

## Percutaneous coronary intervention for chronic total occlusion in patients aged <75 years versus ≥75 years: a systematic review

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### ABSTRACT

**Objective:** To examine the effect of age on procedural and clinical outcomes in patients undergoing percutaneous coronary intervention (PCI) of chronic total occlusion (CTO) lesions.

**Methods:** Literature search was conducted across PubMed, Google Scholar and Web of science, databases till March 2019.

**Results:** Seven studies including 7671 patients with an overall follow-up period of 1.5 to 5 years were included in our review. A total of 6299/1372 patients were included in non-elderly and elderly groups, respectively, with mean age and 67%/61% male patients. CTO-PCI was similarly successful in younger and older patients (82.8%,  $n = 5070$  vs. 78.1%,  $n = 1010$ ). The incidence of short-term outcomes was low across the studies and comparable between the two groups (all-cause mortality: 0.4% younger vs. 0.85% elderly, cerebrovascular accidents: 0.3% vs. 0.4%, major adverse cardiovascular events (MACE): 1.53% vs. 3.72% and major bleeding: 0.57% vs. 2.18%). Long-term outcomes including all-cause mortality (8.89% vs. 29.5%), cardiac mortality (3.72% vs. 15%) and MACE (24.9% vs. 40%) occurred with a higher incidence in elderly patients. When results were segregated according to the success of CTO-PCI, reduced clinical events were noted with successful revascularization in either age group.

**Conclusion:** Compared with the younger age group, CTO-PCI in elderly patients is safe and feasible with a comparable incidence of short-term outcomes. In either population, the incidence of long-term outcomes including survival remains a concern but when successful, CTO-PCI may be associated with improvement in terms of multiple patient-important clinical end-points.

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Chronic total occlusion; percutaneous coronary intervention; age>75; review; angiography

### 1. Introduction

Chronic total occlusion (CTO) of coronary arteries is defined as complete obstruction of a native coronary artery for the duration of  $\geq 3$  months based on estimation from clinical symptoms [1]. The gravity of occlusion is defined by thrombolysis in myocardial infarction (TIMI) grade using angiography as true (TIMI flow grade 0) or functional (TIMI flow grade 1) [2]. Large clinical registries have reported a CTO prevalence of 16–18% in patients with CAD [3,4]. The traditional treatment for CTO has been optimal medical therapy while revascularization therapies, namely, coronary artery bypass graft (CABG) surgery and percutaneous coronary intervention (PCI) were utilized in a lesser proportion of patients (CABG, 22–26% and PCI, 10–22%) [4]. This was due to the uncertainty regarding the post-operative prognosis after revascularization, difficulty in performing CTO-PCI, and the morbidity related to CABG surgery.

With the advancement in treatment strategies, including the use of the hybrid algorithm for guiding crossing strategies and dedicated procedural equipment

combined with increasing expertise of operators and availability of experienced centers, PCI has now become an accepted and valuable revascularization treatment option for CTO lesions as compared to the conservative era. As per a national report in 2013, CTO-PCI represented 4.8% of the total PCI volume in the US whereas a percentage of 5% to 10% was noted worldwide [5].

Studies have shown successful CTO-PCI can improve symptoms, angina, quality of life and left ventricular systolic function as well as reduce the need for repeat CABG [6]. However, most of these studies noted these benefits in a relatively younger patient population. With the improvement in life expectancy in the last few decades, we now have a greater proportion of elderly patients with CTO. However, there remains general reluctance towards revascularization therapy in the elderly, as most are being treated with medical management due to presumed complications, low technical success (60–70%) and lack of enough-published data to support aggressive revascularization [3].

Despite increasing evidence, that CTO-PCI improves survival in the elderly, these patients undergo PCI for

CTO lesions less frequently as compared to younger individuals. In view of these conflicting practices, the aim of our study was to compare the short- and long-term outcomes of patients undergoing CTO-PCI in younger (<75) and older age groups ( $\geq 75$ ).

## 2. Method

### 2.1. Search strategy

A comprehensive systematic literature search was performed across four databases (PubMed, Google Scholar, Web of Science and ScienceDirect) to identify all reports of clinical outcomes in elderly patients who underwent CTO-PCI. The search was conducted from the inception of these databases (till March 2019). To identify any additional studies, the references and footnotes of all retrieved articles were also manually searched to ensure that no studies were missed (Figure 1).

