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Risk of contrast-induced nephropathy in patients undergoing complex percutaneous coronary intervention☆

Lorenzo Azzalini [a,*], Enrico Poletti [a], Francesca Lombardo [a], Alessandra Laricchia [a], Alessandro Beneduce [a], Silvia Moscardelli [a], Barbara Bellini [a], Davide Maccagni [a], Alberto Cappelletti [b], Marco B. Ancona [a], Mauro Carlino [a], Alaide Chieffo [a], Antonio Colombo [a], Matteo Montorfano [a]

[a] Interventional Cardiology Division, Cardio-Thoracic-Vascular Department, San Raffaele Scientific Institute, Milan, Italy

[b] Cardiology Division, Cardio-Thoracic-Vascular Department, San Raffaele Scientific Institute, Milan, Italy

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ABSTRACT

Background: Complex percutaneous coronary intervention (PCI) is associated with increased procedural challenges and high contrast load. We aimed to evaluate the association between complex PCI and contrast-induced nephropathy (CIN).

Methods: This single-center retrospective study included all-comers undergoing PCI between January 2012 and December 2016. Complex PCI was defined as a procedure with ≥1 of the following characteristics: 3 vessels treated, ≥3 stents implanted, two-stent bifurcation intervention, total stent length >60 mm, PCI on a chronic total occlusion, saphenous vein graft, or left main, protected PCI, use of rotational/laser atherectomy. CIN was defined as an increase in post-PCI creatinine of ≥0.3 mg/dl or ≥50% from baseline.

Results: We included 2660 patients ($n = 1128$ complex PCI, $n = 1532$ non-complex PCI). Complex PCI patients tended to be older, and had higher cardiovascular comorbidity and Mehran CIN risk score. They also had a higher prevalence of type B2/C lesions and need for mechanical circulatory support, and received a higher mean contrast volume (284 ± 137 vs. 189 ± 90 ml, $p < 0.001$). CIN incidence was similar in complex vs. non-complex PCI patients (12.1% vs. 11.5%, $p = 0.63$), as was the need for in-hospital dialysis (0.5% vs. 0.2%, $p = 0.25$). Upon multivariable adjustment, age, female sex, diabetes, ejection fraction, periprocedural hypotension, presentation with acute coronary syndrome, and contrast volume were independently associated with CIN, while complex PCI was not.

Conclusions: Complex PCI is not associated with an increased risk of CIN in all-comers. Further studies should confirm our findings and investigate novel effective strategies to decrease the risk of this serious complication.

1. Introduction

Over the last few years, the interventional cardiology community has witnessed an increase in the complexity of the patients treated and the procedures performed in the field of percutaneous coronary intervention (PCI) [1–3]. Indeed, both patient- and procedure-related characteristics can contribute to the complexity and risk of such procedures. In particular, patient comorbidities, hemodynamic conditions and angiographic characteristics drive decision-making with regards to procedural strategy, and the concept of complex and higher-risk patients with an indication for revascularization (CHIP) has recently been defined [3].

Few studies have investigated the outcomes of percutaneous revascularization in CHIP patients [4–6]. As a consequence, no standardized definition of such procedures currently exists. Moreover, even less data exist regarding the concept of complex PCI per se (i.e., a purely angiographic and procedural strategy-related definition) [7]. Complex PCI is associated, among others, with high contrast volume and hypotension, and is often performed in patients with a high cardiovascular comorbidity burden (e.g., diabetes and peripheral arterial disease). Such conditions are known risk factors for contrast-induced nephropathy (CIN), which is a frequent and potentially serious complication of PCI [8,9]. CIN has been associated with irreversible deterioration of renal function, need for dialysis, increased hospital costs, and death [8]. So far, no data exist on the association between complex PCI and the risk of CIN.

☆ ll authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

* Corresponding author at: Interventional Cardiology Division, Cardio-Thoracic-Vascular Department, San Raffaele Scientific Institute, Via Olgettina 60, 20132 Milan, Italy.
E-mail address: azzalini.lorenzo@hsr.it (L. Azzalini).

