Incidence, Management, Immediate and Long-Term Outcome of Guidewire and Device Related Grade III Coronary Perforations (from G3CAP - Cardiogroup VI Registry)

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Ellis grade III coronary artery perforations (G3-CAP) remain a life-threatening complication of percutaneous coronary intervention (PCI), with high morbidity and mortality and lack of consensus regarding optimal treatment strategies. We reviewed all PCIs performed in 10 European centers from 1993 to 2019 recording all G3-CAP along with management strategies, in-hospital and long-term outcome according to Device-related perforations (DP) and Guidewire-related perforations (WP). Among 106,592 PCI (including 7,773 chronic total occlusions), G3-CAP occurred in 311 patients (0.29%). DP occurred in 194 cases (62.4%), more commonly in proximal segments (73.2%) and frequently secondary to balloon dilatation (66.0%). WP arose in 117 patients (37.6%) with chronic total occlusions guidewires involved in 61.3% of cases. Overall sealing success rate was 90.7% and usually required multiple maneuvers (80.4%). The most commonly adopted strategies to obtain hemostasis were prolonged balloon inflation (73.2%) with covered stent implantation (64.4%) in the DP group, and prolonged balloon inflation (53.8%) with coil embolization (41%) in the WP group. Procedural or in-hospital events arose in 38.2% of cases: mortality was higher after DP (7.2% vs 2.6%, p = 0.05) and acute stent thrombosis 3-fold higher (3.1% vs 0.9%, p = 0.19). At clinical follow-up, median 2 years, a major cardiovascular event occurred in one-third of cases (all-cause mortality 8.2% and 7.1% respectively, without differences between groups). In conclusion, although rare and despite improved rates of adequate perforation sealing G3-CAP cause significant adverse events. DP and WP result in different patterns of G3-CAP and management strategies should be based on this classification. **(Am J Cardiol 2021;143:37–45)**

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See supplemental appendix for full list of investigators.

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Ellis grade 3 coronary artery perforation (G3-CAP) or coronary rupture is the most severe form of perforation and a rare but life-threatening complication of percutaneous coronary intervention (PCI).[1,2] The overall incidence of coronary perforation ranges from 0.1% to 3.0%.[3–6] However, most studies do not define the perforation grade or provide data on therapeutic maneuvers attempted to resolve the perforation. The largest experience focusing on G3-CAP was a 2-center study which included only 56 patients[7]: authors reported a high mortality rate (18% intraprocedural and in-hospital mortality; 15% long term mortality) and major adverse cardiac event (MACE) up to 55% during hospitalization, in line with previous reports.[8–11] Although rare, the incidence of perforation has not decreased over time,[3,7,8,11,12] reflecting the increased complexity of PCI including chronic total occlusion (CTO) and extensive use of novel guidewires and devices.[6] The optimal management of G3-CAP is extensively debated and a lack of consensus on its optimal management persists[13] Contemporary

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registries[1,12,14–16] based on national PCI and including large cohorts of patients reported several clinical and procedural predictors of CP and a worse short and long-term outcome compared to an uncomplicated PCI. However, these studies did not specifically define the perforation grade (including together all CP despite their increasing severity) and provided limited data on the coronary equipment causing perforation or the subsequent therapeutic strategy to treat it. In light of these limitations, our registry included only G3-CAP reporting the procedural characteristics, the management strategies and the acute and long-term outcomes according to the underlying mechanism of perforation, differentiating among guidewire and device-related perforations (DP).

Methods

Data from 10 European institutions (9 Italian, 1 Spanish, see Appendix) participating in the G3-CAP registry between 1998 and 2018 were retrospectively collected. All patients who had a CAP as a complication of PCI were initially selected. All procedural angiograms were reviewed by 2 experienced interventional cardiologists in a *core-lab analysis* to identify cases of G3-CAP as defined by the Ellis criteria[2]: grade I, II or IV (cavity-spilling) were excluded. Baseline clinical, angiographic and procedural characteristics, DP or wires-related perforations (WP), immediate management, acute and long-term outcomes were retrospectively entered in a dedicated online database (http://www.cardiogroup.org/GIII-CAP). The therapeutic strategy following G3-CAP was chosen by the operator. Long-term follow-up was obtained during office visits or by phone contact. The research was conducted according to the Local Research Ethic Committee regulations.

G3-CAP or coronary rupture was defined by the Ellis criteria as extravasation of blood through a frank (1mm) perforation (but not into a heart chamber or coronary sinus - Ellis IV).[2] WP was defined as perforation following distal advancement of a guidewire out of the vessel architecture (Figure 1, *left panel*); DP was defined as blood extravasation following the correct (e.g., expansion of a non-compliant balloon) or incorrect (e.g. balloon advancement over the guidewire tip) use of a coronary angioplasty device (Figure 1, *right panel*). Successful treatment of G3-CAP was defined as the absence of angiographic evidence of contrast extravasation or clinical or echocardiographic signs of cardiac tamponade at the end of the procedure. Periprocedural myocardial infarction was defined according to the Fourth Universal Definition of MI.[17] Target lesion revascularization (TLR), Target vessel revascularization (TVR) and Stent thrombosis (ST) were defined using the Academic Research Consortium definitions.[18] MACE was defined as a combination of all-cause mortality, MI, TLR, TVR, and need for coronary artery bypass graft (CABG). Adverse procedural and in-hospital events were defined as the need for cardiopulmonary resuscitation, in-hospital MI, TLR, urgent CABG/surgical repair, and death. The long-term primary end points were defined as death from any cause, TVR, TLR, CABG and MACE at any time during the in-hospital stay or at follow-up. The secondary endpoint was the incidence of ST.[19]

Student's t test or Mann-Whitney test were used for quantitative variables, expressed as mean and standard deviation or median and interquartile range as appropriate. Fisher's exact test or chi-squared test were used for qualitative variables, reported as frequencies and percentages. Multiple logistic regression analysis was performed including the entire sample using a back-ward stepwise logistic regression model and likelihood ratio, including the variables with $p < 0.1$ in the univariate analysis performed among patients with and without in-hospital events and those judged to be of clinical importance from previously published literature. Variables included in the model were: age, left ventricular ejection fraction, gender, ST-elevation myocardial infarction at presentation, DP (vs WP) atherectomy use, perforation in a small vessel (<2.5 mm), presence of tortuous vessels, glycoprotein IIb/IIIa inhibitors use. Results were expressed as an odds ratio (OR) and 95%

