Choice and Duration of Antithrombotics after CTO-PCI: Does it Matter?

David Geffen School of Medicine

UCLA Health

Michael S. Lee, MD, FACC, FSCAI
Interventional Cardiology

What is the ideal anticoagulant?

Heartwire from Medscape

Stone and Stables Spar Over Heparin vs Bivalirudin in STEMI

Shelley Wood

September 22, 2014

WASHINGTON, DC — More than five months after the HEAT-PPCI STEMI trial of **heparin** monotherapy vs **bivalirudin** burst onto the radar of interventional cardiologists, the two men at opposite ends of this controversy took to the public stage to debate the issues.

In fact, at last week's TCT 2014 meeting, they did it not once, but twice.

On one side, **Dr Rod Stables** (Liverpool Heart and Chest Hospital, UK), the principal investigator for HEAT-PPCI, which first called into question bivalirudin's supremacy in primary PCI. The trial has since spurred a change to practice patterns and, at least in Europe, a

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what do the data support? Stone, speaking first, landed the first jab with the provocative opener: "Heparin is a disgusting product," he proclaimed, showing a black and white photo of a chemist with dead swine dangling in the background and a recipe for concocting the drug. "It's made from pork intestines, it has pancreatic extract, ammonia, sodium hydroxide: this is how you made heparin [in the 1930s], and this is how you make it today. . . . It's inexpensive, yes, but it's a terrible drug."


Dr Gregg Stone

From there, Stone launched into the fast-paced clinical-trial review for which he is famous, slides flickering past like strobe lights, providing a sweeping recap of more than a decade's worth of research showing heparin monotherapy in STEMI care to be an inferior strategy.

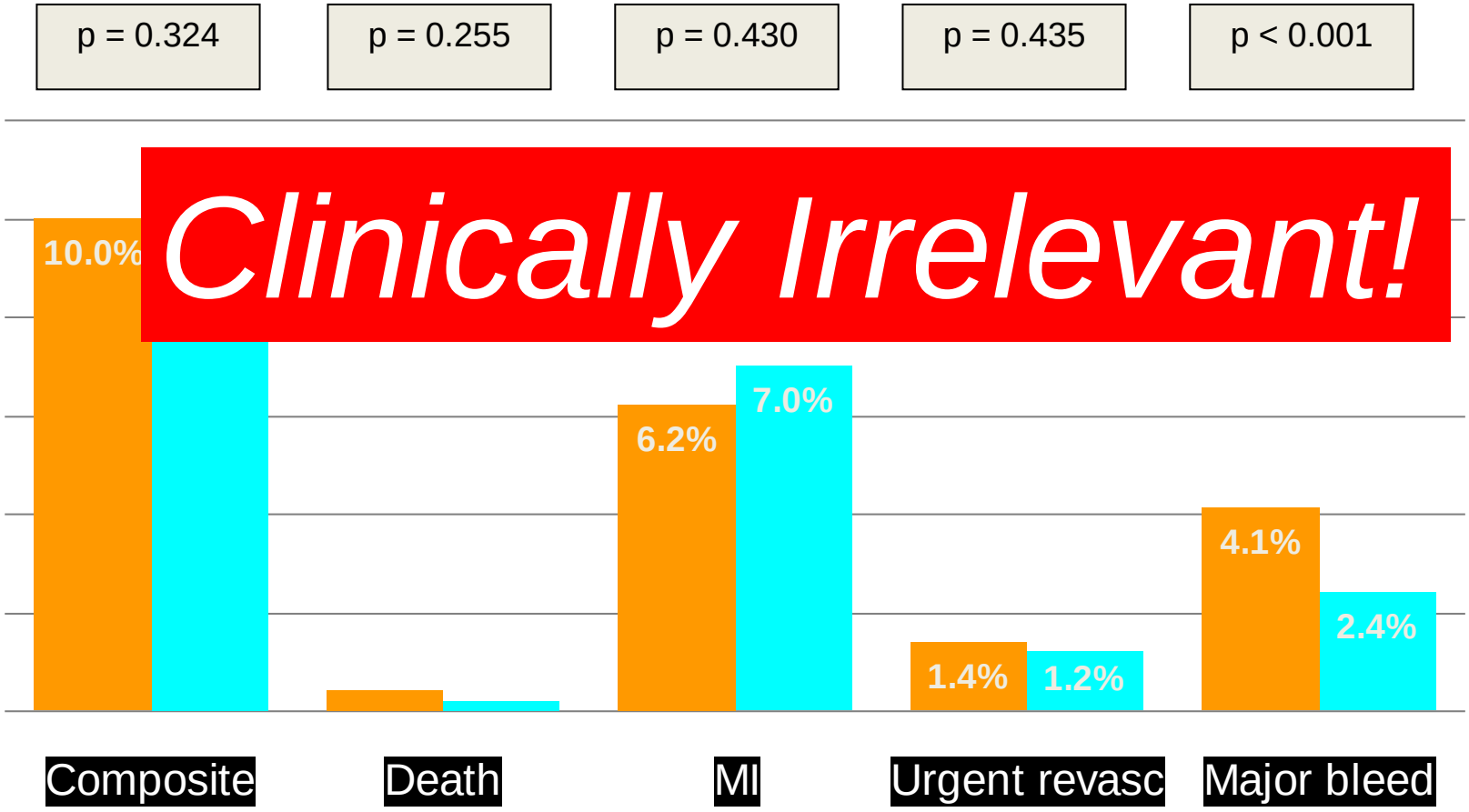
"When did it become okay once again to use heparin only during primary PCI in STEMI?" Stone asked. "Heparin monotherapy is stepping back a decade."

Stone's most pointed remarks zeroed in on the three trials that have looked specifically at heparin monotherapy vs bivalirudin: **BRIGHT** (presented in the US for the first time at TCT), **EUROMAX** ,and HEAT-PPCI, saving his most blistering treatment for the last. The other two, he noted, were large multicenter trials, whereas HEAT-PPCI was a single-center trial, "so you've got to scrutinize the methods and the results."

> "Heparin is a disgusting product.

"Heparin is a disgusting product. It's made from pork intestines. It has pancreatic extract, ammonia, sodium hydroxide. …it's a terrible drug"

