.02$ ), and 3.16 mmol/min (95%CI: 2.17-4.14,  $P < 0.00001$ ), respectively. The net post-LVAD mean value of the cardiac index was significantly higher by 0.49 L/min/m<sup>2</sup> (95%CI: 0.31-0.66,  $P < 0.00001$ ) compared to

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pre-LVAD value. The pulmonary capillary wedge pressure and pulmonary vascular resistance were significantly reduced after LVAD implantation by 8.56 mmHg (95%CI: 3.78-13.35,  $P = 0.0004$ ), and 0.83 Woods U (95%CI: 0.11-1.55,  $P = 0.02$ ), respectively. There was no significant difference observed in the right atrial pressure after LVAD implantation (0.61 mmHg, 95%CI: -2.00 to 3.32,  $P = 0.65$ ). Overall findings appear to be driven by studies using HeartMateII devices.

## CONCLUSION

LVAD implantation might be associated with a significant reduction of the spirometric measures, including FEV1, FVC, and DLCO, and an overall improvement of pulmonary hemodynamics.

**Key Words:** Pulmonary function tests; Left ventricular assist device; Spirometry; Ventricular assist device

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**Core Tip:** Left ventricular assist device (LVAD) implantation can cause worsening of forced expiratory volume in one second, forced vital capacity, and diffusion lung capacity of carbon monoxide in post-LVAD patients. However, the benefits of LVAD implantation outweigh its risks in the context of pulmonary hemodynamics. More large scale studies are required to validate our findings.

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## INTRODUCTION

Since the advent of the left ventricular assist device (LVAD) in 1988, literature has appropriately focused on its survival benefits in heart failure patients<sup>[1,2]</sup>. Over the years, with an increase in its use, many LVAD related complications also started surfacing together. Arena *et al*<sup>[3]</sup> in 1999 were the first to present data, implicating a decrease in spirometric measures in patients with LVAD implantation. These observation was based on the comparison of pre and post-LVAD findings in a 58-year old gentleman<sup>[3]</sup>. Later on, more observational studies attempted to elucidate the complex interplay of pathophysiological dynamics between LVAD and pulmonary system, but had conflicting findings<sup>[4-7]</sup>. Until recently, there has been no concrete evidence in the form of a randomized controlled trial (RCT) or meta-analysis to identify the net clinical benefit of LVAD in the context of worsened pulmonary functions and improved pulmonary hemodynamics.

## MATERIALS AND METHODS

### Search strategy and study collection

A literature search was performed up to December 2019, using PubMed, EMBASE, and Cochrane databases. There was no language or time restriction. The search strategies included various combinations of medical subject headings (MeSH) to generate two subsets of citations: One for LVAD and other for pulmonary function tests (PFTs). The terms from the two subsets were combined in 1:1 combination using boolean operators, and results from all possible combinations were screened for relevant articles. Based on our research question, articles from the reference lists pertinent to the clinical question were also evaluated by an independent author (backward snow bowling). Studies comparing changes in PFTs and pulmonary hemodynamics after LVAD implantation were included in the final analysis.

Pulmonary hemodynamics included cardiac output (CO), right atrial pressure (RAP) and pulmonary capillary wedge pressures (PCWP) assessment; pulmonary vascular resistance (PVR) was calculated by the standard formula  $PVR = (mPAP - PCWP)/CO$ . The studies with insufficient data, case reports, review articles, and conference papers were excluded after detailed discussion (Figure 1).

### Quality of included studies

The overall methodological quality of the included studies was low. Due to the inclusion of single-center retrospective studies, the risk of selection bias could not be assessed. Similarly, randomization and allocation concealment of the subjects at the level of individual study could not be performed. Most studies, however, mentioned the baseline characteristics of the included population except by Imamura *et al*<sup>[5]</sup>. The risk of reporting bias across all studies was minimal due to adequate reporting of outcomes. Only patients who had post-LVAD spirometry measurements were included in the study, minimizing the risk of attrition bias. All included studies used a self-control model in which the same population was assessed before and after an intervention (LVAD implantation); hence, the risk for detection bias was negligible. The detailed and summary bias graphs are given in Figure 2.

### Statistical analysis

The statistical analysis was performed using the random-effects model (inverse variance) to calculate the mean difference and SD for continuous variables. The probability value of  $P < 0.05$  was considered statistically significant. The “test for overall effect” was reported as  $z$  value corroborating the inference from the 95%CI. Higgins  $I^2$ -squared ( $I^2$ ) statistic model was used to assess variations in outcomes of the included studies.  $I^2$  values of 50% or less corresponded to low to moderate, and 75% or higher indicated large amounts of heterogeneity. Publication bias was illustrated graphically using a funnel plot. The quality assessment of the included articles was performed using the Cochrane guidelines for the systematic review and meta-analysis, where each study was screened for five different types of bias (selection, performance, detection, attrition, and reporting bias). All statistical analysis was performed using the Cochrane Review Manager (RevMan) version 5.3.

## RESULTS

### Search results and study selection

The initial search on multiple databases revealed 1086 articles. After removal of irrelevant and duplicate items, 132 articles deemed relevant for full-text review. We further excluded 128 articles based on our selection criteria. Multiple attempts to authors to retrieve data were unsuccessful. Four articles qualified for final analysis<sup>[4-7]</sup>. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram is shown in Figure 1.

A total of 219 patients, with a mean age of  $54 \pm 11$  years, were included. About 73% of the included subjects were males. Two thirds (74%) of the overall population had 2nd generation continuous flow devices (HeartMateII), while 26% of patients had a 3rd generation pulsatile flow device (HeartWare). The overall mean basal metabolic index was  $26 \pm 12$  kg/m<sup>2</sup>. The mean left ventricular ejection fraction was 10%. The indications for LVAD implantation were non-ischemic and ischemic cardiomyopathy in 62% (136/219) and 36% (79/219) of patients, respectively. Sajgalik *et al*<sup>[6]</sup> were the only ones reporting hypertrophic cardiomyopathy in four patients. The functional status of the included population was defined either by a 6-min walk test (Raheja *et al*<sup>[7]</sup>) or by classification of the New York Heart Association (NYHA) (Sajgalik *et al*<sup>[6]</sup>). The mean brain nitric peptide level was 1695 pg/mL. Of the reported comorbidities, diabetes, chronic kidney disease, and hypertension were the most common. Approximately 22% (50/219) of the total population carried a diagnosis of chronic obstructive lung disease (COPD). The mean follow-up duration and timing of post-LVAD spirometry ranged from 6 mo to 12 mo. The detailed study characteristics are given in Supplementary Table 1.

### Pooled estimate of spirometric changes with LVAD implantation

The overall mean forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) values were significantly lower after LVAD implantation by 0.23 L (95%CI: 0.11-0.34,  $P = 0.0002$ ) and 0.18 L (95%CI: 0.03-0.34,  $P = 0.02$ ), respectively. The

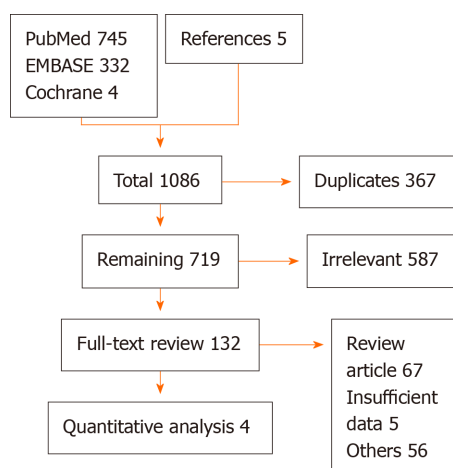


Figure 1 PRISMA flow diagram of the included studies.

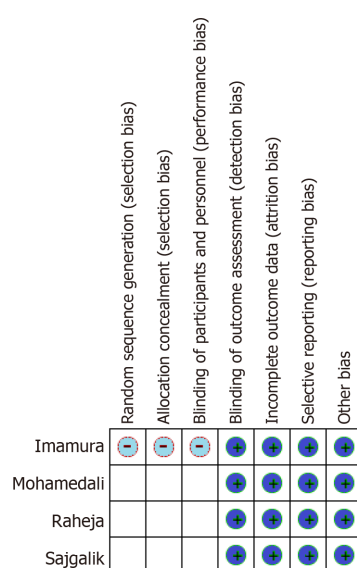
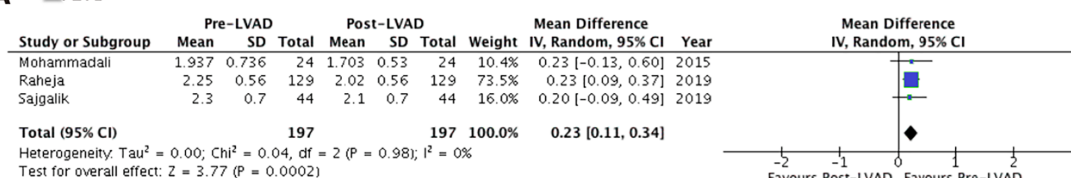
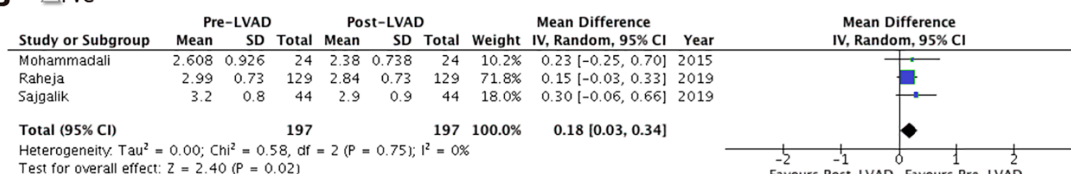
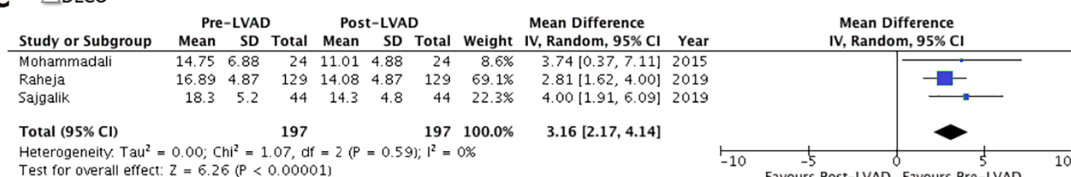


Figure 2 Detailed methodological quality and bias assessment of included studies.

heterogeneity among the outcomes of the included studies was minimal for both FEV1 and FVC with an  $I^2 = 0\%$  ( $P = 0.98$  and  $P = 0.75$ , respectively) (Figure 3A and B). The overall mean value of  $\Delta$ DLCO (diffusion lung capacity of carbon monoxide) was robustly reduced by 3.16 mmol/min (95%CI: 2.17-4.14,  $P < 0.00001$ ) in the post-LVAD state. There was no heterogeneity among the outcomes of individual studies  $I^2 = 0\%$  ( $P = 0.59$ ) (Figure 3C).

### Pooled estimate of pulmonary hemodynamics with LVAD implantation

All indices of pulmonary hemodynamic observed an overall improvement with LVAD implantation. The net post-LVAD implantation mean cardiac index was significantly higher by 0.49 L/min/m<sup>2</sup> (95%CI: 0.31-0.66,  $P < 0.00001$ ) compared to pre-LVAD values with no heterogeneity ( $I^2 = 0$ ). Imamura *et al*<sup>[5]</sup> study contributed more than half to the overall effect size (52% weight) (Figure 4A). Compared to pre-LVAD values, the pooled estimate of PCWP and PVR was significantly reduced after post-LVAD implantation by 8.56 mmHg (95%CI: 3.78-13.35,  $P = 0.0004$ ), and 0.83 Woods U (95%CI: 0.11-1.55,  $P = 0.02$ ), respectively (Figure 4B and C). There was no significant difference observed in RAP in the post-LVAD cohort both at the study level and in the pooled analysis (0.61 mmHg, 95%CI: -2.00 to 3.32,  $P = 0.65$ ). The heterogeneity among the included studies was moderate ( $I^2 = 76\%$ ,  $I^2 = 42\%$ ,  $I^2 = 57\%$ , respectively) (Figure 4D).

**A**  $\triangle$ FEV1**B**  $\triangle$ FVC**C**  $\triangle$ DLCO

**Figure 3** Forest plot depicting the pooled mean difference of forced expiratory volume in one second (A), forced vital capacity (B) and diffusion lung capacity of carbon monoxide (C) between pre- and post-left ventricular assist device patients. FEV1: Forced expiratory volume in one second; FVC: Forced vital capacity; DLCO: Diffusion lung capacity of carbon monoxide; LVAD: Left ventricular assist device.

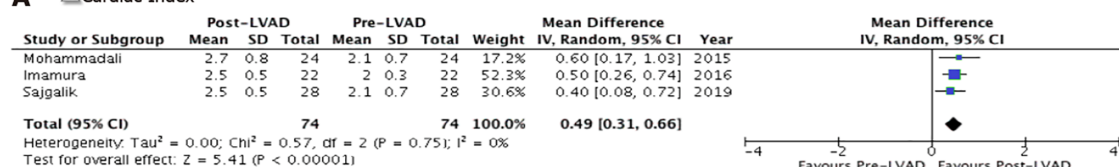
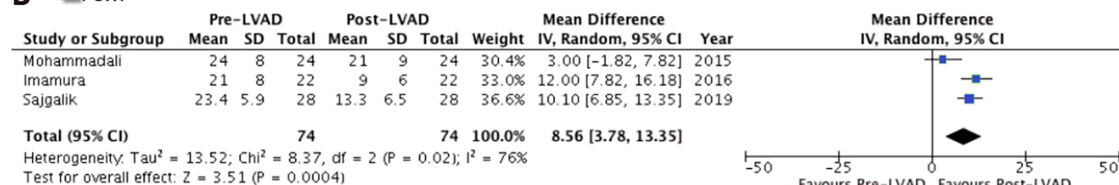
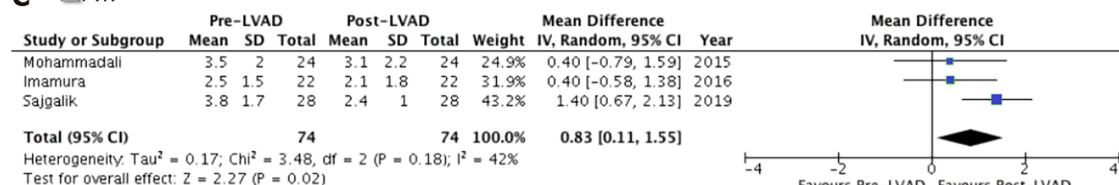
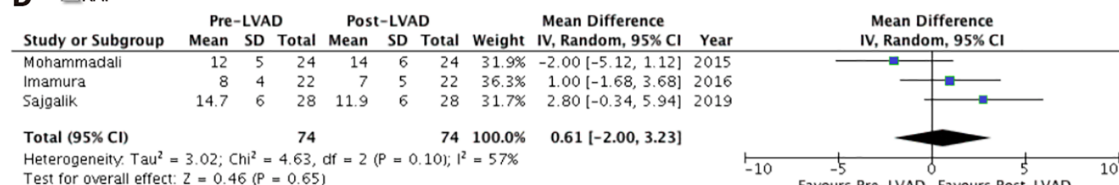
## DISCUSSION

Our meta-analysis shows a substantial decrease in the overall mean spirometric measures (FEV1, FVC, FEV1/FVC, and DLCO) in post-LVAD patients. The pulmonary hemodynamics were, however, significantly improved with an overall mean decrease in the PCWP and PVR. As expected, post-LVAD patients observed a substantial improvement in the cardiac index. Together these changes represented a net decrease in left ventricular filling pressure and an improvement in the left ventricular function. There was no effect seen on the net difference of RAP in patients following LVAD implantation. The detailed pre- and post-LVAD spirometric metrics are given in Figure 5.

Many factors could be accounted for the restrictive pulmonary pattern seen in post-LVAD patients. The initial transient decline in PFTs (FVC and FEV1) could be attributed to anesthesia effects or respiratory muscle weakness due to the major cardiothoracic surgery<sup>[4]</sup>. Long term decrease in post-LVAD FVC can partly be explained by an LVAD patient now having an object that occupies approximately 50 mL (HeartWare) to 63 mL (HeartMateII) of intrathoracic space<sup>[4]</sup>. In addition to the anatomical limitations, a constellation of mechanical and physiological mechanisms compromises the diaphragmatic functions, such as surgical implantation of HeartMateII below the diaphragm, sternotomy, thoracic scarring and respiratory muscle weakness due to cardiac cachexia<sup>[7]</sup>. Moreover, heart failure induced reactive fibrosis, pleural effusion, and cardiomegaly can worsen the post-LVAD spirometric measures by mechanically impeding the lungs from expanding<sup>[6]</sup>. Heart failure can also incite bronchial hypersensitivity or can cause interstitial edema, and compressive atelectasis, further compromising the spirometric metrics of post-LVAD patients. Some post-LVAD patients are at high risk of decline in spirometric measures if they have a compelling indication for pneumotoxic medications such as amiodarone<sup>[4-7]</sup>.