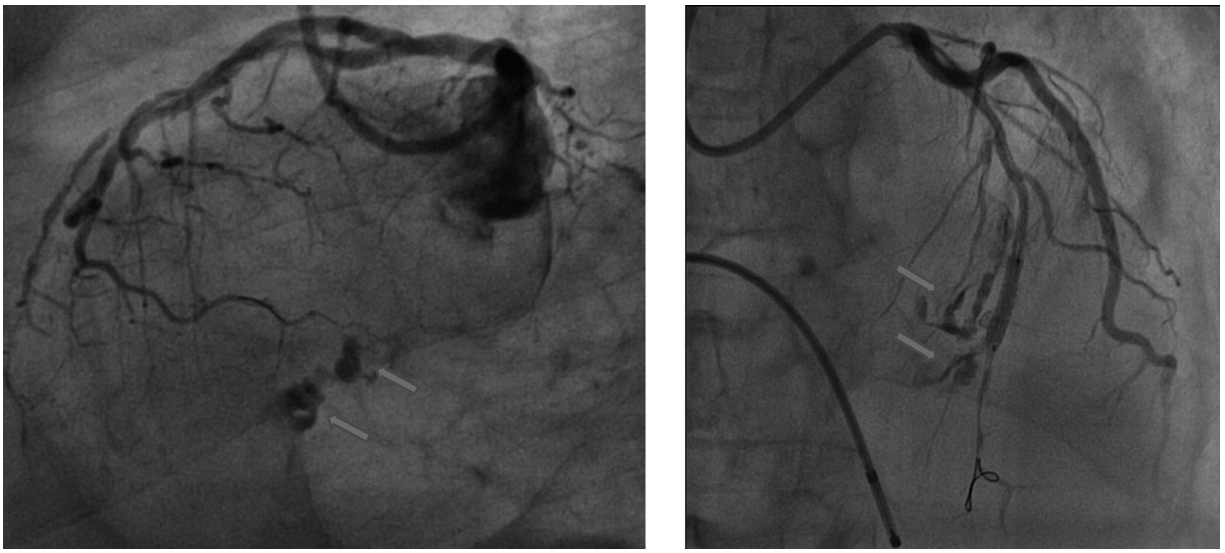

Figure 1. *Left Panel*: Grade III Device related perforation (DP) occurred after postdilatation of a Drug Eluting Stent in distal Left Anterior Descending (LAD). *Right Panel*: Grade III wire related perforation (WP) occurred after distal migration of a rotawire fragment in distal LAD.

confidence interval (95% CI). Long-term survival curves for each group were plotted with the Kaplan−Meier method, and comparisons were performed with the log-rank test. All statistical tests were 2-sided. Results were considered significant if p was <0.05. Statistical analyses were performed using SPSS Version 24 (IBM Corp Armonk, New York) and Graph Pad Prism 6 (GraphPad Software Inc, California).

Results

From 106,592 PCI procedures (including 7,773 CTO PCIs) we identified 311 patients with G3-CAP, giving an overall incidence of 0.29%, ranging from 0.15% (1998 to 2000) to 0.33% (2016 to 2018, see Figures 2, *panel A* and Figure 3). Patients' baseline clinical demographics are shown in Table 1. Amongst them, 194 G3-CAP (62.4%) were caused by a device (DP group), while 117 G3-CAP (37.6%) were related to guidewire manipulation (WP group). Hypertension was more common in the WP group (83.8 vs 73.1%, p = 0.02) with no other significant differences in baseline clinical characteristics between the 2 groups.

Baseline lesion characteristics are outlined in Table 2. Overall, 89% of lesions were complex with no differences between DP and WP (p = 0.39). In the CTO-PCI subgroup, WPs were most prevalent (37.6% vs 22.3% in DP group, p < 0.01). More than half of DPs were caused by balloons dilatations occurring during predilation (47.5%) or postdilation (52.5% of cases). WPs were mainly related to non-workhorse or CTO dedicated guidewires (61.3%; n = 74/117) mainly polymer jacket coated (n = 57) and tapered (n = 28) wires (Table 3).

The treatment of G3-CAP is outlined in Table 4. Following G3-CAP, pericardiocentesis for cardiac tamponade was required in half of cases, similar in both groups, while emergent intra-aortic balloon pump was used more commonly in the DP group (12.4% vs 6.0% in WP group, p= 0.049). The overall success rate in sealing G3-CAPs was 90.7% with no differences between groups and usually required multiple maneuvers (80.4%). Emergency CABG or surgical repair were rarely undertaken (6.7% DP and 3.4% WP group, p = 0.17) with low success rates in both groups.

Combined procedural and in-hospital events were 38.2% (42.3% in DP vs 31.6% in WP; p = 0.06, Table 5). Cardiopulmonary resuscitation was required more frequently in the DP group (13.9%) than the WP group (4.3%; p < 0.01). ST immediately post stent deployment occurred in 7 patients (2.2%; 5 cases after covered stent [CS] implantation). Of note, 5 of these 7 patients received heparin reversal. Intraprocedural mortality was 5.5% for the study population, significantly higher in DP (7.2% vs 2.6%, p = 0.05). During in-hospital follow-up, 9% of patients required pericardial drainage as a second procedure (separate from the index), more commonly in the WP group