REPLACE-2 Trial



NAPLES III trial

Elective PCI in biomarker negative patients at high risk of bleeding

UFH group

70 U/Kg i.v. prior to start the procedure

Additional bolus 20 U/Kg in case ACT <250 sec

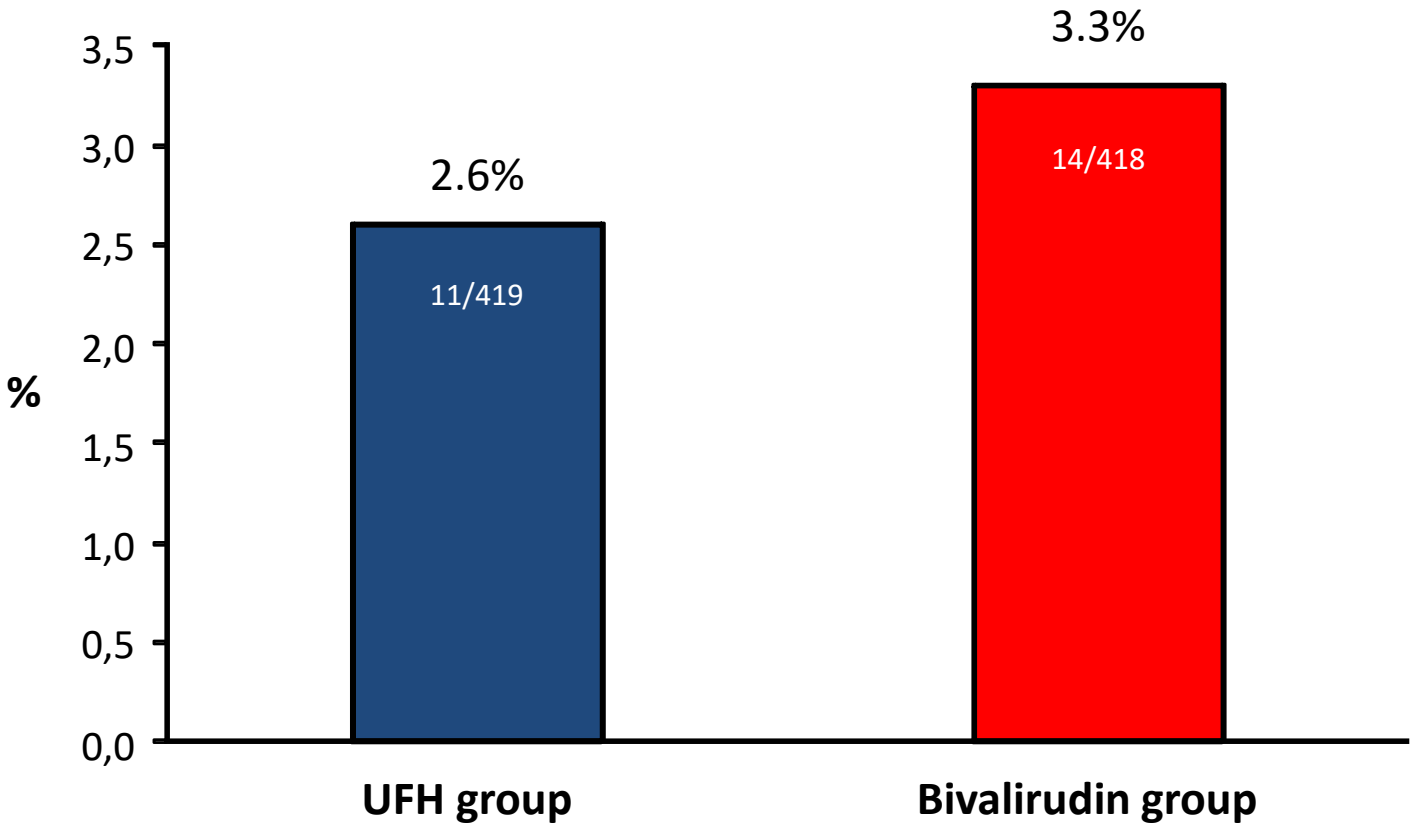
Bivalirudin group

Bolus of 0.75 mg/kg i.v. prior to the start of the procedure, followed by infusion of 1.75 mg/kg per hour for the duration of the procedure

Additional bolus 0.3mg/Kg in case ACT <250 sec

NAPLES III:
Primary endpoint: Major Bleeding

Odds ratio = 1.28; 95% CI= 0.58-2.86
p = 0.54



NAPLES 4
Secondary endpoint 30-day MACE

	Bivalirudin group (N= 418)	UFH Group (N=419)	P
Major bleeding	14 (3.3%)	11 (2.6%)	0.58
Death	10 (2.4%)	6 (1.4%)	0.31
Myocardial infarction	1 (0.2%)	0	0.50
Revascularization	5 (1.2%)	3 (0.7%)	0.47
Stent thrombosis	2 (0.5%)	2 (0.5%)	0.99
Composite	27 (6.5%)	18 (4.3%)	0.17

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STATE-OF-THE-ART REVIEW

Update in the Percutaneous Management of Coronary Chronic Total Occlusions

Peter Tajti, MD,[a,b] M. Nicholas Burke, MD,[a] Dimitri Karmpaliotis, MD, PHD,[c] Khaldoon Alaswad, MD,[d] Gerald S. Werner, MD,[e] Lorenzo Azzalini, MD, PHD, MSc,[f] Mauro Carlino, MD,[f] Mitul Patel, MD,[g] Kambis Mashayekhi, MD,[h] Mohaned Egred, MD,[i] Oleg Krestyaninov, MD,[j] Dmitrii Khelimskii, MD,[j] William J. Nicholson, MD,[k] Imre Ungi, MD, PHD,[b] Alfredo R. Galassi, MD,[l] Subhash Banerjee, MD,[m] Emmanouil S. Brilakis, MD, PHD[a,m]

ABSTRACT

Percutaneous coronary intervention (PCI) for chronic total occlusions (CTOs) has been rapidly evolving during recent years. With improvement in equipment and techniques, high success rates can be achieved at experienced centers, although overall success rates remain low. Prospective, randomized-controlled data regarding optimal use and indications for CTO PCI remain limited. CTO PCI should be performed when the anticipated benefit exceeds the potential risk. New high-quality studies of the clinical outcomes and techniques of CTO PCI are needed, as is the expansion of expert centers and operators that can achieve excellent clinical outcomes in this challenging patient and lesion subgroup. In the current review the authors summarize the latest publications in CTO PCI and provide an overview of the current state of the field. (J Am Coll Cardiol Intv 2018;11:615–25) © 2018 the American College of Cardiology Foundation. Published by Elsevier. All rights reserved.

Circulation

WHITE PAPER

Guiding Principles for Chronic Total Occlusion Percutaneous Coronary Intervention

A Global Expert Consensus Document

ABSTRACT: Outcomes of chronic total occlusion (CTO) percutaneous coronary intervention (PCI) have improved because of advancements in equipment and techniques. With global collaboration and knowledge sharing, we have identified 7 common principles that are widely accepted as best practices for CTO-PCI.

1. Ischemic symptom improvement is the primary indication for CTO-PCI.
2. Dual coronary angiography and in-depth and structured review of the angiogram (and, if available, coronary computed tomography angiography) are key for planning and safely performing CTO-PCI.
3. Use of a microcatheter is essential for optimal guidewire manipulation and exchanges.
4. Antegrade wiring, antegrade dissection and reentry, and the retrograde approach are all complementary and necessary crossing strategies. Antegrade wiring is the most common initial technique, whereas retrograde and antegrade dissection and reentry are often required for more complex CTOs.
5. If the initially selected crossing strategy fails, efficient change to an alternative crossing technique increases the likelihood of eventual PCI success, shortens procedure time, and lowers radiation and contrast use.
6. Specific CTO-PCI expertise and volume and the availability of specialized equipment will increase the likelihood of crossing success and facilitate prevention and management of complications, such as perforation.
7. Meticulous attention to lesion preparation and stenting technique, often requiring intracoronary imaging, is required to ensure optimum stent expansion and minimize the risk of short- and long-term adverse events.

These principles have been widely adopted by experienced CTO-PCI operators and centers currently achieving high success and acceptable complication rates. Outcomes are less optimal at less experienced centers, highlighting the need for broader adoption of the aforementioned 7 guiding principles along with the development of additional simple and safe CTO crossing and revascularization strategies through ongoing research, education, and training.

Emmanouil S. Brilakis, MD, PhD
et al

Full author list is available on page 428

Key Words: coronary occlusion ▪ methods ▪ percutaneous coronary intervention ▪ treatment outcome

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CLINICAL STUDY

Exploration of Bivalirudin Use during Percutaneous Coronary Intervention for High Bleeding Risk Patients with Chronic Total Occlusion

Chenguang Li,[1*] MD, Yi Shen,[2*] MD, Rende Xu,[1] MD, Yuxiang Dai,[1] MD, Shufu Chang,[1] MD, Hao Lu,[1] MD, Lei Ge,[1] MD, Jianying Ma,[1] MD, Juying Qian,[1] MD and Junbo Ge,[1] MD

