

# Angiographic Success and Procedural Complications in Patients Undergoing Percutaneous Coronary Chronic Total Occlusion Interventions

## A Weighted Meta-Analysis of 18,061 Patients From 65 Studies

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**Objectives** This study sought to perform a weighted meta-analysis of the complication risk during chronic total occlusion (CTO) percutaneous coronary intervention (PCI).

**Background** The safety profile of CTO PCI has received limited study.

**Methods** We conducted a meta-analysis of 65 studies published between 2000 and 2011 reporting procedural complications of CTO PCI. Data on the frequency of death, emergent coronary artery bypass graft surgery, stroke, myocardial infarction, perforation, tamponade, stent thrombosis, major vascular or bleeding events, contrast nephropathy, and radiation skin injury were collected.

**Results** A total of 65 studies with 18,061 patients and 18,941 target CTO vessels were included. Pooled estimates of outcomes were as follows: angiographic success 77% (95% confidence interval [CI]: 74.3% to 79.6%); death 0.2% (95% CI: 0.1% to 0.3%); emergent coronary artery bypass graft surgery 0.1% (95% CI: 0.0% to 0.2%); stroke <0.01% (95% CI: 0.0% to 0.1%); myocardial infarction 2.5% (95% CI: 1.9% to 3.0%); Q-wave myocardial infarction 0.2% (95% CI: 0.1% to 0.3%); coronary perforation 2.9% (95% CI: 2.2% to 3.6%); tamponade 0.3% (95% CI: 0.2% to 0.5%); and contrast nephropathy 3.8% (95% CI: 2.4% to 5.3%). Compared with successful procedures, unsuccessful procedures had higher rates of death (0.42% vs. 1.54%,  $p < 0.0001$ ), perforation (3.65% vs. 10.70%,  $p < 0.0001$ ), and tamponade (0% vs. 1.65%,  $p < 0.0001$ ). Among 886 lesions treated with the retrograde approach, success rate was 79.8% with no deaths and low rates of emergent coronary artery bypass graft surgery (0.17%) and tamponade (1.2%).

**Conclusions** CTO PCI carries low risk for procedural complications despite high success rates. (J Am Coll Cardiol Intv 2013;6:128–36) © 2013 by the American College of Cardiology Foundation

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Chronic total occlusions (CTO) are encountered in 15% to 30% of patients undergoing coronary angiography (1). Compared with failed CTO PCI, successful CTO percutaneous coronary intervention (PCI) has been associated with improvement in angina, left ventricular function, and increased survival (2,3). Despite these benefits, CTO PCI is performed infrequently (2), likely due to historically low procedural success rates, technical complexity,

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high equipment use, and the potential for major periprocedural complications (4). In the past decade, new devices, increased operator experience, and new crossing techniques, such as the retrograde approach have helped overcome technical complexities leading to improved procedural success rates (5). However, there remain concerns that CTO PCI may be associated with high risk for procedural complications. Thus, we performed a meta-analysis of published CTO PCI series to better characterize the incidence of procedural complications.

## Methods

**Search strategy and eligibility criteria.** We performed a comprehensive search of the PubMed and Cochrane Library databases for manuscripts on coronary CTO. Bibliographies of the retrieved studies were searched by hand for other relevant studies. Human studies in English published between the years 2000 and 2011 were included if they reported any of the following procedural complications of CTO PCI: death; emergent or urgent coronary artery bypass graft (CABG); stroke; myocardial infarction (MI); perforation; tamponade; stent thrombosis; major vascular complications; major bleeding; contrast nephropathy; and radiation skin injury. Major adverse cardiovascular events were defined as the composite of death, emergent CABG, stroke, and MI. Review articles, letters to the editor, case reports, and studies in which procedural complications could not be accurately assessed from the published manuscript were excluded. Series of balloon uncrossable CTO or anomalous coronaries were also excluded. Series consisting exclusively of successful CTO PCI procedures were excluded from the overall study; however, these were included in a separate analysis comparing procedural complications of successful versus unsuccessful CTO PCI procedures. A list of the included studies is shown in Online Table 1. Because there are no validated scales for assessment of quality of observational series (6), the proportion of studies reporting each individual outcome was used as a measure of robustness (Table 1) (7). There was robust assessment of angiographic success, death, emergent CABG, stroke, MI, coronary perforation, and tamponade.

