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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

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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 \leq 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%, $p\leq 0.001$), mainly driven by MI (4.4% vs. 1.5% vs. 3%, $p\leq 0.001$) and overall ST (4.3% vs. 1.5% vs. 1.8%, $p\leq 0.001$). 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 bifurcationN 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 $eGFR \leq 60$ 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 $\text{DAPT} \leq 3$ 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 figures 1,2)

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 cardiology 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 paid 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.

These 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 P₂Y₁₂-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.

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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			P Value
		< 3 (n=117)	3-12 (n=200)	12 (n=1958)	
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			P Value
	3 Months DAPT (117)	3-12 Months DAPT (200)	12 Months DAPT (1958)	
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

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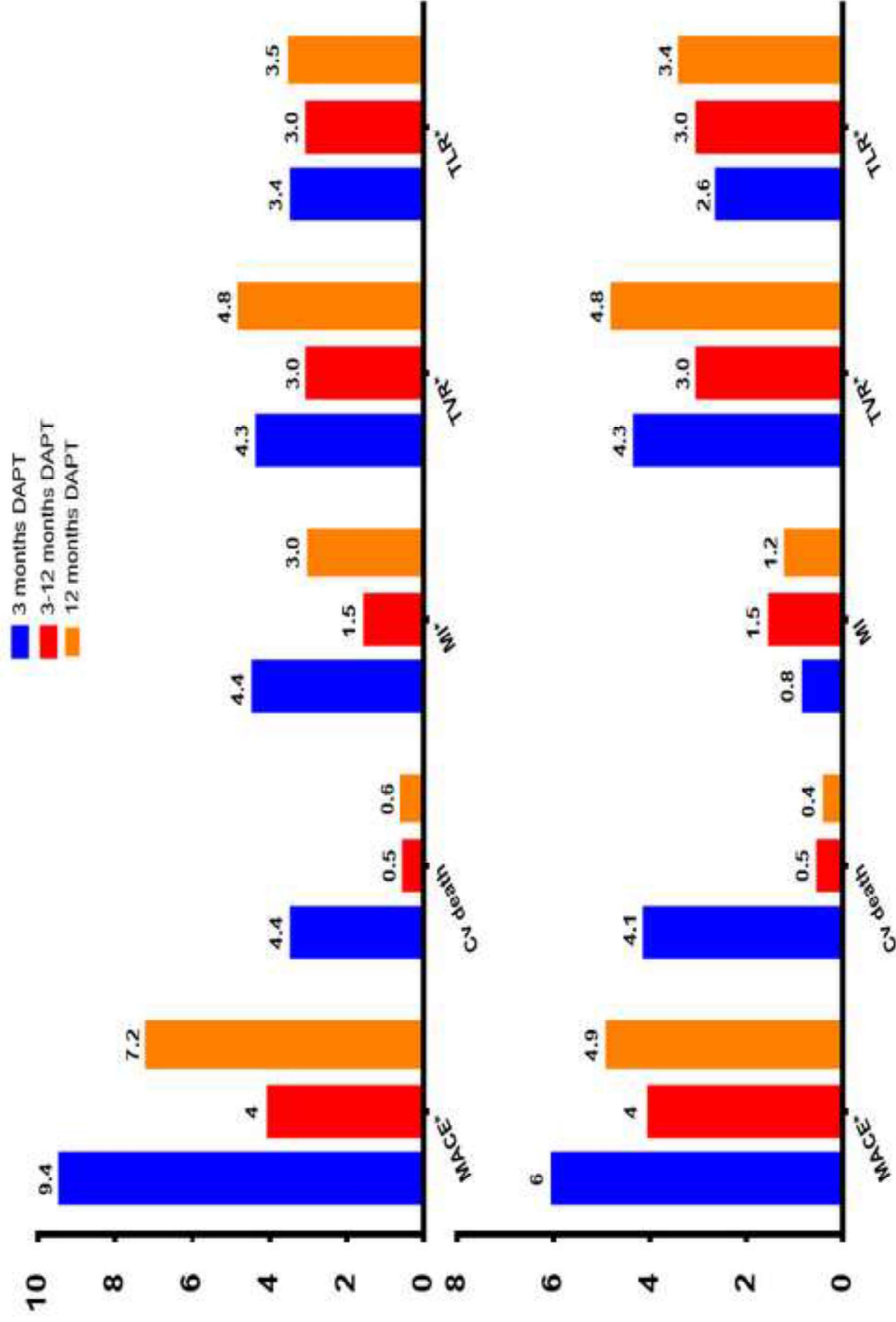