The literature on the post-LVAD pulmonary dynamics is scarce. Our extensive literature search identified four studies for quantitative analysis<sup>[4-7]</sup>. All these studies unanimously agreed on the decline of pulmonary functions and the improvement of pulmonary hemodynamics in post-LVAD patients. These studies, however, should be interpreted in the context of its methodological limitations. Most studies used older generation devices (HeartMateII), while more contemporary studies used the newer



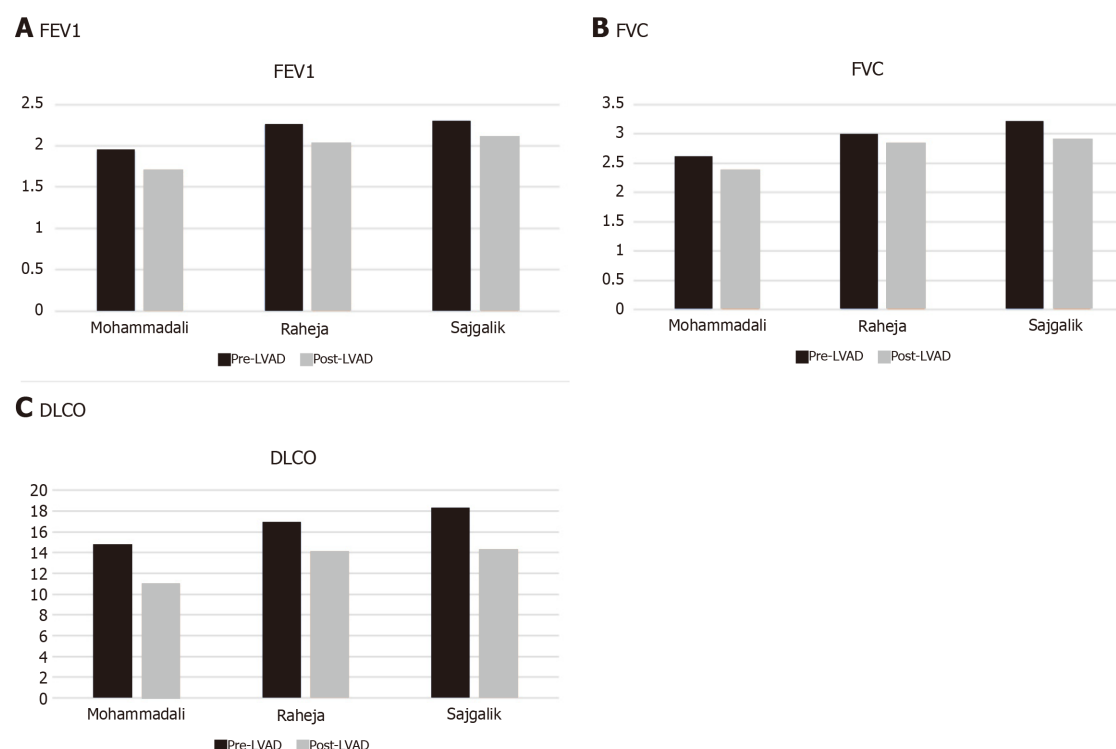
**A**  $\triangle$ Cardiac Index**B**  $\triangle$ PCWP**C**  $\triangle$ PVR**D**  $\triangle$ RAP

**Figure 4** Forest plot showing pooled comparison of mean difference in cardiac index (A), pulmonary capillary wedge pressures (B), pulmonary vascular resistance (C), and right atrial pressure (D) between pre- and post-left ventricular assist device groups. PCWP: Pulmonary capillary wedge pressures; PVR: Pulmonary vascular resistance; RAP: Right atrial pressure; LVAD: Left ventricular assist device.

generation pulsatile LVAD devices (HeartWare). This potentially skewed the overall results of the studies. Mohamedali *et al*<sup>[4]</sup> in 2015, were the first to recognize that a decrease in the spirometric measures (FEV1, FVC, and DLCO) was actually driven by the HeartMateII devices, rather than HeartWare. They attributed these findings to the surgical resection related paralysis of the diaphragm, post-procedure lung fibrosis, and restriction of the left hemidiaphragm by a relatively larger device size in the former<sup>[4]</sup>. Raheja *et al*<sup>[7]</sup> subsequently validated the overall results of the prior study. They also quantified the effect of LVAD on the functional status of heart failure patients using a six-minute walk distance (MWD). A significant correlation between the MWD and LVAD induced change in FEV1 ( $P = 0.0466$ ), and DLCO ( $P = 0.0032$ ) was demonstrated; however, these findings were never adjusted for the duration of follow up<sup>[7]</sup>. Sajgalik *et al*<sup>[6]</sup> hurdled these limitations by performing a stratified analysis based on different follow-up durations. Although a substantial amount of decline in FEV1 ( $P = 0.04$ ) and FVC ( $P = 0.01$ ) was observed at 12-mo, there was no significant decrease in PFTs on a shorter follow-up duration of 6-mo (FVC  $P = 0.07$ , FEV1  $P = 0.27$ ). Similarly, the observed predictive effect of survival with the change of DLCO at 6-mo ( $P = 0.03$ ) was attenuated at an extended follow-up duration of 12-mo ( $P = 0.22$ )<sup>[6]</sup>.

Mohamedali *et al*<sup>[4]</sup> exclusively used the 2nd generation (HeartMateII) devices, while about 77% LVADs in the Sajgalik *et al*<sup>[6]</sup> and 88% of devices used by Raheja *et al*<sup>[7]</sup> study were HeartMateII devices. Despite a higher percentage of HeartMateII devices in the later studies, the overall outcomes were never stratified based on the device type<sup>[5-7]</sup>. Therefore, a clear distinction between the relative safety of HeartMateII and HeartWare could not be ascertained. This, along with the fact that all studies had substantial limitations due to non-randomized data, call into question the generalizability of individual results.

One can also argue that spirometric changes observed in post-LVAD patients could



**Figure 5** Trend of decrease in forced expiratory volume in one second (A), forced vital capacity (B), and diffusion lung capacity of carbon monoxide (C) in the included studies. FEV1: Forced expiratory volume in one second; FVC: Forced vital capacity; DLCO: Diffusion lung capacity of carbon monoxide; LVAD: Left ventricular assist device.

be a transient decline of the pre-existing lung disease, and might not have long-term consequences. As claimed by Imamura *et al*<sup>[5]</sup> in his analysis, that the post-LVAD PFTs worsening is a reversible phenomenon with heart transplantation. However, more studies are needed to shed light on the long-term impacts of LVAD implantation on pulmonary dynamics. It should also be noted that, approximately 36% of patients from Sajgalik *et al*<sup>[6]</sup> study had obstructive sleep apnea, while 29% of patients in Mohamedali *et al*<sup>[4]</sup>, and 22% of Raheja *et al*<sup>[7]</sup> patients had COPD. It is unclear if the decrease of post-LVAD spirometric measures in the mentioned cohorts was an actual device effect or was merely worsening of their underlying lung condition.

Given apparent differences in the outcomes and significant effect of covariates on the results, one should be cautious about the clinical interpretations of individual results. This, along with the fact that previous small studies were either underpowered to detect clinical outcomes, or had conflicting findings, prompted us to integrate the findings of these studies.

In contrast to individual data, our meta-analysis provides strong evidence that LVAD related beneficial effects outweigh its potential spirometric decline in heart failure patients. A minimal mean decrease in post-LVAD measures of FEV1 and FCV by only 0.23 L and 0.18 L respectively is massively offset by a significantly higher increase in the cardiac index by 0.49 L/min/m<sup>2</sup>, and improvement of PCWP by 8.56 mmHg and PVR by 0.83 Woods U, respectively. Our meta-analysis also illustrates the paucity of randomized data in post-LVAD patients and highlights the limits on our ability to draw definitive conclusions due to the retrospective nature of data.

Our study is constrained by the limitations of the available data. A significant barrier was our inability to perform a stratified subgroup analysis based on different LVAD types and variable follow up durations. The inherent heterogeneity in the inclusion criteria of studies could not be accounted for in the pooled analysis. This, in addition to the biases and confounding factors inherent in observational non-randomized studies, call for caution when interpreting the results of this meta-analysis.

To determine the actual effect of LVAD implantation on spirometric metrics, it is imperative to account for all the confounding variables in a controlled population. One way would be to determine the causation of lung findings on a prospective scale or conduction of a RCT. This will enable the researchers not only to assess the risk of post-LVAD spirometric changes but can also help in the identification of instantaneous

event rates such as mortality and survival benefits.

## CONCLUSION

LVAD implantation might be associated with worsening of FEV1, FVC, and DLCO in post-LVAD patients. However, the overall benefits of LVAD in the context of pulmonary hemodynamics outweigh the presumed harm to spirometric metrics. More large scale studies are needed to validate our findings.

## ARTICLE HIGHLIGHTS

### **Research background**

Recent studies suggest that left ventricular assist device (LVAD) implantation has not been associated with an improvement in pulmonary function tests. However, the improvement seen in post-LVAD pulmonary hemodynamics outweighs the observed decrease in spirometry.

### **Research motivation**

The studies investigating these parameters are not expansive and the overall methodological quality of the studies available is low. Further inquiry into the effects of the LVAD implantation on pulmonary hemodynamics, objective pulmonary function testing and on the observed clinical outcomes is needed.

### **Research objectives**

This meta-analysis aims to stratify the observed outcomes in studies assessing these parameters, in order to better understand the factors contributing to the changes seen on pulmonary function testing and the correlation with pulmonary hemodynamics.

### **Research methods**

Our study literature search was performed on published data until December 2019, using PubMed, EMBASE, and Cochrane databases. After screening the studies 132 articles deemed relevant were reviewed. 128 articles were excluded based on our selection criteria. Four studies were analysed and included in this meta-analysis.

### **Research results**

A total of four studies comprising 219 patients were included. The overall mean forced expiratory volume in one second (FEV1), forced vital capacity (FVC) and diffusion lung capacity of carbon monoxide (DLCO) after LVAD implantation were significantly lower by 0.23 L (95% CI: 0.11-0.34,  $P = 0.0002$ ), 0.18 L (95% CI: 0.03-0.34,  $P = 0.02$ ), and 3.16 mmol/min (95% CI: 2.17-4.14,  $P < 0.00001$ ), respectively. The pulmonary capillary wedge pressure and pulmonary vascular resistance were significantly reduced after LVAD implantation by 8.56 mmHg (95% CI: 3.78-13.35,  $P = 0.0004$ ), and 0.83 Woods U (95% CI: 0.11-1.55,  $P = 0.02$ ), respectively. There was no significant difference observed in the right atrial pressure after LVAD implantation (0.61 mmHg, 95% CI: -2.00 to 3.32,  $P = 0.65$ ).

### **Research conclusions**

LVAD implantation might be associated with a significant reduction of the spirometric measures, including FEV1, FVC, and DLCO, and an overall improvement of pulmonary hemodynamics.

### **Research perspectives**

The short term and long-term effects of LVAD on the pulmonary hemodynamics on and pulmonary function tests need to be expanded and are essential in order to better assess outcomes. The need for randomized control trials exists to identify confounding factors that may affect the outcomes seen in the studies analyzed. Also, further studies with extended follow-up are needed to assess the clinical outcomes of the changes seen on PFTs and hemodynamics.

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## Medical therapy vs early revascularization in diabetics with chronic total occlusions: A meta-analysis and systematic review

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### Abstract

#### BACKGROUND

Management of chronic total occlusions (CTO) in diabetics is challenging, with a recent trend towards early revascularization [ER: Percutaneous coronary intervention (PCI) and bypass grafting] instead of optimal medical therapy (OMT). We hypothesize that ER improves morbidity and mortality outcomes in diabetic patients with CTOs as compared to OMT.

#### AIM

To determine the long term clinical outcomes and to compare morbidity and mortality between OMT and ER in diabetic patients with CTOs.

#### METHODS

Potentially relevant published clinical trials were identified in Medline, Embase, chemical abstracts and Biosis (from start of the databases till date) and pooled hazard ratios (HR) computed using a random effects model, with significant *P*



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Authors report no conflict of interest.

**PRISMA 2009 Checklist statement:**

The Authors have read the PRISMA checklist and the manuscript was prepared and revised according to the 2009 PRISMA check list.

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value < 0.05. Primary outcome of interest was all-cause death. Secondary outcomes included cardiac death, prompt revascularization (ER) or repeat myocardial infarction (MI). Due to scarcity of data, both Randomized control trials and observational studies were included. 4 eligible articles, containing 2248 patients were identified (1252 in OMT and 1196 in ER). Mean follow-up was 45-60 mo.

**RESULTS**

OMT was associated with a higher all-cause mortality [HR: 1.70, 95% confidence interval (CI): 0.80-3.26,  $P = 0.11$ ] and cardiac mortality (HR: 1.68, 95%CI: 0.96-2.96,  $P = 0.07$ ). Results were close to significance. The risk of repeat MI was almost the same in both groups (HR: 0.97, 95%CI: 0.61-1.54,  $P = 0.90$ ). Similarly, patients assigned to OMT had a higher risk of repeat revascularization (HR: 1.62, 95%CI: 1.36-1.94,  $P < 0.00001$ ). Sub-group analysis of OMT *vs* PCI demonstrated higher all-cause (HR: 1.98, 95%CI: 1.36-2.87,  $P = 0.0003$ ) and cardiac mortality (HR: 1.87, 95%CI: 0.96-3.62,  $P = 0.06$ ) in the OMT group. The risk of repeat MI was low in the OMT group *vs* PCI (HR: 0.53, 95%CI: 0.31-0.91,  $P = 0.02$ ). Data on repeat revascularization revealed no difference between the two (HR: 1.00, 95%CI: 0.52-1.93,  $P = 1.00$ ).

**CONCLUSION**

In diabetic patients with CTO, there was a trend for improved outcomes with ER regarding all-cause and cardiac death as compared to OMT. These findings were reinforced with statistical significance on subgroup analysis of OMT *vs* PCI.

**Key Words:** Coronary angiography; Diabetes mellitus; Percutaneous coronary Intervention; Coronary bypass grafts; Chronic total occlusions; Mortality

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**Core Tip:** There is a well-known association with worse outcomes from chronic total occlusions in diabetics. These lesions have been traditionally treated with optimal medical therapy (OMT) with the standard of care for revascularization being coronary artery bypass grafting with little evidence of superiority over OMT. Our results reveal for the first time a trend towards superiority of the prompt revascularization group to OMT in terms of all cause and cardiac death in diabetics with chronic total occlusions. These findings were reinforced on subgroup analysis. However, patients undergoing percutaneous coronary intervention had a higher risk of repeat fatal and non-fatal myocardial infarction as compared to OMT. The risk for repeat revascularization was similar in both groups.

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**INTRODUCTION**

Chronic total occlusion (CTO) of a coronary artery is defined as a 100% stenosis with thrombolysis in myocardial infarction 0/I flow for greater than 3 mo<sup>[1,2]</sup>. The prevalence of CTOs ranges from 18%-26% in all patients with coronary artery disease (CAD) and almost 50% in patients with previous coronary artery bypass grafting (CABG)<sup>[3]</sup>. Around 10% of patients with acute myocardial infarction (MI) are also found to have CTOs<sup>[3]</sup>. Presence of CTO is associated with lifestyle impairment, reduced cardiac performance and poor long-term outcomes<sup>[3,4]</sup>. Given the complex nature and uncertainty regarding mortality benefit from revascularization, these lesions were traditionally treated with optimal medical therapy (OMT). However, with recent advancement in percutaneous techniques and greater operator experience along



with better patient selection, there has been an increase in the trend of CTO interventions in contemporary practice.

In this complex subset of CAD population, diabetic patients are particularly at higher risk of poor outcomes as compared to their non-diabetic counter-parts<sup>[5-7]</sup>. Despite lack of sufficient studies, recent evidence suggest that successful CTO revascularization is associated with improved outcomes of quality of life, left ventricular systolic function and potentially survival in general population<sup>[8,9]</sup>. However, limited data exists regarding long-term outcomes in diabetic patients with CTO treated with revascularization. We, therefore, conducted this meta-analysis of randomized clinical and observational studies to compare clinical outcomes with revascularization *vs* optimal medical therapy in diabetic patients with CTO.

## MATERIALS AND METHODS

We followed the preferred reporting items for systematic reviews and meta-analyses guidelines, a checklist of which is available as supplementary material<sup>[10]</sup>.

### Search strategy

A predefined inclusion criterion was established in advance. Potentially relevant published clinical trials were identified in Medline, Embase, chemical abstracts and Biosis (from start of the databases till date). The following search items were used to search titles and abstracts: (Optimal medical therapy? or OMT? Or intensive medical therapy or IMT or revascularization? Or prompt revascularization or early revascularization? And diabetic or type 2 diabetes or DM and chronic total occlusion or CTO and clinical trials. Due to scarcity of data, both observational and interventional studies were included. Studies were limited to involving humans only.

### Selection criteria

Two researchers independently performed an electronic search of pub med and web of science databases. No language restrictions were made. Studies were included if they met the following criteria; intervention with OMT and early revascularization (PCI or CABG) in diabetics as variables and primary outcome of interest as all cause death. Secondary outcomes included cardiac death, prompt revascularization (ER) or repeat MI. Studies were included if successful revascularization (CABG or PCI) was performed within six weeks of randomization or start of study. Both short and long term follow ups were included in literature review. 48 articles were identified after the search. The second selection step involved proof-reading of those articles to ensure the first step was performed correctly. Articles were excluded if data on OMT or prompt revascularization (ER) was missing, trials did not include diabetic subjects or primary and secondary outcomes of interest were not available. In case of un-clarity, inclusion of the studies was discussed amongst the authors to arrive at a final decision.

### Data extraction and statistical analysis

Data was extracted from each study using a standardized spread sheet which involved study identification (Author, year of publication and country), study type, percent males, subject baseline characteristics with history of coronary artery disease, number of cases in OMT and ER arms, time of follow up, type of stent used (Drug eluting *vs* bare-metal), exclusion criteria and quality scoring.

To calculate the overall effect outcome, generic inverse variance tool under the random effects model to calculate pooled hazard ratios (HR) was performed using Cochrane's review manager. The "test for overall effect" was reported as z value corroborating inference from the 95% confidence interval (CI), and the probability value of  $P < 0.05$  was considered statistically significant. Higgins I-squared (I<sup>2</sup>) statistic model was used to assess variations in outcomes of included studies. I<sup>2</sup> values of 50% or less corresponded to low to moderate, and 75% or higher indicated large amounts of heterogeneity. Publication bias was illustrated graphically using a funnel plot asymmetry. The methodological quality of included articles was performed using the Cochrane guidelines for systematic review and meta-analysis.

We also assessed quality using a scoring system based on the Delphi consensus for meta-analysis<sup>[11]</sup>. The following criteria were used for scoring: Proper randomization (Score: 1 point), similarity of treatment groups in relevant variables at baseline (1 point), blinding of subjects and investigators (1 point for each), specified eligibility criteria (1 point), valid point estimates and measures of variability (1 point) and data on degree of compliance (1 point). Thus, a combined score was calculated for each

study which could range from 0 to 7 points. For the observational studies, a score of 0 was given for randomization. Quality scores for each study have been illustrated in Table 1.

## RESULTS

The search through Pub med and Med of science databases yielded 48 potentially relevant articles. Based on predefined exclusion criteria, 44 papers were excluded for various reasons. 1 Randomized control trial<sup>[12]</sup> and 3 observational studies<sup>[13-15]</sup> involving a total of 2448 subjects were included in the meta-analysis. The number of subjects ranged from 236 in Yan *et al*<sup>[15]</sup> to 972 in Damluji *et al*<sup>[12]</sup>. Mean age ranged from 59.2 years in Yan *et al*<sup>[15]</sup> to 68.5 years in Flores-Umanzor *et al*<sup>[13]</sup>. Reported compliance was 100%. Follow up time ranged from 45 mo in Yan *et al*<sup>[15]</sup> To 60 mo in Damluji *et al*<sup>[12]</sup> as above, studies were included if successful revascularization (CABG or PCI) was performed within six weeks of randomization or start of study. OMT included pharmacological therapy as well as lifestyle modification. Pharmacologic therapy across the studies included antiplatelet therapy (as needed), maximum tolerated dose of anti-anginals (B-Blocker plus a long acting nitrate and/or a calcium channel blocker) and statins. Baseline characteristics of all studies have been illustrated in Table 1, with the major co-morbidities across all studies in Table 2. Among studies with reported data, right coronary artery was the vessel most commonly diseased (Table 3).

### Primary effect outcome

Three out of four studies reported long term all-cause mortality. There was a 70% increase in risk of pooled all-cause mortality in the OMT group, although the confidence interval did cross 1, (HR: 1.70, 95%CI: 0.80-3.26,  $P = 0.11$ , see Figure 1A). Significant heterogeneity was observed, ( $I^2 = 88\%$ ,  $P = 0.0003$ ). After removing the study by Flores-Umanzor *et al*<sup>[13]</sup>, no significant heterogeneity was seen, ( $I^2 = 28\%$ ,  $P = 0.24$ ) however, pooled results were similar, (HR: 1.21, 95%CI: 0.79-4.19,  $P = 0.38$ , Figure 1B). In order to assess for publication bias, a funnel plot for each study was constructed against their respective precisions. Absence of publication bias is reflected in an intercept close to zero with the slope of regression line close to overall effect size. Although the small number of studies limited its interpretation however, a subjective impression of funnel plot demonstrated no publication bias.

