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**Benefit of Extended Dual Antiplatelet Therapy Duration in Acute Coronary
Syndrome Patients Treated with Drug Eluting Stents for Coronary Bifurcation
Lesions (from the BIFURCAT Registry).**

Ovidio De Filippo*¹ MD, Jeehoon Kang*² MD, Francesco Bruno¹ MD, Jung-Kyu Han² MD, Andrea Saglietto¹ MD, Han-Mo Yang² MD, Giuseppe Patti³ MD, Kyung-Woo Park² MD, Radoslaw Parma⁴ MD, Hyo-Soo Kim² MD, Leonardo De Luca⁵ MD, Hyeon-Cheol Gwon⁶ MD, Mario Iannaccone⁷ MD, Woo Jung Chun⁸ MD, Grzegorz Smolka⁴ MD, Seung-Ho Hur⁹ MD, Enrico Cerrato¹⁰ MD, Seung Hwan Han¹¹ MD, Carlo di Mario¹² MD, Young Bin Song⁶ MD, Javier Escaned¹³ MB, BCh, Ki Hong Choi⁶ MD, Gerard Helft¹⁴ MD, Joon-Hyung Doh¹⁵ MD, Alessandra Truffa Giachet¹⁶ MD, Soon-Jun Hong¹⁷ MD, Saverio Muscoli¹⁸ MD, Chang-Wook Nam⁹ MD, Guglielmo Gallone¹ MD, Davide Capodanno¹⁹ MD, Daniela Trabattoni²⁰ MD, Yoichi Imori²¹ MD, Veronica Dusi²² MD, Bernardo Cortese²³ MD, Antonio Montefusco¹ MD, Federico Conrotto¹ MD, Iacopo Colonnelli²⁴, Imad Sheiban²⁵ MD, Gaetano Maria de Ferrari¹ MD, Bon-Kwon Koo² MD**, Fabrizio D'Ascenzo¹ MD, PhD**

*joint first authors; **joint last authors

Affiliations:

- 1) Division of Cardiology, Department of Medical Sciences, University of Turin, Torino, Italy
- 2) Department of Internal Medicine and Cardiovascular Center, Seoul National University Hospital, Seoul, Republic of Korea
- 3) Coronary Care Unit and Catheterization laboratory, A.O.U. Maggiore della Carità, Novara, Novara, Italy
- 4) Department of Cardiology and Structural Heart Diseases, Medical University of Silesia, Katowice, Poland.
- 5) Department of Cardiosciences, A.O. San Camillo-Forlanini, Roma, Italy
- 6) Department of Cardiology Sungkyunkwan University Samsung Medical Center Seoul Republic of Korea
- 7) Dipartimento di Cardiologia, Ospedale San Giovanni Bosco, Torino, Italy
- 8) Department of Internal Medicine, Samsung Changwon Hospital, Changwon, Republic of Korea
- 9) Department of Internal Medicine, Keimyung University Dongsan Medical Center, Daegu, Republic of Korea
- 10) Department of Cardiology, San Luigi Gonzaga Hospital, Orbassano, Turin, Italy
- 11) Division of Cardiology, Department of Internal Medicine, Gachon University Gil Hospital, Incheon, Republic of Korea
- 12) Structural Interventional Cardiology, Careggi University Hospital, Florence, Italy
- 13) Department of Cardiology, Hospital Clínico San Carlos IDISSC and Universidad Complutense de Madrid, Madrid, Spain.
- 14) Pierre and Marie Curie University, Paris, France
- 15) Division of Cardiology, Department of Internal Medicine, Inje University Ilsan Paik Hospital, Goyang, Republic of Korea
- 16) Division of Cardiology Ospedale di Asti, Asti, Italy
- 17) Department of Cardiology, Cardiovascular Center, Korea University Anam Hospital, Seoul, Republic of Korea
- 18) Department of Medicine, Università degli Studi di Roma 'Tor Vergata', Rome, Italy

- 19) Division of Cardiology, Cardio-Thoracic-Vascular Department, Azienda Ospedaliero Universitaria "Policlinico-Vittorio Emanuele," Catania, Italy
- 20) Invasive Cardiology Unit 3, Centro Cardiologico Monzino, IRCCS, Milano, Italy
- 21) Department of Cardiovascular Medicine, Nippon Medical School, Tokyo, Japan
- 22) Department of Molecular Medicine, Section of Cardiology, University of Pavia, Pavia, Italy
- 23) Department of Interventional Cardiology, ASST Fatebenefratelli-Sacco, Milano, Italy
- 24) Department of Computer Science, University of Torino, Torino, Italy
- 25) Pederzoli Hospital, Peschiera del Garda, Italy

Corresponding author:

Bon-Kwon Koo,

Seoul National University Hospital, Seoul, South Korea, bkkoo@snu.ac.kr

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ABSTRACT.