**Data extraction.** Data from included studies were extracted by 2 authors (V.P. and E.B.) and controversies were reviewed by both; in case of disagreement, a third reviewer (S.B.) was used to reach a consensus. Extracted data included the total number of patients and lesions, age, sex, history of prior CABG, frequency and outcomes of the retrograde approach, target vessel, angiographic success, and occurrence of complications. The country and institute of origin, author, and enrollment period were reviewed to identify and exclude duplicate publications from the same cohort.

**Statistical analysis.** The frequency of each evaluated outcome was abstracted from each study and presented as minimum, maximum, and cumulative rates. To assess heterogeneity across trials, we used the Cochrane Q statistic (a p value  $\leq 0.1$  was considered significant) and  $I^2$  statistic (25%, 50%, and 75% correlate with low, moderate, and high heterogeneity, respectively) for each outcome. Due to its conservative or “worst-case scenario” estimates, a random-effects model as described by DerSimonian and Laird (8) was used to obtain a summary estimate and 95% confidence intervals (CI). However, the cumulative proportion and corresponding confidence intervals are presented in Online Tables 2 and 3. Data collection, study selection, processing of the data, and reporting of the results were performed according to accepted principles related to systematic review and meta-analysis (7,9–11). Publication bias for angiographic success and death rates

### Abbreviations and Acronyms

**CABG** = coronary artery bypass graft

**CI** = confidence interval

**CTO** = chronic total occlusion

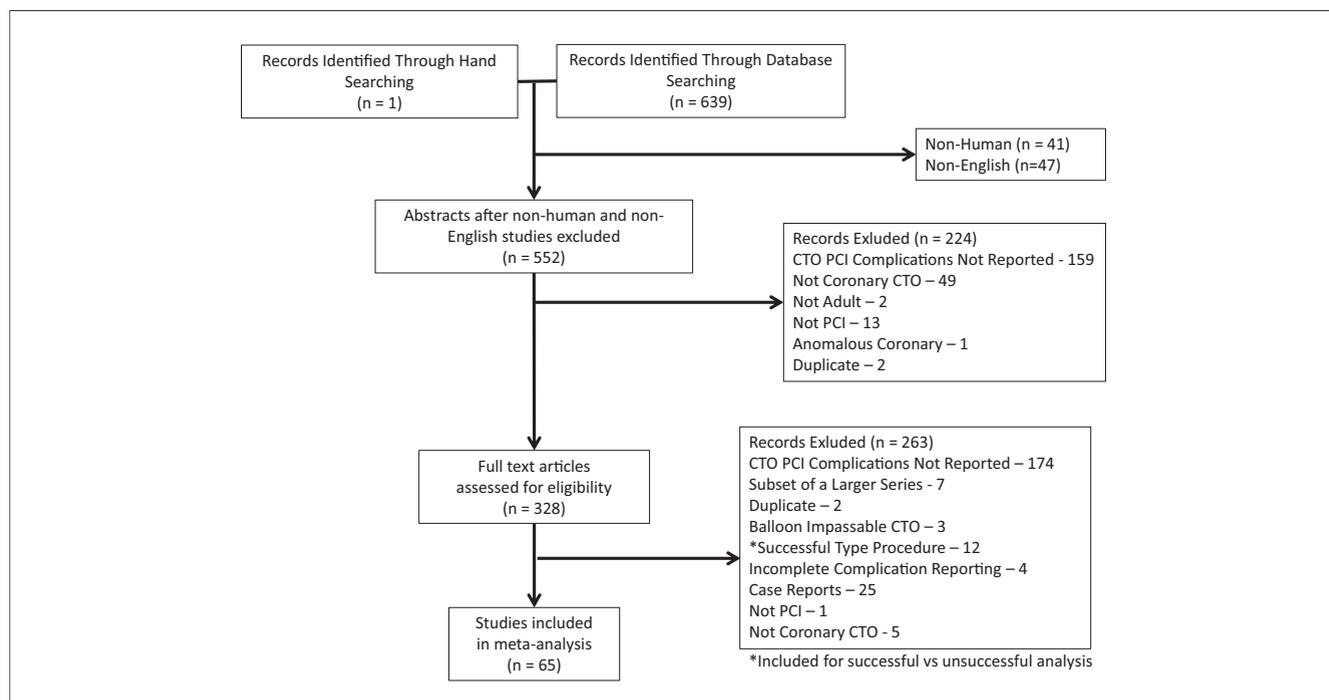
**MI** = myocardial infarction

**OR** = odds ratio

**PCI** = percutaneous coronary intervention

**Table 1. Proportion of Studies Reporting Success and Various Complication Rates of CTO PCI**

Variable	Proportion of Studies Reporting Outcome
Angiographic success	64/65 (98.5)
Death	65/65 (100)
Emergent coronary artery bypass graft	65/65 (100)
Stroke	65/65 (100)
Myocardial infarction	55/65 (84.6)
Q-wave myocardial infarction	46/65 (70.8)
Coronary perforation, per lesion	49/65 (75.4)
Tamponade	54/65 (82.8)
Acute stent thrombosis	25/65 (38.5)
Vascular complication	15/65 (23.1)
Major bleed	13/65 (20.0)
Contrast nephropathy	13/65 (20.0)
Radiation injury	7/65 (10.8)
Values are n/N (%).	



**Figure 1. Flow Diagram of the Literature Search and Study Selection**

CTO = chronic total occlusion; PCI = percutaneous coronary intervention.