### 2.2. Inclusion and exclusion criteria

Studies were considered eligible if they reported clinical outcomes in elderly patients (age  $\geq 75$ ) who underwent PCI for CTO lesions with a younger population (age < 75) acting as a comparison group. Two authors independently screened the titles and abstracts of all citations obtained from the initial search. Any disagreement was resolved through discussion and consensus.

### 2.3. Data extraction

After deciding on the studies to be included, the data was extracted and verified by two authors. When provided, we extracted study design, the name of the first author, publication year, regions of study, study period, sample size, case size, duration of follow up, gender, mean age or age range, co-morbidities and concurrent pharmacological treatment and clinical outcomes.

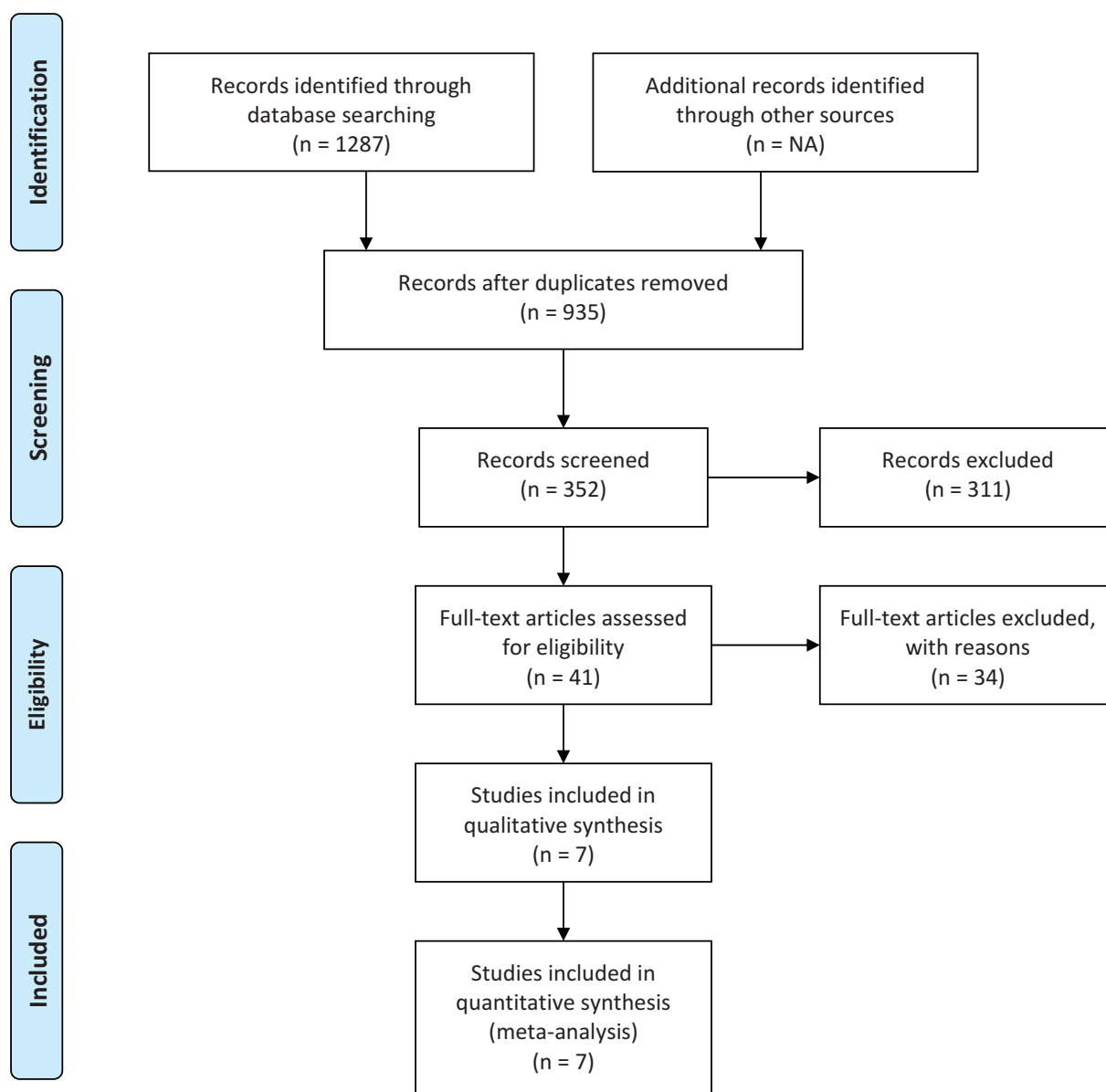


Figure 1. PRISMA flowsheet showing literature search and study selection details.

### 3. Result

#### 3.1. Baseline characteristics

A total of seven studies were included with 7671 patients [7–12, 14]. Two studies were prospective and five were retrospective. The overall follow-up period ranged from 1.5 to 5 years. The mean age ranged from 59 ± 9 to 80 ± 4. A total of 6184 patients were included in younger age group and 1538 patients were enrolled in older age group. In the younger age group, 67% (n = 4320) were males while 32% (n = 2009) were females. Among the elderly, 61% of patients were males (n = 839) while 39% (n = 549) were females. The BMI reported by only three studies [7,10,14] was higher in younger patients and showed a statistically significant difference (p < 0.01) between the two cohorts in these studies. Among other cardiovascular risk factors, younger patients had higher prevalence of current smoker status [30% (n = 1929) vs. 16% (n = 219)] and lower prevalence of hypertension (HTN) [76% (n = 4789) vs. 82% (n = 1166)], whereas the percentages of patients with diabetes mellitus type 2 and hyperlipidemia were comparable between the two groups.

