Coronary Artery Perforations after Contemporary Percutaneous Coronary Interventions: Evaluation of Incidence, Risk Factors, Outcomes and Predictors of Mortality

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Abstract

Objectives: We sought to evaluate the incidence, risk factors, in-hospital and long term outcomes and predictors of mortality of coronary artery perforations (CAP) in the contemporary percutaneous coronary intervention (PCI) era.

Background: CAP is a rare but serious complication of PCI associated with increased risk of morbidity and mortality.

Methods: We included 181,590 procedures performed across 47 hospitals in Michigan from 1/1/2010-12/31/2015. Endpoints evaluated included the incidence of CAP and its association with in-hospital outcomes. Logistic regression analysis was utilized to determine independent risk factors for CAP and to examine whether the effect of CAP on mortality varied by gender.

Results: CAP occurred in 625 (0.34%) of patients. Independent predictors for CAP included older age, peripheral arterial disease, presence of left ventricular dysfunction or cardiomyopathy, lower body mass index, pre-PCI insertion of a mechanical ventricular support device, treatment of complex lesions (Type C), and treatment of chronic total occlusions, the latter of which was the strongest predictor of perforation (adjusted odds ratio 7.01, $p < 0.001$). After adjusting for baseline risk, the incidence of adverse outcomes remained substantially greater in patients with a perforation, with an adjusted odds ratio estimate of 5.00 for mortality (95% CI 3.42-7.31), 3.25 for acute kidney injury (95% CI 2.30-4.58), and 5.26 for transfusion (95% CI 4.03-6.87) (all $p < 0.001$). Perforation was associated with a higher mortality in women than men (interaction p-value = 0.01).

Conclusions: CAP is a rare complication but is associated with high morbidity and mortality especially in women. Further investigation is warranted to determine why women fare worse after CAP.

Key words: Coronary Aneurysm/Dissection/Perforation, Gender, Outcomes/Studies, Health Care Outcomes

Abbreviations:

1. CAP: Coronary artery perforations
2. PCI: percutaneous coronary interventions
3. CABG: coronary artery bypass grafting
4. CTO: Chronic total occlusion
5. BMC2: Blue Cross Blue Shield of Michigan Cardiovascular Consortium
6. MVC: Michigan Value Collaborative
7. BCBSM: Blue Cross Blue Shield of Michigan
8. CI-AKI: Contrast-induced acute kidney injury
9. IABP: intra-aortic balloon pump
10. STEMI: ST-segment elevation myocardial infarction

Introduction

The incidence of coronary artery perforation (CAP) during percutaneous coronary interventions (PCI) is estimated at 0.1% to 0.84%.[1] Although rare, CAP is associated with an increased risk of adverse outcomes including tamponade, myocardial infarction, need for emergency coronary artery bypass grafting (CABG), and death.[2-4] The majority of studies thus far have included a modest number of patients and it is unclear which pre-procedural patient factors are associated independently with an increased risk of CAP as well as which factors increase the risk of adverse outcomes after CAP. In addition, given improvement of equipment and therapies, advancing age of the population and changing guidelines, PCI utilization in certain higher risk subgroups, including the elderly or those with chronic total occlusions (CTO), has been increasing.[5-8] This study represents a large cohort of patients developing CAP after PCI and provides an updated analysis of the incidence, risk factors, and inpatient and long term outcomes associated with CAP in contemporary practice.

Methods

We included data from patients undergoing PCI at 47 hospitals participating in the Blue Cross Blue Shield of Michigan Cardiovascular Consortium (BMC2). The details of the BMC2 registry and its data collection and auditing process have been described previously.[9] Briefly, procedural data on all patients undergoing PCI at participating hospitals are collected using standardized data collection forms. Baseline data include clinical, demographic, procedural, and angiographic characteristics as well as medications used before, during, and after the procedure, and in-hospital outcomes. All data elements have been prospectively defined, and the protocol is approved by local institutional review boards at each hospital. In addition to a random audit of 2% of all cases, medical records of all patients undergoing multiple procedures or coronary artery bypass grafting and of patients who died in the hospital are reviewed routinely to ensure data accuracy.

The study population for this analysis included all consecutive patients who underwent PCI between January 2010 and December 2015. If a patient underwent more than one PCI

procedure during a hospital stay, only procedural data reflecting the earliest procedure is included in this analysis. For a subset of Medicare beneficiaries in the dataset, 90-day readmission and long term survival data were available through indirect matching on admission, discharge and procedure dates for the index hospitalization, patient gender and date of birth, and hospital and operator NPI numbers with Medicare data for PCI episodes in collaboration with the Michigan Value Collaborative (MVC).[10, 11]

Study endpoints

Inpatient mortality was defined as mortality from any cause during the initial hospitalization following PCI. Contrast-induced acute kidney injury (CI-AKI) was defined as an increase in pre-procedural to post-procedural serum creatinine ≥ 0.5 mg/dl, since this definition has been strongly associated with inpatient mortality and new requirement for dialysis.[12] Pre-procedural serum creatinine values were measured within 30 days prior to PCI, with the value closest to time of PCI chosen as the baseline value. Peak post-procedural serum creatinine was defined as the highest value after PCI and prior to the next procedure or discharge.

Statistical analysis

Univariate comparisons were performed using student T-tests for continuous measures, and Fisher exact tests for dichotomous measures. The Cochrane-Armitage trend test was used to assess whether the rate of CAP and the rate of treatment of CTO lesions changed over time. Multivariate logistic regression with stepwise variable selection using Akaike Information Criteria was utilized to identify pre-procedural clinical and demographic patient characteristics associated with the development of CAP. Patient characteristics included as candidate predictors were chosen based on both significant univariate differences as well as associations with CAP observed in previous studies.[1-3]

Pre-procedural patient risk of in-hospital outcomes including mortality, transfusion, and CI-AKI were estimated using the current BMC2 random Forest risk models from baseline patient clinical and demographic characteristics. The models are implemented for patient pre-procedural

risk prediction, and model inputs are described at the SCAI/BMC2 PCI online risk prediction tool available at both the BMC2 https://bmc2.org/calculators/multi and SCAI http://www.scai.org/PCIRiskAssessmentTools/default.aspx websites.[13-16] Risk adjusted mortality, transfusion, and CI-AKI rates were estimated for sub-groups by the overall collaborative outcome incidence multiplied by the ratio of observed to expected outcome rates for the subgroup (overall rate * O/E ratio for subgroup).

The association of CAP with adverse outcomes of inpatient mortality, need for transfusion and development of CI-AKI was assessed using multivariate logistic regression models adjusting for baseline patient risk. To assess whether the effect of CAP on outcomes potentially varied by gender, likelihood ratio tests were utilized to determine whether inclusion of a gender by CAP interaction term significantly improved model fit.

In the subset of Medicare patients for which long term survival data was available, propensity score matching was employed to account for baseline patient clinical and demographic variables that could confound the analysis of the impact of CAP on post-discharge survival. Logistic regression was utilized to construct the propensity score, and each CAP patient was matched to 10 similar non-CAP cases without replacement using a greedy algorithm. Variables included in the propensity score model and comparison of the cohorts are included in Supplementary Table 1 and 2. Kaplan-Meier incidence curves were used to visualize post discharge survival by group, and Cox proportional hazard regression was utilized to assess differences in survival between groups.

Results

Baseline demographics and clinical characteristics

Between January 2010 and December 2015, 181,590 patients underwent PCI in the state of Michigan and were included in this analysis. Of these patients, 625 (0.34%) suffered CAP during the PCI procedure, and 41 (6.56%) patients with perforation died prior to discharge. The rate of perforation overall was relatively stable over the 6 years included in the analysis

(Supplementary Figure 1A). The proportion of PCI cases where a CTO lesion was treated increased in statistically significant fashion over this same 6-year period, from 1.6% to 2.8% of all cases (Cochran Armitage trend test p value < 0.001), while the incidence of perforation among the subgroup of CTO cases did not demonstrate a statistically significant trend (Cochrane Armitage trend test p-value=0.06) (Supplementary Figure 1B-C).

Baseline clinical, demographic and procedural characteristics for patients with and without perforation are provided in Table 1. Patients with CAP were older, more likely to be female, have peripheral arterial disease or heart failure, require intra-aortic balloon pump (IABP) or other mechanical ventricular support prior to PCI, and to be in cardiogenic shock at the start of the procedure compared to those without CAP. Conversely, patients with perforations were less likely to have diabetes.

Of the 625 patients who developed CAP, 22 (3.52%) underwent post-procedural CABG, of which 2 (9.90%) died prior to discharge.

Association of CAP with intracoronary devices and coronary lesion variables

Among the 625 cases of CAP, 524 (83.8%) involved only one treated vessel and these cases were utilized to examine the association of CAP with specific devices or coronary lesion variables (Table 2). Lesion length was significantly longer in vessels that developed CAP (29.24 ± 13.46 mm) compared to those without CAP (23.74 ± 13.46 mm) (p-value<0.001). The use of atherectomy and laser were each associated with significantly higher rates of CAP with odds ratio of 3.05 and 8.88, respectively (both p<0.001). When analyzing the treatment of specific coronary lesion variables, CAP occurred in 1.91% of patients with a treated CTO lesion compared to only 0.3% of patients without CTO, and a CTO PCI was the strongest univariate predictor of increased risk of CAP (odds ratio 6.51, Fisher Exact test p-value < 0.001).

Predictors of CAP

Multivariate stepwise logistic regression identified older age, peripheral arterial disease, presence of left ventricular dysfunction or cardiomyopathy, treatment of high complexity (type

C) lesions, treatment of CTO, and use of a mechanical ventricular support prior to PCI as predictors of CAP (Table 3). Treatment of CTO remained associated with the greatest estimated risk of CAP after adjusting for other covariates, with patients treated for CTO having a seven-fold greater odds of developing CAP, odds ratio 7.01 (95% CI 5.48 – 8.98; p – value < 0.001). Greater height, higher body mass index and presence of diabetes were associated with a lower risk for the development of CAP.

In-hospital outcomes

Mean baseline risk estimates and outcomes of patients with and without perforations are provided in Supplementary Table 3. Mean predicted risks were significantly higher in patients with perforation, reflecting a greater burden of comorbidites in these patients. After adjusting for baseline predicted risk in a logistic regression model, patients with perforations remained at a substantially higher risk of adverse outcomes, with an adjusted odds ratio estimate of 5.00 (95% CI 3.42 – 7.31) for mortality, 3.25 (95% CI 2.30 – 4.58) for CI-AKI, and 5.26 (95% CI 4.03 – 6.87) for transfusion (all p < 0.001).

Predictors of in-hospital mortality

Table 4 provides a comparison of baseline and procedural patient characteristics of patients with CAP who died during the hospitalization and those discharged alive. Among the 41 patients that died, multiple pre-procedural patient characteristics, clinical presentations, procedural outcomes and complications occurred more frequently including: older age, female gender, ST-segment elevation myocardial infarction (STEMI) presentation, recent heart failure, cardiogenic shock or cardiac arrest, and pre-PCI insertion of IABP or other mechanical ventricular support. Of the 41 perforation patients who died, 29 (70.7%) were female, compared to only 40.1% of those discharged alive (p <0.001). Thirteen of the 41 perforation deaths (31.7%) occurred in the catheterization lab, and 20 deaths occurred on the same calendar date as the index PCI procedure (48.8%).

Figure 1 (a, b and c) provides risk adjusted mortality, CI-AKI, and transfusion rates for subgroups defined by gender and perforation. The effect of CAP on mortality was significantly greater in women compared to men when assessed by multivariate logistic regression model (gender by perforation interaction p-value = 0.01). No significant CAP by gender interaction was observed for the CI-AKI (p = 0.32) or transfusion (p = 0.50).

Subsequent analysis stratified by gender demonstrated a statistically significant increase in mortality with CAP in both men with adjusted OR=2.70 (95% CI: 1.37 - 5.30; p-value = 0.004) and women with an OR= 7.32 (95% CI: 4.60 – 11.65; p<0.001). By contrast, no significant weight by CAP interaction was observed in the mortality model (p = 0.80), indicating no significant evidence that the relationship between CAP and mortality varied across the spectrum of patient weights

Of the 625 cases of CAP, covered stents were successfully deployed in 70 (11.2%). Of the 70 CAP cases where covered stents were used, 12 (17.1%) patients died versus 29 deaths (5.23%) among 555 patients where covered stents were not utilized. After adjusting for predicted risk of death in logistic regression, the odds ratios for inpatient mortality for cases of CAP treated with covered stents vs. no covered stent was 4.46 (p < 0.001) likely related to the fact that covered stent use is reserved for perforations that are more likely to be hemodynamically significant.

Long term outcomes

Using propensity score matching, 1,030 Medicare patients without CAP having similar baseline clinical and demographic characteristics to the 103 available Medicare patients with CAP (Supplementary Tables 1 and 2) were selected. Median post-discharge follow-up in this cohort was 23 months for both groups, with 34 (33.0%) deaths observed among CAP patients, and 205 (19.9%) deaths among non-CAP patients during follow up. Kaplan-Meier survival curves with confidence band shading are provided in Figure 2. In Cox proportional hazards regression, CAP was associated with significantly greater mortality (HR = 1.63, p = .008). In

contrast to in-hospital mortality, no significant gender by CAP interaction was observed in Cox regression (p = 0.430), and women and men with CAP had comparable estimated mortality at 2 years (men 31.1% (95% CI 14.4% - 44.6%), women 23.6% (95% CI 10.2% - 35.0%)). No significant difference was observed for 90-day readmission (30.1% for CAP, 23.8% no CAP, p = 0.185)

Discussion

This study includes one of the largest patient cohorts describing the risk of CAP during PCI in contemporary practice. The incidence of CAP in our population was 0.34%, confirming that CAP remains an uncommon event. However, the high in-hospital mortality rate of 6.56% confirms the associated high mortality and highlights the need for further investigation into understanding risk factors, outcomes and potential therapies for this serious complication.

Small retrospective studies have identified various patient and angiographic characteristics as potential risk factors for CAP including older age, female gender, presence of chronic kidney disease, hypertension, and previous PCI or CABG as well as angiographic characteristics such as type C lesions, chronic total occlusions, calcified lesions, and culprit lesions in the right coronary artery.[1-4] In addition, certain procedural characteristics including a higher balloon to artery ratio and the use of atheroablative devices were shown in these limited studies to increase the risk of this serious event.[1, 3, 4]

Our study adds to the existing literature by identifying more than 600 patients with CAP. Some factors that have been suggested to be associated with CAP were not found to be independently associated with CAP in this large study, including hypertension, chronic kidney disease and prior coronary artery bypass grafting.[3, 4] However, consistent with prior studies, our analysis identified several patient and procedural characteristics as independent risk factors for CAP, including older age and treatment of chronic total occlusions.[2-4] In fact, treatment of CTO was the strongest risk factor for CAP development, which is an important consideration as

recently there has been an increasing interest in treatment of these higher risk lesions as techniques and technology have improved.

Consistent with prior work, we found CAP to be associated with an increased risk of in-hospital mortality.[1, 2] However, we also identified that CAP was associated with increased risk of long term mortality and with other adverse in-hospital outcomes, including development of CI-AKI and the need for transfusion. Possible mechanisms to explain the increased risk of CI-AKI and need for transfusion include hemodynamic compromise related to development of complications of tamponade or myocardial infarction as well as need for additional procedures or surgical repair.