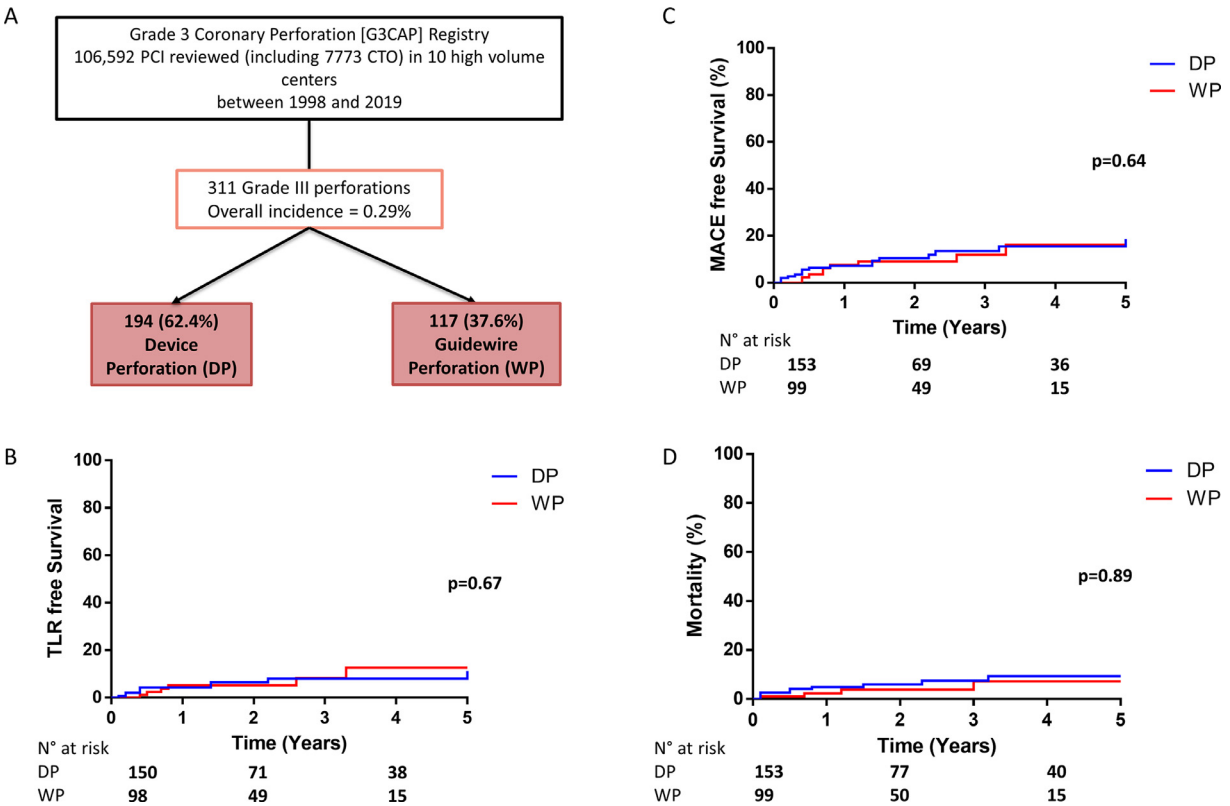

Figure 2. Study flow chart (*panel A*) and Kaplan−Meier curves (*panels B, C, and D*) (*B*)MACE free survival at long follow-up in patients experienced a grade 3 Device Perforation (DP) versus Wire Perforation (WP). (*C*) TLR free survival at long follow-up in patients experienced a grade 3 Device Perforation (DP) versus Wire Perforation (WP). (*D*) Survival (mortality) at long follow-up in patients experienced a grade 3 Device Perforation (DP) versus Wire Perforation (WP).

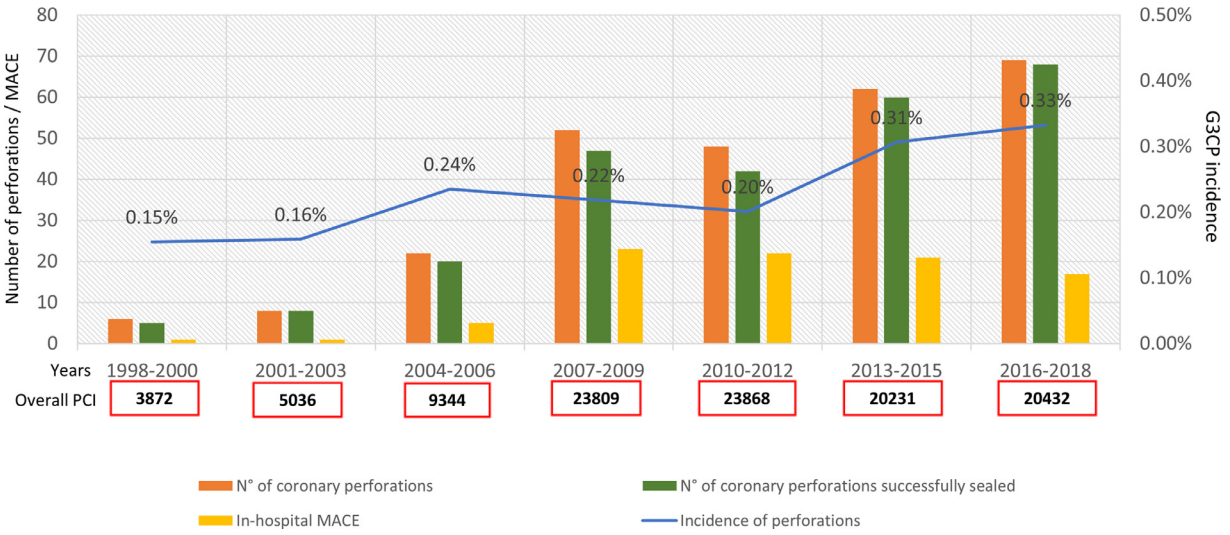

Figure 3. Incidence, treatment and in-hospital MACE of grade 3 Coronary Perforations from 1998 to 2018. Graph showing number of cases of grade III coronary perforation (orange), number of cases of successfully treated (green), and combined in-hospital and procedural major adverse event rates over each 3-year period from 1998 to 2018. Figures in white boxes represent total number of percutaneous coronary intervention procedures performed within each period. MACE: major adverse cardiac event. Blue line shows per period incidence of perforation among the overall number of PCI performed within each period. (Color version of figure is available online.)

(13.7% vs 6.2%, p = 0.04). The overall in-hospital mortality was 6.1%, nonsignificantly higher in the DP group (7.2% vs 4.3%, p = 0.18). At multivariate logistic regression, female sex (OR 7.18 [95% CI 2.16 to 23.80]; p = 0.001) and glycoprotein IIb-IIIa inhibitors use (OR 8.94 [95% CI 2.01 to 39.66]; p = 0.004) were independent predictors of in-hospital adverse events.

Long-term follow-up was available in 87% of the cohort (median 2.0 years [IQR 0.8 to 3.6], angiographic follow-up in approximately 30%. The overall mortality rate during follow-up was 8.2% with no significant differences among groups (Figure 2, *panels B, C, and D*). Definite ST occurred in 5 patients (2.0%), all treated with CS implantation following a DP. Overall, MACE occurred in one-third of cases (Table 6).

A subgroup of 32 patients (10.2%) had history of previous CABG. Graft perforations accounted for 2.6% of cases (n = 8, 2 arterial grafts and 6 vein grafts) and procedural pericardiocentesis was necessary for 5 patients (15.6%), while in-hospital pericardial drainage for only 1 patient. Death and MACE rates at follow-up were 21.8% (7/32 patients) and 25.0% (8/32 patients) respectively.

