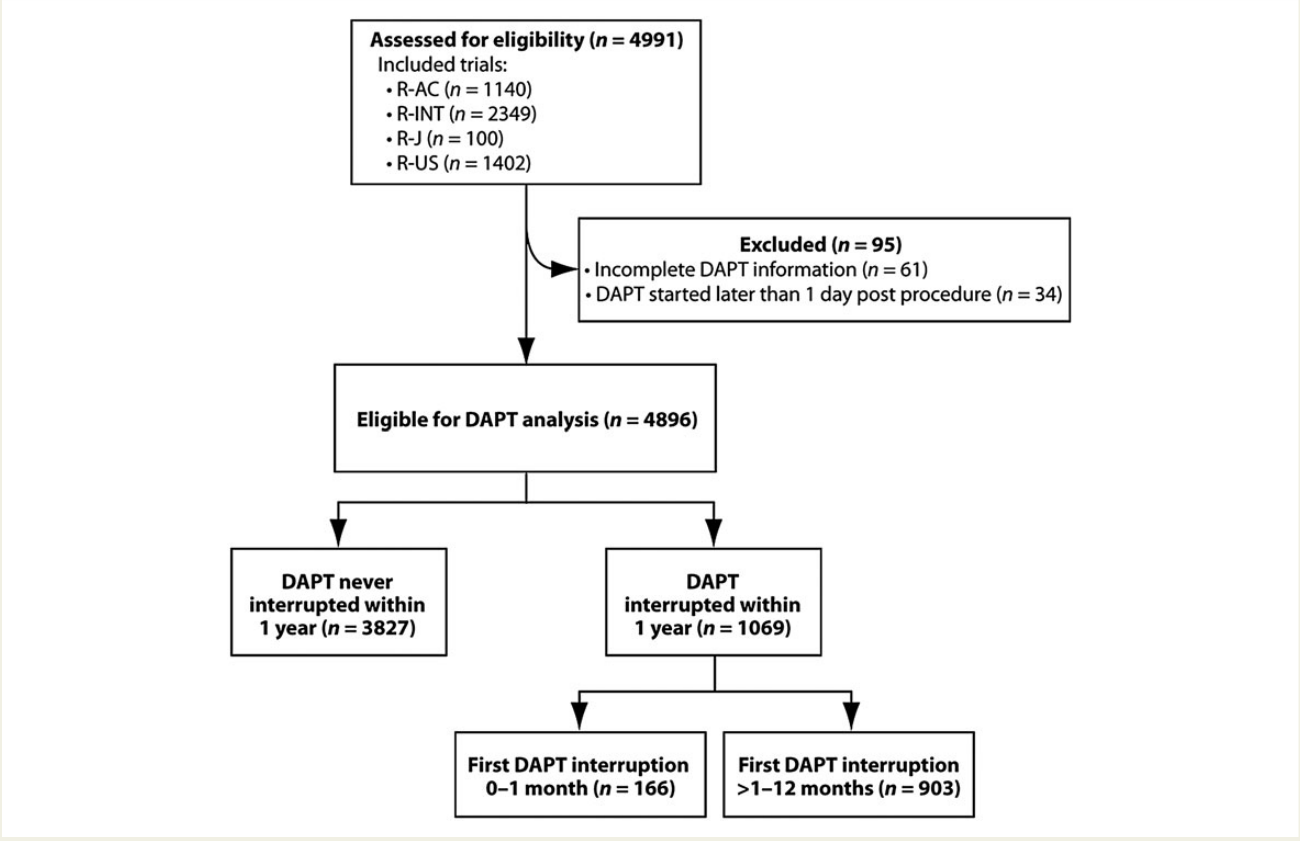

Figure 1 Patient disposition according to dual antiplatelet therapy interruption status. DAPT, dual antiplatelet therapy; R-AC, RESOLUTE-All comers; R-INT, RESOLUTE-International; R-J, RESOLUTE-Japan; R-US, RESOLUTE-US.