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The aim of the present study is to ascertain whether patients undergoing complex PCI suffer an increased risk for CIN, compared with subjects undergoing non-complex PCI.

2. Methods

2.1. Patient population

This single-center retrospective study included all patients undergoing PCI between January 2012 and December 2016, for whom both baseline and post-procedural serum creatinine measurements were available. Baseline, procedural, and hospitalization data were recorded. All patients signed an informed consent, approved by the local ethics committee, for procedural data collection and for the anonymous use of data for retrospective evaluation.

2.2. CIN prophylaxis

All patients received intravenous administration of normal saline (1.0–1.5 ml/kg/h; 0.5 ml/kg/h in cases of volume overload or left ventricular ejection fraction [LVEF] <45%), initiated 12 h before PCI (or in the catheterization laboratory for emergency cases) and continued up to 24 h afterwards.

2.3. Definitions

The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease equation. For stable patients, the most recent pre-procedural serum creatinine value was used. For unstable subjects (decompensated heart failure, acute renal failure, cardiac arrest, cardiogenic shock, etc.), the last stable known serum creatinine value was employed. If no prior stable value was known, admission serum creatinine concentration was utilized. The Mehran risk score [10] was calculated to estimate CIN risk.

Complex PCI was defined according to an expanded version of the definition by Giustino et al. [7], as a procedure with at least one of the following characteristics: 3 vessels treated, ≥3 stents implanted, bifurcation treated with two stents, total stent length >60 mm, chronic total occlusion (CTO) PCI, saphenous vein graft (SVG) PCI, left main PCI, protected PCI (use of mechanical circulatory support device in non-emergency settings, namely ST-elevation myocardial infarction, cardiogenic shock, or cardiac arrest), or rotational or laser atherectomy. Hypotension during/before PCI was defined as a period >10 min in which blood pressure was <90/60 mmHg. Technical success was defined as the achievement of a final stenosis <30% with TIMI 3 flow.

The study endpoint was CIN, which was diagnosed, in patients not undergoing dialysis before PCI, using the change from pre-procedural to peak serum creatinine levels within 72 h after PCI. CIN was defined and graded according to the Acute Kidney Injury Network (AKIN) definition [11]: stage 1, increase in serum creatinine of ≥0.3 mg/dl or ≥50% to 100% from baseline; stage 2, increase in serum creatinine >100% to 200%; stage 3, increase in serum creatinine >200% or to ≥4.0 mg/dl with an acute increase of ≥0.5 mg/dl. CIN requiring dialysis was defined as the new need for in-hospital renal replacement therapy in patients not undergoing chronic dialysis before PCI. A sensitivity analysis was conducted utilizing the CIN definition by Mehran et al. [10] (increase in serum creatinine ≥0.5 mg/dl or ≥25% from baseline).

2.4. Statistical analysis

Continuous variables are presented as mean ± standard deviation and compared with Student's *t*-test. Categorical variables are presented as frequency (percentages) and compared with chi-square test.

Unadjusted rates of the study endpoint were calculated and compared according to complex PCI status. A sensitivity analysis was then performed, focusing on patients presenting with acute coronary syndrome (ACS). An additional analysis was performed to explore the relationship between the degree of complexity of PCI (number of complexity characteristics, as described above and outlined in Online Fig. 1) and the risk of CIN. Moreover, the rates of CIN for each complexity characteristic group were analyzed.

Finally, multivariate logistic regression analysis with stepwise backward selection (p-entry = 0.05, p-exit = 0.10) was performed to identify independent predictors of CIN. The final model included variables previously identified to be predictors of CIN [8–10,12,13]: complex vs. non-complex PCI, age, sex, eGFR, diabetes, prior coronary artery bypass graft, LVEF, heart failure on presentation, hypotension during/before PCI, number of diseased vessels, ACS, emergency PCI, vascular access, and contrast media type and volume.