were estimated visually by funnel plots and are presented in Online Figures 1 and 2. Proportions were compared using the chi-square test, and  $p < 0.05$  was considered statistically significant. A logistic regression model using study publication year was developed to evaluate for temporal trends in angiographic success rates and major complications. Statistical analyses were performed using Stata (version 11, StataCorp, College Station, Texas).

## Results

**Search results.** Of 640 studies retrieved through electronic and manual search, 65 studies met the inclusion criteria and were included in the final pooled analysis (Fig. 1). A full listing of all 65 articles is provided in Online Table 1. Table 1 shows the number of articles that reported success and various complication rates of CTO PCI. The 65 published studies reported outcomes on 18,061 patients who underwent CTO PCI of 18,941 target vessels (Table 2). Mean age of the cohort was 62.4 years, most patients (81.9%) were men, and 15.2% had prior CABG. The most common target vessel was the right coronary artery followed by the left anterior descending and the left circumflex arteries.

**Incidence of angiographic success and procedural complications.** The overall angiographic success rate ranged between 41.2% and 100% with a pooled estimate of 77% (95% CI: 74.3% to 79.6%) (Table 3). The reported major adverse cardiovascular events rate in 15,718 patients ranged from

0% to 19.4% with a pooled estimate of 3.1% (95% CI: 2.4% to 3.7%). Most of the major adverse cardiovascular events consisted of MI, with a pooled estimate rate of 2.5%. There were 77 deaths in the cohort with a reported range from 0% to 3.6%, yielding a pooled estimate of 0.2%. Emergent CABG, stroke, and radiation injury were the least common complications with rates of 0.1%, <0.01%, and <0.01%, respectively, in pooled analyses. The most commonly observed complications were perforation (2.9%, 95% CI: 2.2% to 3.6%) and contrast nephropathy (3.8%, 95% CI: 2.4% to 5.3%). Inspection of funnel plots demonstrated no evidence

**Table 2. Patient Demographics and CTO Target Vessel**

Patients	18,061
Lesions	18,941
Age, yrs	62.4 ± 3.1
Male	14,660/17,893 (81.9)
Previous CABG	2,171/14,244 (15.2)
Retrograde approach	1,440/5,449 (26.4)
CTO target vessel	17,942
Left main	59 (0.3)
Left anterior descending artery	6,126 (34.1)
Circumflex	3,818 (21.3)
Right coronary artery	7,486 (41.7)
Bypass graft	110 (0.6)
Other	343 (1.9)

Values are mean ± SD, n/N (%) or n (%).

CABG = coronary artery bypass graft surgery; CTO = chronic total occlusion.