Discussion

To our knowledge this is the largest multicenter registry focusing on G3-CAP. The main findings of this study are: (1)

Table 1
Baseline clinical characteristics

Variable	All (n = 311)	Device perforation (n = 194)	Wire perforation (n = 117)	p value
Age (years)	70.5 ± 10.7	70.9 ± 10.6	69.9 ± 11	0.40
Men	233, 74.9%	144, 74.2%	89, 76.1%	0.41
Ejection fraction (%)	52 ± 9	52 ± 9	51 ± 10	0.68
Prior CAD	163, 53.1%	97/, 50.8%	66, 56.9%	0.18
Prior PCI	134, 43.6%	81, 42.4%	53, 45.7%	0.33
Prior CABG	32, 10.4%	20, 10.5%	12, 10.3%	0.57
Cardiovascular risk factors				
Family history of CAD	79, 25.5%	49, 25.4%	30, 25.6%	0.53
Hypertension	239, 77.1%	141, 73.1%	98, 83.8%	0.02
Hypercholesterolemia	179, 57.7%	111, 57.5%	68, 58.1%	0.51
Smoke (current/former)	112, 36.1%	67, 34.5%	41, 39.3%	0.35
Diabetes mellitus	106, 33.2%	63, 32.6%	34, 36.8%	0.48
Clinical presentation				
Stable angina pectoris	175, 56.3%	110, 56.7%	65, 55.6%	0.47
Acute coronary syndrome	136, 43.7%	84, 43.3%	51, 43.6%	0.50
Multivessel coronary disease	249, 80.1%	153, 78.9%	96, 82.1%	0.30
eGFR <30 mL/min	15, 5.6%	10, 5.7%	5, 5.3%	0.57

CABG = coronary artery by-pass graft; CAD = coronary artery disease; eGFR = estimated glomerular filtration rate; PCI = percutaneous coronary intervention.

All values are numbers and percentages or mean and standard deviation.

Table 2
Lesion characteristics

Variable	All (n = 311)	Device perforation (n = 194)	Wire perforation (n = 117)	p value
Native vessel perforation	303, 97.4%	188, 96.9%	115, 98.3%	0.36
Left Main	7, 2.3%	6, 3.1%	1, 0.9%	0.19
Left Anterior Descending	140, 45%	96, 49.5%	44, 37.6%	0.08
Diagonal	16, 6.2%	3, 1.5%	13, 11.3%	0.03
Septal	7, 2.3%	1, 0.5%	6, 5.2%	0.03
Left circumflex	58, 18.6%	37, 19.1%	21, 17.9%	0.46
Marginal	12, 3.9%	7, 3.6%	5, 4.3%	0.85
Right	91, 29.3%	48, 24.7%	43, 36.8%	0.02
Posterior Descending Artery	6, 1.9%	1, 0.5%	5, 4.3%	0.04
Posterolateral branch	28, 9.1%	10, 5.2%	18, 15.7%	<0.01
Ramus Intermedius	7, 2.3%	5, 2.6%	2, 1.7s%	0.41
Graft perforation	8, 2.6%	6, 3.1%	2, 1.7%	0.37
LIMA/RIMA graft	2, 0.64%	2, 1.0%	0	N/A
SVG	6, 1.9%	4, 2.1%	2, 1.7%	0.37
Lesion and vessel morphology				0.50
Type A	5, 1.6%	4, 2.1%	1, 0.9%	0.33
Type B1	14, 4.5%	10, 5.2%	4, 3.4%	
Type B2	90, 28.9%	67, 34.5%	23, 19.6%	
Type C	202, 65%	113, 58.2%	89, 76.1%	
Moderate/severe calcium	132, 42.4%	84, 43.3%	48, 41.0%	0.39
Small vessel < 2.5 mm	92, 29.6%	42, 21.6%	50, 42.7%	<0.01
Bifurcation	80, 25.7%	50, 25.8%	30, 25.6%	0.65
Tortuous vessels	72, 23.2%	47, 24.2%	25, 21.4%	0.33
CTO	87, 28.1%	43, 22.3%	44, 37.6%	<0.01
- J-CTO score	1.76 ± 1.4	2.0 ± 1.6	1.5± 1.3	0.14

CTO = chronic total occlusion; LIMA = left internal mammary artery; RIMA = right internal mammary artery; SVG = saphenous vein graft.
All values are numbers and percentages or mean and standard deviation.

G3-CAP rates increased over time but treatment became more effective; (2) DP and WP produce different patterns of G3-CAP and management strategies should be based on this classification: balloons were the leading cause of DP while WPs were usually due to CTO wires; prolonged balloon inflation with CS implantation and prolonged balloon inflation with coil embolization were the most feasible and commonly adopted hemostatic strategies in DP and WP, respectively; (3) Hard event rates -including mortality and ST- remain high in the short- and long-term especially in DP.

Table 3
Procedural characteristics and equipment causing perforation

Variable	Device perforation (n = 194)	Wire perforation (n = 117)	p value
Glycoprotein IIb/IIIa inhibitors	14, 7.2%	12, 10.3%	0.23
Unfractioned heparin	186, 95.9%	115, 98.3%	0.20
Device causing rupture			
Semi-compliant balloon	49, 25.3%	–	–
Non-compliant balloon	79, 40.7%	–	–
Cutting balloon	5, 2.6%	–	–
Stent	43, 22.2%	–	–
Rotational atherectomy	10, 5.2%	–	–
Directional atherectomy	2, 1.0%	–	–
Microcatheter	5, 2.0%	–	–
Guideliner	1, 0.5%	–	–
IVUS/OCT	0		
Wire causing rupture			
Workhorse guidewires	–	43, 38.7%	–
Non-workhorse/CTO guidewires*	–	68, 61.3%	–
- Tip load >3gr	–	16	–
- Polymer-jacketed	–	57	–
- Tapered	–	28	–
- Extra support	–	7	–
- Tip load > 3gr, polymer-jacketed	–	8	–
- Tip load > 3gr, non-tapered, non-polymer -jacketed	–	8	–

IVUS = intravascular ultrasound; OCT = optical coherence tomography.
All values are numbers and percentages.