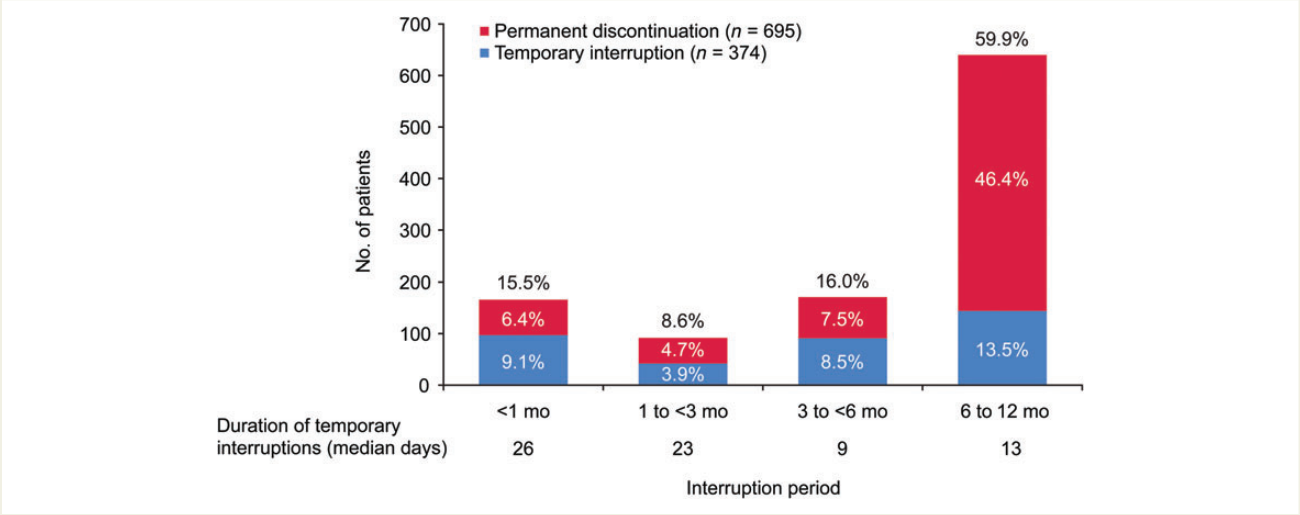

Figure 2 Distribution of patients according to time of first dual antiplatelet interruption.

interruption in the first month were older and had lower left ventricular ejection fractions. In addition, these patients had more B2/C class lesions and smaller reference vessel diameter, but shorter lesion lengths.

Timing of stent thrombosis

In total, 39 cases of ST occurred during the first year following R-ZES implantation. Overall, 32 (82.1%) cases of ST occurred when patients were on DAPT and 7 (17.9%) ST events occurred when patients were

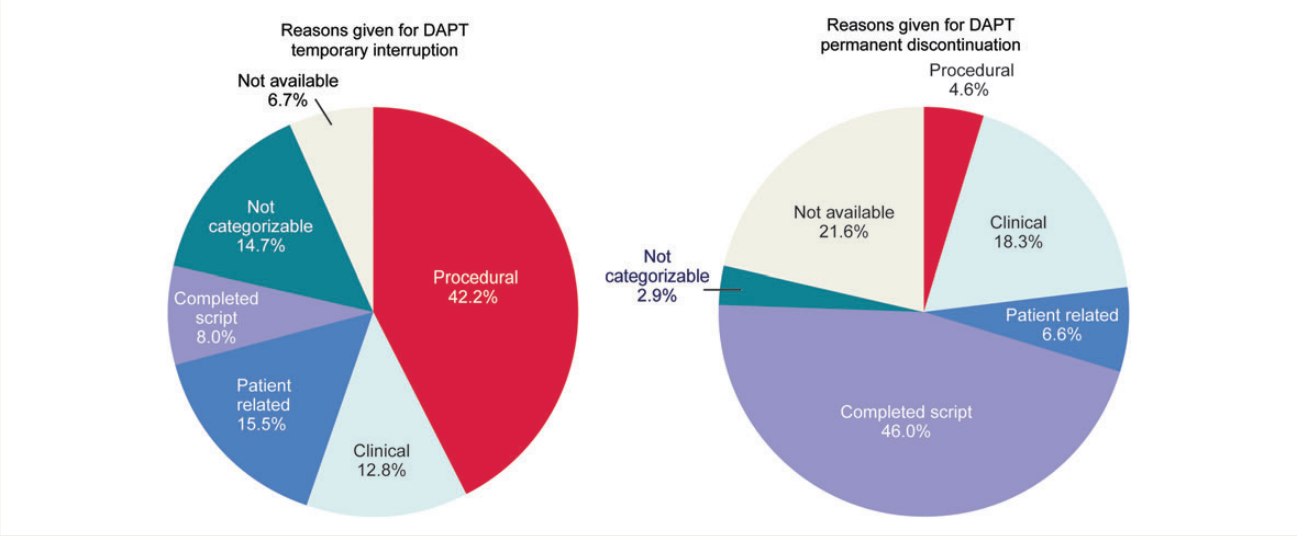

Figure 3 Reasons given for dual antiplatelet therapy interruptions.