Figure number 1. Adverse outcomes according to length of DAPT (above for all events,* significant values between 3 m. and 3-12 and 12 m for MACE, death ,*significant values between 3 months and 3-12 for MI, TVR and TLR; below only event after 3 months, $p < 0.001$ (TLR and TVR))

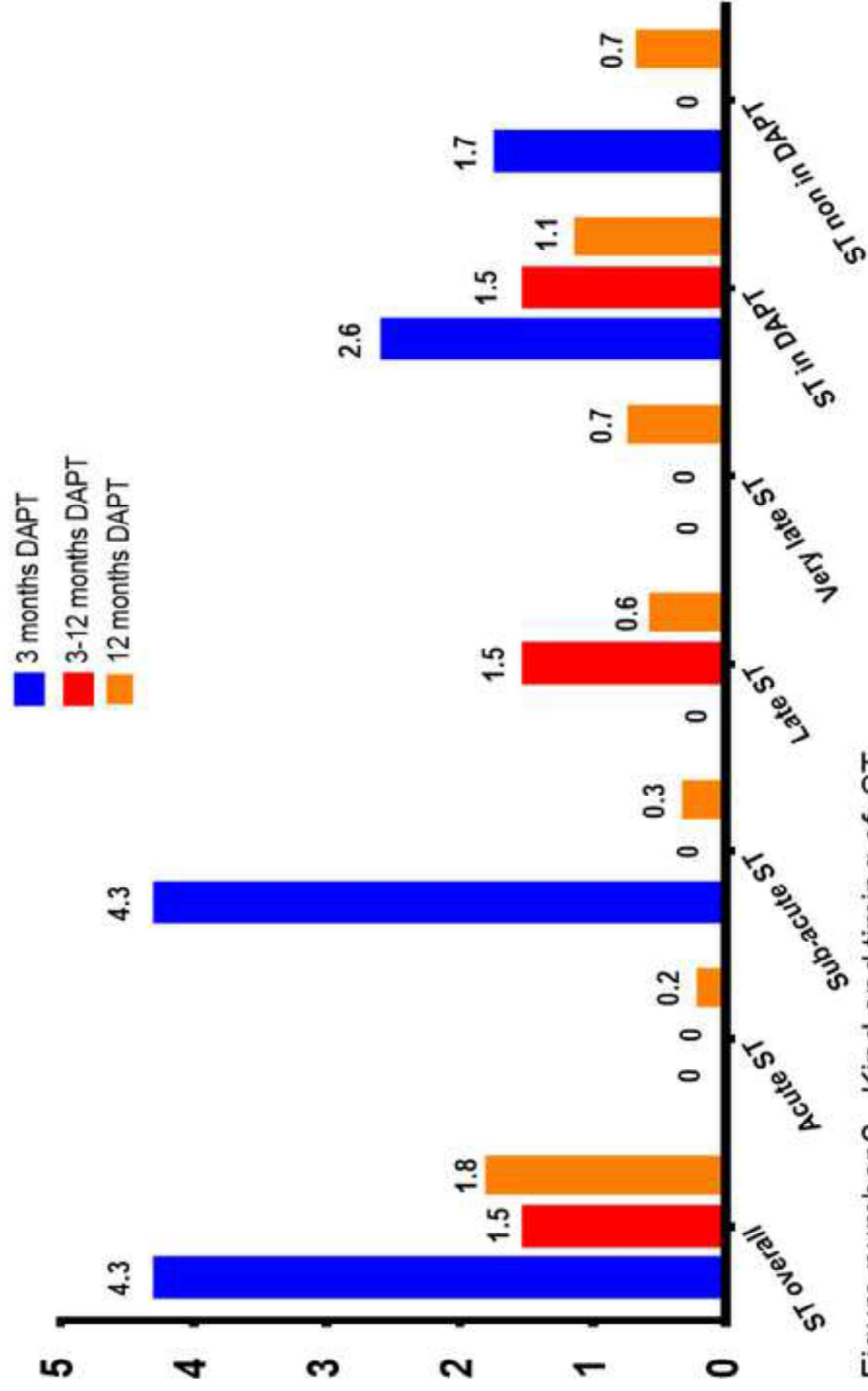


Figure number 2. Kind and timing of ST

Figure 3.tif

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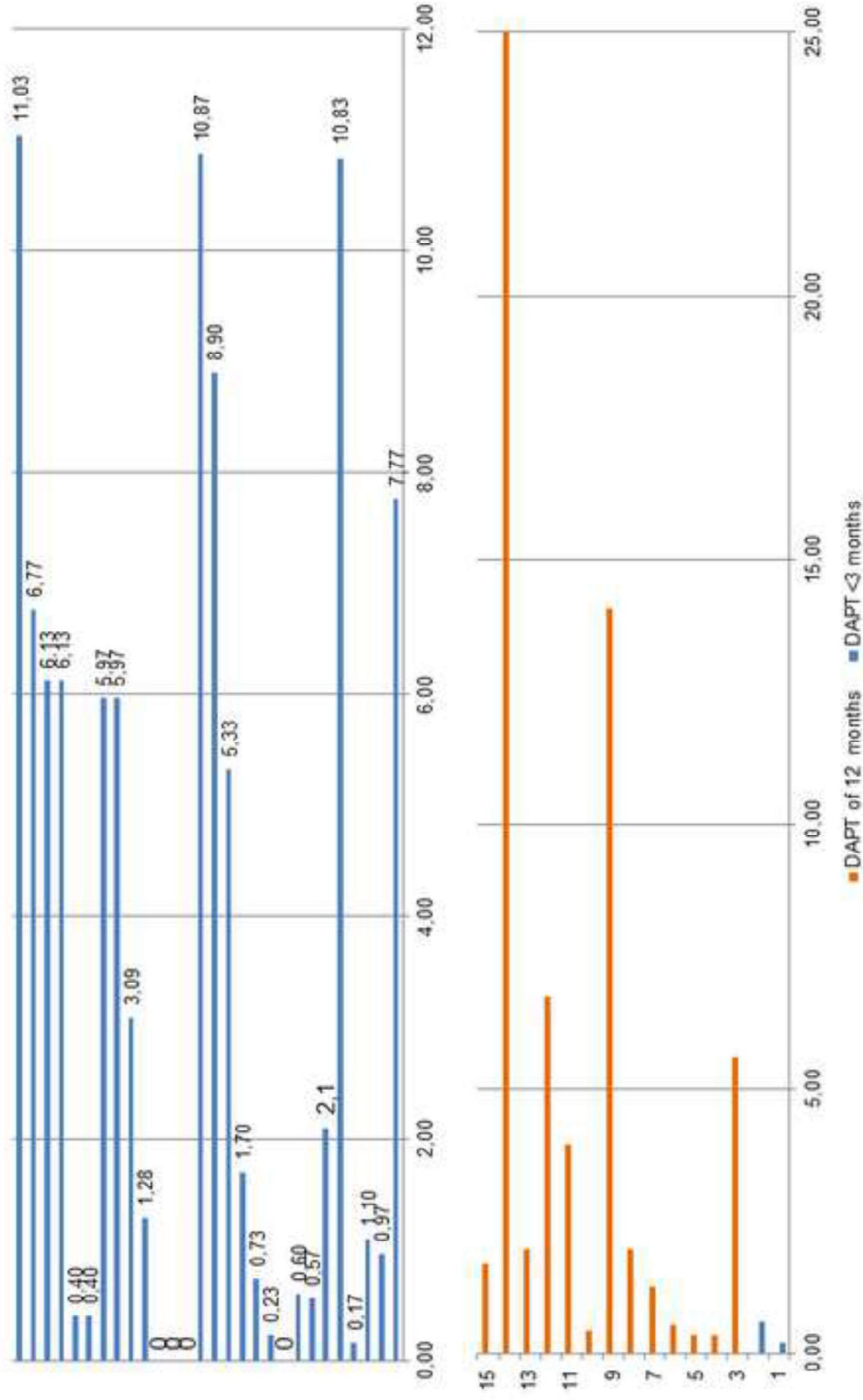