Summary

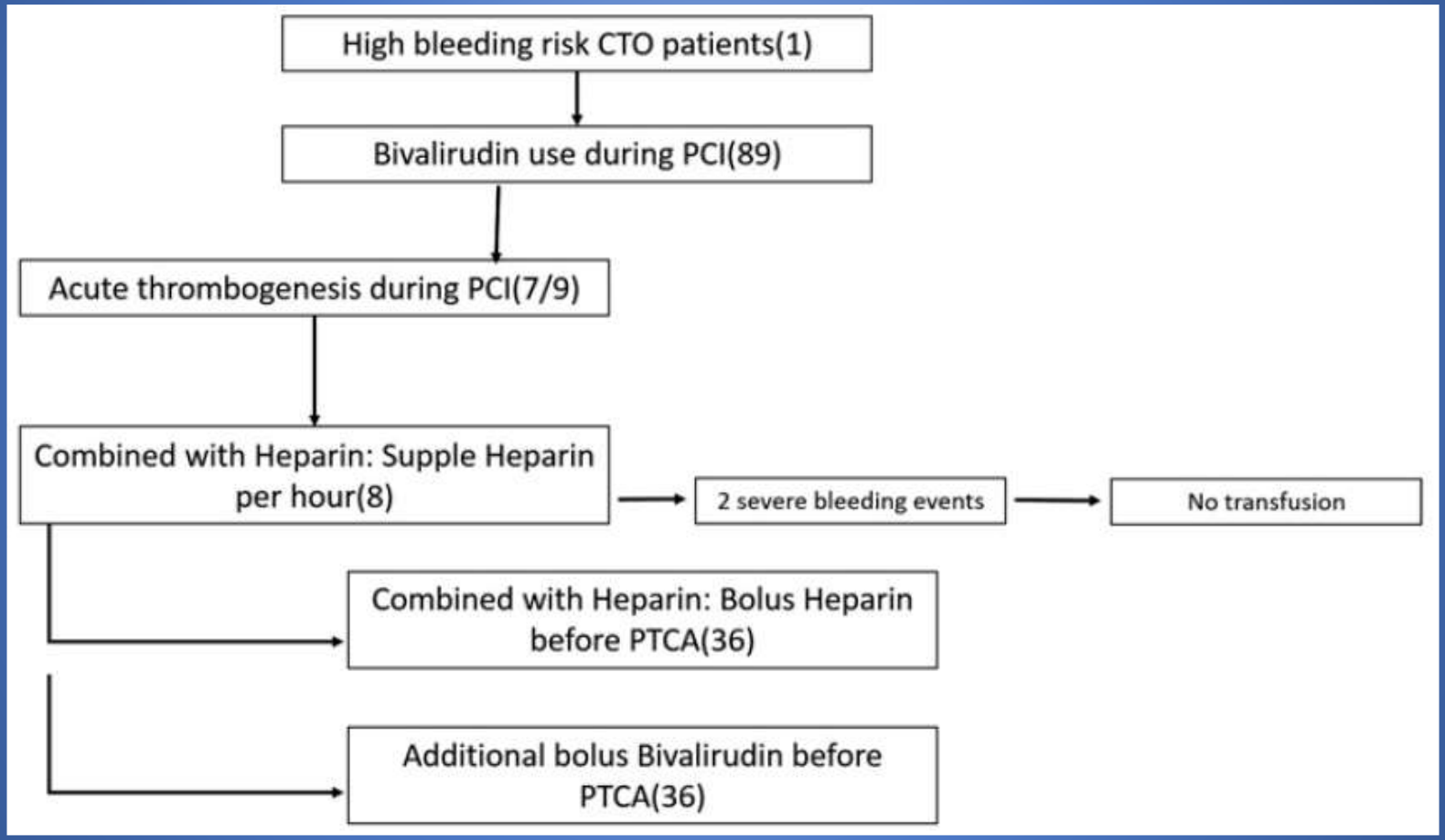
The safety and efficacy of bivalirudin during percutaneous coronary intervention (PCI) in high bleeding risk patients with chronic total occlusion lesions (CTO) has not been studied till date. The use of bivalirudin may increase the thrombotic events during CTO-PCI.

Between May 2013 and April 2014, a total of 117 high bleeding risk patients with CTOs underwent PCI. Bivalirudin was used in 89 cases with different strategies, including standard usage, combination of heparin, and additional bolus of bivalirudin on the basis of standard usage. The clinical characteristics, procedural details and antithrombotic strategies were assessed, and the bleeding and ischemic events were evaluated. The first 7 of 9 patients with standard application of bivalirudin exhibited acute thrombogenesis in the procedure. Heparin was then added in decreasing amounts in the next 8 patients wherein no thrombosis occurred; however, 2 patients had bleeding complications. The subsequent 72 patients were randomly assigned to the heparin bolus or additional bivalirudin bolus groups before the percutaneous transluminal coronary angioplasty (PTCA) was performed. The baseline clinical characteristics and procedure information were identical in both the groups. There were no ischemic and bleeding events in both the groups during the 6-month follow-up.

Monotherapy with bivalirudin in CTO-PCI should be treated with caution, as the potential risk of thrombogenesis may be due to the long procedure time, the frequent change of equipment and temporary blood flow convection. Combination of heparin or an additional bolus of bivalirudin before PTCA was observed to be likely to decrease the incidence of thrombogenesis.

(Int Heart J 2018; 59: 293-299)

Schematic Representation of the Process of Exploring the Usage of Bivalirudin



Procedural Data

Variable	Total (89)	Bivalirudin plus heparin bolus group (36)	Standard usage plus additional bivalirudin bolus group (36)	*P*
Access, radial *n* %	65 (74.7%)	28 (77.8%)	30 (83.3%)	0.195
Target occlusion vessel				0.061
LAD	32 (36.8%)	13 (36.1%)	15 (33.3%)	
LCx	17 (19.5%)	7 (33.3%)	5 (16.7%)	
RCA	38 (43.7%)	16 (41.7%)	16 (50.0%)	
Occlusion lesion length (mm)	50.87 ± 24.95	45.50 ± 13.35	43.40 ± 19.16	0.087
Retrograde	38 (43.7%)	16 (44.4%)	17 (47.2%)	0.429
ACT Index (Highest)	625.13 ± 79.37	626.08 ± 71.53	625.8 ± 35.2	0.096
(Lowest)	319.10 ± 34.44	319.33 ± 39.89	312.60 ± 20.96	0.055
(Average)	412.38 ± 31.90	419.17 ± 29.67	415.50 ± 19.17	0.11
Combined use of GPI IIb/IIIa	10 (11.5%)	0	0	
Contrast volume (mL)	275.26 ± 158.37	213.33 ± 72.78	300.00 ± 49.39	0.072
Procedure time (minutes)	179.49 ± 104.90	126.67 ± 45.99	156.00 ± 65.18	0.285
Coronary perforation	4 (4.60%)	1 (2.78%)	2 (5.56%)	0.545
Dissection after PTCA (NHLBI C-E Type)	32 (36.8%)	11 (30.6%)	13 (36.1%)	0.515
Acute thrombosis	7 (8.05%)	0	0	
Location of thrombosis				
Target vessel	5 (71.4%)	0	0	
Other vessel	2 (28.6%)	0	0	
Treatment for the thrombosis				
Simply Aspiration	3 (42.9%)	0	0	
PTCA	4 (57.1%)	0	0	
Outcome of intervention				
PCI	36 (92.3%)	100%	11 (91.7%)	0.121
PTCA	3 (7.7%)	0	1 (8.33%)	0.109
Stents				
Number of stents per patient	1.97 ± 0.96	2.17 ± 0.83	2.00 ± 0.82	0.944
Stent length (mean, mm)	61.56 ± 30.56	62.67 ± 25.47	64.00 ± 26.05	0.755
Stent diameter (mean, mm)	2.75 ± 0.69	2.81 ± 0.19	3.00 ± 0.26	0.927