**Table 3. Frequency of Angiographic Success and Complications in CTO PCI**

Outcome	Pooled Estimate Rate, %	95% CI	Reported Rate, Min–Max %	Cumulative Rate, n/N	I <sup>2</sup> , %	Cochran's Q	p Value Heterogeneity
Angiographic success	77.0	74.3–79.6	41.2–100.0	14,414/18,828	94.4	1,120.6	<0.0001
MACE	3.1	2.4–3.7	0–19.4	500/15,718	79.4	262.0	<0.0001
Death	0.2	0.1–0.3	0.0–3.6	77/18,061	0.0	39.3	0.994
Emergent CABG	0.1	0–0.2	0–2.3	52/18,061	0.0	29.7	1.000
Stroke	<0.01	0–0.1	0–0.7	11/18,061	0.0	6.0	1.000
Myocardial infarction	2.5	1.9–3.0	0–19.4	490/15,718	77.3	238.4	<0.0001
Q-wave myocardial infarction	0.2	0.1–0.3	0–2.6	61/13,353	0.0	38.2	0.752
Coronary perforation, per lesion	2.9	2.2–3.6	0–11.9	418/12,254	79	228.6	<0.0001
Tamponade	0.3	0.2–0.5	0–4.7	74/13,103	0.0	27.9	0.998
Acute stent thrombosis	0.3	0.1–0.5	0–2.0	51/9,338	31.9	35.3	0.065
Vascular complication	0.6	0.3–0.9	0–2.8	66/7,308	35.7	21.8	0.084
Major bleed	0.4	0–0.7	0–3.7	32/5,108	54.6	26.5	0.009
Contrast nephropathy	3.8	2.4–5.3	2.4–18.1	165/4,796	89.5	114.3	<0.0001
Radiation skin injury	<0.01	0–0.1	0–11.1	3/2,857	0.0	2.18	0.902

CI = confidence interval; MACE = major adverse cardiac events (composite of death, emergency CABG, stroke, and myocardial infarction); PCI = percutaneous coronary intervention; other abbreviations as in Table 2.

for publication bias for procedural success but a possibility for publication bias for death (Online Figs. 1 and 2).

**Successful versus unsuccessful procedures and use of the retrograde approach.** Compared with successful procedures, unsuccessful procedures had significantly higher rates of death (1.5% vs. 0.4%), stroke (0.4% vs. 0.07%), perforation (10.7% vs. 3.7%), and tamponade (1.7% vs. 0%) (Table 4). However, the frequency of emergent CABG, MI, Q-wave MI, and contrast nephropathy was similar between successful and unsuccessful procedures.

Among 884 patients undergoing CTO PCI of 886 lesions using a retrograde approach, angiographic success was reported from 55.6% to 100% with a pooled estimate rate of 83.8% (95% CI: 76.9% to 90.7%) (Table 5). The most commonly observed complications in patients who received a retrograde CTO PCI approach were MI (1.8%; 95% CI: 1.5% to 4.1%), perforation (3.2%; 95% CI: 0.8% to 5.5%), and contrast nephropathy (1.2%, 95% CI: 0% to

2.7%). Major complications, such as death, emergent CABG, and stroke were rare, with each occurring in 0.1% of patients.

**Temporal trends.** To evaluate changes over time, studies were divided into 4 groups based on publication year (Table 6). Most studies were published within the last 6 years. The pooled angiographic success rate increased in each successive quartile from 68.2% in studies published between the years 2000 and 2002 to 79.4% in studies published between 2009 and 2011 (Fig. 3). With each successive year, the rate of angiographic success increased significantly (odds ratio [OR]: 1.06, 95% CI: 1.05 to 1.07). There was also significant decrease in the rate of major complications over time, with studies published between 2000 and 2002 reporting a rate of 1.6%, which decreased to 0.5% for studies published between 2009 and 2011 (Fig. 3). For each successive year, the rate of major complications decreased significantly (OR: 0.93, 95% CI: 0.89 to 0.97).

