Incidence of adverse events at 3 months versus at 12 months after dual antiplatelet therapy cessation in patients treated with thin stents with unprotected left main or

Availability:
This version is available at: 11583/2842974 since: 2020-09-01T15:18:04Z

Publisher:
Elsevier Inc.

Incidence of Adverse Events at 3 Months versus at 12 Months after Dual Antiplatelet Therapy Cessation in Patients Treated with Thin Stents with Unprotected Left Main or Coronary Bifurcations

Fabrizio D'Ascenzo MD , Umberto Barbero MD, Mohamed Abdirashid MD, Daniela Trabattoni MD, Giacomo Boccuzzi MD, Nicola Ryan MB Giorgio Quadri MD Davide Capodanno PhD, ,BCh, Giuseppe Venuti MD, Saverio Muscoli MD, Francesco Tomassini MD, Michele Autelli MD, Andrea Montabone MD, Wojciech Wojakowski MD, , Andrea Rognoni MD, Diego Gallo PhD, Radoslaw Parma MD, Leonardo De Luca MD, Filippo Figini MD, Satoru Mitomo MD, Antonio Montefusco MD, Giacomo Boccuzzi MD, Alessio Mattesini MD, Wojciech Wańha MD, Marcin Protasiewicz MD, Grzegorz Smolka PhD, Zenon Huczek MD, Cristina Rolfo MD, Bernardo Cortese MD, Alaide Chieffo MD, Wiktor Kuliczowki MD, Ivan Nuñez-Gil MD, Umberto Morbiducci PhD, Fabrizio Ugo MD, Giorgio Marengo MD, Mario Iannaccone MD, Enrico Cerrato MD Carlo di Mario PhD, Claudio Moretti MD, Maurizio D'Amico MD, Ferdinando Varbella MD, Thomas F. Lüscher, Imad Sheiban PhD, Javier Escaned PhD, Francesco Romeo PhD, Mauro Rinaldi PhD, Gaetano Maria De Ferrari, Gerard Helft MD.

Division of Cardiology, Departement of Internal Medicine, Città della Salute e della Scienza (FDA, MA, FC, PO, CM, MDA); Coronary Care Unit and Catheterization laboratory , A.O.U. Maggiore della Carità , Novara , Italy (AR); Structural Interventional Cardiology, Careggi University Hospital, Florence, Italy (AM, CDM); Division of Cardiology, Cardio-Thoracic-Vascular Department, Azienda Ospedaliero Universitaria "Policlinico-Vittorio Emanuele," Catania, Italy (GV, DC); Department of Cardiovascular Medicine, Nippon Medical School, 1-1-5, Sendagi, Bunkyo-ku, Tokyo, Japan (YI); Department of Cardiovascular Sciences, IRCCS Centro Cardiologico Monzino, Milan, Italy; University of Milan, Milan, Italy. (DT); Interventional Cardiology, ASST Fatebenefratelli-Sacco, Milano, Italy (BC); Dipartimento di Cardiologia, Ospedale San Giovanni Bosco, Italy (FU; GB); University Clinical Hospital, Warsaw, Poland (RP; ZH); Department of Cardiology, Hospital Clinico San Carlos, Madrid, Spain (NR, INGJE); San Raffaele Scientific Institute, Milan, Italy (SM, AC); Pederzoli Hospital, Peschiera del Garda, Italy (FF; IS); Department of Cardiology, Medical University of Silesia, Katowice, Poland (WW, WW, GS); Department of Cardiology, Infermi Hospital, Rivoli, Italy- Department of Cardiology, San Luigi Gonzaga Hospital, Orbassano, Turin, Italy (EC, GQ, FV); Division of Cardiology, S. Giovanni Evangelista Hospital, Tivoli, Rome, Italy (LdL), Pierre and Marie Curie University, Paris, France (GH), Division of Cardioloy, Universityspirtal of Zurich (CT, SG); Polito^{BIO}Med Lab, Department of Mechanical and Aerospace Engineering, Politecnico di Torino (DG;UM) and Royal Brompton and Harefield Hospital Trust and Imperial College, London, United Kingdom; Department of Medicine, Università degli Studi di Roma 'Tor Vergata', Rome, Italy (SM, FR)

Corresponding Author: Mohamed Abdirashid MD

Division of Cardiology, Departement of Medical Science University of Turin, Città della Salute e Della Scienza; Tel: +390116335945 email: baashi90@gmail.com

ABSTRACT.

Incidence and predictors of adverse events after dual antiplatelet therapy (DAPT) cessation in patients treated with thin stents (< 100 microns) in unprotected Left Main (ULM) or coronary bifurcation remain undefined. All consecutive patients presenting with a critical lesion of an ULM or involving a main coronary bifurcation who were treated with very thin strut stents were included. MACE (a composite end point of cardiovascular death, myocardial infarction (MI), target lesion revascularization (TLR) and stent thrombosis (ST) was the primary endpoint, while target vessel revascularization (TVR) was the secondary endpoint, with particular attention to type and occurrence of ST and occurrence of ST, CV death and MI during DAPT or after DAPT discontinuation. All analyses were performed according to length of DAPT dividing the patients in 3 groups: short DAPT (3-months), intermediate DAPT (3-12 months) and long DAPT (12-months). 117 patients were discharged with an indication for DAPT≤3 months (median 1:1-2.5), 200 for DAPT between 3 and 12 months (median 8:7-10) and 1958 with 12 months DAPT. After 12.8 months (8-20), MACE was significantly higher in the 3-month group compared to 3-12 and 12-month groups (9.4% vs. 4.0% vs. 7.2%, p≤0.001), mainly driven by MI (4.4% vs. 1.5% vs. 3%, p≤0.001) and overall ST (4.3% vs. 1.5% vs. 1.8%, p≤0.001). Independent predictors of MACE were low GFR and a 2 stent strategy. Independent predictors of ST were DAPT duration < 3 months and the use of a 2-stent strategy. In conclusion even stents with very thin strut when implanted in real-life ULM or coronary bifurcation patients discharged with short DAPT have a relevant risk of ST, which remains high although not significant after DAPT cessation.

Key Words: Coronary artery disease; Thin stents; Unprotected Left Main; Coronary Bifurcations; Stent Thrombosis

INTRODUCTION.

The higher performance of 2nd and 3rd generation DES and their use lead to a reduced duration of DAPT compared to the classical 12 months of the 1st generation DES era [1-9]. Recently, both American and European guidelines had recommendation to reduce to 3 months the duration of the DAPT in patients with high bleeding risk [10, 11, 12]. Reduction of DAPT duration therefore has become a common clinical scenario, even involving complex PCI (Percutaneous Coronary Intervention) patients with high bleeding risk or requiring early surgical intervention for malignancy after revascularization. A more liberal use of thin stents in complex lesions such as left main coronary artery (LMCA) and bifurcations should allow a safer shortening of the DAPT duration when required [2,3,7,8,13]. However, there is a lack of evidence surrounding the outcome of thin stents in high-risk vessels when treated with shorter DAPT protocols**.** For this reason we performed this subgroup analysis of the RAIN registry (veRy thin stents for patients with left mAIn or bifurcatioN in real life, NCT03544294).

METHODS.

All consecutive patients presenting with a critical lesion of an ULM (**see Appendix web only for definition**) or involving a main coronary bifurcation in our centers were included, if treated with thin stent (Supplementary material 1).