Our study also demonstrated that the effect of CAP on mortality may vary by gender with our results indicating that perforation is significantly more deleterious in women than men. The etiology of the increased risk of death in women with CAP is unknown but potentially relates to anatomical or hormonal differences between sexes. One hypothesis relates to a presumed smaller vessel diameter or differences in vessel wall thickness size in women that could increase the risk of development of CAP and/or higher grades of CAP.[17] The influence of estrogen on coagulation factors and inflammatory markers has been proposed as a mechanism to explain the increased susceptibility for vascular injury. Our study did not examine the influence of smaller vessel size on the development of CAP, since the BMC2 database does not include information on vessel diameter.

The manner in which CAP is treated is dependent on the severity of the CAP, often graded by Ellis type classification, and whether certain complications associated with CAP, such as tamponade, are present.[18] Potential therapies include the use of prolonged balloon occlusion, deployment of covered stents, thrombin or gelfoam embolization, coils or CABG. We found that covered stents were utilized in the minority of patients with CAP, however these patients experienced higher rates of inpatient mortality. We hypothesize that this is related to the use of these therapies in more severe cases of CAP and that the worse outcomes in these patients are

related to this underlying higher grade perforation than the use of the covered stent itself. However, there is also evidence that covered stents are at higher risk for restenosis and thrombosis.[19] We do not have data on the exact reason why these patients died and further investigation into optimal treatment of CAP is needed.

There are several limitations to our study. First, our study was a retrospective analysis utilizing data from a large database which does not include details on the severity of CAP (such as Ellis type classification) or vessel size, which would be important to examine when attempting to identify the etiology of the potentially worse prognosis of CAP in women than men. In addition, various outcomes that may develop after CAP, including tamponade, need for emergency surgery or subsequent development of MI, could not be evaluated in our population based on database restrictions. Evaluating incidence and efficacy of various treatments for CAP was limited to assessing the use of covered stents in our population with CAP.

In conclusion, CAP remains an uncommon but serious complication of PCI, associated with an increased incidence of inpatient mortality, CI-AKI and need for transfusion as well as long term mortality. Treatment of CTO lesions was the strongest independent predictor of CAP. Coronary artery perforations were more harmful in women than men in our study. Further investigation into the etiology of the poorer prognosis of CAP in women as well as efficacy of various therapies to treat CAP is needed.

Tables and Figures

Table 1: Characteristics of patients with and without coronary artery perforation

Table 2: Perforations by device type and type of coronary lesion

Table 3: Independent adjusted risk factors for the development of coronary artery perforations

Table 4: Characteristics of patients with coronary artery perforations who were discharged alive versus deceased

Figure 1: Risk adjusted mortality, transfusion and contrast-induced acute kidney injury (CI-AKI) rates for subgroups defined by gender and perforation

1A. Risk adjusted mortality associated with coronary perforation in men and women
1B. Risk adjusted transfusion associated with coronary perforation in men and women
1C. Risk adjusted CI-AKI associated with coronary perforation in men and women

Figure 2: Long term mortality of propensity matched patients with and without coronary artery perforation among those discharged alive after PCI.

Supplementary Tables and Figures

Supplementary Table 1: Covariates included in propensity matching of patients with and without coronary artery perforation

Supplementary Table 2: Comparison of propensity matched cohorts of patients with and without coronary artery perforation

Supplementary Table 3: Baseline mean predicted risks, outcomes, and adjusted odds ratios of patients with and without coronary artery perforation

Supplementary Figure 1A-C: Overall incidence of CAP, proportion of PCI performed for treatment of CTO and incidence of CAP among CTO cases over a 5-year period

Supplementary Figure 1A: Perforation rate by year
Supplementary Figure 1B: Treated CTO lesion rate by year
Supplementary Figure 1C: Perforation rate by year in patients with a treated CTO lesion

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References

1. Shimony A, Joseph L, Mottillo S, Eisenberg MJ. Coronary artery perforation during percutaneous coronary intervention: A systematic review and meta-analysis. Can J Cardiol. 2011;27:843-850
2. Stankovic G, Orlic D, Corvaja N, et al. Incidence, predictors, in-hospital, and late outcomes of coronary artery perforations. Am J Cardiol. 2004;93:213-216
3. Fasseas P, Orford JL, Panetta CJ, et al. Incidence, correlates, management, and clinical outcome of coronary perforation: analysis of 16,298 procedures. Am Heart J. 2004;147:140-145
4. Shimony A, Zahger D, Van Straten M, et al. Incidence, risk factors, management and outcomes of coronary artery perforation during percutaneous coronary intervention. Am J Cardiol. 2009;104:1674-1677
5. Antonsen L, Jensen LO, Terkelsen CJ, et al. Outcomes after primary percutaneous coronary intervention in octogenarians and nonagenarians with ST-segment elevation myocardial infarction: from the western Denmark heart registry. Catheter Cardiovasc Interv. 2013;81:912-919
6. Sandhu K, Nadar SK. Percutaneous coronary intervention in the elderly. Int J Cardiol 2015;199:342-355
7. Galassi AR, Brilakis ES, Boukhris M,et al. Appropriateness of percutaneous revascularization of coronary chronic total occlusions: an overview. Eur Heart J. 2015 August 7, [Epub ahead of print]
8. Galassi AR, Boukhris M, Azzarelli S, Marza F, Tomasello SD. Percutaneous coronary interventions for chronic total occlusions: More benefit for the patient or for the interventionist's ego? Can J Cardiol. 2015;31:974-979
9. Gurm HS, Smith DE, Collins JS, et al. The relative safety and efficacy of abciximab and eptifibatide in patients undergoing primary percutaneous coronary intervention: insights

from a large regional registry of contemporary percutaneous coronary intervention. J Am Coll Cardiol. 2008;51:529-535

0. Michigan Value Collaborative. Accessed June 1, 2016. Available at: http://michiganvalue.org/

1. Herrel L, Syrjamaki JD, Linsell SM, et al. Identifying drivers of episode cost variation with radical prostatectomy. *Urology*. 2016;In press

2. Slocum NK, Grossman PM, Moscucci M, et al. The changing definition of contrast-induced nephropathy and its clinical implications: Insights from the Blue Cross Blue Shield of Michigan Cardiovascular Consortium (BMC2). Am Heart J. 2012;163:829-834

3. Gurm HS, Kooiman J, LaLonde T, Grines C, Share D, Seth M. A random forest based risk model for reliable and accurate prediction of receipt of transfusion in patients undergoing percutaneous coronary intervention. *PloS One*. 2014;9:e96385

4. Gurm HS, Seth M, Kooiman J, Share D. A novel tool for reliable and accurate prediction of renal complications in patients undergoing percutaneous coronary intervention. J Am Coll Cardiol. 2013;61:2242-2248

5. BMC2 Collaboration for Quality Improvement. BMC2 PCI-VIC. Available at: https://bmc2.org/calculators/multi. Accessed May 1, 2015.

6. PCI Risk Assessment Tool. The Society for Cardiovascular Angiography and Interventions. Available at: http://www.scai.org/PCIRiskAssessmentTools/default.aspx. Accessed May 1, 2015.

7. Argulian E, Patel AD, Abramson JL, et al. Gender differences in short-term cardiovascular outcomes after percutaneous coronary interventions. Am J Cardiol. 2006;98:48-53

8. Ellis SG, Ajluni S, Arnold AZ, et al. Increased coronary perforation in the new device era. Incidence, classification, management, and outcome. Circulation. 1994;90:2725-2730

9. Romaguera R, Waksman R. Covered stents for coronary perforations: Is there enough evidence? Catheter Cardiovasc Interv. 2011;78:246-253

Table 1: Characteristics of patients with and without coronary artery perforation

Characteristic	Coronary Perforation – no. (%)		p-value
	No N = 180,965	Yes N = 625	
Demographic			
Age (years) ± SD	65.08 ± 12.02	67.35 ± 12.04	p < 0.001
Female gender	60,349 (33.3%)	263 (42.1%)	p < 0.001
Current or recent smoker	52,677 (29.1%)	177 (28.4%)	p = 0.696
Height (cm)	171.15 ± 10.59	168.95 ± 10.86	p < 0.001
Weight (kg)	89.70 ± 21.43	84.21 ± 19.84	p < 0.001
Historical			
Hypertension	154,589 (85.5%)	553 (88.8%)	p = 0.019
Dyslipidemia	148,315 (82.0%)	516 (82.7%)	p = 0.668
Diabetes Mellitus	69,556 (38.4%)	221 (35.4%)	p = 0.113
Peripheral Arterial Disease	29,069 (16.1%)	126 (20.2%)	p = 0.005
Prior MI	63,507 (35.1%)	244 (39.0%)	p = 0.039
Prior PCI	82,465 (45.6%)	294 (47.0%)	p = 0.464
Prior CABG	33,415 (18.5%)	136 (21.8%)	p = 0.034
Cardiomyopathy or Left Ventricular Systolic Dysfunction	19,177 (10.6%)	91 (14.6%)	p = 0.001
Procedural			
PCI Status: Elective	66,218 (36.6%)	237 (38.0%)	p = 0.478
PCI Status: Urgent	83,790 (46.3%)	287 (46.0%)	p = 0.868
PCI Status: Emergency	30,498 (16.9%)	96 (15.4%)	p = 0.325
PCI Status: Salvage	364 (0.2%)	4 (0.6%)	p = 0.015
Arterial Access Site: Radial	37,473 (20.7%)	123 (19.7%)	p = 0.538
Pre-PCI insertion of IABP or other mechanical ventricular support device	2,467 (1.4%)	25 (4.0%)	p < 0.001
Pre-PCI Left Ventricular Ejection Fraction ± SD	51.90 ± 12.84	49.89 ± 14.42	p = 0.003
Cardiogenic Shock at Start of PCI	3,765 (2.1%)	24 (3.8%)	p = 0.002

SD: standard deviation, MI: myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary artery bypass grafting, IABP: intraaortic balloon pump

Table 2: Perforations by device type and type of coronary lesion

	Percent of cases where device was used or lesion variable present	Perforation rate in cases with device or lesion variable	Perforation rate in cases without device or lesion variable	Odds Ratio	P-value (Fisher exact test)
Intracoronary device type					
Thrombectomy	5.67%	0.31%	0.33%	0.940	0.850
Cutting Balloon	4.92%	0.42%	0.32%	1.301	0.155
Atherectomy	1.03%	0.98%	0.32%	3.051	< 0.001
Bare Metal Stent	17.69%	0.32%	0.33%	0.952	0.731
Drug Eluting Stent	72.13%	0.26%	0.50%	0.524	< 0.001
Extraction Catheter	3.51%	0.18%	0.33%	0.535	0.043
Embolic Protection	2.10%	0.42%	0.33%	1.281	0.357
Laser	0.13%	2.82%	0.33%	8.876	< 0.001
Type of coronary lesion					
Chronic Total Occlusion	1.91%	1.91%	0.30%	6.514	< 0.001
Type C lesion	56.62%	0.36%	0.29%	1.242	0.017
Thrombus Present	15.91%	0.26%	0.34%	0.761	.036
Bifurcation Lesion	5.67%	0.31%	0.33%	0.940	0.850

Table 3: Independent adjusted risk factors for the development of coronary artery perforations

	Odds Ratio	P-value	95% Confidence Interval
Age (per 5 year increase)	1.05	0.005	1.015-1.089
Height (per 5 cm increase)	0.91	< 0.001	0.872-0.941
BMI (per 1 unit increase)	0.98	0.001	0.965-0.991
PAD	1.21	0.064	0.989-1.483
Diabetes	0.86	0.090	0.723-1.024
Cardiomyopathy or LV dysfunction	1.30	0.026	1.032-1.633
IABP or MV support device implanted prior to PCI	2.04	0.002	1.302-3.207
Pre-PCI creatinine	0.90	0.061	0.803-1.005
Type C/high complexity lesion	1.15	0.100	0.973-1.364
CTO lesion	7.01	< 0.001	5.478-8.980
Cardiogenic shock at start of PCI	1.41	0.138	0.896-2.211

BMI: body mass index, PAD: peripheral arterial disease, LV: left ventricle, MV: mechanical ventricular, CTO: chronic total occlusions

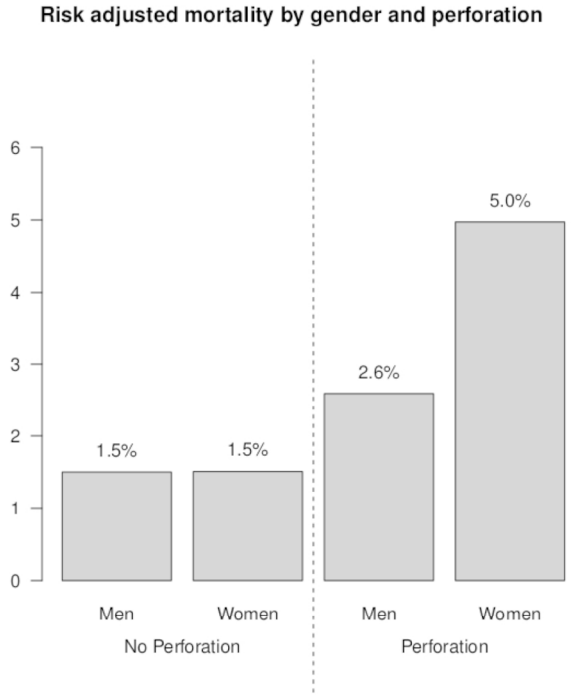
Table 4: Characteristics of patients with coronary artery perforations who were discharged alive versus deceased

Characteristic	Discharged alive N = 584	In-hospital death N = 41	p-value	Absolute Standard Difference
Demographic				
Age ± SD	66.98 ± 11.94	72.66 ± 12.28	p = 0.006	46.87
Female Gender	234 (40.1%)	29 (70.7%)	p < 0.001	64.85
Current or recent smoker	162 (27.8%)	15 (36.6%)	p = 0.230	18.81
Historical				
Hypertension	518 (89.0%)	35 (85.4%)	p = 0.476	10.90
Dyslipidemia	487 (83.5%)	29 (70.7%)	p = 0.036	30.84
Diabetes Mellitus	207 (35.4%)	14 (34.1%)	p = 0.867	2.73
Prior MI	226 (38.7%)	18 (43.9%)	p = 0.509	10.58
Prior PCI	279 (47.8%)	15 (36.6%)	p = 0.165	22.80
Prior CABG	134 (22.9%)	2 (4.9%)	p = 0.007	54.08
CAD Presentation				
STEMI or equivalent	77 (13.2%)	13 (31.7%)	p = 0.001	45.53
Heart failure within two weeks	87 (14.9%)	14 (34.1%)	p = 0.001	45.91
Cardiogenic shock within 24 hours	10 (1.7%)	8 (19.5%)	p < 0.001	60.37
Cardiac arrest within 24 hours	10 (1.7%)	4 (9.8%)	p < 0.001	35.11
Pre-PCI insertion of IABP or other mechanical ventricular support device	16 (2.7%)	9 (22.0%)	p < 0.001	61.04
PCI Status: Elective	231 (39.6%)	6 (14.6%)	p = 0.001	58.56
PCI Status: Urgent	267 (45.8%)	20 (48.8%)	p = 0.711	5.98
PCI Status: Emergency	85 (14.6%)	11 (26.8%)	p = 0.036	30.58
PCI Status: Salvage	0 (0.0%)	4 (9.8%)	p < 0.001	46.50
Post procedural outcomes				
Cardiogenic Shock	58 (9.9%)	30 (73.2%)	p < 0.001	167.30
Heart Failure	36 (6.2%)	8 (19.5%)	p = 0.001	40.72

