Trends in Outcomes After Percutaneous Coronary Intervention for Chronic Total Occlusions
A 25-Year Experience From the Mayo Clinic

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Objectives
The aim of our study was to examine the trends in procedural success, in-hospital, and long-term outcomes after percutaneous coronary intervention (PCI) for chronic total occlusions (CTO) over the last 25 years from a single PCI registry and to examine the impact of drug-eluting stents.

Background
The percutaneous treatment of CTO remains a major challenge. Past studies have used variable definitions of CTO, and there are limited data available from contemporary practice.

Methods
We evaluated the outcomes of 1,262 patients from the Mayo Clinic registry who required PCI for a CTO. The patients were divided into 4 groups according to the time of their intervention: group 1 (percutaneous transluminal coronary angioplasty era), group 2 (early stent era), group 3 (bare-metal stent era), and group 4 (drug-eluting stent era).

Results
Procedural success rates were 51%, 72%, 73%, and 70% (p = 0.001), respectively, in the 4 groups. In-hospital mortality (2%, 1%, 0.4%, and 0%, p = 0.005), emergency coronary artery bypass grafting (15%, 3%, 2%, and 0.7%, p < 0.001), and rates of major adverse cardiac events (8%, 5%, 3%, and 4%, p = 0.052) decreased over time. During follow-up, the combined end point of death, myocardial infarction, or target lesion revascularization, was significantly lower in the 2 most recent cohorts compared with those patients treated before (p = 0.001 for trend). Technical failure to treat the CTO was not an independent predictor of long-term mortality (hazard ratio 1.16 [95% confidence interval 0.90 to 1.5], p = 0.25).

Conclusions
Procedural success rates for CTO have not improved over time in the stent era, highlighting the need to develop new techniques and devices. Compared with the prestent era, in-hospital major adverse cardiac events and 1-year target vessel revascularization rates have declined by approximately 50%.

J Am Coll Cardiol 2007;49:1611–8 © 2007 by the American College of Cardiology Foundation

There have been numerous technical and pharmacological advances in the field of percutaneous coronary intervention (PCI) since its inception more than a quarter of a century ago. However, the treatment of chronic total occlusion (CTO) remains a major challenge and is a frequent reason for a patient’s referral for coronary artery bypass surgery (CABG), leading some to refer to it as the “last frontier” of PCI (1). Physicians frequently encounter CTOs in current practice; they are found in as many as one-third of patients with at least one vessel with >50% stenosis (2), and they account for 10% of all percutaneous revascularization (3).

A concerted effort is underway to encourage the development of novel techniques and devices for the treatment of chronically occluded coronary arteries (1,4,5).

However, there are limited published data on the short- and long-term outcomes after PCI for CTO in contemporary practice. Previous studies on CTO have suggested that there has been an improvement in procedural success over time (6). Comparison between long- and short-term outcomes to establish temporal trends is difficult because of the variable inclusion criteria, definitions of procedural success, and clinical end points. These studies may have included patients with recent myocardial infarction (MI) and are not contemporaneous because they lack information on the influence of drug-eluting stents (DES) on the outcomes (3).

Thus, the aim of our study was to examine the trends in procedural success, in-hospital, and long-term outcomes after PCI for CTO during the last 25 years from a single PCI registry and to examine the impact of DES.
Methods

Since 1979, all patients undergoing percutaneous revascularization at the Mayo Clinic in Rochester, Minnesota, have been prospectively followed in a registry. The registry includes demographic, clinical, angiographic, and procedural data. Immediate and in–hospital events are recorded, and each patient is surveyed by telephone using a standardized questionnaire at 6 months, 1 year, and then annually after the procedure. All adverse events are confirmed by reviewing the medical records of the patients followed at our institution and by contacting the patients’ physicians and reviewing the hospital records of patients followed elsewhere.

We identified 1,262 patients undergoing PCI of a CTO lesion; these patients were divided into 4 groups according to the time of their intervention: group 1, October 1979 to December 1989 (n = 169); group 2, January 1990 to December 1996 (n = 459); group 3, January 1997 to March 2003 (n = 482); and group 4, April 2003 to July 2005 (n = 152). Group 1 consisted of patients who principally underwent percutaneous transluminal coronary angioplasty alone. Group 2 consisted of patients from the early stent era in whom stents were predominantly used as a bailout strategy. Group 3 included patients from the bare-metal stent (BMS) era in whom stenting was the preferred strategy in conjunction with dual oral antiplatelet therapy. Finally, group 4 consisted of patients whose PCI reflects contemporary practice and includes treatment with DES. Inclusion criteria were patients requiring nonemergency PCI to treat a 100% occlusion of a coronary artery. Patients were excluded if they suffered myocardial infarction in the 3 months before PCI. The study was approved by the Institutional Review Board at the Mayo Clinic and Mayo Foundation.