Table 1 Baseline demographic and lesion characteristics

Baseline characteristics	Never interrupted, $n = 3827$ patients	Interrupted first month, $n = 166$ patients	Interrupted >1–12 months, $n = 903$ patients	*P*-value
Age (years)	63.4 ± 10.8 (3827)	66.6 ± 12.0 (166)	65.5 ± 11.3 (903)	<0.001
History of smoking	59.1% (2261/3827)	53.0% (88/166)	58.4% (527/903)	0.289
Prior percutaneous coronary revascularization	30.7% (1176/3827)	27.1% (45/166)	33.1% (299/903)	0.204
Diabetes mellitus	29.6% (1134/3827)	32.5% (54/166)	31.8% (287/903)	0.354
Insulin dependent	8.5% (327/3827)	10.8% (18/166)	10.2% (92/903)	0.201
Prior MI	25.6% (974/3800)	22.7% (37/163)	27.1% (242/893)	0.435
Left ventricular ejection fraction <30%	1.8% (48/2630)	5.7% (6/105)	2.1% (14/671)	0.020
Lesion class B2/C	65.9% (3271/4960)	72.7% (152/209)	68.5% (791/1154)	0.040
ACS	42.4% (1621/3827)	42.2% (70/166)	40.0% (361/903)	0.427
STEMI	8.5% (327/3827)	8.4% (14/166)	6.9% (62/903)	0.255
NSTEMI	7.8% (297/3827)	7.8% (13/166)	8.3% (75/903)	0.861
Unstable angina	26.1% (997/3827)	25.9% (43/166)	24.8% (224/846)	0.744
Pre-procedure RVD (mm)	2.79 ± 0.51 (4767)	2.70 ± 0.56 (198)	2.76 ± 0.53 (1092)	0.010
Lesion length (mm)	15.93 ± 9.66 (4744)	14.77 ± 8.33 (198)	15.09 ± 8.95 (1091)	0.010
Number of stents per patient	1.56 ± 0.94 (3827)	1.53 ± 1.10 (166)	1.52 ± 0.90 (903)	0.615
Total stent length per patient (mm)	29.38 ± 19.56 (3826)	27.84 ± 22.49 (166)	27.83 ± 18.84 (903)	0.071
Stent diameter (mm)	2.95 ± 0.45 (6367)	2.93 ± 0.46 (271)	2.94 ± 0.45 (1467)	0.476

Data are presented as means ± SD or % (*n*/*N*).

off DAPT at the time of ST (*Figure 4*). Among the 29 ST events occurring early (within 30 days), 25 of these events occurred on DAPT and 4 occurred off DAPT. Among the 10 cases of late ST, 7 occurred on DAPT and 3 occurred off DAPT.

Dual antiplatelet therapy interruption

Among the 3827 patients with no DAPT interruption, there were 32 ST events (0.84%). Among patients with DAPT interruption, 166 patients interrupted DAPT in the first month, with 6 ST events occurring in this group (3.61%). Among 903 patients with a DAPT interruption between 1 and 12 months, one ST event occurred (0.11%). Kaplan–Meier estimates of the cumulative incidence of ST events showed a significant difference between patients interrupted in the first month and patients with a DAPT interruption between 1 and 12 months (log-rank $P < 0.001$; *Figure 5*). In addition to the ST assessment at 12 months, when the 1069 patients with any DAPT

interruption were followed for one full year after the time of DAPT interruption, no additional ST events were identified beyond the seven events described here.

Dual antiplatelet therapy interruption longer than14 days

Among the 874 patients with a DAPT interruption longer than 14 days, 122 interrupted in the first month. All of the six ST events that occurred in the first month were in these patients who had a prolonged DAPT interruption. Among the 752 patients with a longer than 14 day DAPT interruption between 1 and 12 months, there was no ST event.

