Title: Cessation of dual antiplatelet therapy and cardiovascular events following acute coronary syndrome

Short title: DAPT cessation post-ACS

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Abstract and Keywords

Objective To assess whether cardiovascular events are increased after cessation of dual antiplatelet therapy (DAPT) following acute coronary syndrome and to explore predictors for recurrent events after DAPT cessation during long-term follow-up.

Methods We did a retrospective observational cohort study. **We included consecutive people with acute coronary syndrome (ACS) who were discharged from Scottish hospitals between January 2008 and December 2013 and who received DAPT after discharge followed by antiplatelet monotherapy.** The rates of cardiovascular events were assessed during each 90-day period of DAPT treatment and 90-day period after stopping DAPT. Cardiovascular events were defined as a composite of death, ACS, transient ischaemic attack or stroke. Cox regression was used to identify predictors of cardiovascular events following DAPT cessation.

Results 1340 patients were included **(62% male, mean age 64.9(13.0) years).** Cardiovascular events occurred in 15.7% (n=211) during the DAPT period **(mean DAPT duration 175.1(155.3) days)** and in 16.7% (n=188) following DAPT cessation **(mean of 2.7 years follow-up).** Independent predictors for a cardiovascular event following DAPT cessation were age (hazard ratio (HR) 1.07; 95% confidence interval (CI) 1.05-1.08; p<0.001), DAPT duration (HR 0.997; 95% CI 0.995-0.998; p<0.001) and having revascularization therapy during the index admission (HR 0.58; 95% CI 0.39-0.85; p=0.005).

Conclusions The rate of cardiovascular events was not significantly increased in the early period post DAPT cessation compared to later periods in this ACS population. Increasing age, DAPT duration and lack of revascularization therapy were associated with increased risk of cardiovascular events during long term follow up after DAPT cessation.

Keywords: antiplatelets, DAPT, cardiovascular events, ACS;

Word count : 250 words

Key messages

What is already known on this subject?

Discontinuation of dual antiplatelet therapy (DAPT) is associated with an increased risk of cardiovascular disease in previous studies. The association between the duration of DAPT and DAPT cessation is unknown.

What might this study add?

We found that increasing age, DAPT duration and lack of revascularization therapy for the ACS were associated with increased risk of cardiovascular events during long term follow up after DAPT cessation.

How might this impact on clinical practice?

Our findings indicate that longer duration of DAPT and use of revascularization therapy may be related to a reduced risk of cardiovascular event after ACS and DAPT cessation.

INTRODUCTION

Antiplatelet therapy is indicated after an acute coronary syndrome (ACS) because it lowers mortality and reduces the early risk of recurrence. Dual antiplatelet therapy (DAPT), typically using aspirin and an ADP receptor antagonist such as clopidogrel, ticagrelor or prasugrel, is superior to use of a single antiplatelet agent. Clopidogrel, when given together with aspirin and fibrinolytic therapy has been shown to reduce the rate of death or re-infarction without major increased bleeding risk following ST-elevation myocardial infarction (STEMI) when compared with aspirin alone.[1 2] Furthermore, patients with a non-STEMI ACS treated with both clopidogrel and aspirin had a lower rate of death from cardiovascular causes, non-fatal myocardial infarction or stroke than patients treated with aspirin alone.[3]

Typically, DAPT is given for a defined period of time after which patients continue with antiplatelet monotherapy. There are reports that the risk of cardiovascular events increases after DAPT is stopped,[4 5] perhaps due to a rebound in platelet activity.[6] Studies have shown that use of DAPT beyond 12 months significantly reduces risk of cardiovascular events.[7 8] Whether duration of DAPT is associated with risk of events after DAPT cessation is unclear. Most studies of risk after DAPT cessation also have short follow-up duration between 6 to 18 months,[4 9] included predominantly male patients[4] or patients with health insurance in specific health care plans.[5 10] A better understanding of the long term outcomes after DAPT cessations and the predictors of events thereafter may help develop strategies to mitigate this risk.

The National Health Service (NHS) Scotland has set up regional data Safe Havens which aim to facilitate rapid access to high quality health data for research purposes.[11] We used data contained in NHS Greater Glasgow and Clyde (NHS GGC) Safe Haven to assess the incidence and predictors of cardiovascular events after discontinuation of DAPT in patients who have suffered

ACS. We hypothesised that discontinuation of DAPT would increase the risk of cardiovascular events in the first 90 days interval after stopping DAPT.