In terms of past medical history, both the groups had a similar history of prior MI (38% in each group), whereas the higher prevalence of stroke was noted in the older age group [15% (n = 89) vs. 10% (n = 262)]. Similarly, in regards to previous cardiovascular interventions, both the groups had undergone PCI with a similar frequency (~43% in each group) but higher prevalence of prior CABG surgery was seen in older patients [29% (n = 350) vs. 22% (n = 1273)] (Table 1).

#### 3.2. Angiographic and procedural characteristics

Regarding the coronary angiography results, CTO lesions were more frequently seen in the left anterior

descending (LAD) artery in older patients (43% vs. 28%), whereas the prevalence of right circumflex artery and left circumflex artery disease was comparable between both groups. Sufficient data was not reported for single versus multivessel disease and location of left main disease in majority of the studies but the available data showed that single vessel disease was more prevalent in younger patients, 21% (n = 387) vs. 14% (n = 69). Six studies reported comparable volume of contrast used during the procedure ranging from a mean value of 176 ± 80 to 482 ± 23 ml in younger patients as compared to 164 ± 79 to 404 ± 197 ml in older patients. Procedural success was reported by five studies and it showed that CTO-PCI was successful in 82% (n = 4744) younger patients and 86% (n = 1039) older patients. Technical success was reported by seven studies and was achieved with a similar frequency in both age groups (76.7% versus 73.1%) (Table 2).

#### 3.3. Short-term outcomes

The overall clinical outcomes are summarized in Table 3. The all-cause mortality was reported by three studies and neither of them found any statistically significant differences between the two groups. It occurred in 0.4% (n = 14) younger patients and 0.85% (n = 7) in elderly patients. Major adverse cardiovascular events (MACE), reported by four studies, was lower in the younger group: 1.53% (n = 65) vs. 3.72% (n = 37). Similarly, major bleeding events or drop-in Hemoglobin level >3 g/dl that required transfusion were lower in younger patients (0.57%, n = 20) compared to older patients (2.18%, n = 18). Overall, the incidence of short-term outcomes in the two age groups was low across all studies.

Table 1. Baseline participant characteristics.