Data regarding cardiovascular risk factors, clinical presentation, angiographic features, use of IVUS, OCT, and fractional flow reserve (FFR) were collected, along with characteristics of the implanted stents. Data were derived from electronic charts at each Center on pre-specified forms and recorded online (http://www.cardiogroup.org/RAIN/index.php?cat=home). IVUS or OCT was used before

stent implantation to assess side branch involvement and after to optimize stent implantation. Post-dilatation, final kissing balloon (FKB), use of imaging and the choice of stenting techniques (provisional vs. 2-stents) were left to the treating physicians' discretion. Patients on oral anticoagulation therapy (OAT) were excluded. For each patient, PARIS [14] thrombotic and bleeding risk scores were evaluated.

Follow up was performed through dedicated clinical assessment, telephonic follow up or formal query to the primary care physician. Internal investigators in each center collected the events, and then they were adjudicated through submission to a panel of experts for blinded assessment.

MACE (a composite end point of cardiovascular death, myocardial infarction (MI), target lesion revascularization (TLR) and ST) was the primary endpoint, while target vessel revascularisation (TVR) was the secondary endpoint. Moreover, type and occurrence of ST and occurrence of ST during DAPT or after DAPT discontinuation were also evaluated along with CV death and MI. ARC (Academic Research Consortium) definition of ST were used and definite stent thrombosis were confirmed when there was angiographic confirmation of stent thrombosis**.** All analysis were performed, including all events and after left censoring for those occurring before 3 months, according to the length of DAPT prescribed at discharge dividing the patients in 3 groups: short DAPT (≤3 months), intermediate DAPT (3 to 12 months of DAPT) and long DAPT (12 months DAPT or more). Decision about the length of DAPT was made by caring physicians according to the concept that a short DAPT (3 to 6 months) decreases major bleeding while maintains antithrombotic efficacy compared with an extended DAPT (≥ 12 months) with a 3-to-6-month DAPT usually considered to be preferable for a broad group of patients undergoing DES implantation**.** Moreover, supplementary analysis comparing baseline and

interventional features between patients with ST occurring during DAPT or after DAPT cessation were carried out.

Categorical variables are reported as count and percentages, whereas continuous variables as mean and standard deviations or interquartile range (IQR). Gaussian or non-Gaussian distribution was evaluated by Kolmogorov-Smirnoff test. The t-test has been used to assess differences between parametric continuous variables, Man-Whitney U test for non-parametric variables, the chi-square test for categorical variables and Fisher exact test for 2x2 tables. Cox multivariate analysis was performed to assess the independent predictors of MACE and ST overall and of ST after DAPT discontinuation. The dependent variables included in the multivariate analysis were those statistically significant at the univariate analysis.

Proportional hazards assumption was not violated in statistical analysis.
A two-sided P value <=0.05 was considered statistically significant; all analyses were performed with SPSS 21.0 (IBM, Armonk, NY, USA).

RESULTS

A total of 2275 patients were included, with a median age of 68.7±11.12 years, 77.5% were male and 29.5% had diabetes mellitus, with a prevalence of renal disease (defined as eGFR≤60 ml/min) of 16.7%. One hundred and seventeen patients were discharged with indication for DAPT ≤3 months (median 1:1-2.5), 200 for DAPT between 3 and 12 months (median 8:7-10) and 1958 with 12 months DAPT.

Patients receiving ≤3 months DAPT were older compared to other 2 groups, with a lower ejection fraction (EF) **(Table 1),** with higher rates of kidney disease and more often presenting with positive stress test as an indication for PCI. Moreover these patients have higher rates of both bleeding and ischemic PARIS score. From an angiographic point of

view, the most frequently treated vessel in this group was the LAD/Diagonal bifurcation with ULM lesions less common **(Table 2)**. A 2-stent technique was rare, and clopidogrel was the most common P2Y12i drug at discharge (70.9% vs. 63.5% vs. 59.2%, p<0.001, (see **appendix web only, Figure 1**).

After a mean follow up of 12.8 months (range 8-20), the incidence of MACE was significantly higher in the ≤3 months DAPT group compared to the 3-12 and 12-month groups (9.4% vs. 4.0% vs. 7.2%, p<0.001); this difference was mainly driven by MI (4.4% vs. 1.5% vs. 3%, p<0.001) and overall ST (4.3% vs. 1.5% vs. 1.8%, p<0.001, see **Table 3 and Figure 1**). After censoring the events in the first 3-months, the incidence of MACE was 6% vs. 4% vs. 4.9% (p<0.01), with no significant difference in MI (0.8% vs. 1.5% vs. 1.2%, p 0.45). When analyzing in detail the ST data patients with ≤3 months DAPT had higher rates of sub-acute ST (4.3% vs. 0% vs. 0.3%, p=0.001), while rates of ST during DAPT and post DAPT were similar among groups (2.6% vs. 1.5% vs. 1.1%, p=0.42, and 1.7% vs. 0% vs. 0.7%, p=0.4; **see Table 4 and Figure 2).** Median time to ST after DAPT discontinuation was 1.67 months (0.48-4.7), while time from index PCI to ST was 1.49 months (0.4-6.13, **see Figure 3**). In patients undergoing PCI in ULM, a comparable tendency was noted with higher rates of overall ST in DAPT≤3 months (7.1% vs. 1.9% vs. 2.5%, p<0.001), while only a trend was noted for ST during DAPT and after DAPT cessation (**Figure 4**). Similarly, in the first 2 groups the whole of CV death occurred after DAPT cessation, while in the group with longer DAPT 44.8% of all the CV death occurred in DAPT and just 55.2% after DAPT cessation. Regarding MI, 65% occurred during DAPT for the first group and 35% after DAPT cessation, 100% in DAPT for the second group and 87.5% in DAPT and 12.5% after DAPT cessation for the longer DAPT group.

At multivariate analysis, short DAPT did not impact on the risk of MACE, which was instead increased by the presence of renal disease (OR 1.8:1.2-2.7, 95% CI) and by the adoption of a 2-stent strategy (OR 1.6: 1.1-2.3, 95%CI).

Regarding ST overall, DAPT longer than 12 months compared to a 3 months strategy reduces its risk (OR 0.103: 0.019-.0563, 95%CI) while only a trend was noted for DAPT between 3 and 12 months (OR 0.61:0.186-2.005, 95%CI). ST after DAPT cessation was only predicted by a 2-stent strategy (OR 3.241: 1.048-10.026, 95%CI) and reduced by use of FKB (OR 0.101:0.01-0.872, 95%CI), irrespective of the DAPT duration. (see Supplementary Table 3-5, Figures 5,6). Interestingly, independently from the kind of P2Y12-inhibitor, the risk of ST was significantly higher in the 3 months DAPT groups, while prasugrel and ticagrelor showed a trend for lowering risk of ST in ultrashort DAPT (0% vs. 1.4% vs. 1.3%; see Supplementary figures1,2)

Similar baseline clinical features were seen in patients with ST during DAPT or after DAPT cessation. Angiographically, ST during DAPT was seen more frequently in mid-distal LM disease (87% vs. 67%, p 0.04) and in patients with diffuse coronary disease (43% vs. 13%, p 0.049). No differences were observed when analyzed by stent strategy and use of imaging (see Supplementary tables 1 and 2).

DISCUSSION

With the present registry we aimed to appraise incidence of thrombotic events for patients treated with thin stents on ULM and bifurcation according to length of DAPT.

The novelty of the present registry relies on the inclusion of patients with short DAPT (even shorter than 3 months) who received PCI on bifurcation or ULM and stenting with thin stents, which should be protective by themselves from ST due to reduced shear stress

in coronary arteries [15]. Our data fill a gap among randomized controlled trials (RCTs) and observational registries.