METHODS

Study design

We undertook a retrospective observational cohort study using healthcare records obtained from NHS Greater Glasgow and Clyde (GGC). NHS GGC is the largest health board in Scotland, serving a catchment area including the City of Glasgow, Inverclyde, Renfrewshire, East Renfrewshire, East Dunbartonshire and West Dunbartonshire. **Approval was obtained from the NHSGGC Safe Haven advisory committee, which has approval from the West of Scotland Research Ethics Committee (GSH/13/CA/005).** The study adhered to strict information governance and security protocols. All data are held within the NHSGGC Safe Haven with restricted access.

Data source

NHS GGC and the Robertson Centre for Biostatistics provide access to anonymised local healthcare data in the West of Scotland subject to the approvals described. We incorporated data from the Scottish Morbidity Record, the General Register Office for Scotland death registration records, the Prescribing Information System, the Scottish Care Information – Diabetes Collaboration (SCI-DC) and the General Practice database. The Scottish Morbidity Record database was used to search all admission for ACS that occurred in the West of Scotland from January 2008 through December 2013.

Study setting and study population

Patients were included in the study if they experienced an ACS, continued on DAPT following discharge (defined as cashing a prescription for DAPT within 60 days of hospital discharge) and subsequently stopped DAPT and then continued with single antiplatelet therapy. An ACS event was defined as emergency hospital admission with a main discharge diagnosis of ACS (International Classification of Diseases – Tenth revisions [ICD-10] codes I20, I21 or I22).

Baseline demographic data were obtained from the Scottish Morbidity Record dataset. Medical history data were obtained from the General Practice and the Scottish Care Information – Diabetes Collaboration databases. These comorbidities were defined as a condition reported from general practitioners before the ACS event. A coronary revascularization procedure was defined as a procedure listed in operation field from Scottish Morbidity Record dataset during the index admission. Revascularization procedures include coronary artery bypass graft (English Office of Population Censuses and Surveys (OPCS-4) codes K40-46) and percutaneous coronary intervention (PCI) (OPCS-4 codes K49-50 and K75).

DAPT use

The usage of DAPT was identified and verified through the Prescribing Information System database. DAPT use included and combination of aspirin-clopidogrel, aspirin-dipyridamole, aspirin-ticagrelor and aspirin-prasugrel. The number of pills dispensed for each prescription was used to calculate the duration of DAPT use. In the primary analysis, the last day of DAPT use was based on the date of last DAPT prescription refill plus the number of days supplied for that refill. Discontinuation of DAPT was defined when there was no refill prescription or dispense date of DAPT more than 14 days after this date.

Study endpoints

The primary endpoint of the study was a cardiovascular event, which consists of composite of all-cause mortality, ACS (myocardial infarction (MI) or unstable angina), transient ischaemic attack or stroke after cessation of DAPT. Information on death was obtained through General Register Office for Scotland database. The ICD-10 codes were used to identified hospitalizations for ACS (I20 – I25), TIA (G458-G459) and stroke (I63-I64). The safety endpoint of the study was a major bleeding event following the first admission of ACS. Major bleedings were based on ICD-10 (I60-I62, H11.3, H31.3, H35.6, H43.1 and R58)

Statistical methods

Descriptive statistics are given for the whole population and separately for patients treated with medical or revascularization therapy for the index ACS. Categorical variables were summarised using frequencies and proportions and continuous variables as mean [standard deviation (SD)] or median [interquartile range (IQR)]. Patients were censored at the end of the follow-up period.

The life table method was used to calculate unadjusted incidence rates per 1000 patient-days of the primary endpoint for each 90-day interval during DAPT and after DAPT cessation. Incidence rate ratios (IRR) with 95% confidence interval (95% CI) were calculated to compare incidence rates in medical and revascularization-treated patients during the same intervals.