Author, Year, Study design	Groups	N	Age	Gender M/		HTN	HLD	DM Type 2	Current Smoker	Prior MI	Prior PCI	Prior CABG	Prior stroke	CHF	CKD
				F											
Toma, 2017, Retrospective	<75	1593	61.5 ± 9	224/1369	1276	1369	461	377	390	241	221	NA	262	172	
	≥75	409	79.5 ± 4	108/301	371	340	129	24	103	69	71	NA	86	222	
Karatasakis, 2017, Retrospective	<75	1391	63.1 ± 6	1217/174	1244	1307	633	389	619	883	487	146	396	NA	
	≥75	253	80.1 ± 3	192/61	235	248	104	30	114	162	109	40	78	NA	
Zhang, 2017, Retrospective	<75	325	63	246/79	214	NA	111	200	72	NA	NA	NA	52	NA	
	≥75	120	78	81/39	87	NA	40	49	29	NA	NA	NA	24	NA	
Iwentu, 2016, Retrospective	<75	932	62.8 ± 5	805/127	824	899	444	299	405	599	312	97	269	NA	
	≥75	217	79.6 ± 4	168/49	219	227	97	34	102	145	106	40	71	NA	
Andre, 2015, Prospective	<75	263	60.6 ± 9	231/32	134	199	85	182	134	116	15	19	263	51	
	≥75	93	80.5 ± 4	68/25	70	59	37	34	50	44	17	9	93	39	
Tanaka, 2013, Retrospective	<75	217	63.1 ± 9	193/24	139	142	88	51	38	NA	NA	NA	NA	15	
	≥75	67	78.5 ± 3	44/23	46	45	23	6	12	NA	NA	NA	NA	1	
Hobers, 2013, Prospective	<75	1578	59.1 ± 9	1377/201	932	1032	369	431	775	NA	238	NA	NA	46	
	≥75	213	79 ± 3	166/47	138	120	37	42	115	NA	47	NA	NA	16	

M, Male; F, Female; HTN, Hypertension; HLD, Hyperlipidemia; DM, Diabetes Mellitus; MI, Myocardial Infarction; PCI, Percutaneous coronary intervention; CABG, Coronary artery bypass grafting; CHF, Congestive heart failure; CKD, Chronic kidney disease; NA, Not available.

**Table 2.** Procedural and angiographic characteristics.

		Overall result	Andre, 2015	Toma, 2017	Iwentu, 2016	Tankana, 2013	Karatasakis, 2017	Zhang, 2017	Hobers, 2013
<b>Procedural characteristics</b>									
Procedural success	<75	2073 (89.2%)	–	–	863 (89.7%)	–	1210 (87%)	–	–
	≥75	396 (84.2%)	–	–	191 (82.8%)	–	205 (81%)	–	–
Technical success	< 75	5070 (82.8%)	226 (78%)	1355 (85%)	874 (90.9%)	189 (79%)	1231 (88.5%)	105 (82.7%)	1090 (69%)
	≥75	1010 (78.1%)	75 (74.3%)	307 (75%)	199 (85.7%)	57 (77%)	213 (84%)	23 (69.7%)	136 (63.9%)
<b>Angiographic characteristics</b>									
LAD	<75	1680 (27.6%)	–	431 (27%)	214 (22%)	68 (31.3%)	327 (23.5%)	99 (30.5%)	541 (34.3%)
	≥75	564 (43.4%)	–	125 (30.6%)	231 (97.5%)	25 (37.3%)	71 (28%)	35 (29.2%)	77 (36.2%)
LCX	<75	1904 (30%)	78 (29.7%)	765 (48%)	204 (20.8%)	59 (27.2%)	313 (22.5%)	116 (35.7%)	369 (23.4%)
	≥75	386 (27.8%)	29 (31.2%)	166 (40.6%)	45 (19%)	17 (25.4%)	45 (18%)	46 (38.3%)	38 (17.8%)
RCA	<75	2171 (44.8%)	152 (57.8%)	388 (24.4%)	561 (57%)	111 (51.2%)	765 (55%)	163 (50.2%)	31 (42%)
	≥75	603 (42.8%)	42 (45.2%)	112 (27.4%)	127 (53.6%)	32 (47.8%)	139 (55%)	54 (45%)	97 (42%)

LAD, Left anterior descending; LCX, Left circumflex; RCA, Right coronary artery.

