

## ORIGINAL RESEARCH ARTICLE

# Extended dual antiplatelet therapy after acute coronary syndrome in Spain: Results from the EPICOR study

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## Summary

**Introduction:** Real-world, country-specific studies of dual antiplatelet therapy (DAPT) duration among survivors of acute coronary syndrome (ACS) are important for improving long-term prognosis.

**Aims:** To investigate DAPT duration after hospital discharge for ACS in Spain.

**Results:** Data from patients enrolled in the Spanish cohort of the EPICOR (long-term follow-up of antithrombotic management Patterns In acute CORonary syndrome patients) study (NCT01171404) were analyzed for changes to antithrombotic medication up to 2 years postdischarge according to index event diagnosis and patient characteristics. Deaths, coronary events, and bleeding events were analyzed over the same period. Overall, a high proportion of patients remained on DAPT at 2 years (53.1%). Among patients who experienced any on-treatment bleeding event, almost two-thirds remained on DAPT at the end of follow-up. Patients >65 years, diabetic, or those that were medically managed were more likely to continue with DAPT until 2 years following discharge. At 2 years, the incidence of bleeding events requiring hospitalization was low compared with the incidence of coronary events (1.4% vs 6.6%). There was a numerical reduction in coronary events, but no increase in bleeding events, with DAPT continuation compared with single antiplatelet therapy.

**Conclusions:** More than half of patients in this unselected cohort study remained on DAPT at 2 years following discharge for ACS. Continuation with DAPT was greater among patients with additional cardiovascular risk factors, which suggests that treating physicians in Spain prioritizes ischemic risk reduction over bleeding risk in patients with ACS, according to patient's risk profile.

## KEYWORDS

Acute coronary syndrome, ADP Receptor antagonists, Antiplatelet agents, Coronary artery disease, Myocardial infarction, Secondary prevention

## 1 | INTRODUCTION

European Society of Cardiology (ESC) guidelines recommend administration of dual antiplatelet therapy (DAPT) with low-dose aspirin and

a P2Y<sub>12</sub> receptor antagonist for at least 12 months following an acute coronary syndrome (ACS) event, irrespective of index event diagnosis and management.<sup>1,2</sup>

Several studies have shown that the risk of a recurrent cardiovascular event persists beyond the first year following discharge from hospital, even in patients who have remained event-free during this period.<sup>3–6</sup> A number of trials and meta-analyses also

suggest that prolonged DAPT reduces the incidence of ischemic events compared with standard duration, although at the expense of increased potential for bleeding.<sup>7-9</sup> Importantly, the net benefit of prolonged DAPT is likely to be dependent on the ischemic- and bleeding-risk profiles of individual patients.<sup>10-12</sup> Country-specific analyses of DAPT duration are important for improving patient care according to current practice, but recent data for Spain are lacking in the literature.

Using data from the Spanish patient population enrolled in the EPICOR (long-term follow-up of antithrombotic management patterns in acute CORonary syndrome patients) registry (NCT01171404), the aim of this analysis was to investigate the proportion of patients remaining on DAPT beyond the 12-month guideline period, and to explore the relationship between DAPT continuation and patient characteristics. We also explored the rate of cardiovascular and bleeding events on extended DAPT versus single antiplatelet therapy.

## 2 | METHODS

EPICOR is a prospective, real-world, multinational, observational study. A total of 10,568 patients who experienced an ACS event, and who survived to discharge, were enrolled (between September 2010 and March 2011) in 555 hospitals across 20 countries.<sup>13</sup>

Patients were eligible for inclusion if they were hospitalized within 24 hours of symptom onset of the index event with a final diagnosis of ST-segment elevation myocardial infarction (STEMI) or non-ST-segment elevation ACS (NSTEMI-ACS, comprising both non-STEMI and unstable angina) at discharge. Patients were excluded if previously enrolled in EPICOR, they had a life expectancy <6 months, or presented with circumstances that would prevent complete follow-up.

Baseline characteristics along with pre- and in-hospital diagnostic and therapeutic management strategies were recorded and have been described for the overall population previously.<sup>13,14</sup> Patients were followed up via scheduled telephone interviews at 6 weeks after the index event and then every 3 months up to 2 years post-discharge (final follow-up call at 23 months), and data regarding antithrombotic therapy used, and coronary and bleeding events were recorded. Coronary events comprised stable angina, unstable angina, and myocardial infarction. Bleeding events were defined as those requiring hospitalization, physician consultation, or those occurring during hospitalization.

The present analysis used data from 782 patients enrolled in EPICOR in 50 centers in Spain. Analysis of DAPT patterns in the total EPICOR cohort has been published previously.<sup>15</sup> As one of the top recruiting countries in EPICOR, Spain's enrolled patients provide a representative selection of the overall EPICOR population with which to further investigate DAPT duration. In addition, country-specific information on DAPT patterns is important to identify potential inter-country differences and highlight room for improvement in the management of patients with ACS.