Optimal dual antiplatelet therapy (DAPT) duration for patients undergoing percutaneous coronary intervention (PCI) for coronary bifurcations is an unmet issue. The BIFURCAT registry was obtained by merging two registries on coronary bifurcations. Three groups were compared in a two-by-two fashion: short-term DAPT (≤ 6 months), intermediate-term DAPT (6-12 months) and extended DAPT (>12 months). Major adverse cardiac events (MACE) (a composite of all-cause death, myocardial infarction (MI), target-lesion revascularization and stent thrombosis) were the primary endpoint. Single components of MACE were the secondary endpoints. Events were appraised according to the clinical presentation: chronic coronary syndrome (CCS) vs acute coronary syndrome (ACS). 5537 patients (3231 ACS, 2306 CCS) were included. After a median follow-up of 2.1 years (IQR 0.9-2.2), extended DAPT was associated with a lower incidence of MACE compared with intermediate-term DAPT (2.8% vs 3.4%, adjusted HR 0.23 [0.1-0.54], $p < 0.001$), driven by a reduction of all-cause death in the ACS cohort. In the CCS cohort, an extended DAPT strategy was not associated with a reduced risk of MACE. In conclusion, among real-world patients receiving PCI for coronary bifurcation, an extended DAPT strategy was associated with a reduction of MACE in ACS but not in CCS patients.

Keywords: Dual antiplatelet therapy; percutaneous coronary intervention; coronary bifurcation lesions.

INTRODUCTION.

Coronary bifurcation stenosis account for 15-20% of lesions treated with percutaneous coronary intervention (PCI)¹. Despite PCI is currently a routine practice in this setting², it has been historically characterized by a lower procedural success rate and worse clinical outcomes as compared with stenting of noncomplex coronary lesions³. The most suitable dual antiplatelet therapy (DAPT) strategy in this context, in which suboptimal procedural results (i.e. malapposed stent struts, inadequate stent expansion, excessive metal scaffolding) are often observed, is yet to be determined. Latest years' research focused on the optimal intensity and duration of antiplatelet treatments following PCI with discordant findings⁴⁻⁵, mostly suggesting that the benefit of an extended DAPT strategy is modulated by the individual thrombotic risk and by clinical presentation. Yet, patients with high-risk anatomical features such as coronary bifurcation lesions or unprotected left main (ULM) involvement were mostly underrepresented or excluded in these trials, thus limiting the inferential aim of these findings in the context of complex coronary disease. Consequently, we explored the impact of different DAPT duration strategy in a large cohort of patients treated with PCI with DES for coronary bifurcation lesions across different clinical presentations.

METHODS.

Two large datasets (COBIS III, NCT01642992 and RAIN, NCT03544294) of patients treated with PCI for coronary bifurcations were merged in prespecified forms to create the BIFURCAT (comBined Insights From the Unified RAIN and COBIS bifurcAtion regisTries) registry, encompassing 5537 patients. Details about both registries are reported in the

supplementary appendix. Patients were classified in groups based on DAPT duration after PCI and to evaluate prognosis from landmark time-points. We identified three groups of interest:

Short-term DAPT: patients with a DAPT duration \leq six months

Intermediate-term DAPT: patients with a DAPT duration $>$ six months and

Extended DAPT: patients with a DAPT duration $>$ 12 months

The groups were compared in a two-by-two fashion. For each comparison only the events occurring after the shortest landmark time-point of DAPT withdrawal after PCI were accounted for. For instance, to compare outcomes of intermediate-term DAPT vs short-term DAPT, only events occurring after 6 months were considered. Likewise, to compare extended-term DAPT vs intermediate-term DAPT we only included events occurring after 12 months. Details about PCI, pharmacologic therapy and data collection are reported in the supplementary appendix (see supplementary methods). Major adverse cardiac events [(MACE), defined as a composite of all-cause death, myocardial infarction (MI), target-lesion revascularization (TLR) and definite or probable stent thrombosis (ST)] were the primary endpoint. Single outcomes constituting the composite of MACE were the secondary endpoints. All clinical events were classified based on the recommendations from the Academic Research Consortium (ARC)⁶. Endpoints of interest were appraised according to the clinical presentation (ACS vs chronic coronary syndrome, CCS). Subgroup analyses according to the presence of disease involving distal ULM, DAPT score⁷ and stenting technique (provisional vs 2 stents) were also performed. Categorical variables are reported as count and percentages. Continuous variables as mean and standard deviations or interquartile range (IQR). Parametric (T-test) and non-parametric (Mann-Whitney test) tests were used to assess differences between continuous variables, while chi-square test was