**Table 3.** Short and long-term outcomes.

Outcomes	Groups	Overall result	Andre, 2015	Toma, 2017	Iwentu, 2016	Tankana, 2013	Karatasakis, 2017	Zhang, 2017	Hobers, 2013
<b>Short-term outcomes</b>									
All-cause mortality	<75	14 (0.4%)	1 (0.4%)	7 (0.4%)	–	0	6 (0.5%)	–	–
	≥75	7 (0.8%)	2 (2.2%)	2 (0.5%)	–	1 (1.5%)	2 (0.8%)	–	–
MACE	<75	65 (1.5%)	1 (0.4%)	15 (0.9%)	19 (1.9%)	–	30 (2.2%)	–	–
	≥75	37 (3.7%)	5 (5.4%)	4 (0.9%)	12 (5.1%)	–	16 (6.3%)	–	–
TVR	<75	10 (0.3%)	0 (0%)	5 (0.3%)	–	1 (0.5%)	4 (0.3%)	–	–
	≥75	6 (0.7%)	2 (2.2%)	3 (0.7%)	–	0	1 (0.4%)	–	–
CVA	<75	16 (0.3%)	0	1 (0.7%)	3 (0.3%)	0	12 (0.8%)	–	–
	≥75	4 (0.4%)	0	1 (0.2%)	1 (0.4%)	1 (1.4%)	1 (0.4%)	–	–
Cardiac tamponade	<75	22 (0.5%)	–	8 (0.5%)	3 (0.7%)	4 (1.7%)	7 (1.1%)	–	–
	≥75	14 (1.4%)	–	2 (0.5%)	5 (2.2%)	0	7 (2.8%)	–	–
Major bleeding	<75	20 (0.6%)	1 (0.4%)	3 (0.2%)	–	4 (1.8%)	12 (0.9%)	–	–
	≥75	18 (2.2%)	5 (5.4%)	9 (2.2%)	–	0	4 (1.4%)	–	–
<b>Long-term outcomes</b>									
All-cause mortality	<75	208 (6.6%)	–	133 (8.3%)	–	–	–	–	75 (4.8%)
	≥75	155 (24.9%)	–	109 (26.7%)	–	–	–	–	46 (21.6%)
Cardiac mortality	<75	18 (3.7%)	–	–	–	3 (1.4%)	–	15 (5.6%)	–
	≥75	27 (15%)	–	–	–	9 (13.4%)	–	18 (5.6%)	–
MACE	<75	730 (21.5%)	–	457 (28.6%)	–	50 (23%)	–	–	223 (14.13%)
	≥75	252 (36.5%)	–	162 (39.6%)	–	22 (32.8%)	–	–	68 (32%)

MACE, Major Adverse Cardiovascular Events; TVR, Target vessel revascularization; CV, Cerebrovascular accident.

### 3.4. Long-term outcomes

Although not reported by all studies, the long-term mortality was lower in the younger age group. In the younger age group, the all-cause mortality was 8.89%

( $n = 282$ ) and cardiac mortality was 3.72% ( $n = 18$ ). These adverse clinical events had a much higher incidence in the older age group with an all-cause mortality of 29.5% ( $n = 211$ ) and cardiac mortality of

15% (*n* = 27). Regarding long-term MACE, 24.9% (*n* = 844) younger patients experienced MACE as compared to 40% (*n* = 276) of elderly patients.

### 3.5. Successful vs. failed PCI

Comparison of outcomes between patients with successful versus failed PCI was reported by five studies, with the study by Andre et al. reporting outcomes in the elderly age group only (Table 4). In the younger age group, studies report a lower incidence of all-cause mortality, MI, MACE and cardiac mortality in those with successful PCI than those with failed PCI (2% vs. 4.8%, 2.6% vs. 3.4%, 6.5% vs. 15.1% and 2.1% vs. 6.8%, respectively). On the other hand, a higher incidence of TVR was seen in successful vs. failed PCI patients (2.1% vs. 1%).

In the older age group patients, a lower incidence of outcomes including MI, MACE, TVR, cardiac mortality and all-cause mortality was seen in patients with successful PCI as compared to those with failed PCI (3.9% vs. 5%, 1.2% vs. 2%, 2.5% vs. 4.4%, 5.2% vs. 16.3% and 8.8% vs. 10.9%, respectively).