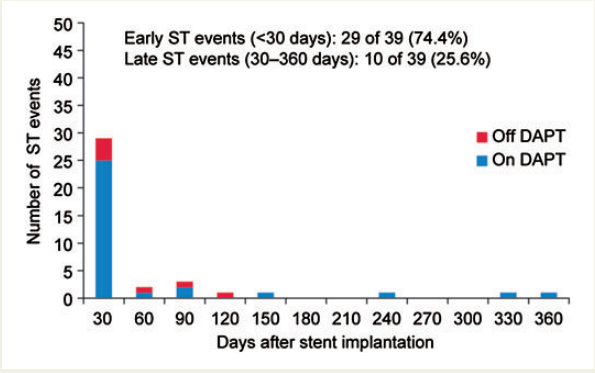

Figure 4 Timing of stent thrombosis regardless of time of dual antiplatelet therapy interruption. DAPT, dual antiplatelet therapy; ST, stent thrombosis.

Thienopyridine interruption

In patients with a DAPT interruption, the thienopyridine alone was interrupted in 662 (61.9%) patients; there were three total ST events in this group. Among patients interrupting thienopyridine only, 67 patients interrupted the thienopyridine within 1 month [with two ST events (3.0%)], and 595 patients interrupted the thienopyridine between 1 and 12 months [with one ST event (0.2%)].

Acetylsalicylate interruption

In patients with a DAPT interruption, the ASA alone was interrupted in 196 (18.3%) patients; there were four total ST events in this group. Among patients interrupting ASA only, 78 patients interrupted ASA within 1 month [with four ST events (5.1%)], and 118 patients interrupted ASA between 1 and 12 months (no ST events).

Simultaneous interruption

In patients with a DAPT interruption, simultaneous interruption of both the thienopyridine and ASA therapies occurred in 211 (19.7%) patients. Among these patients, 21 interrupted DAPT within the first month and 190 patients interrupted between 1 and 12 months. Notably, there were no ST events in either group.

Permanent discontinuation of dual antiplatelet therapy

Among patients with a DAPT interruption, there were 695 patients (65.0%) who stopped DAPT permanently; of these, 69 occurred within the first month. All four ST events among patients with permanent DAPT discontinuation occurred in patients who permanently discontinued DAPT within the first month.

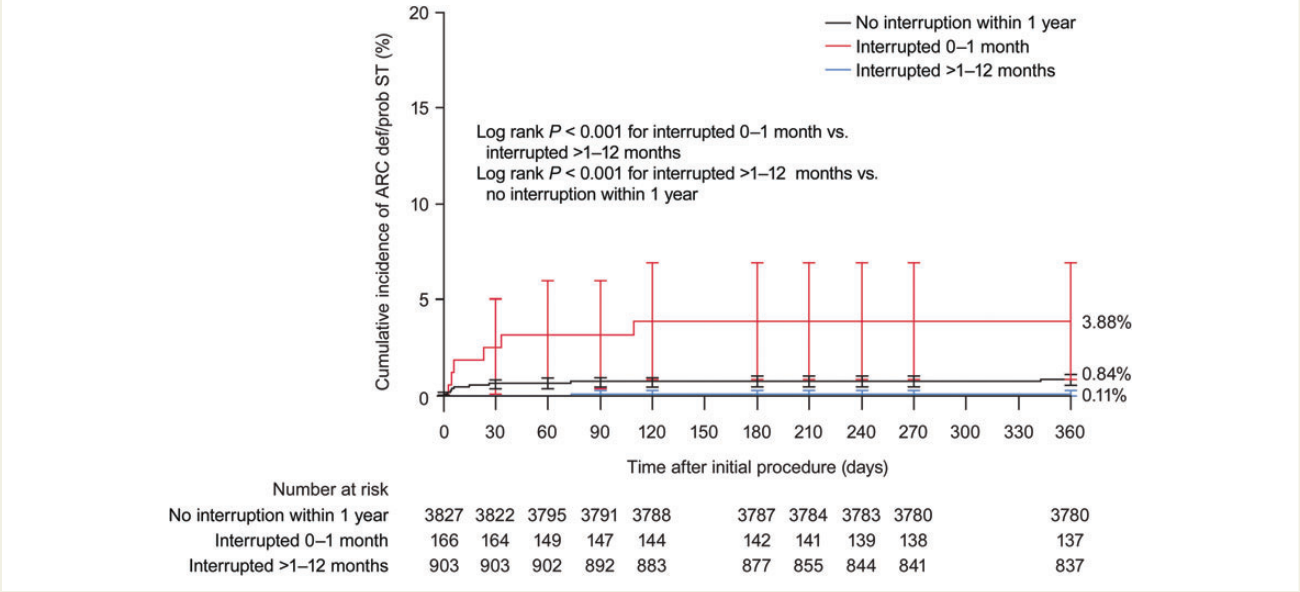

Figure 5 Cumulative incidence of definite or probable stent thrombosis through 1 year after stent implantation according to dual antiplatelet therapy interruption status. ST, stent thrombosis.