A p-value <0.05 was considered statistically significant. Analyses were performed using SPSS 24 (IBM Corp., Armonk, NY).

3. Results

3.1. Study population

During study period, $n = 5823$ PCIs were performed at our institution: $n = 2241$ were complex PCI and $n = 3582$ were non-complex PCI. Of those, 2660 (46%) had at least one post-procedural creatinine value available ($n = 1128$ [50%] with complex PCI and $n = 1532$ [43%] with non-complex PCI, $p < 0.001$). These patients represented the study population. A comparison between the study population and patients for whom no post-PCI creatinine values were available is presented in the Online Table 1 (clinical characteristics) and Online Table 2 (angiographic and procedural characteristics). Patients with available post-procedural creatinine data were older (68.1 ± 11.4 vs. 66.3 ± 9.8 years, $p < 0.001$), had lower eGFR (73.0 ± 28.1 vs. 89.1 ± 23.2 ml/min/1.73 m^2, $p < 0.001$) and higher Mehran CIN risk score (7.4 ± 5.0 vs. 4.4 ± 3.4, $p < 0.001$), and received higher contrast volume (229 ± 122 vs. 214 ± 95 ml, $p < 0.001$). In the study population, serum creatinine measurements were available for 93% of patients on day 1 post-PCI (93% vs. 93% in complex vs. non-complex PCI, $p > 0.99$), 50% on day 2 (46% vs. 53%, $p < 0.001$), and 38% on day 3 (34% vs. 41%, $p < 0.001$). Creatinine values were available only on day 1 post-PCI in 45% (49% vs. 42%, $p = 0.001$).

Online Fig. 1A shows the prevalence of complexity characteristics in the complex PCI population. Approximately half of such cases received ≥3 stents and a total stent length >60 mm. CTO PCI was performed in 28% and left main PCI in 22% of subjects. A two-stent strategy for bifurcation intervention was performed in 14%. As shown in Online Fig. 1B, almost half of the complex PCI cohort presented with one complexity characteristic, while two characteristics were observed in 28% of cases, and three characteristics in 19%. Only a small minority of patients (6% overall) had higher complexity.

3.2. Clinical characteristics

Table 1 outlines the clinical characteristics of the study population. Patients undergoing complex PCI tended to be older (68.6 ± 11.1 vs. 67.7 ± 11.6, $p = 0.06$), and had higher prevalence of most cardiovascular risk factors (including diabetes, 39% vs. 33%, $p = 0.001$) and comorbidities (including prior myocardial infarction, 42% vs. 30%, $p < 0.001$; peripheral arterial disease, 33% vs. 24%, $p < 0.001$; and chronic heart failure, 19% vs. 15%, $p = 0.001$). However, there were no differences in baseline eGFR (72.0 ± 26.7 vs. 73.7 ± 29.0 ml/min/1.73 m^2, $p = 0.12$) and LVEF. Mehran CIN risk score was higher in subjects undergoing complex PCI (8.4 ± 5.1 vs. 6.6 ± 4.8, $p < 0.001$), who however had a lower incidence of ACS on presentation (28% vs. 50%, $p < 0.001$), compared with subjects undergoing non-complex PCI.

3.3. Angiographic and procedural characteristics

As shown in Table 2, patients undergoing complex PCI had a higher number of diseased vessels (2.4 ± 0.7 vs. 2.0 ± 0.8, $p < 0.001$), a higher prevalence of type B2/C lesions (85% vs. 48%, $p < 0.001$), and were treated more frequently via a transfemoral access (41% vs. 27%, $p < 0.001$). The need for mechanical circulatory support (mostly intra-aortic balloon pump) was also higher in such patient population (8% vs. 4%, $p = 0.001$). Complex PCI patients more often underwent intravascular imaging (13% vs. 5%, $p < 0.001$), and received a higher total stent length (59.7 ± 34.5 vs. 26.2 ± 13.6 mm, $p < 0.001$) and contrast volume (284 ± 137 vs. 189 ± 90 ml, $p < 0.001$). A contrast-volume-to-creatinine-clearance >3, which had previously been associated with higher incidence of CIN [14], was more frequently observed in complex PCI patients (68% vs. 38%, $p < 0.001$). Technical success was lower in complex PCI compared with non-complex PCI subjects (88% vs. 97%, $p < 0.001$).