Figure number 3. Months from index PCI to ST for patients experiencing ST in DAPT (above) and time from cessation of DAPT to ST for patients with ST after stopping DAPT (below;).

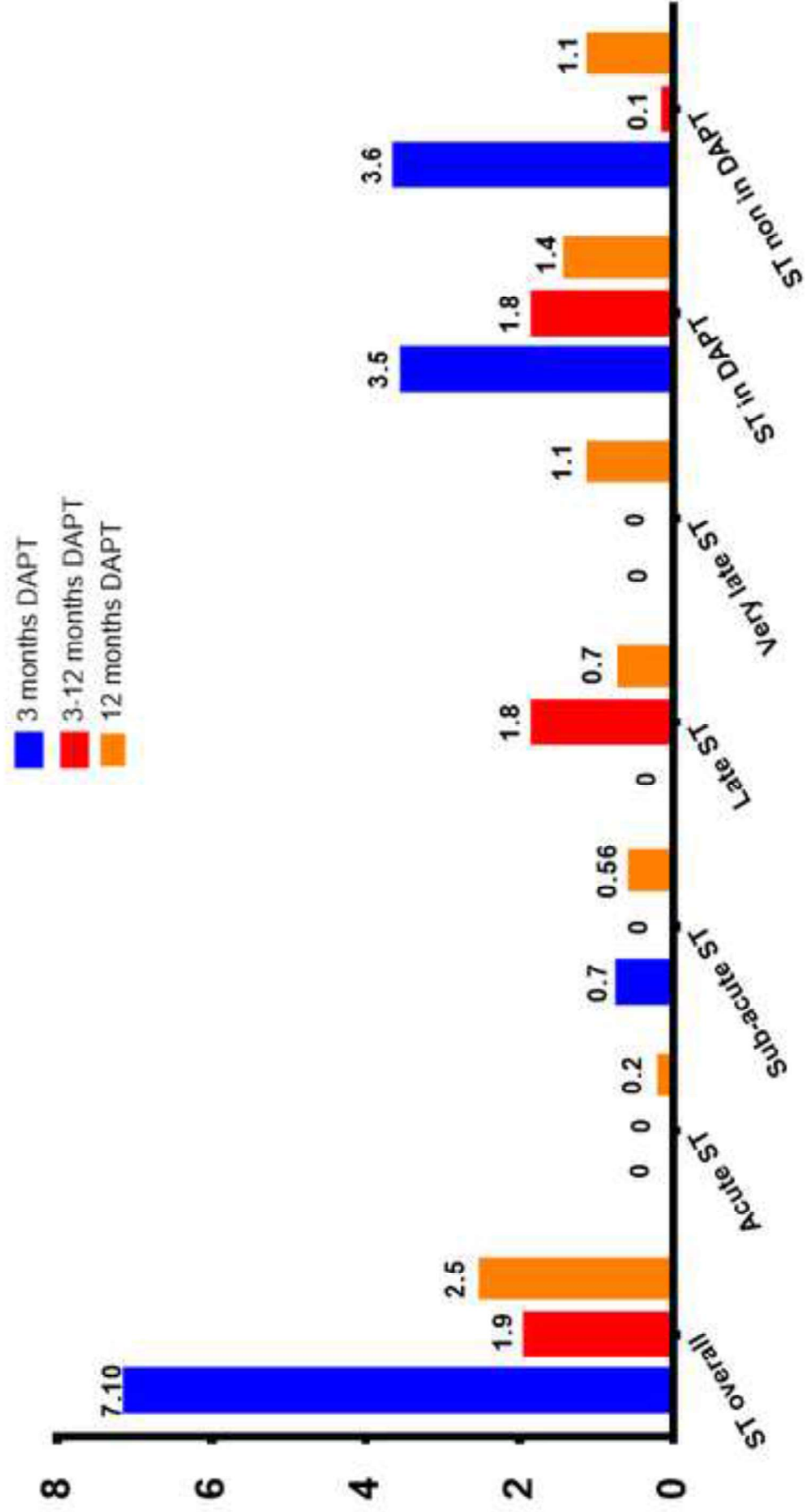


Figure number 4. Kind and timing of ST for ULM

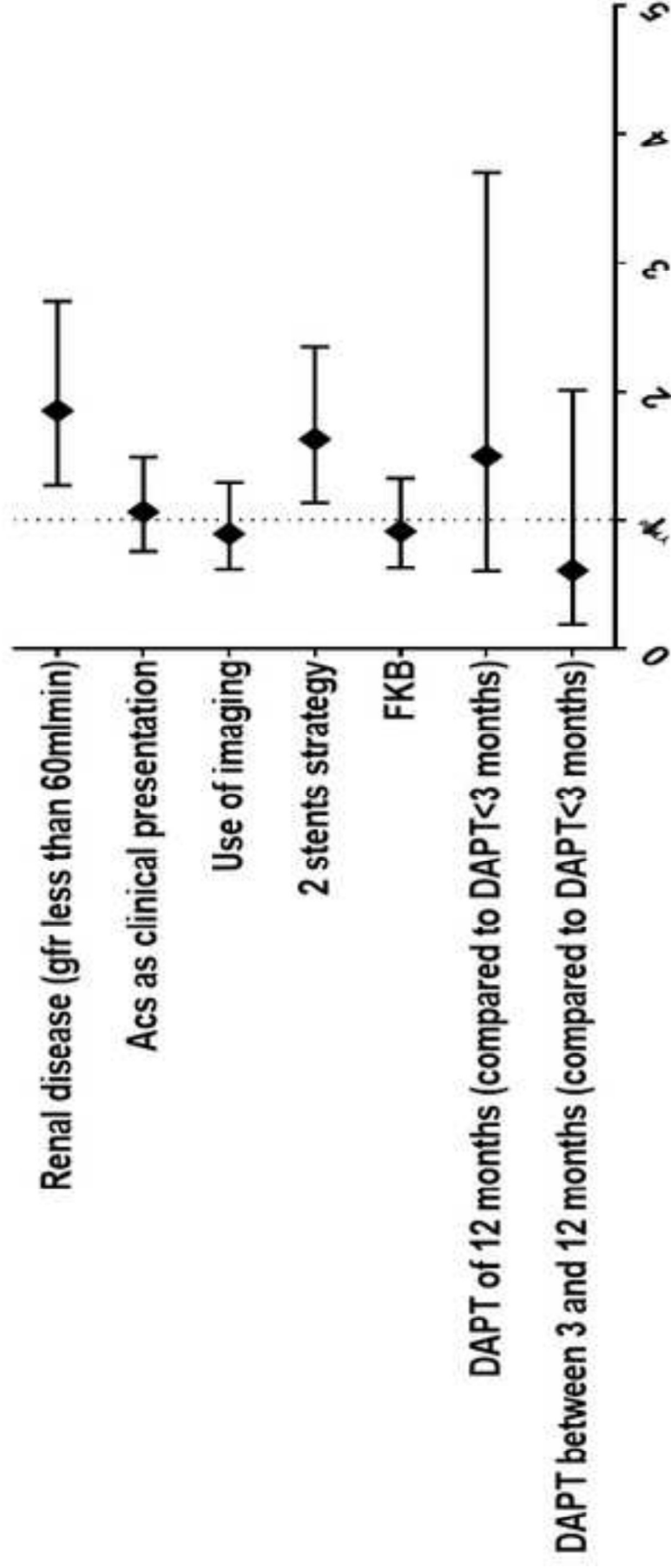


Figure number 5. Cox multivariate analysis for MACE

