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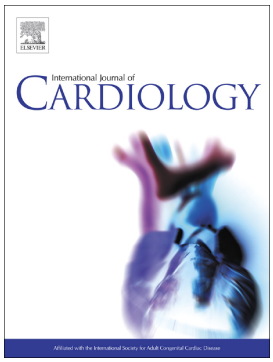
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ABSTRACT

Introduction: Percutaneous coronary intervention (PCI) for complex lesions, including unprotected left main (ULM) and bifurcations, is gaining a relevant role in treating coronary artery disease with good outcomes, also thanks to new generation stents. The daily risk of adverse cardiovascular events and their temporal distribution after these procedures is not known.

Methods: All consecutive patients presenting with a critical lesion of ULM or bifurcation treated with very thin struts stents, enrolled in the RAIN-Cardiogroup VII study, were analyzed. The daily risk of major acute cardiovascular events (MACE), target lesion revascularization (TLR) and stent thrombosis (ST) and their temporal distribution in the first year of follow-up was the primary endpoint. Differences among subgroups (ULM, patient presentation, kind of stent polymer) was the secondary endpoint.

Results: 2745 patients were included, mean age 68± 11 years, 33.3% diabetics, 54.5% had an acute coronary syndrome (ACS); 88.5% of treated lesions were bifurcations, 27.2% ULM. Average daily risk was 0.022% for MACE, 0.005% for TLR and 0.004% for ST, in the first year. Bimodal distribution of adverse events, especially TLR, with an early peak in the first 50 days and a late one after 150 days, was observed. Patients with ULM presented a significantly higher daily risk of events, and ACS patients presented higher MACE risk. No difference emerged according to the type of stent polymer.

Conclusions: The daily risk of adverse events in the first year after complex PCI in our study is acceptably low. PCI on ULM carries a higher risk of complications

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INTRODUCTION.

In the last years, PCI (percutaneous coronary Intervention) has gained a role over surgical revascularization, due to a marked speed up in technologies related to intracoronary imaging, functional assessment of stenosis, and intracoronary stent devices. (1-6)

In particular, satisfactory outcomes for PCI can be now obtained also for patients with high complexity lesions, like coronary bifurcations and unprotected left main (ULM) coronary artery, However, risks for restenosis and thrombosis still represent two of the major limitations for this procedure, being strictly related to clinical (diabetes mellitus and comorbidities, 7-9) and procedural issues (calcification, bifurcation with 2-stents, 6, 10, 11).

An open question is still the risk management related to subsequent events. Regarding the time duration of DAPT (Dual Antiplatelet Therapy), a tailored approach is now largely advocated, due to reduced risk of thrombotic events (both in stent thrombosis and de novo) in patients treated with longer DAPT, although they are burdened by a higher risk of bleeding (12,13). In parallel risk of restenosis appears to be in relation with the features of the lesions, to angiographic procedures, and to adherence to therapy, while angiographic follow up has not demonstrated clinical benefit, apart from non randomized evidence regarding ULM (1, 11, 14).

Recently, analysis of daily risk of events have been introduced also in cardiology (15), with the aim to understand better the timing of recurrent ischemic and bleeding events in patients with myocardial infarction (16), thus offering useful instruments to select properly the time duration of the antiplatelet therapy.

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Aiming at getting more insight into the patterns of restenosis and thrombosis, and to contribute to tailor both type and time duration of DAPT and clinical or instrumental follow up, we analyzed daily risk of thrombosis and restenosis in patients treated with ultrathin stents on ULM or on bifurcation (RAIN-CARDIOGROUP VII study (veRy thin stents for patients with left mAIn or bifurcatioN in real life).

METHODS

The RAIN study is a multicenter study (see Appendix web only for sites of enrollment) that has been recruiting patients prospectively from June 2015 to January 2017.

Inclusion criteria

All consecutive patients presenting with ULM or bifurcation critical lesion (see Appendix web only for definition) in RAIN centers were included, if treated with one of the following stents:

- Platinum-chromium coated with a permanent polymer loading everolimus with strut thickness of 81 µm and diameters from 2.25 to 3.5 mm (Promus Element, Boston Scientific);
- Cobalt-chromium coated with a permanent polymer loading everolimus with a strut thickness of 80 µm (XIence Alpine, Abbot);
- Cobalt-chromium coated with a biodegradable polymer loading sirolimus with strut thickness of 80 µm (Ultimaster, Terumo Corporation);
- Platinum-chromium coated with a biodegradable polymer loading everolimus with strut thickness of 74 µm (diameter in the range 2.25-2.75 mm), 79 µm (diameter in the range 3.00-3.50 mm), and 81 µm for diameter equal to 4.0 mm (Synergy, Boston Scientific);

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- Platinum-chromium coated with a biodegradable polymer loading zotarolimus with a strut thickness of 74 µm (diameter ≤2·5 mm), 79 µm (diameter in the range 3.0-3.50 mm), and 81 µm (diameter equal to 4.0 mm) (Resolute Onyx, Medtronic).