Definitions used were as follows. The number of diseased coronary arteries was defined by at least one coronary artery with 70% stenosis and 50% stenosis in the others. Patients with ≥50% stenosis in the left main coronary artery were considered to have 2-vessel disease if there was right dominance and 3-vessel disease if there was left dominance. Major adverse cardiovascular events (MACEs) were defined as one or more of the following: 1) in–hospital death; 2) Q-wave myocardial infarction; 3) urgent or emergent CABG during the index hospitalization; and 4) cerebrovascular accident defined as transient ischemic attack or stroke. Myocardial infarction was diagnosed in the presence of 2 of the following 3 criteria: 1) typical chest pain for at least 20 min; 2) elevation of creatine kinase (or the MB fraction) >2 times normal; and 3) a new Q wave on electrocardiogram.

In–hospital deaths included all deaths during the index hospital admission. Procedural success was defined as a reduction of residual luminal diameter stenosis to <50% without in–hospital death, Q-wave MI, or need for emergency CABG. Technical success was defined as a reduction of residual luminal diameter stenosis to <50% in the chronic total occlusion segment. Long-term outcome studied included all–cause mortality, death or any MI, and death/MI or target lesion revascularization (TLR). Other procedural complications, such as those related to the vascular access site, were not included in the present analysis. Target lesion revascularization was defined as any attempted percutaneous or surgical revascularization of the target lesion after the initial procedure.

Statistical analysis. Data are presented as the mean ± SD or as a frequency (percentage). Kaplan–Meier methods were used to estimate survival curves. Survival was analyzed in all patients, with follow–up starting on the day of the PCI. Tests for trends across time groups were made using linear contrasts of means in a one–way analysis of variance model for numerical data (with square root transformation for number of stents placed), the Armitage trend test for categorical data, and linear contrasts of group effects in a Cox proportional hazards survival model for time–to–event data. Comparisons between successful and unsuccessful PCIs are made using the Student t test, Pearson’s chi–square statistic, the Mann–Whitney rank–sum test, and the log–rank test for continuous, nominal, ordinal, and survival data, respectively. Although the data represent a population rather than a sample, p values are reported as an indicator of the magnitude of group differences and effect sizes. Cox proportional hazards survival models were used to estimate partial hazard ratios. Covariates were selected on the basis of clinical relevance. Nonlinear relationships between the hazard and continuous variables were considered but were simplified to linear without significant change in the model. Missing data were imputed using the aregImpute function in the Hmisc S–Plus library created by Harrell. All but 2 of the variables in the regression model had less than 6.6% missing values. Ejection fraction was missing in 37%. Chronic renal failure was missing in 33%, predominantly resulting from the fact that the variable was not recorded in the registry before 1993.

Results

Baseline characteristics. The clinical characteristics of patients in the 4 groups are summarized in Table 1. The mean age and proportion of each gender were similar during the time periods. However, there has been a progressive increase in the prevalence of diabetes mellitus, hyperlipidemia, hypertension, congestive heart failure, and ejection fraction <40% over the course of time. A history of revascularization doubled from the nonstent era to the stent era and has been fairly steady since. The body mass index of the patients also increased steadily, but the frequency of active smokers...
diminished. Chest pain remained the predominant indication for PCI, but a positive stress was a more common indication in the recent cohorts. The prevalence of severe angina and unstable angina decreased over time.

**Angiographic and procedural characteristics.** Table 2 summarizes the angiographic and procedural characteristics. There was no significant difference in the prevalence of single versus multivessel disease or the distribution of the target vessel treated among the groups. The number of stents used remained similar over the most recent 2 time periods, although glycoprotein IIb/IIIa inhibitor use declined in the recent period (*p* < 0.01 for comparison between the 2 most recent cohorts). Procedural success rate was 51% in the earliest cohort, increasing to 72% for patients treated between 1990 and 1996, but did not significantly improve (73% and 70%, respectively) in the 2 most recent time periods. Technical success rate were 54%, 76%, 75%, and 74%, respectively.

**Outcomes.** In-hospital mortality decreased over time (*p* = 0.009) (Table 3). There was a trend toward a reduction in any periprocedural myocardial infarction (*p* = 0.081), but there was no change in rate of Q-wave MIs (2% to 3%) among the 4 groups. There was a dramatic reduction in the need for emergency or urgent CABG from the first to the second time periods (15% and 3%), which continued to decrease over time (*p* < 0.001). There was a borderline significant trend toward lower MACE rates over the course of time (*p* = 0.052). The incidence of cardiac tamponade has held steady at 1%.