3.4. Rates of CIN

As shown in Fig. 1, CIN developed in 11.8% of patients overall, with a similar incidence in complex vs. non-complex PCI patients (12.1% vs. 11.5%, $p = 0.63$). The need for in-hospital dialysis was very low (0.3%), with no difference between groups (0.5% vs. 0.2%, $p = 0.25$).

Table 1
Baseline clinical characteristics.

Variable	Overall ($n = 2660$)	Complex PCI ($n = 1128$)	Non-complex PCI ($n = 1532$)	p-Value
Age (years)	68.1 ± 11.4	68.6 ± 11.1	67.7 ± 11.6	0.06
Men	2145 (81%)	940 (83%)	1205 (79%)	0.002
Body mass index (kg/m^2)	26.7 ± 4.0	26.8 ± 4.0	26.7 ± 4.1	0.50
Diabetes mellitus	923 (35%)	435 (39%)	488 (33%)	0.001
Dyslipidemia	1595 (61%)	751 (67%)	844 (56%)	<0.001
Hypertension	1994 (76%)	890 (80%)	1104 (74%)	<0.001
Current smoker	431 (17%)	146 (13%)	285 (19%)	<0.001
Prior myocardial infarction	923 (35%)	467 (42%)	456 (30%)	<0.001
Prior percutaneous coronary intervention	1224 (47%)	577 (52%)	647 (43%)	<0.001
Prior coronary artery bypass graft surgery	423 (16%)	246 (22%)	177 (12%)	<0.001
Peripheral arterial disease	735 (28%)	369 (33%)	366 (24%)	<0.001
Chronic heart failure	434 (17%)	215 (19%)	219 (15%)	0.001
eGFR (ml/min/1.73 m^2)	73.0 ± 28.1	72.0 ± 26.7	73.7 ± 29.0	0.12
eGFR <60 ml/min/1.73 m^2	917 (35%)	393 (35%)	524 (34%)	0.75
eGFR <30 ml/min/1.73 m^2	131 (5%)	59 (5%)	72 (5%)	0.54
Dialysis	52 (2%)	26 (2%)	26 (2%)	0.27
Left ventricular ejection fraction (%)	49.3 ± 11.7	49.2 ± 11.6	49.3 ± 11.8	0.82
Left ventricular ejection fraction <50%	889 (38%)	379 (38%)	510 (38%)	0.91
Heart failure on presentation	184 (7%)	66 (6%)	118 (8%)	0.06
Hypotension during/before PCI	167 (6%)	72 (6%)	95 (6%)	0.85
Mehran risk score	7.4 ± 5.0	8.4 ± 5.1	6.6 ± 4.8	<0.001
Indication of PCI				
Stable coronary artery disease	943 (36%)	521 (46%)	422 (28%)	<0.001
UA/NSTEMI	644 (24%)	235 (21%)	409 (27%)	
STEMI	426 (16%)	78 (7%)	348 (23%)	
Shock/cardiac arrest	77 (3%)	25 (2%)	52 (3%)	
Heart failure/low ejection fraction	103 (4%)	50 (4%)	53 (4%)	
Complete revascularization	265 (10%)	137 (12%)	128 (8%)	
Other	197 (7%)	78 (7%)	119 (8%)	

Abbreviations: eGFR, estimated glomerular filtration rate; STEMI, ST-elevation myocardial infarction. UA/NSTEMI, unstable angina/non-ST-elevation myocardial infarction.

When Mehran's CIN definition was considered, there was still no difference between groups (overall $n = 382$, 14.9%; complex PCI $n = 166$, 15.2% vs. non-complex PCI $n = 216$, 14.6%, $p = 0.66$).