Table 2 Details of stent thrombosis events in patients with dual antiplatelet therapy interruption within 1 year of PCI procedure

Patient	Time of interruption	Duration of interruption	Interrupted medication	Time of ST event (duration of interruption until ST)	ARC classification of ST event
DAPT interruption 0–1 month					
1	Day 1	Permanent[a]	ASA	Day 108 (108)	Probable
2	Day 1	Permanent[b]	ASA	Day 2 (2)	Probable
3	Day 3	33 days	ASA	Day 22 (20)	Definite
4	Day 2	Permanent[b]	Clopidogrel	Day 4 (3)	Probable
5	Day 2	Permanent	ASA	Day 5 (4)	Probable
6	Day 2	30 days	Clopidogrel	Day 32 (31)	Definite
DAPT interruption 1–12 months					
7	Day 69	2	Clopidogrel	Day 71(3)	Definite

[a]Patient was permanently off DAPT for 108 days before ST event and death.
[b]Patients died after ST event within 2–3 days of DAPT interruption.

Details of stent thrombosis events in dual antiplatelet therapy interrupted patients

Of the seven ST events that occurred in DAPT interrupted patients within 1 year after the interruption, three were definite and four were probable (*Table 2*). Two definite ST and four probable ST events were in patients who had a DAPT interruption within the first month. The median number of days to interruption following the PCI for all six patients in this group was 2 days.

For the single case of ARC definite ST that occurred in the interrupted group between 1 and 12 months, the patient had a history of ST prior to the PCI procedure and had two total occlusions close to the previously implanted stents that were treated during the PCI procedure (*Table 2*). The median number of days to interruption for all patients was 211 days.

Cardiac death/target-vessel myocardial infarction by dual antiplatelet therapy interruption longer than 14 days

Overall there were 4071 patients who never interrupted DAPT >14 days or were on DAPT at the time of the CD or TVMI. Among patients who never interrupted DAPT longer than 14 days, the rate of CD/TVMI was 4.08% (166/4071). The rate of CD/TVMI was 6.84% in patients with a longer than 14 day DAPT interruption within the first month; lower rates of CD/TVMI occurred in patients interrupted longer than 14 days between 1–3, 3–6 and 6–12 months (*Figure 6*).

Bleeding outcomes

Of the 2309 patients from R-INT with bleeding data ascertained, 1896 patients had no DAPT interruption prior to any bleeding event; there were 34 bleeding events in these patients (1.79%). No patient who had a DAPT interruption within the first month ($n = 56$) had a bleeding event, and two bleeding events occurred in the 357 patients (0.56%) with a DAPT interruption from 1 to 12 months.

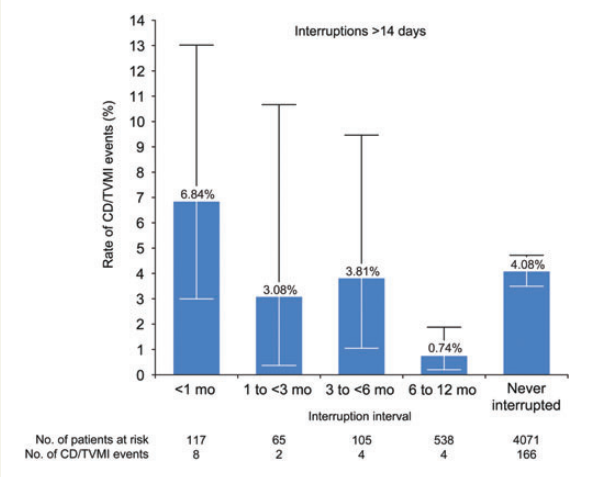

Figure 6 Distribution of patients with cardiac death or target-vessel myocardial infarction per interval of dual antiplatelet interruption longer than 14 days. The mean value for the grouped interruption interval of 1 to <12 months was 1.41%.