Table 4
Treatment of grade III coronary perforation

Variable	All (n = 311)	Device perforation (n = 194)	Wire perforation (n = 117)	p value
Treatment of rupture				
Pericardiocentesis	155, 49.8%	101, 52.1%	52, 44.4%	0.36
Emergency IABP	31, 10.0%	24, 12.4%	7, 6.0%	0.049
Heparin reversal	114, 36.7%	73, 37.6%	41, 35.0%	0.37
Successful	71, 62.3%	47, 64.3%	24, 58.5%	0.54
Prolonged balloon inflation	205, 65.9%	142, 73.2%	63, 53.8%	<0.01
Successful	15, 7.3%	4, 2.8%	11, 17.5%	0.03
Non covered stent implantation	32, 10.2%	27, 14.4%	4, 3.4%	0.03
Successful	7, 21.9%	6, 22.2%	1, 25.0%	0.33
Covered stent implantation	150, 48.2%	125, 64.4%	25, 21.4%	<0.01
Successful	131, 84%	109, 87.2%	22, 88%	0.37
Ping pong technique	18, 5.8%	16, 8.2%	2, 1.7%	0.01
Successful	17, 94%	15, 93.4%	2, 100%	0.50
Coil embolization	58, 18.6%	10, 5.2%	48, 41.0%	<0.01
Successful	54, 77.1%	8, 80%	46, 95.8%	<0.01
Glue embolization	0	0	0	N/A
Fat embolization	1, 0.3%	0	1, 0.9%	0.38
Successful	1, 100%	0	1, 100%	0.06
Surgical repair of perforation	17, 5.5%	13, 6.7%	4, 3.4%	0.17
Successful	8, 47.1%	6, 46.1%	2, 50%	0.28
Other maneuver	7, 2.5%	6, 3.5%	1, 0.9%	0.17
Successful	5, 71.4%	5, 83.3%	0, 0.0%	0.28
Multiple maneuvers used	250, 80.4 %	159, 82%	91, 77.8%	0.06
Overall successful of maneuvers	282, 90.7%	176, 90.7%	106, 90.6%	0.56

IABP = intra-aortic balloon pump.
All values are numbers and percentages.

G3-CAP remains a challenging situation for interventional cardiologists. The incidence appears to increase over time in our study, probably due to a more complex disease such as calcific, tortuous, multivessel disease or CTOs being routinely treated, even in older and frail patients in current clinical practice. All recently published registries support this nonsignificant trend of a progressive increase in G3-CAPs over time.[1,12,15,16,22] Approximately 30% of perforations in our registry involved CTO procedures. Spread of CTO expertise among the interventional community, with the hybrid algorithm being widely adopted to increase success rates[23] may explain this perforation rate. Furthermore, CTO techniques are increasingly implemented in everyday practice to resolve common complications[20] or to treat complex high-risk patients,[21] developments in operator skills and device therapy have increased the feasibility of attempting more complex (and higher risk) interventions. However, the same improvement

Table 5
Procedural and in-hospital complications

Variable	All (n = 311)	Device perforation (n = 194)	Wire perforation (n = 117)	p value
Procedural complications				
TIMI flow 0-1 (end of procedure)	106, 34.1%	53, 27.3%	53, 45.3%	<0.01
Residual dissection	21, 6.8%	15, 7.7%	6, 5.1%	0.26
Residual thrombosis	19, 6.1%	15, 7.7%	4, 3.4%	0.09
Residual stenosis > 30	42, 13.5%	26, 13.5%	16, 13.7%	0.49
Cardiopulmonary resuscitation	32, 10.3%	27, 13.9%	5, 4.3%	<0.01
Death	17, 5.5%	14, 7.2%	3, 2.6%	0.05
In-hospital events				
Acute stent thrombosis	7, 2.2%	6, 3.1%	1, 0.9%	0.19
CABG	3, 1%	2, 1.0%	1, 0.9%	0.67
Pericardial drainage*	28, 9.0%	12, 6.2%	16, 13.7%	0.03
MI (including PMI)	88, 28.3%	58, 29.9%	30, 25.6%	0.17
TLR	9, 2.9%	8, 4.1%	1, 0.9%	0.11
Overall in-hospital mortality	19, 6.1%	14, 7.2%	5, 4.3%	0.18
Combined procedural and in-hospital events	119, 38.2%	82, 42.3%	37, 31.6%	0.06

CABG = coronary artery by-pass graft; MI = myocardial infarction; PMI = periprocedural myocardial infarction; TIMI = thrombolysis in myocardial infarction; TLR = target lesion revascularization.
All values are numbers and percentages.
* Pericardial drainage occurred during PCI where not count as "in-hospital."

Table 6
Long-term outcome during follow-up

	All255/311 (96)	Device perforation153/194 (97)	Wire perforation102/117 (95)	p value
Follow-up time, years (median [IQR])	2.0 [0.8-3.6]	3.4 [1.8-8.2]	2.4 [1.6-5.1]	0.84
Death	21, 8.3%	14, 9.3%	7, 6.8%	0.32
Cardiovascular death	11, 4.6%	7, 5.0%	4, 4.0%	0.49
Target Lesion Revascularization	18, 7.1%	12, 7.8%	6, 5.9%	0.37
Target Vessel Revascularization	22, 8.7%	14, 9.2%	8, 7.9%	0.45
Stent thrombosis (subacute/late/very late)	5, 2.0%	5, 3.3%	0, 0.0%	0.08
Coronary Artery By-pass Graft	5, 2.0%	2, 1.3%	3, 2.9%	0.32
Major Adverse Cardiac Event	71, 27.8%	47, 30.7%	24, 23.5%	0.95

in devices and techniques made improve and simplify the treatment of complications such as coronary perforations, which appear to translate into a reduction of in-hospital MACE over time with a higher rate of successful sealing of the perforation (Figure 3). As a matter of fact, in contrast with previous studies, our registry meticulously analyzed the specific cause of G3-CAP which represents a unique aspect of our study.

Prolonged balloon inflation was the initial strategy in a large percentage of patients in both groups, with subsequent treatment strategies differing between the WP and DP groups. CS implantation was more commonly used to obtain hemostasis in DP patients, while coil embolization was the treatment strategy in almost half of WP cases, with successful deployment in 95% of cases.