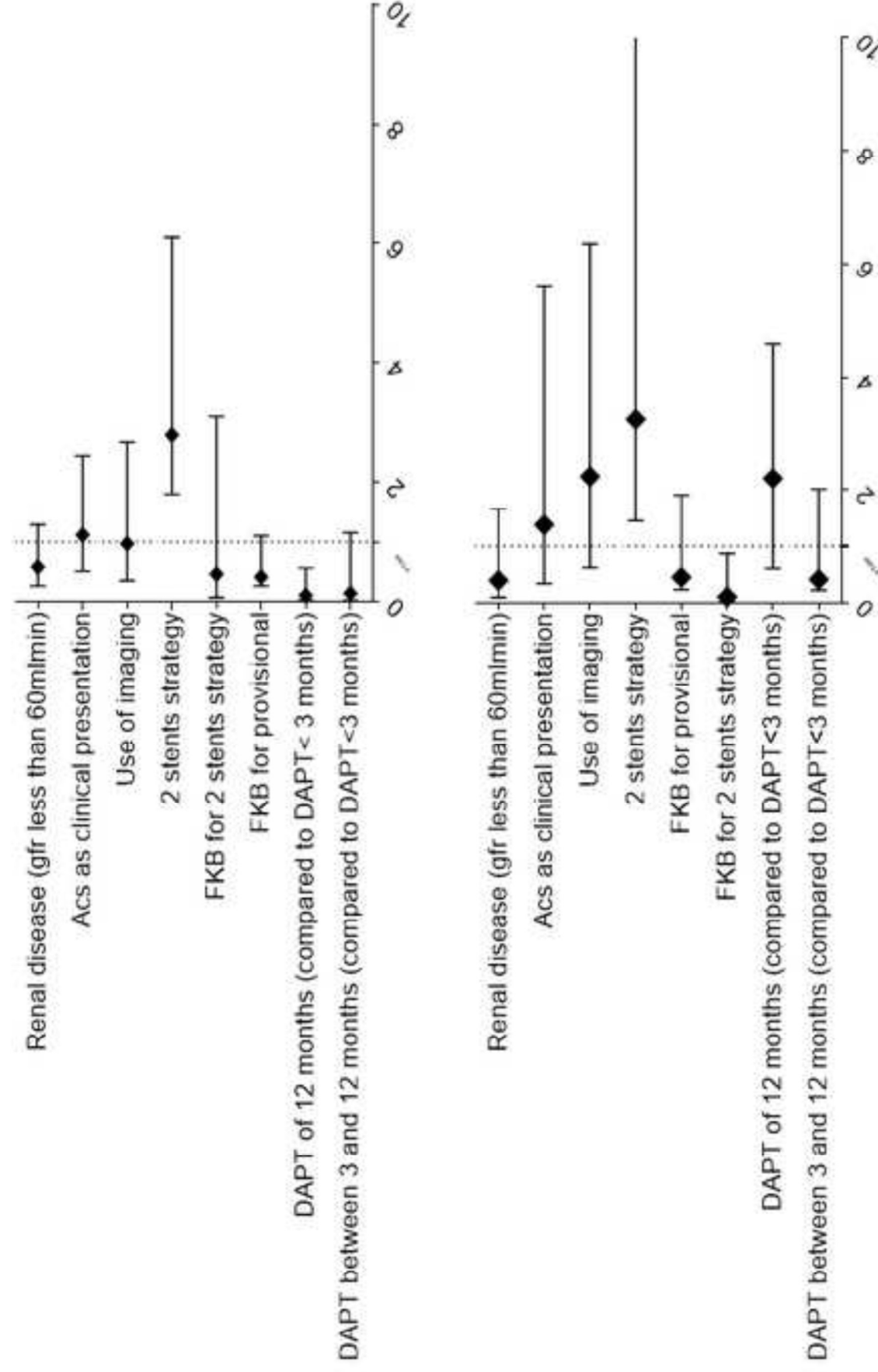


Figure number 6. Cox multivariate analysis for ST overall and for ST after DAPT cessation (from above to below)