Shorter DAPT protocols have been introduced to minimize bleeding risk. Accordingly, all recently published guidelines and position papers from major cardiologic societies recommend personalizing DAPT duration depending on the balance between thrombotic and bleeding risk. Unfortunately, since such tailoring is commonly dictated by a perceived increased hemorrhagic risk, the payed price is an increased thrombotic risk [15]. Moreover it should be noted that patients in the short DAPT group had higher rates of PARIS ischemic risk but also more evident elevated bleeding risk.

This findings are also influenced by clinical characteristics such as kidney disease and technical aspects like complexity of PCI (i.e. two stents technique or the use of FKB). Of note, patients referred to a shorter DAPT regimen because of an increased hemorrhagic risk usually had important comorbidities: in line with other studies they were more frequently older, diabetic, hypertensive, with a lower ejection fraction and impaired kidney function [16, 17]. In addition, they were usually treated with clopidogrel rather than with novel potent P_2Y_{12}-inhibitors. These facts could explain the relatively high level of MACE and ST (which are all sub-acute) in those prescribed short DAPT. In this group of patients when ST occurred after stopping DAPT, the only predisposing factor was a two-stent strategy, while the use of final kissing balloon appeared protective.

In the literature rebound platelet activation has been proposed to explain the increase in very late ST when DAPT length was over 12 months or even longer [18]. A rebound effect on platelet activation after stopping DAPT cannot be excluded in these anatomically complex patients when looking at the percentage increase of events at follow-up in the long-DAPT group compared to mid-length DAPT. Notably, in our study, we

enrolled consecutive ACS patients who t have an intrinsic higher thrombotic risk [19]. Furthermore, as IVUS guided PCI is undeniably able to reduce in-stent restenosis as well as ST [20] and the level of imaging-guided procedures was less than 50% in our series, this could have further contributed.

Thus, our results suggest that a short DAPT strategy requires extensive clinical considerations, particularly in patients with anatomical complexity and/or two stents techniques. The correct identification of sicker patients may help identify the safest PCI technique that permits the shorter DAPT regimen. On the other hand, lesion complexity (i.e. left main and bifurcation lesions) *per se* is associated with an increased risk of MACE [21,22]. This is supported by the analysis of ST on DAPT compared that after DAPT cessation. ST on DAPT presented more often with stenosis of the mid-distal rather than ostial LM, which is a site more prone to shear stress, atherothrombotic and diffuse disease which itself carries a higher risk of such an event. Notably and in line with a previous study [23], the mid-term DAPT group, which included patients that had an intermediate anatomical and technical thrombotic risk, had the best clinical outcomes at follow-up. The ischemic risk may be stratified using validated risk scores like the DAPT score or PRECISE-DAPT, helping to identify patients who still have an increased ischemic risk irrespective of their hemorrhagic one [24, 25].

Timing of ST after DAPT discontinuation appears to be in line with previous reports [25-27]. Actually, the relationship between time from DES revascularization and likelihood for ST when DAPT therapy is discontinued (or interrupted) is strictly depending from the total DAPT length: within the initial 6 months, the time from drug cessation to ST is brief. Beyond 6 months, however, the relationship between time from thienopyridine discontinuation and event is less distinct [26, 27].

There are many limitations to this study. First, it is not a randomized controlled trial; therefore the ability to differentiate between DAPT groups is limited. Second, the duration of the DAPT was at discretion of the operators/clinicians before the discharge of the patients and the reasons of the discontinuation were not reported. Third, PARIS score may be less accurate because patients with OAT therapy were excluded. Fourth, the short DAPT groups are smaller than the conventional 12 months DAPT group, but it is actually uncommon to have patients with bifurcations or ULM PCI receiving short DAPT because of concerning related to bleeding issue; nevertheless the number hereby presented are not negligible and we think that data are worth of reporting. Moreover, we did not record data about bleeding complications, because it was beyond the aim of the present registry. However, PARIS bleeding risk was higher in patients discharged with short DAPT, predicting relevant rates of hemorrhages. Finally, some of the patients were enrolled in 2015 and early 2016, before more standardized guidelines had been published which might have affected the heterogeneity of the enrolling criteria. Despite such limitations, we think that this study nicely fits into the evolving field of the safety of newer generation DES.

In conclusion, left main and bifurcation lesions are a thorny PCI subset, in which anatomical complexity is often complemented by unfavorable comorbidities of the patients. All the clinical factors known to increase the ischemic risk should be adequately balanced against hemorrhagic risk considering the high rate of MACE (particularly ACS and ST) that such patients like the one enrolled in our study can encounter on follow-up when a short-term DAPT is chosen. When a patient needs short DAPT, a provisional approach to bifurcation stenting and imaging-guided PCI with extensive post-dilation should be used to reduce the risk of subsequent events.

References

[1] DAPT Study Investigators.Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med* 2014;371:2155-2166.

[2] Bonaca MP, Bhatt DL, Steg PG, Storey RF, Cohen M, Im K, Oude Ophuis T, Budaj A, Goto S, López-Sendón J, Diaz R, Dalby A, Van de Werf F, Ardissino D, Montalescot G, Aylward P, Magnani G, Jensen EC, Held P, Braunwald E, Sabatine MS. Ischaemic risk and efficacy of ticagrelor in relation to time from P2Y12 inhibitor withdrawal in patients with prior myocardial infarction: insights from PEGASUS-TIMI 54. *Eur Heart J* 2016;37:1133-1142.

[3] D'Ascenzo F, Moretti C, Bianco M, Bernardi A, Taha S, Cerrato E, Omedè P, Montefusco A, Frangieh AH, Lee CW, Campo G, Chieffo A, Quadri G, Pavani M, Zoccai GB, Gaita F, Park SJ, Colombo A, Templin C, Lüscher TF, Stone GW. Meta-Analysis of the Duration of Dual Antiplatelet Therapy in Patients Treated With Second-Generation Drug-Eluting Stents. *Am J Cardiol* 2016;117:1714-1723.

[4] Kim BK, Hong MK, Shin DH, Nam CM, Kim JS, Ko YG, Choi D, Kang TS, Park BE, Kang WC, Lee SH, Yoon JH, Hong BK, Kwon HM, Jang Y. A new strategy for discontinuation of dual antiplatelet therapy: the RESET Trial (REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation). *J Am Coll Cardiol* 2012;60:1340-1348.

[5] Gwon HC, Hahn JY, Park KW, Song YB, Chae IH, Lim DS, Han KR, Choi JH, Choi SH, Kang HJ, Koo BK, Ahn T, Yoon JH, Jeong MH, Hong TJ, Chung WY, Choi YJ, Hur SH, Kwon HM, Jeon DW, Kim BO, Park SH, Lee NH, Jeon HK, Jang Y, Kim HS. Six-month versus 12-month dual antiplatelet therapy after implantation of drug-eluting stents:

the Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting (EXCELLENT) randomized, multicenter study. *Circulation* 2012;125:505-513.

[6] Valgimigli M, Campo G, Monti M, Vranckx P, Percoco G, Tumscitz C, Castriota F, Colombo F, Tebaldi M, Fucà G, Kubbajeh M, Cangiano E, Minarelli M, Scalone A, Cavazza C, Frangione A, Borghesi M, Marchesini J, Parrinello G, Ferrari R. Short- versus long-term duration of dual-antiplatelet therapy after coronary stenting: a randomized multicenter trial. *Circulation* 2012;125:2015-2026.