Discussion

In patients with stable coronary artery disease, current recommendations for DES call for a minimum of 6 months in the European[7,8] and 12 months in the US guidelines.[9] The recently revised American College of Cardiology Foundation/American Heart Association guidelines for management of ST-elevation myocardial infarction recommend 12 months DAPT duration and a strict minimum of 6 months following DES placement for these high-risk patients.[10] In patients with acute coronary syndromes, both guidelines recommend DAPT for 12 months, irrespective of stent type.[7–9,11–13] However, prolonged DAPT has been associated with higher bleeding rates,[34] and optimal DAPT duration with new generation DES is unknown. In this analysis, >4800 patients treated with the R-ZES,

we found that most ST events occurred within 30 days of the index procedure, irrespective of DAPT status. Moreover, DAPT interruptions beyond 30 days were associated with a low risk of ST and no increased risk of CD/TVMI.

Data from other newer generation stent platforms also show that the greatest risk of ST is within the first 30 days and that the risk of ST does not differ between patients on DAPT and off DAPT following this time point.[35] These data suggest that other factors such as procedural factors, implantation technique, and patient-related factors impacting the risk for ST are especially important during the first 30 days post-procedure.[36–39] It is known that ~4–7% of patients undergoing PCI and stent placement will require non-cardiac surgery in each year after treatment and thus it is often unavoidable to interrupt DAPT before the 6–12 months post-procedure recommended.[40] For patients that interrupted DAPT in the current analysis, nearly all ST events (six of seven) occurred in patients who interrupted DAPT between 0 and 1 month and only one patient that interrupted DAPT after 1 and before 12 months had a ST.

While event numbers are small, interruption of DAPT after 1 month appeared to confer no additional risk for ST, compared with no interruption of DAPT. However, interruption of DAPT during the first month was associated with a greater risk of ST. The log-rank *P*-value for the difference in ST rates between patients interrupted between 1 and 12 months and patients interrupted within the first month is <0.0001, which would imply that the patients that interrupted between 1–12 months has a lower risk of ST than patients that interrupted within a month of R-ZES. These data do not address patients who may be at a higher risk for ST regardless of stent type but suggest that DAPT interruption after 1 month may not confer increased risk for ST, CD, or MI for many patients receiving a Resolute stent. While observational studies of the first generation DES consistently showed a correlation between early discontinuation of DAPT and higher rates of ST, it is not clear that the same observations apply to new generation DES such as the R-ZES, as evidenced by our observation that the rate of ST in patients with a DAPT interruption after 1 month is quite low.

It is also important to consider the role of duration of interruption. The thienopyridines, ticlopidine, and clopidogrel are pro-drugs metabolized in the liver to active metabolites that are non-competitive antagonists of the platelet adenosine diphosphate receptor, P2Y12. Inhibition of platelet aggregation by these drugs is delayed until 24–48 h after administration, with maximal inhibition achieved after 3–5 days. Studies have shown that it takes up to 14 days for the platelet function to recover after DAPT withdrawal,[32] which supports the relevance and importance of assessing ST status for subjects that interrupt for longer than 14 days given that a DAPT effect on platelet function could still be active during shorter interruption durations. Consistent with these data, the DAPT Study being conducted in over 20 000 subjects uses a duration of DAPT longer than 14 days to define compliance.[41] In this analysis, no ST events occurred in patients with longer than 14 day interruption in the 1–12-month interruption group. All six ST events in patients with longer than 14 day interruption occurred in the 1-month interruption group.

When the reasons for DAPT interruption were investigated, we noted no difference in the incidence of ST according to reason for interruption although the small number of events precludes any definitive conclusions. However a recently published observational study of over 5000 patients looking at cessation of DAPT and cardiac events after PCI observed a significantly greater risk for major adverse cardiac events when patients disrupted their therapy than when physicians chose to discontinue or interrupt DAPT.[42]

Prolonged use of antiplatelet drugs is a known risk for bleeding events and there is evidence to suggest that for some patients, DAPT extension beyond 3 months confers no additional benefit in terms of reduction in ST events, but is associated with more major bleeding events.[43] Even mild-to-moderate bleeding events are associated with a poorer long-term prognosis compared with those patients without bleeding.[44] These results (1.79% bleeding with no DAPT interruption and 0.56% bleeding in DAPT interrupted patients) are consistent with observations that there is an increased risk for bleeding in the presence of DAPT.