**Table 4. Incidence of Procedural Complications in Successful Versus Unsuccessful CTO PCI**

Outcome	Successful	Unsuccessful	Chi-Square	p Value
MACE	84 (3.7)	14 (4.3)	0.2	0.68
Death	19 (0.4)	17 (1.5)	15.1	<0.0001
Emergent CABG	1 (0.03)	1 (0.17)	0.1	0.74
Stroke	3 (0.07)	4 (0.4)	4.1	0.04
Myocardial infarction	106 (2.8)	25 (3.0)	0.03	0.87
Q-wave myocardial infarction	10 (0.3)	6 (0.5)	1.3	0.26
Coronary perforation, per lesion	67 (3.7)	55 (10.7)	39.2	<0.0001
Tamponade	0 (0)	7 (1.7)	16.8	<0.0001
Vascular complication	33 (1.7)	6 (0.9)	1.7	0.20
Contrast nephropathy	18 (5.0)	5 (4.6)	0.03	0.86

Values are n (%).  
 Abbreviations as in Tables 2 and 3.

**Table 5. Incidence of Angiographic Success and Procedural Complications in Retrograde CTO PCI**

Outcome	Pooled Estimate Rate, %	95% CI	Reported Rate, Min–Max %	Cumulative Rate, n/N	I <sup>2</sup> , %	Cochran's Q	p Value Heterogeneity
Angiographic success	83.8	76.9–90.7	55.6–100	707/886	84.9	72.7	<0.0001
MACE	3.1	1.7–4.4	0–7.1	31/853	0.0	6.41	0.780
Death	0.1	0–0.7	0–0.4	1/884	0.0	0.4	1.000
Emergent CABG	0.1	0–0.6	0–0.6	1/884	0.0	0.5	1.000
Stroke	0.1	0–0.6	0–0.6	1/884	0.0	0.5	1.000
Myocardial infarction	2.8	1.5–4.1	0–7.1	28/853	0.0	5.6	0.848
Q-wave myocardial infarction	0.2	0–0.9	0–0.6	2/803	0.0	0.6	1.000
Coronary perforation, per lesion	3.2	0.8–5.5	0–14	31/828	62.1	21.1	0.007
Tamponade	0.5	0–1.2	0–4.5	9/817	0.0	4.0	0.912
Acute stent thrombosis	0.1	0–0.8	0–1.2	1/428	0.0	0.5	0.974
Contrast nephropathy	1.2	0–2.7	0–11.1	6/378	0.0	1.4	0.701
Radiation injury	<0.01	0–0.8	0–11.1	1/293	0.0	0.8	0.662

Abbreviations as in Tables 2 and 3.

**CTO duration definition.** The 44 studies that had a strict CTO duration requirement of  $\geq 3$  months were compared with the remaining 21 studies to assess the effect of CTO duration on angiographic success and major procedural complications. There was a nonsignificant trend toward more recent publication in studies that had a strict CTO duration criteria of  $\geq 3$  months versus those without (median year of publication 2009 vs. 2008,  $p = 0.07$ ). Compared with studies that included CTO duration  $< 3$  months, studies that included only CTO duration  $\geq 3$  months reported higher angiographic success rates without significant differences in the rate of major procedural complications (Table 7).

**Operator volume.** Although operator volume could not be directly assessed, a surrogate defined by study size greater than the median was used to assess the impact of CTO case volume on angiographic success and major procedural complications. The median study size was 134 patients. There was no difference in the angiographic success rate (76.2% vs. 76.6%,  $p = 0.7$ ) or major complication rate (0.2% vs. 0.8%,  $p = 0.06$ ) between smaller and larger studies.

## Discussion

Our meta-analysis is the first to evaluate the pooled angiographic success and procedural complication rates of CTO

PCI. The main findings are that CTO PCI: 1) is performed with increasing success rates; and 2) carries low risk of major complications; 3) compared to successful CTO PCI, unsuccessful CTO PCI is associated with significantly higher rates of death, stroke, coronary perforation, and tamponade; and 4) retrograde CTO PCI is associated with low procedural complication risk.