Poisson regression (or negative binomial if overdispersion was present) model was used to assess incidence of the primary endpoint after stopping DAPT. Incidence rate ratios were calculated with adjustment for age, medical or revascularization therapy and duration of DAPT. In these models, the risk of cardiovascular events in the first 90 days interval after stopping DAPT was compared with 91 to 180 days after stopping and with 91 to 360 days interval consistent with prior studies.[4 5] Cox regression analysis was used to model the predictors of

cardiovascular events after stopping DAPT. The models were adjusted for age, medical or revascularization therapy and duration of DAPT. Adjustment was not made for other risk factors such as hypertension, diabetes, hyperlipidaemia, chronic renal failure and ischaemic heart disease because of missing data. **The proportional hazards assumption was tested by using of log-minus-log plots. We found no evidence of violation of this assumption**. The adjusted hazard ratios (HRs) and 95% CI for cardiovascular event were estimated and adjusted to age, medical or revascularization therapy and duration of DAPT. **The Harrell's C-statistic result for the overall model prediction accuracy was reported. The Fine-Gray model for the competing risk of death was used as a sensitivity analysis[12] and the sub-distribution hazard ratio (SHR) and 95% CI of SHR were estimated.**

Statistical analyses were performed using IBM SPSS Statistics version 21.0[13] and for competing risk analyses were performed using STATA version 15.0 (University of Glasgow). A value of $p<0.05$ was considered statistically significant.

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None.

RESULTS

Of the 7232 patients admitted with an ACS during the study period, 2899 (40%) patients received only single antiplatelet therapy, 1531 (21%) had no documented antiplatelet information leaving 2802 (38.7%) patients who were dispensed with DAPT. Of these 2802 patients, 1872 patients were confirmed to refill a prescription for DAPT within 60 days of hospital discharge. Of these, 1340 (71.6%) had DAPT then continued with a single antiplatelet in

the longer term and were (Figure 1) included in the study. Baseline characteristics are shown in Table 1. Mean follow-up after DAPT cessation was 1009 days, median 1067 days **(supplementary figure).** Following DAPT cessation, antiplatelet monotherapy with aspirin was commonly prescribed (79.1%), followed by clopidogrel (19.8%), then dipyridamole (0.6%) and ticagrelor (0.4%).

Study endpoints

Cardiovascular events occurred in 211 (15.7%) whilst taking DAPT, leaving1129 (84.3%) event-free at DAPT cessation. After DAPT cessation 188 cardiovascular events occurred (16.7%) (Table 2). Major bleeding occurred in 6 (0.45%) and 5 (0.44%) while on DAPT and after DAPT cessation respectively.

Cardiovascular events

The incidence rate was higher in first 90-days of DAPT treatment compared to the following 90-days of DAPT treatment (IRR, 5.73; 95% CI, 3.48-10.06; $p<0.001$) (Table 3). After cessation of DAPT, the incidence rate was not different in the first 90-days compared to the next 90-days (IRR, 0.65; 95% CI, 0.31-1.31; $p=0.190$). Medically-treated had a higher incidence of cardiovascular events during DAPT in the first 90-days (IRR, 2.57; 95% CI, 1.71-3.99; $p<0.001$) (Figure 2(a)) compared with revascularization-treated patients. After cessation of DAPT, there was no difference in the incidence rate of cardiovascular event between medically-treated patients and revascularization-treated patients in the first 90-day interval (IRR, 3.30; 95% CI, 0.75-30.12; $p=0.096$) (Figure 2(b)).

Adjusted incidence rate ratios following DAPT cessation

After adjusting for age, medical or revascularization therapy and total duration of DAPT treatment, there was no increased risk of cardiovascular events in the first 90 days after DAPT cessation (adjusted IRR, 0.70; 95% CI, 0.32 to 1.55; p=0.375) compared to day 91-180 (Table 4).

Predictors of cardiovascular events following DAPT cessation

The univariable and multivariable analysis of possible predictors of risk of cardiovascular events after stopping DAPT is presented in Table 5. Multivariable analysis of the Cox model, indicated that increased age (HR, 1.07; 95% CI, 1.05-1.08; p<0.001) was significantly associated with an increased risk of cardiovascular event, whereas patients treated with revascularization (HR, 0.58; 95% CI, 0.39-0.85; p=0.005) and longer duration of DAPT (HR, 0.997; 95% CI, 0.995-0.998; p<0.001) had lower risk (Harrell's C statistic=0.77). Results were broadly consistent with Fine-Gray model.