## 4. Discussion

The results of our review show: (1) similar procedural and technical success rates in elderly and younger age group patients, (2) comparable frequency of short-term outcomes with the overall incidence being low between the two age groups and (3) higher incidence of long-term outcomes in the elderly group.

Elderly patients are more likely to have complex coronary artery lesions and extensive CAD. This combined with the comorbidity burden accounts for the perception of poor outcomes and subsequent reluctance of physicians towards performing complex PCI in this high-risk group [8]. However, in recent years' multiple factors such as the use of hybrid algorithms, including antegrade versus retrograde approach and true lumen strategy versus dissection re-entry, improved wire designs, use of drug-eluting stents and increased skills of operating physicians have significantly improved the success rates of CTO-PCI [13]. In line with this, the combined result of these studies in our review showed a comparable technical success rate between the two age groups (76.7% vs 73.1%).

This is in contrast to the report from the NCDR (National Cardiovascular Data Registry) which reported a success rate of 59% and identified older age as an independent predictor of technical failure [5]. However, the same study also reported high success rate with participation of more experienced high volume operators as was the case in the studies by Iwentu et al. and Tanaka et al. Similarly, the study by Karatasakis et al. was also performed in a high CTO volume center but it showed greater odds of technical failure in patients >75 years of age (odds ratio [OR], 2.28; 95% confidence interval [CI], 1.20--4.28). However, residual confounding from examined variables (such as previous CABG, PAD) and unexamined variables (such as frailty) was a concern with this study.

**Table 4.** Comparison of outcomes between successful vs. failed CTO-PCI in both young and elderly patients.

Study	Outcomes	Age < 75		Age > 75	
		Successful PCI	Failed PCI	Successful PCI	Failed PCI
Andre, 2016	Mortality	–	–	<i>N</i> = 71	<i>N</i> = 22
	MI	–	–	15 (21.1)	2 (9.1)
	Unstable Angina	–	–	2 (2.8)	4 (18.2)
	Cardiogenic shock	–	–	1 (1.4)	1 (4.5)
	Angina CCS >2	–	–	2 (2.8)	1 (4.5)
	TVR	–	–	4 (5.6)	7 (31.8)
Hoebbers, 2013		–	–	2 (2.8)	5 (22.7)
		<i>N</i> = 1090	<i>N</i> = 488	<i>N</i> = 136	<i>N</i> = 77
	MACE	123 (11.2)	102 (20.8)	35 (25.8)	33 (42.3)
	CABG	40 (3.6)	62 (12.7)	0 (0)	16 (20.4)
	MI	56 (5.1)	25 (5.1)	16 (11.5)	6 (8)
Toma, 2017	Mortality	48 (4.4)	30 (6.1)	27 (19.6)	19 (24.6)
		<i>N</i> = 1355	<i>N</i> = 238	<i>N</i> = 307	<i>N</i> = 102
	MACE	10 (0.7)	5 (2.1)	3 (1)	1 (1)
	Mortality	2 (0.1)	5 (2.1)	3 (1)	1 (1)
	MI	7 (0.5)	0 (0)	2 (0.7)	0 (0)
	TVR	3 (0.2)	0 (0)	1 (0.2)	0 (0)
Zhang, 2017	CVA	0 (0)	1 (0.4)	1 (0.3)	1 (1)
		<i>N</i> = 90	<i>N</i> = 177	<i>N</i> = 20	<i>N</i> = 94
	Cardiac mortality	1 (1.1)	14 (7.9)	3 (15)	15 (16)
	3-year primary end-point*	12 (13.3)	66 (37.3)	5 (25)	31 (33)
Tanaka, 2013		<i>N</i> = 189	<i>N</i> = 28	<i>N</i> = 57	<i>N</i> = 10
	Cardiac mortality	5 (2.4)	0 (0)	1 (2.4)	2 (23.1)
	MACE	39 (20.8)	7 (25.3)	20 (35.6)	3 (30.8)
	TVR	30 (15.9)	5 (17.6)	8 (14.4)	1 (8.3)

\*For Zhang, 2017 – 3-year primary end-point was the combined incidence of hospitalization from angina, reinfarction, heart failure or repeat revascularization and cardiac death.