When the analysis was limited to subjects presenting with an ACS (Online Fig. 2A), however, patients treated with complex PCI tended to have a higher incidence of CIN (19.2% vs. 14.8%, $p = 0.07$) and had a higher incidence of CIN requiring in-hospital dialysis (1.6% vs. 0.3%, $p = 0.01$).

When we analyzed the association between the number of complexity characteristics and development of CIN (Online Fig. 2B), subjects with 0, 1–2, and 3–4 complexity characteristics presented a similar incidence of CIN (ranging from 11.5% to 12.6%), whereas this figure markedly increased up to 37.5% in subjects with 5–6 characteristics (although this finding was driven by only six cases). Mean contrast volume gradually increased across the four groups.

Finally, no clear association was found between the specific type of complexity characteristic and contrast volume (Online Fig. 3). Patients undergoing protected PCI had a CIN incidence of 31.1%, despite receiving a not particularly high contrast volume (on average, 265 ml).

3.5. Other in-hospital adverse events

Subjects undergoing complex PCI suffered higher rates of other in-hospital adverse events, compared with non-complex PCI patients (Table 3), including coronary perforation (2.7% vs. 0.3%, $p < 0.001$), major bleeding (1.5% vs. 0.8%, $p = 0.08$), periprocedural myocardial

Table 2
Angiographic characteristics and procedural data.

Variable		Overall ($n = 2660$)	Complex PCI ($n = 1128$)	Non-complex PCI ($n = 1532$)	p-Value
Number of diseased vessels		2.2 ± 0.8	2.4 ± 0.7	2.0 ± 0.8	<0.001
Femoral access		733 (32%)	361 (41%)	372 (27%)	<0.001
Complex lesion (B2/C type)		1679 (63%)	952 (85%)	727 (48%)	<0.001
Mechanical circulatory support	None	2504 (94%)	1038 (92%)	1466 (96%)	0.001
	IABP	139 (5%)	78 (7%)	61 (4%)	
	ECMO	1 (0.04%)	1 (0.1%)	0	
	Impella	9 (0.3%)	7 (0.6%)	2 (0.1%)	
	More than one device	7 (0.3%)	4 (0.4%)	3 (0.2%)	
Intravascular imaging		232 (9%)	151 (13%)	81 (5%)	<0.001
Number of stents implanted		1.8 ± 1.2	2.6 ± 1.4	1.3 ± 0.6	<0.001
Drug-eluting stent(s) implanted		2117 (82%)	945 (89%)	1172 (78%)	<0.001
Total stent length (mm)		40.3 ± 29.7	59.7 ± 34.5	26.2 ± 13.6	<0.001
Contrast volume (ml)		229 ± 122	284 ± 137	189 ± 90	<0.001
Contrast-volume-to-creatinine-clearance ratio		4.0 ± 3.1	4.7 ± 3.4	3.4 ± 2.8	<0.001
Contrast-volume-to-creatinine-clearance ratio >3		1352 (51%)	771 (68%)	581 (38%)	<0.001
Low-osmolar contrast media		2165 (82%)	938 (84%)	1227 (80%)	0.02
Radiation dose (Gy·cm^2)		141 ± 118	194 ± 139	102 ± 79	<0.001
Fluoroscopy time (min)		24.8 ± 21.1	36.4 ± 23.9	16.3 ± 13.4	<0.001
Technical success		2472 (93%)	993 (88%)	1479 (97%)	<0.001

Abbreviations: ECMO, extracorporeal membrane oxygenator; IABP, intra-aortic balloon pump.