DISCUSSION

We assessed the rate of cardiovascular events following DAPT cessation and explored predictors of events during long-term follow-up after DAPT cessation. The incidence was not higher in the first 90 days post DAPT cessation compared to later periods suggesting no rebound increase in risk in this population. Cardiovascular events did occur in the long-term follow period after DAPT cessation and we found that increasing age, lack of revascularization treatment for the ACS and duration of DAPT treatment to be independent predictors of cardiovascular event following DAPT cessation.

The incidence of cardiovascular events following DAPT cessation in the literature varies between studies (4-17%). The incidence in the present study (16.7%) is at the higher end of this range and

this could be due to longer follow-up period i.e. 2.7 year follow-up, which allowed us to capture more events. We did not see an increase in risk following DAPT cessation. This is in contrast to many other studies.[4 5 10 14] There are several differences between our and other studies to note. These differences may be due to differences in definitions used of cardiovascular event between studies,[15] and differences in the duration of DAPT after ACS (in the present study was 177 (155) days, which was shorter than previous studies).[10 14] **The shorter duration of DAPT in this study was 5.8 months and this is probably due to the recommendation made by the Cardiac Prescribing Group West of Scotland. This recommends 3 and 6 months of DAPT following a STEMI or NSTEMI, for use of bare metal stent and drug eluting stents respectively.** More patients in our study were treated with medical therapy alone for their ACS 67% compared to 50% and 25% in the studies by Ho *et.al.*[4] and Stephenson *et.al.*[10]

We explored predictors of long-term events after DAPT cessation. We found that increasing age, DAPT duration and lack of revascularization therapy for the ACS were associated with increased risk of cardiovascular events after DAPT cessation. Previous studies have demonstrated that usage of clopidogrel for more than six months was associated with lower rates of death, myocardial infarction and/or stent thrombosis.[16 17] These data suggest that ACS patients may benefit when the duration of DAPT is more than six months. **In contrast, a network meta-analysis by D'Ascenzo *et.al.*[18] found shorter DAPT duration (<12 months) is associated with lower rates of ischemic events in everolimus/zotarolimus eluting stents than bioresorbable stents. These data suggest that type of stent and DAPT duration may affect the cardiovascular events at follow-up.**

Strengths

Our study had full information on antiplatelet use through the Prescribing Information System database. Thus, we were able to confirm that all patients included in this study were taking aspirin plus either clopidogrel or prasugrel or ticagrelor and which antiplatelet they took following DAPT cessation. This is in contrast to some previous studies where this information was not available.[5 10 19]

We included ACS population in the West of Scotland. Ours is a study of all individuals in a community with an ACS identified through resources of the NHS GGC Safe Haven, regardless of sex and health care insurance. In previous studies, they only able to include predominantly male patients[4] or patients with treated within a particular health care plan.[5 10]

Study limitations

Many patients with a diagnosis of ACS were not included in our analysis. This is because many received only single antiplatelet therapy, many did not continue receiving prescriptions for DAPT and many did not stop DAPT and then continue with antiplatelet monotherapy. There are several reasons for this. First, patients may be coded as an ACS in hospital records but not have met criteria for DAPT use. Patients who did not receive a further prescription for DAPT within 60 days of discharge may have stopped DAPT due to side effects or bleeding complications meaning our estimates of bleeding may be falsely low. Patients admitted near the end of the study window may not have reached the end of their DAPT treatment course.

This was an observational analysis and the combinations of DAPT were not randomly assigned. We excluded all patients that did not have their antiplatelet therapy recorded in the Prescribing Information System database. Due to exclusion of these patients from the analysis, could raise the likelihood that the observed effect estimate is biased. We included 33 ACS patients who

were prescribed with aspirin and dipyridamole, however, we were unable to determine the rationale for this treatment decision. We assume it us due to ischaemic stroke.

We lack specific measures of indications for stopping DAPT such as bleeding, switching to other antiplatelet, stopping for surgery or lack of adherence. We assume that in most cases the cessation of DAPT was planned. Although we could not directly measure medication adherence, we did use pharmacy dispensing data, which is strongly correlated with a broad range of patient outcomes.[20] Use of prescriptions filled has been shown to reflect medication use by the patient with a high degree of accuracy.[21] We also lack information on the type of coronary lesion and the type of stents used in revascularization group. The use of over-the-counter medicines were not available[22] in this study that could be potential confounding factors. Patients in the Scotland receive free prescriptions, which should reduce the possibility of over-the-counter medicine use. The present study included patients admitted with ACS in the West of Scotland, thus, generalizability to other populations and practice setting is unknown. The differences incidence rate between medical and revascularized treated patients in the early period did not show a significant difference because of the low number of events in each group and the wide confidence intervals.