Baseline and procedural data.

Data on cardiovascular risk factors, clinical presentation, angiographic features, use of IVUS (IntraVascular UltraSound), OCT (Optical Coherence Tomography), and FFR (Fractional Flow Reserve) were collected, along with features of implanted stents design. 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 were applied before stent implantation to assess the severity of the stenosis and side branch involvement, and after stent implantation to evaluate dissection and to drive postdilatation. The decision of applying post-dilatation, FKB (Final Kissing Balloon), use of imaging, and choice of stenting technique (provisional *vs.* 2-stents), was left to the physician.

Follow up was performed through dedicated clinical assessment, telephonic follow up or formal query to primary care physicians.

Data about adverse outcomes, i.e., target lesion revascularization (TLR), stent thrombosis (ST), all cause death and myocardial infarction (MI) were collected along with the date of the event. MACE was calculated as a composite end point of all cause death, MI, TLR and ST.

At follow-up MI were defined according to the European Society of Cardiology “Third universal definition of myocardial infarction”, while ST according to ARC classification (17, 18)

End points.

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Primary endpoint was the calculation, along the first year after revascularization, of the average and punctual daily risk of MACE, TLR and ST. Secondary endpoints were the calculation of the same data for defined subpopulations, i.e. ULM, bifurcations, ACS, stable CAD (SCAD), biodegradable and permanent stent polymer, and the analysis of differences between subpopulations.

Statistical analysis.

Categorical variables were reported as count and percentage, continuous variables as mean and standard deviation. Events occurring on a specific day after revascularization were aggregated and divided by the number of patients still “actively” in the protocol on the same day (i.e. the total study population minus the number of deaths, loss at follow-up and patients who already experienced the event up to that day) to calculate the daily risk of MACE, TLR, ST. After that, the average risk was calculated at one, three and six month and at one year. The paired t-test was used to assess differences between subpopulations. A two-sided P value equal to 0.05 was considered statistically significant. The statistical analysis was performed with SPSS version 21.0 statistic software package (IBM, Armonk, NY, USA).

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RESULTS

Data from 2745 patients were analyzed: baseline features and procedural data are summarized in **table 1**. The average age was 68 years, 76.6% of patients were males, 33.3% had diabetes, and 32.6% already had a PCI and 5% a CABG. Revascularization procedure was performed for STEMI in 16.8% of the patients, NSTEMI in 23.6%, UA in 14.1%, stable CAD in 38.9%, and in 6.5% it was a planned angiography (a planned procedure not due to symptoms or evidence of ischemia - e.g. an angiographic or pressure wire control of a subcritical stenosis or a control after one year of a complex procedure). Concerning angiographic and procedural data, 88.5% of lesions were bifurcations, 38.6% were type C according to ACC/AHA classification, and in 27.2% of cases left main (LM) was the first lesion vessel. 66.6% of the patients was initiated on clopidogrel, 25.8% on ticagrelor, and 7.5% on prasugrel.

In general, the rate of reported adverse events during the follow-up was low, with an average daily risk of MACE of 0.022%, risk of TLR of 0.005%, and risk of ST of 0.004%, during the first year – full data presented in **appendix table 1**. The time distribution of risks is presented in figures **1, 2 and 3**, where it clearly emerges the occurrence of two clusters of TLR and ST events: the early one in the first 50 days, and the second one after five months. Moreover, it can be observed that from 150 days risk of TLR markedly increases, while risk of ST is characterized by a moderate increasing trend along the first year of observation.

In the subpopulation analysis (shown in **appendix tables 2)**, patients who underwent PCI because of an ACS had a significantly higher daily risk of MACE than SCAD patients at one, six months and one year, but the rate of TLR and ST did not differ among the two groups.

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Patients with PCI on LM had a significantly higher daily risk of MACE at three, six months and one year, a higher daily risk of TLR at six months and one year, and a higher daily risk of ST at six months.