SD: Standard deviation, CAD: coronary artery disease, MI: myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary artery bypass grafting, STEMI: ST-segment elevation myocardial infarction, IABP: intra-aortic balloon pump, CK-MB: creatinine kinase, CVA: cerebral vascular accident

Figure 1. Risk adjusted mortality, transfusion and contrast-induced acute kidney injury (CI-AKI) rates for subgroups defined by gender and perforation

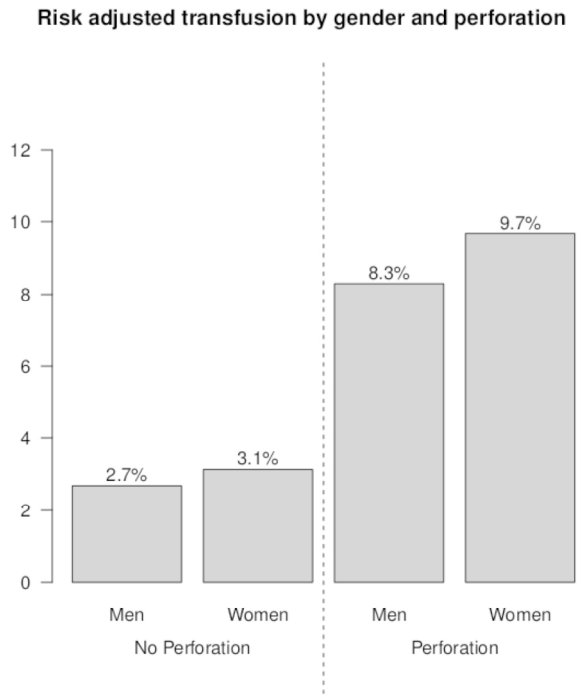
1A. Risk adjusted mortality associated with coronary perforation in men and women



Risk adjusted mortality, transfusion and contrast-induced acute kidney injury (CI-AKI) rates for subgroups defined by gender and perforation
1A. Risk adjusted mortality associated with coronary perforation in men and women

127x118mm (300 x 300 DPI)

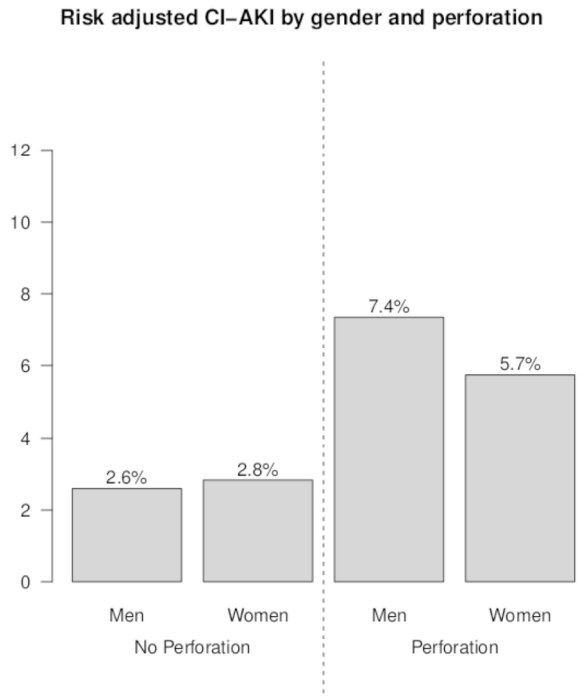
1B. Risk adjusted transfusion associated with coronary perforation in men and women



Risk adjusted mortality, transfusion and contrast-induced acute kidney injury (CI-AKI) rates for subgroups defined by gender and perforation
1B. Risk adjusted transfusion associated with coronary perforation in men and women

127x103mm (300 x 300 DPI)

1C. Risk adjusted CI-AKI associated with coronary perforation in men and women



Risk adjusted mortality, transfusion and contrast-induced acute kidney injury (CI-AKI) rates for subgroups defined by gender and perforation
1C. Risk adjusted CI-AKI associated with coronary perforation in men and women

127x110mm (300 x 300 DPI)

Figure 2: Long term mortality of propensity matched patients with and without coronary artery perforation among those discharged alive after PCI

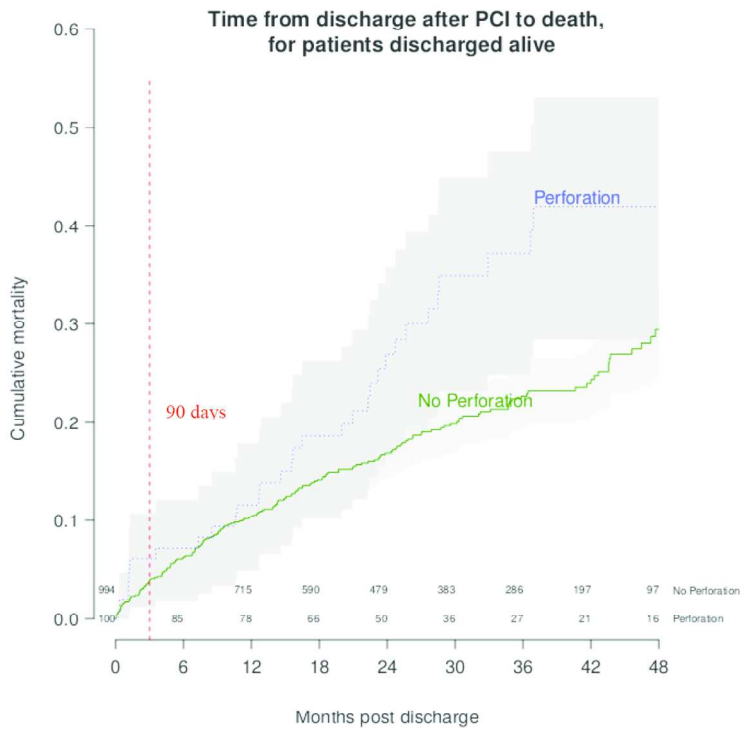


Figure 2: Long term mortality of propensity matched patients with and without coronary artery perforation among those discharged alive after PCI

127x123mm (300 x 300 DPI)

Supplementary Table 1: Covariates included in propensity matching of patients with and without coronary artery perforation

PCI Indication: 1) Immediate PCI for STEMI 2) PCI for STEMI (Unstable) 3) PCI for STEMI (Stable) 4) PCI for STEMI, stable after successful full-dose Thrombolysis) 5) Rescue PCI for STEMI (after failed full-dose lytics) 6) PCI for high risk Non-STEMI or unstable angina 7) Staged PCI 8) Other	CAD presentation: 1) No symptom, no angina 2) Symptom unlikely to be ischemic 3) Stable angina 4) Unstable angina 5) Non-STEMI 6) STEMI or equivalent
PCI status: 1) elective 2) urgent 3) emergency 4) salvage	Admission source: 1) admitted from emergency department 2) transfer 3) other
Smoking status (current smoker)	Prior CABG
Hypertension	Height
Dyslipidemia	Weight
Family history of CAD	Currently on dialysis
Prior MI	Prior cerebrovascular disease
Prior heart failure	Prior peripheral artery disease
Prior valve surgery	Chronic lung disease
Prior PCI	Diabetes
Heart failure within the past 2 weeks	LV ejection fraction less than 40%
Pre-procedural Hemoglobin	Race (white, black, Asian, other – allowing selection of multiple categories)
Cardiomyopathy and/or left ventricular dysfunction	Prior cardiogenic shock (within 24 hours)
Prior cardiac arrest (within 24 hours)	Cardiogenic shock at start of PCI procedure
Age	Gender
Predicted patient mortality risk based on BMC2 mortality risk model.	

CAD: coronary artery disease, MI: myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary artery bypass grafting, NSTEMI: non-ST segment elevation myocardial infarction, STEMI: ST segment elevation myocardial infarction, BMC2: Blue Cross Blue Shield of Michigan Cardiovascular Consortium, LV: left ventricular

Supplementary Table 2: Comparison of propensity matched cohorts of patients with and without coronary artery perforation

Characteristic	No Perforation	Perforation	p-value	Absolute Standard Difference
Age	74.74 ± 9.51	74.16 ± 10.75	p = 0.597	5.75
Sex				
Male	483/1,030 (46.9%)	50/103 (48.5%)	p = 0.749	3.30
Female	547/1,030 (53.1%)	53/103 (51.5%)	p = 0.749	3.30
Height	166.37 ± 10.69	166.63 ± 11.26	p = 0.822	2.38
Weight	80.45 ± 19.71	80.83 ± 20.16	p = 0.856	1.90
Race				
White	978/1,030 (95.0%)	98/103 (95.1%)	p = 0.931	0.90
Black	32/1,030 (3.1%)	3/103 (2.9%)	p = 0.913	1.14
Asian	8/1,030 (0.8%)	1/103 (1.0%)	p = 0.832	2.09
Admit Source				
Emergency department	464/1,030 (45.0%)	45/103 (43.7%)	p = 0.791	2.74
Transfer in from another acute care facility	239/1,030 (23.2%)	26/103 (25.2%)	p = 0.641	4.76
Other	327/1,030 (31.7%)	32/103 (31.1%)	p = 0.888	1.46
Current/Recent Smoker	154/1,030 (15.0%)	15/103 (14.6%)	p = 0.916	1.10
Hypertension	925/1,030 (89.8%)	92/103 (89.3%)	p = 0.877	1.59
Dyslipidemia	862/1,030 (83.7%)	86/103 (83.5%)	p = 0.960	0.52
Family History of Premature CAD	197/1,030 (19.1%)	19/103 (18.4%)	p = 0.867	1.74
Prior MI	406/1,030 (39.4%)	42/103 (40.8%)	p = 0.788	2.77
Prior Heart Failure	214/1,030 (20.8%)	22/103 (21.4%)	p = 0.890	1.43
Prior PCI	447/1,030 (43.4%)	46/103 (44.7%)	p = 0.805	2.54
Prior CABG	259/1,030 (25.1%)	27/103 (26.2%)	p = 0.812	2.44
Cerebrovascular Disease	258/1,030 (25.0%)	25/103 (24.3%)	p = 0.862	1.80
Peripheral Arterial Disease	282/1,030 (27.4%)	29/103 (28.2%)	p = 0.866	1.73
Chronic Lung Disease	210/1,030 (20.4%)	21/103 (20.4%)	p = 1.000	0
Diabetes Mellitus	440/1,030 (42.7%)	44/103 (42.7%)	p = 1.000	0
CAD Presentation				
No angina	24/1,030 (2.3%)	2/103 (1.9%)	p = 0.802	2.69
Symptom unlikely to be ischemic	18/1,030 (1.7%)	2/103 (1.9%)	p = 0.886	1.44
Stable angina	95/1,030 (9.2%)	10/103 (9.7%)	p = 0.871	1.66
Unstable angina	434/1,030 (42.1%)	43/103 (41.7%)	p = 0.939	0.79
NSTEMI	254/1,030 (24.7%)	26/103 (25.2%)	p = 0.896	1.35
STEMI	205/1,030 (19.9%)	20/103 (19.4%)	p = 0.906	1.22
PCI Status				
Elective	350/1,030 (34.0%)	36/103 (35.0%)	p = 0.843	2.04
Urgent	481/1,030 (46.7%)	48/103 (46.6%)	p = 0.985	0.19
Emergency	199/1,030 (19.3%)	19/103 (18.4%)	p = 0.830	2.23
PCI Indication				
Immediate PCI for STEMI	156/1,030 (15.1%)	16/103 (15.5%)	p = 0.917	1.08
PCI for STEMI (Unstable, >12 hours from symptom onset)	49/1,030 (4.8%)	4/103 (3.9%)	p = 0.689	4.30
PCI for high risk NSTEMI or unstable angina	581/1,030 (56.4%)	59/103 (57.3%)	p = 0.865	1.76
Staged PCI	9/1,030 (0.9%)	1/103 (1.0%)	p = 0.920	1.02
Other	235/1,030 (22.8%)	23/103 (22.3%)	p = 0.911	1.16
Heart Failure within two weeks	193/1,030 (18.7%)	19/103 (18.4%)	p = 0.942	0.75
Cardiomyopathy or left ventricular systolic dysfunction	124/1,030 (12.0%)	13/103 (12.6%)	p = 0.863	1.77
Cardiogenic Shock at start of PCI	50/1,030 (4.9%)	5/103 (4.9%)	p = 1.000	0
Pre-Procedure Hemoglobin	12.73 ± 1.80	12.73 ± 1.71	p = 0.975	0.32

CAD: coronary artery disease, MI: myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary artery bypass grafting, NSTEMI: non-ST segment elevation myocardial infarction, STEMI: ST segment elevation myocardial infarction

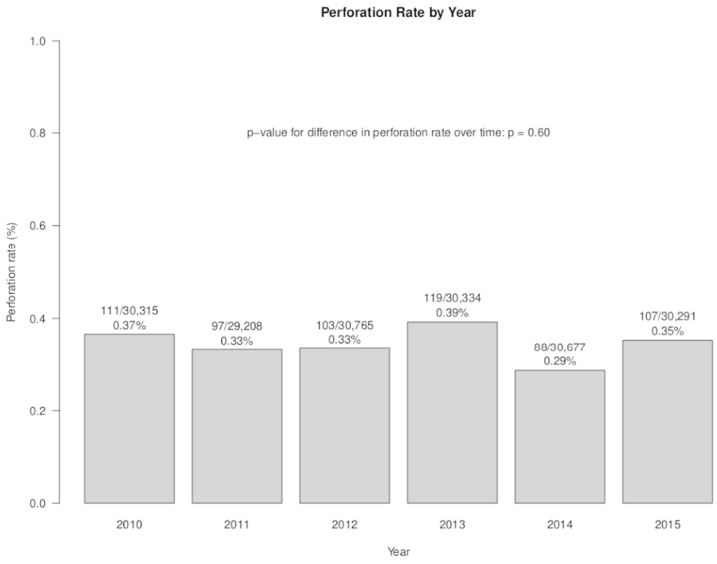
Supplementary Table 3: Baseline mean predicted risks, outcomes, and adjusted odds ratios of patients with and without coronary artery perforation

	Estimated baseline risk of death	Estimated baseline risk of CI-AKI	Estimated baseline risk of transfusion
No Perforation	1.51%	2.70%	2.94%
Perforation	2.54%	3.28%	4.09%
p-value	p = .001	p = .026	p < .001
	Mortality	CI-AKI incidence	Transfusion incidence
No Perforation	1.50%	2.68%	2.91%
Perforation	6.56%	7.95%	12.64%
Overall rate:	1.52%	2.70%	2.95%
O/E ratio:	Death	CI-AKI	Transfusion
No Perforation	0.99	0.99	0.99
Perforation	2.58	2.42	3.09
Adjusted OR	5.00 (95% CI 3.42 – 7.31)	3.25 95% CI 2.30 – 4.58)	5.26 (95% CI 4.03-6.87)
p-value:	p < .001	p < .001	p < .001