CONCLUSIONS

In ACS population, the incidence of cardiovascular events was not higher early post DAPT cessation than in later periods. Cardiovascular events post DAPT cessation did occur and were associated with increasing age, DAPT duration and lack of revascularization therapy.

Contributor WMK and JD contributed to study design. All authors contributed to interpretation of results, reviewed and approved the manuscript prior to submission. WMK wrote the first manuscript and performed all analyses.

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Conflict of interest The authors declare that there is no conflict of interest.

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Table 1: Baseline characteristics whilst on DAPT

Characteristics	All patients (n=1340)	Medical treated (n=933)	Revascularization treated (n=407)
Age, years			
Mean (SD)	64.9(13.0)	66.7(13.1)	60.9(11.9)
Median (IQR)	64(55-75)	67(57-77)	60(52-69)
Sex			
Female	510(38.1)	377(40.4)	133(32.7)
Male	830(61.9)	556(59.6)	274(67.3)
Current smoker	296(28.3)	178(25.6)	118(33.4)
Medical history			
Hypertension	463(34.6)	336(36.0)	127(31.2)
Diabetes	234(17.5)	157(16.8)	77(18.9)
Hyperlipidaemia	867(64.7)	591(63.3)	276(67.8)
CRF	194(14.5)	140(15.0)	54(13.3)
IHD	323(24.1)	218(23.4)	105(25.8)
Prior AP therapy			
No prior AP	885(66.0)	576(61.7)	309(75.9)
Aspirin	316(23.6)	234(25.1)	82(20.1)
Clopidogrel	35(2.6)	29(3.1)	6(1.5)
Dipyridamole	6(0.4)	6(0.6)	0(0)
Aspirin + clopidogrel	59(4.4)	52(5.6)	7(1.7)
Aspirin + dipyridamole	33(2.5)	30(3.2)	3(0.7)
Aspirin + ticagrelor	5(0.4)	5(0.5)	0(0)
DAPT combinations			
Aspirin + clopidogrel	1261(94.2)	861(92.3)	400(98.3)
Aspirin + dipyridamole	33(2.4)	30(3.2)	3(0.7)
Aspirin + ticagrelor	42(3.1)	38(4.0)	4(1.0)
Aspirin + prasugrel	3(0.2)	3(0.3)	0(0)
Duration of DAPT			
Mean (SD)	175.09(155.30)	164.28(148.17)	199.85(168.10)
Median (IQR)	113(78-208)	109(76-185)	126(85-311)
≤ 6 months	955(71.3)	695(74.5)	260(63.9)
> 6 months	385(28.7)	238(25.5)	147(36.1)
≤ 12 months	1139(85.0)	812(87.0)	327(80.3)
> 12 months	201(15.0)	121(13.0)	80(19.7)

All values are reported as no. (%) unless otherwise noted. Revascularization includes CABG and PCI. AP, antiplatelet; CABG, coronary artery bypass graft; CRF, chronic renal failure; DAPT, dual antiplatelet therapy; IHD, ischaemic heart disease; PCI, percutaneous coronary intervention; SD, standard deviation; IQR, interquartile range.

Table 2: Incidence of cardiovascular events (composite of death, ACS, transient ischaemic attack or stroke)

	During DAPT			After DAPT cessation		
	All (n=1340)	Medical treated (n=933)	Revascularization treated (n=407)	All (n=1129)	Medical treated (n=754)	Revascularization treated (n=375)
Cardiovascular events	211 (15.7)	179 (19.2)	32 (7.9)	188 (16.7)	154 (20.4)	34 (9.1)
ACS	179 (13.4)	155 (16.6)	24 (5.9)	60 (5.3)	46 (6.1)	14 (3.7)
Ischaemic stroke/TIA	2 (0.1)	2 (0.2)	0 (0)	24 (2.1)	16 (2.1)	8 (2.1)
All death	44 (3.3)	35 (3.8)	9 (2.2)	135 (12.0)	120 (15.9)	15 (4.0)

All values are reported as no. (%) unless otherwise noted.