Median follow-up (interquartile range) was available for 216 (197, 230), 134 (112, 158), 63 (47, 84), and 12 (7, 20) months, respectively, for the 4 groups. During follow-up, there was no significant difference in the mortality rates (*p* = 0.84 for comparison between group). There appeared to be a reduction in the combined endpoint of death or MI but this did not reach statistical significance (*p* = 0.16) (Fig. 1).
The combined end point of death, MI, or TLR was significantly lower in the 2 most recent cohorts compared with those patients treated before 1997 (p < 0.001 for trend) (Fig. 1). At 1 year, the respective event rates for the combined end point were 36%, 37%, 26%, and 21% in the 4 groups of patients. The rates of TLR in the 4 groups were 26%, 24%, 13%, and 11% at 6 months and 28%, 29%, 17%, and 14%, respectively, at 1 year (p < 0.001). Percutaneous TLR rates at 6 months were 6%, 14%, 7%, and 6% at 6 months and 7%, 18%, 10%, and 8% at 1 year, respectively (p = 0.017 for trend in last 3 groups).

**Technical failure.** There were no significant differences in the age, gender, presenting symptom, history of diabetes mellitus, hyperlipidemia, hypertension, congestive heart failure, peripheral vascular disease, cerebrovascular disease, previous PCI or CABG, single versus multivessel disease, and ejection fraction between patients who did and did not have technically successful procedures. A history of MI and smoking was more frequent in those with unsuccessful PCI (Table 4). In-hospital death and MI were not significantly different based on PCI technical success; CABG, however, was significantly greater (11% vs. 1%) in unsuccessful procedures (Table 4). Long-term mortality was significant greater in patients with technical failure (p = 0.025) (Fig. 2), although the separation in curves is not distinct until after 6 years. When using multivariate analysis, we determined that technical failure was not an independent predictor of mortality (hazard ratio 1.16 [95% confidence interval 0.90 to 1.5], p = 0.25). Table 5 shows the covariates used for adjustment. Age, diabetes mellitus, history of smoking, history of congestive heart failure, ejection fraction, triple-vessel disease, chronic renal failure, and the date of the procedure were independent predictors of mortality during follow-up.

**Discussion**

The major findings of the present study are that, during the past 25 years, among patients requiring PCI for the treatment of a CTO: 1) the procedural success rate in the stent era has held steady at approximately 70%; 2) there has been a progressive reduction in periprocedural major adverse events; 3) survival and myocardial infarction rates during follow-up were not significantly different; and 4) there has been a progressive reduction in the need for target vessel revascularization, a trend that appears to be continuing in the DES era.

**Procedural success rates.** Our study illustrates the trends in procedural success rates for CTO from the time PCI was first introduced as a treatment for coronary artery disease.

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**Table 2 Angiographic and Procedural Characteristics**

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<tbody>
<tr>
<td>Number of vessels diseased</td>
<td>0.37</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>45 (28)</td>
<td>134 (31)</td>
<td>112 (25)</td>
<td>47 (36)</td>
<td></td>
</tr>
<tr>
<td>Double</td>
<td>67 (42)</td>
<td>166 (39)</td>
<td>192 (43)</td>
<td>43 (33)</td>
<td></td>
</tr>
<tr>
<td>Triple</td>
<td>49 (30)</td>
<td>141 (32)</td>
<td>143 (32)</td>
<td>40 (31)</td>
<td></td>
</tr>
<tr>
<td>Total number of stents placed</td>
<td>0.0 ( \pm ) 0.0</td>
<td>0.5 ( \pm ) 1.1</td>
<td>1.7 ( \pm ) 1.5</td>
<td>1.5 ( \pm ) 1.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Drug-eluting stent use</td>
<td></td>
<td></td>
<td>0.017</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>54 (32)</td>
<td>168 (37)</td>
<td>179 (37)</td>
<td>58 (38)</td>
<td>0.62</td>
</tr>
<tr>
<td>Left anterior descending</td>
<td>59 (35)</td>
<td>175 (38)</td>
<td>177 (37)</td>
<td>55 (36)</td>
<td>0.89</td>
</tr>
<tr>
<td>Circumflex artery</td>
<td>57 (34)</td>
<td>120 (26)</td>
<td>134 (28)</td>
<td>41 (27)</td>
<td>0.30</td>
</tr>
<tr>
<td>Procedural success</td>
<td>87 (51)</td>
<td>331 (72)</td>
<td>354 (73)</td>
<td>107 (70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Technical success</td>
<td>91 (54)</td>
<td>347 (76)</td>
<td>363 (75)</td>
<td>112 (74)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiac tamponade</td>
<td>3 (1.4)</td>
<td>4 (0.8)</td>
<td>2 (1.3)</td>
<td></td>
<td>0.88</td>
</tr>
</tbody>
</table>

The p values are test for trend across time groups. GP = glycoprotein.