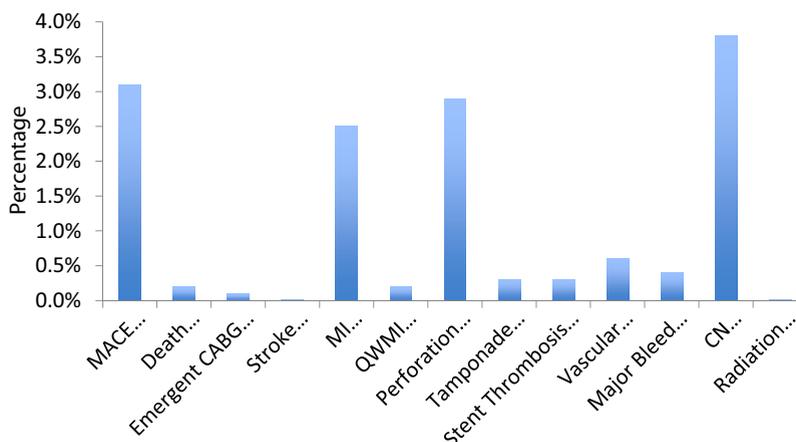
**Success rate.** The pooled angiographic success rate in this analysis is 77% and has increased over time (Fig. 3). This is likely the result of improved equipment and CTO PCI techniques. The advent and subsequent widespread use of stents in the late 1990s to early 2000s was the first major step toward a significant increase in CTO PCI success rates from approximately 50% in the pre-stent era to 70% afterward (12). The development of new crossing and re-entry devices, microcatheters, and guidewires contributed to further increases in the success rates in recent years. Finally, the introduction of new CTO PCI techniques and crossing strategies, such as the use of contralateral injections, dissection/re-entry techniques, and the retrograde approach coupled with dedicated high volume CTO PCI operators likely accounts for the higher success rates in modern CTO PCI demonstrated in this analysis (13–15).

We used study size as a surrogate for operator volume to understand the effect of operator volume on angiographic

**Table 6. Temporal Trends in Cumulative Angiographic Success Rates and Major Procedural Complication Rates by Study Publication Year**

Publication Year	Studies	Patients	Lesions	Angiographic Success, n (%)	Chi-Square	p Value*	Major Complications, n (%)†	Chi-Square	p Value*
2000–2002	6	2,766	2,833	1,933 (68.2)			45 (1.6)		
2003–2005	7	1,607	1,677	1,149 (73.5)‡	0.03	0.8691	9 (0.6)	8.6	0.0033
2006–2008	20	5,331	5,770	4,457 (77.2)	52.7	<0.0001	43 (0.8)	0.7	0.4012
2009–2011	32	8,357	8,661	6,875 (79.4)	9.2	0.0024	43 (0.5)	4.0	0.0457

\*Compared to prior 3 years. †Combined death, emergent coronary artery bypass graft, and stroke. ‡Out of 1,564 lesions.



**Figure 2. Pooled Complication Rates**

Pooled complication rates of chronic total occlusion percutaneous coronary interventions. CABG = coronary artery bypass graft; CN = contrast nephropathy; MACE = major adverse cardiac events; MI = myocardial infarction; QWMI = Q-wave myocardial infarction.

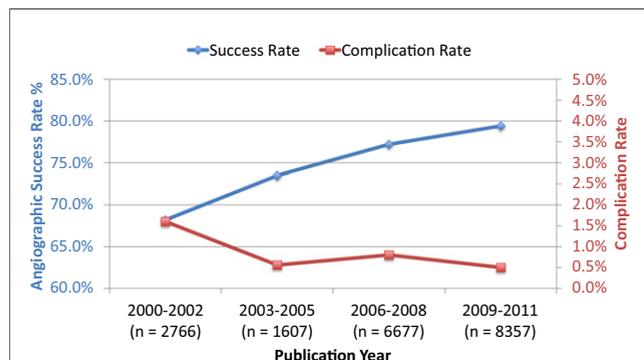
success rates. Although we did not find a difference in angiographic success and complication rates between smaller and larger studies, study size is likely a poor surrogate for operator volume. Indeed, several investigators who may be traditionally considered “high-volume” CTO operators have also published small-size studies.

Contrary to what might be expected, angiographic success rates were higher in studies that used a strict definition of CTO duration greater than 3 months as compared to those allowing CTO of shorter duration. A number of possible explanations may account for these findings. First, studies that allowed shorter duration occlusions may still have included a significant number of patients with occlusions of longer duration. Second, studies that required a CTO duration of >3 months tended to be published later

and thus may be more reflective of modern techniques that have resulted in higher rates of angiographic success. Finally, determining the duration of occlusion is an inexact science when serial angiograms are unavailable and relies largely on clinical history; it is possible that some patients deemed to have occlusions >3 months in age may actually have had occlusions that were <3 months in age.