[7] OPTIMIZE Trial Investigators. Three vs twelve months of dual antiplatelet therapy after zotarolimus-eluting stents: the OPTIMIZE randomized trial. *JAMA 2013;310:2510-2522.*

[8] Colombo A, Chieffo A, Frasheri A, Garbo R, Masotti-Centol M, Salvatella N, Oteo Dominguez JF, Steffanon L, Tarantini G, Presbitero P, Menozzi A, Pucci E, Mauri J, Cesana BM, Giustino G, Sardella G. Second-generation drug-eluting stent implantation followed by 6- versus 12-month dual antiplatelet therapy: the SECURITY randomized clinical trial. *J Am Coll Cardiol* 2014;64:2086-2097.

[9] D'Ascenzo F, Iannaccone M, Saint-Hilary G, Bertaina M, Schulz-Schüpke S, Wahn Lee C, Chieffo A, Helft G, Gili S, Barbero U, Biondi Zoccai G, Moretti C, Ugo F, D'Amico M, Garbo R, Stone G, Rettegno S, Omedè P, Conrotto F, Templin C, Colombo A, Park SJ, Kastrati A, Hildick-Smith D, Gasparini M, Gaita F. Impact of design of coronary stents and length of dual antiplatelet therapies on ischaemic and bleeding events: a network meta-analysis of 64 randomized controlled trials and 102 735 patients. *Eur Heart J* 2017;38:3160-3172.

[10] Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, Granger CB, Lange RA, Mack MJ, Mauri L, Mehran R, Mukherjee D, Newby LK, O'Gara PT, Sabatine

MS, Smith PK, Smith SC. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2016;68:1082-1115.

[11] 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;37:2893-2962.

[12] 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2018;39:213-260.

[13] Iannaccone M, Gatti P, Barbero U, Bassignana A, Gallo D, de Benedictis M, Helft G, Morbiducci U, Doronzo B, D'Ascenzo F. Impact of strut thickness and number of crown and connectors on clinical outcomes on patients treated with second-generation drug eluting stent. Catheter Cardiovasc Interv. 2019 Apr 13. doi:10.1002/ccd.28228. [Epub ahead of print] PubMed PMID: 30980471.

[14] Baber U, Mehran R, Giustino G, Cohen DJ, Henry TD, Sartori S, Ariti C, Litherland C, Dangas G, Gibson CM, Krucoff MW, Moliterno DJ, Kirtane AJ, Stone GW, Colombo A, Chieffo A, Kini AS, Witzenbichler B, Weisz G, Steg PG, Pocock S. Coronary Thrombosis and Major Bleeding After PCI With Drug-Eluting Stents: Risk Scores From PARIS. *J Am Coll Cardiol* 2016;67:2224-2234.

[15] Kolandaivelu K, Swaminathan R, Gibson WJ, Kolachalama VB, Nguyen-Ehrenreich KL, Giddings VL, Coleman L, Wong GK, Edelman ER. Stent thrombogenicity

early in high-risk interventional settings is driven by stent design and deployment and protected by polymer-drug coatings. *Circulation* 2011;123:1400-1409.

[16] Zimarino M, Briguori C, Amat-Santos IJ, Radico F, Barbato E, Chieffo A, Cirillo P, Costa RA, Erglis A, Gamra H, Gil RJ, Kanic V, Kedev SA, Maddestra N, Nakamura S, Pellicano M, Petrov I, Strozzi M, Tesorio T, Vukcevic V, De Caterina R, Stankovic G. Mid-term outcomes after percutaneous interventions in coronary bifurcations. *Int J Cardiol* 2019;283:78-83.

[17] Jang WJ, Ahn SG, Song YB, Choi SH, Chun WJ, Oh JH, Cho SW, Kim BS, Yoon JH, Koo BK, Yu CW, Jang YS, Tahk SJ, Kim HS, Gwon HC, Lee SY, Hahn JY. Benefit of Prolonged Dual Antiplatelet Therapy After Implantation of Drug-Eluting Stent for Coronary Bifurcation Lesions: Results From the Coronary Bifurcation Stenting Registry II. *Circ Cardiovasc Interv* 2018;11:e005849.

[18] Brener SJ, Serruys PW, Morice MC, Mehran R, Kappetein AP, Sabik JF, Liu Y, Dressler O, Ben-Yehuda O, Stone GW. Optimal Duration of Dual Antiplatelet Therapy After Left Main Coronary Stenting. *J Am Coll Cardiol* 2018;72:2086-2087.

[19] D'Ascenzo F, Colombo F, Barbero U, Moretti C, Omedè P, Reed MJ, Tarantini G, Frati G, Di Nicolantonio JJ, Biondi Zoccai G, Gaita F. Discontinuation of dual antiplatelet therapy over 12 months after acute coronary syndromes increases risk for adverse events in patients treated with percutaneous coronary intervention: systematic review and meta-analysis. *J Interv Cardiol* 2014;27:233-241.

[20] Rhee TM, Park KW, Kim CH, Kang J, Han JK, Yang HM, Kang HJ, Koo BK, Kim HS. Dual Antiplatelet Therapy Duration Determines Outcome After 2- But Not 1-Stent Strategy in Left Main Bifurcation Percutaneous Coronary Intervention. *JACC Cardiovasc Interv* 2018;11:2453-2463.

[21] Cerrato E, Barbero U, Quadri G, Ryan N, D'Ascenzo F, Tomassini F, Quirós A, Bellucca S, Conrotto F, Ugo F, Kawamoto H, Rolfo C, Pavani M, Mejia-Renteria H, Gili S, Iannaccone M, Debenedictis M, Baldassarre D, Biondi-Zoccai G, Colombo A, Varbella F, Escaned J. Prediction of long-term patient outcome after contemporary left main stenting using the SYNTAX and SYNTAX II scores: A comparative analysis from the FAIL-II multicenter registry (failure in left main study with 2nd generation stents-Cardiogroup III study). *Catheter Cardiovasc Interv* 10.1002/ccd.28468

[22] Barbero U, Kanji R, Cerrato E, Di Summa R, Conrotto F, Kawamoto H, Biondi-Zoccai G, Gili S, Ugo F, Iannaccone M, Gagliardi M, De Benedictis M, Doronzo B, Varbella F, D'Amico M, Moretti C, Colombo A, Escaned J, D'Ascenzo F. Unprotected Left Main Coronary Artery Disease: Outcomes of Treatment With Second-Generation Drug-Eluting Stents - Insight From the FAILS-2 Study. *J Invasive Cardiol* 2018;30:283-288.

[23] Yeh RW, Kereiakes DJ, Steg PG, Cutlip DE, Croce KJ, Massaro JM, Mauri L. Lesion Complexity and Outcomes of Extended Dual Antiplatelet Therapy After Percutaneous Coronary Intervention. *J Am Coll Cardiol* 2017;70:2213-2223.

[24] Kereiakes DJ, Yeh RW, Massaro JM, Cutlip DE, Steg PG, Wiviott SD, Mauri L. DAPT Score Utility for Risk Prediction in Patients With or Without Previous Myocardial Infarction. *J Am Coll Cardiol* 2016;67:2492-2502.

[25] Costa F, van Klaveren D, James S, Heg D, Räber L, Feres F, Pilgrim T, Hong MK, Kim HS, Colombo A, Steg PG, Zanchin T, Palmerini T, Wallentin L, Bhatt DL, Stone GW, Windecker S, Steyerberg EW, Valgimigli M. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. *Lancet* 2017;389:1025-1034.

[26] Airoldi F, Colombo A, Morici N, Latib A, Cosgrave J, Buellesfeld L, Bonizzoni E, Carlino M, Gerckens U, Godino C, Melzi G, Michev I, Montorfano M, Sangiorgi GM, Qasim A, Chieffo A, Briguori C, Grube E. Incidence and predictors of drug-eluting stent thrombosis during and after discontinuation of thienopyridine treatment. *Circulation* 2007;116:745-754.