used for categorical variables. Adjustment was performed with Cox multivariate analysis and inverse probability of treatment weighting (IPTW). For Cox multivariate analysis, variables with significant differences at univariate analysis ($p < 0.05$) or clinically relevant were included in the multivariable model, along with the referral registry (COBIS vs. RAIN) and the year of enrolment (meant as before and after 2015). Adjusted survival analysis with Cox adjustment was performed for MACE. For IPTW, the following steps were performed: (a) variables with $>10\%$ missing values were excluded from the merged study dataset; (b) multiple imputation was carried with polytomous logistic regression, logistic regression using the R mice package (version 3.8.0), leading to five imputed different datasets; (c) matching and weighting of the multiple imputed datasets were performed using the R MatchThem package (version 0.9.3), (d) Rubin's rule was used to get pooled propensity score-adjusted hazard ratio (HR) estimates for each endpoint according to this method. A formal sample size calculation is reported in the appendix. The a priori statistical significance level was set at $\alpha = 0.05$. Statistical analyses were conducted using R Statistical Software version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS (version 24.0, SPSS Inc., Chicago, Illinois, US).

RESULTS

A total of 5537 patients were included in the final population (Figure 1): 3231 (58%) presenting with ACS and 2306 (42%) with CCS. The median follow-up was 2.1 years (IQR 0.9-2.2). 204 patients (3.8%) were lost at follow up and therefore not considered for the outcome analysis. Most of the patients enrolled before 2015 were treated with extended DAPT, whereas starting from 2015 onwards the majority both in ACS and CCS subgroup received intermediate-term DAPT, (**Appendix Tables 1 and 2**). In the ACS cohort, 238 (7%) patients received short-term DAPT (median length of DAPT 3 months, IQR 1-4), 1536 (48%) intermediate-term DAPT (12 months, IQR 12-12) and 1457 (45%) extended DAPT (24

months, IQR 23-24). In the CCS cohort, 144 (6%) patients received short-term DAPT (median length 1 month, IQR 1-3), 1208 (52%), intermediate-term DAPT (12 months, IQR 12-12) and 954 (42%) extended DAPT (24 months, IQR 23-24). Baseline clinical features are reported in **Table 1**. Procedural features are outlined in **Supplementary Table 3**. Among ACS patients, extended DAPT was associated with a lower incidence of MACE as compared with intermediate-term DAPT (2.8% vs. 3.4%, adjusted HR 0.23, 95% CI 0.11-0.54, $p < 0.001$ and adjusted HR 0.27, 95% CI 0.18-0.43, $p = 0.04$, with Cox multivariate analysis and with IPTW, respectively). No significant differences were observed in the incidence of MACE when comparing the intermediate-term DAPT group with the short-term DAPT group (5.3 % vs 8%, HR 0.45, 95% CI 0.29-1.32, $p = 0.17$ and HR 0.67 95% CI 0.33-1.34, $p = 0.26$ after Cox multivariate adjustment and IPTW, respectively), **Table 2 and Figure 2**. For CCS patients, extended DAPT and intermediate DAPT regimens were not associated with a reduced risk of MACE after multivariate as well as IPTW adjustment (**Table 2 and Figure 2**). Among ACS patients, extended DAPT compared with intermediate-term DAPT was associated with a reduced risk of all-cause death after Cox multivariate adjustment (1.4% vs. 1.6%, HR 0.16, 95% CI 0.04-0.9, $p = 0.04$) but not at IPTW analysis (HR 0.86, 95% CI 0.64-1.73, $p = 0.71$), **Table 2**. No differences were observed between the intermediate and the short-term DAPT groups. For CCS patients, a similar adjusted risk of all-cause death was observed among the three subgroups when compared in a two-by-two fashion, **Table 2**. A lower unadjusted incidence of MI (0.6% vs 0.9%), TLR (0.9% vs 1.4%) and ST (0.1% vs 0.3%) was observed among ACS patients treated with an extended DAPT strategy as compared with those treated with DAPT for 6-12 months, **Table 2**. However, such differences were not significant after IPTW adjustment. Among CCS patients, a lower incidence of ST was observed with longer DAPT regimens (0.5% vs 1.4% for intermediate DAPT vs short-DAPT and 0% vs 0.4% for extended DAPT vs intermediate DAPT), with a significant difference for patients treated for 6-12 months as compared to those on DAPT

for ≤ 6 months after IPTW adjustment (HR 0.14 95%CI 0.03-0.74, $p=0.02$), but not with Cox multivariate analysis (HR 0.45, 95% CI 0.04-4.34, $p=0.66$). The risk of MI and TLR according to DAPT duration subgroups within the CCS cohort was not significantly different.