### Secondary effect outcomes

All four studies reported long term cardiac mortality. The long-term HR for cardiac mortality was 1.68 with 95%CI: 0.96-2.96 and  $P = 0.07$  in the OMT group with an overall 68% increased risk as compared to the ER group, results were close to significance (Figure 1C). Significant heterogeneity was again observed, ( $I^2 = 76\%$ ,  $P = 0.006$ ). After removing Flores-Umanzor *et al*<sup>[13]</sup> from the analysis, mortality was higher in the OMT group, however the CI crossed 1, (HR: 1.24, 95%CI: 0.85-1.81,  $P = 0.27$ ).

Data for repeat MI was available for all four studies. No significant differences in the hazard ratio were observed between the two groups. (HR: 0.97, 95%CI: 0.61-1.54,  $P = 0.90$ , Figure 2A). No significant heterogeneity was observed, ( $I^2 = 41\%$ ,  $P = 0.16$ ).

All four studies reported data on repeat revascularization (PCI and CABG). There was a 62% increase in risk of repeat revascularization in patients assigned to medical therapy, and results were statistically significant, (HR: 1.62, 95%CI: 1.36-1.94,  $P < 0.00001$ , Figure 2B). No publication bias or study heterogeneity was observed,  $I^2 = 0\%$ .

### Subgroup analysis

Sub-group analysis stratified by mode of revascularization *i.e.* CABG or PCI was also performed for both primary and secondary effect outcomes. Only Flores-Umanzor *et al*<sup>[13]</sup> provided data on both PCI and CABG where as two studies provided data on PCI only. Thus, subgroup analysis was done only for PCI.

For all-cause mortality, sub group analysis of OMT *vs* PCI revealed a 98% increased risk in the OMT group, (HR: 1.98, 95%CI: 1.36-2.87,  $P = 0.0003$ , Figure 3A). This was statistically significant with no significant heterogeneity, ( $I^2 = 0$ ,  $P = 0.83$ ).

Similarly, sub-group analysis for cardiac mortality was also done comparing PCI *vs* OMT. Three out of four studies *i.e.*, Flores-Umanzor *et al*<sup>[13]</sup> and Yan *et al*<sup>[15]</sup> provided data on PCI. There was an 87% increased risk of cardiac mortality in the OMT *vs* PCI group, (HR: 1.87, 95%CI: 0.96-3.62,  $P = 0.06$ , Figure 3B). Results were not statistically significant with moderate heterogeneity, ( $I^2 = 60\%$ ,  $P = 0.08$ ).

Table 1 Baseline characteristics of all studies

Ref.	Damluji <i>et al</i> <sup>[12]</sup>	Flores-Umanzor <i>et al</i> <sup>[13]</sup>	Yan <i>et al</i> <sup>[15]</sup>	Choi <i>et al</i> <sup>[14]</sup>
Type of study	Randomized control trial (Post Hoc analysis of BARI-2D)	Cohort (prospective)	Cohort (retrospective)	Cohort (retrospective)
Country	United States	Spain	China	South Korea
Period during which study was done	2001-05	2010-14	2007-17	2003-12
Study size (Patients with DM and CTO)	972	538	2361	702
Follow up in months	60	48	45	46
Male (%)	78	82	78	77
Age, mean (yr)	62.5	68.5+/-3.5	60	64.6
Type of stent used if PCI	DES or BMS	-	DES	DES
Exclusion criteria	Need for immediate revascularization, left main coronary disease, a creatinine level > 2.0 mg/dL, a glycated hemoglobin level > 13.0%, heart failure class III or IV, hepatic dysfunction, or previous PCI or CABG within the last 12 mo	No exclusion criteria	(1) Patients who had a history of CABG; (2) Patients who had acute myocardial infarction (MI) due to non-CTO vessels 1 mo before the study; (3) Patients who had left main coronary artery disease; and (4) Patients who had histories of cancer or other diseases that could confuse the end points	History of previous CABG; history of cardiogenic shock or cardiopulmonary resuscitation; ST-segment elevation acute MI during the preceding 48 h
Quality score <sup>2</sup>	7	5	5	5

<sup>1</sup>Propensity Matched Population.

<sup>2</sup>Criteria used for scoring: Proper Randomization (Score: 1 point), similarity of treatment groups in relevant variables at baseline (1 point), blinding of subjects and investigators (1 point for each), specified eligibility criteria (1 point), valid point estimates and measures of variability (1 point) and data on degree of compliance (1 point). More details in text. DM: Diabetes mellitus; CTO: Chronic total occlusion; PCI: Percutaneous coronary intervention; RCT: Randomized control trial; DES: Drug eluting stent; BMS: Bare metal stent; CABG: Coronary artery bypass grafting.

Three out of four studies *i.e.* Flores-Umanzor *et al*<sup>[13]</sup>, Choi *et al*<sup>[14]</sup> and Yan *et al*<sup>[15]</sup> provided data on risk of repeat MI. OMT was relatively safer in regards to occurrence of repeat MI as compared with PCI with a decreased HR, (HR: 0.53, 95%CI: 0.31-0.91,  $P = 0.02$ , Figure 3C). No heterogeneity was observed,  $I^2 = 0\%$ ,  $P = 0.87$ .

For repeat revascularization, sub group analysis of OMT *vs* PCI revealed no difference in HR between the two groups. (HR: 1.00, 95%CI: 0.52-1.93,  $P = 1.00$ , Figure 3D).

## DISCUSSION

In this meta-analysis of randomized controlled and observational studies comparing diabetic patients with CTOs, patients in the OMT group were found to have a higher risk of all-cause and cardiac death as compared to ER. We included 4 studies for a total of 2448 patients. 1252 patients were treated with OMT while 1196 patients underwent early revascularization. Damluji *et al*<sup>[12]</sup> which is a post hoc analysis of the bypass angioplasty revascularization investigation 2 diabetes trial, evaluated the influence of CTO on long term clinical outcomes of patients with coronary artery disease and diabetes mellitus. We extracted the data for CTO only from Damluji *et al*<sup>[12]</sup> to calculate mortality and morbidity outcomes in diabetics, however, our results were non-significant as shown in Figures 1A-1C further 3 observational studies were added to our meta-analysis to achieve the above results. We found that there was a trend of improved survival with ER either with CABG or PCI in terms of cardiac and all cause

**Table 2 Percentage prevalence of co-morbidities across studies (actual prevalence in brackets)**

Ref.	Damluji <i>et al</i> <sup>[12]</sup>		<sup>1</sup> Flores- Umanzor <i>et al</i> <sup>[13]</sup>			Yan <i>et al</i> <sup>[15]</sup>		Choi <i>et al</i> <sup>[14]</sup>	
	OMT ( <i>n</i> = 490)	ER ( <i>n</i> = 482)	OMT ( <i>n</i> = 326)	ER	ER	OMT ( <i>n</i> = 118)	ER ( <i>n</i> = 118)	OMT ( <i>n</i> = 318)	ER ( <i>n</i> = 384)
				PCI ( <i>n</i> = 76)	CABG ( <i>n</i> = 136)				
HTN	80 (385)	81 (387)	85 (276)	82 (62)	86 (117)	66.9 (79)	71.2 (84)	70.7 (225)	70.3 (270)
Previous MI	44 (214)	41 (197)	33 (108)	28 (21)	28 (21)	56.8 (67)	55.9 (66)	34.9 (111)	18.0 (69)
Prior CHF	7 (36)	9 (43)	-	-	-	14.4 (17)	10.2 (12)	-	-
Prior Stent/PCI	11 (56)	12 (59)	-	-	-	48.3 (57)	42.4 (50)	30.5 (97)	22.1 (85)
Prior CVA/TIA	10 (49)	10 (46)	-	-	-	5.1 (6)	5.9 (7)	12.3 (39)	11.2 (43)
Prior Revascularization	31 (151)	26 (124)	-	-	-	-	-	-	-
Previous CABG	-	-	14 (45)	5 (4)	4 (5)	-	-	0	0
HbA1c mean	7.4	7.3	7.6 ± 0.1	7.6 ± 0.2	7.3 ± 0.1	-	-	-	-
Dyslipidemia	83 (402)	84 (400)	75 (246)	71 (54)	74 (100)	51.7 (61)	50 (59)	21.7 (69)	31.3 (120)
Smoking	-	-	52 (169)	55 (42)	59 (80)	55.9 (66)	57.6 (68)	28.6 (91)	32.8 (126)
Peripheral vascular disease	-	-	45 (145)	33 (25)	35 (47)	3.4 (4)	3.4 (4)	6.0 (19)	3.4 (13)

<sup>1</sup>Data given separately for percutaneous coronary intervention and Coronary Artery Bypass Grafting group. OMT: Optimal medical therapy; ER: Early revascularization; N: Number of subjects; PCI: Percutaneous coronary intervention; CABG: Coronary Artery Bypass Grafting; HTN: Hypertension; MI: Myocardial infarction; CHF: Heart failure; CVA: Cerebrovascular accident, HbA1c: Hemoglobin A1c.

**Table 3 Chronic total occlusions location with number of chronic total occlusions lesions among studies in percentages (actual prevalence in brackets)**

Ref.	Damluji <i>et al</i> <sup>[12]</sup>		Flores-Umanzor <i>et al</i> <sup>[13]</sup>		Yan <i>et al</i> <sup>[15]</sup>		Choi <i>et al</i> <sup>[14]</sup>	
	OMT	ER	OMT ( <i>n</i> = 326)	ER ( <i>n</i> = 212)	OMT ( <i>n</i> = 118)	ER ( <i>n</i> = 118)	OMT ( <i>n</i> = 318)	ER ( <i>n</i> = 384)
Number of CTO lesions								
1	-	-	80 (261)	75 (159)			-	-
2	-	-	79 (60)	24 (50)			-	-
3	-	-	1.5 (5)	1.4 (3)			-	-
CTO location								
LAD artery	-	-	18 (60)	24 (51)	30.5 (36)	28.0 (33)	26.4 (84)	38.5 (148)
LCX artery	-	-	19 (62)	20 (42)	28.0 (33)	26.3 (31)	36.5 (116)	29.2 (112)
RCA	-	-	52 (170)	47 (100)	41.5 (49)	45.8 (54)	56.3 (117)	47.9 (184)
Other coronary artery branches	-	-	10 (34)	9 (19)	-	-	-	-

LAD: Left anterior descending; LCX: Left circumflex; RCA: Right coronary artery; OMT: Optimal medical therapy; ER: Early revascularization; N: number of subjects.



death. To our knowledge, this is the first ever meta-analysis of clinical trials comparing morbidity and mortality outcomes in diabetic patients with a CTO. Our subgroup analysis also revealed poor performance of PCIs *vs* OMT in terms of incidence of combined fatal and non-fatal MI. Further stratification could not be performed due to paucity of data.

Given the complex nature and uncertainty regarding mortality or morbidity benefits from percutaneous or surgical revascularization, CTO lesions have been traditionally treated with OMT. Historically, the standard of care for revascularization of CTO lesions has been CABG with little evidence of superiority over OMT. However, with recent advancement in percutaneous techniques and greater operator experience along with better patient selection, there has been an increase in trend of CTO interventions in contemporary practice<sup>[16,17]</sup>. Although observational data has shown a reduction in Major Adverse Cardiac Events, global left ventricular ejection fraction and quality of life after revascularization of CTO, results from these trials are inconsistent<sup>[18,19]</sup>.

Currently the global expert consensus statement recommends PCI revascularization for ischemic symptom improvement for which data is more unanimous<sup>[20]</sup>.

Diabetes mellitus is a major risk factor of CTO. Around 34%-40% of patients with CTO have a history of diabetes<sup>[13]</sup> and there is a well-known association with worse outcomes from CTO in diabetics<sup>[5-7,13]</sup>. Diabetes leads to endothelial cell dysfunction and changes in microcirculation, a prothrombotic/proinflammatory state along with impaired formation of coronary collaterals<sup>[7,8,21]</sup>. This causes aggressive progression of atherosclerosis within the arterial bed including the coronary arteries leading to poorer outcomes in patients with CAD<sup>[22]</sup>. PCI in diabetic patients also has a higher risk of in-stent restenosis, repeat revascularization, MI, stent thrombosis and death when compared to non-diabetics<sup>[23-25]</sup>.

By performing a post hoc analysis of the bypass angioplasty revascularization investigation 2 diabetes trial, Damluji *et al*<sup>[12]</sup> was the first to compare clinical outcomes in patients with both diabetes and coronary artery disease. They found that a lot of diabetic patients with CAD had a high prevalence of CTOs, approximately 41%. Although the primary outcome studied was the effect of CTOs on mortality in diabetics with a strongly positive correlation, we extracted the data for the CTO subgroup only for our analysis and found that OMT was associated with a higher risk of all cause and cardiac mortality in diabetics. Patients undergoing early revascularization were also noted to have a lower risk of repeat MI and repeat revascularization at long term follow up. Damluji *et al*<sup>[12]</sup> and Choi *et al*<sup>[14]</sup> however did not perform a subgroup analysis on the revascularization modality chosen *i.e.*, CABG *vs* PCI.

Our subgroup analysis (OMT *vs* PCI) revealed inferiority of PCI as a revascularization strategy in terms of repeat MI and repeat revascularization to the combined PCI and CABG group. This discrepancy in results is an interesting observation from the PCI subset as compared to the combined revascularization pool. This could imply superiority of CABG over PCI in these patients but these results might be confounded by disease anatomy and various comorbidities. Studies designed to compare CABG and PCI for this purpose can be helpful in the future. Also, the current success rates of CTO-PCI in the general population are from 80%-85%, however the majority of our trials demonstrated a lower success rate<sup>[26]</sup>. One possible explanation for this discrepancy could be recent advancements in percutaneous techniques and equipment, however it is well known that diabetic patients have a higher burden of CAD with more complex disease anatomy which might be difficult to completely re-vascularize<sup>[27]</sup>. In a meta-analysis of 35 studies including 89883 patients, Garcia *et al*<sup>[28]</sup> demonstrated that CABG was twice as likely as PCI to achieve complete revascularization in patients with CTOs. The study by Flores-Umanzor *et al*<sup>[13]</sup> included in our meta-analysis also noted higher rates of anatomic and functional complete revascularization in CABG *vs* PCI patients (63% and 62% *vs* 36% and 32%,  $P < 0.01$ ). Subsequently, they also reported statistically significant lower all-cause and cardiac mortality with CABG when compared to MT group but not with PCI.

Another important factor to consider in these patients is the presence or absence of chronic kidney disease (CKD). Studies have shown that renal dysfunction is an independent risk factor for cardiovascular disease, with higher mortality rates for both myocardial infarction and sudden cardiac death<sup>[29,30]</sup>. Our patients in Choi *et al*<sup>[14]</sup> and Yan *et al*<sup>[15]</sup> were case-control matched according to the presence or absence of CKD, however, further data on this sub-group was not available for us to perform analysis. Similarly, the study referenced by Damluji *et al*<sup>[12]</sup> excluded patients with a creatinine of 2.0 mg/dL or higher. Flores-Umanzor *et al*<sup>[13]</sup> did not comment on CKD. Hopefully, further studies in the future shall enable us to look at the effect of CKD on clinical

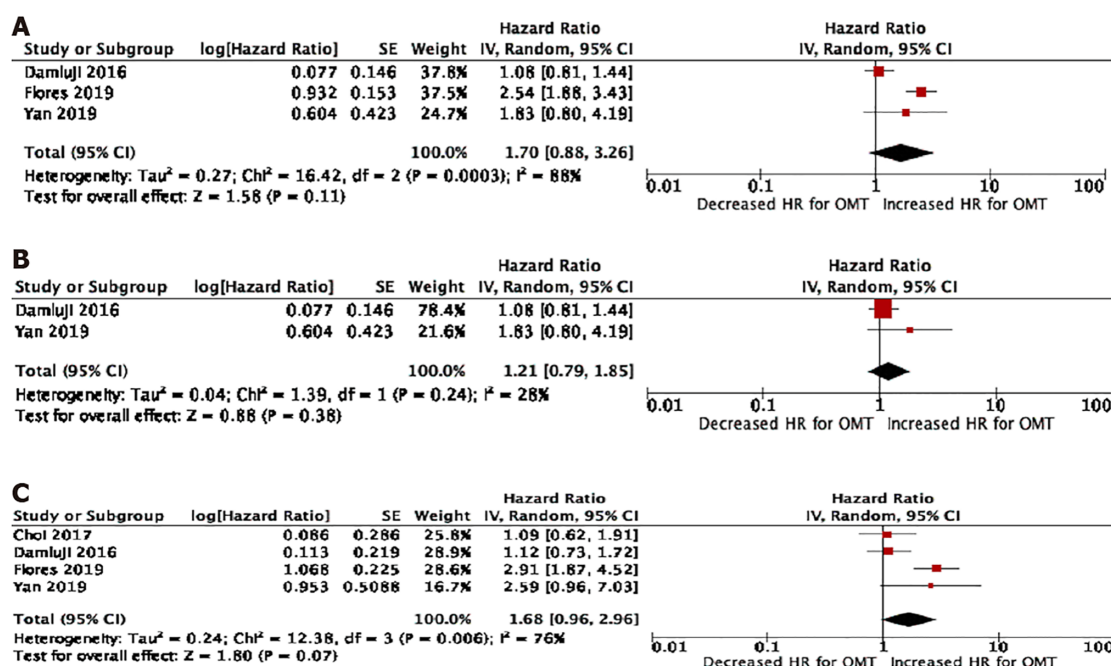


Figure 1 Random effects meta-analysis and forest plot of hazard ratios for all cause long term and cardiac mortality. A: All-cause Mortality; B: All-cause mortality after removing Flores-Umanzor *et al*<sup>[13]</sup>; and C: Cardiac Mortality.