[27] van Werkum JW, Heestermans AA, Zomer AC, Kelder JC, Suttorp MJ, Rensing BJ, Koolen JJ, Brueren BR, Dambrink JH, Hautvast RW, Verheugt FW, ten Berg JM. Predictors of coronary stent thrombosis: the Dutch Stent Thrombosis Registry. *J Am Coll Cardiol* 2009;53:1399-1409.

Table 1. Baseline Characteristics

		Months of Dual Antiplatelet Therapy			
		< 3 (n=117)	**3-12 (n=200)**	**12 (n=1958)**	**P Value**
Men		91 (77%)	167 (83.5%)	1506 (76.9%)	0.104
Age (years)		72.29±10.9	64.84±12.7	68.88±10.9	<0.001
Body Mass Index (kg/m2)		27.54±11.22	26.71±7.82	24.56±12.3	0.056
Ejection Fraction (%)		49.4 ±13.27	53.76 ± 9.96	52.07±9.13	0.006
Hypertension		95 (81.2%)	135 (67.5%)	1428 (72.9%)	0.030
Hyperlipidemia		73 (62.4%)	118 (59%)	1092 (55.8%)	0.276
Diabetes (Non-Insulin-Dependent Diabetes)		40 (34.2%)	52 (26%)	423 (21.6%)	0.003
Diabetes (Insulin-Dependent Diabetes)		10 (8.5%)	16 (8%)	132 (6.7%)	0.627
Previous smoker		31 (26.5%)	54 (27%)	547 (27.9%)	0.087
Current smoker		23 (18.7%)	55 (27.5%)	378 (19.3%)	
Renal disease (GFR< 60 ml/min)		43 (36.8%)	21 (15.6%)	307 (15.7%)	<0.001
Anemia at discharge		43 (36.5%)	54 (29.7%)	314 (17.6%)	<0.001
Previous percutaneous coronary intervention		38 (32.5%)	63 (31.5%)	573 (29.7%)	0.731
Previous Coronary Artery Bypass Graft surgery		9 (7.7%)	6 (3%)	99 (5.1%)	0.177
Previous myocardial infarction		46 (41.4%)	100 (50%)	567 (30.6%)	<0.001
Paris bleeding risk:					<0.001
- **Low**		26 (22%)	93 (46%)	864 (44%)	
- **Moderate**		41 (35%)	85 (43%)	996 (51%)	
- **High**		50 (43%)	22 (11%)	100 (5%)	
Paris ischemic risk:					0.001
- **Low**		64 (55%)	103 (52%)	1221 (63%)	
- **Moderate**		31 (27%)	72 (36%)	558 (28.5%)	
- **High**		22 (19%)	25 (13%)	181 (9.2%)	
Percutaneous coronary intervention indication	**Stent thrombosis segment elevation myocardial infarction**	20 (17.4%)	20 (10%)	307 (15.8%)	<0.001
	Non Stent	31 (27%)	59 (29.5%)	462 (23%)	

thrombosis segment elevation myocardial infarction			
Unstable angina	11 (9.6%)	33 (16.5%)	310 (16%)
Stable angina	19 (16.5%)	53 (26.5%)	451 (23.3%)
Positive stress test	34 (29.6%)	30 (15%)	220 (11.3%)
Planned angiographic follow up	0	4 (2%)	189 (9.7%)

Table 2. Angiographic Characteristics.

		Months of Dual Antiplatelet Therapy			
		< 3 (n=117)	**3-12 (n=200)**	**12 (n=1958)**	**P Value**
Left main lesion	**Ostial**	14 (41.2%)	16 (25.8%)	93 (12.9%)	<0.001
	Mid-distal	20 (58.8%)	46 (74.2%)	626 (87.1%)	
Radial access		77 (65.8%)	146 (73%)	1348 (69.2%)	0.712
Diffuse disease		56 (47.9%)	143 (72.6%)	652 (36.8%)	<0.001
Bifurcation		97 (82.9%)	182 (91.5%)	1689 (87.4%)	0.077
Type of bifurcation	**Distal LM**	31 (31.3%)	48 (26.2%)	547 (31.8%)	0.089
	LAD/Diag	50 (50.5%)	87 (47.5%)	776 (45.1%)	
	Cx/OM	14 (14.1%)	29 (15.8%)	282 (16.4%)	
	RCA/PL	3 (3%)	19 (10.4%)	92 (5.4%)	
Bifurcation Strategy	**Provisional**	75 (87.2%)	152 (80%)	1408 (77.9%)	0.027
	2-stent	8 (9.3%)	38 (20%)	349 (19.3%)	
Use of imaging	**IVUS**	16 (14%)	34 (17.3%)	408 (21.2%)	<0.001
	OCT	1 (0.9%)	9 (4.6%)	19 (1%)	
Postdilatation		53 (45.7%)	149 (75.3%)	1360 (76.6%)	0.142
FInal kissing balloon		29 (26%)	78 (41%)	847 (49%)	<0.001
Dual Antiplatelet Therapy	**Clopidogrel**	83 (70.9%)	127 (63.5%)	1161 (59.2%)	<0.001
	Ticagrelor	30 (25.6%)	65 (32.5%)	617 (31.5%)	
	Prasugrel	2 (1.7%)	8 (4%)	132 (6.7%)	

Table 3. Long term outcome.

Outcome	Months of Dual Antiplatelet Therapy			
	3 Months DAPT (117)	3-12 Months DAPT (200)	12 Months DAPT (1958)	P Value
MACE				
- **Overall**	11 (9.4%)	8 (4.0%)	141 (7.2%)	<0.001
- **After 3 months**	7 (6.0%)	8 (4.0%)	97 (4.9%)	0.01
CV death				
- **Overall**	4 (4.4%)	1 (0.5%)	13 (0.6%)	0.36
- **After 3 months**	2 (4.1%)	1 (0.5%)	7 (0.4%)	0.61
MI				
- **Overall**	6 (4.4%)	3 (1.5%)	59 (3%)	0.001
- **After 3 months**	1 (0.8%)	3 (1.5%)	23 (1.2%)	0.45
TVR				
- **Overall**	5 (4.3%)	6 (3%)	95 (4.8%)	0.004
- **After 3 months**	5 (4.3%)	6 (3%)	95 (4.8%)	
TLR				
- **Overall**	4 (3.4%)	6 (3%)	68 (3.5%)	0.002
- **After 3 months**	3 (2.6%)	6 (3%)	67 (3.4%)	0.002