OR=odds ratio, CI-AKI=contrast-induced acute kidney injury, CI=confidence interval, O/E = observed/expected

Supplementary Figure 1: Overall incidence of CAP, proportion of PCI performed for treatment of CTO and incidence of CAP among CTO cases over a 5 year period

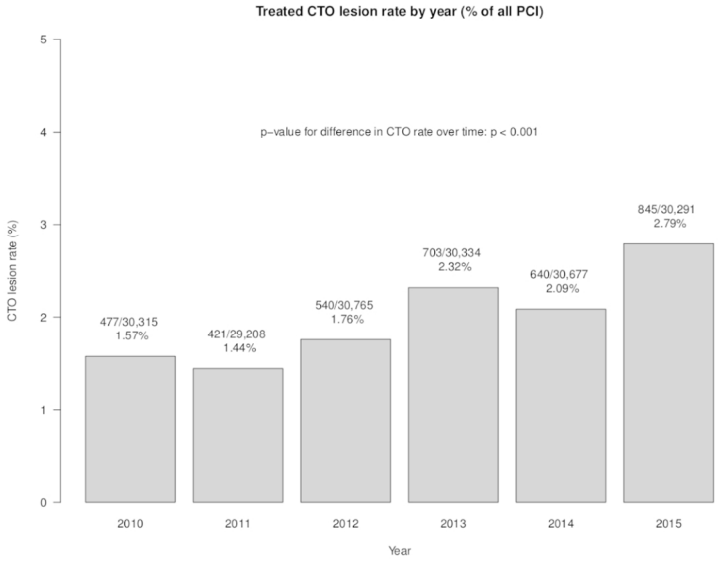
Supplementary Figure 1A: Perforation rate by year



1A-C: Overall incidence of CAP, proportion of PCI performed for treatment of CTO and incidence of CAP among CTO cases over a 5-year period
Supplementary Figure 1A: Perforation rate by year

127x112mm (300 x 300 DPI)

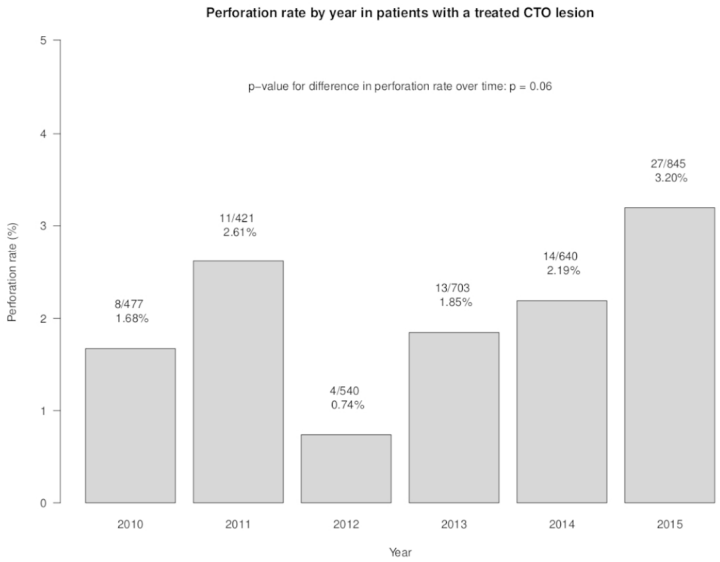
Supplementary Figure 1B: Treated CTO lesion rate by year



1A-C: Overall incidence of CAP, proportion of PCI performed for treatment of CTO and incidence of CAP among CTO cases over a 5-year period
Supplementary Figure 1B: Treated CTO lesion rate by year

127x99mm (300 x 300 DPI)

Supplementary Figure 1C: Perforation rate by year in patients with a treated CTO lesion



CAP: coronary artery perforations, PCI: percutaneous coronary interventions, CTO: chronic total occlusions

1A-C: Overall incidence of CAP, proportion of PCI performed for treatment of CTO and incidence of CAP among CTO cases over a 5-year period
Supplementary Figure 1C: Perforation rate by year in patients with a treated CTO lesion

127x109mm (300 x 300 DPI)

Subject: JINT041916-0818 Decision Letter

"Coronary Artery Perforations after Contemporary Percutaneous Coronary Interventions: Evaluation of Incidence, Risk Factors, Outcomes and Predictors of Mortality"

Dear Dr. Gurm,

Thank you for your recent manuscript submission to JACC: Cardiovascular Interventions. Unfortunately, after careful consideration by the editors and by expert external reviewers, the consensus is that its priority is not sufficient to warrant publication.

The comments of the reviewers are enclosed for your information.

We recognize the thought and effort that went into your work. Regrettably, we are able to publish less than one-fifth of the papers we receive, and must decline many of considerable merit. Thank you for your interest in the journal, and we look forward to reviewing other submissions from you in the future.

Sincerely,

Spencer B. King III, MD, MACC
Editor-in-Chief
JACC: Cardiovascular Interventions
Heart House, 2400 N Street NW, Washington, DC, 20037
Ph: 202-375-6136
Fax: 202-375-6819
Email: jaccint@acc.org

Associate Editor (Comments for the Author):

There are discrepancies in your numbers and percentages. These should all be reviewed and reconciled.

Reviewer #1 (Comments for the Author (Required)):

The authors submit and interesting retrospective analysis of coronary perforation from a very large database. Perhaps they would consider whether attention to the following might strengthen their paper:

1. Please clarify some numbers: in the results section you state that 563 patients, or 0.37% of all PCI cases during the enrollment window, had a coronary performation. In the discussion you state that your paper 'adds...more than 600 patients with CAP' (pg 10) and on pg 9 you state that 'the incidence of CAP in our population was 0.67%'. Why do these numbers differ?

2. I understand the limitations of a retrospective database study such as this in gathering more granular data but such is tremendously important to interventionalists. For starts, who entered the data into the database and what source documentation was used?

3. You suggest that additional data might be sampled, could not the procedure reports be gathered? Could claims data be used to determine if pericardiocentesis and or cardiac surgery was performed during the index hospitalization?

4. The observation that less than 10% of the patients received a covered stent suggests that most of perforations identified might have been more 'incidental' than life threating. Of course there are cases, especially CTO procedures using epicardial collaterals in which a covered stent might not be deliverable. When you say covered stents were utilized does this imply that the device was actually deployed successfully or migh it also include when such a stent was asked for and taken out of the box but never successfully deployed?

5. Can you provide data as to how many of the patients died on the same day as the index procedure?

Reviewer #2 (Comments for the Author (Required)):

The study by Parsh et al is a retrospective report from the BCBS PCI database of Michigan. The authors sought to evaluate the incidence, clinical predictors, and in hospital prognosis of pts undergoing PCI who had coronary perforations (CAP). The authors observed an incidence of 0.63%, with PCI of CTO as the strongest predictor of CAP. CAP was also associated with higher rates of transfusion, AKI, and death. This represents one of the largest contemporary registry reports of CAP, and is thus of potential interest. There are a few issues that merit discussion:

1. The Ellis classification of CAP has been shown to correlate with adverse outcomes, with class I CAP having a more benign outcome. Although the authors acknowledge this as a limitation this study would be strengthened by stratifying outcomes and predictors using the Ellis classification.

2. In the absence of more detailed lesion characteristics such as extent of calcification, lesion length, reference diameters etc evaluating clinical and limited procedural characteristics and their influence on CAP and outcomes is potentially biased. Including known important lesion characteristics would substantially strengthen the study (not sure why this information is not available since one would assume most sites also participate in the NCDR which does collect this type of information).

Associate Editor:

There are discrepancies in your numbers and percentages. These should all be reviewed and reconciled.

We apologize for these errors. All numbers have been verified from the original data and then corrected in the manuscript. In addition, our data has been updated to include all patients undergoing PCI in the state of Michigan from January 2010 and December 2015.

Page 11:

The incidence of CAP in our population was 0.34%, confirming that CAP remains an uncommon event.

Page 11:

Our study adds to the existing literature by identifying more than 600 patients with CAP.

Reviewer #1

The authors submit and interesting retrospective analysis of coronary perforation from a very large database. Perhaps they would consider whether attention to the following might strengthen their paper:

1. Please clarify some numbers: in the results section you state that 563 patients, or 0.37% of all PCI cases during the enrollment window, had a coronary perforation. In the discussion you state that your paper 'adds...more than 600 patients with CAP' (pg 10)

and on pg 9 you state that 'the incidence of CAP in our population was 0.67%'. Why do these numbers differ?

We again apologize for these errors. As noted above in response to the associate editor comments, all numbers have been verified.

2. I understand the limitations of a retrospective database study such as this in gathering more granular data but such is tremendously important to interventionalists. For starts, who entered the data into the database and what source documentation was used?

The data collected by the BMC2 collaborative registry is abstracted by trained personnel at the individual member hospitals directly from the medical record and is subject to periodic random audit of 2% of cases, and 100% audit of all cases resulting in mortality.

3. You suggest that additional data might be sampled, could not the procedure reports be gathered? Could claims data be used to determine if pericardiocentesis and or cardiac surgery was performed during the index hospitalization?

The BMC2 registry does collect data on whether coronary artery bypass grafting was performed during admission and we have added this data to the manuscript. Performance of pericardiocentesis is not recorded and procedure reports are not available for further review.

Page 8:

Of the 625 patients who developed CAP, 22 (3.52%) underwent post-procedural CABG, of which 2 (9.90%) died prior to discharge.

4. The observation that less than 10% of the patients received a covered stent suggests that most of perforations identified might have been more 'incidental' than life threating. Of course there are cases, especially CTO procedures using epicardial collaterals in which a covered stent might not be deliverable. When you say covered stents were utilized does this imply that the device was actually deployed successfully or might it also include when such a stent was asked for and taken out of the box but never successfully deployed?

We appreciate the reviewer's comment and would like to clarify the coding of covered stents in the BMC2 registry. Per the coder dictionary, when the use of a covered stent is recorded, this refers only to cases where covered stents were actually deployed (and not merely taken out of the box). We have clarified this as follows:

Page 10:

Of the 625 cases of CAP, covered stents were successfully deployed in 70 (11.2%). Of the 70 CAP cases where covered stents were used, 12 (17.1%) patients died versus 29 deaths (5.23%) among 555 patients where covered stents were not utilized.

5. Can you provide data as to how many of the patients died on the same day as the index procedure?

We appreciate the reviewer's suggestion to include this data.

Page 9:

Thirteen of the 41 perforation deaths (31.7%) occurred in the catheterization lab, and 20 deaths occurred on the same calendar date as the index PCI procedure (48.8%).

Reviewer #2

The study by Parsh et al is a retrospective report from the BCBS PCI database of Michigan. The authors sought to evaluate the incidence, clinical predictors, and in hospital prognosis of pts undergoing PCI who had coronary perforations (CAP). The authors observed an incidence of 0.63%, with PCI of CTO as the strongest predictor of CAP. CAP was also associated with higher rates of transfusion, AKI, and death. This represents one of the largest contemporary registry reports of CAP, and is thus of potential interest. There are a few issues that merit discussion:

1. The Ellis classification of CAP has been shown to correlate with adverse outcomes, with class I CAP having a more benign outcome. Although the authors acknowledge this as a limitation this study would be strengthened by stratifying outcomes and predictors using the Ellis classification.

We appreciate the reviewer's comments and we do acknowledge that lack of data on Ellis classification of CAP is a limitation of our study. Going forward, there is interest in integrating Ellis classification into the BMC2 database as this would allow for more robust investigation of CAP.

2. In the absence of more detailed lesion characteristics such as extent of calcification, lesion length, reference diameters etc evaluating clinical and limited procedural characteristics and their influence on CAP and outcomes is potentially biased. Including known important lesion

characteristics would substantially strengthen the study (not sure why this information is not available since one would assume most sites also participate in the NCDR which does collect this type of information).

We appreciate the reviewer's comments. We have extended our analysis to include lesions characteristic information that is available through our BMC2 database. In addition to investigating the risk of CAP in treated chronic total occlusions and type C lesions, risk of CAP in bifurcation lesions and lesions with thrombus was studied and is presented in Table 2.

Page 17:

Table 2: Perforations by device type and type of coronary lesion

	Percent of cases where device was used or lesion variable present	Perforation rate in cases with device or lesion variable	Perforation rate in cases without device or lesion variable	Odds Ratio	P-value (Fisher exact test)
Intracoronary device type					
Thrombectomy	5.67%	0.31%	0.33%	0.940	0.850
Cutting Balloon	4.92%	0.42%	0.32%	1.301	0.155
Atherectomy	1.03%	0.98%	0.32%	3.051	< 0.001
Bare Metal Stent	17.69%	0.32%	0.33%	0.952	0.731
Drug Eluting Stent	72.13%	0.26%	0.50%	0.524	< 0.001
Extraction Catheter	3.51%	0.18%	0.33%	0.535	0.043
Embolic Protection	2.10%	0.42%	0.33%	1.281	0.357
Laser	0.13%	2.82%	0.33%	8.876	< 0.001
Type of coronary lesion					
Chronic Total Occlusion	1.91%	1.91%	0.30%	6.514	< 0.001
Type C lesion	56.62%	0.36%	0.29%	1.242	0.017
Thrombus Present	15.91%	0.26%	0.34%	0.761	.036
Bifurcation Lesion	5.67%	0.31%	0.33%	0.940	0.850

Coronary Artery Perforations after Contemporary Percutaneous Coronary Interventions: Evaluation of Incidence, Risk Factors, Outcomes and Predictors of Mortality

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Word count: 5956

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Abstract

Objectives: We sought to evaluate the incidence, risk factors, in-hospital and long term outcomes and predictors of mortality of coronary artery perforations (CAP) in the contemporary percutaneous coronary intervention (PCI) era.

Background: CAP is a rare but serious complication of PCI associated with increased risk of morbidity and mortality.

Methods: We included 181,590 procedures performed across 47 hospitals in Michigan from 1/1/2010-12/31/2015. Endpoints evaluated included the incidence of CAP and its association with in-hospital outcomes. Logistic regression analysis was utilized to determine independent risk factors for CAP and to examine whether the effect of CAP on mortality varied by gender.

Results: CAP occurred in 625 (0.34%) of patients. Independent predictors for CAP included older age, peripheral arterial disease, presence of left ventricular dysfunction or cardiomyopathy, lower body mass index, pre-PCI insertion of a mechanical ventricular support device, treatment of complex lesions (Type C), and treatment of chronic total occlusions, the latter of which was the strongest predictor of perforation (adjusted odds ratio 7.01, $p < 0.001$). After adjusting for baseline risk, the incidence of adverse outcomes remained substantially greater in patients with a perforation, with an adjusted odds ratio estimate of 5.00 for mortality (95% CI 3.42-7.31), 3.25 for acute kidney injury (95% CI 2.30-4.58), and 5.26 for transfusion (95% CI 4.03-6.87) (all $p < 0.001$). Perforation was associated with a higher mortality in women than men (interaction p-value = 0.01).

Conclusions: CAP is a rare complication but is associated with high morbidity and mortality especially in women. Further investigation is warranted to determine why women fare worse after CAP.