MI, Myocardial infarction; TVR, Target vessel revascularization; MACE, Major Adverse Cardiovascular Events; CABG, Coronary artery bypass grafting; CVA, Cerebrovascular accident.

Even though the incidence of short-term outcomes was low in both the age groups, these events occurred with relatively higher frequency in elderly patients. This can be related to the higher prevalence of comorbid conditions such as HTN, prior stroke, CABG and angiographic risk such as more severe coronary calcification in elderly patients in most of our studies. Despite this, with the recent technological advances, the advent of drug-eluting stents and more prolonged antithrombotic medications, the incidence of short-term outcomes after CTO-PCI has decreased as noted in the report from NCDR which did not reveal an association between age and in-hospital MACEs [5,15,16].

In regards to long-term outcomes, a much higher incidence of hard end-points was noted in the elderly group as compared to younger patients. These findings resonate with the results of large observational studies performed by Tomasello et al. and Jang et al. which primarily included patients aged <75 and reported a decreased incidence of cardiac death and MACEs with CTO revascularization [17,18]. However, results from randomized controlled trials have been ambiguous. DECISION-CTO and EUROCTO trials evaluated angina relief and quality of life with EUROCTO trial reporting improvement in health status assessed via Seattle Angina Questionnaire in the CTO-PCI group. However, both the studies reported no difference in regards to MACEs [19,20]. In contrast, the recently published REVASC trial including 205 patients showed reduced MACEs with CTO-PCI at 12 months [21]. Hence, based on our studies, there may be a trend towards better long-term outcomes in younger age populations, however, convincing proof of survival benefit in either age group remains elusive. This is also in congruence with current guidelines that recommend considering PCI for CTO lesions in patients with angina burden and for improving LV function and degree of ischemia as compared to mortality benefit [22,23].

An important consideration here is the comparison of outcomes between successful versus failed CTO revascularization. A meta-analysis of 25 studies including more than 28,000 CTO-PCI patients with a median follow-up of 3 years showed that successful PCI was associated with improved clinical outcomes including overall survival (odds ratio (OR), 0.52), angina burden (OR 0.38), stroke (OR 0.72) and need for subsequent bypass surgery (OR 0.18) [24]. Similarly, compared with failed PCI, combined results from studies included in our review showed better outcomes with successful CTO revascularization in both elderly and younger age group patients.

Following are the limitations of our study: first, five out of the seven included studies were retrospective analysis and are thus subject to selection bias. Second, given heterogeneity for several clinical end-points and success rates, a pooled analysis was not possible, hence, the

reported results should only be considered suggestive and hypothesis-generating. Third, only the study by Andre et al. assessed myocardial viability. As expected, whether CTO supplies viable or non-viable myocardium has significant clinical importance as it correlates with the burden of ischemia and might dictate benefit achieved post-CTO recanalization. Fourth, only the study by Iwentu et al. reported definitions for technical and procedural success which can partly explain the observed varied success rates. Fifth, four out of the seven studies were performed at single centers which questions the generalizability of results of these studies.

## 5. Summary

In conclusion, when compared with the younger age group, CTO-PCI in elderly patients is safe and feasible with a comparable incidence of short-term outcomes. However, there seems to be a trend towards better long-term outcomes in younger patients requiring further research to convincingly establish proof of survival in either age group.

## Author contributions

Noman Lateef conceptualized and designed the review; Noman Lateef, Muhammad Junaid Ahsan carried out the analysis; Noman Lateef, Muhammad Junaid Ahsan and Hafiz Muhammad Fazeel, Abdul Haseeb and Omar Kousa drafted the initial manuscript; Mohsin Mirza, Mark Holmberg reviewed and approved the final manuscript as submitted.

## Disclosure statement

A conflict-of-interest statement is required for all articles and study types. In the interests of transparency and helping reviewers to assess any potential bias in a study's design, interpretation of its results, or presentation of its scientific/medical content, the BPG requires all authors of each paper to declare on the title page any conflicting interests (including but not limited to commercial, personal, political, intellectual or religious interests) that are related to the work submitted for consideration of publication.

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