In the ACS cohort, extended DAPT reduced the risk of MACE compared with intermediate-term DAPT for all the subgroups explored (ULM vs non-ULM, stenting strategy and DAPT score $<$ or ≥ 2). Intermediate-term DAPT compared to short-term DAPT reduced the risk of MACE only for patients with DAPT score ≥ 2 (HR 0.36, 95% CI 0.13-0.99, $p 0.04$), while there were no differences in the other subgroups analyzed (Figure 3, panel A and Appendix Table 4). In the CCS cohort, no differences in MACE incidence according to DAPT duration were observed across all the explored subgroups (Figure 3, panel B and Appendix Table 4).

DISCUSSION

The main findings of this study, investigating the issue of the optimal DAPT duration in patients treated with PCI for coronary bifurcation according to clinical presentation can be resumed as follows: ACS patients undergoing PCI for coronary bifurcation lesions who received an extended (>12 months) DAPT had a lower incidence of MACE compared with those treated with an intermediate-term DAPT (6-12 months); the lower incidence of MACE in ACS patients receiving DAPT for > 12 months compared to those receiving DAPT for of 6-12 months was confirmed after multivariate and IPTW adjustment and was consistent despite the stenting technique (one vs 2 stents), the site of bifurcation (ULM vs no ULM) and the DAPT score. Furthermore, a higher incidence of MACE was observed in patients with a DAPT score ≥ 2 and a DAPT duration ≤ 6 months compared to those treated for 6-12 months. A similar risk of MACE was instead observed among patients admitted for CCS and treated with different DAPT regimens. Such result was confirmed among all the analyzed subgroups.

Complex interventional scenarios intuitively represent a driver in favor of a prolonged antithrombotic treatment, although actual evidence supporting this approach is scant. The current ESC guidelines mostly rely on patients' clinical presentation (ACS vs CCS) to recommend a diversification in DAPT strategy, with a weak recommendation to consider prolonged DAPT duration in patients undergoing complex PCI (class of recommendation IIb)⁸. Such indication relies on a pooled analysis of six RCTs assessing the impact of DAPT duration according to PCI complexity (frequently but not always on the basis of a bifurcation treatment), where authors found that patients who underwent complex PCI had a two-fold increase risk of MACE (5.0% vs. 2.5%; P = 0.001) and that long-term DAPT (\geq 12 months) compared with short-term (3 or 6 months) was associated with a reduction in MACE in this group as compared with the noncomplex PCI cohort at a median follow up of 392 days⁹. Of interest, despite a non-significant interaction, the benefit of prolonged DAPT among complex PCI groups appeared more relevant in high-risk ACS patients (HR 0.37, 95%CI 0.16-0.83) as compared with those admitted for unstable angina (HR 0.75, 95%CI 0.45-1.23), thus being overall consistent with our findings. In a previous analysis from the COBIS registry, Jang et al¹⁰ found that a prolonged DAPT (>12 months) was associated with a reduction in MI and all-cause death as compared to DAPT < 12 months. However, in contrast with such work, we found the admission diagnosis to modulate this benefit with only ACS patients taking advantage from a long-term antithrombotic treatment. Both patient- (clinical presentation and extent of CAD) and procedural-related (PCI complexity) features may influence the future thrombotic risk and therefore the overall clinical benefit of an extended DAPT regimen. The extended cohort considered in the BIFURCAT registry as compared with the solely COBIS population is characterized by a larger use of very-thin strut-stents (as per RAIN registry inclusion criteria)¹¹. This difference may have translated in the selection of a cohort in whom patients-related factors (rather than stent- and lesion-related