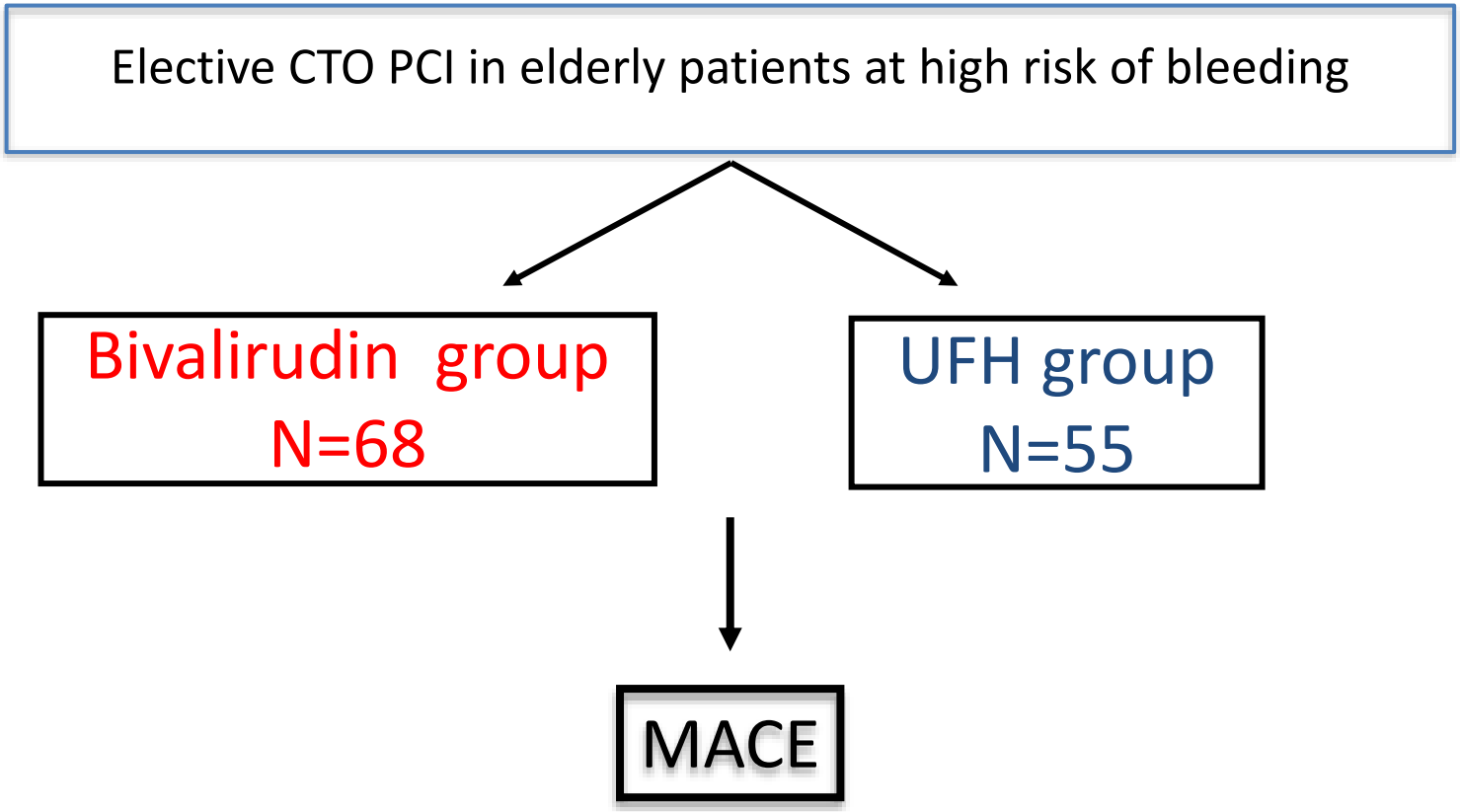
Clinical Outcomes

Variable	Total (89)	Bivalirudin plus heparin bolus group (36)	Standard usage plus additional bivalirudin bolus group (36)	*P*
In-hospital follow-up				
Cardiac death (definite)	0	0	0	
Total death	0	0	0	
STEMI	0	0	0	
NonSTEMI	0	0	0	
Clinically driven TLR	2 (2.3%)	0	0	
Stroke	2 (2.3%)	0	0	
Total MACCE	4 (4.6%)	0	0	
PMI	12 (13.8%)	2 (5.56%)	3 (8.34%)	0.545
Bleeding				
BARC Type 1-2	1 (1.2%)	0	0	
BARC Type 3-5	2 (2.3%)	0	0	
6-month follow-up				
Total death	1 (1.2%)	0	0	
Cardiac death	0	0	0	
Myocardial infarction	0	0	0	
TVR	2 (2.3%)			
Bleeding				
BARC Type 1-2	0	0	0	
BARC Type 3-5	1 (2.6%)	0	0	

Authors' Conclusion

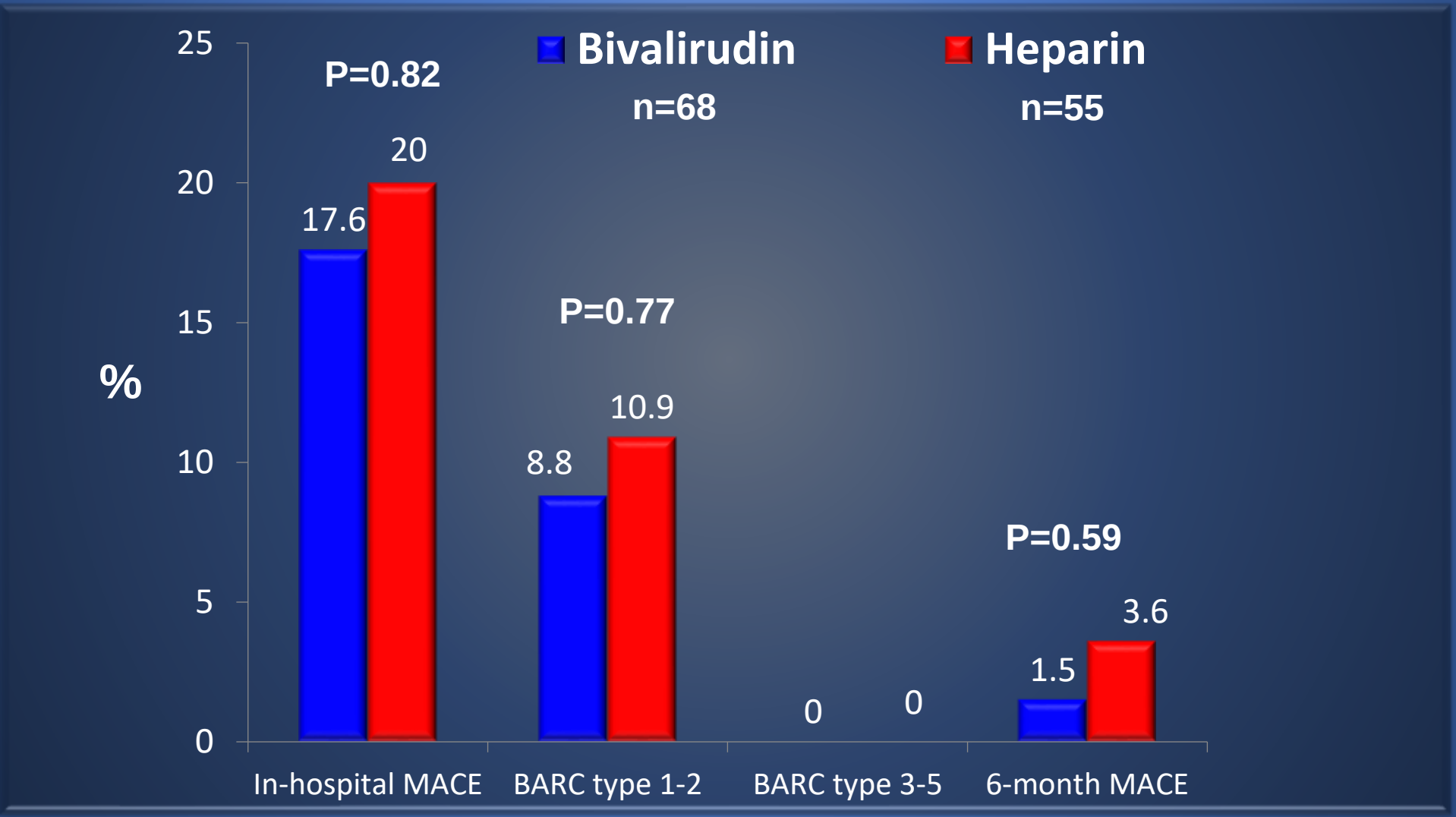
- *"Monotherapy with bivalirudin in CTO-PCI should be treated with caution, as the potential risk of thrombogenesis may be due to the long procedure time, the frequent change of equipment and temporary blood flow convection."*
- *"Combination of heparin or an additional bolus of bivalirudin before PTCA …likely decreased the incidence of thrombogenesis."*

DESIGN: Prospective, randomized, double-blind, single center, investigator-initiated clinical study from China