Figure 1.tif
Click here to download high resolution image

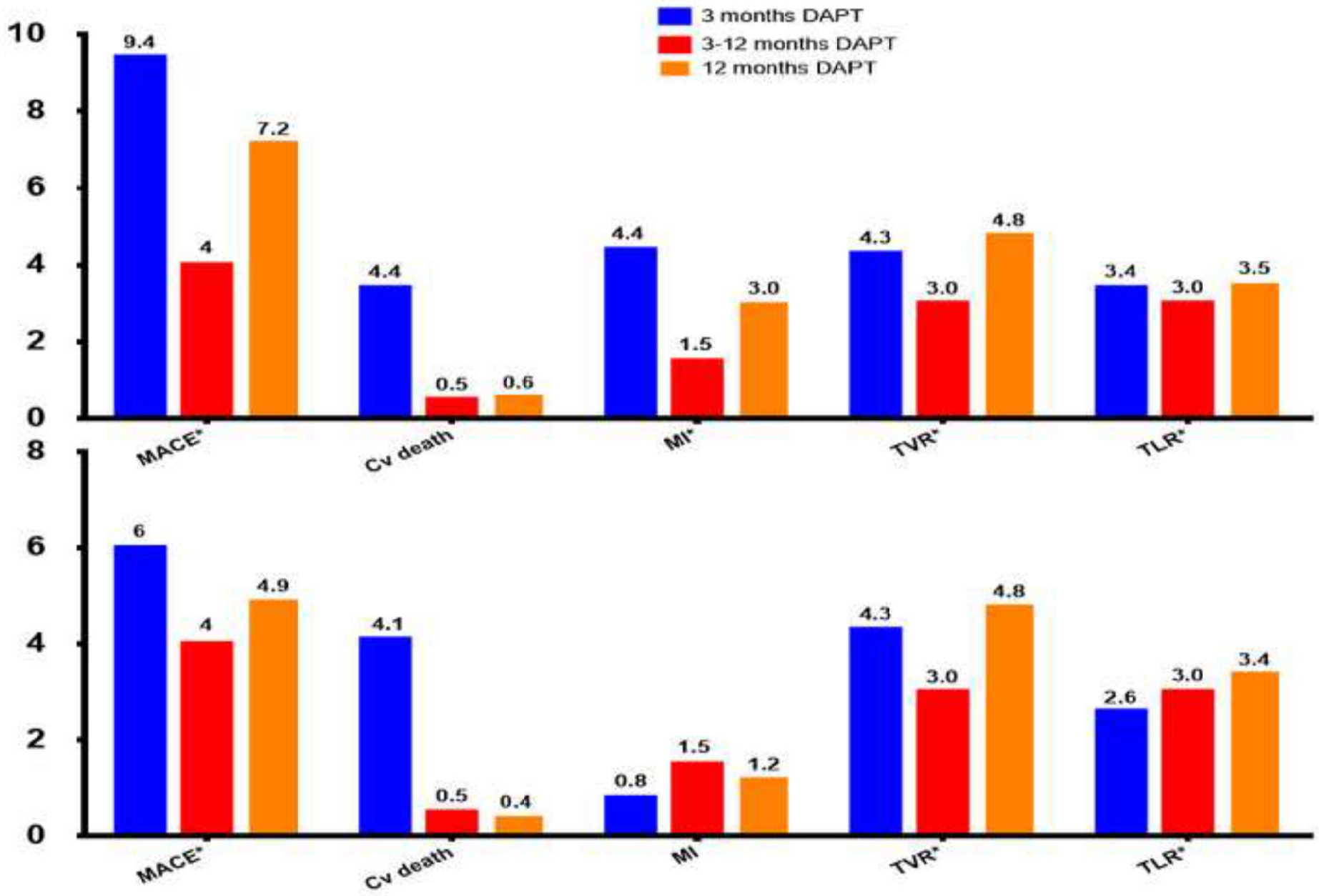

Figure number 1. Adverse outcomes according to lenght of DAPT (above for all events,* significant values between 3 m. and 3-12 and 12 m for MACE, death , *significant values between 3 months and 3-12 for MI, TVR and TLR; below only event after 3 months, p<0.001 fTLR and TVR)