No significant difference was observed with the use of permanent *vs.* biodegradable stents. The difference in temporal distribution of events among subpopulations is presented in **appendix figures 1-3**.

Analysis on the use of imaging with IVUS/OCT showed no significant difference, but only a trend towards a reduction in ST (daily ST risk in non-imaging 0.005%, imaging 0.002%, p 0.055). Analysis between use of IVUS vs OCT in LM disease was not performed due to the small sample (257 and 10 patients respectively).

The highest daily risk values of MACE, TLR and ST were recorded during the first month of follow-up in patients who underwent PCI for LM lesions, with values of 0.073%, 0.014% and 0.037%, respectively.

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DISCUSSION.

To the best of our knowledge, this is one of the first papers evaluating temporal distribution of restenosis and thrombosis in patients treated with ultrathin stents on LM and on coronary bifurcations. The main findings of the study are:

1) A substantial very low rates of adverse events was observed in patients treated with ultrathin stents in challenging lesions;
2) Two more relevant cluster of events were noted at 50 and at 150 days, irrespective of clinical presentation and of site of coronary lesions;
3) No difference was noted according to kind of implanted polymer stent design.

The observed low rates of events reflects findings already reported in literature, suggesting a satisfactory performance for ultrathin stents, even in high risk anatomical settings. It should be noted here that the observed rates of restenosis and ST are markedly lower than those reported with first generation DESs like Taxus or Cypher. For example, in the 5-year analysis of the Syntax trial focused on LM treated with Taxus (16) the rate of TLR was 26.7%, while in the NOBLE trial, where second generation DES were implanted, this incidence decreased (at 5 years) to 12% (19). A similar trend has been reported for non LM bifurcations: in the paper by Kaplan et al (20), the rate of TLR with Culotte strategy performed with first generation DES was 11.1% at 9 months, while use of ultrathin stents with the same techniques reduced this incidence to 1.4% at the same follow up period (21).

Two more relevant pattern of restenosis events, especially concerning TLR and ST, were reported at 50 days and at 150 days, independent of the site of coronary lesion and of presentation with ACS or not. These different time points may be ascribable to different etiological features. Probably the events in the first 50 days were related to sub-optimal

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index procedures, for example underexpansion of implanted stents or residual dissection. Stent underexpansion results from poor expansion during implantation rather than from chronic stent recoil (22) and may be undetectable at angiography in many cases. Only suspicion may be raised in an area of fluoroscopically under-expanded stent struts (compared with the rest of the struts), in the context of calcified lesions or inability to fully expand the balloon inside the stent. Clinically, these procedural features translated into early re-hospitalization after PCI, normally scheduled as 30 days readmission (23). In a study of Wasfy et al (24), 9.8% of the patients were admitted to hospital 30 days after PCI. However, for only less than 12% of them a revascularization procedure was needed, with only 2.6% requiring revascularization of the vessel treated during index procedure. The second pattern of restenosis was noted at 150 days, and it might be explained in terms of impact of antiproliferative drugs. Drug release kinetics directly impact drug retention in the wall and can influence vascular healing, and the therapeutic effect as well. A balance between drug release rate and arterial drug uptake, i.e., neither too rapid release exceeding the tissue absorption rate nor too slowly limiting the amount of drug transferred to the artery (25), is an essential feature assuring DES efficacy. The absolute duration of drug release also plays a fundamental role in the dynamics of the restenosis process, since molecular biology studies demonstrate a pro-restenosis gene activation for periods up to 3 weeks, implying the need for drug-induced inhibition for at least a minimum time period (26). For example, OCT study of Guagliumi et al (27) has demonstrated a better suppression of the neointimal response but higher proportion of uncovered and malapposed struts at 6-months, for sustained release *vs.* fast release from different formulations of zotarolimus eluting stents. Most of the drugs charged in stent models evaluated in the present study are fully released at 100 days after implantation (28), hence it is more than reasonable to conjecture that the observed increase in TLR events at 150 days is a consequence of the response of the vessel to a general inflammation condition

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due to a lack of antiproliferative drugs. Clinically these results may be helpful to physicians to focus clinical or instrumental follow up (example for complex lesions) after no more than 6 months after PCI. (29) The fact that the bimodal distribution of events is primarily observed in the case of TLR and ST can be attributed to the fact that TLR and ST are primarily dependent on procedure result, while MACE depends also a lot more on patient-related complications (e.g. cardiovascular death due to fatal arrhythmias). So, the temporal distribution of TLR and ST is strictly linked to PCI outcome over time, while MACE distribution is "smoothed" by patient related features.