In addition to the lack of safety benefit demonstrated with extended use of DAPT, there is increasing evidence to show comparable safety outcomes in terms of ST and cardiac death with a shorter DAPT duration than is currently recommended by guidelines. Analysis from multiple publications shows the greatest risk for ST and cardiac death is observed when DAPT interruption occurs within 30 days after stent implantation.[17,45–48] These observations highlight the need for randomized controlled trials to evaluate the risk vs. benefit of very short (1 month) vs. longer durations of DAPT after DES implantation.

Cardiac death/target-vessel myocardial infarction

The clinical consequences of ST can be serious, with death and myocardial infarction being the most severe. A pooled analysis of multicentre coronary stent trials and registries has shown that ST is a rare but usually catastrophic event, frequently associated with a myocardial infarction or death. The use of DAPT for a period longer than 12 months in patients who had received DESs was not significantly more effective than aspirin monotherapy in reducing the rate of myocardial infarction or death from cardiac causes in a previously randomized study.[22] Although not all cardiac deaths and myocardial infarctions are ST-related, we analysed the occurrence of CD/TVMI in patients with and without a longer than 14 day DAPT interruption to provide a more inclusive assessment of ST. Results support the conclusion that the antiplatelet therapy discontinuation was not necessarily followed by major cardiovascular events, at least in patients with a prolonged DAPT interruption later than 1 month after stenting.

There are several possible mechanisms explaining the relative safety of the R-ZES. Pre-clinical studies of the Biolinx™ polymer blend used on the R-ZES demonstrate that the hydrophilic surface of this polymer coating does not induce an inflammatory response and provides excellent biocompatibility.[49] This observation was confirmed in a porcine coronary artery model showing minimal inflammation following implantation of the R-ZES.[50] Clinical studies have also supported the safety of ZES. For example, some of these findings might be explained by better neointimal coverage in the early post-implant period compared with earlier generation DES.[51,52] In optical coherence tomography studies, most of the stent struts were covered with neointima at 3 months after R-ZES implantation

and the rates of malapposition (0.7 ± 2.2%) and thrombus (1/18, 5.6%) were quite low,[52] and exposure of stent struts and thrombi was observed less frequently in patients undergoing PCI with ZES than in those undergoing PCI with SES at 9-month follow-up.[51]

Although 1 year of clinical follow-up may not be sufficient to assess the very late outcomes, the data presented here are meaningful given that the majority of the ST events occurs within the first year following stent implantation. Moreover, the optimal duration of DAPT might be different according to DES types. These data suggest for R-ZES, DAPT use for the first month after stent placement is important but the necessity for continued DAPT beyond this time is unclear. DES that can offer both safety and efficacy are desirable, especially for those who may need to stop DAPT early after DES implantation.

Limitations

This is a *post hoc* analysis of pooled datasets that may not reflect the higher ST risk likely to occur in routine clinical practice. Specifically, the RESOLUTE-Japan and RESOLUTE-US trials enrolled subjects likely to be at a lower risk for clinical events; however, the majority (70%) of the patients included in this analysis was taken from the RESOLUTE-International Registry ($n = 2349$) and the RESOLUTE-All Comers trial ($n = 1140$) which enrolled a high proportion of high-risk 'real world' patients. These results should not be overinterpreted in this observational database given that physicians may have appropriately selected those patients who could safely interrupt DAPT and the small number of ST events that occurred after R-ZES implantation. Additionally, most of the DAPT interruptions (often temporary and brief) occurred after 6 months making it difficult to sort out the exact role of nature of the association between DAPT interruptions and adverse clinical events. The generalized application of these results to the entire population demands careful attention given that a larger sample size and a randomized trial might be required to provide a definite answer regarding low frequency events such as ST. The findings reported here apply only to R-ZES. Because safety and efficacy differ according to the DES type, additional analyses that determine the feasibility of short duration DAPT after implantation of other DES are needed.

Conclusion

In a large pooled population of patients treated with an R-ZES, DAPT interruptions between 1 and 12 months were associated with low rates of ST and adverse cardiac outcomes. It would be inappropriate to suggest any changes to the ESC or ACC/AHA/SCAI guidelines for PCI post-stent implantation; however, the current analysis may provide reassurance for clinicians and patients implanted with an R-ZES who may need to interrupt or discontinue the medications before the recommended duration for a variety of unplanned reasons. Randomized clinical trials are needed to determine whether early temporary or permanent interruption of DAPT is truly safe.

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