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**Table 3 In-Hospital Outcomes**

<table>
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<tbody>
<tr>
<td>Death</td>
<td>4 (2.4)</td>
<td>6 (1.3)</td>
<td>2 (0.4)</td>
<td>0 (0)</td>
<td>0.009</td>
</tr>
<tr>
<td>Any myocardial infarction</td>
<td>17 (10)</td>
<td>41 (9)</td>
<td>39 (8)</td>
<td>7 (5)</td>
<td>0.081</td>
</tr>
<tr>
<td>Q-wave myocardial infarction</td>
<td>4 (2.4)</td>
<td>9 (2.0)</td>
<td>12 (2.5)</td>
<td>5 (3.3)</td>
<td>0.48</td>
</tr>
<tr>
<td>CABG</td>
<td>26 (15)</td>
<td>16 (3)</td>
<td>8 (1.7)</td>
<td>1 (0.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MACE</td>
<td>13 (8)</td>
<td>21 (5)</td>
<td>16 (3.3)</td>
<td>6 (3.9)</td>
<td>0.052</td>
</tr>
</tbody>
</table>

The p values are test for trend across time groups. CABG = coronary artery bypass grafting; MACE = major adverse cardiac event.
through to contemporary practice. We observed that, in the present era, successful revascularization was achieved in approximately one-half (51%) of the patients. Procedural success rates increased sharply to approximately 70% from 1990 onward, almost certainly as the result of the introduction of stents. However, more widespread use of stents and advances in their design has not been associated with further improvement in procedural success. These findings are consistent with previous individual studies published during different time periods (3,6–15). Suero et al. (6) reported an overall procedural success rate of 69.9% in their cohort during the period of 1980 to 1999 in which 7% of patients were treated with a stent. In more recent time periods, Olivari et al. (15), as well as Hoye et al. (3), have reported procedural success rates of 73.3% and 65.1%, respectively, among patients who were predominantly (>80%) treated with stents. In current practice, the predominant reason for the low success rate in the treatment of CTO is the failure to cross the lesion (16), highlighting the need for developing new devices and techniques for tackling this lesion subset (1,4,5). Moreover, our data suggest that advances in guidewire technology during the most recent time period are yet to have a major effect on procedural success rates, although continued surveillance is required to establish their full impact. In addition it is possible that their efficacy is, in part, negated by the use in increasingly complex lesion morphology. Regardless, our findings challenge the notion that there has been a progressive improvement in success rates in the stent era (4).

Clinical outcomes. As with other lesion subsets, there has been a steady decrease in in-hospital death associated with PCI over time, with mortality rates being <0.5% in the stent era. Similarly, there has been a progressive decrease (p < 0.08) in postprocedural MI with a rate of 5% in our most recent cohort of patients. In contrast, the frequency of large (Q-wave) infarcts has not decreased during the last 25 years, emphasizing the fact that there is potential for harm even when treating occluded vessels. Myocardial ischemic injury may result from damage to the collateral circulation, branch vessel occlusion, or distal embolization. The improvement in outcomes have occurred despite the patients in the recent cohorts having more adverse clinical characteristics such as diabetes and reduced ejection fraction, reflecting the improvement in PCI techniques and adjunctive therapy. In addition, there has been a major reduction in the need for urgent CABG after PCI, with the greatest change coinciding with the introduction of stents in the 1990s. The current rate of 0.7% is similar to the frequency

Figure 1  Long-Term Outcomes

Kaplan-Meier estimates for (A) death, (B) death or myocardial infarction, and (C) death, myocardial infarction (MI), or target lesion revascularization in the 4 groups. The sudden survival decrease around 8 years for the 1997 to March 2003 group was the result of an event occurring among a small number of patients still at risk and reflects the instability of the estimator when few patients remain. However, we present the curves to 10 years for the benefit of comparing the 10-year estimates of the 2 earliest groups.
of urgent CABG reported in our larger patient population from the Mayo PCI registry (17).