The low but continuous risk of ST represents a well-known phenomenon. Similar to restenosis, very early and early ST have been related to procedural features, while late ST may be ascribable to the permanence of uncovered struts, or to poor adherence of antiplatelet drugs (30, 31). In this optic, the results of this study may stimulate physicians to evaluate more appropriate time duration of DAPT (Dual Antiplatelet Therapy) in these patients, stressing the importance of procedures and their technical and anatomic challenges.

Concerning the use of coronary imaging with IVUS/OCT we could not draw any conclusion both because the sample size was not large enough, both because of the protocol of the study: the use of IVUS/OCT was up to the operator, creating a possible bias so that these techniques were used more often in more complex procedures, thus equalizing the outcomes.

Our paper shares some limitations. First, it does not derive from randomized study, with all the well known limitations related to observational design. Second, it may be limited by absence of follow up in some patients, although in all centers attrition bias was low due to loss of no more than 15% of patients at follow up.

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CONCLUSIONS

In our registry of 2745 patients undergoing complex PCI on LM or bifurcation, daily risks of adverse events resulted to be acceptably low; the average daily risk of MACE, TLR and ST in the first year resulted to be 0.022%, 0.005% and 0.004%, respectively. The highest risks (0.073% for MACE, 0.014% for TLR, and 0.037% for ST) were observed during the first month of follow-up in patients who underwent PCI for LM lesions.

Patients undergoing revascularization on LM coronary artery as first vessel presented a higher daily risk of MACE, TLR and ST than people with bifurcations not involving LM. Patients with ACS were at higher daily risk of MACE but not TLR and ST, while no difference was reported in the usage of permanent and biodegradable polymer stent designs.

Temporal distribution of events appeared to be bimodal, especially concerning TLR, with the two clusters of events occurring in the first 50 days the first, and after 150 days the second one. As for ST, a small but continuous risk was noted.

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FIGURE LEGEND:

Figure 1 – Daily MACE risk over time

Figure 2 – Daily TLR risk over time

Figure 3 – Daily ST risk over time

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Table 1 Baseline Characteristics and procedural data

Age - years	68.7±11.22
Male no. (%)	2086 (76.6)
Hypertension no. (%)	1997 (74.9)
Hyperlipidemia no. (%)	1601 (60.1)
Diabetes Mellitus no. (%)	860 (33.3)
Previous Smoker no. (%)	773 (29.4)
Current Smoker no. (%)	531 (20.2)
Chronic Kidney Disease no. (%)	514 (72.2)
Previous PCI no. (%)	886 (32.6)
Previous CABG no. (%)	135 (5.0)
Previous MI no. (%)	801 (30.2)
Indications for PCI	
STEMI no. (%)	456 (16.8)
NSTEMI no. (%)	642 (23.6)
UA no. (%)	384 (14.1)
Stable CAD no. (%)	1058 (38.9)
Planned angiography no. (%)	176 (6.5)
Kind of DAT	
Clopidogrel no. (%)	1828 (66.6)
Ticagrelor no. (%)	708 (25.8)
Prasugrel no. (%)	206 (7.5)
Other (e.g. Ticlopidine) no. (%)	3 (0.1)
Severe calcification no. (%)	304 (13.0)
Diffuse disease no. (%)	990 (39.4)
Bifurcation no. (%)	2350 (88.5)
Predilatation no. (%)	2260 (88.8)
Postdilation no. (%)	1573 (74.0)
Final kissing balloon no. (%)	1026 (40.9)
Rotablator no. (%)	55 (2.4)

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Type C Lesion no. (%)	943 (38.6)
First lesion vessel	
LM no. (%)	730 (27.2)
LAD no. (%)	1271 (47.4)
Cx/Mo no. (%)	463 (17.3)
RCA no. (%)	175 (6.5)
RI no. (%)	40 (1.5)
Kind of strategy	
Provisional no. (%)	2024 (80.7)
2 Stents no. (%)	418 (16.7)
Use of imaging	
No no. (%)	1787 (66.2)
IVUS no. (%)	881 (32.7)
OCT no. (%)	30 (1.1)
Kind of stent	
Resolute Onyx no. (%)	768 (28.6)
Xience Alpine no. (%)	673 (25.1)
Synergy no. (%)	565 (21.0)
Ultimaster no. (%)	249 (9.3)
Biomatrix Alfa no. (%)	5 (0.2)
Promus no. (%)	402 (15.0)