features) had a dominant role in driving the benefit of a prolonged DAPT regimen, thus probably accounting for the different findings according to the clinical admission setting. In accordance with such hypothesis, we found a significant reduction of MACE in ACS patients treated with extended DAPT regardless of the stenting technique (one vs 2 stent) used. RCTs in the modern DES era showed that short-term DAPT should be considered as the safest strategy, being consistently associated with a significant reduction in bleeding events without increase in ischemic events, both in the ACS setting and in unselected cohorts¹²⁻¹⁴. Of note, none of these trials was specifically designed to determine the optimal DAPT duration in complex anatomical settings and patients with coronary bifurcations were therefore underrepresented (20% and 15% in HOST-REDUCE-ACS and TICO trial, respectively). Moreover, in a post-hoc analysis of the TWILIGHT Trial, among 2342 patients undergoing complex PCI who completed three months of DAPT, the continuation of ticagrelor monotherapy was associated with a lower incidence of bleeding events without increasing the risk of ischemic events as compared to continuing DAPT¹⁵. However, such analysis was not adequately powered for ischemic endpoints and differently from the BIFURCAT population patients with STEMI were not included as per study protocol inclusion criteria. In our ACS cohort, the reduction of all-cause mortality may suggest that in peculiar settings like coronary bifurcation disease, the benefits from reducing ischemic events may offset the potential increase in bleeding risk with prolonged DAPT. Such hypothesis should be further confirmed in future studies and should be interpreted with caution in the absence of data about bleeding events.

Our results should be interpreted in the context of some limitations. First, this study has an observational design. The choice of different DAPT strategies was not based on randomization. Despite IPTW adjustment, a potential bias coming from unmeasured variables that would be adequately prevented only through a randomized design cannot be excluded. However, to our knowledge no RCT is currently ongoing to address the issue of

optimal DAPT duration in the specific setting of coronary bifurcations. Second, data on bleeding events were not available. We inferred the net clinical benefit of a prolonged DAPT strategy by performing a subgroup analysis according to DAPT score. Despite our findings were consistent with the main analysis, the potential harm coming from such strategy could not be directly assessed. Due to the observational nature of the study, the groups analyzed were not balanced in their size, especially regarding the short-term DAPT group. However, this may reflect the contemporary practice and the physicians' preference for a long-term DAPT in this setting. In conclusion, in this large real-world cohort of patients treated with PCI on bifurcation coronary lesions we found that an extended DAPT strategy (>12 months) compared with a short- and intermediate-term DAPT (<6 months and 6-12 months, respectively) was associated with a reduction of MACE in patients admitted with ACS, regardless of DAPT score, distal ULM involvement and stenting technique (provisional vs two stents). In patients admitted for CCS, the risk of MACE was not affected by DAPT duration, but the risk of all-cause death was significantly lower in the extend-term DAPT group compared to the short-term DAPT group. These results suggest that a prolonged DAPT strategy may improve long-term clinical outcomes in patients treated with PCI for bifurcation coronary lesions, particularly in the setting of ACS.

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Supplementary material

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.amjcard.2021.07.005>.

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TABLES:

Table 1: Baseline features of the population.

VARIABLE	ACS cohort				CCS cohort			
	Months of dual antiplatelet therapy				Months of dual antiplatelet therapy			
	≤6 months (238, 7%)	6-12 months (1536, 48%)	>12 months (1457, 45%)	p-value	<6 months (144, 6%)	6-12months (1208, 52%)	>12 months (954, 42%)	p-value
Age (years)	69±13	68±13	63±11	<0.001	64±11	66±10	67±106	0.56
Male gender	179 (75.5%)	1151 (74.9%)	1098 (75.4%)	0.947	113 (79.0%)	945 (78.2%)	742 (77.8%)	0.938
Hypertension	157 (66.2%)	1129 (73.5%)	795 (54.6%)	<0.001	102 (71.3%)	902 (74.6%)	572 (60.0%)	<0.001
Hyperlipidemia	93 (39.2%)	866 (56.3%)	550 (37.7%)	<0.001	81 (56.6%)	744 (61.5%)	402 (42.1%)	<0.001
Diabetes mellitus	93 (39.2%)	506 (32.9%)	470 (32.3%)	0.104	48 (33.6%)	382 (31.6%)	335 (35.1%)	0.224
Current smoker	81 (34.2%)	404 (26.3%)	486 (33.4%)	<0.001	22 (15.4%)	182 (15.1%)	233 (24.4%)	<0.001
Renal disease [eGFR <60 ml/min] at presentation	53 (23.2%)	330 (21.5%)	49 (3.5%)	<0.001	20 (14.9%)	234 (19.4%)	32 (3.5%)	<0.001
Previous PCI	45 (19.0%)	370 (24.1%)	173 (11.9%)	<0.001	37 (25.9%)	490 (40.5%)	129 (13.5%)	<0.001
Previous CABG	5 (2.1%)	71 (4.6%)	5 (0.3%)	<0.001	10 (7.0%)	60 (5.0%)	6 (0.6%)	<0.001
Previous MI	46 (19.4%)	480 (31.2%)	68 (4.7%)	<0.001	23 (16.1%)	291 (24.1%)	36 (3.8%)	<0.001
Indication to PCI	STEMI	58 (24.5%)	474 (30.8%)	271 (18.6%)	<0.001	-	-	-
	NSTEMI	96 (40.5%)	662 (43.1%)	405 (27.8%)	0.03	-	-	-
	UA	83 (35.0%)	401 (26.1%)	781 (53.6%)	0.01	-	-	-
Stable angina	-	-	-	-	91 (63.6%)	714 (59.1%)	953 (99.9%)	<0.001
Other	-	-	-	-	52 (36.4%)	495 (40.9%)	1 (0.1%)	<0.001