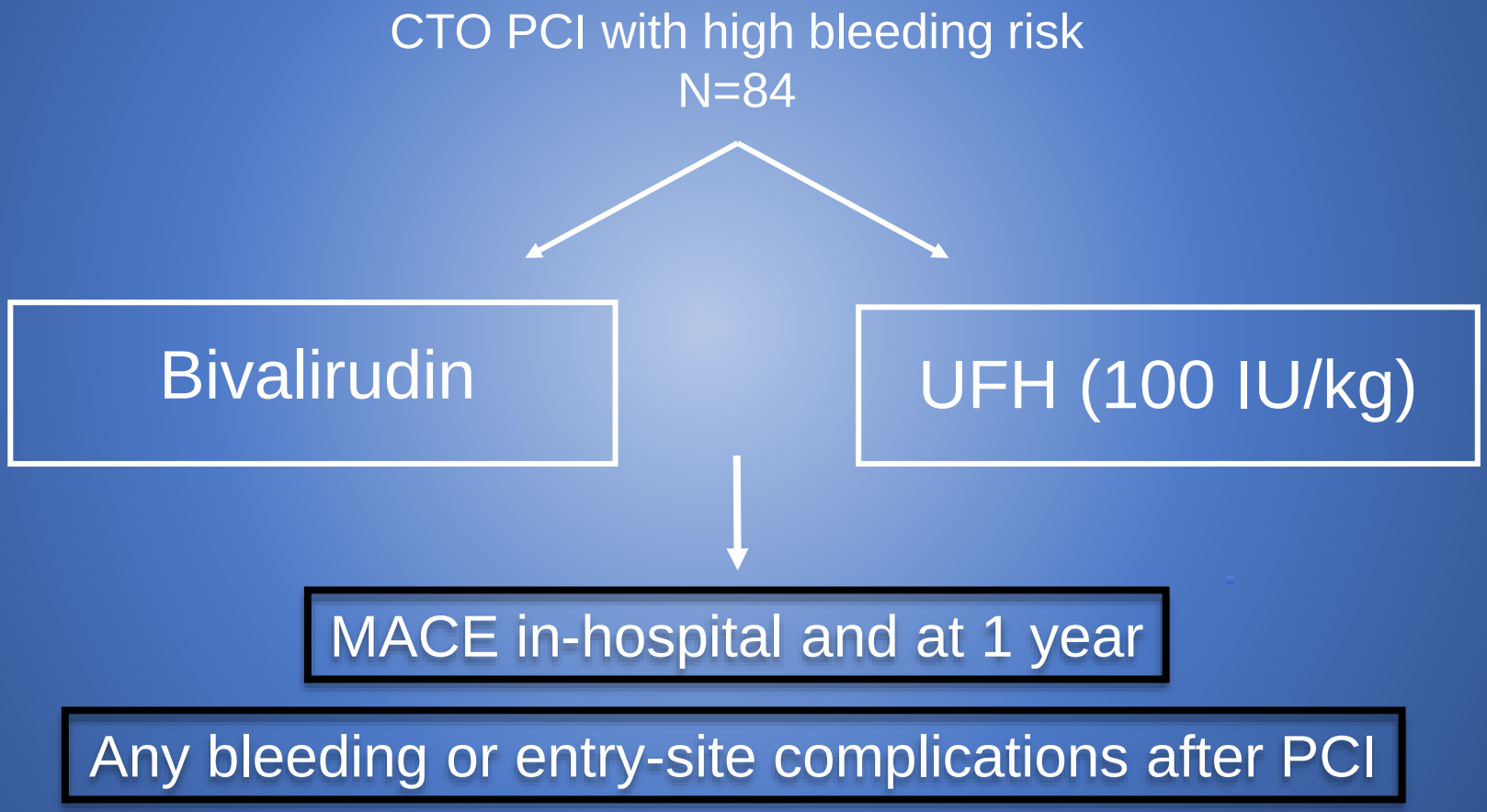
Primary Endpoint

MACE In-Hospital and 6 months



Wang et al. Catheter Cardiovasc Interv 2019.

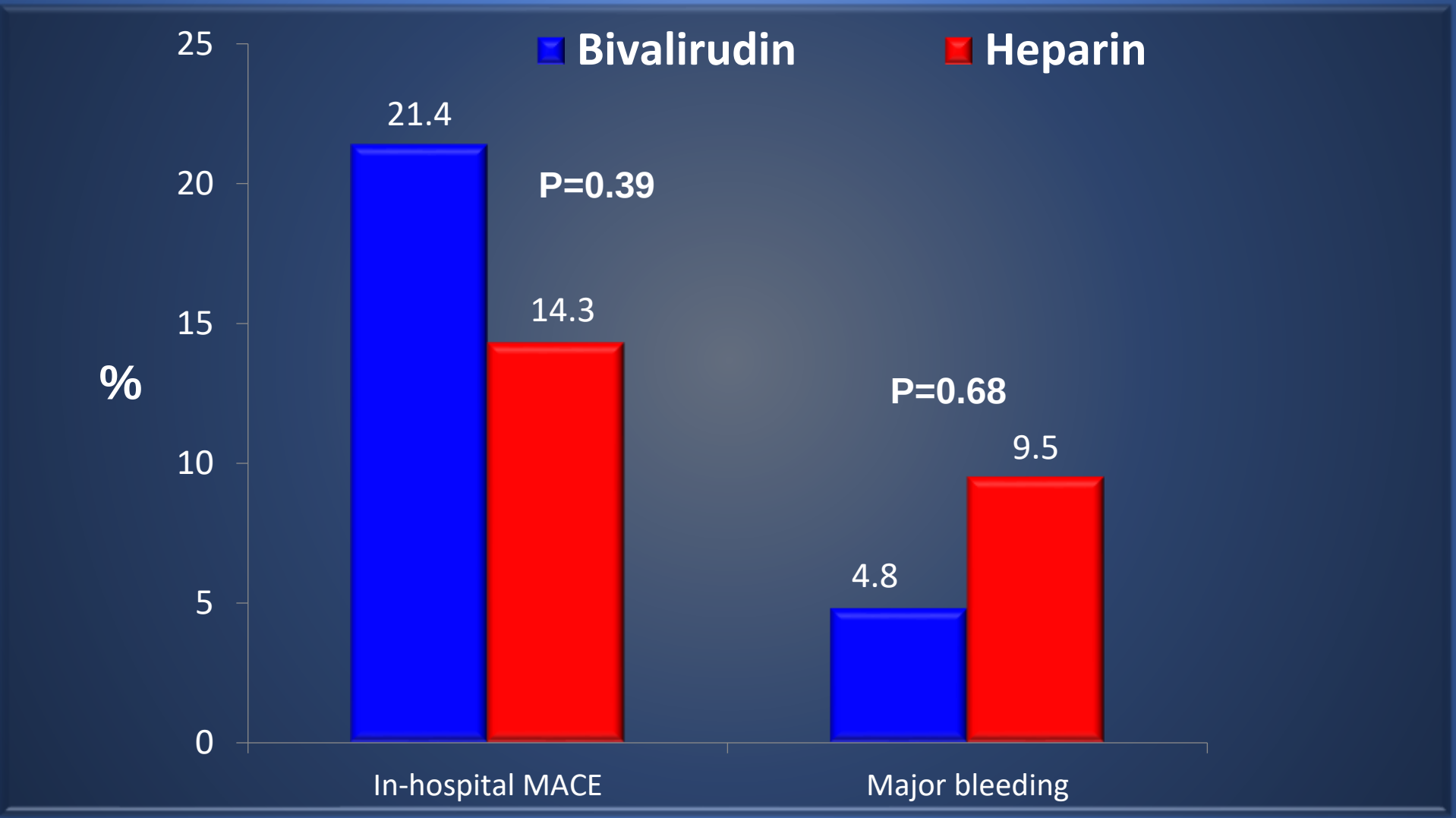
- *DESIGN: Prospective, randomized, single center, clinical study from China*



Li et al. Catheter Cardiovasc Interv 2018.