Current flow-charts[13,24] for CAP treatment suggest prompt reversal of anticoagulation with protamine administration as the first line therapeutic option to treat G1 and G2 CAP, after removal of all the intracoronary equipment, along with prolonged balloon inflation. Conversely, in patients with G3-CAP protamine use and its timing still remain a matter of debate: indeed, it may predispose to ST especially in the setting of CS stent deployment. In previous studies intraprocedural ST was described in up-to 4.7% of cases and subacute/late and very late ST in 5% to 23.8%.[25–28] In our registry we found an overall ST rate of approximately 4%. However, our findings are limited to the previous generation of polytetrafluoroethylene CS while newer single-layered device[29,30] showed favorable efficacy especially with regard to thrombotic events.[31]

Emergency intra-aortic balloon pump and cardiopulmonary resuscitation were more frequently required in the DP group, likely due to the abrupt hemodynamic instability after a proximal-segment perforation leading to cardiac

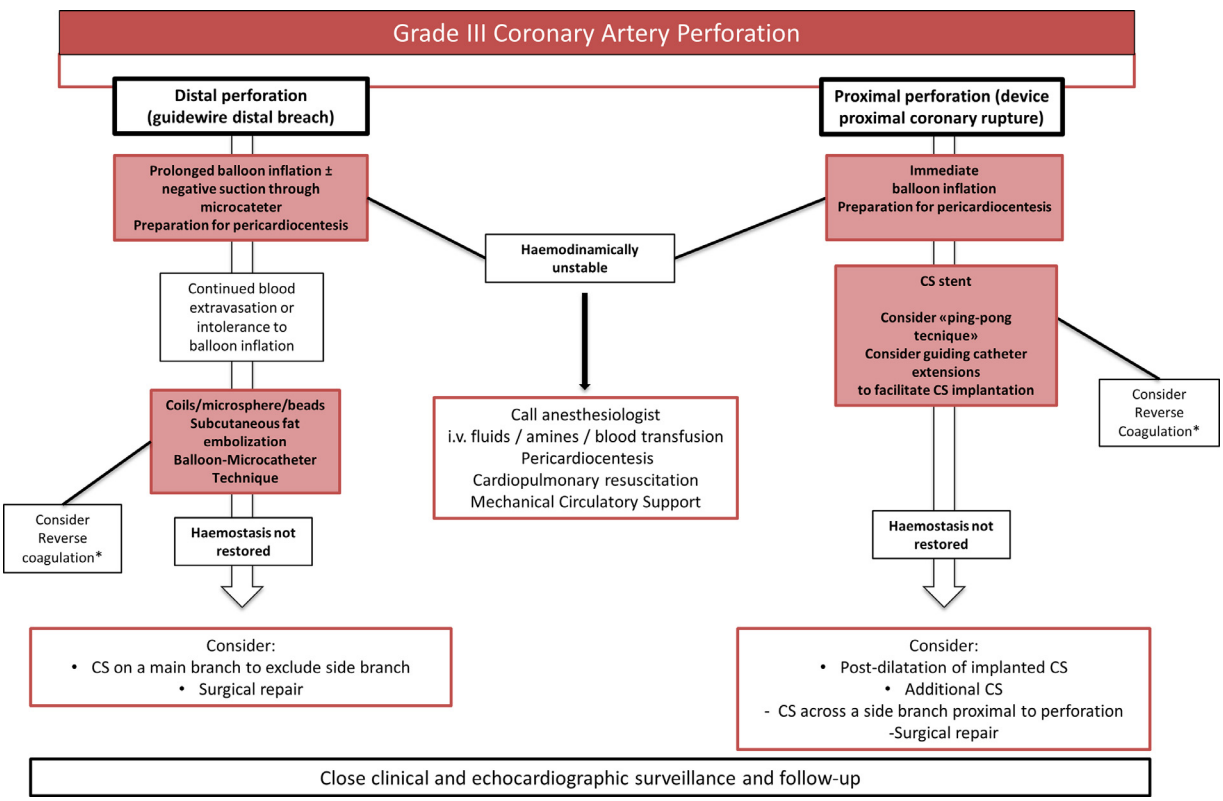

Figure 4. Flow-chart of grade III coronary artery perforation treatment. *Coagulation reversal is indicated as a final step after achieving adequate hemostasis and after removal all the equipment from the coronary artery. CS = covered stent.

tamponade whereas. Otherwise, late in-hospital events were more common in the WP group, mainly driven by a higher need for pericardial drainage, due to pericardial tamponade probably caused by the incomplete sealing of the distal perforation leading to continuous spillage into the pericardial cavity. This has been previously reported,[32] and stresses the importance of a close surveillance of these patients in the intensive care unit.[33] Of note, in the WP group, 41 patients (48%) underwent coil implantation and of those only 2 required in-hospital pericardial drainage.

As previously described,[34] we found that CABG-related G3-CAP, even if uncommon, were associated with high risk of death and MACE at follow-up. Our study also confirms that post-CABG patients are at equal risk for tamponade compared to non-CABG patients, refuting the misleading concept of "protection" associated with previous pericardiotomy.

Potential strategies to minimize pericardial effusion differs between DP and WP (Figure 4) including the use of a dual catheter approach ("*ping-pong technique*")[21] to enable rapid CS implantation minimizing the risk of pericardial tamponade and the *Balloon-Microcatheter-Technique*[35] to allow coil embolizations in the DP site during a controlled occlusion of the targed vessel. Both techniques demonstrate a very high success rate in our registry.

Despite the overall high success rate of 1 or more maneuvers to obtain hemostasis (>90% of patients), in-hospital and long term mortality remained high (6.4% and 8.3%), in line with previously reported studies.[7,8] Finally, female sex resulted linked to a worse in-hospital prognosis after a G3-CAP, in line with contemporary national-bases CP registries[12,15,16,22] and other studies[36] focusing on sex-based differences in complications rate and outcome after PCI.

The main limitation of this study is its retrospective nature, with all the inherent bias. Given the emergency setting of a potentially fatal G3-CAP, some specific information may be lost (eg. timing of hepatin reversal). Finally, although the mortality rate was numerically higher in DP, the present registry was not conceived and powered to assess differences in short and long term outcome in DP vs WP.

Conclusions

Although G3-CAP remains a rare complication of PCI, its incidence has been steadily rising over time, likely due to the increasing patient and lesion complexity in current clinical practice. We noted an improvement in the rates of adequate perforation sealing over time. DP and WP produce different patterns of G3-CAP and management strategies should be based on this classification. All interventional cardiology laboratories must be adequately equipped, and its staff trained, to deal with this challenging situation.