Legend: ACS: acute coronary syndrome; CCS: Chronic Coronary Syndrome; eGFR: estimated glomerular filtration rate; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; MI: myocardial infarction; STEMI: ST-segment elevation myocardial; NSTEMI: non ST-segment elevation myocardial infarction; UA: unstable angina. p-value for unadjusted between-group comparisons.

Table 2: Long term outcomes.

	ACS cohort			CCS cohort		
	DAPT 6-12 months versus DAPT≤6 months			DAPT 6-12 months versus DAPT≤6 months		
	Univariate analysis**	Cox multivariate analysis (HR, CI 95%)*	IPTW (HR; CI 95%)	Univariate analysis**	Cox multivariate analysis (HR, CI 95%)*	IPTW (HR; CI 95%)
MACE	5.3% versus 8.0 %, p 0.101	0.45 (0.29-1.32), p 0.17	0.67 (0.33-1.34), p 0.26	3.6% versus 6.9% p 0.05	0.44 (0.21-1.02) p 0.03	0.81 (0.41-1.12) p 0.67
Death	18.5% versus 5.5% p <0.001	0.48 (0.21-1.3), p 0.07	0.47 (0.10-1.15), p 0.09	3.3% versus 6.9% p 0.03	0.67 (0.12-5.91) p 0.63	0.35 (0.16-1.6) p 0.16
MI	2.2% versus 1.3%, p 0.34	1.66 (0.44-5.52), p 0.56	2.12 (0.67-2.78), p 0.07	0.8% versus 0.2% p 0.27	0.78 (0.34-5.67.) p 0.57	0.89 (0.71-1.67) p 0.31
TLR	0.8% versus 1.7%, p 0.17	0.23 (0.04-1.8), p 0.68	0.32 (0.09-1.12), p 0.06	1.6% versus 2.1% p 0.65	0.45 (0.12-4.56) p 0.51	0.44 (0.11-1.82) p 0.99
ST	0.3% versus 0.2% p 0.56	0.41 (0.23-9.1), p 0.45	0.46 (0.35-4.7), p 0.89	0.5% versus 1.4% p 0.18	0.45 (0.04-4.34) p 0.66	0.14 (0.03-0.74) p 0.02
DAPT >12 months versus DAPT 6-12 months	DAPT >12 months versus DAPT 6-12 months					
MACE	2.8% versus 3.4% p 0.56	0.23 (0.11-0.54), p <0.001	0.27 (0.18-0.43), p0.04	3.6% versus 3.2%, p 0.67	0.51 (0.31-1.45) p 0.78	1.12 (0.64-1.73) p 0.85
Death	1.4% versus 1.6% p 0.81	0.16 (0.04-0.9), p 0.04	0.86 (0.64-1.73), p 0.71	1.3% versus 1.3%, p 0.89	0.45 (0.23-4.51) p 0.43	1.27 (0.50-3.21) p 0.62
MI	0.6% versus 0.9% p 0.08	0.25 (0.18-0.88), p 0.03	1.11 (0.88-3.56), p 0.65	0.3% versus 0.7%, p 0.67	0.31 (0.03-3.41) p 0-18	0.33 (0.21-4.12) p 0.55
TLR	0.9% versus 1.4%, p 0.17	0.45 (0.21-1.7), p 0.89	0.79 (0.36-1.81), p 0.55	1.7% versus 1.6%, p 0.89	0.51 (0.14-1.41) p 0.36	0.90 (0.44-1.85) p 0.78
ST	0.1% versus 0.3%, p 0.28	2.1 (0.2-4.9), p 0.67	0.49 (0.21-4.51), p 0.66	0.0% versus 0.4% p 0.04	-	-

Legend: DAPT: dual antiplatelet therapy; ACS: acute coronary syndrome; CCS: Chronic Coronary Syndrome; MACE: major adverse cardiovascular events; MI: myocardial infarction; TLR: target lesion revascularization; ST: stent thrombosis. HR: hazard ratio; CI: confidence interval; IPTW: Inverse probability of treatment weighting.