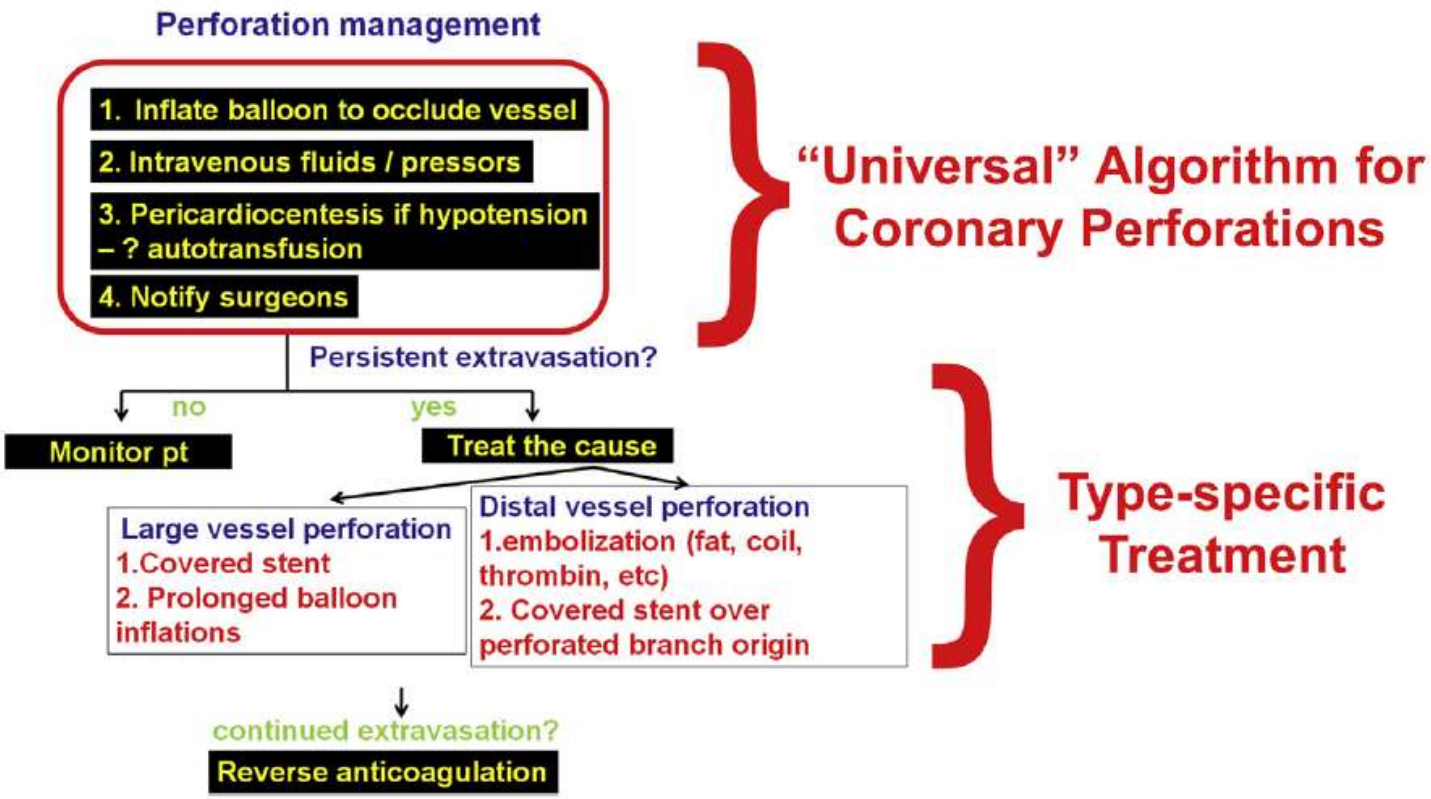
Primary Endpoint

In-Hospital MACE



Li et al. Catheter Cardiovasc Interv 2018

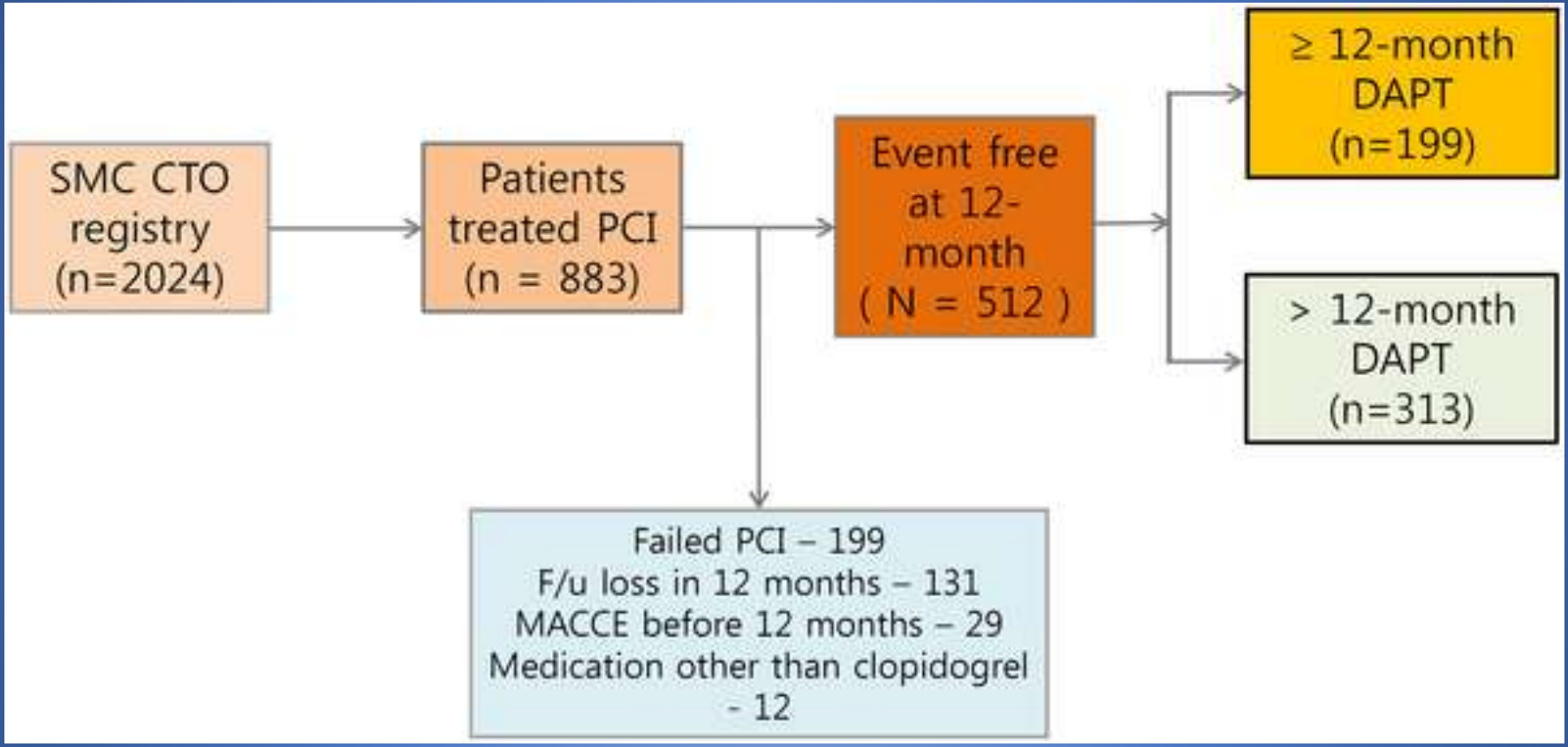
FIGURE 2 Perforation Management Algorithm



The first step in management of coronary perforations is balloon inflation to stop bleeding into the pericardium, followed by fluid/vasopressor administration, pericardiocentesis in case of hypotension and notification of cardiac surgery in case emergency surgery is needed. If the perforation is not sealed further management depends on perforation type: large vessel perforations are usually treated with a covered stent whereas distal vessel perforations are treated with embolization. Anticoagulation should not be reversed until all equipment is removed from the coronary arteries to minimize the risk for coronary thrombosis. Reproduced with permission from Brilakis (6).

What is the ideal duration of DAPT?