Table 3: The risk of cardiovascular events[a] following ACS and up to two years after stopped DAPT

	Period, days	All patients			Medically-treated			Revascularization-treated		
		Number at risk	Number of events	Incidence rate per 1000 patient-days	Number at risk	Number of events	Incidence rate per 1000 patient-days	Number at risk	Number of events	Incidence rate per 1000 patient-days
During DAPT	0-90	1340	181	1.882	933	153	2.335	407	28	0.914
	91-180	797	17	0.328	523	15	0.455	274	2	0.106
	181-270	354	5	0.184	209	4	0.255	145	1	0.087
	271-360	250	3	0.152	140	2	0.179	110	1	0.117
	361-450	189	1	0.088	109	1	0.149	80	0	0
	451-540	64	1	0.231	40	1	0.370	24	0	0
	541-630	32	1	0.453	20	0	0.823	12	0	0
	631-720	17	0	0.000	7	2	0	10	0	0
After DAPT cessation	0-90	1129	15	0.151	754	13	0.199	375	2	0.060
	91-180	1072	22	0.234	706	20	0.325	366	2	0.062
	181-270	1017	21	0.234	660	18	0.311	357	3	0.094
	271-360	978	10	0.115	628	10	0.180	350	0	0.000
	361-450	950	17	0.203	605	14	0.263	345	3	0.100
	451-540	910	16	0.119	577	12	0.237	333	4	0.135
	541-630	876	17	0.220	550	14	0.290	326	3	0.104
	631-720	840	15	0.205	522	10	0.221	318	5	0.179

[a]Cardiovascular events consist of composite of all-cause mortality, ACS, transient ischaemic attack or stroke.

Table 4: Adjusted incidence rate ratios for the cardiovascular event after DAPT cessation

Patient cohort	After DAPT cessation (n=1129)			Medical treated (n=754)			Revascularization treated (n=375)		
	n	Adjusted IRR (95% CI)	p-value	n	Adjusted IRR (95% CI)	p-value	n	Adjusted IRR (95% CI)	p-value
All patients[a]	1129	0.79 (0.45-1.42)	0.443	754	0.77 (0.42-1.41)	0.390	375	1.17 (0.13-10.81)	0.889
All patients[b]	1129	0.69 (0.42-1.13)	0.141	754	0.67 (0.39-1.13)	0.133	375	0.79 (0.16-3.87)	0.777

[a]comparing the initial 90-day interval versus the 91 to 180-day interval after stopping DAPT.
[b]comparing the initial 90-day interval versus the 91 to 360-day interval after stopping DAPT.
Cardiovascular events consist of composite of all-cause mortality, ACS, TIA or stroke. All the Poisson regression models (or negative binomial if overdispersion is present) adjusted for age, medical or revascularization therapy and duration of DAPT. IRR, incidence rate ratio.

Table 5: Univariable and multivariable analyses of possible predictors of cardiovascular events after stopping DAPT

Predictive variables	Cox analysis						Fine-Gray analysis					
	Univariable analysis			Multivariable analysis[a]			Univariable analysis			Multivariable analysis[b]		
	HR	95% CI	p-value	Adjusted HR	95% CI	p-value	SHR	95% CI	p-value	SHR	95% CI	p-value
Age	1.08	(1.06-1.09)	<0.001	1.07	(1.05-1.08)	<0.001	1.04	(1.02-1.06)	<0.001	1.02	(1.01-1.05)	0.002
Male	0.52	(0.39-0.69)	<0.001				0.48	(0.30-0.76)	0.002	0.61	(0.38-1.01)	0.053
Current smoker	1.35	(0.69-2.66)	0.380				1.00	(1.00-1.00)	<0.001			
Hypertension[b]	3.72	(2.44-5.66)	<0.001				1.08	(0.66-1.78)	0.754			
Diabetes[b]	5.85	(2.75-12.45)	<0.001				1.92	(0.88-4.18)	0.099			
Hyperlipidaemia[b]	1.56	(1.17-2.08)	0.002				1.00	(0.62-1.63)	0.998			
Chronic renal failure[b]	1.76	(1.08-2.85)	0.023				0.59	(0.34-1.03)	0.063			
Ischaemic heart disease[b]	5.34	(2.97-9.58)	<0.001				1.82	(0.96-3.46)	0.065			
Revascularization vs medical therapy	0.38	(0.26-0.55)	<0.001	0.58	(0.40-0.85)	0.005	0.63	(0.34-1.06)	0.083			
Prior vs no prior AP	2.02	(1.51-2.70)	<0.001				1.94	(1.21-3.09)	0.006			
DAPT duration	0.995	(0.994-0.997)	<0.001	0.997	(0.995-0..998)	<0.001	0.994	(0.991-0.998)	0.001	0.995	(0.992-0.998)	0.003
Monotherapy Clopidogrel vs aspirin	1.40	(1.01-1.94)	0.046				1.63	(0.97-2.75)	0.065			

[a]Final multivariable analysis. [b]These variables were not included in the multivariable analysis due to missing data.
SHR, subdistribution hazard ratio.