Condensed Abstract

In this retrospective study including 181,590 PCI procedures performed in the state of Michigan, treatment of CTO was the strongest independent predictor of CAP. Development of CAP was associated with increased risk of inpatient and long term mortality, transfusion and acute kidney injury. We also found that women fare worse than men after development of CAP with a greater risk of inpatient mortality. Further prospective investigation is required to further identify risk factors for the poor prognosis after CAP, the etiology of possible gender discrepancies in outcomes and to assess the efficacy of various treatment options for CAP.

Key words: perforation, gender, mortality

Abbreviations:

1. CAP: Coronary artery perforations
2. PCI: percutaneous coronary interventions
3. CABG: coronary artery bypass grafting
4. CTO: Chronic total occlusion
5. BMC2: Blue Cross Blue Shield of Michigan Cardiovascular Consortium
6. MVC: Michigan Value Collaborative
7. BCBSM: Blue Cross Blue Shield of Michigan
8. CI-AKI: Contrast-induced acute kidney injury
9. IABP: intra-aortic balloon pump
10. STEMI: ST-segment elevation myocardial infarction

Introduction

The incidence of coronary artery perforation (CAP) during percutaneous coronary interventions (PCI) is estimated at 0.1% to 0.84%.[1] Although rare, CAP is associated with an increased risk of adverse outcomes including tamponade, myocardial infarction, need for emergency coronary artery bypass grafting (CABG), and death.[2-4] The majority of studies thus far have included a modest number of patients and it is unclear which pre-procedural patient factors are associated independently with an increased risk of CAP as well as which factors increase the risk of adverse outcomes after CAP. In addition, given improvement of equipment and therapies, advancing age of the population and changing guidelines, PCI utilization in certain higher risk subgroups, including the elderly or those with chronic total occlusions (CTO), has been increasing.[5-8] This study represents a large cohort of patients developing CAP after PCI and provides an updated analysis of the incidence, risk factors, and inpatient and long term outcomes associated with CAP in contemporary practice.

Methods

We included data from patients undergoing PCI at 47 hospitals participating in the Blue Cross Blue Shield of Michigan Cardiovascular Consortium (BMC2). The details of the BMC2 registry and its data collection and auditing process have been described previously.[9] Briefly, procedural data on all patients undergoing PCI at participating hospitals are collected using standardized data collection forms. Baseline data include clinical, demographic, procedural, and angiographic characteristics as well as medications used before, during, and after the procedure, and in-hospital outcomes. All data elements have been prospectively defined, and the protocol is approved by local institutional review boards at each hospital. In addition to a random audit of 2% of all cases, medical records of all patients undergoing multiple procedures or coronary artery bypass grafting and of patients who died in the hospital are reviewed routinely to ensure data accuracy.

The study population for this analysis included all consecutive patients who underwent PCI between January 2010 and December 2015. If a patient underwent more than one PCI

procedure during a hospital stay, only procedural data reflecting the earliest procedure is included in this analysis. For a subset of Medicare beneficiaries in the dataset, 90-day readmission and long term survival data were available through indirect matching on admission, discharge and procedure dates for the index hospitalization, patient gender and date of birth, and hospital and operator NPI numbers with Medicare data for PCI episodes in collaboration with the Michigan Value Collaborative (MVC).[10, 11]

Study endpoints

Inpatient mortality was defined as mortality from any cause during the initial hospitalization following PCI. Contrast-induced acute kidney injury (CI-AKI) was defined as an increase in pre-procedural to post-procedural serum creatinine ≥ 0.5 mg/dl, since this definition has been strongly associated with inpatient mortality and new requirement for dialysis.[12] Pre-procedural serum creatinine values were measured within 30 days prior to PCI, with the value closest to time of PCI chosen as the baseline value. Peak post-procedural serum creatinine was defined as the highest value after PCI and prior to the next procedure or discharge.

Statistical analysis

Univariate comparisons were performed using student T-tests for continuous measures, and Fisher exact tests for dichotomous measures. The Cochrane-Armitage trend test was used to assess whether the rate of CAP and the rate of treatment of CTO lesions changed over time. Multivariate logistic regression with stepwise variable selection using Akaike Information Criteria was utilized to identify pre-procedural clinical and demographic patient characteristics associated with the development of CAP. Patient characteristics included as candidate predictors were chosen based on both significant univariate differences as well as associations with CAP observed in previous studies.[1-3]

Pre-procedural patient risk of in-hospital outcomes including mortality, transfusion, and CI-AKI were estimated using the current BMC2 random Forest risk models from baseline patient clinical and demographic characteristics. The models are implemented for patient pre-procedural

risk prediction, and model inputs are described at the SCAI/BMC2 PCI online risk prediction tool available at both the BMC2 https://bmc2.org/calculators/multi and SCAI http://www.scai.org/PCIRiskAssessmentTools/default.aspx websites.[13-16] Risk adjusted mortality, transfusion, and CI-AKI rates were estimated for sub-groups by the overall collaborative outcome incidence multiplied by the ratio of observed to expected outcome rates for the subgroup (overall rate * O/E ratio for subgroup).

The association of CAP with adverse outcomes of inpatient mortality, need for transfusion and development of CI-AKI was assessed using multivariate logistic regression models adjusting for baseline patient risk. To assess whether the effect of CAP on outcomes potentially varied by gender, likelihood ratio tests were utilized to determine whether inclusion of a gender by CAP interaction term significantly improved model fit.

In the subset of Medicare patients for which long term survival data was available, propensity score matching was employed to account for baseline patient clinical and demographic variables that could confound the analysis of the impact of CAP on post-discharge survival. Logistic regression was utilized to construct the propensity score, and each CAP patient was matched to 10 similar non-CAP cases without replacement using a greedy algorithm. Variables included in the propensity score model and comparison of the cohorts are included in Supplementary Table 1 and 2. Kaplan-Meier incidence curves were used to visualize post discharge survival by group, and Cox proportional hazard regression was utilized to assess differences in survival between groups.

Results

Baseline demographics and clinical characteristics

Between January 2010 and December 2015, 181,590 patients underwent PCI in the state of Michigan and were included in this analysis. Of these patients, 625 (0.34%) suffered CAP during the PCI procedure, and 41 (6.56%) patients with perforation died prior to discharge. The rate of perforation overall was relatively stable over the 6 years included in the analysis

(Supplementary Figure 1A). The proportion of PCI cases where a CTO lesion was treated increased in statistically significant fashion over this same 6-year period, from 1.6% to 2.8% of all cases (Cochran Armitage trend test p value < 0.001), while the incidence of perforation among the subgroup of CTO cases did not demonstrate a statistically significant trend (Cochrane Armitage trend test p-value=0.06) (Supplementary Figure 1B-C).

Baseline clinical, demographic and procedural characteristics for patients with and without perforation are provided in Table 1. Patients with CAP were older, more likely to be female, have peripheral arterial disease or heart failure, require intra-aortic balloon pump (IABP) or other mechanical ventricular support prior to PCI, and to be in cardiogenic shock at the start of the procedure compared to those without CAP. Conversely, patients with perforations were less likely to have diabetes.

Of the 625 patients who developed CAP, 22 (3.52%) underwent post-procedural CABG, of which 2 (9.90%) died prior to discharge.

Association of CAP with intracoronary devices and coronary lesion variables

Among the 625 cases of CAP, 524 (83.8%) involved only one treated vessel and these cases were utilized to examine the association of CAP with specific devices or coronary lesion variables (Table 2). Lesion length was significantly longer in vessels that developed CAP (29.24 ± 13.46 mm) compared to those without CAP (23.74 ± 13.46 mm) (p-value<0.001). The use of atherectomy and laser were each associated with significantly higher rates of CAP with odds ratio of 3.05 and 8.88, respectively (both p<0.001). When analyzing the treatment of specific coronary lesion variables, CAP occurred in 1.91% of patients with a treated CTO lesion compared to only 0.3% of patients without CTO, and a CTO PCI was the strongest univariate predictor of increased risk of CAP (odds ratio 6.51, Fisher Exact test p-value < 0.001).

Predictors of CAP

Multivariate stepwise logistic regression identified older age, peripheral arterial disease, presence of left ventricular dysfunction or cardiomyopathy, treatment of high complexity (type

C) lesions, treatment of CTO, and use of a mechanical ventricular support prior to PCI as predictors of CAP (Table 3). Treatment of CTO remained associated with the greatest estimated risk of CAP after adjusting for other covariates, with patients treated for CTO having a seven-fold greater odds of developing CAP, odds ratio 7.01 (95% CI 5.48 – 8.98; p – value < 0.001). Greater height, higher body mass index and presence of diabetes were associated with a lower risk for the development of CAP.

In-hospital outcomes

Mean baseline risk estimates and outcomes of patients with and without perforations are provided in Supplementary Table 3. Mean predicted risks were significantly higher in patients with perforation, reflecting a greater burden of comorbidites in these patients. After adjusting for baseline predicted risk in a logistic regression model, patients with perforations remained at a substantially higher risk of adverse outcomes, with an adjusted odds ratio estimate of 5.00 (95% CI 3.42 – 7.31) for mortality, 3.25 (95% CI 2.30 – 4.58) for CI-AKI, and 5.26 (95% CI 4.03 – 6.87) for transfusion (all p < 0.001).

Predictors of in-hospital mortality

Table 4 provides a comparison of baseline and procedural patient characteristics of patients with CAP who died during the hospitalization and those discharged alive. Among the 41 patients that died, multiple pre-procedural patient characteristics, clinical presentations, procedural outcomes and complications occurred more frequently including: older age, female gender, ST-segment elevation myocardial infarction (STEMI) presentation, recent heart failure, cardiogenic shock or cardiac arrest, and pre-PCI insertion of IABP or other mechanical ventricular support. Of the 41 perforation patients who died, 29 (70.7%) were female, compared to only 40.1% of those discharged alive (p <0.001). Thirteen of the 41 perforation deaths (31.7%) occurred in the catheterization lab, and 20 deaths occurred on the same calendar date as the index PCI procedure (48.8%).

Figure 1 (a, b and c) provides risk adjusted mortality, CI-AKI, and transfusion rates for subgroups defined by gender and perforation. The effect of CAP on mortality was significantly greater in women compared to men when assessed by multivariate logistic regression model (gender by perforation interaction p-value = 0.01). No significant CAP by gender interaction was observed for the CI-AKI (p = 0.32) or transfusion (p = 0.50).

Subsequent analysis stratified by gender demonstrated a statistically significant increase in mortality with CAP in both men with adjusted OR=2.70 (95% CI: 1.37 - 5.30; p-value = 0.004) and women with an OR= 7.32 (95% CI: 4.60 – 11.65; p<0.001). By contrast, no significant weight by CAP interaction was observed in the mortality model (p = 0.80), indicating no significant evidence that the relationship between CAP and mortality varied across the spectrum of patient weights

Of the 625 cases of CAP, covered stents were successfully deployed in 70 (11.2%). Of the 70 CAP cases where covered stents were used, 12 (17.1%) patients died versus 29 deaths (5.23%) among 555 patients where covered stents were not utilized. After adjusting for predicted risk of death in logistic regression, the odds ratios for inpatient mortality for cases of CAP treated with covered stents vs. no covered stent was 4.46 (p < 0.001) likely related to the fact that covered stent use is reserved for perforations that are more likely to be hemodynamically significant.

Long term outcomes

Using propensity score matching, 1,030 Medicare patients without CAP having similar baseline clinical and demographic characteristics to the 103 available Medicare patients with CAP (Supplementary Tables 1 and 2) were selected. Median post-discharge follow-up in this cohort was 23 months for both groups, with 34 (33.0%) deaths observed among CAP patients, and 205 (19.9%) deaths among non-CAP patients during follow up. Kaplan-Meier survival curves with confidence band shading are provided in Figure 2. In Cox proportional hazards regression, CAP was associated with significantly greater mortality (HR = 1.63, p = .008). In

contrast to in-hospital mortality, no significant gender by CAP interaction was observed in Cox regression (p = 0.430), and women and men with CAP had comparable estimated mortality at 2 years (men 31.1% (95% CI 14.4% - 44.6%), women 23.6% (95% CI 10.2% - 35.0%)). No significant difference was observed for 90-day readmission (30.1% for CAP, 23.8% no CAP, p = 0.185)

Discussion

This study includes one of the largest patient cohorts describing the risk of CAP during PCI in contemporary practice. The incidence of CAP in our population was 0.34%, confirming that CAP remains an uncommon event. However, the high in-hospital mortality rate of 6.56% confirms the associated high mortality and highlights the need for further investigation into understanding risk factors, outcomes and potential therapies for this serious complication.

Small retrospective studies have identified various patient and angiographic characteristics as potential risk factors for CAP including older age, female gender, presence of chronic kidney disease, hypertension, and previous PCI or CABG as well as angiographic characteristics such as type C lesions, chronic total occlusions, calcified lesions, and culprit lesions in the right coronary artery.[1-4] In addition, certain procedural characteristics including a higher balloon to artery ratio and the use of atheroablative devices were shown in these limited studies to increase the risk of this serious event.[1, 3, 4]

Our study adds to the existing literature by identifying more than 600 patients with CAP. Some factors that have been suggested to be associated with CAP were not found to be independently associated with CAP in this large study, including hypertension, chronic kidney disease and prior coronary artery bypass grafting.[3, 4] However, consistent with prior studies, our analysis identified several patient and procedural characteristics as independent risk factors for CAP, including older age and treatment of chronic total occlusions.[2-4] In fact, treatment of CTO was the strongest risk factor for CAP development, which is an important consideration as

recently there has been an increasing interest in treatment of these higher risk lesions as techniques and technology have improved.

Consistent with prior work, we found CAP to be associated with an increased risk of in-hospital mortality.[1, 2] However, we also identified that CAP was associated with increased risk of long term mortality and with other adverse in-hospital outcomes, including development of CI-AKI and the need for transfusion. Possible mechanisms to explain the increased risk of CI-AKI and need for transfusion include hemodynamic compromise related to development of complications of tamponade or myocardial infarction as well as need for additional procedures or surgical repair.

Our study also demonstrated that the effect of CAP on mortality may vary by gender with our results indicating that perforation is significantly more deleterious in women than men. The etiology of the increased risk of death in women with CAP is unknown but potentially relates to anatomical or hormonal differences between sexes. One hypothesis relates to a presumed smaller vessel diameter or differences in vessel wall thickness size in women that could increase the risk of development of CAP and/or higher grades of CAP.[17] The influence of estrogen on coagulation factors and inflammatory markers has been proposed as a mechanism to explain the increased susceptibility for vascular injury. Our study did not examine the influence of smaller vessel size on the development of CAP, since the BMC2 database does not include information on vessel diameter.

The manner in which CAP is treated is dependent on the severity of the CAP, often graded by Ellis type classification, and whether certain complications associated with CAP, such as tamponade, are present.[18] Potential therapies include the use of prolonged balloon occlusion, deployment of covered stents, thrombin or gelfoam embolization, coils or CABG. We found that covered stents were utilized in the minority of patients with CAP, however these patients experienced higher rates of inpatient mortality. We hypothesize that this is related to the use of these therapies in more severe cases of CAP and that the worse outcomes in these patients are

related to this underlying higher grade perforation than the use of the covered stent itself. However, there is also evidence that covered stents are at higher risk for restenosis and thrombosis.[19] We do not have data on the exact reason why these patients died and further investigation into optimal treatment of CAP is needed.