Samsung Medical Center CTO Registry



Lee SH, Yang JH, Choi SH, Park TK, Jang WJ, et al. (2017) Duration of dual antiplatelet therapy in patients treated with percutaneous coronary intervention for coronary chronic total occlusion. PLOS ONE 12(5): e0176737. https://doi.org/10.1371/journal.pone.0176737

Clinical outcomes of ≤12-month DAPT vs >12-month DAPT in the crude population

	≤ 12-month DAPT	> 12-month DAPT	Unadjusted HR (95% CI)	p-value	Multivariate analysis‡	
					Adjusted HR (95% CI)	p-value
MACCE	43 (21.6)	55 (17.6)	1.05 (0.70–1.56)	0.83	1.27 (0.83–1.94)	0.26
Stent thrombosis*	4 (2.0)	5 (1.6)	1.08 (0.29–4.03)	0.91	0.96 (0.90–7.00)	0.53
All cause death	13 (6.5)	16 (5.1)	1.18 (0.56–2.45)	0.67	1.60 (0.73–3.53)	0.24
Cardiac death	6 (3.0)	5 (1.6)	1.67 (051–5.50)	0.40	2.12 (0.60–7.56)	0.25
Myocardial infarction	3 (1.5)	10 (3.2)	0.41 (0.11–1.49)	0.18	0.54 (0.14–2.12)	0.38
Stroke	2 (1.0)	4 (1.3)	0.72 (0.13–3.92)	0.33	1.13 (0.19–6.57)	0.89
Repeat revascularizaton	29 (14.6)	36 (11.5)	1.05 (0.64–1.71)	0.72	1.21 (0.72–2.03)	0.47
BARC type 2, 3 or 5	4 (2.0)	11 (3.5)	0.52 (0.17–1.64)	0.27	0.75 (0.82–2.77)	0.75
GUSTO severe or moderate	1 (0.5)	8 (2.6)	0.17 (0.02–1.40)	0.10	0.26 (0.03–2.23)	0.22
TIMI major or minor	1 (0.5)	7 (2.2)	0.20 (0.02–1.61)	0.13	0.31 (0.04–2.67)	0.29

Data are presented as n (%).

DAPT, dual antiplatelet therapy; BARC, Bleeding Academic Research Consortium; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries; TIMI, Thrombolysis in Myocardial Infarction; CI, confidence interval; HR, hazard ratio

‡ Covariates include age, diabetes, hypertension, chronic kidney disease, history of PCI, history of stroke, newer generation stent, total stent length, and minimum stent diameter

* Stent thrombosis includes definite or probable stent thrombosis

https://doi.org/10.1371/journal.pone.0176737.t003

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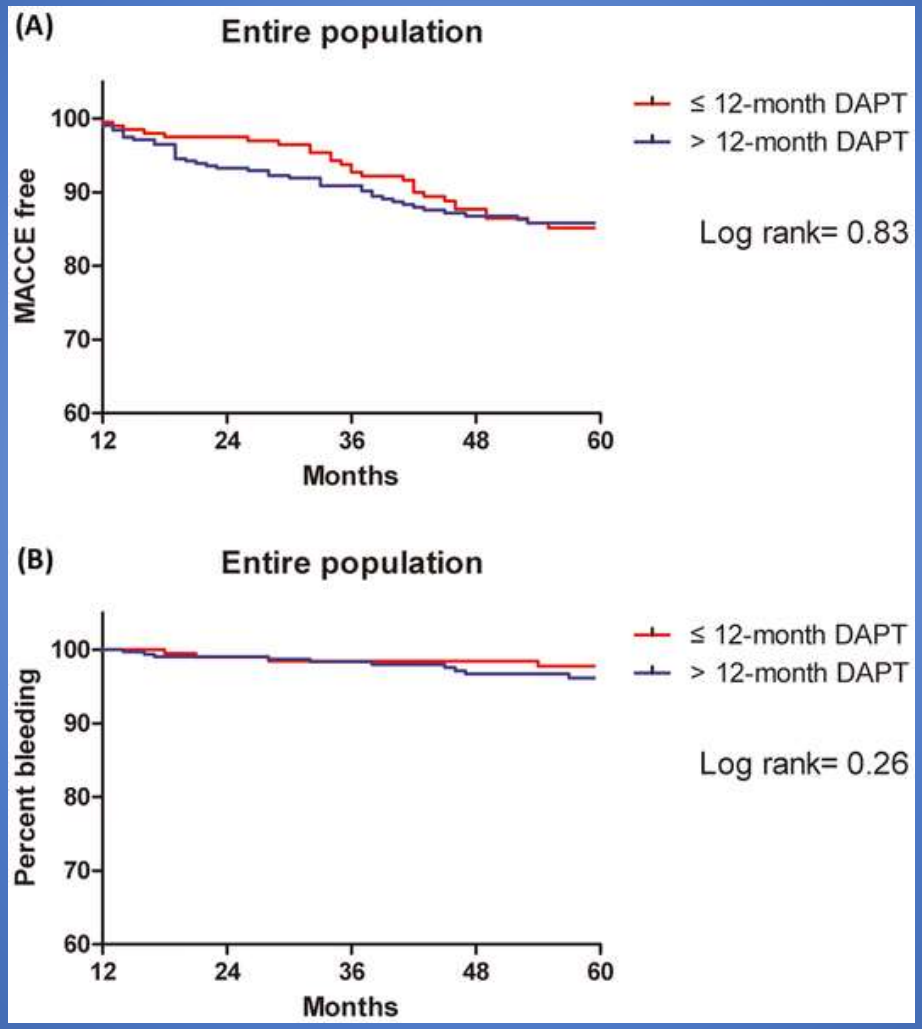
Kaplan-Meier curves for MACCE and moderate to severe bleeding between ≤ 12-month and >12-month DAPT groups in the entire population.



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Clinical outcomes of ≤12-month DAPT vs >12-month DAPT in the propensity-matched population

	≤ 12-month DAPT	> 12-month DAPT	Adjusted HR (95% CI)	p-value
MACCE	41 (22.2)	31 (16.8)	1.32 (0.81–2.18)	0.26
Stent thrombosis*	4 (2.2)	4 (2.2)	0.99 (0.30–3.26)	0.98
All cause death	11 (5.9)	7 (3.8)	1.58 (0.60–4.17)	0.35
Cardiac death	5 (2.7)	3 (1.6)	1.67 (0.40–7.07)	0.48
MI	3 (1.6)	6 (3.2)	0.50 (0.15–1.68)	0.30
Stroke	2 (1.1)	0		
Repeat revascularizaton	29 (15.7)	24 (13.0)	1.22 (0.69–2.13)	0.50
BARC type 2, 3 or 5	3 (1.6)	4 (2.2)	0.76 (0.17–3.44)	0.72
GUSTO severe or moderate	1 (0.5)	4 (2.2)	0.25 (0.03–2.30)	0.22
TIMI major or minor	1 (0.5)	3 (1.6)	0.34 (0.03–3.30)	0.35

Values are n (%).

DAPT, dual antiplatelet therapy; BARC, Bleeding Academic Research Consortium; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries; TIMI, Thrombolysis in Myocardial Infarction; CI, confidence interval; HR, hazard ratio

* Stent thrombosis includes definite or probable stent thrombosis

https://doi.org/10.1371/journal.pone.0176737.t004

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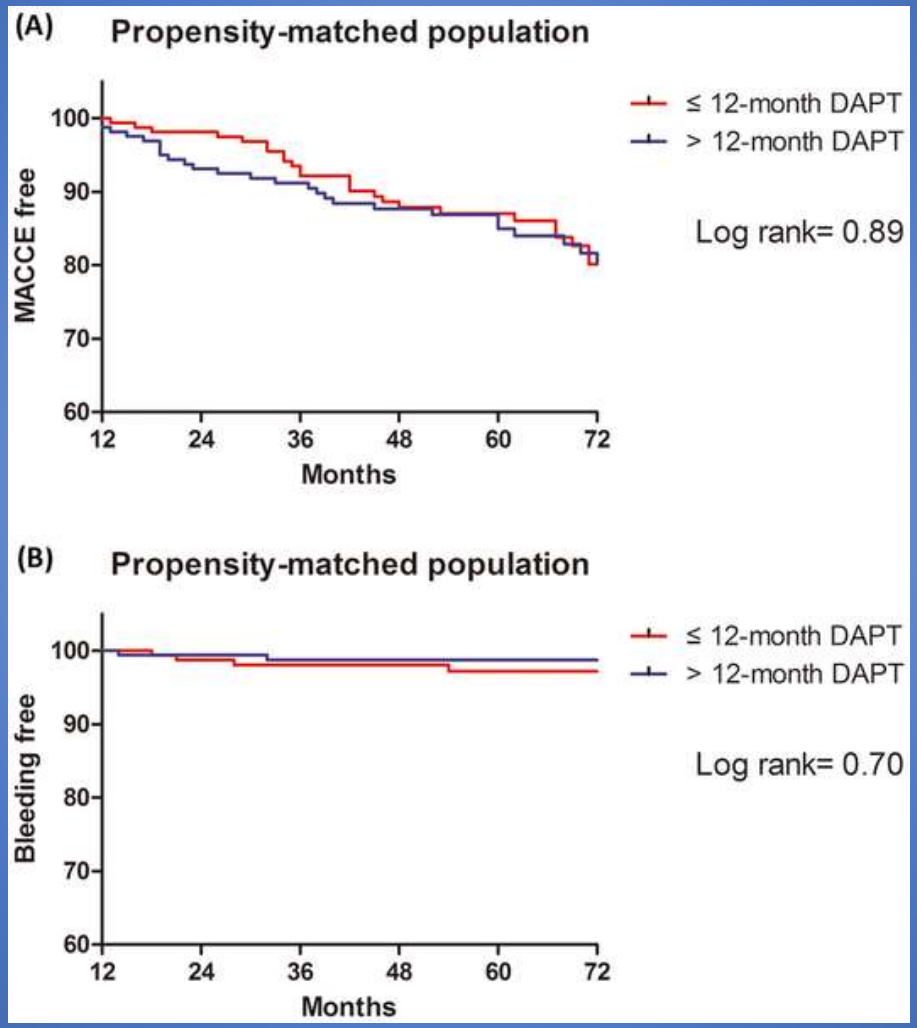
Kaplan-Meier curves for MACCE and moderate to severe bleeding between ≤12-month and >12-month DAPT groups in the propensity-matched population.