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Highlights

- PCI for complex lesions with new stents carries a low daily risk of adverse events
- Daily risks are 0.022% for MACE, 0.005% for TLR and 0.004% for ST in the first year
- Daily risks of TLR and ST show a bimodal distribution
- PCI on ULM carries a higher risk of complications
- Stent polymer is not associated with a difference in the daily risk of events

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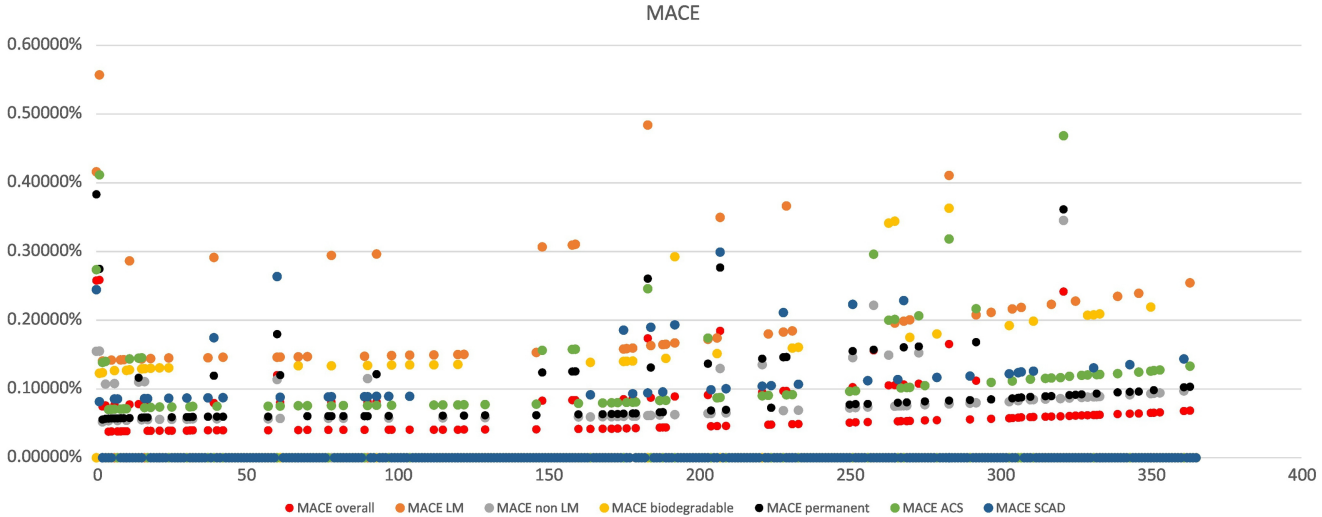

MACE
0.60000%
0.50000%
0.40000%
0.30000%
0.20000%
0.10000%
0.00000%
0
50
100
150
200
250
300
350
400
MACE overall
MACE LM
MACE non LM
MACE biodegradable
MACE permanent
MACE ACS
MACE SCAD