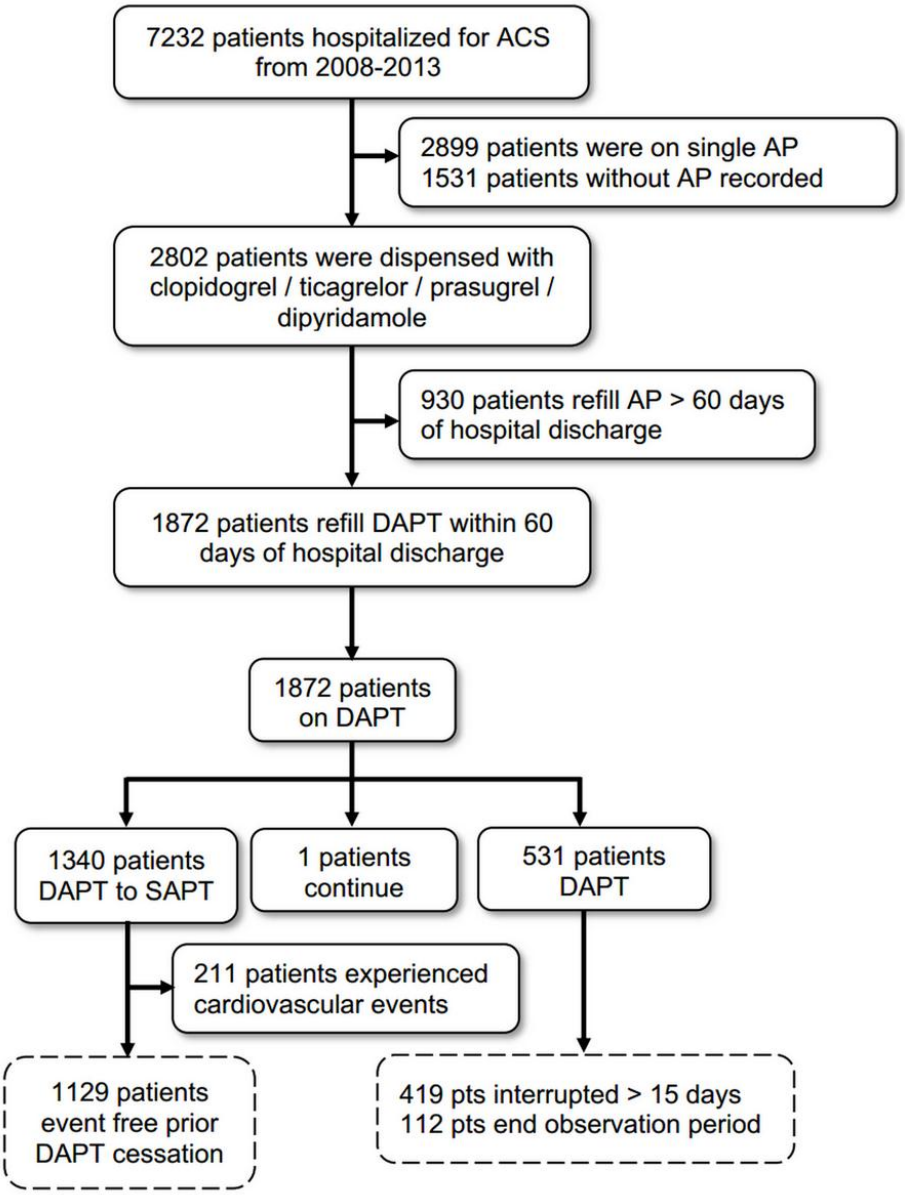

Figure 1 Flow diagram describing the selection of data for the analysis reported. ACS, acute coronary syndrome; AP, antiplatelet; DAPT, dual antiplatelet therapy; SAPT, single antiplatelet therapy.