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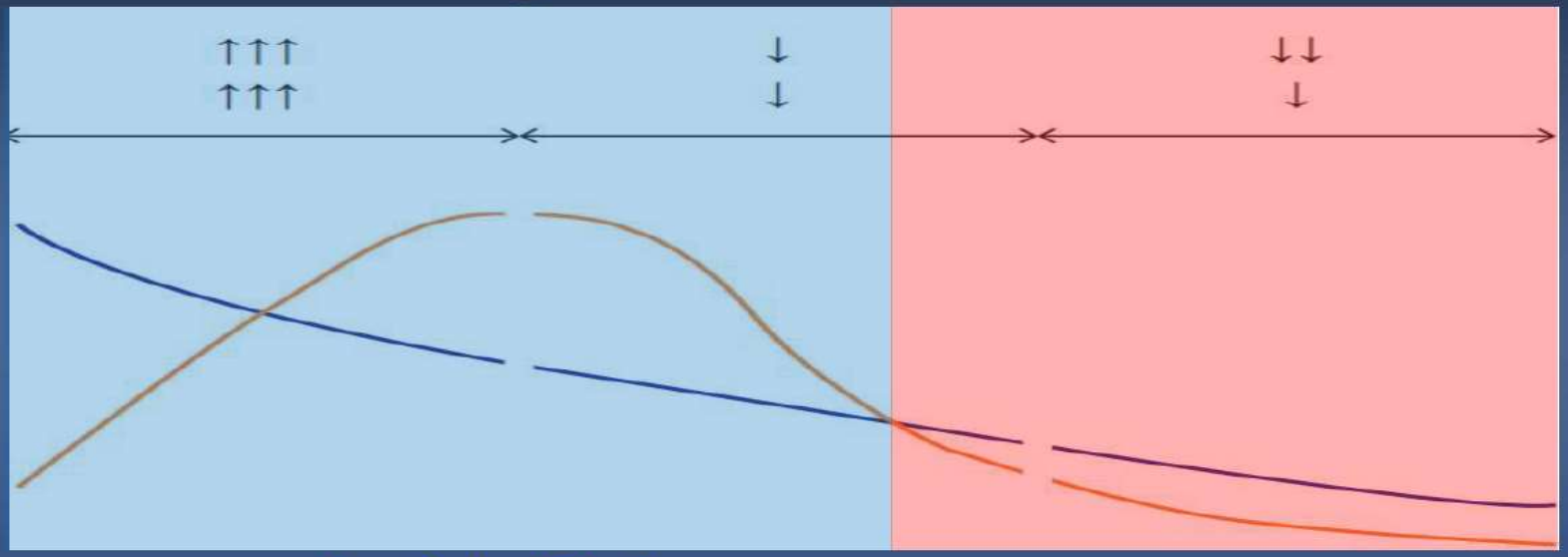
TAILORED-CHIP Trial: Rationale

Complex High-Risk PCI (CHIP Patients)

"Ischemic vs. Bleeding Balancing Over Time in High-Risk PCI"

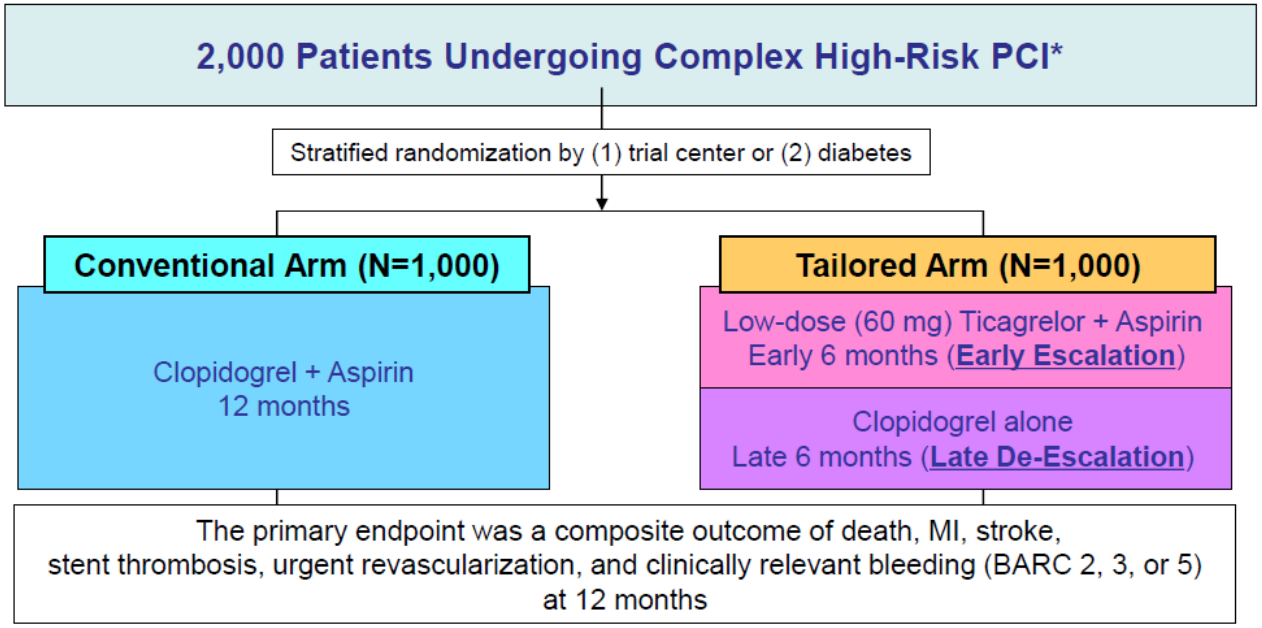


More Potent Strategy
For Ischemic Risk
"Low-Dose Ticagrelor + ASA"

Less Potent Strategy
For Bleeding Risk
"Clopidogrel Only"

TAILored versus C***O***nventional Antith***R***ombotic Strat***E***gy
Inten***D***ed for ***C***omplex ***HI***gh-Risk ***P***CI

TAILORED-CHIP Trial



***Complex High-Risk PCI**
: Left main PCI, chronic total occlusion, bifurcation with 2 stents implanted, severe calcification, diffuse long lesion (lesion length ≥ 30mm), multivessel PCI (≥ 2 vessels stented), ≥3 stents implanted, ≥3 lesions treated, total stent length >60mm, diabetes, CKD (Cr-clearance <60ml/min) or severe LV dysfunction (EF <40%).

Conclusions

- Data on the safety of bivalirudin in CTO PCI are conflicting.
- Heparin is the most commonly used anticoagulant for CTO PCI, inexpensive, safe, and effective
- Heparin can be reversed with protamine if perforation occurs
- Among patients treated with CTO-PCI, DAPT for <12 months showed similar long-term outcomes compared to >12 months
- Results of these East Asian studies may not be generalizable to all patients

Thank you!