**Death, emergent CABG, and stroke.** The most serious potential complications of any PCI are death, need for emergency CABG, and stroke. Such complications are of particular concern in the context of CTO PCI, as most of these patients are presenting electively for stable angina (5). The rates of death, emergent CABG, and stroke in 1 of the largest previously published series of 2,007 patients undergoing CTO PCI were 1.3%, 0.7%, and 0.01%, respectively (16). On the other end of the spectrum, a study of 1,463 patients undergoing elective PCI from April 2003 to 2006 reported 0.1% mortality (17). Our analysis falls between these studies, demonstrating low rates of each of the major complications in pooled estimates. Ultimately, the data suggest that the risk of major complications from CTO PCI is likely slightly higher than that of routine elective PCI, but lower than the common perception.

**Myocardial infarction.** Periprocedural myocardial infarction is among the most common complications of CTO PCI. However, most MI are non-Q-wave MI diagnosed by asymptomatic cardiac biomarker elevation. The MI rates in our study ranged widely from 0% to 19.4%, likely reflecting significant variability in the frequency of systematic cardiac biomarker measurement after PCI. This is consistent with previously published data from the National Cardiovascular Data Registry, in which a median of only 7% of patients had cardiac biomarker measurements after PCI (18). Whereas



**Figure 3. Temporal Trends in Cumulative Angiographic Success Rates and Major Procedural Complication Rates**

Temporal trends in cumulative angiographic success rates and major procedural complication rates, presenting according to the study publication year.

**Table 7. Incidence of Angiographic Success and Major Procedural Complications Stratified by CTO Duration and Study Size**

Outcome	CTO Duration ≥ 3 Months, n/N (%)	CTO Duration < 3 Months or No Specific Criteria, n/N (%)	Chi-Square	p Value	Study Size		Chi-Square	p Value
					≤ Median, n/N (%)	> Median n/N (%)		
Angiographic success	9,889/12,345 (80.1)	4,525/6,483 (69.8)	251.0	<0.0001	1,471/1,930 (76.2)	12,943/16,897 (76.6)	0.1	0.7288
Major complications*	80/11,650 (0.7)	60/6,411 (0.9)	3.0	0.0821	8/1,997 (0.2)	132/16,064 (0.8)	3.6	0.0590
Death	42/11,650 (0.4)	35/6,411 (0.5)	2.9	0.0871	3/1,997 (0.2)	74/16,064 (0.5)	3.3	0.0679
Emergent CABG	29/11,650 (0.2)	23/6,411 (0.4)	1.4	0.2408	5/1,997 (0.3)	47/16,064 (0.3)	<0.1	0.9179
Stroke	9/11,650 (0.8)	2/6,411 (<0.1)	0.8	0.3760	0/1,997 (0.0)	11/16,064 (0.1)	0.5	0.4909

\*Combined death, emergent CABG, stroke.  
Abbreviations as in Table 2.

cardiac biomarker elevation after routine PCI is associated with higher immediate and long-term mortality, the clinical and therapeutic implications of these events remain unclear (19). Studies that report results of systematic cardiac biomarker measurements following CTO PCI are needed.

**Coronary perforation and tamponade.** Coronary perforation is among the most feared complications of CTO PCI, due to the risk of tamponade. CTO PCI carries increased risk of perforation due to routine use of stiff and polymer-jacketed guidewires and frequent uncertainty about the vessel course. The incidence of coronary perforation in non-CTO PCI is approximately 0.19% and occurs more commonly in heavily calcified tortuous vessels using hydrophilic wires and atheroablative devices (20–22). Most of these cases do not result in tamponade and can be managed conservatively (20). Similarly, in our analysis, coronary artery perforation occurred in 2.9% of patients; however, only 0.3% of patients developed tamponade. Hence, most of the perforations were self-limited. Perforation can occur in a major vessel (usually after balloon or stent placement) or at a distal vessel branch or a collateral vessel (23). Despite its relatively rare occurrence, it is important for every CTO PCI program to have the necessary equipment for managing perforations, such as covered stents and coils (23).