Authors' Contributions

Enrico Cerrato: Conceptualization, Methodology. Francesco Colombo, Antonio Mangieri, Barbara Bellini, Fabrizio D'Ascenzo Alfonso Ielasi, Michele De Benedictis: Data curation. Enrico Cerrato, Marco Pavani, Umberto Barbero: Writing- original draft preparation. Massimo Mancone Javier Escaned, Matteo Montorfano, Ferdinando Varbella: Visualization, investigation. Enrico Cerrato Lorenzo Azzalini: Supervision. Nicola Ryan Giorgio Quadri, Francesco Tomassini, Davide Giacomo Presutti, Simone Calcagno, Alfonso Franzè: Writing- reviewing and editing.

Disclosures

The authors have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.12.041.

1. Guttmann OP, Jones DA, Gulati A, Kotecha T, Fayed H, Patel D, Crake T, Ozkor M, Wragg A, Smith EJ, Weerackody R, Knight CJ, Mathur A, O'Mahony C. Prevalence and outcomes of coronary artery perforation during percutaneous coronary intervention. *EuroIntervention J Eur Collab Work Group Interv Cardiol Eur Soc Cardiol* 2017;13:e595–e601.
2. Ellis SG, Ajluni S, Arnold AZ, Popma JJ, Bittl JA, Eigler NL, Cowley MJ, Raymond RE, Safian RD, Whitlow PL. Increased coronary perforation in the new device era. Incidence, classification, management, and outcome. *Circulation* 1994;90:2725–2730.
3. Gruberg L, Pinnow E, Flood R, Bonnet Y, Tebeica M, Waksman R, Satler LF, Pichard AD, Kent KM, Leon MB, Lindsay J. Incidence, management, and outcome of coronary artery perforation during percutaneous coronary intervention. *Am J Cardiol* 2000;86:680–682. A8.
4. Gunning MG, Williams IL, Jewitt DE, Shah AM, Wainwright RJ, Thomas MR. Coronary artery perforation during percutaneous intervention: incidence and outcome. *Heart Br Card Soc* 2002;88:495–498.
5. Ramana RK, Arab D, Joyal D, Steen L, Cho L, Lewis B, Liu J, Loeb H, Leya F. Coronary artery perforation during percutaneous coronary intervention: incidence and outcomes in the new interventional era. *J Invasive Cardiol* 2005;17:603–605.
6. Kinnaird T, Anderson R, Ossei-Gerning N, Cockburn J, Sirker A, Ludman P, deBelder M, Walsh S, Smith E, Hanratty C, Spratt J, Strange J, Hildick-Smith D, Mamas MA, British Cardiovascular Intervention Society and the National Institute for Cardiovascular Outcomes Research. Legacy effect of coronary perforation complicating percutaneous coronary intervention for chronic total occlusive disease: an analysis of 26 807 cases from the British cardiovascular intervention society database. *Circ Cardiovasc Interv* 2017;10.
7. Al-Lamee R, Ielasi A, Latib A, Godino C, Ferraro M, Mussardo M, Arioli F, Carlino M, Montorfano M, Chieffo A, Colombo A. Incidence, predictors, management, immediate and long-term outcomes following grade III coronary perforation. *JACC Cardiovasc Interv* 2011;4:87–95.
8. Shimony A, Zahger D, Van Straten M, Shalev A, Gilutz H, Ilia R, Cafri C. Incidence, risk factors, management and outcomes of coronary artery perforation during percutaneous coronary intervention. *Am J Cardiol* 2009;104:1674–1677.
9. Javaid A, Buch AN, Satler LF, Kent KM, Suddath WO, Lindsay J, Pichard AD, Waksman R. Management and outcomes of coronary artery perforation during percutaneous coronary intervention. *Am J Cardiol* 2006;98:911–914.
10. Fukutomi T, Suzuki T, Popma JJ, Hosokawa H, Yokoya K, Inada T, Hayase M, Kondo H, Ito S, Suzuki S, Itoh M. Early and late clinical outcomes following coronary perforation in patients undergoing percutaneous coronary intervention. *Circ J Off J Jpn Circ Soc* 2002;66:349–356.
11. Hendry C, Fraser D, Eichhofer J, Mamas MA, Fath-Ordoubadi F, El-Omar M, Williams P. Coronary perforation in the drug-eluting stent era: incidence, risk factors, management and outcome: the UK experience. *EuroIntervention J Eur Collab Work Group Interv Cardiol Eur Soc Cardiol* 2012;8:79–86.