There are several limitations to our study. First, our study was a retrospective analysis utilizing data from a large database which does not include details on the severity of CAP (such as Ellis type classification) or vessel size, which would be important to examine when attempting to identify the etiology of the potentially worse prognosis of CAP in women than men. In addition, various outcomes that may develop after CAP, including tamponade, need for emergency surgery or subsequent development of MI, could not be evaluated in our population based on database restrictions. Evaluating incidence and efficacy of various treatments for CAP was limited to assessing the use of covered stents in our population with CAP.

In conclusion, CAP remains an uncommon but serious complication of PCI, associated with an increased incidence of inpatient mortality, CI-AKI and need for transfusion as well as long term mortality. Treatment of CTO lesions was the strongest independent predictor of CAP. Coronary artery perforations were more harmful in women than men in our study. Further investigation into the etiology of the poorer prognosis of CAP in women as well as efficacy of various therapies to treat CAP is needed.

Tables and Figures

Table 1: Patient characteristics of patients with and without coronary artery perforation

Table 2: Perforations by device type and type of coronary lesion

Table 3: Independent adjusted risk factors for the development of coronary artery perforations

Table 4: Characteristics of patients with coronary artery perforations who were discharged alive versus deceased

Figure 1: Risk adjusted mortality, transfusion and contrast-induced acute kidney injury (CI-AKI) rates for subgroups defined by gender and perforation

1A. Risk adjusted mortality associated with coronary perforation in men and women
1B. Risk adjusted transfusion associated with coronary perforation in men and women
1C. Risk adjusted CI-AKI associated with coronary perforation in men and women

Figure 2: Long term mortality of propensity matched patients with and without coronary artery perforation among those discharged alive after PCI.

Supplementary Tables and Figures

Supplementary Table 1: Covariates included in propensity matching of patients with and without coronary artery perforation

Supplementary Table 2: Comparison of propensity matched cohorts of patients with and without coronary artery perforation

Supplementary Table 3: Baseline mean predicted risks, outcomes, and adjusted odds ratios of patients with and without coronary artery perforation

Supplementary Figure 1A-C: Overall incidence of CAP, proportion of PCI performed for treatment of CTO and incidence of CAP among CTO cases over a 5-year period

Supplementary Figure 1A: Perforation rate by year
Supplementary Figure 1B: Treated CTO lesion rate by year
Supplementary Figure 1C: Perforation rate by year in patients with a treated CTO lesion

Acknowledgments

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Table 1: Characteristics of patients with and without coronary artery perforation

Characteristic	Coronary Perforation – no. (%)		p-value
	No N = 180,965	Yes N = 625	
Demographic			
Age (years) ± SD	65.08 ± 12.02	67.35 ± 12.04	p < 0.001
Female gender	60,349 (33.3%)	263 (42.1%)	p < 0.001
Current or recent smoker	52,677 (29.1%)	177 (28.4%)	p = 0.696
Height (cm)	171.15 ± 10.59	168.95 ± 10.86	p < 0.001
Weight (kg)	89.70 ± 21.43	84.21 ± 19.84	p < 0.001
Historical			
Hypertension	154,589 (85.5%)	553 (88.8%)	p = 0.019
Dyslipidemia	148,315 (82.0%)	516 (82.7%)	p = 0.668
Diabetes Mellitus	69,556 (38.4%)	221 (35.4%)	p = 0.113
Peripheral Arterial Disease	29,069 (16.1%)	126 (20.2%)	p = 0.005
Prior MI	63,507 (35.1%)	244 (39.0%)	p = 0.039
Prior PCI	82,465 (45.6%)	294 (47.0%)	p = 0.464
Prior CABG	33,415 (18.5%)	136 (21.8%)	p = 0.034
Cardiomyopathy or Left Ventricular Systolic Dysfunction	19,177 (10.6%)	91 (14.6%)	p = 0.001
Procedural			
PCI Status: Elective	66,218 (36.6%)	237 (38.0%)	p = 0.478
PCI Status: Urgent	83,790 (46.3%)	287 (46.0%)	p = 0.868
PCI Status: Emergency	30,498 (16.9%)	96 (15.4%)	p = 0.325
PCI Status: Salvage	364 (0.2%)	4 (0.6%)	p = 0.015
Arterial Access Site: Radial	37,473 (20.7%)	123 (19.7%)	p = 0.538
Pre-PCI insertion of IABP or other mechanical ventricular support device	2,467 (1.4%)	25 (4.0%)	p < 0.001
Pre-PCI Left Ventricular Ejection Fraction ± SD	51.90 ± 12.84	49.89 ± 14.42	p = 0.003
Cardiogenic Shock at Start of PCI	3,765 (2.1%)	24 (3.8%)	p = 0.002

SD: standard deviation, MI: myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary artery bypass grafting, IABP: intraaortic balloon pump

Table 2: Perforations by device type and type of coronary lesion

	Percent of cases where device was used or lesion variable present	Perforation rate in cases with device or lesion variable	Perforation rate in cases without device or lesion variable	Odds Ratio	P-value (Fisher exact test)
Intracoronary device type					
Thrombectomy	5.67%	0.31%	0.33%	0.940	0.850
Cutting Balloon	4.92%	0.42%	0.32%	1.301	0.155
Atherectomy	1.03%	0.98%	0.32%	3.051	< 0.001
Bare Metal Stent	17.69%	0.32%	0.33%	0.952	0.731
Drug Eluting Stent	72.13%	0.26%	0.50%	0.524	< 0.001
Extraction Catheter	3.51%	0.18%	0.33%	0.535	0.043
Embolic Protection	2.10%	0.42%	0.33%	1.281	0.357
Laser	0.13%	2.82%	0.33%	8.876	< 0.001
Type of coronary lesion					
Chronic Total Occlusion	1.91%	1.91%	0.30%	6.514	< 0.001
Type C lesion	56.62%	0.36%	0.29%	1.242	0.017
Thrombus Present	15.91%	0.26%	0.34%	0.761	.036
Bifurcation Lesion	5.67%	0.31%	0.33%	0.940	0.850

Table 3: Predictors of coronary artery perforation selected by stepwise logistic regression.

	Odds Ratio	P-value	95% Confidence Interval
Age (per 5 year increase)	1.05	0.005	1.015-1.089
Height (per 5 cm increase)	0.91	< 0.001	0.872-0.941
BMI (per 1 unit increase)	0.98	0.001	0.965-0.991
PAD	1.21	0.064	0.989-1.483
Diabetes	0.86	0.090	0.723-1.024
Cardiomyopathy or LV dysfunction	1.30	0.026	1.032-1.633
IABP or MV support device implanted prior to PCI	2.04	0.002	1.302-3.207
Pre-PCI creatinine	0.90	0.061	0.803-1.005
Type C/high complexity lesion	1.15	0.100	0.973-1.364
CTO lesion	7.01	< 0.001	5.478-8.980
Cardiogenic shock at start of PCI	1.41	0.138	0.896-2.211

BMI: body mass index, PAD: peripheral arterial disease, LV: left ventricle, MV: mechanical ventricular, CTO: chronic total occlusions

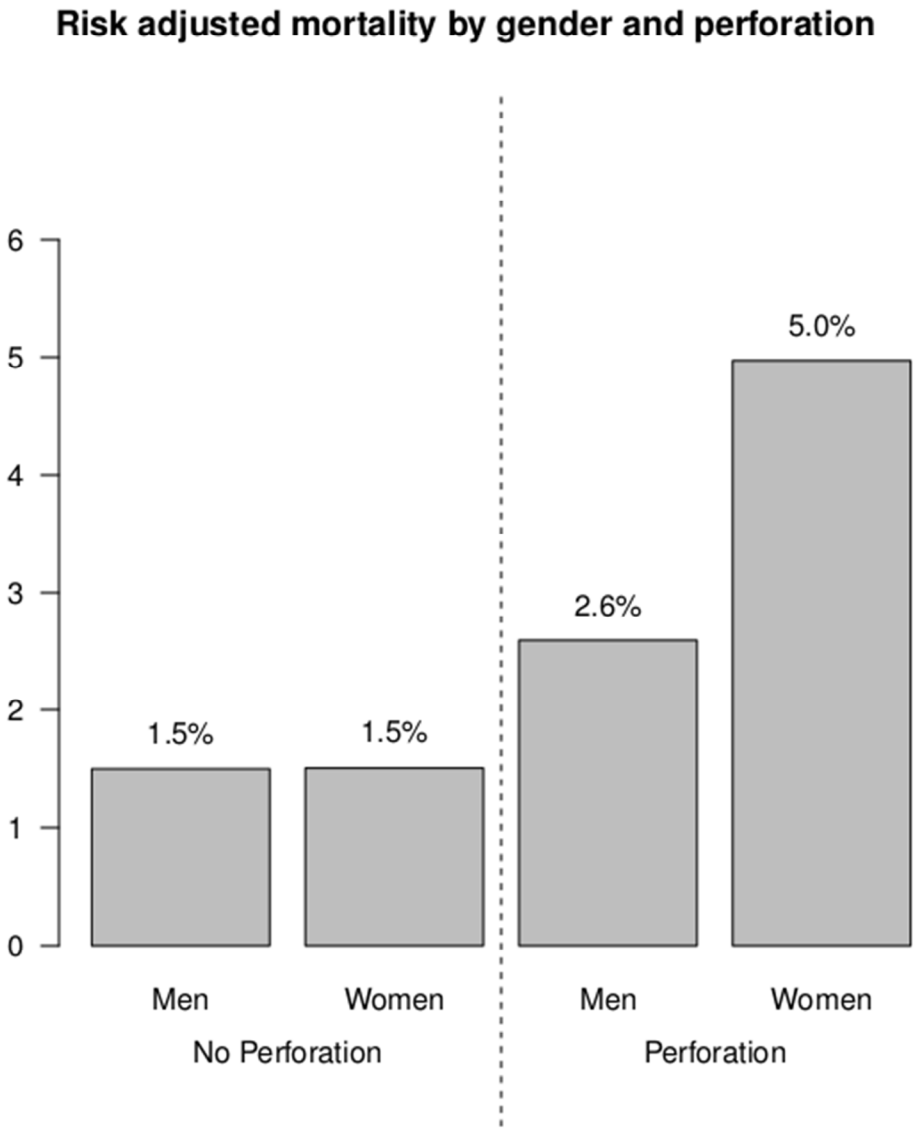
Table 4: Characteristics of patients with coronary artery perforations who were discharged alive versus deceased

Characteristic	Discharged alive N = 584	In-hospital death N = 41	p-value	Absolute Standard Difference
Demographic				
Age ± SD	66.98 ± 11.94	72.66 ± 12.28	p = 0.006	46.87
Female Gender	234 (40.1%)	29 (70.7%)	p < 0.001	64.85
Current or recent smoker	162 (27.8%)	15 (36.6%)	p = 0.230	18.81
Historical				
Hypertension	518 (89.0%)	35 (85.4%)	p = 0.476	10.90
Dyslipidemia	487 (83.5%)	29 (70.7%)	p = 0.036	30.84
Diabetes Mellitus	207 (35.4%)	14 (34.1%)	p = 0.867	2.73
Prior MI	226 (38.7%)	18 (43.9%)	p = 0.509	10.58
Prior PCI	279 (47.8%)	15 (36.6%)	p = 0.165	22.80
Prior CABG	134 (22.9%)	2 (4.9%)	p = 0.007	54.08
CAD Presentation				
STEMI or equivalent	77 (13.2%)	13 (31.7%)	p = 0.001	45.53
Heart failure within two weeks	87 (14.9%)	14 (34.1%)	p = 0.001	45.91
Cardiogenic shock within 24 hours	10 (1.7%)	8 (19.5%)	p < 0.001	60.37
Cardiac arrest within 24 hours	10 (1.7%)	4 (9.8%)	p < 0.001	35.11
Pre-PCI insertion of IABP or other mechanical ventricular support device	16 (2.7%)	9 (22.0%)	p < 0.001	61.04
PCI Status: Elective	231 (39.6%)	6 (14.6%)	p = 0.001	58.56
PCI Status: Urgent	267 (45.8%)	20 (48.8%)	p = 0.711	5.98
PCI Status: Emergency	85 (14.6%)	11 (26.8%)	p = 0.036	30.58
PCI Status: Salvage	0 (0.0%)	4 (9.8%)	p < 0.001	46.50
Post procedural outcomes				
Cardiogenic Shock	58 (9.9%)	30 (73.2%)	p < 0.001	167.30
Heart Failure	36 (6.2%)	8 (19.5%)	p = 0.001	40.72

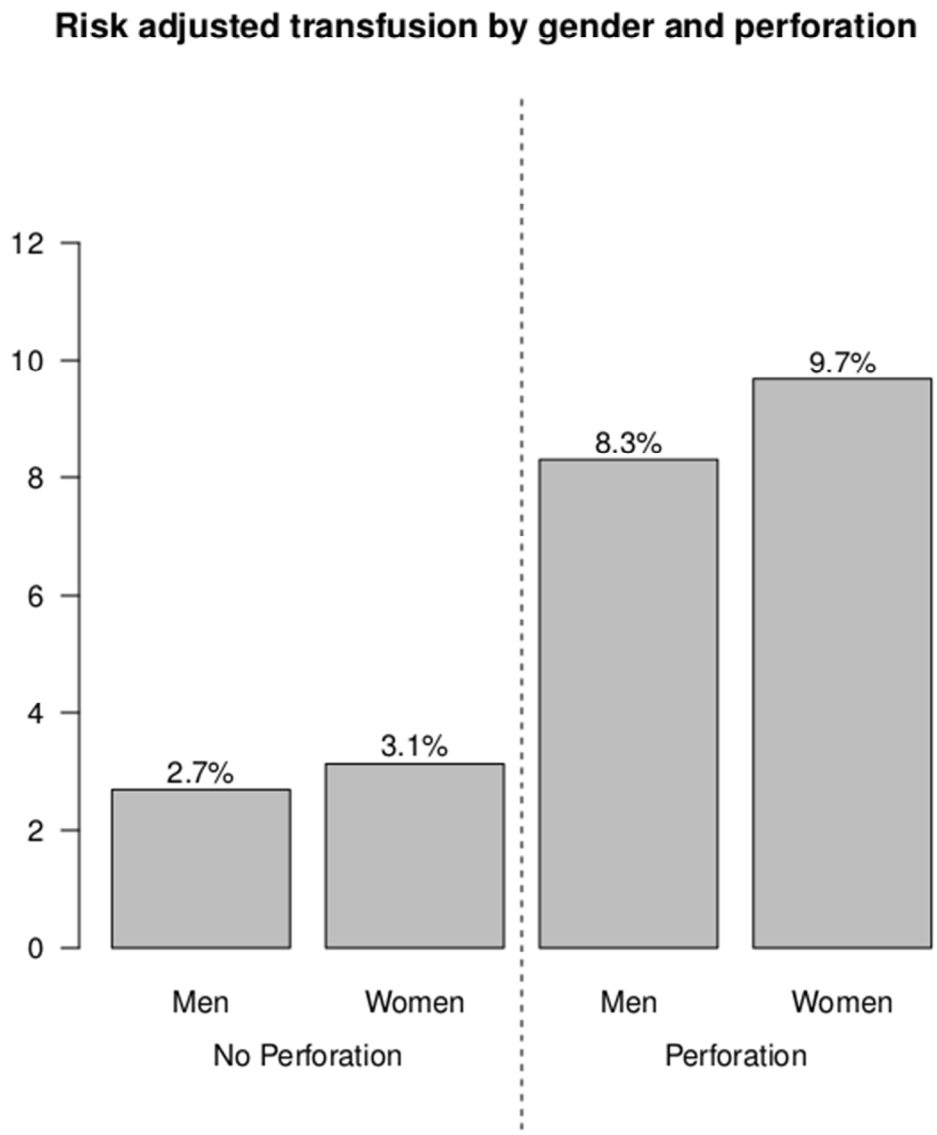
SD: Standard deviation, CAD: coronary artery disease, MI: myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary artery bypass grafting, STEMI: ST-segment elevation myocardial infarction, IABP: intra-aortic balloon pump, CK-MB: creatinine kinase, CVA: cerebral vascular accident