Figure 2.tif
Click here to download high resolution image

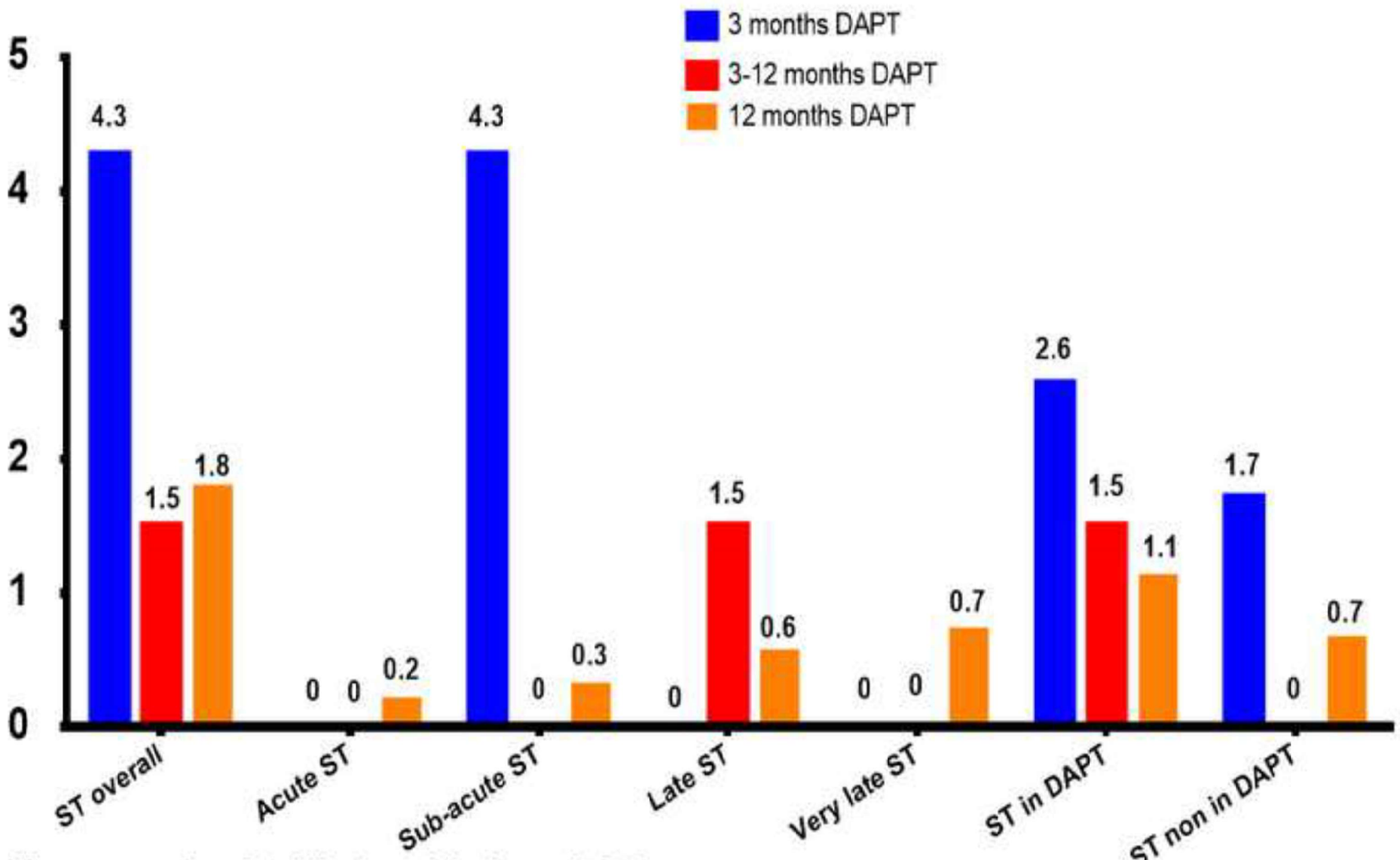

Figure number 2. Kind and timing of ST

Figure 3.tif
Click here to download high resolution image

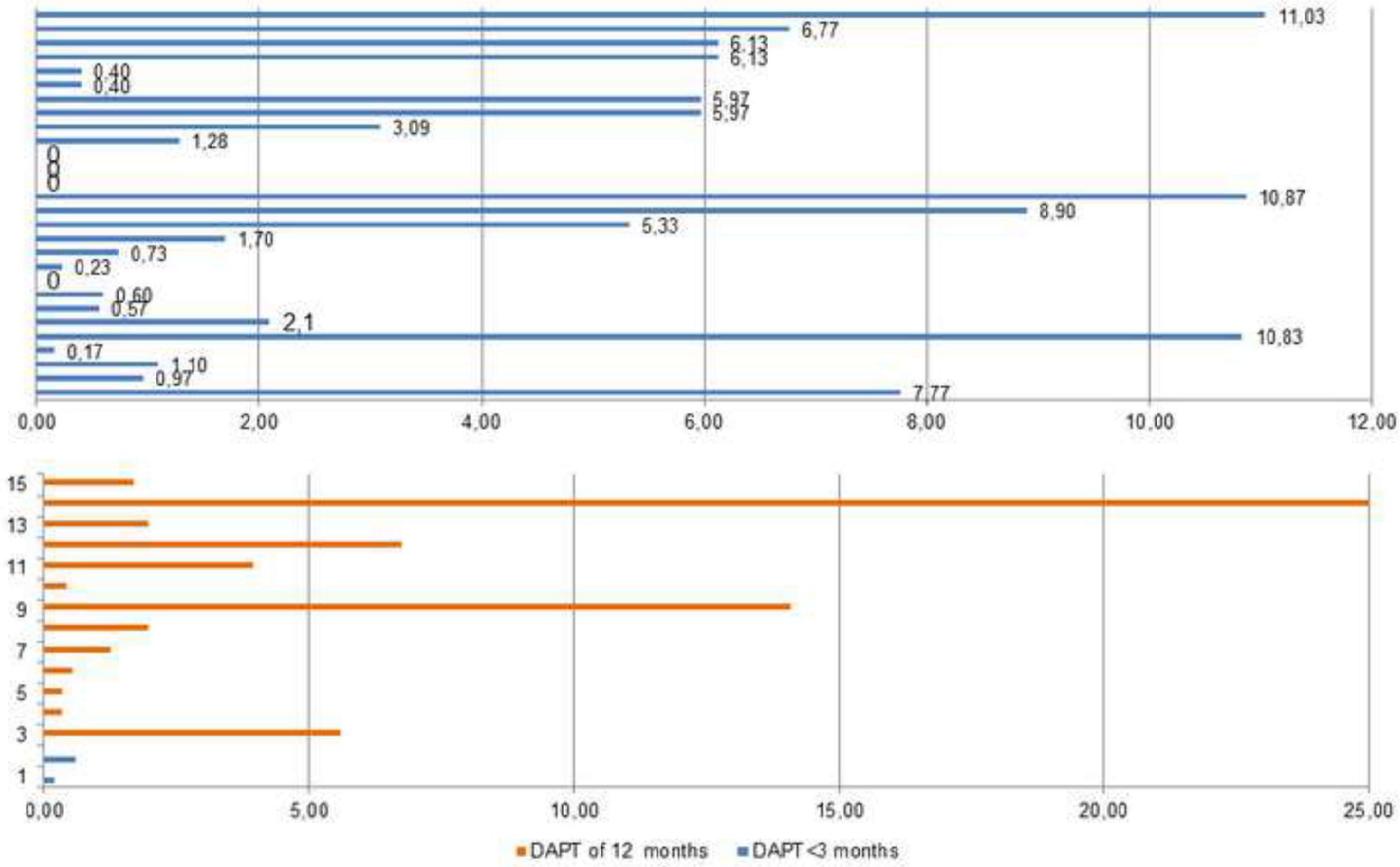

Figure number 3. Months from index PCI to ST for patients experiencing ST in DAPT (above) and time from cessation of DAPT to ST for patients with ST after stopping DAPT (below;).