12. Kinnaird T, Kwok CS, Kontopantelis E, Ossei-Gerning N, Ludman P, deBelder M, Anderson R, Mamas MA, British Cardiovascular Intervention Society and the National Institute for Cardiovascular Outcomes Research. Incidence, determinants, and outcomes of coronary perforation during percutaneous coronary intervention in the United Kingdom between 2006 and 2013: an analysis of 527 121 cases from the British cardiovascular intervention society database. *Circ Cardiovasc Interv* 2016;9.
13. Giannini F, Candilio L, Mitomo S, Ruparelia N, Chieffo A, Baldetti L, Ponticelli F, Latib A, Colombo A. A practical approach to the management of complications during percutaneous coronary intervention. *JACC Cardiovasc Interv* 2018;11:1797–1810.
14. Harnek J, James S, Lagerqvist B. Coronary artery perforation and tamponade − incidence, risk factors, predictors and outcomes from 12 years' data of the SCAAR registry −. *Circ J* 2019;84:43–53.
15. Parsh J, Seth M, Green J, Sutton NR, Chetcuti S, Dixon S, Grossman PM, Khandelwal A, Dupree JM, Gurm HS. Coronary artery perforations after contemporary percutaneous coronary interventions: Evaluation of incidence, risk factors, outcomes, and predictors of mortality. *Catheter Cardiovasc Interv Off J Soc Card Angiogr Interv* 2017;89:966–973.
16. Rakowski T, Węgiel M, Siudak Z, Plens K, Dziewierz A, Birkemeyer R, Kleczyński P, Tokarek T, Rzeszutko Ł, Dudek D. Prevalence and predictors of coronary artery perforation during percutaneous coronary interventions (from the ORPKI National Registry in Poland). *Am J Cardiol* 2019;124:1186–1189.
17. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD, Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction. Fourth universal definition of myocardial infarction (2018). *J Am Coll Cardiol* 2018;72:2231–2264.
18. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, Es G-A van, Steg PG, Morel M, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW, Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation* 2007;115:2344–2351.
19. Spitzer E, McFadden E, Vranckx P, Garcia-Garcia HM, Seltzer JH, Held C, Vries T de, Menon V, Brown KJ, Soliman OII, Onuma Y, Lopes RD, Stone GW, Cutlip DE, Serruys PW. Critical appraisal of contemporary clinical endpoint definitions in coronary intervention trials. *JACC Cardiovasc Interv* 2019;12:805–819.
20. Ben-Gal Y, Weisz G, Collins MB, Genereux P, Dangas GD, Teirstein PS, Singh VP, Rabbani LE, Kodali SK, Sherman W, Leon MB, Moses JW. Dual catheter technique for the treatment of severe coronary artery perforations. *Catheter Cardiovasc Interv Off J Soc Card Angiogr Interv* 2010;75:708–712.
21. Azzalini L, Tzanis G, Mashayekhi K, Uretsky BF, Ojeda S, Pan M, Rinfret S, Avran A, Alaswad K, Yamane M, Karmpaliotis D, Brilakis ES, Carlino M, Ybarra LF. Solving challenging situations and complications in everyday percutaneous coronary intervention using chronic total occlusion techniques. *J Invasive Cardiol* 2020;32:E63–E72.
22. Harnek J, James S, Lagerqvist B. Coronary artery perforation and tamponade - incidence, risk factors, predictors and outcomes from 12 years' data of the SCAAR registry. *Circ J Off J Jpn Circ Soc* 2019;84:43–53.
23. Brilakis ES, Banerjee S, Karmpaliotis D, Lombardi WL, Tsai TT, Shunk KA, Kennedy KF, Spertus JA, Holmes DR, Grantham JA. Procedural outcomes of chronic total occlusion percutaneous coronary intervention: a report from the NCDR (National Cardiovascular Data Registry). *JACC Cardiovasc Interv* 2015;8:245–253.
24. Muller O, Windecker S, Cuisset T, Fajadet J, Mason M, Zuffi A, Doganov A, Eeckhout E. Management of two major complications in the cardiac catheterisation laboratory: the no-reflow phenomenon and coronary perforations. *EuroIntervention J Eur Collab Work Group Interv Cardiol Eur Soc Cardiol* 2008;4:181–183.
25. Pavani M, Cerrato E, Latib A, Ryan N, Calcagno S, Rolfo C, Ugo F, Ielasi A, Escaned J, Tespili M, Conrotto F, Mancone M, Colombo A, Varbella F. Acute and long-term outcomes after polytetrafluoroethylene or pericardium covered stenting for grade 3 coronary artery perforations: Insights from G3-CAP registry. *Catheter Cardiovasc Interv Off J Soc Card Angiogr Interv* 2018;92:1247–1255.
26. Copeland KA, Hopkins JT, Weintraub WS, Rahman E. Long-term follow-up of polytetrafluoroethylene-covered stents implanted during percutaneous coronary intervention for management of acute coronary perforation. *Catheter Cardiovasc Interv Off J Soc Card Angiogr Interv* 2012;80:53–57.
27. Kawamoto H, Tanaka K, Ruparelia N, Takagi K, Yabushita H, Watanabe Y, Mitomo S, Matsumoto T, Naganuma T, Fujino Y, Ishiguro H, Tahara S, Kurita N, Nakamura S, Hozawa K, Nakamura S. Short-term and long-term outcomes after polytetrafluoroethylene-covered stent implantation for the treatment of coronary perforation. *Am J Cardiol* 2015;116:1822–1826.
28. Lee W-C, Hsueh S-K, Fang C-Y, Wu C-J, Hang C-L, Fang H-Y. Clinical outcomes following covered stent for the treatment of coronary artery perforation. *J Intervent Cardiol* 2016;29:569–575.
29. Hachinohe D, Latib A, Laricchia A, Iannopollo G, Demir OM, Ancona MB, Mangieri A, Regazzoli D, Giannini F, Azzalini L, Mitomo S, Chieffo A, Montorfano M, Carlino M, Colombo A. Long-term follow-up of covered stent implantation for various coronary artery diseases. *Catheter Cardiovasc Interv* 2019;94:571–577.
30. Barbero U, Cerrato E, Secco GG, Tedeschi D, Belliggiano D, Pavani M, Moncalvo C, Tomassini F, Benedictis MD, Doronzo B, Varbella F. PK Papyrus coronary stent system: the ultrathin struts polyurethane-covered stent. *Future Cardiol* 2020;16:405–411.
31. Kufner S, Schacher N, Ferenc M, Schlundt C, Hoppmann P, Abdel-Wahab M, Mayer K, Fusaro M, Byrne RA, Kastrati A. Outcome after new generation single-layer polytetrafluoroethylene-covered stent implantation for the treatment of coronary artery perforation. *Catheter Cardiovasc Interv Off J Soc Card Angiogr Interv* 2019;93:912–920.
32. Azzalini L, Poletti E, Ayoub M, Ojeda S, Zivelonghi C, La Manna A, Bellini B, Lostalo A, Luque A, Venuti G, Montorfano M, Agostoni P, Pan M, Carlino M, Mashayekhi K. Coronary artery perforation during chronic total occlusion percutaneous coronary intervention: epidemiology, mechanisms, management, and outcomes. *EuroIntervention J Eur Collab Work Group Interv Cardiol Eur Soc Cardiol* 2019;15:e804–e811.
33. Moroni F, Magni V, Cappelletti A, Capogrosso C, Godino C, Montorfano M, Azzalini L. Contrast-enhanced echocardiography to rule-out active intrapericardial bleeding following coronary artery perforation. *Cardiol J* 2019;26:810–811.
34. Hirai T, Nicholson WJ, Sapontis J, Salisbury AC, Marso SP, Lombardi W, Karmpaliotis D, Moses J, Pershad A, Wyman RM, Spaedy A, Cook S, Doshi P, Federici R, Nugent K, Gosch KL, Spertus JA, Grantham JA, OPEN-CTO Study Group. A detailed analysis of perforations during chronic total occlusion angioplasty. *JACC Cardiovasc Interv* 2019;12:1902–1912.
35. Garbo R, Oreglia JA, Gasparini GL. The Balloon-Microcatheter technique for treatment of coronary artery perforations. *Catheter Cardiovasc Interv Off J Soc Card Angiogr Interv* 2017;89:E75–E83.
36. Potts J, Sirker A, Martinez SC, Gulati M, Alasnag M, Rashid M, Kwok CS, Ensor J, Burke DL, Riley RD, Holmvang L, Mamas MA. Persistent sex disparities in clinical outcomes with percutaneous coronary intervention: insights from 6.6 million PCI procedures in the United States. *PLOS ONE* 2018;13:e0203325.