* adjusted for age, gender, hyperlipidemia, diabetes mellitus, renal disease, distal ULM, provisional versus 2 stents strategy, use of imaging, registry (COBIS versus RAIN) kind of DAPT and 2010-2014 versus 2015-2017

** the percentages are reported as number of events/number of patients at the follow up achieved by each patient

FIGURES:

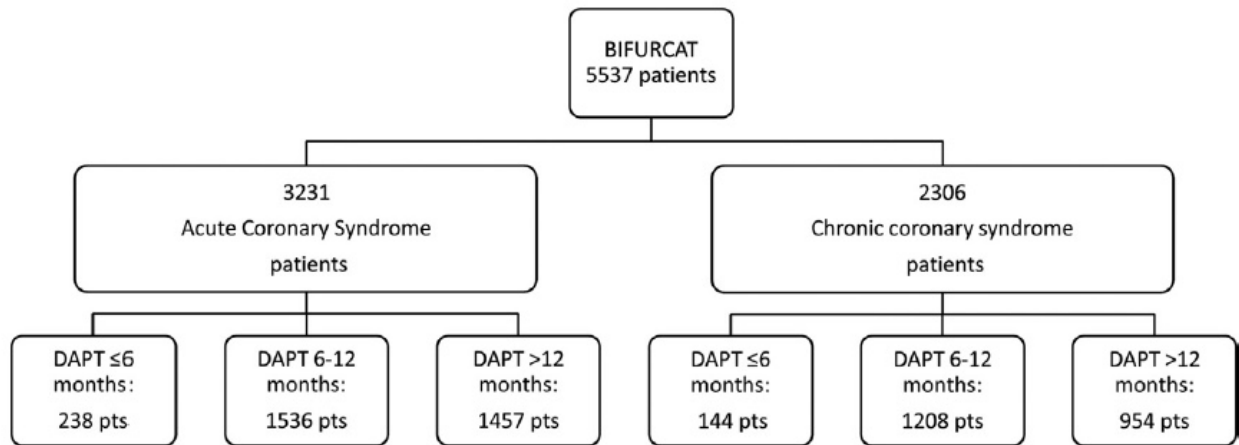


Figure 1: Study Design. DAPT: dual antiplatelet therapy.