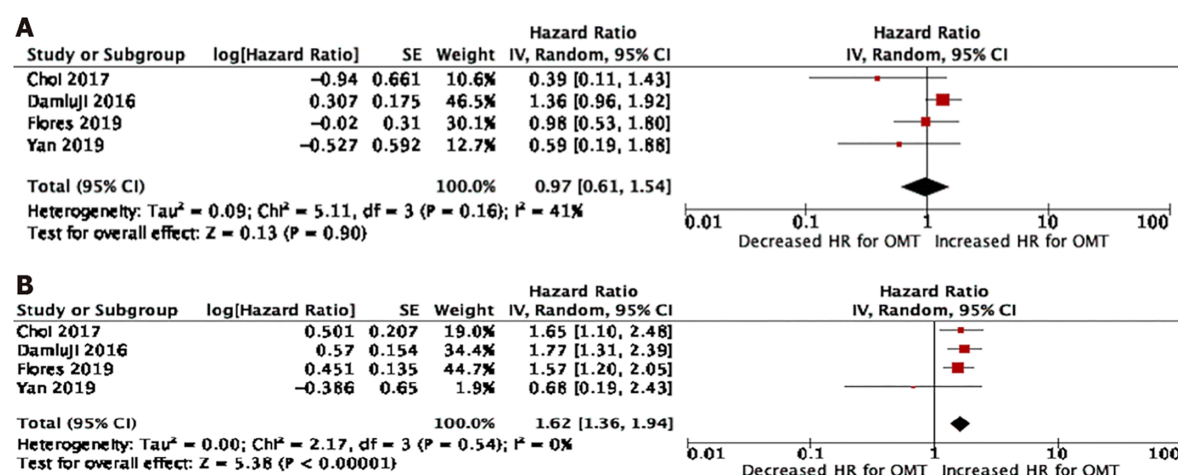


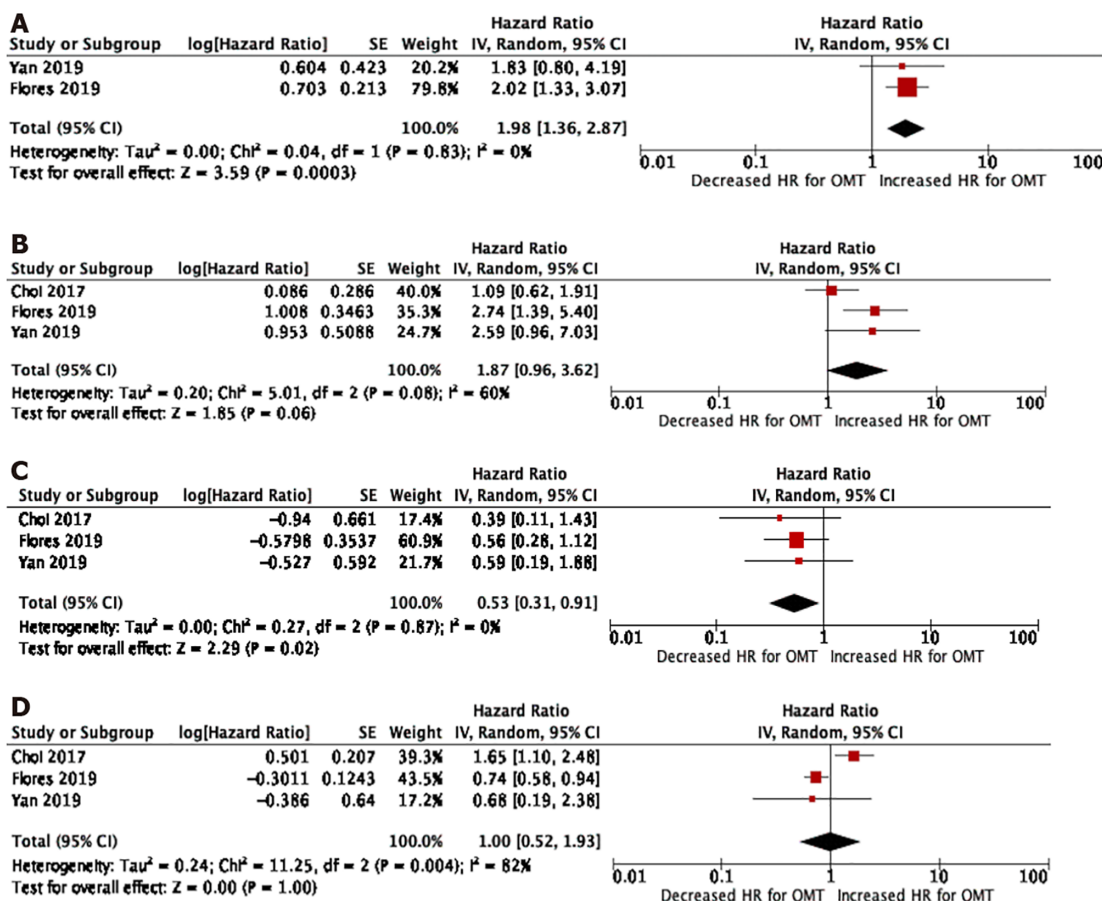
Figure 2 Random effects meta-analysis and forest plot of hazard ratios for repeat myocardial infarction and repeat revascularization. A: Repeat Myocardial Infarction; and B: Repeat revascularization.

outcomes in diabetics with CTO.

It is also not clear why revascularization in CTO is beneficial and associated with improved survival rates in diabetics. CTOs are usually associated with a larger scar and most of all with a bigger border zone which causes arrhythmias and sudden cardiac death in most patients<sup>[31]</sup>. Thus, it might be the beneficial effects of early revascularization in preventing the formation of scar myocardium which may lead to improvement in mortality and morbidity. It also might be worthwhile to attempt CABG instead of PCI in patients with a difficult anatomy particularly in the diabetic sub group as these patients have a lower success rate as compared to the general population and might save unnecessary side effects from an unsuccessful procedure in itself.

### Limitations

Our studies have various limitations. Because of the observational design of three out of four studies (Figures 1 and 2), there was an inherent risk of selection bias which



**Figure 3** Sub-group analysis and forest plot of hazard ratios for all-cause and cardiac mortality, repeat MI and repeat revascularization. A: All-Cause Mortality; B: Cardiac mortality; C: Repeat myocardial infarction; and D: Repeat revascularization.

may have affected the results through confounding factors. One of the potential explanations for the mortality benefits with ER may be potential confounders as high-risk patients are less likely to undergo ER. This was reinstated across all studies as patients assigned to OMT were older and with more co-morbidities. A major concern for selection bias in Flores-Umanzor *et al.*<sup>[13]</sup> was the inclusion of failed PCI group into the medical therapy group as a failed PCI might itself be a risk factor for adverse events in the future. Yan and colleagues also only studied one vessel CTO but the other three studies also included more than one vessel CTO. Although this might not be significant as Flores-Umanzor *et al.*<sup>[13]</sup> demonstrated that in majority of patients, only one vessel was diseased with the most common culprit being the right coronary artery. The selection of only PCI as revascularization modality by Choi *et al.*<sup>[14]</sup> and Yan *et al.*<sup>[15]</sup> also introduced bias as patients treated with CABG were not studied. Significant heterogeneity was observed in some effect outcomes, however we used sensitivity analysis to analyze which study was causing the effect and recalculated data after dropping the study. Also, as with all met-analysis, the quality of the study is as good as the quality of the trials itself.

## CONCLUSION

Despite our limitations, we report the results of the first meta-analysis specifically done on diabetic patients with CTO lesions treated with OMT *vs* ER. The results reveal a trend towards superiority of the ER group (PCI and CABG) to OMT in terms of all cause and cardiac death although we could not achieve statistical significance. These findings were reinforced on subgroup analysis of OMT *vs* PCI, specifically regards to all-cause death where the results were statistically significant. However, patients undergoing PCI had a higher risk of repeat fatal and non-fatal MI as compared to OMT and the risk for repeat revascularization was similar in both groups. Overall patients in the OMT only group had a higher risk of repeat revascularization

as compared to ER group (PCI and CABG). In patients with extensive CAD and CTO, CABG may be attempted as PCI in diabetics has a higher risk of failure as compared to non-diabetics. Further data including larger patient population from future studies is needed to clarify outcome benefits from revascularization or medical therapy in these patients.

## ARTICLE HIGHLIGHTS

### Research background

The thought process behind this manuscript was our motivation upon literature review of a scarcity of data involving clinical outcomes of diabetics with chronic total occlusion (CTO) of coronary vessels.

### Research motivation

Our motivation came from the scarcity of data in this sub group of population. There exists a lot of literature comparing the mortality and morbidity outcomes of medical therapy (OMT) *vs* early re-vascularization [ER: Percutaneous coronary intervention (PCI) + Coronary artery bypass grafting] in patients with chronic total occlusions but none in the diabetic subset.

### Research objectives

To compare the mortality and morbidity outcomes in diabetic population with CTO treated with OMT *vs* ER.

### Research methods

Multiple electronic data-bases including Pubmed, Embase were searched involving human studies comparing OMT *vs* ER in patients having CTO of coronary vessels. Data was analyzed using Cochrane review manager with hazard ratios using the random effects model. Primary effect estimate was all cause mortality with secondary effect estimates as cardiac mortality, repeat myocardial infarction (MI) and repeat re-vascularization.

### Research results

Statistical analysis revealed a higher risk for all-cause mortality, cardiac mortality and repeat re-vascularization in the OMT group. For repeat MI, data analysis revealed no significant differences in between the two groups. Sub-group analysis was also done for OMT *vs* PCI. This revealed a higher risk for all-cause mortality but not for cardiac mortality or repeat re-vascularization in the OMT group. Interestingly, patients in the OMT group were found to have a lower incidence of repeat MI *vs* PCI group.

### Research conclusions

There is a trend towards superiority of the ER group as compared to OMT group in diabetic patients with a CTO. These findings were reinforced on sub-group analysis of OMT *vs* PCI.

### Research perspectives

Despite our limitations, we present the first ever meta-analysis specifically involving diabetic patients only with CTO treated with OMT or ER. Although we were able to demonstrate a trend towards superiority of the ER group, this was not statistically significant for some sub-groups including all-cause and cardiac mortality. Although this manuscript provides a relatively new insight into management of such patients, further studies may be needed before a consensus is developed.

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## Transradial vs transfemoral secondary access outcomes in transcatheter aortic valve implantation: A systematic review and meta-analysis

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Radhakrishnan SL completed conceptualization, methodology and formal analysis, wrote original draft, reviewed and edited the manuscript; Ho KKL provided resources and supervision, reviewed and edited the manuscript.

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## Abstract

### BACKGROUND

Complications of transcatheter aortic valve implantation (TAVI) procedures include bleeding, vascular complications, and strokes. These complications are often associated with the type of access used. The two types of access in TAVI procedures are primary and secondary. The main use of the primary access is for valve delivery, while secondary access is used for angiography and hemodynamic monitoring. While there are many options for primary access, those for secondary access are transfemoral and transradial.

### AIM

To compare outcomes between transradial *vs* transfemoral secondary access (TFSA).

### METHODS

A systematic search was conducted using major databases (EMBASE, PubMed, Cochrane Central, Google Scholar), which resulted in 5 studies that met the criteria for study selection. Outcomes of interest were 30-d rates each of major/life-threatening bleeding, vascular complications, strokes, and mortality. All 5 studies were observational. Only adjusted or matched data were used when available in this meta-analysis.

### RESULTS

A total of 5065 patients underwent TAVI, with 1453 patients (28.7%) having undergone transradial secondary access (TRSA) and 3612 patients (71.3%) TFSA. Irrespective of the site of primary access, the odds of having major or life-threatening bleeding were 60% lower in the TRSA group than the TFSA group (*P*

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< 0.00001). The odds of having major vascular complications were 52% lower in the TRSA group ( $P < 0.0001$ ) with no difference in minor vascular complications between the 2 groups. Similarly, the odds of mortality in 30-d after the procedure were 41% lower ( $P = 0.006$ ) and the odds of stroke were 54% lower ( $P = 0.001$ ) in the TRSA group than the TFSA group.

## CONCLUSION

The transradial secondary approach appears to be a safer alternative to the transfemoral secondary approach in TAVI procedures.

**Key Words:** Transcatheter aortic valve implantation; Meta-analysis; Femoral access; Radial access; Secondary access; Transcatheter aortic valve replacement

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**Core Tip:** Transcatheter aortic valve implantation (TAVI) procedures can result in complications due to secondary access site. This meta-analysis looks into 5 observational studies that compared outcomes in TAVI related to secondary access. The outcomes included 30-d bleeding, vascular complications, strokes, and mortality. Meta-analysis showed decreased odds of outcomes when transradial secondary access was used over transfemoral.

**Citation:** Radhakrishnan SL, Ho KKL. Transradial vs transfemoral secondary access outcomes in transcatheter aortic valve implantation: A systematic review and meta-analysis. *World J Cardiol* 2020; 12(11): 571-583

**URL:** <https://www.wjgnet.com/1949-8462/full/v12/i11/571.htm>

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## INTRODUCTION

The transcatheter aortic valve implantation (TAVI) procedure is a promising alternative to surgical aortic valve replacement in patients with aortic stenosis. As with any procedure, TAVI is not without complications. Bleeding, vascular complications, and strokes are some of the most common adverse events associated with TAVI. These complications are often associated with the type of access used in the procedure.

TAVI utilizes two vascular access sites—primary and secondary. The valve itself is delivered through the primary access site, while the secondary access site is used for the introduction of catheters for angiography, aiding in device placement, and obtaining invasive hemodynamic data<sup>[1]</sup>. Options for primary access include transfemoral, transaortic, transapical, and subclavian, among others, out of which transfemoral has been the most popular. The two main sites used for secondary access are the contralateral femoral artery and either radial artery. Historically, the transfemoral site was chosen as the preferred secondary access site. However, during recent years, the transradial site has shown promising results with lower complication rates. There are a handful of studies, mostly with relatively small sample sizes, directly comparing outcomes in transfemoral (TF) and transradial (TR) access sites<sup>[1-6]</sup>. These studies have suggested that the transradial site for secondary access has better outcomes than the transfemoral site for bleeding and vascular complications. The aim of this review is to pool data from available relevant studies to compare outcomes between TR and TF secondary accesses.

## MATERIALS AND METHODS

### Search strategy

This study was registered on PROSPERO on May 7, 2020, and the meta-analysis was conducted using PRISMA guidelines. A comprehensive literature search was conducted through June 10, 2020 using PubMed, EMBASE, Google Scholar, and

Cochrane databases. Search words included “transfemoral *vs* transradial secondary access in transcatheter aortic valve replacement” and “radial *vs* femoral secondary access in TAVI.” Literature search was conducted independently by two investigators (Radhakrishnan SL and Darmoch F—see acknowledgement) using the above search strategy. There was uniform agreement between both investigators on what studies to include and exclude, resulting in a kappa correlation of 1.

### **Inclusion criteria**

All observational or experimental trials which aimed at comparing data related to secondary access in patients who underwent TAVI were considered in this review, irrespective of primary access. We included studies if they reported data comparing outcomes between transradial and transfemoral secondary access. Studies considered had to include tables comparing demographics and other baseline characteristics and outcomes. The outcomes considered for the purpose of this review were 30-d all-cause mortality, 30-d stroke, 30-d bleeding complications, and 30-d vascular complications. Studies were included if they reported at least one of the four outcomes in the format desired (comparing TR *vs* TF).

### **Exclusion criteria**

Studies that did not meet inclusion criteria based on title were excluded. Studies that did not report data specifically related to secondary access in TAVI procedures in the format desired were also excluded. Letters to the editor, abstracts, and posters were excluded.

### **Statistical analysis**

Statistical analysis was performed using Review Manager 5.3. Subgroup analysis was only done if data were reported in at least four studies to increase confidence in the findings. The test statistic calculated in this meta-analysis was the odds ratio. A random-effect model was chosen over a fixed-effect model since the underlying population in each study was thought to be different. Heterogeneity was determined by the  $I^2$  value to describe the percentage of variability due to heterogeneity rather than due to sampling bias. The higher the  $I^2$  value, the higher the heterogeneity. That is, an  $I^2$  of < 50% indicates more similarity between studies. A  $P$  value of 0.05 or less was considered to be significant for all test statistics. Funnel plots were created to assess for evidence of bias and to determine heterogeneity. Results are expressed as mean  $\pm$  standard deviation, with 95% confidence intervals for odds ratio denoted by square brackets.

## **RESULTS**

### **Identification of eligible studies**

Using the search strategy described above resulted in 2701 articles (2690 from Google scholar, 5 from PubMed, 5 from Embase, and 1 from Cochrane Central). Of these, 2690 articles were excluded after title and/or abstract review, and 1 trial was still in process and unpublished. Each of the remaining 10 articles was reviewed in full. Of these, 2 letters, 1 poster, and 1 duplication were excluded. Although a study by Wynne *et al*<sup>[1]</sup> was an observational study which focused on the topic of interest, results reported were not dichotomized based on the type of secondary access and hence excluded from the meta-analysis. Five remaining studies were included in the meta-analysis<sup>[2-6]</sup>. Detailed results of the search strategy are outlined in [Figure 1](#).

### **Study characteristics**

All 5 studies included were observational cohort studies. Definitions of bleeding and vascular events were based on Valve Academic Research Consortium-2 (VARC-2) criteria in 4 studies and the original VARC criteria in 1 study (Curran *et al*<sup>[3]</sup>). All studies provided outcomes comparing transradial secondary access (TRSA) with transfemoral secondary access (TFSA). The primary access was solely femoral in 2 studies (Fernandez-Lopez *et al*<sup>[6]</sup> and Curran *et al*<sup>[3]</sup>). Allende *et al*<sup>[4]</sup> and Jackson *et al*<sup>[5]</sup> reported data on all primary accesses (APA, *i.e.*, femoral and non-femoral primary accesses) with distinction in comparative outcomes based on transfemoral primary access (TFPA) *vs* non-TFPA. In Junquera *et al*<sup>[2]</sup>, the study included APA subjects. However, it did not separately provide comparative data on TFPA subjects. Due to the lack of uniformity in the type of primary access, most of the analyses in the study

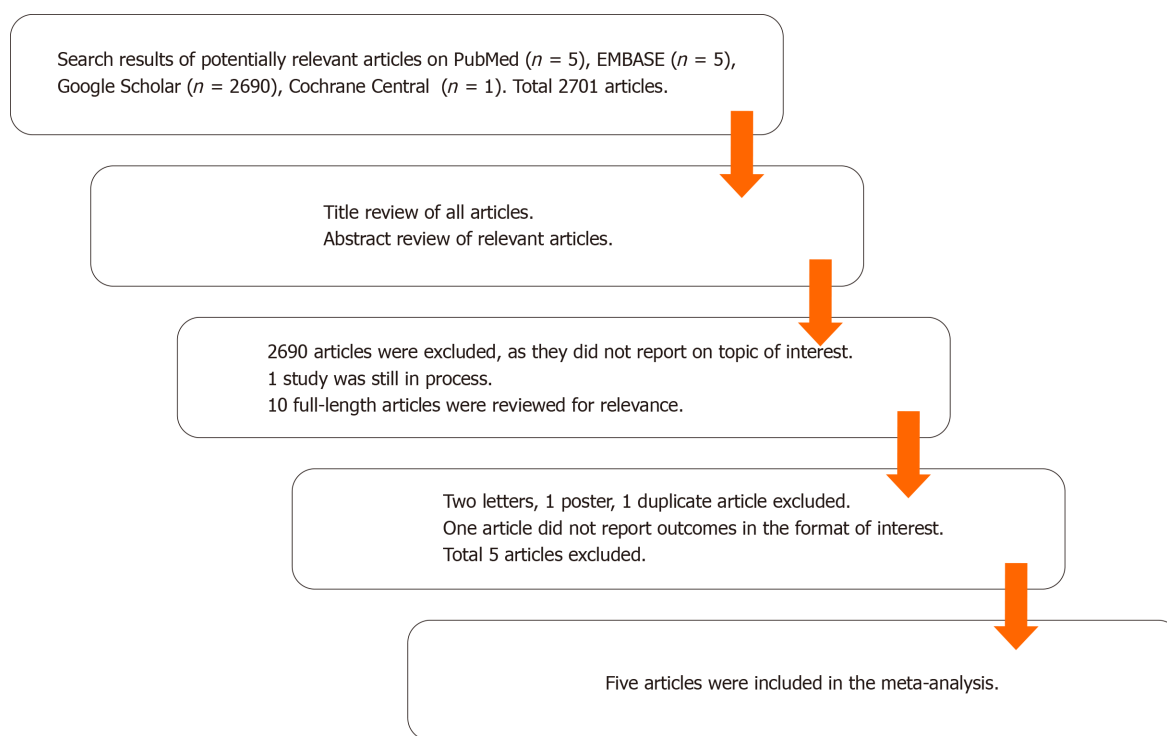


Figure 1 Flowchart outlining search strategy and article-selection process.

mainly focused on APA. The 2 studies that reported only TFPA outcomes were considered as APA for practical purposes. A separate analysis was also done for TFPA alone, thus excluding Junquera *et al*<sup>[2]</sup>. Relevant study characteristics are outlined in Table 1.