Figure 1

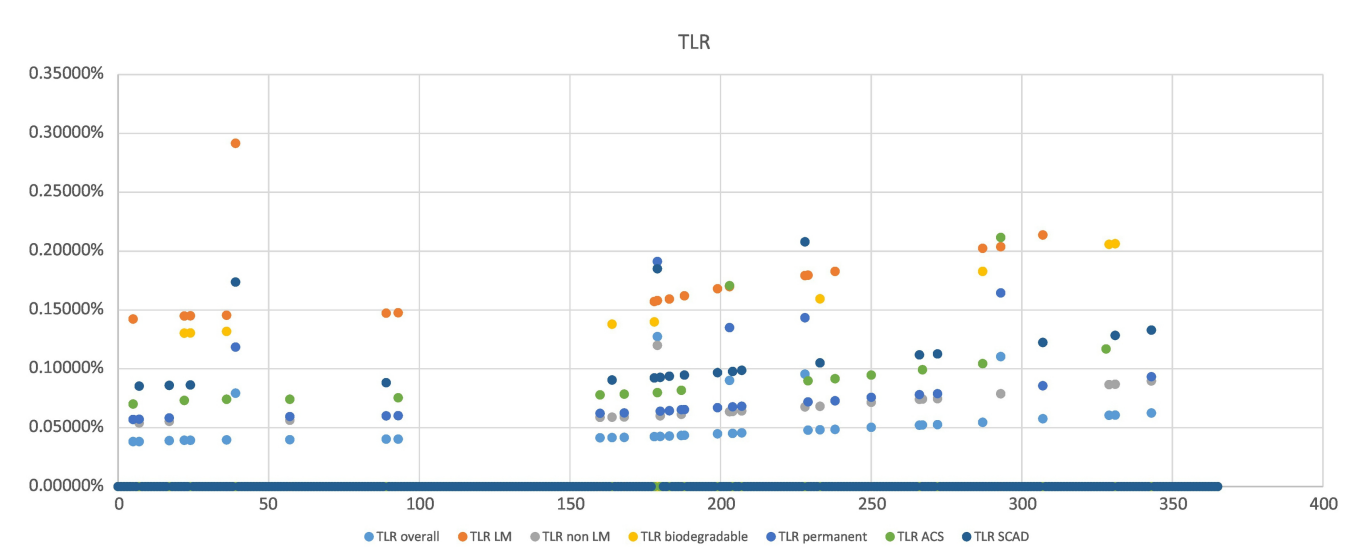

TLR
0.35000%
0.30000%
0.25000%
0.20000%
0.15000%
0.10000%
0.05000%
0.00000%
0
50
100
150
200
250
300
350
400
TLR overall
TLR LM
TLR non LM
TLR biodegradable
TLR permanent
TLR ACS
TLR SCAD

Figure 2

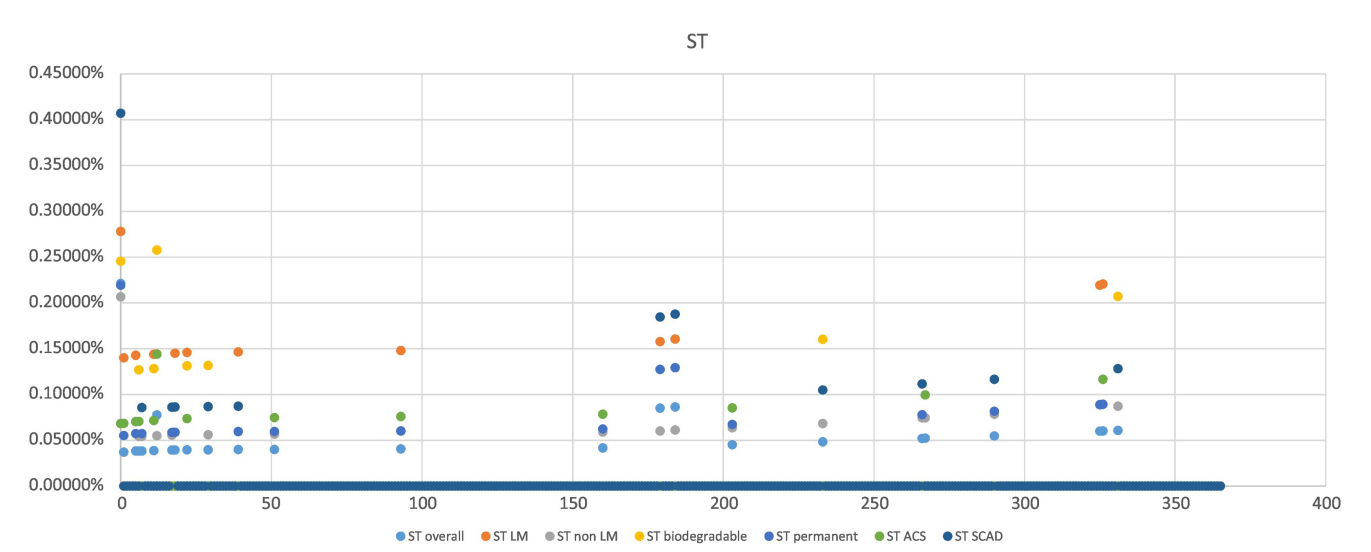

ST
0.45000%
0.40000%
0.35000%
0.30000%
0.25000%
0.20000%
0.15000%
0.10000%
0.05000%
0.00000%
0
50
100
150
200
250
300
350
400
ST overall
ST LM
ST non LM
ST biodegradable
ST permanent
ST ACS
ST SCAD

Figure 3