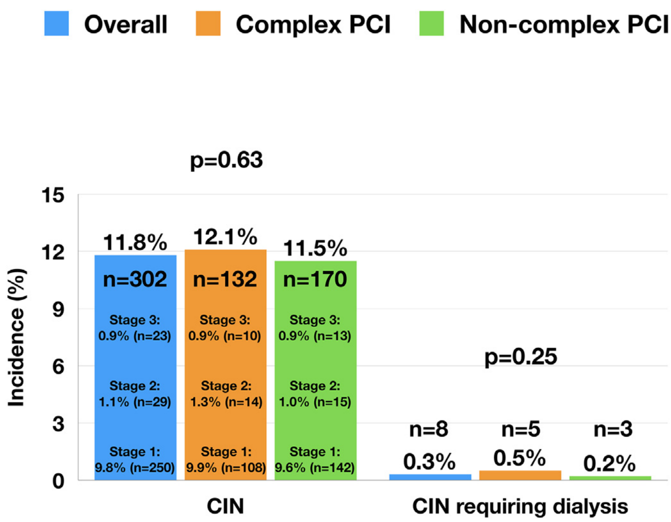

Fig. 1. Rates of CIN (with AKIN stages), according to complex vs. non-complex PCI in the overall population.

infarction (2.1% vs. 0.5%, $p < 0.001$). However, there were no differences in the incidence of cardiac tamponade, stroke, or death.

3.6. Predictors of CIN

Online Table 3 shows the univariate and multivariate analysis for the prediction of CIN. Upon multivariable adjustment, age (OR 1.54, $p < 0.001$), female sex (OR 1.51, $p = 0.02$), diabetes mellitus (OR 1.49, $p = 0.01$), LVEF (OR 0.64, $p < 0.001$), periprocedural hypotension (OR 2.86, $p < 0.001$), presentation with ACS (OR 1.86, $p < 0.001$), and contrast volume (OR 1.17, $p = 0.02$) were independently associated with CIN. Complex PCI was not a predictor of CIN.

4. Discussion

Our study findings are: 1) complex PCI is frequently performed at a high-volume tertiary-care center (38% of overall PCI volume), and 2) is associated with a similar incidence of CIN, compared with subjects undergoing non-complex PCI (12.1% vs. 11.5%); 3) these findings persisted upon multivariable adjustment; 4) however, cases who presented a high number of complexity characteristics and the subgroup of ACS patients treated with complex PCI were exposed to a higher risk of CIN.

The last decade has witnessed a global decrease in the number of PCIs performed in the U.S. [15], particularly in the context of stable coronary artery disease (CAD) [16]. However, the overall complexity of PCI has increased, due to both patient-related and angiographic factors. Bortnick et al. [17] observed that, between 1999 and 2011, there was a significant change in the characteristics of CAD patient population undergoing PCI, including an increase in mean age and in the prevalence of diabetes, hypertension, hypercholesterolemia, and chronic kidney disease, among others. Similarly, the frequency of triple-vessel and left main disease, as well as PCI on calcified and type C lesions also increased. However, overall 5-year rates of death, myocardial infarction, and repeat PCI did not change significantly, in the context of increased comorbidities and complex disease.

A variety of percutaneous interventions to treat specific subsets of CAD lesions have been developed, widely adopted, and perfected, during the last few years. For example, left main PCI has witnessed an increase in angiographic (association with multivessel disease) and procedural (treatment of distal bifurcation, utilization of two-stent techniques) complexity over the last two decades, with concomitant improvement in long-term outcomes (including mortality) [1]. Similarly, the utilization of CTO PCI in the U.S. has grown between 2009 and 2013, in parallel with an increase in procedural success and a decrease in in-hospital adverse events [2]. Additionally, rotational atherectomy is now performed routinely at specialized centers, with low rates of adverse events, even in challenging lesion subsets like CTO [6,18]. Finally, the availability and adoption of percutaneous mechanical circulatory support devices has allowed pursuing complete revascularization even in challenging settings such as high-risk patients with left main and multivessel disease, with good in-hospital and short-term outcomes [19].