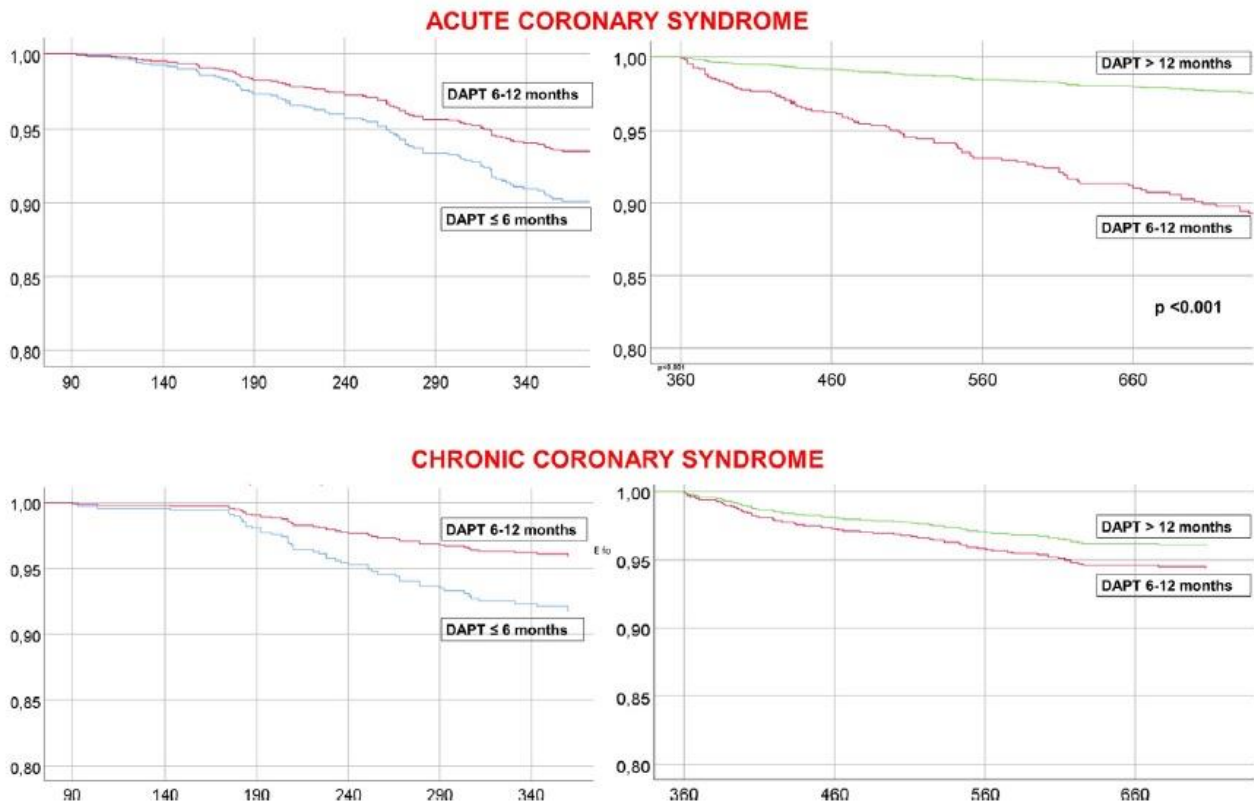


Figure 2: Adjusted survival from MACE for DAPT \leq 6 months, DAPT 6-12 months and DAPT > 12 months (above: acute coronary syndrome; below: chronic coronary syndrome cohort). Only significant p values (< 0.05) are reported. For the comparison between DAPT \leq 6 months and 6-12 months, time on the x axis starts from 6 months after the index PCI. For the comparison between DAPT 6-12 months and DAPT > 12 months, x axis starts from 12 months after the index PCI procedure.

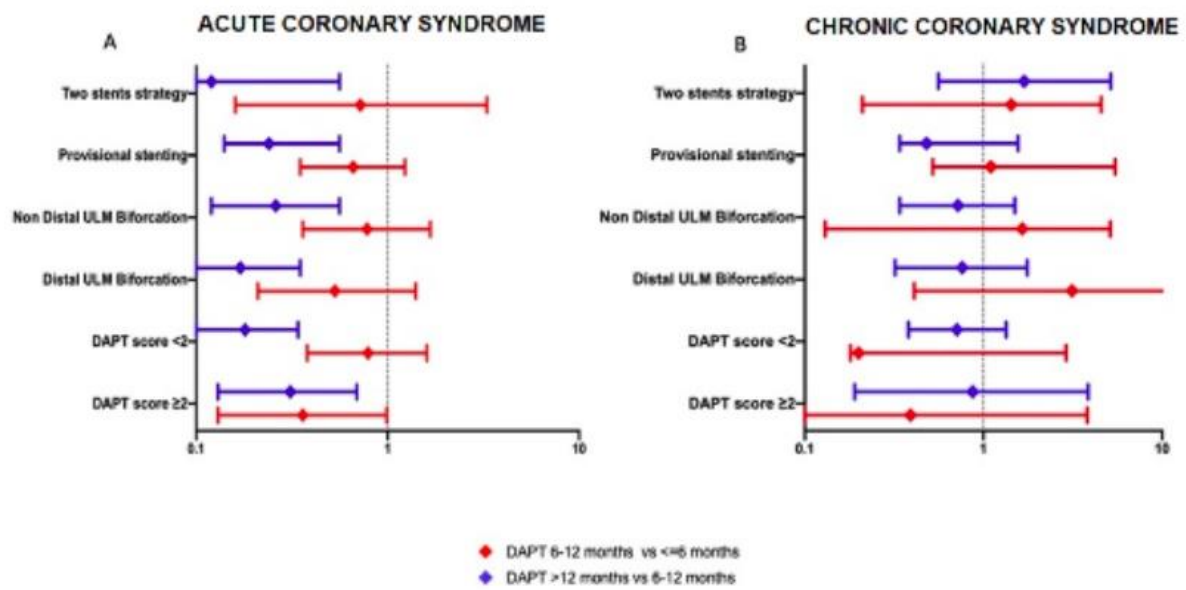


Figure 3: Subgroup analysis for MACE. ULM: unprotected left main. DAPT: dual antiplatelet therapy