Figure 4.tif
Click here to download high resolution image

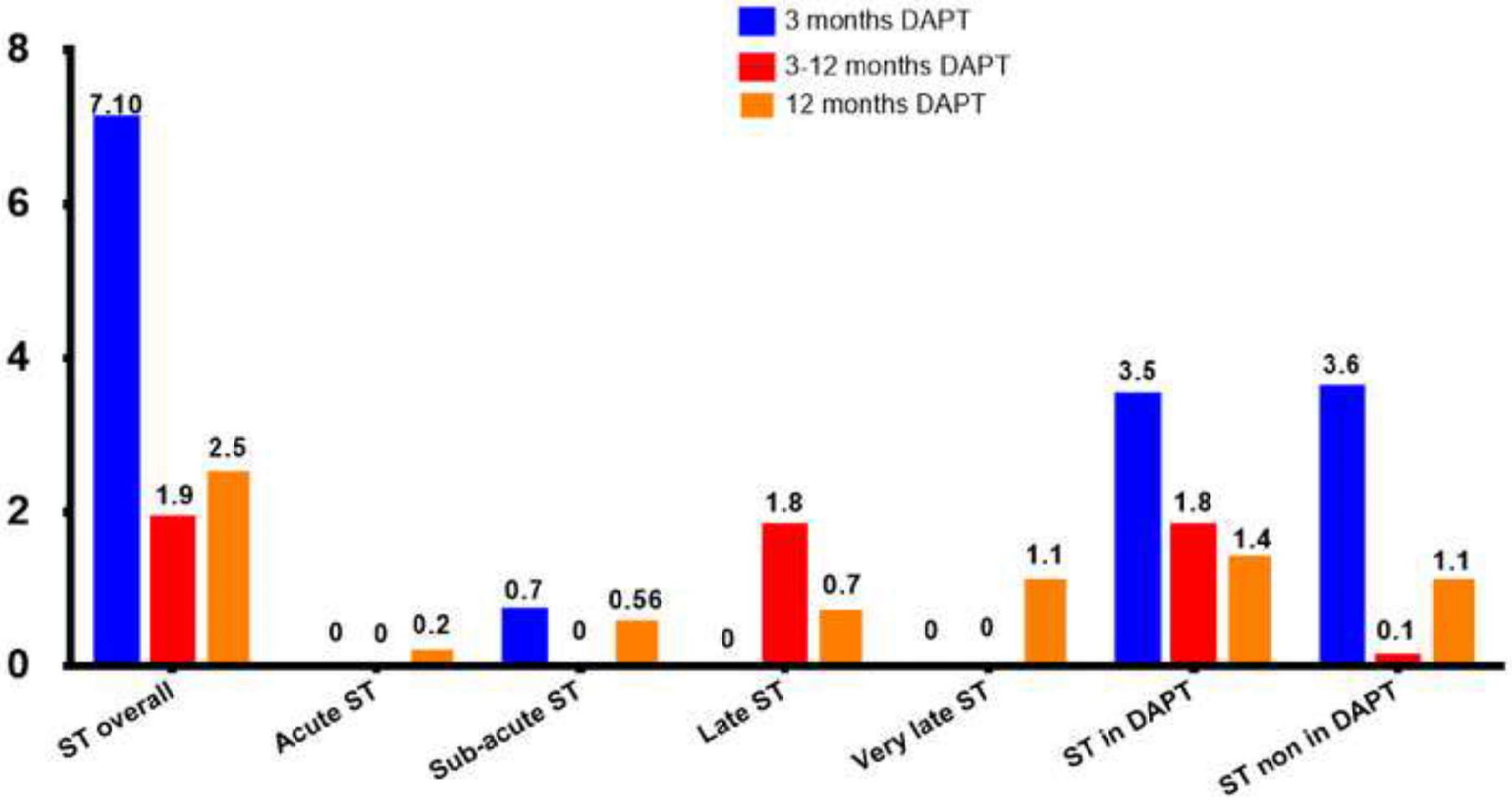

Figure number 4. Kind and timing of ST for ULM

Figure 5.tif
Click here to download high resolution image

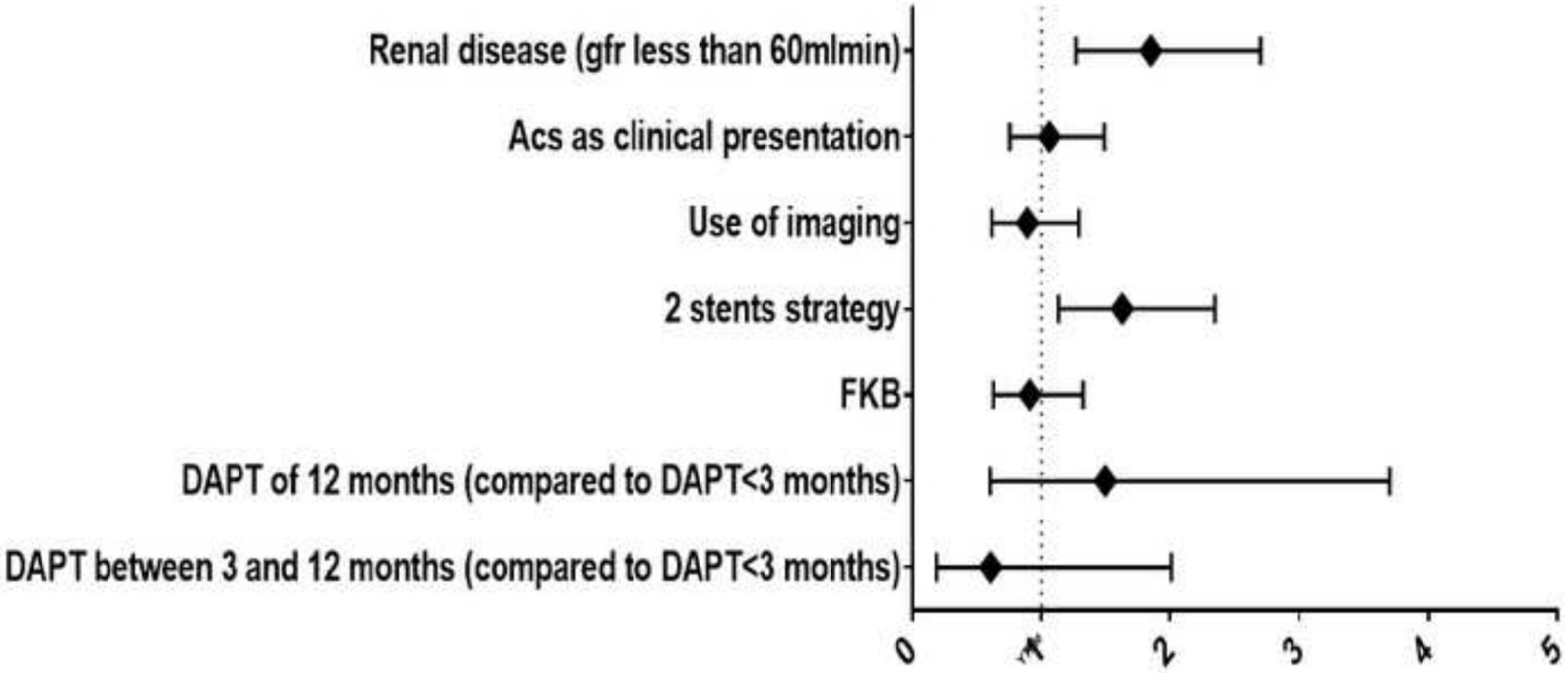

Figure number 5. Cox multivariate analysis for MACE

Figure 6.tif
Click here to download high resolution image

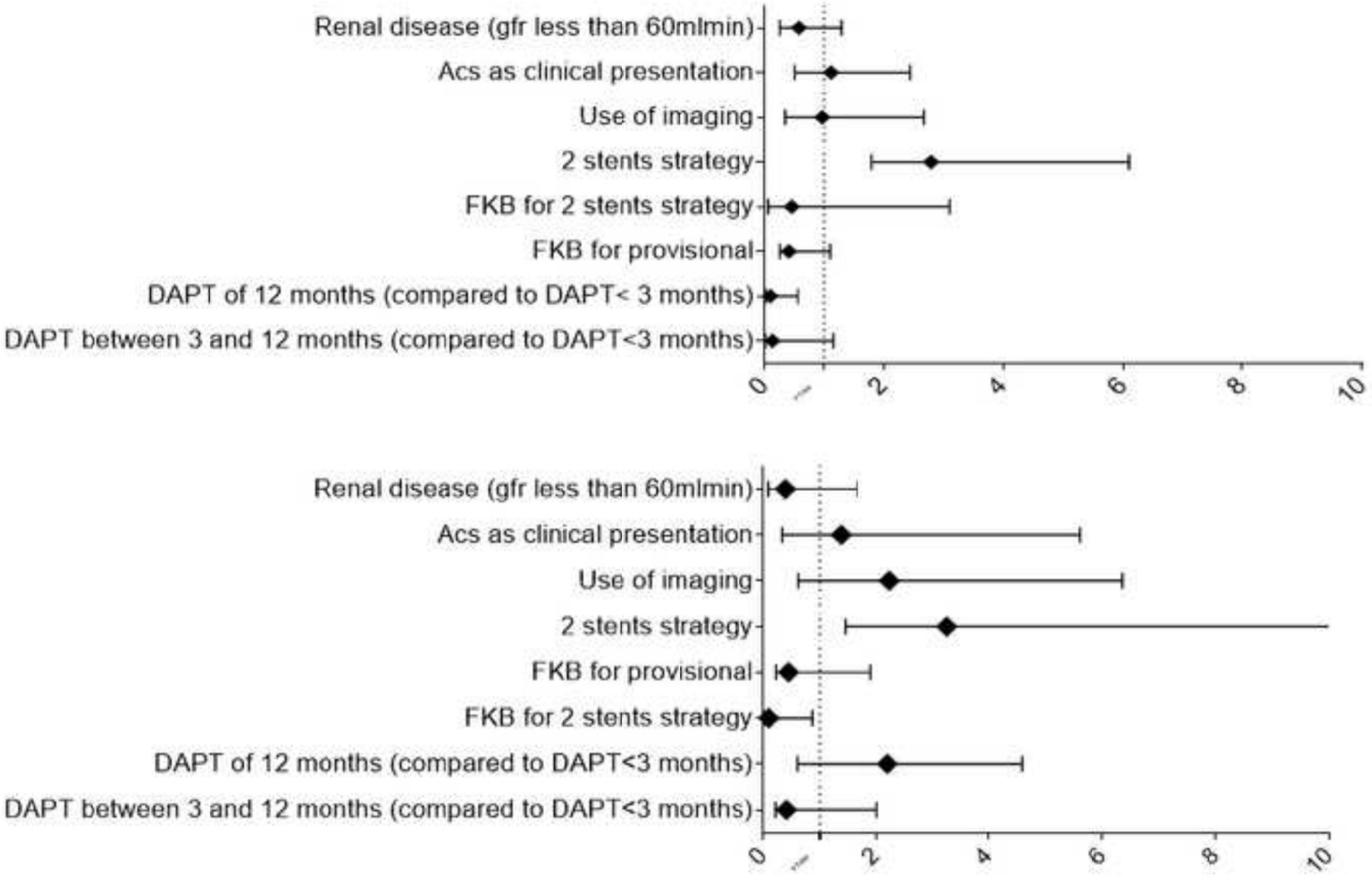

Figure number 6. Cox multivariate analysis for ST overall and for ST after DAPT cessation (from above to below)