Of the 5 studies, risk adjustment in some manner was reported in 3 of 5 studies. When available, matched/adjusted scores were used; however, if no adjustment or matching was reported, the study was still included in this review. Allende *et al*<sup>[4]</sup> adjusted data for differences in gender and peripheral disease. Fernandez-Lopez *et al*<sup>[6]</sup> reported that results were adjusted for age, Euroscore, body mass index, New York Heart Association (NYHA) functional class, type and size of valve. Junquera *et al*<sup>[2]</sup> reported both overall unadjusted data and propensity score-matched data. Jackson *et al*<sup>[5]</sup> and Curran *et al*<sup>[3]</sup> did not report having performed specific risk adjustment or matching.

In Junquera *et al*<sup>[2]</sup>, both unadjusted as well as propensity score-matched data were reported. For the purpose of this study, only propensity score-matched data was included.

### Study results

A total of 5065 patients underwent TAVI inclusive of APA, with 1453 patients (28.7%) having TRSA and 3612 patients (71.3%) having TFSA. A secondary analysis was conducted in patients that underwent TAVI with TFPA. Four out of 5 studies qualified for the TFPA sub-group analysis. The total population of this cohort was 898 patients, out of which 496 patients (55.2%) underwent TRSA and 402 (44.8%) patients underwent TFSA.

Baseline demographics in each study are compared in Table 2. The mean age of the study population was  $81.1 \pm 7.2$  in the TFSA group and  $81.3 \pm 7.1$  in the TRSA group. Forty six percent (46%) were males in the TFSA group and 53% in the TRSA group. Atrial fibrillation was present in 26% of subjects in the TFSA group and 28% in the TRSA group. The mean STS-PROM score was 6.4 in the TFSA group and 6.0 in the TRSA group.

### Results of APA procedures

**All-cause mortality:** When APA-TAVI procedures were considered, the 30-d all-cause mortality rate was 2.6% in the TRSA group and 4.4% in the TFSA group, odds ratio (OR) 0.59 [0.41, 0.86] ( $P = 0.006$ , Figure 2A).

**Stroke:** The 30-d stroke rate was 1.5% in the TRSA group and 3.2% in the TFSA group,



**Table 1 Characteristics and procedure details of included studies**

	<b>Junquera <i>et al</i><sup>[2]</sup></b>	<b>Fernandez-Lopez <i>et al</i><sup>[6]</sup></b>	<b>Jackson <i>et al</i><sup>[5]</sup></b>	<b>Allende <i>et al</i><sup>[4]</sup></b>	<b>Curran <i>et al</i><sup>[3]</sup></b>
Study details					
Year of publication	2020	2018	2018	2014	2014
Country of origin	Multinational (Canada, Europe)	France	The United Kingdom	Canada	Italy
Number of centers	Multicenter	Single center	Single center	Single center	Single center
Study design	Retrospective and prospective cohort study	Retrospective and prospective cohort study	Retrospective cohort study	Retrospective cohort study	Retrospective cohort study
Study subjects	A total of 4949 patients who underwent TAVI between 2007 and 2018 in 10 tertiary centers were included. Selection of secondary access was up to the heart team. 3906 subjects had matched outcomes	Retrospective cohort of 194 patients underwent TFSA TAVI between Sept 2015 and Apr 2016. Prospective cohort of 217 pts underwent TRSA TAVI between April 2016 and May 2017	All consecutive TAVI cases between May 2015 and June 2017 included. Default TRSA used for all non-TF TAVIs from Jan 2016. Prior to this, secondary access was selected based on clinical grounds	Consecutive patients who underwent TAVI from 2007 to 2014 enrolled. From May 2007-Jan 2013, TFSA was chosen. From Jan 2013 onwards, TRSA was chosen in TFPA TAVI and some non-TFPA TAVI	A total of 87 consecutive patients who underwent TFPA TAVI between June 2011 and March 2012 were included in the study. The first 46 TRSA candidates and 41 TFSA candidates were considered
Primary access	TF + non-TF	TF only	TF + non-TF	TF + non-TF	TF only
Total No. of study subjects (APA) with matched or adjusted data if available	3906 (TRSA = 928, TFSA = 2978)	411 (TRSA = 217, TFSA = 194)	199 (TRSA = 135, TFSA = 64)	462 (TRSA = 127, TFSA = 335)	87 (TRSA = 46, TFSA = 41)
Total No. of study subjects (TFPA) with matched or adjusted data	NA	411 (TRSA = 217, TFSA = 194)	179 (TRSA = 115, TFSA = 64)	221 (TRSA = 118, TFSA = 103)	87 (TRSA = 46, TFSA = 41)
Definition of bleeding and vascular events	VARC-2 criteria	VARC-2 criteria	VARC-2 criteria	VARC-2 criteria	Original VARC criteria
Limitations of study	Nonrandomized study	(1) Non-randomized study; (2) Relatively small sample size; (3) TFSA technique was novel resulting in a learning curve	(1) Non-randomized study; (2) Relatively small sample size; (3) Unclear if there was a difference in the populations (risk adjustment not reported)	(1) Non-randomized study; (2) Relatively small sample size; (3) Low use of percutaneous closure devices (13%) for obtaining hemostasis in TFSA	(1) Non-randomized study; (2) Relatively small sample size; (3) TFSA technique was novel resulting in a learning curve
Was risk-adjustment done?	Both unadjusted and propensity score-matched data available	Adjusted for age, Euroscore, BMI, NYHA class, type, and size of valve	Not reported	Adjusted for gender and peripheral disease	Not reported
TAVI Procedure details					
Hemostasis of PA	TFPA—Percutaneous in 76.3%, surgical cutdown in 23.7%	TFPA—ProGlide device	TFPA—2 ProGlide devices	TFPA—surgical cutdown	NA
Hemostasis of TF	Manual compression (24%), ProGlide (39%),	Angio-Seal or ProGlide	NA	Manual compression (87%), ProGlide	NA

secondary access	Angio-Seal (37%)	(8%), Angio-Seal (5%)	
Post-closure angiography?			No angiography was performed systematically in TFPA

TF: Transfemoral; TR: Transradial; APA: All primary access; TFPA: Transfemoral primary access; TFSA: Transfemoral secondary access; TRSA: Transradial secondary access; TAVI: Transcatheter aortic valve implantation; NYHA: New York Heart Association; BMI: Body mass index; VARC: Valve Academic Research Consortium; NA: Not available.

OR 0.45 [0.29, 0.74] ( $P = 0.001$ , [Figure 2B](#)).

**Bleeding complications:** The incidence of major and life-threatening bleeding complications by 30 d post-TAVI was 3.4% in TRSA patients and 6.3% in TFSA, OR 0.40 [0.28, 0.56] ( $P < 0.00001$ , [Figure 2C](#)).

**Vascular complications:** Major vascular complications by 30 d post-TAVI were seen in 2.8% of TRSA patients and 5.9% in TFSA, OR 0.48 [0.33, 0.69] ( $P < 0.0001$ , [Figure 2D](#)). The incidence of 30-d minor vascular complications was 11.7% in TRSA patients and 12.4% in TFSA, OR 0.92 [0.75, 1.12] ( $P = 0.41$ , [Figure 2E](#)).

[Figure 3](#) shows funnel plots for the main outcomes. The plots were symmetric, and all studies lie within the triangular region, close to the mean, without outliers. This indicates minimal heterogeneity in this review. [Figure 4](#) shows traffic light plots of the domain-level judgements for each individual result to assess risk of bias.

### Results of TFPA procedures

**All-cause mortality:** The 30-d all-cause mortality rate was 2.8% in the TRSA group and 4.7% in the TFSA group, OR 0.62 [0.31, 1.26] ( $P = 0.19$ , [Figure 5A](#)).

**Stroke:** The 30-d stroke rate was 1.2% in the TRSA group and 4.2% in the TFSA group, OR 0.31 [0.12, 0.77] ( $P = 0.01$ , [Figure 5B](#)).

**Bleeding complications:** In patients who had TFPA during their TAVI, major/Life-threatening bleeding complications were seen by 30 d in 6.3% of TRSA patients and 11.2% in TFSA, OR 0.52 [0.32, 0.85] ( $P = 0.008$ , [Figure 5C](#)).

**Vascular complications:** This was not analyzed for the TFPA group, as only 3 out of 5 studies reported on this outcome in the TFPA group.

## DISCUSSION

### Main findings

In this meta-analysis, we found that patients who underwent TRSA had significantly

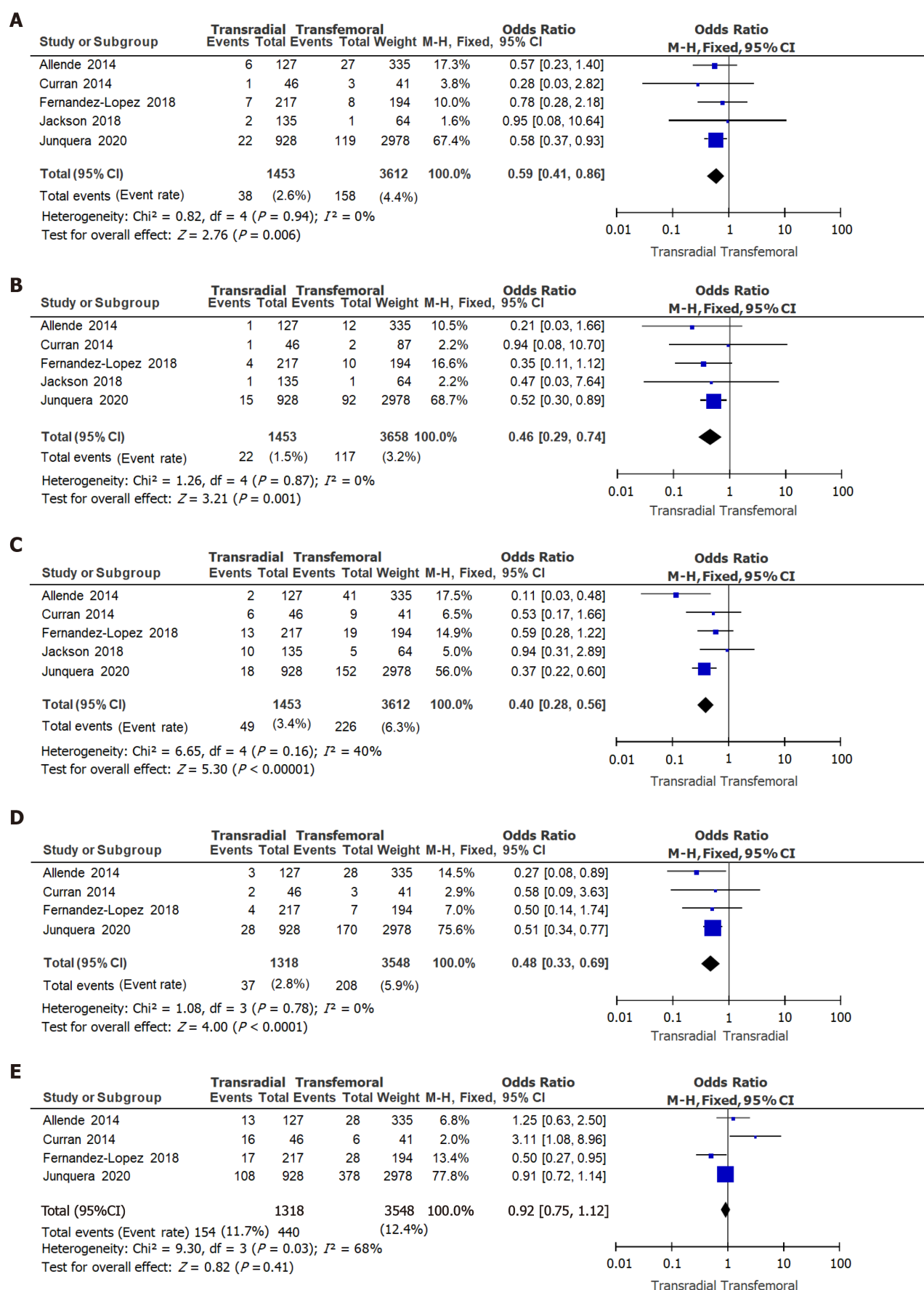
Table 2 Demographic comparison based on secondary access of matched/adjusted data (if available)

	Junquera <i>et al</i> <sup>[2]</sup>		Fernandez-Lopez <i>et al</i> <sup>[6]</sup>		Jackson <i>et al</i> <sup>[5]</sup>		Allende <i>et al</i> <sup>[4]</sup>		Curran <i>et al</i> <sup>[3]</sup>	
	TFSA (n = 2978)	TRSA (n = 928)	TFSA (n = 194)	TRSA (n = 217)	TFSA (n = 64)	TRSA (n = 135)	TFSA (n = 335)	TRSA (n = 127)	TFSA (n = 41)	TRSA (n = 46)
Baseline characteristics of patients										
Age	81 ± 4	81 ± 8	83 ± 7	82 ± 6	82 ± 6	82 ± 7	79 ± 8	80 ± 9	80 ± 10	80 ± 5
%Male	52.60%	53.20%	44.80%	53.50%	57.00%	43.00%	45.00%	61.00%	31.70%	52.20%
Baseline comorbidities										
Diabetes	26.90%	27.00%	31.40%	24.40%	20.00%	20.00%	35.00%	31.00%	30.00%	26.10%
HTN	-	-	56.70%	55.30%	-	-	88.00%	84.00%	92.50%	80.40%
CAD	51.20%	50.30%	-	-	53.00%	52.60%	67.00%	63.00%	-	-
Previous CABG	19.80%	19.60%	4.10%	6.00%	20.00%	19.30%	39.00%	33.00%	17.10%	17.40%
AFib	33.50%	34.70%	27.80%	33.60%	25.00%	25.00%	17.00%	20.00%	-	-
PVD	16.30%	19.20%	13.40%	14.30%	18.00%	26.70%	40.00%	24.00%	-	-
Prior CVA	-	-	10.30%	10.60%	17.00%	16.30%	19.00%	16.00%	-	-
eGFR < 60 mL/min/1.73 m <sup>2</sup>	67.60%	69.40%	-	-	-	-	57.00%	51.00%	-	-
COPD/Pul disease	21.30%	20.90%	11.90%	13.40%	25.00%	25.90%	29.00%	25.00%	20.00%	13.00%
STS-PROM score	4.5	4.7	5.0 ± 3.0	4.8 ± 3.6	-	-	7.1 ± 4.5	7.2 ± 5.0	9.0 ± 7.8	7.2 ± 7.5
Valve type										
Balloon-expandable	60.00%	63.50%	NA	NA	NA	NA	96.00%	88.00%	NA	NA
Self-expandable	40.00%	36.50%	NA	NA	NA	NA	3.00%	10.00%	NA	NA
1° Access										
TFPA	88.50%	89.90%	100%	100%	100%	85.20%	30.80%	93.00%	100%	100%
Non-TFPA	11.50%	10.10%	0	0	0	14.80%	69.20%	7.00%	0	0
Transapical	9.10%					3.70%	58.20%	6.00%		
Transaortic	1.90%					8.80%	10.70%	1.00%		
Subclavian	1.50%					2.20%	0.30%	0		
Transcarotid	4.06%					0	0	0		
Transcaval	0.12%					0	0	0		

TFSA: Transfemoral secondary access; TRSA: Transradial secondary access; HTN: Hypertension; CAD: Coronary artery disease; CABG: Coronary artery bypass graft; AFib: Atrial fibrillation; PVD: Peripheral vascular disease; CVA: Cerebrovascular event; eGFR: Estimated glomerular filtration rate; COPD: Chronic obstructive pulmonary disease; STS-PROM: Society of thoracic surgeons predicted risk of mortality; TFPA: Transfemoral primary access.

lower odds than those with TFSA of developing 30-d mortality, stroke, bleeding, and major vascular complications. When APA site procedures were considered, the odds of mortality up to 30 d after the procedure were found to be 41% lower, and the odds of 30-d stroke 54% lower in the TRSA group than the TFSA group. Similarly, the odds of having major or life-threatening bleeding were 60% lower in the TRSA group than the TFSA group. The odds of having major vascular complications were 52% lower in the TRSA group. Our findings are consistent with previously published data<sup>[1-10]</sup>, which have also reported that TRSA has lower odds of complications.

When TFPA alone was considered, there was no significant difference in 30-d mortality between the TRSA and TFSA groups as opposed to the APA group which showed a significant decrease in mortality in the TRSA group. The absolute mortality



**Figure 2 Forest plots for all primary access outcomes.** Transradial vs transfemoral secondary access. A: All primary access 30-d all-cause mortality; B: All primary access 30-d stroke/transient ischemic attack; C: All primary access 30-d major/life threatening bleeding complications; D: All primary access 30-d major vascular complications; E: All primary access 30-d minor vascular complications. CI: Confidence interval.

rates and odds ratio in the APA and TFPA cohorts were, however, comparable. This discrepancy in statistical significance can be attributed to the smaller sample size in the TFPA group. There were significantly lower odds of having a stroke or major/life-threatening bleeding in the TRSA group compared with the TFSA group in the TFPA cohort.

The transradial access has some advantages over transfemoral access. For one, the transradial site is more easily compressible in case of bleeding complications<sup>[11-13]</sup>. It also avoids the need to puncture both femoral arteries<sup>[3]</sup>. These advantages could lead to improved rates of vascular complications when compared with femoral secondary access. The disadvantage of radial access is that it does not allow the use of other interventional devices<sup>[11,13]</sup>. Some other challenges include difficulty navigating in case of anatomical variations and the possibility of developing radial artery occlusion with larger catheter diameters.

This review has several limitations. One major limitation of this meta-analysis is that all studies included were non-randomized. No randomized studies on this topic have been published yet. Hence there is high risk for selection bias. Risk adjustment or propensity score-matching was done in some studies. Two studies did not report on risk adjustment or matching in their study, hence there is a possibility of differences in their study populations. Moreover, unmeasured confounders cannot be accounted for. To improve confidence in the results, subgroup analysis was done only if data were reported in at least four studies. On another note, there was no uniformity in the type of primary access among studies. Few studies reported outcomes in the TFPA subgroup. This was a small fraction of the overall study population and results were mostly similar to APA results. Lastly, the presence of a learning curve should be considered, with the assumption that complication rates improve with experience. Due to the novelty of the procedure when initially adapted in some of these studies, one could assume that complications were more likely to occur in the early phase of implementing this procedure. In experienced operators, complication rates would likely be lower. This could skew the study results accordingly, especially if radial secondary access was adopted later in institutional experience.