Figure 1. Risk adjusted mortality, transfusion and contrast-induced acute kidney injury (CI-AKI) rates for subgroups defined by gender and perforation

1A. Risk adjusted mortality associated with coronary perforation in men and women



1B. Risk adjusted transfusion associated with coronary perforation in men and women



1C. Risk adjusted CI-AKI associated with coronary perforation in men and women

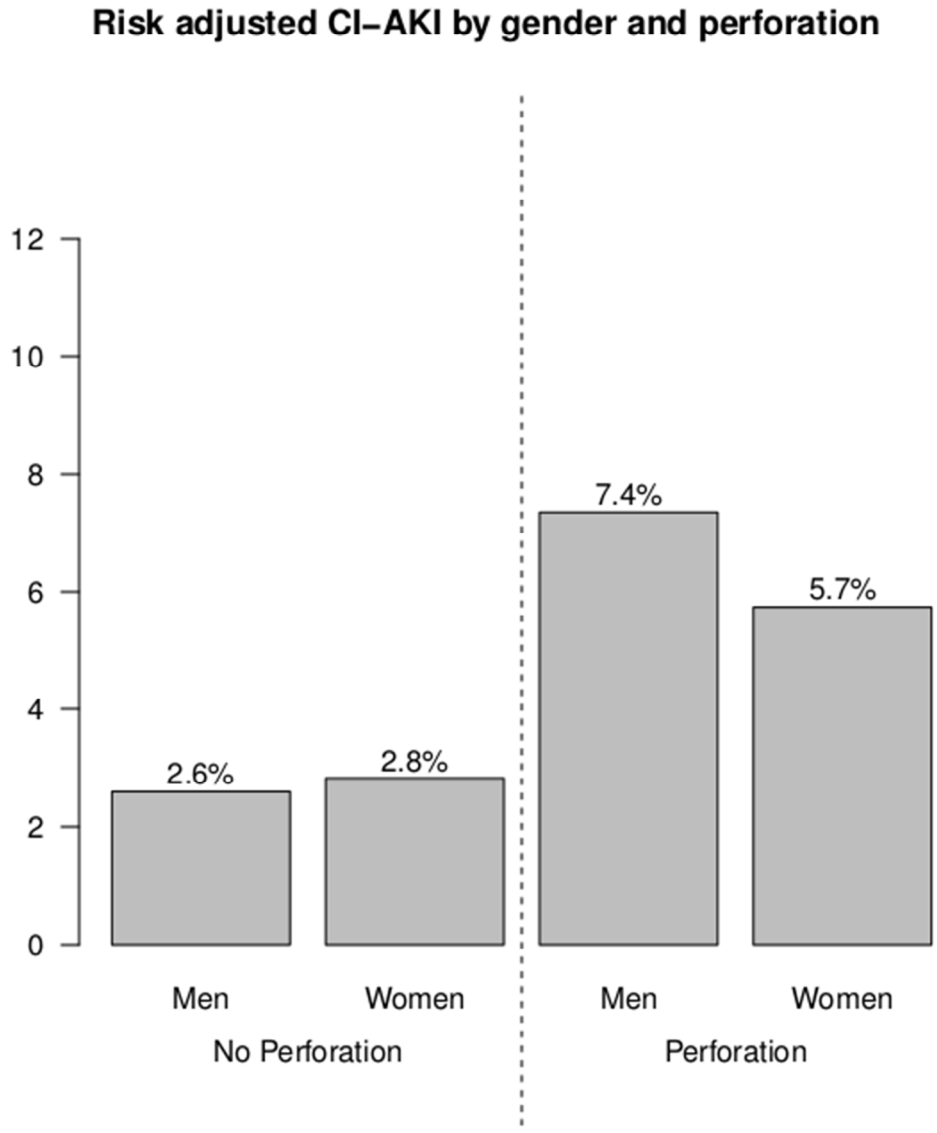
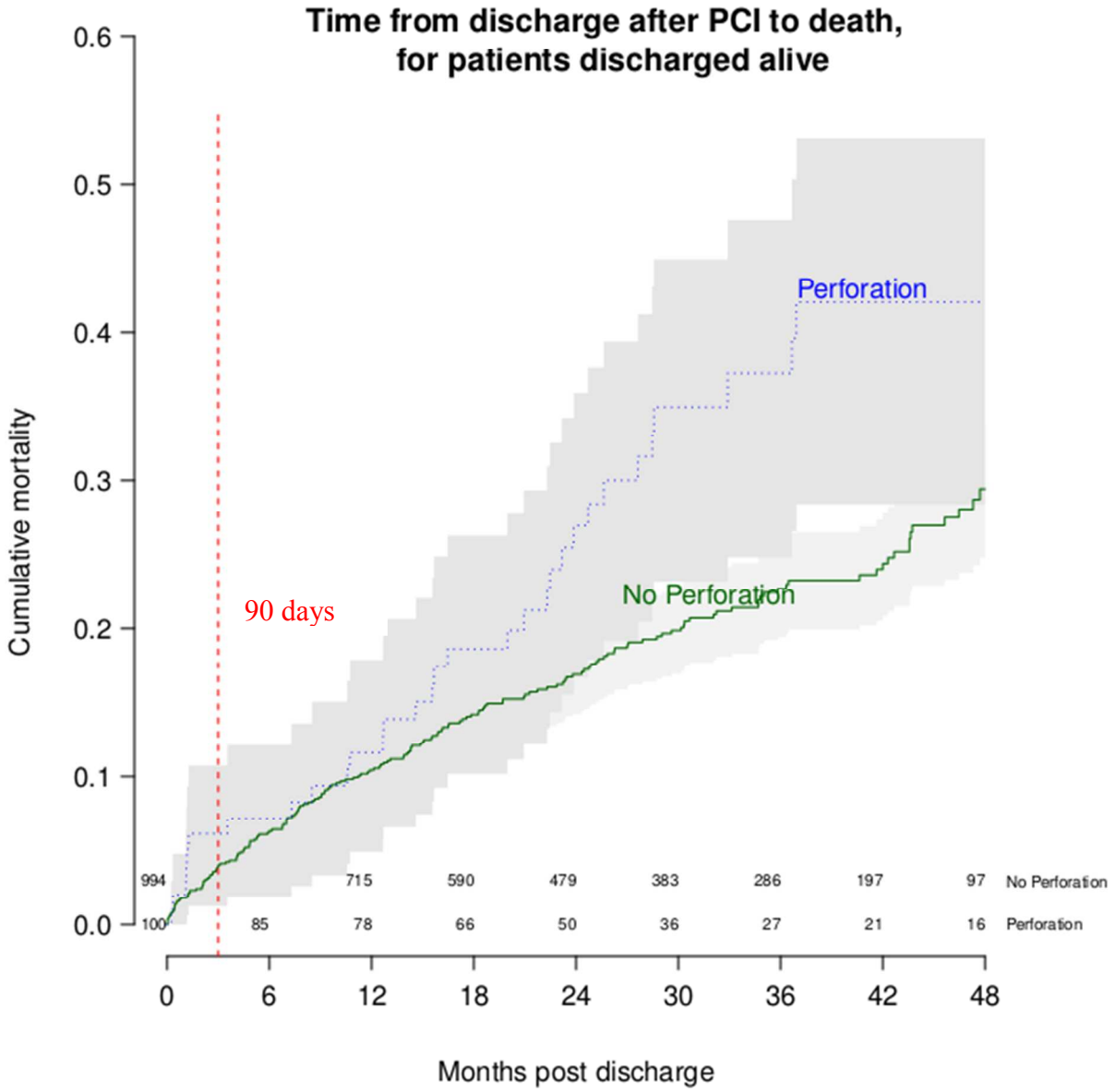


Figure 2: Long term mortality of patients with and without coronary artery perforation among those discharged alive after PCI.



Supplementary Table 1: Covariates included in propensity matching of patients with and without coronary artery perforation

PCI Indication: 1) Immediate PCI for STEMI 2) PCI for STEMI (Unstable) 3) PCI for STEMI (Stable) 4) PCI for STEMI, stable after successful full-dose Thrombolysis) 5) Rescue PCI for STEMI (after failed full-dose lytics) 6) PCI for high risk Non-STEMI or unstable angina 7) Staged PCI 8) Other	CAD presentation: 1) No symptom, no angina 2) Symptom unlikely to be ischemic 3) Stable angina 4) Unstable angina 5) Non-STEMI 6) STEMI or equivalent
PCI status: 1) elective 2) urgent 3) emergency 4) salvage	Admission source: 1) admitted from emergency department 2) transfer 3) other
Smoking status (current smoker)	Prior CABG
Hypertension	Height
Dyslipidemia	Weight
Family history of CAD	Currently on dialysis
Prior MI	Prior cerebrovascular disease
Prior heart failure	Prior peripheral artery disease
Prior valve surgery	Chronic lung disease
Prior PCI	Diabetes
Heart failure within the past 2 weeks	LV ejection fraction less than 40%
Pre-procedural Hemoglobin	Race (white, black, Asian, other – allowing selection of multiple categories)
Cardiomyopathy and/or left ventricular dysfunction	Prior cardiogenic shock (within 24 hours)
Prior cardiac arrest (within 24 hours)	Cardiogenic shock at start of PCI procedure
Age	Gender
Predicted patient mortality risk based on BMC2 mortality risk model.	

CAD: coronary artery disease, MI: myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary artery bypass grafting, NSTEMI: non-ST segment elevation myocardial infarction, STEMI: ST segment elevation myocardial infarction, BMC2: Blue Cross Blue Shield of Michigan Cardiovascular Consortium, LV: left ventricular

Supplementary Table 2: Comparison of propensity matched cohorts of patients with and without coronary artery perforation

Characteristic	No Perforation	Perforation	p-value	Absolute Standard Difference
Age	74.74 ± 9.51	74.16 ± 10.75	p = 0.597	5.75
Sex				
Male	483/1,030 (46.9%)	50/103 (48.5%)	p = 0.749	3.30
Female	547/1,030 (53.1%)	53/103 (51.5%)	p = 0.749	3.30
Height	166.37 ± 10.69	166.63 ± 11.26	p = 0.822	2.38
Weight	80.45 ± 19.71	80.83 ± 20.16	p = 0.856	1.90
Race				
White	978/1,030 (95.0%)	98/103 (95.1%)	p = 0.931	0.90
Black	32/1,030 (3.1%)	3/103 (2.9%)	p = 0.913	1.14
Asian	8/1,030 (0.8%)	1/103 (1.0%)	p = 0.832	2.09
Admit Source				
Emergency department	464/1,030 (45.0%)	45/103 (43.7%)	p = 0.791	2.74
Transfer in from another acute care facility	239/1,030 (23.2%)	26/103 (25.2%)	p = 0.641	4.76
Other	327/1,030 (31.7%)	32/103 (31.1%)	p = 0.888	1.46
Current/Recent Smoker	154/1,030 (15.0%)	15/103 (14.6%)	p = 0.916	1.10
Hypertension	925/1,030 (89.8%)	92/103 (89.3%)	p = 0.877	1.59
Dyslipidemia	862/1,030 (83.7%)	86/103 (83.5%)	p = 0.960	0.52
Family History of Premature CAD	197/1,030 (19.1%)	19/103 (18.4%)	p = 0.867	1.74
Prior MI	406/1,030 (39.4%)	42/103 (40.8%)	p = 0.788	2.77
Prior Heart Failure	214/1,030 (20.8%)	22/103 (21.4%)	p = 0.890	1.43
Prior PCI	447/1,030 (43.4%)	46/103 (44.7%)	p = 0.805	2.54
Prior CABG	259/1,030 (25.1%)	27/103 (26.2%)	p = 0.812	2.44
Cerebrovascular Disease	258/1,030 (25.0%)	25/103 (24.3%)	p = 0.862	1.80
Peripheral Arterial Disease	282/1,030 (27.4%)	29/103 (28.2%)	p = 0.866	1.73
Chronic Lung Disease	210/1,030 (20.4%)	21/103 (20.4%)	p = 1.000	0
Diabetes Mellitus	440/1,030 (42.7%)	44/103 (42.7%)	p = 1.000	0
CAD Presentation				
No angina	24/1,030 (2.3%)	2/103 (1.9%)	p = 0.802	2.69
Symptom unlikely to be ischemic	18/1,030 (1.7%)	2/103 (1.9%)	p = 0.886	1.44
Stable angina	95/1,030 (9.2%)	10/103 (9.7%)	p = 0.871	1.66
Unstable angina	434/1,030 (42.1%)	43/103 (41.7%)	p = 0.939	0.79
NSTEMI	254/1,030 (24.7%)	26/103 (25.2%)	p = 0.896	1.35
STEMI	205/1,030 (19.9%)	20/103 (19.4%)	p = 0.906	1.22
PCI Status				
Elective	350/1,030 (34.0%)	36/103 (35.0%)	p = 0.843	2.04
Urgent	481/1,030 (46.7%)	48/103 (46.6%)	p = 0.985	0.19
Emergency	199/1,030 (19.3%)	19/103 (18.4%)	p = 0.830	2.23
PCI Indication				
Immediate PCI for STEMI	156/1,030 (15.1%)	16/103 (15.5%)	p = 0.917	1.08
PCI for STEMI (Unstable, >12 hours from symptom onset)	49/1,030 (4.8%)	4/103 (3.9%)	p = 0.689	4.30
PCI for high risk NSTEMI or unstable angina	581/1,030 (56.4%)	59/103 (57.3%)	p = 0.865	1.76
Staged PCI	9/1,030 (0.9%)	1/103 (1.0%)	p = 0.920	1.02
Other	235/1,030 (22.8%)	23/103 (22.3%)	p = 0.911	1.16
Heart Failure within two weeks	193/1,030 (18.7%)	19/103 (18.4%)	p = 0.942	0.75
Cardiomyopathy or left ventricular systolic dysfunction	124/1,030 (12.0%)	13/103 (12.6%)	p = 0.863	1.77
Cardiogenic Shock at start of PCI	50/1,030 (4.9%)	5/103 (4.9%)	p = 1.000	0
Pre-Procedure Hemoglobin	12.73 ± 1.80	12.73 ± 1.71	p = 0.975	0.32

CAD: coronary artery disease, MI: myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary artery bypass grafting, NSTEMI: non-ST segment elevation myocardial infarction, STEMI: ST segment elevation myocardial infarction,