**Contrast nephropathy.** Contrast nephropathy is a common PCI complication, occurring in 10% to 15% of all PCI patients (24,25), and has been linked with adverse clinical outcomes, including prolonged hospital stay, progression of chronic kidney disease, MI, and death (26,27). Given that higher contrast volume is associated with higher risk for contrast nephropathy, it is not surprising that contrast nephropathy is among the most common complications of CTO PCI (28). Studies included in our analysis reported rates of contrast nephropathy that varied from 2.4% to 18.1%, with a pooled estimate rate of 3.4%. However, this is likely an underestimate of the true incidence of contrast nephropathy, as only 20% of studies reported the data on contrast nephropathy and even those studies likely did not perform systematic serial assessment of renal function. As CTO PCI may require administration of a large amount of

contrast, prophylactic measures, such as hydration, are important to minimize the risk for contrast nephropathy.

**Major vascular and bleeding complications.** Bleeding is a common noncardiac complication in patients undergoing PCI and is associated with a poor prognosis (29). Presenting with acute coronary syndrome, cardiogenic shock, female sex, advanced age (≥85 years), and renal dysfunction are all predictive of increased bleeding risk (30). In addition to these established risk factors, CTO PCI has the potential to carry increased risk for bleeding due to use of large caliber sheaths and high frequency of dual (or occasionally triple) arterial access (31). However, use of intensive anticoagulation and antiplatelet regimens (such as glycoprotein IIb/IIIa inhibitors) is generally limited in CTO PCI due to the possibility of coronary perforation, which potentially lessens the risk for vascular access bleeding. Moreover, men have a lower risk of access complications than women do, and men composed most of the CTO PCI patients in our study. Indeed, in the present study, the pooled rate of major bleeding was 0.4%, which could, however, be underreported (only 20% of studies reported major bleeding complications and the definition of major bleeding varied from study to study).

**Radiation skin injury.** Radiation skin injury is of particular concern in patients undergoing CTO PCI, as long fluoroscopy and cine-angiography exposure may be required to cross and treat the lesion. As a result, careful attention to the radiation dose administered is recommended during the case with abortion of the procedure if crossing has not occurred after 8 to 10 Gy of air kerma exposure. Radiation skin injury was the least studied CTO complication in the present meta-analysis with only 11% of studies reporting on its occurrence and only 3 reported cases among 2,857 patients. Similar under-reporting of radiation exposure is true for most PCI studies (32). In part, this systematic under-reporting of radiation skin injury may be because this complication may not become apparent until weeks or months after the procedure. Regardless, studies, including systematic screening for radiation skin injury weeks and

months after PCI are needed to better define its incidence and implications.

**Study limitations.** First, only complication rates that were clearly reported in each article were included. Although this is unlikely to affect major complications, such as death or emergent CABG, less serious complications, such as MI, vascular complications, or bleeding, could be either under- or over-reported (as some investigators may not report an outcome because it did not occur). Second, systematic evaluation for certain complications, such as MI, contrast nephropathy, and radiation skin injury, was not performed. Third, publication bias is always possible in meta-analyses. Visual assessment of the funnel plot for angiographic success rates appeared symmetrical and unbiased; however, the funnel plot for death suggested that publication bias was possible. Publication bias may have also affected other periprocedural complications of CTO PCI, leading to underestimation of other complication rates. Fourth, many of the published studies were from dedicated high CTO PCI volume centers and expert operators; thus, these event rates may not reflect “real-world” event rates. However, this effect could be mitigated, at least in part, in our study by inclusion of multiple small series from low-volume centers worldwide. Fifth, whereas a patient-level meta-analysis would be ideal, this is unlikely to ever be performed and the present study-level pooled analysis provides the best currently available data on the frequency of CTO PCI complications. Sixth, the definitions for some of the complications may have varied across studies, highlighting the importance of defining and using universally acceptable definitions for future studies.

## Conclusions

Our meta-analysis demonstrates that CTO PCI is currently performed with high and improving success and low and decreasing complication rates, suggesting that CTO PCI carries a favorable risk/benefit ratio and supporting its increasing use for the treatment of this complex lesion and patient group.

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**Key Words:** chronic total occlusion ■ complications ■ percutaneous coronary intervention.

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 **APPENDIX**

**For additional tables and figures, please see the online version of this paper.**