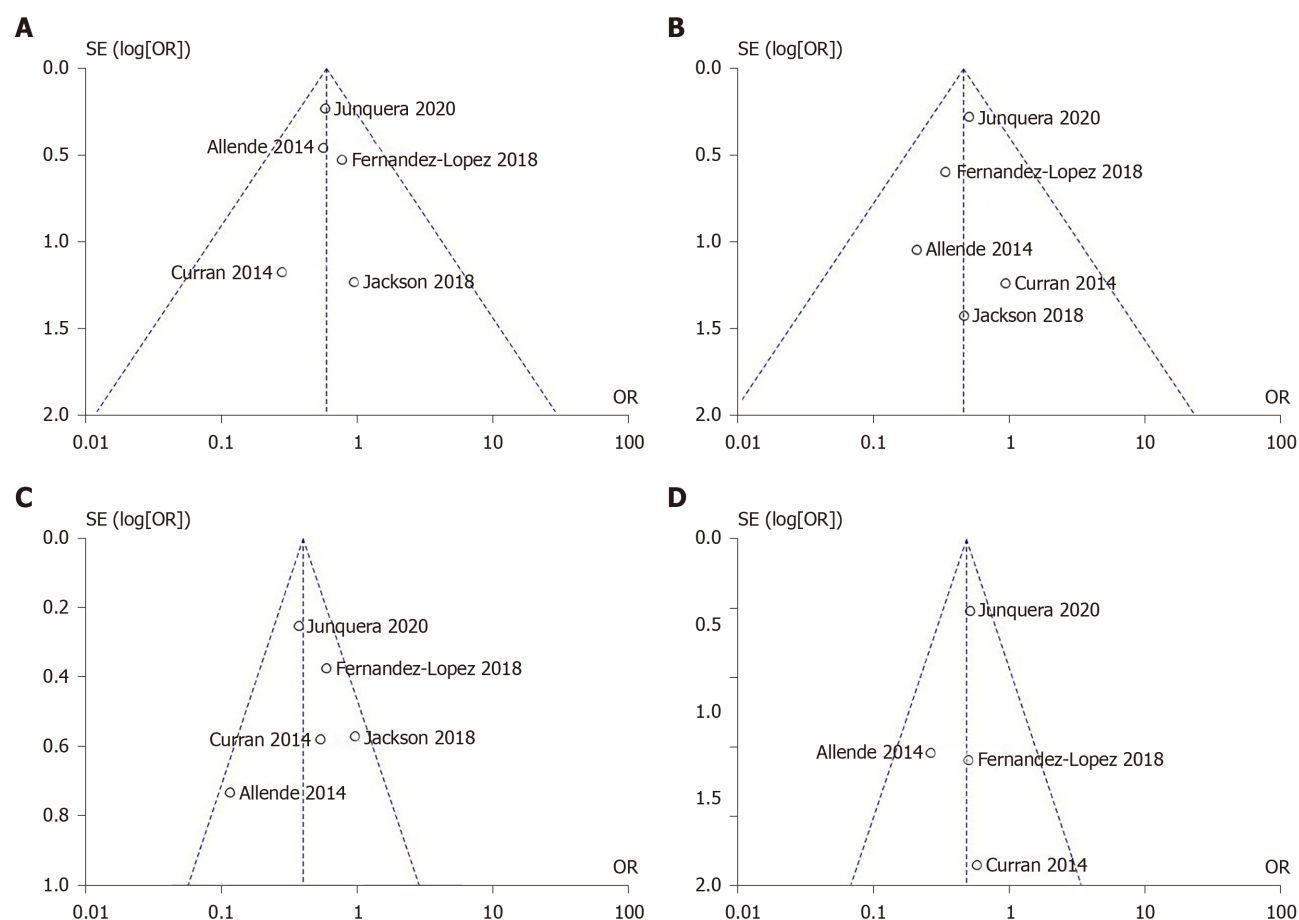
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## CONCLUSION

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In patients undergoing transcatheter aortic valve implantation (TAVI), irrespective of primary access, those who underwent TRSA had lower complication rates than those who underwent TFSA. In the absence of contraindications, a transradial approach for secondary access seems preferable in TAVI procedures. Confirmation by randomized controlled studies of TAVI procedures stratified by primary access site would be useful to adjust for primary access while comparing secondary access-related outcomes.

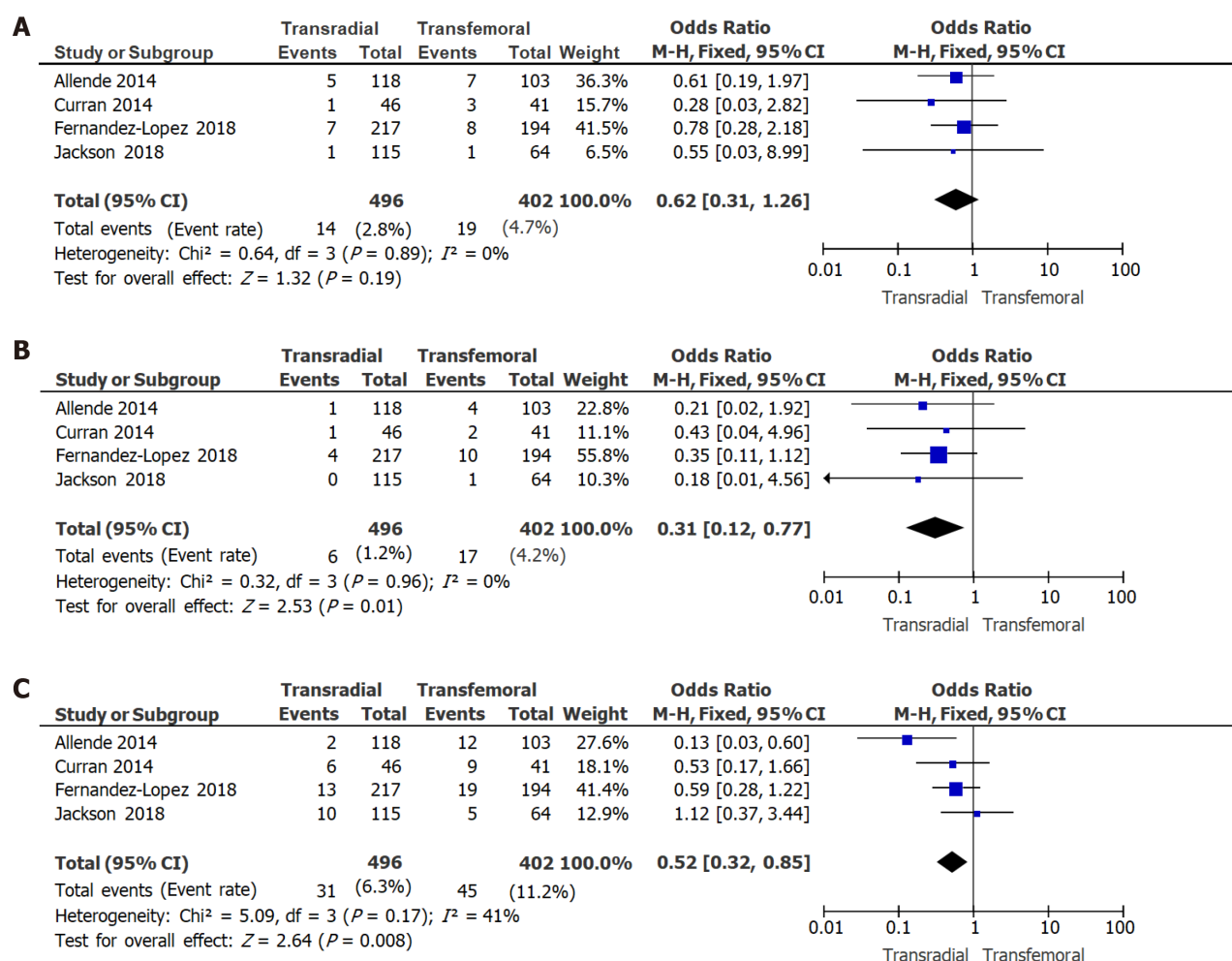




**Figure 3** Funnel plot for all primary access outcomes. Transradial vs transfemoral secondary access. A: 30-d all-cause mortality; B: 30-d stroke/transient ischemic attack; C: 30-d major/life threatening bleeding complications; D: 30-d major vascular complications. OR: Odds ratio.

		Risk of bias domains						Overall
		D1	D1b	D2	D3	D4	D5	
Study	Allende 2014	⊗	○	⊕	⊕	⊕	⊕	⊕
	Curran 2014	⊗	○	⊖	⊕	⊕	⊖	⊖
	Fernandez-Lopez 2018	⊗	○	⊕	⊕	⊕	⊕	⊕
	Jackson 2018	⊗	○	⊕	⊕	⊕	⊖	⊕
	Junquera 2020	⊗	○	⊖	⊕	⊕	⊕	⊕
Domains:								
D1: Bias arising from the randomization process								
D1 b: Bias arising from the timing of identification and recruitment of Individual participants in relation to timing of randomization								
D2: Bias due to deviations from intended intervention.								
D3: Bias due to missing outcome data.								
D4: Bias in measurement of the outcome.								
D5: Bias in selection of the reported result.								
Judgement								
⊗ High								
⊖ Some concerns								
⊕ Low								
○ Not applicable								

**Figure 4** Traffic light plots of the domain-level judgements for each individual result to assess risk of bias.



**Figure 5 Forest plots for trans femoral primary access outcomes.** A: Transfemoral primary access (TFPA) 30-d all-cause mortality; B: TFPA 30-d stroke; C: TFPA 30-d major/life threatening bleeding complications. CI: Confidence interval.

## ARTICLE HIGHLIGHTS

### Research background

Complications of transcatheter aortic valve implantation (TAVI) procedures include bleeding, vascular complications, and strokes. These complications are often associated with the type of access used. Access can be primary or secondary. Few studies have been published on the effect of secondary access on outcomes.

### Research motivation

The objective of this meta-analysis is to investigate if transradial secondary access (TRSA) has fewer complications than transfemoral or vice versa, with the hope of reducing complications in TAVI procedures related to access.

### Research objectives

This systematic review aims to compare outcomes between transradial *vs* transfemoral secondary access (TFSA).

### Research methods

A systematic search was conducted using major databases (EMBASE, PubMed, Cochrane Central, Google Scholar), which resulted in 5 studies that met criteria for study selection. Outcomes of interest were 30-d rates each of major/life-threatening bleeding, vascular complications, strokes, and mortality. All 5 studies were observational. Adjusted or matched data were used if reported.

### Research results

A total of 5065 patients underwent TAVI, with 1453 patients (28.7%) having

undergone TRSA and 3612 patients (71.3%) TFSA. Irrespective of the site of primary access, the odds of having major or life-threatening bleeding were 60% lower in the TRSA group than the TFSA group ( $P < 0.00001$ ). The odds of having major vascular complications were 52% lower in the TRSA group ( $P < 0.0001$ ) with no difference in minor vascular complications between the 2 groups. Similarly, the odds of mortality in 30d after the procedure were 41% lower ( $P = 0.006$ ) and the odds of stroke were 54% lower ( $P = 0.001$ ) in the TRSA group than the TFSA group.

### Research conclusions

TRSA appears to be a safer alternative to the TFSA in TAVI procedures.

### Research perspectives

Our findings need to be confirmed in randomized clinical trials, which should minimize selection bias and both measured and unmeasured confounding.

## ACKNOWLEDGEMENTS

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## Cardiac adverse events of immune checkpoint inhibitors in oncology patients: A systematic review and meta-analysis

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### Abstract

#### BACKGROUND

Immune checkpoint inhibitors (ICIs) are novel therapeutic agents used for various types of cancer. ICIs have revolutionized cancer treatment and improved clinical outcomes among cancer patients. However, immune-related adverse effects of ICI therapy are common. Cardiovascular immune-related adverse events (irAEs) are rare but potentially life-threatening complications.

#### AIM

To estimate the incidence of cardiovascular irAEs among patients undergoing ICI therapy for various malignancies.

#### METHODS

We conducted this systematic review and meta-analysis by searching PubMed, Cochrane CENTRAL, Web of Science, and SCOPUS databases for relevant



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interventional trials reporting cardiovascular irAEs. We performed a single-arm meta-analysis using OpenMeta [Analyst] software of the following outcomes: Myocarditis, pericardial effusion, heart failure, cardiomyopathy, atrial fibrillation, myocardial infarction, and cardiac arrest. We assessed the heterogeneity using the *I*<sup>2</sup> test and managed to solve it with Cochrane's leave-one-out method. The risk of bias was performed with the Cochrane's risk of bias tool.

**RESULTS**

A total of 26 studies were included. The incidence of irAEs follows: Myocarditis: 0.5% [95% confidence interval (CI): 0.1%-0.9%]; Pericardial effusion: 0.5% (95%CI: 0.1%-1.0%); Heart failure: 0.3% (95%CI: 0.0%-0.5%); Cardiomyopathy: 0.3% (95%CI: -0.1%-0.6%); atrial fibrillation: 4.6% (95%CI: 1.0%-14.1%); Myocardial infarction: 0.4% (95%CI: 0.0%-0.7%); and Cardiac arrest: 0.4% (95%CI: 0.1%-0.8%).

**CONCLUSION**

The most common cardiovascular irAEs were atrial fibrillation, myocarditis, and pericardial effusion. Although rare, data from post market surveillance will provide estimates of the long-term prevalence and prognosis in patients with ICI-associated cardiovascular complications.

**Key Words:** Atrial fibrillation; Cancer; Immune checkpoint inhibitors; Immunotherapy; Cardiovascular adverse events; Pericardial effusion

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**Core Tip:** Cardiovascular immune-related adverse events (irAEs) are rare but potentially life-threatening complications that can occur in patients receiving immune checkpoint inhibitor (ICI) therapy. The most common ICI-associated adverse events are atrial fibrillation, myocarditis, and pericardial effusion. Risk factors for cardiovascular irAEs include treatment with combination immunotherapy, male sex, and a history of cardiac disease. Ongoing post-market surveillance is imperative to characterize long-term risks and improve outcomes among patients receiving ICIs.

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**INTRODUCTION**

Immune checkpoint inhibitors (ICIs) have demonstrated remarkable efficacy in various malignancies, including lung cancer, melanoma, Hodgkin's lymphoma, bladder cancer, and microsatellite instability<sup>[1]</sup>. ICIs exert their effects through blocking inhibitory receptors on tumor cells [programmed cell death 1 Ligand-1 (PD-L1)]<sup>[2,3]</sup> or T-lymphocytes [programmed cell death protein-1 (PD-1) or cytotoxic T lymphocyte-associated protein-4 (CTLA-4)]<sup>[4,5]</sup>. The blockade of these receptors activates the effector T cells to target neoplastic cells<sup>[2]</sup>. Many studies have demonstrated significant survival benefits of ICIs<sup>[6-8]</sup> and over 1200 trials are currently ongoing<sup>[9]</sup>.

The mechanism of action of ICIs involves non-specific activation of the immune system<sup>[10]</sup>. Consequently, autoimmune inflammatory reactions frequently occur; this can ultimately lead to a broad spectrum of immune-related adverse events (irAEs) affecting both on-target and off-target organs<sup>[11]</sup>. Reactions involving the skin, gastrointestinal tract, and endocrine system are relatively common among cancer patients on ICIs<sup>[12,13]</sup>. Approximately 80% of patients treated with agents targeting CTLA-4, 70% of patients treated with anti-PD-1 drugs, and 40% of those treated with anti-PD-L1 agents develop irAEs<sup>[13,14]</sup>. Severe events are common and up to 40% of patients on ICIs require treatment discontinuation due to irAEs<sup>[10]</sup>.

Cardiovascular irAEs are rare, but potentially life-threatening<sup>[15]</sup>. Although the initial trials on ICIs did not assess myocardial activity, growing evidence from case reports, case series, and cohort studies have raised awareness of unexpected cardiac toxicities associated with ICI therapy<sup>[16-18]</sup>. Dual therapy appears to markedly increase the risk of cardiovascular irAEs; using the Bristol-Myers Squibb safety database, the estimated rate of myocarditis in patients receiving combination immunotherapy (ipilimumab plus nivolumab) was 0.27% as compared to 0.06% in those receiving nivolumab monotherapy<sup>[18]</sup>.

Data on other ICI-related cardiac toxicities are scarce. This study aims to provide high-class evidence on the incidence of ICI-related cardiovascular adverse events through a systematic review and meta-analysis.

## MATERIALS AND METHODS

This systematic review and meta-analysis complies with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement<sup>[19]</sup> and Cochrane's Handbook of Systematic Reviews of Interventions<sup>[20]</sup>.

### Eligibility criteria

Our analysis included interventional trials involving patients receiving an ICI in which an adverse cardiovascular event was reported. We excluded the following: Non-randomized trials, trials involving concurrent use of other anticancer interventions, animal studies, non-clinical studies, reviews, and meta-analyses. We also excluded studies without accessible data, conference abstracts, and studies for which there was no English language translation.

### Literature search

We searched PubMed, Cochrane CENTRAL, SCOPUS, and Web of Science databases for possible included articles according to our eligibility criteria from May 1<sup>st</sup>, 2020 through May 15<sup>th</sup>, 2020. We retrieved articles using a combination of the following keywords: "cardiotoxicity", "adverse", "events", "myocard\*", "pericard\*", "neoplasm", "cancer", and "immune checkpoint inhibitor."

### Study selection, data collection, and analysis

**Screening of results:** We performed the screening of retrieved studies through two stages. The first stage involved the inclusion and exclusion of studies based on title and abstract review. Selected studies underwent full-text screening against the inclusion criteria. Studies that had a mismatch with a single inclusion criterion were excluded. We conducted another search through the references of the included trials to ensure that no trials were inadvertently excluded. We considered studies which included multiple treatment arms as separate studies based on the adverse event reporting and refer to them as first author last name, year of publication followed by a, b, or c in the forest plot diagrams and Table 1<sup>[3,6-8,21-42]</sup>. Figure 1 shows a PRISMA flow chart of the literature search.

**Data extraction:** We used a data extraction form specifically designed for this study. Three main categories of data were extracted. The first category included baseline data about the study participants, such as patients' age, gender, cancer type, and drug administered and dose. The second category included different outcome endpoints for analysis (any reported cardiovascular adverse event). The third category involved data used to assess the risk of bias among the included studies.

**Quality and risk of bias assessment:** This systematic review and meta-analysis were conducted in accordance with the principles of the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE). We included clinical trials only to ensure high-quality evidence. For assessment of the risk of bias, we used the Cochrane's Risk of Bias tool<sup>[43]</sup>.