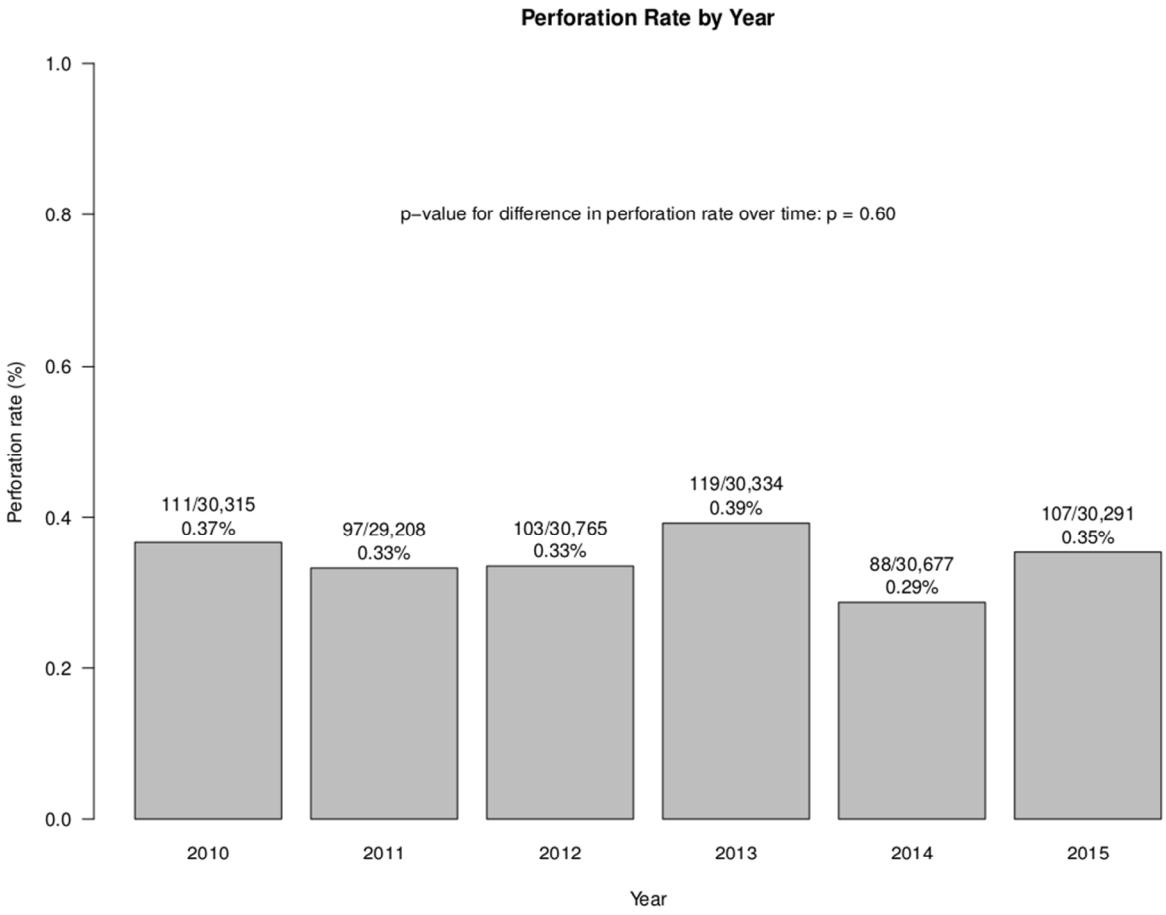
Supplementary Table 3: Baseline mean predicted risks, outcomes, and adjusted odds ratios of patients with and without coronary artery perforation

	Estimated baseline risk of death	Estimated baseline risk of CI-AKI	Estimated baseline risk of transfusion
No Perforation	1.51%	2.70%	2.94%
Perforation	2.54%	3.28%	4.09%
p-value	p = .001	p = .026	p < .001
	Mortality	CI-AKI incidence	Transfusion incidence
No Perforation	1.50%	2.68%	2.91%
Perforation	6.56%	7.95%	12.64%
Overall rate:	1.52%	2.70%	2.95%
O/E ratio:	Death	CI-AKI	Transfusion
No Perforation	0.99	0.99	0.99
Perforation	2.58	2.42	3.09
Adjusted OR	5.00 (95% CI 3.42 – 7.31)	3.25 95% CI 2.30 – 4.58)	5.26 (95% CI 4.03-6.87)
p-value:	p < .001	p < .001	p < .001

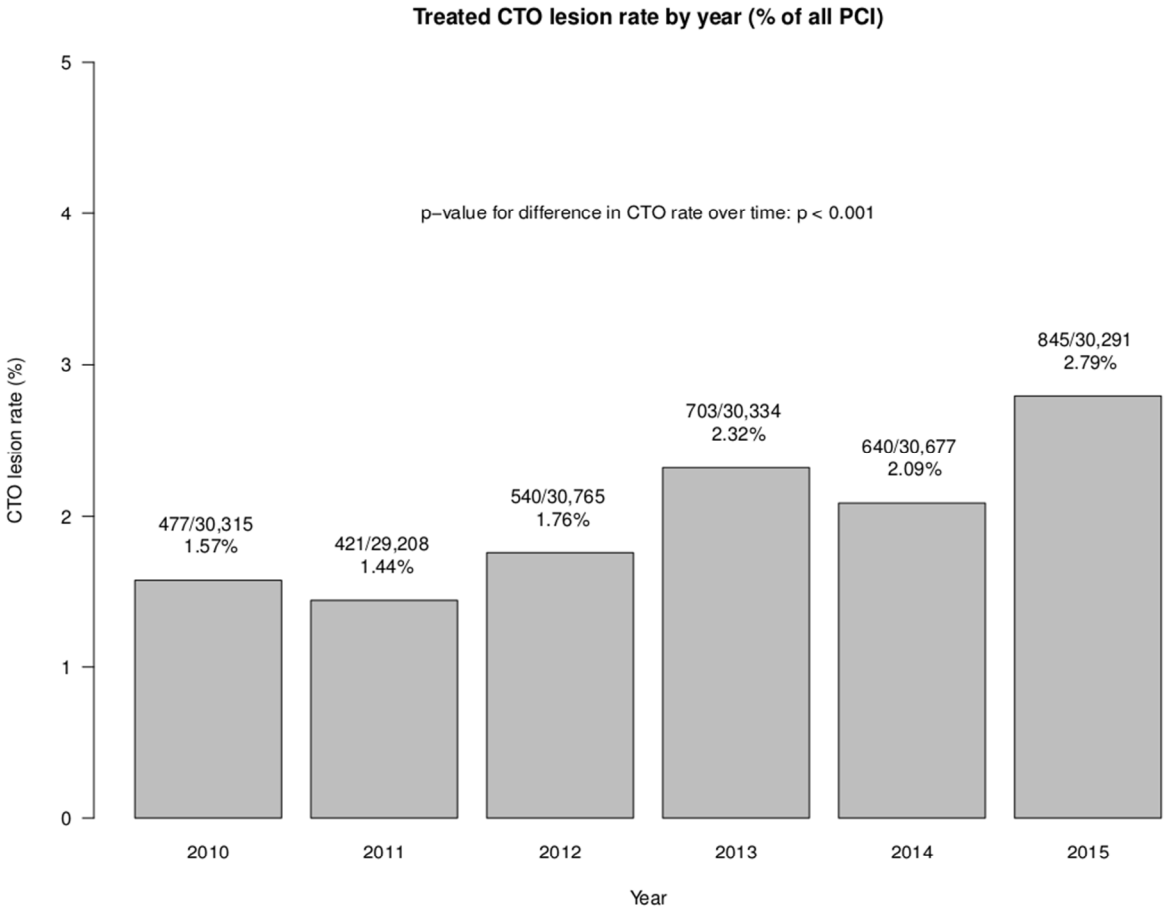
OR=odds ratio, CI-AKI=contrast-induced acute kidney injury, CI=confidence interval, O/E = observed/expected

Supplementary Figure 1: Overall incidence of CAP, proportion of PCI performed for treatment of CTO and incidence of CAP among CTO cases over a 5 year period

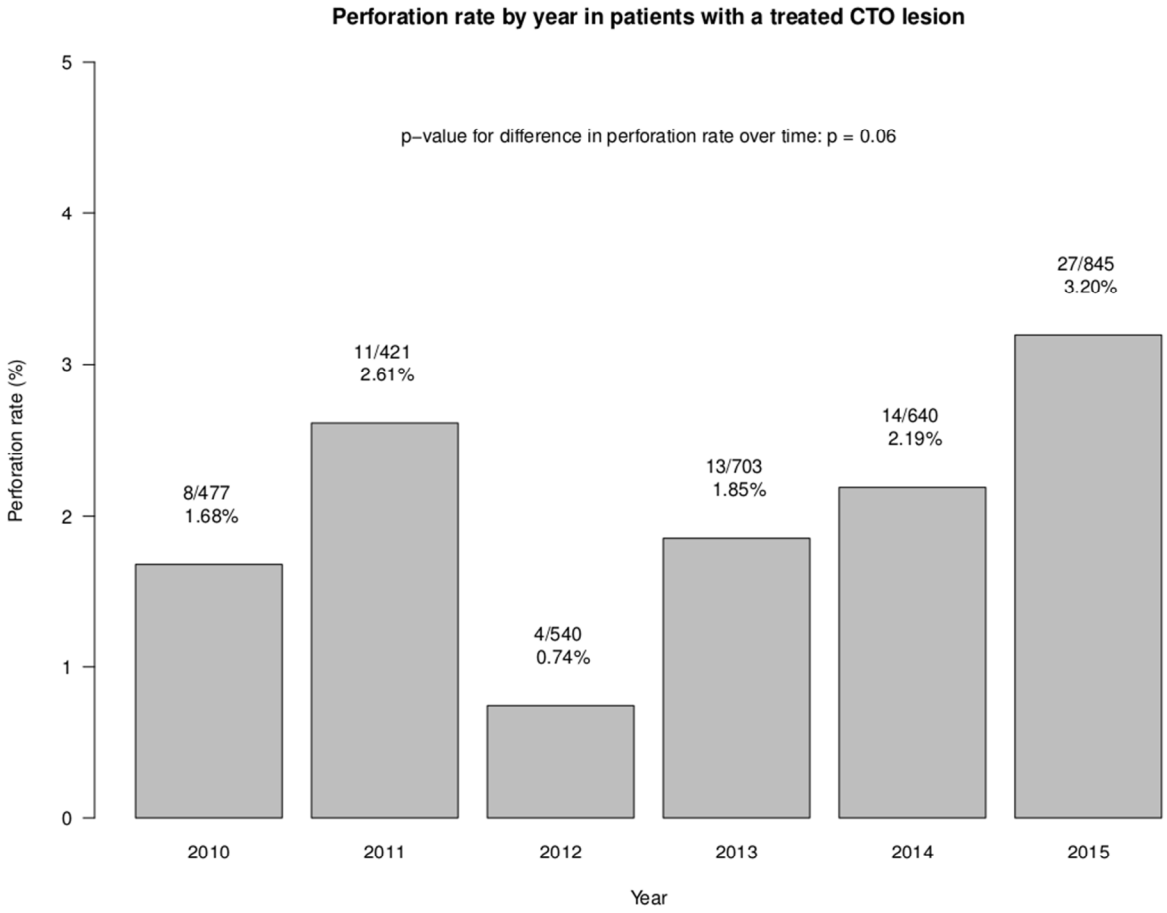
Supplementary Figure 1A: Perforation rate by year



Supplementary Figure 1B: Treated CTO lesion rate by year



Supplementary Figure 1C: Perforation rate by year in patients with a treated CTO lesion



CAP: coronary artery perforations, PCI: percutaneous coronary interventions, CTO: chronic total occlusions

References

1. Shimony A, Joseph L, Mottillo S, Eisenberg MJ. Coronary artery perforation during percutaneous coronary intervention: A systematic review and meta-analysis. Can J Cardiol. 2011;27:843-850
2. Stankovic G, Orlic D, Corvaja N, et al. Incidence, predictors, in-hospital, and late outcomes of coronary artery perforations. Am J Cardiol. 2004;93:213-216
3. Fasseas P, Orford JL, Panetta CJ, et al. Incidence, correlates, management, and clinical outcome of coronary perforation: analysis of 16,298 procedures. Am Heart J. 2004;147:140-145
4. Shimony A, Zahger D, Van Straten M, et al. Incidence, risk factors, management and outcomes of coronary artery perforation during percutaneous coronary intervention. Am J Cardiol. 2009;104:1674-1677
5. Antonsen L, Jensen LO, Terkelsen CJ, et al. Outcomes after primary percutaneous coronary intervention in octogenarians and nonagenarians with ST-segment elevation myocardial infarction: from the western Denmark heart registry. Catheter Cardiovasc Interv. 2013;81:912-919
6. Sandhu K, Nadar SK. Percutaneous coronary intervention in the elderly. Int J Cardiol 2015;199:342-355
7. Galassi AR, Brilakis ES, Boukhris M,et al. Appropriateness of percutaneous revascularization of coronary chronic total occlusions: an overview. Eur Heart J. 2015 August 7, [Epub ahead of print]
8. Galassi AR, Boukhris M, Azzarelli S, Marza F, Tomasello SD. Percutaneous coronary interventions for chronic total occlusions: More benefit for the patient or for the interventionist's ego? Can J Cardiol. 2015;31:974-979
9. Gurm HS, Smith DE, Collins JS, et al. The relative safety and efficacy of abciximab and eptifibatide in patients undergoing primary percutaneous coronary intervention: insights

from a large regional registry of contemporary percutaneous coronary intervention. J Am Coll Cardiol. 2008;51:529-535

0. Michigan Value Collaborative. Accessed June 1, 2016. Available at: http://michiganvalue.org/

1. Herrel L, Syrjamaki JD, Linsell SM, et al. Identifying drivers of episode cost variation with radical prostatectomy. *Urology*. 2016;In press

2. Slocum NK, Grossman PM, Moscucci M, et al. The changing definition of contrast-induced nephropathy and its clinical implications: Insights from the Blue Cross Blue Shield of Michigan Cardiovascular Consortium (BMC2). Am Heart J. 2012;163:829-834

3. Gurm HS, Kooiman J, LaLonde T, Grines C, Share D, Seth M. A random forest based risk model for reliable and accurate prediction of receipt of transfusion in patients undergoing percutaneous coronary intervention. *PloS One*. 2014;9:e96385

4. Gurm HS, Seth M, Kooiman J, Share D. A novel tool for reliable and accurate prediction of renal complications in patients undergoing percutaneous coronary intervention. J Am Coll Cardiol. 2013;61:2242-2248

5. BMC2 Collaboration for Quality Improvement. BMC2 PCI-VIC. Available at: https://bmc2.org/calculators/multi. Accessed May 1, 2015.

6. PCI Risk Assessment Tool. The Society for Cardiovascular Angiography and Interventions. Available at: http://www.scai.org/PCIRiskAssessmentTools/default.aspx. Accessed May 1, 2015.

7. Argulian E, Patel AD, Abramson JL, et al. Gender differences in short-term cardiovascular outcomes after percutaneous coronary interventions. Am J Cardiol. 2006;98:48-53

8. Ellis SG, Ajluni S, Arnold AZ, et al. Increased coronary perforation in the new device era. Incidence, classification, management, and outcome. Circulation. 1994;90:2725-2730

9. Romaguera R, Waksman R. Covered stents for coronary perforations: Is there enough evidence? Catheter Cardiovasc Interv. 2011;78:246-253