The long-term mortality and the combined occurrence of death or MI did not change over time. Survival at 2 years was approximately 95% in all 4 cohorts and remained similar out to 10 years’ follow-up. Thus, the improvement in procedural success rates in the stent era did not appear to confer a long-term survival benefit after PCI. However, this finding needs to be evaluated, bearing in mind that PCI has not been shown to improve survival in any other lesion subset among patients with stable disease and generally is performed with the aim of relieving ischemia. Moreover, the observational design of our study makes it likely that the greater prevalence of adverse clinical characteristics, such as diabetes, hypertension, hyperlipidemia, greater body mass index, congestive heart failure, and reduced ejection fraction among patients in the recent cohorts would confound the ability to demonstrate temporal improvement in outcomes as the result of advances in medical therapy (18). This result is supported by the observation that the date when the PCI was performed was an independent predictor of survival in a multivariable model. After adjustment for the differences in patient characteristics, there was a 4% relative reduction in mortality per year.

Repeat revascularization. There has been a marked reduction (>50%) in the need for TLR from 1997 onward, coinciding with the widespread use of stents. This finding is consistent with several randomized trials that have established the efficacy of BMS over balloon angioplasty in reducing angiographic restenosis in CTO by approximately 50% (19–22). Recent data from several registries suggest that the use of DES in CTO, as with all other lesion subsets, is effective in further decreasing restenosis and the need for revascularization when compared with BMS (23–26). We also observed a trend in reduction in target vessel revascularization in our DES cohort compared with the BMS cohort. However, this trend did not reach statistical significance, potentially because of the relatively small number of patients in the DES group. Data from a small randomized trial of 200 patients in the PRISON II (Prospective Randomized Trial of Sirolimus-Eluting and Bare Metal Stents in Patients With Chronic Total Occlusions) study comparing BMS with DES have demonstrated that the use of DES significantly reduces angiographic restenosis and TLR in patients with CTO (27). The rates of target vessel revascularization and TLR at 6 months were 8% and 4%, respectively, which is similar to our patients with DES.
Recently, the TOSCA-4 (Total Occlusion Study of Canada) registry has been established in the U.S. to facilitate Food and Drug Administration approval for the use of DES in the treatment of patients with CTO. **Impact of technical failure.** As reported previously, patients who underwent a failed PCI did not have greater in-hospital death or MI but, not surprisingly, they were much more likely to be referred for surgical revascularization (3). We have previously reported that successful recanalization of a CTO does not significantly impact long-term survival (7). In contrast, several subsequent studies have indicated that a successful procedure confers a long-term survival benefit (3,6,28). In the present study, patients with a technical success did appear to have slightly greater survival at 6 years after PCI, but no immediate survival advantage was observed. There are at least 2 potential explanations for the association between technical success and survival. First, as suggested by others (6), there may be a direct benefit of restoring coronary patency and myocardial perfusion on ventricular function and the risk of life threatening arrhythmia. However, this benefit can only be definitively evaluated by a randomized trial comparing optimal medical therapy with PCI. Alternatively, patients who undergo a failed procedure may have more severe atherosclerosis that is associated with fibrosis and calcification of the vessels accounting for both technical failure and higher mortality. Previous studies have reported that technical failure is more frequent among patients with multivessel disease (3,6,28). Although this was not observed in our study, patients with failed procedures were more likely to have had a previous MI. Furthermore, technical failure was not an independent predictor of mortality by multivariable analysis. Survival did correlate with left ventricular dysfunction, and patient attributes associated with greater atherosclerotic burden, supporting the hypothesis that technical failure may be a marker of disease severity. **Study limitations.** Although the data were collected prospectively, this is a retrospective single center analysis and is subject to the limitations of such analyses. The precise duration of the occlusion was not angiographically documented, a limitation applicable to all observational studies of CTO. Independent core angiographic laboratory analysis to investigate lesion characteristics and collateral blood flow was not performed, which may have provided insight into the determinants of procedural success and MACE in current practice. The study is limited to patients treated with PCI, and we cannot comment on the trends in outcomes for patients with CTO who are managed with medical therapy or surgical revascularization. **Conclusions** The introduction of coronary stents has resulted in a marked improvement in procedural success for CTO, but the rate has remained around 70% and has not improved during the past decade. It is imperative that there is continued focus on developing new techniques and devices to improve the success rates. It is encouraging that PCI for CTO has become much safer over time, with MACE rates of <5% in current practice. The use of stents, including DES, has been accompanied by a marked reduction in TLR, but there has been no apparent improvement in the long-term survival of patients. Thus, we recommend that PCI should primarily be considered for the treatment of angina or extensive myocardial ischemia in patients with CTO.

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**REFERENCES**