Prior to this study, the concept of complex PCI per se (based on angiographic and procedural characteristics) had received little study. Giustino et al. [7] performed a patient-level pooled analysis of randomized controlled trials designed to investigate the efficacy and safety of long- versus short-term dual antiplatelet therapy in patients undergoing PCI. Complex PCI was defined as a procedure with at least one of the following characteristics: 3 vessels treated, ≥3 stents implanted, ≥3 lesions treated, bifurcation with 2 stents implanted, total stent length >60 mm, or CTO as target lesion. At a median follow-up 392 days, patients who underwent complex PCI had a higher risk of major adverse cardiac events. The study by Giustino et al. is the first providing an angiographic definition of complex PCI, which we adopted and modified, incorporating other markers of procedural complexity not available in their report (e.g., rotational/laser atherectomy).

While the available literature has focused on the impact of complex PCI on stent outcomes (mainly stent thrombosis), to the best of our knowledge no study investigated the association between complex PCI and CIN prior to our report. Globally, our data indicate that complex PCI is a safe procedure with regards to CIN risk, if patients receive adequate intravenous hydration. Upon multivariable adjustment, complex PCI was not independently associated with CIN. Older age, female sex, diabetes mellitus, lower LVEF, periprocedural hypotension, presentation with ACS, and higher contrast volume were identified as independent predictors of CIN. These associations had been previously reported in the literature [8–10,12,13], which confers strength to our findings. However, subanalyses revealed a signal towards an increased risk of CIN (including CIN requiring dialysis) in patients undergoing complex PCI in the context of an ACS, in cases presenting 5–6 complexity characteristics, and in those undergoing protected PCI. Subjects with ACS present systemic inflammation and hypotensive episodes, which, in conjunction with the higher contrast volumes and risk for stent thrombosis [7] associated with complex PCI in such context, might expose patients to an increased risk of CIN. Moreover, very complex PCI (i.e., with 5–6 complexity characteristics) might be linked to CIN via extremely high contrast volumes, periprocedural hypotension, and patients baseline comorbidities. Additionally, protected PCI - which in our series was almost exclusively provided by intra-aortic balloon pump - might still be insufficient to prevent the transient episodes of hypotension that are associated with renal hypoperfusion. However, given their post-hoc nature, such analyses should be considered hypothesis-generating only.

Our study has some limitations. First, it is an observational study, with all the bias ascribed to such type of design. Second, being a real-world registry, post-procedural creatinine was not available for

Table 3
Procedural complications and in-hospital adverse events.

Variable	Overall ($n = 2660$)	Complex PCI ($n = 1128$)	Non-complex PCI ($n = 1532$)	p-Value
Any adverse event	126 (4.7%)	87 (7.7%)	39 (2.6%)	<0.001
Coronary perforation	34 (1.3%)	30 (2.7%)	4 (0.3%)	<0.001
Cardiac tamponade	8 (0.3%)	5 (0.4%)	3 (0.2%)	0.25
Major bleeding	29 (1.1%)	17 (1.5%)	12 (0.8%)	0.08
Periprocedural myocardial infarction	31 (1.2%)	23 (2.1%)	8 (0.5%)	<0.001
Stroke	9 (0.3%)	3 (0.3%)	6 (0.4%)	0.58
In-hospital death	56 (2.1%)	25 (2.2%)	31 (2.0%)	0.73

approximately half of patients, although such problem is commonly found at a similar extent also in large national registries [13]. Third, patients for whom post-PCI creatinine data were not available had a lower CIN risk profile, so that the actual rate of CIN might have been overestimated, making our estimates more conservative. Fourth, post-PCI creatinine measurements were not performed in equal proportions on post-procedural day 1, 2, and 3. Since creatinine already starts rising within 24 h following contrast media administration in cases who will subsequently develop CIN [20], it is likely that the vast majority of those subjects were detected promptly and followed with repeated creatinine measurements on the following days. Finally, follow-up of our cohort was limited to in-hospital stay only.

5. Conclusions

Complex PCI is not associated with an increased risk of CIN in all-comers. However, it might be linked to increased rates of such complication in subjects presenting with ACS, in cases presenting extreme procedural complexity, and in those undergoing protected PCI. Further larger multicenter studies should confirm our findings and investigate novel effective strategies to decrease the risk of this serious complication.

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