### Statistical analysis

The extracted data were restricted to dichotomous outcomes, as all the data for the analysis are adverse events expressed as events/total. Using the OpenMeta[Analyst] Software, the intended scores were pooled as risk ratios (RR), and the presence of heterogeneity was assessed using two main tests<sup>[44]</sup>, the I-square test ( $I^2$ ) and the  $P$  value of the Chi-square test. The analysis is said to be heterogeneous if values of  $I^2 >$

Table 1 Summary of baseline characteristics of included studies, *n* (%)

Study	<i>n</i>	ICI	Cancer type	Males	Median age (range), yr	Median follow-up (range), mo	Race, Asian	Race, Black	Tobacco users
Antonia <i>et al</i> <sup>[8]</sup> , 2016a	98	Nivolumab	Small cell carcinoma of the lung	61 (62)	63 (57-68)	10.07 (NR)	NR	3 (3)	95 (97)
Antonia <i>et al</i> <sup>[8]</sup> , 2016b	61	Nivolumab plus ipilimumab	Small cell carcinoma of the lung	35 (57)	66 (58-71)	12.03 (9.10-15.67)	NR	1 (2)	57 (93)
Antonia <i>et al</i> <sup>[8]</sup> , 2016c	54	Nivolumab plus ipilimumab	Small cell carcinoma of the lung	32 (59)	61 (56-65)	8.68 (8.27-9.6)	NR	0	48 (89)
Antonia <i>et al</i> <sup>[21]</sup> , 2017	476	Durvalumab	Stage III non-small cell lung cancer	334 (70.2)	64 (NR)	14.5 (0.2-29.9)	120 (25.2)	12 (2.5)	433 (91)
Balar <i>et al</i> <sup>[22]</sup> , 2017	370	Pembrolizumab plus cisplatin	Advanced, unresectable metastatic urothelial cancer	286 (77)	74 (34-94)	5 (30-8.6)	NR	NR	NR
Barlesi <i>et al</i> <sup>[23]</sup> , 2018	393	Avelumab	Advanced non-small-cell lung cancer	269 (68)	64 (59-70)	18.9 (IQR 13.2-23)	102 (26)	5 (1)	324 (82)
Bott <i>et al</i> <sup>[24]</sup> , 2018	21	Nivolumab	Resectable non-small cell lung cancer	10 (48)	67 (55-84)	1.1 (0.57-1.13)	NR	NR	18 (86)
Brohl <i>et al</i> <sup>[25]</sup> , 2016	31	Ipilimumab plus peginterferon	Unresectable melanoma	18 (58.1)	65 (38-83)	35.8 (19.7-50.2)	NR	NR	NR
Cho <i>et al</i> <sup>[26]</sup> , 2018	33	Pembrolizumab	Relapsed thymic epithelial tumor	21 (63.6)	57 (26-78)	14.9 (IQR 6.25-20.7)	NR	NR	NR
Choueiri <i>et al</i> <sup>[3]</sup> , 2018	55	Avelumab plus axitinib	Advanced clear cell renal cell carcinoma	42 (76)	60 (55-68)	13 (9.35-14.02)	6 (11)	3 (6)	NR
Chung <i>et al</i> <sup>[27]</sup> , 2019	11	p53MVA vaccine combined with pembrolizumab	Advanced breast, pancreatic, hepatocellular, or head and neck cancer	NR	NR	16.26 (15.42-17.27)	NR	NR	NR
Dudnik <i>et al</i> <sup>[28]</sup> , 2018	260	Nivolumab	Non-small cell lung cancer	176 (68)	67 (41-99)	8.4 (2-16.8)	NR	NR	197 (76)
Eggermont <i>et al</i> <sup>[29]</sup> , 2015	475	Ipilimumab	High-risk stage III melanoma	296 (62)	51 (20-84)	7.5 (7-11.4)	NR	NR	NR
Giaccone <i>et al</i> <sup>[30]</sup> , 2018	40	Pembrolizumab	Thymic carcinoma	28 (70)	57 (25-80)	8.4 (2-16.8)	4 (10)	2 (5)	NR
Herbst <i>et al</i> <sup>[31]</sup> , 2020	26	Ramucirumab plus pembrolizumab	Advanced non-small-cell lung cancer	21 (78)	65 (56-72)	33.3 (IQR 27.7-39.2)	NR	1 (4)	26 (96)
Hodi <i>et al</i> <sup>[32]</sup> , 2018	313	Nivolumab plus ipilimumab	Advanced melanoma	NR	NR	20 (IQR 14-26)	NR	NR	NR
Juergens <i>et al</i> <sup>[7]</sup> , 2020	136	Durvalumab with or without tremelimumab and platinum-doublet	Lung cancer (unspecified)	67 (49)	61.9 (30.1-83.2)	32.8 (IQR 28.1-33.6)	8 (6)	1 (1)	NR
Loi <i>et al</i> <sup>[33]</sup> , 2019	58	Pembrolizumab plus trastuzumab	Lung cancer (unspecified)	0	52 (43-92)	46.9 (48-NR)	NR	NR	NR
Maio <i>et al</i> <sup>[34]</sup> , 2017	382	Tremelimumab	Malignant mesothelioma	283 (74)	66 (60-72)	19.61 (0.23-26.48)	7 (2)	3 (<1%)	NR
Mateos <i>et al</i> <sup>[35]</sup> , 2019	125	Pembrolizumab plus pomalidomide and dexamethasone	Multiple myeloma	77 (62)	65 (60-72)	25.7 (IQR 25.6-25.8)	NR	NR	NR
Motzer <i>et al</i> <sup>[36]</sup> , 2019	550	Nivolumab plus ipilimumab	Advanced renal cell carcinoma	NR	NR	2 (1-3)	NR	NR	NR
Sarocchi <i>et al</i> <sup>[37]</sup> , 2018	59	Nivolumab	Advanced non-small cell lung cancer	41 (NR)	69 (44-81)	8.1 (IQR 4.5-10.9)	NR	NR	51 (86)
Scherpereel <i>et al</i> <sup>[6]</sup> , 2019	63	Nivolumab or nivolumab plus ipilimumab	Relapsed malignant pleural mesothelioma	47 (75)	72.3 (32.5-87)	32.4 (IQR 13.4-36.3)	NR	NR	34 (54)
Tawbi <i>et al</i> <sup>[38]</sup> , 2018	94	Nivolumab plus ipilimumab	Melanoma with brain metastases	65 (69)	59 (22-81)	NR	NR	NR	NR
Ueno <i>et al</i> <sup>[39]</sup> , 2018	30	Nivolumab alone	Unresectable or recurrent	NR	NR	20.1 (IQR 19.6-	NR	NR	NR

2019a			biliary tract cancer				20.3)			
Ueno <i>et al</i> <sup>[39]</sup> , 2019b	30	Nivolumab in combination with cisplatin	Unresectable or recurrent biliary tract cancer	NR	NR	14 (6-NR)	NR	NR	NR	
Usmani <i>et al</i> <sup>[40]</sup> , 2019a	151	Pembrolizumab	Multiple myeloma	70 (46)	74 (70-79)	5.1 (IQR 3.4-7)	NR	NR	NR	
Usmani <i>et al</i> <sup>[40]</sup> , 2019b	150	Lenalidomide	Multiple myeloma	71 (47)	74 (70-78)	8.2 (IQR 7-14)	NR	NR	NR	
Wrangle <i>et al</i> <sup>[41]</sup> , 2018	21	ALT-803, an IL-15 superagonist, in combination with nivolumab	Metastatic non-small cell lung	15 (71)	55 (46-67)	6.6 (IQR 3.4-9.6)	NR	NR	12 (57)	
Yang <i>et al</i> <sup>[42]</sup> , 2018a	42	Preoperative chemotherapy	Non-small cell lung cancer	21 (50)	NR	6.6 (IQR 3.4-9.6)	NR	7 (17)	NR	
Yang <i>et al</i> <sup>[42]</sup> , 2018b	13	Ipilimumab	Non-small cell lung cancer	5 (38)	NR	6.9 (IQR 5.5-12.0)	NR	3 (23)	NR	

ICI: Immune checkpoint inhibitor; NR: Not report; IQR: Inter-quartile range.

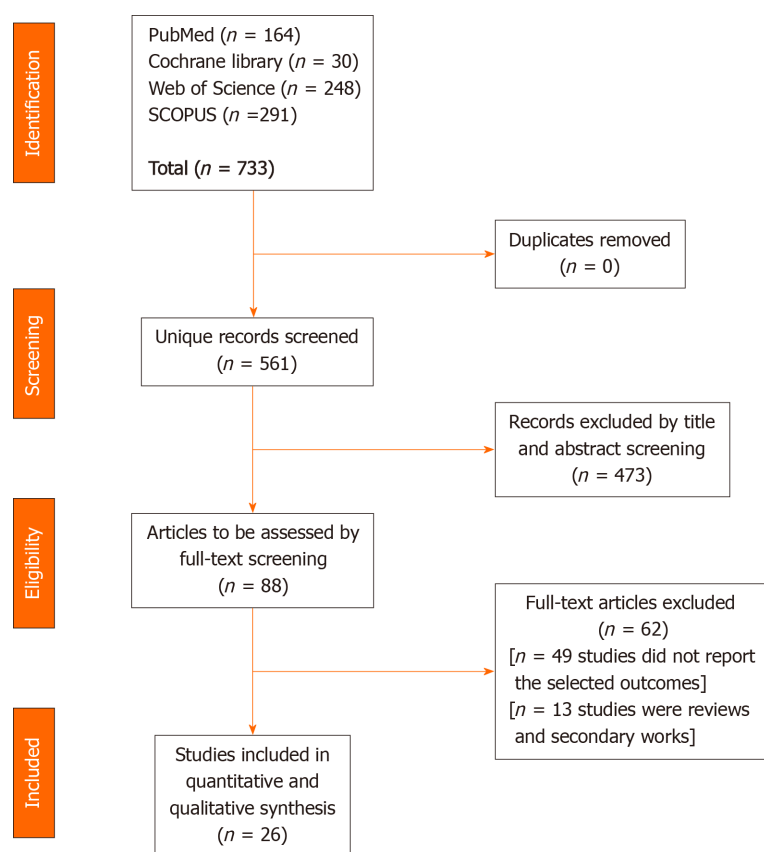


Figure 1 PRISMA diagram for our literature search.

50% and  $P < 0.1$  were present, according to the Cochrane Handbook<sup>[20]</sup>. We performed the analysis of homogeneous data under a fixed-effects model, while heterogeneous data were analyzed under the random-effects model.

## RESULTS

### Summary of included studies

We present the analysis of 4622 cancer patients from 26 studies. Figure 1 presents a flow diagram of the number of studies at each stage of the study selection process. Males were slightly overrepresented as compared to females [2420 (52.4%) vs 2202

(47.6%)]]. The mean age was 63.7 years. Further details pertaining to study characteristics, cancer type, ICI administered, and demographic data are illustrated in [Table 1](#).

### Results of risk of bias

The overall risk of bias was high among the included studies. Studies reported various data regarding randomization of patients, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, attrition bias, and selective reporting. The risk of bias status is summarized in [Figure 2](#).

### Results of analysis of outcomes

**Incidence of myocarditis:** Twelve studies reported the incidence of myocarditis as a cardiovascular irAE. The overall effect estimate showed that the incidence of myocarditis was 0.5%; the analysis was significant (95%CI: 0.1%-0.9%) and homogeneous ( $I^2 = 0\%$ ,  $P = 0.5$ ) ([Figure 3](#)).

**Incidence of pericardial effusion:** Nine studies reported the incidence of pericardial effusion as a cardiovascular irAE. The overall effect estimate showed that the incidence of pericardial effusion was 0.5%; the analysis was significant (95%CI: 0.1%-1.0%) and homogeneous ( $I^2 = 36.7\%$ ,  $P = 0.1$ ) ([Figure 4](#)).

**Incidence of heart failure:** Seven studies reported the incidence of heart failure as a cardiovascular irAE. The overall effect estimate showed that the incidence of heart failure was 0.3%; the analysis was homogeneous ( $I^2 = 0\%$ ,  $P = 0.1$ ) but not significant (95%CI: 0.0%-0.5%) ([Figure 5](#)).

**Incidence of cardiomyopathy:** Five studies reported the incidence of cardiomyopathy as a cardiovascular irAE. The overall effect estimate showed that the incidence of cardiomyopathy was 0.3%; the analysis was homogeneous ( $I^2 = 0\%$ ,  $P = 0.6$ ) but not significant (95%CI: -0.1%-0.6%) ([Figure 6](#)).

**Incidence of atrial fibrillation:** Four studies reported the incidence of atrial fibrillation as a cardiovascular irAE. The overall effect estimate showed that the incidence of atrial fibrillation was 7.6%; the analysis was significant (95%CI: 1.0%-14.1%) and heterogeneous ( $I^2 = 66\%$ ,  $P = 0.02$ ) ([Figure 7A](#)). Using Cochrane's leave-one-out method, we solved the heterogeneity by excluding one study (Bott *et al*). Homogeneous results revealed an incidence rate of atrial fibrillation of 4.6%. The results were not significant (95%CI: -0.2%-9.4%) ([Figure 7B](#)).

**Incidence of myocardial infarction:** Six studies reported the incidence of myocardial infarction as a cardiovascular irAE. The overall effect estimate showed that the incidence of MI was 0.4%; the analysis was homogeneous ( $I^2 = 0\%$ ,  $P = 0.1$ ) but not significant (95%CI: 0.0%-0.7%) ([Figure 8](#)).

**Incidence of cardiac arrest:** Four studies reported the incidence of cardiac arrest as a cardiovascular irAE. The overall effect estimate showed that the incidence of cardiac arrest was 0.4%; the analysis was significant (95%CI: 0.1%-0.8%) and homogeneous ( $I^2 = 0\%$ ,  $P = 0.6$ ) ([Figure 9](#)).

## DISCUSSION

Cardiotoxicity is a rare but potentially fatal adverse effect of ICI therapy. The incidence of cardiovascular irAEs remains to be established<sup>[45]</sup>. Our meta-analysis of 26 studies including a total of 4622 ICI-treated cancer patients showed that 0.5% of cancer patients treated with ICIs developed myocarditis, 0.3% developed heart failure, and 4.6% developed atrial fibrillation. In addition, pericardial effusion occurred in 0.5% of patients, cardiomyopathy in 0.3% of patients, myocardial infarction in 0.4% of patients, and cardiac arrest in 0.4% of patients. These results are relatively consistent as evidenced by the low level of statistical heterogeneity.

The underlying pathogenesis of cardiovascular irAEs has yet to be fully elucidated. However, several mechanisms have been proposed. The most frequently postulated mechanism underlying myocarditis is that T-lymphocytes could target an antigen common to both neoplastic tissue and the heart. Indeed, in a recent report by Johnson *et al*<sup>[18]</sup> the authors described a common high-frequency T-lymphocyte sequence found in both tumor and cardiac muscles. Preclinical studies of mouse models have also shown that PD-1 and CTLA-4 deficiency is associated with myocarditis. The deletion



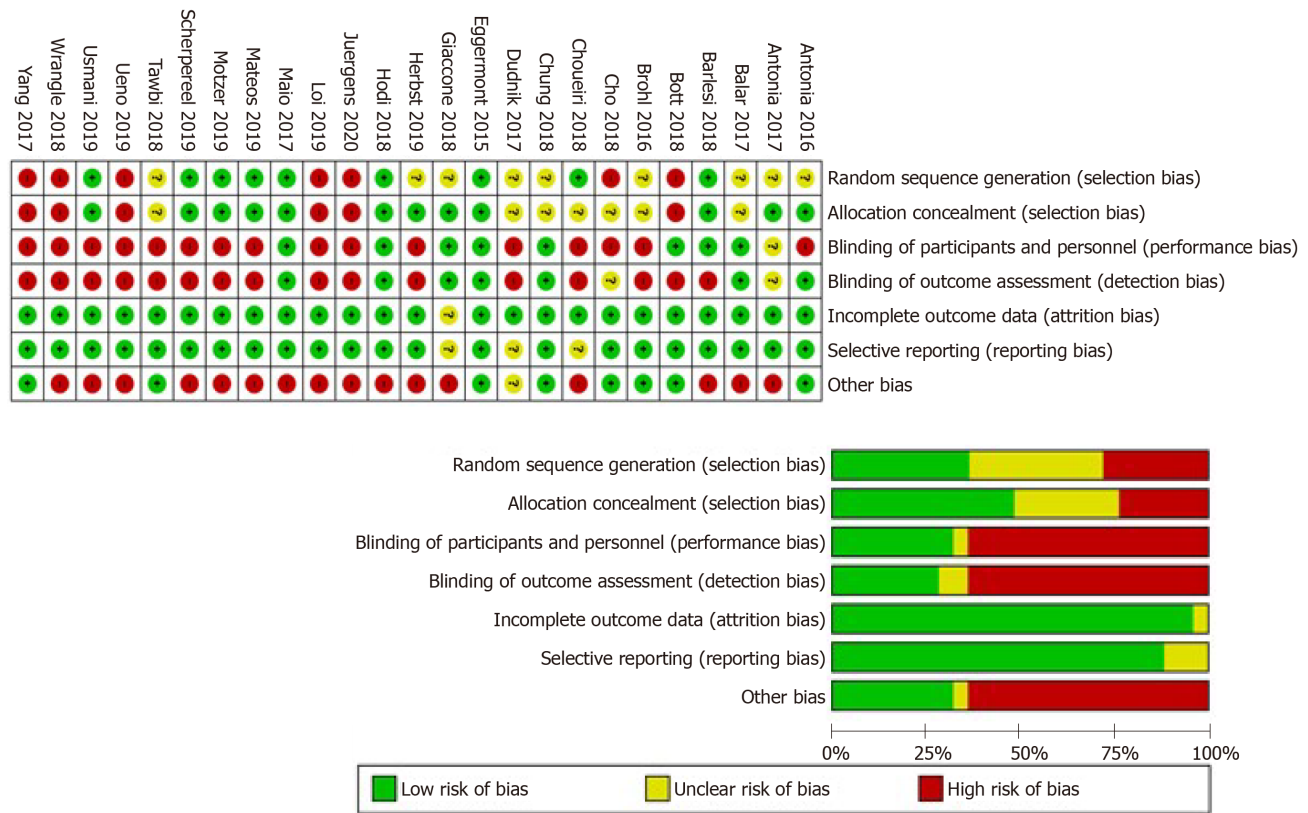


Figure 2 Results of risk of bias assessment among included trials.