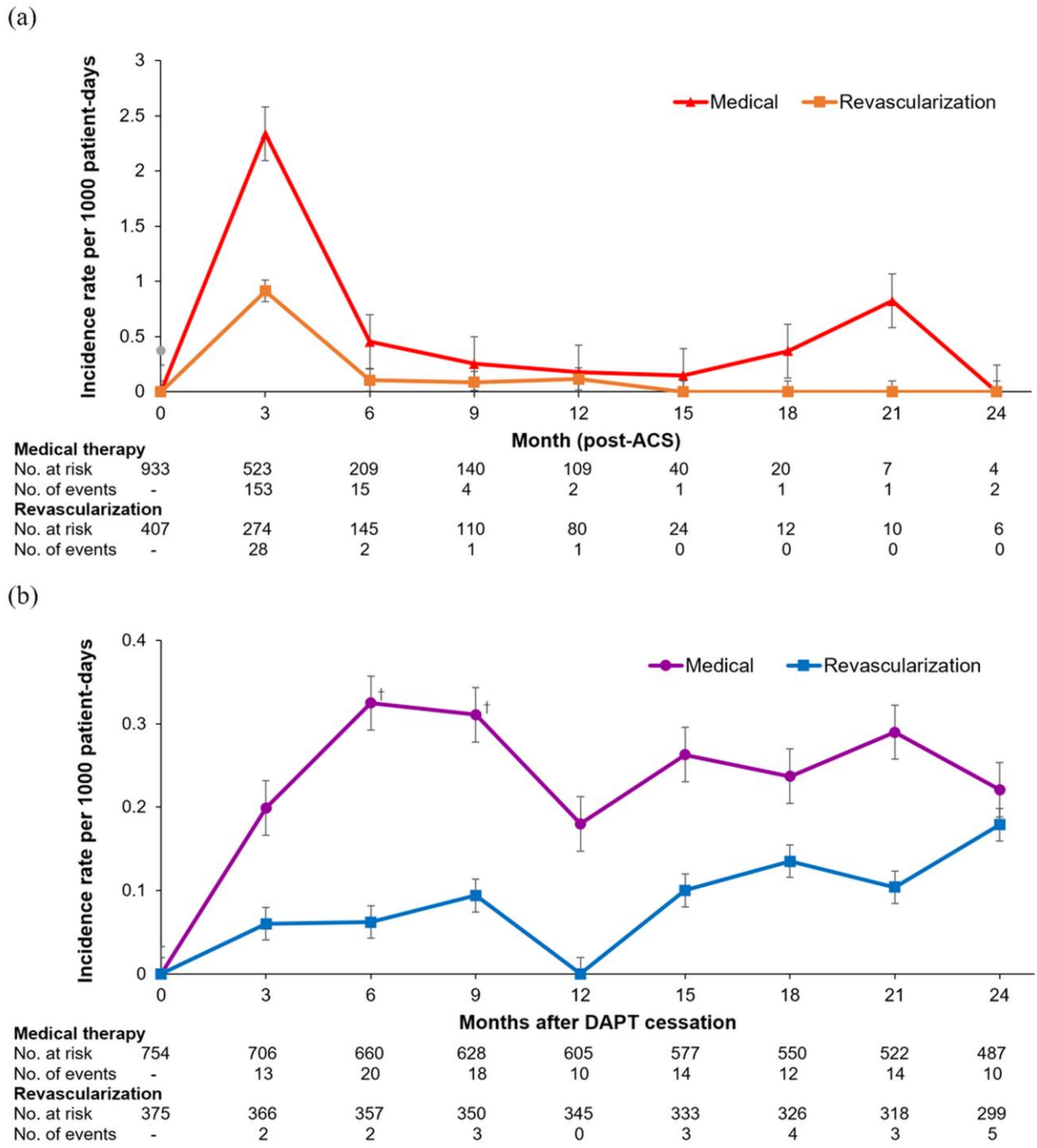

Figure 2 Incidence rate (A) during DAPT and (B) after DAPT cessation for patients treated with medical and revascularisation therapy. *p<0.01, †p<0.05, compared with patients treated with revascularisation therapy from the same interval. ACS, acute coronary syndrome; DAPT, dual antiplatelet therapy.