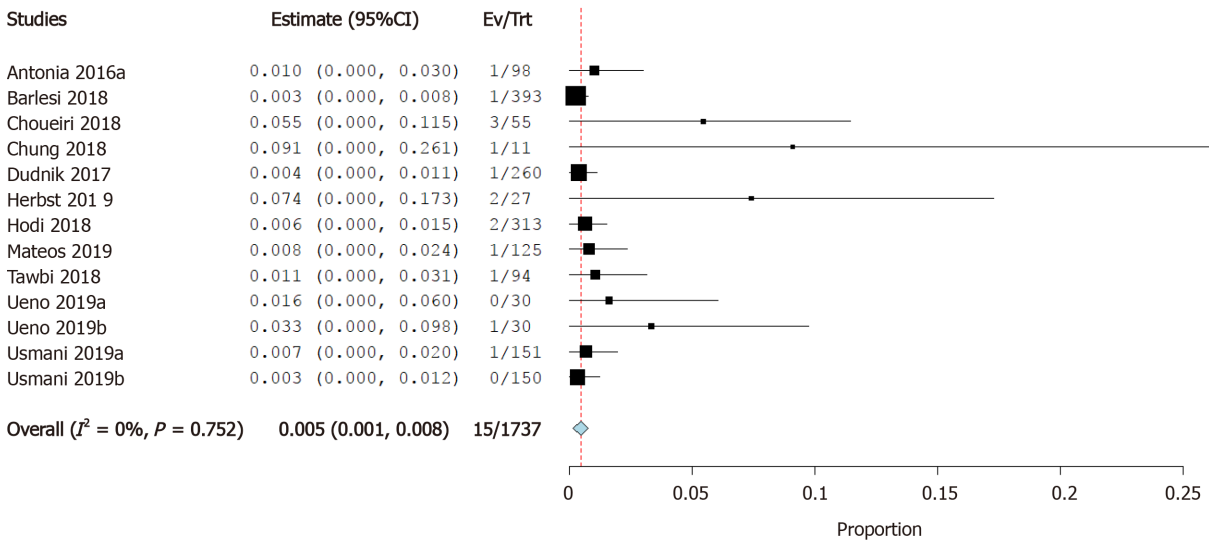
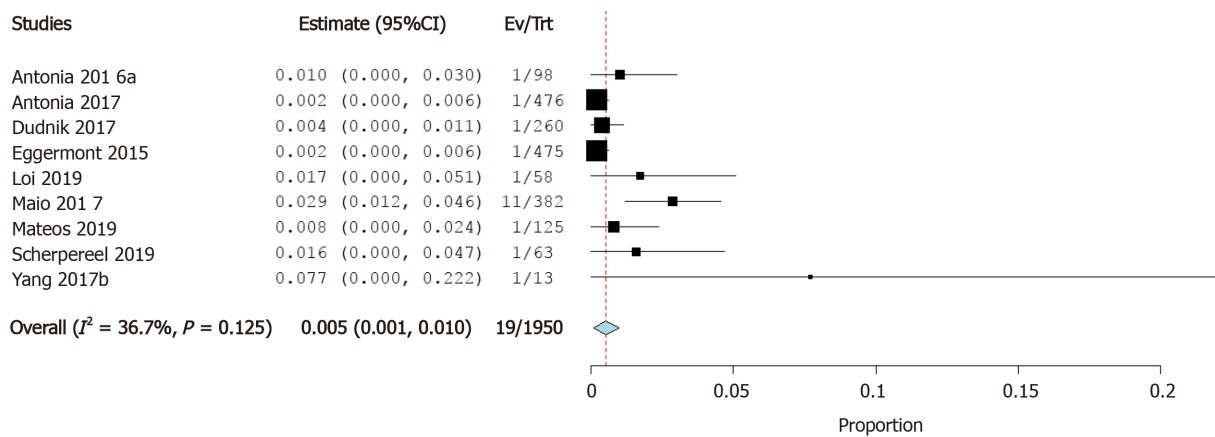


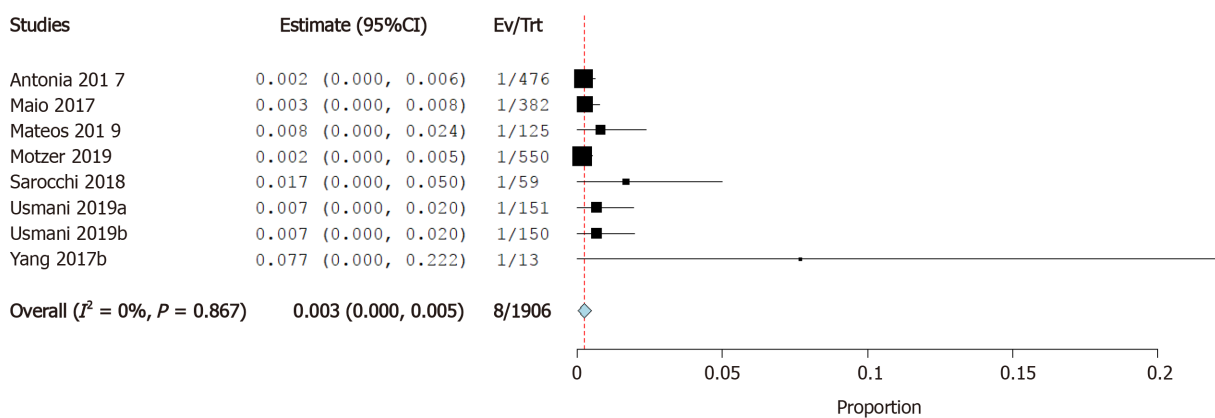
Figure 3 Incidence of myocarditis. CI: Confidence interval.

of the PD-1 and CTLA-4 axes induces autoimmune myocarditis, indicating that the PD-1/PD-L1 interaction and CTLA-4 play important roles in protecting against T-lymphocyte-mediated inflammation<sup>[46-48]</sup>. Injury usually occurs within first three months of initiating ICI; however, late presentation is not uncommon<sup>[49,50]</sup>.

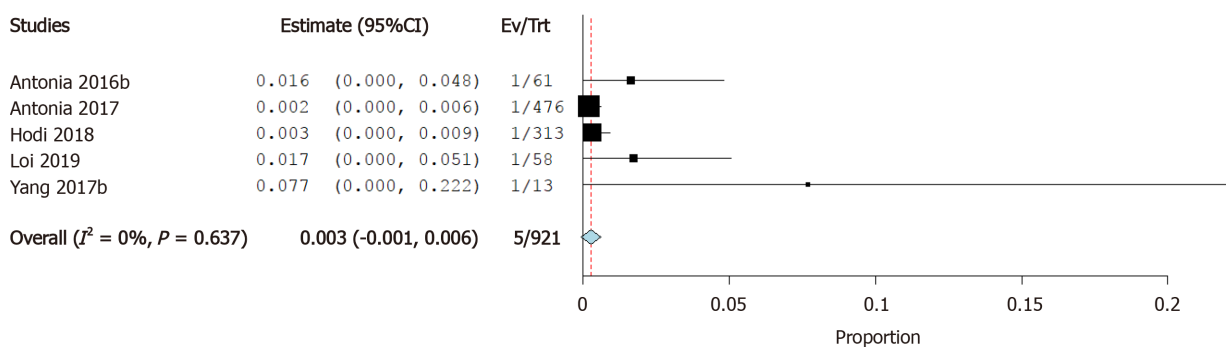
T-lymphocyte-mediated inflammation may also be implicated in the pathogenesis of ICI-related atrial fibrillation. In one recent case report, histopathologic analysis of a patient with atrial fibrillation displayed patchy infiltrations of lymphocytes in the sinoatrial and atrioventricular nodes<sup>[18]</sup>; this suggests that T-lymphocytes are intricately involved in the development of atrial fibrillation and other ICI-induced conduction disorders. In addition, it has been hypothesized that the increased risk of atrial fibrillation among patients taking ICIs may be attributed to the direct connection



**Figure 4** Incidence of pericardial effusion. CI: Confidence interval.



**Figure 5** Incidence of heart failure. CI: Confidence interval.

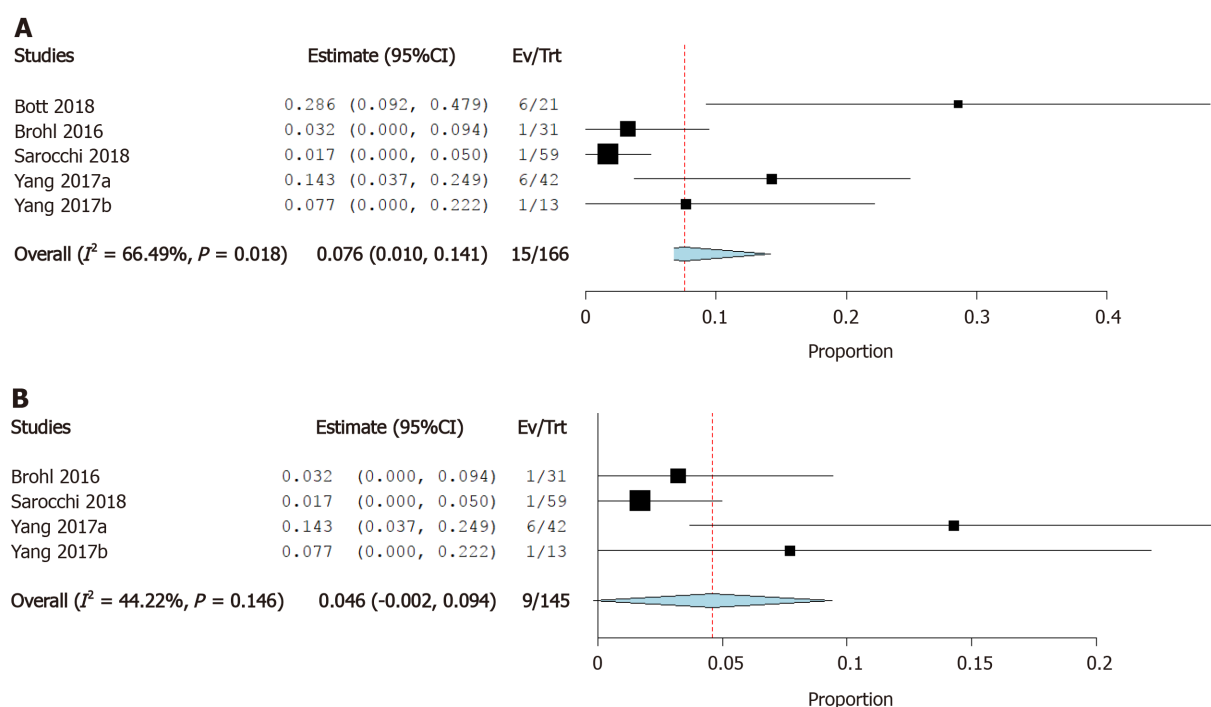


**Figure 6** Incidence of cardiomyopathy. CI: Confidence interval.

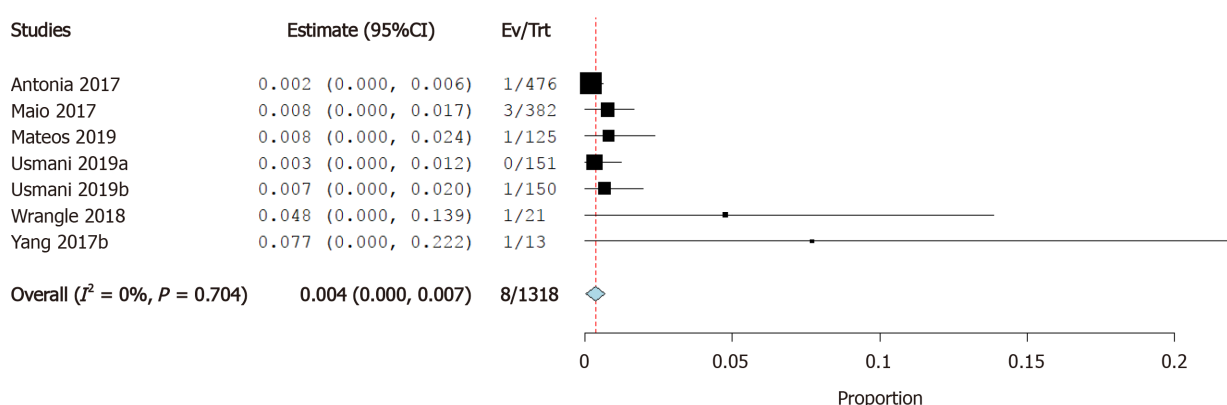
between the sinoatrial node and the autonomic nervous system, which make the atria sensitive indicators of any disruptive processes in the body<sup>[10]</sup>.

T-lymphocyte-related inflammatory processes are also suspected in pericardial effusion<sup>[51]</sup> and myocardial infarction<sup>[52]</sup>. Lyon *et al*<sup>[52]</sup> suggested that the development of ICI-induced myocardial infarction could be due to the activation of an inflammatory reaction that triggers atherosclerotic coronary plaque formation and acute infarction. Conversely, Nykl *et al*<sup>[53]</sup> argued that the PD-1 inhibitory effect of ICIs leads to coronary vasospasm and ST-segment elevation. The mechanism by which coronary vasospasm develops is unclear but could be associated with systemic inflammatory response syndrome<sup>[43]</sup>.

The incidence of cardiovascular irAEs is affected by many risk factors. Patients



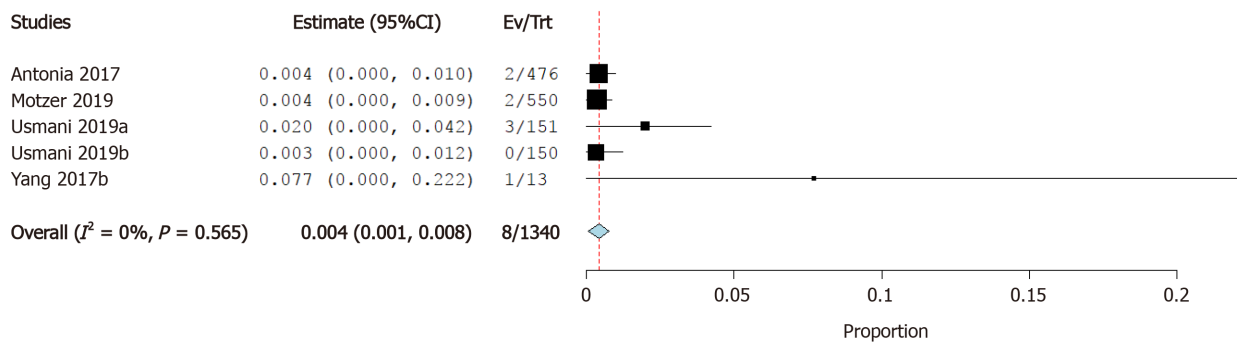
**Figure 7 Incidence of atrial fibrillation.** A: Incidence of atrial fibrillation with heterogeneity; B: Incidence of atrial fibrillation after correction with Cochrane's leave-one-out method. CI: Confidence interval.



**Figure 8 Incidence of myocardial infarction.** CI: Confidence interval.

treated with combination therapy were more susceptible to cardiac complications as compared to those treated with ICI monotherapy<sup>[49]</sup>. In addition, male patients are at higher risk of developing cardiovascular irAEs. A retrospective analysis showed that 77% of cases with ICI-related cardiac toxicity were males<sup>[48]</sup>. In addition, another multicenter study found that 23 out of 35 irAEs (71%) occurred in male patients<sup>[54]</sup>. However, data is limited and based on retrospective analyses of a small number of cases (65 cases). Furthermore, concomitant cardiovascular disease is a potential risk factor for cardiovascular irAEs<sup>[55]</sup>.

Cardiovascular irAEs are classified into four grades by the Society for Immunotherapy of Cancer<sup>[56]</sup>. The management of patients with cardiovascular irAEs differs based on the grade and severity of the symptoms. Grade I is usually asymptomatic and requires neither treatment nor discontinuation of immunotherapy. Grade II is characterized by mild cardiac symptoms that should be controlled by holding cancer immunotherapy and management of the coexisting cardiac disease and its risk factors. Grade III cardiovascular symptoms are significant and require the withdrawal of ICI therapy as well as urgent initiation of high-dose prednisone (1-2 mg/kg). Grade IV cardiovascular irAEs are life-threatening conditions characterized by decompensated cardiac function with moderate-to-severe symptoms; corticosteroid therapy is the first-line treatment. The addition of intravenous immunoglobulins,



**Figure 9 Incidence of cardiac arrest.** CI: Confidence interval.

infliximab, or anti-thymocyte globulin should be considered as second-line treatments for patients with grade IV cardiovascular irAEs<sup>[10,56]</sup>.

Long-term data regarding the prognosis of patients with cardiovascular irAEs are limited. However, the available findings suggest a high fatality rate. In a systematic review that included 99 patients with cardiovascular irAEs, the fatality rate was 35%<sup>[50,57]</sup>. In addition, observational studies report a 50% rate of major adverse cardiac events in ICI-associated myocarditis, which is significantly higher than that of non-ICI-related myocarditis<sup>[58,59]</sup>.

This study represents an attempt to estimate the overall incidence of cardiovascular irAEs in cancer patients receiving ICI therapy. The quality of the included studies ranged from low to moderate according to the Cochrane Risk of Bias Assessment tool<sup>[43]</sup>. The main limitation of our analysis is that the included studies were not primarily designed to investigate the incidence of ICI-induced cardiac adverse events. In addition, there was a high risk of bias resulting from the difficulty in blinding and randomization of some studies. The definitions to determine adverse events were slightly different across all studies. We did not consider medication dose, which may influence the severity of adverse effects. Furthermore, although some trials noted an increased risk of cardiovascular irAEs among males, patients receiving multiple ICIs, and patients with pre-existing cardiovascular disease, raw data were not available to perform further subgroup analysis<sup>[48,49,54,55]</sup>. It is also important to note that malignancy in and of itself is a risk factor for coronary artery disease and other cardiovascular comorbidities and hence it is difficult to differentiate a concomitant cardiovascular irAE<sup>[60]</sup>. It is therefore reasonable to perform cardiovascular magnetic resonance to distinguish a pre-existing cardiovascular disease from a cardiovascular irAE<sup>[58,60]</sup>. Nevertheless, we believe this analysis provides a valuable framework for further studies on ICI-associated cardiovascular events.

## CONCLUSION

Cardiovascular irAEs are rare but potentially life-threatening complications that can occur in patients receiving ICI therapy. Our analysis revealed that the most frequent ICI-associated adverse events are atrial fibrillation, myocarditis, and pericardial effusion. Risk factors for cardiovascular irAEs include treatment with combination immunotherapy, male sex, and a history of cardiac disease. Data on the prognosis of cardiac irAEs are limited. Ongoing post-market surveillance is therefore imperative to characterize long-term risks and improve outcomes among patients receiving ICIs.

## ARTICLE HIGHLIGHTS

### Research background

Immune checkpoint inhibitors (ICIs) are novel antineoplastic agents that are used with increasing frequency throughout the developed world. However, although ICIs have demonstrated remarkable efficacy for the treatment of many malignancies, a range of adverse events have been reported.

### Research motivation

Cardiovascular adverse events have been associated with numerous anticancer agents. ICIs have been available for nearly a decade, however, and yet the rate of cardiovascular ICI-related adverse events (irAEs) remains to be definitively established.

### Research objectives

We reviewed the medical literature in order to identify, quantify, and characterize the risk of cardiovascular irAEs.

### Research methods

We conducted a systematic review and meta-analysis by searching PubMed, Cochrane CENTRAL, Web of Science, and SCOPUS databases for relevant interventional trials reporting cardiovascular irAEs. We performed a single-arm meta-analysis using OpenMeta [Analyst] software of the following outcomes: Myocarditis, pericardial effusion, heart failure, cardiomyopathy, atrial fibrillation, myocardial infarction, and cardiac arrest. A total of 26 studies were included.

### Research results

New-onset atrial fibrillation was the most common cardiovascular irAE observed among patients taking ICIs, occurring in 4.6% of individuals included in the analysis. Other relatively common cardiovascular adverse events included pericardial effusion and myocarditis, both of which occurred in 0.5% of patients receiving ICI therapy. The mechanism underlying cardiovascular irAEs remains to be definitively established, but it has been hypothesized that T-lymphocyte-mediated inflammation causes direct myocardial injury and disrupts sinoatrial node activity.

### Research conclusions

Cardiovascular irAEs—including atrial fibrillation, pericardial effusion, and myocarditis—are uncommon but potentially life-threatening complications of ICI therapy. Mechanisms of pathogenesis and patient- and ICI-associated risk factors warrant further investigation.

### Research perspectives

Cardiovascular irAEs represent rare but potentially life-threatening complications of ICIs. Data from post-market surveillance will play a vital role in clarifying the risk of cardiovascular irAEs. Based on the available evidence, however, close cardiac monitoring of patients receiving ICIs may be warranted.

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