## 2.1 | Statistical analysis

Patients were grouped according to antithrombotic medication at the time of discharge: DAPT, comprising patients on aspirin plus a P2Y<sub>12</sub> inhibitor (clopidogrel, prasugrel, or ticlopidine), or single antiplatelet therapy (SAPT). Patterns of DAPT continuation were analyzed over the 2-year follow-up period. Mortality, adverse coronary events, and bleeding events were analyzed for both SAPT and DAPT up to 2 years.

The percentage of patients on DAPT was calculated for all follow-up time points, excluding those patients who had died or were lost to follow-up since discharge. The chi-square test was used to compare characteristics across discharge medication groups. The association between antiplatelet use and clinical outcomes at 2 years was evaluated by fitting a Cox proportional hazards model for time to the applicable event, with the antithrombotic-management-pattern group (SAPT/DAPT) as the only explanatory variable. All analyses were performed in SAS Version 9.3 (SAS Institute Inc., USA, 2010).

## 3 | RESULTS

### 3.1 | DAPT use at discharge and follow-up

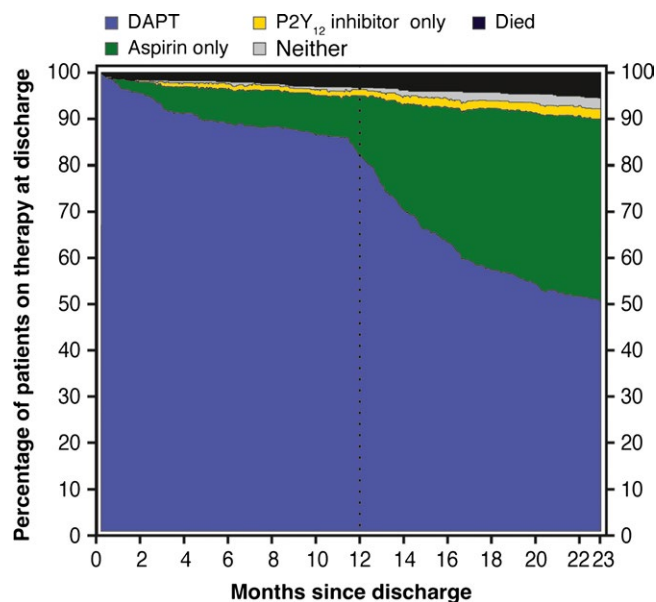
Oral antiplatelet treatment and adverse events were recorded for a total of 782 (340 STEMI and 442 NSTEMI-ACS) patients enrolled in Spain over a 2-year period following discharge for ACS.

Overall, 86.3% (675/782) patients were discharged on DAPT with aspirin and a P2Y<sub>12</sub> inhibitor, that is, clopidogrel, prasugrel, or ticlopidine; ticagrelor was not available in Spain at the time the study was conducted. Of those discharged on DAPT, 96.7% (653/675) of patients received clopidogrel in combination with aspirin. The majority of patients discharged on DAPT remained on DAPT at 1 year (84.4% [539/639]) and a high proportion were still on DAPT at 2 years (53.1% [324/610]), excluding patients who died or were lost to follow-up (Figure 1, Table 1). Considering the total patient population, 68.9% (539/782) were on DAPT at 1 year, and 41.4% (324/782) at 2 years.

Among patients with at least one bleeding event during follow-up (2.7% at 1 year and 4.4% at 2 years), nearly two-thirds remained on DAPT at 1 year (61.1% [11/18]) and at 2 years (61.5% [16/26]). At 2 years, the proportion of patients remaining on DAPT was similar among those who experienced a bleeding event (61.5%) compared with those who experienced a cardiovascular event during follow-up (64.2%).

### 3.2 | Continuation on DAPT by patient subgroup

A higher proportion of STEMI patients were discharged on DAPT compared with NSTEMI-ACS patients (STEMI, 91.5% [311/340] vs NSTEMI-ACS, 82.4% [364/442];  $P < .01$ ). Continuation on DAPT after discharge, however, was comparable between STEMI and NSTEMI-ACS patients. At 1 year, 83.7% (252/301) of STEMI patients and 84.9% (287/338) NSTEMI-ACS patients remained on DAPT ( $P = .68$ ). At 2 years,



**FIGURE 1** Change in percentage of patients remaining on dual antiplatelet therapy (DAPT) from discharge to end of follow-up. Of the patients discharged on DAPT ( $n=675$ ), 84.4% remained on DAPT at 1 year and 53.1% remained on DAPT at 2 years after discharge. DAPT, dual antiplatelet therapy

approximately half of those discharged on DAPT remained on DAPT in both subgroups, excluding those who died or were lost to follow-up (2 years: STEMI, 49.8% [143/287] vs NSTEMI-ACS, 56.0% [181/323];  $P=.13$ ) (Table 1). Looking at each diagnostic group as a whole, 74.1% (252/340) and 42.1% (143/340) of STEMI patients were on DAPT at 1 and 2 years, respectively, compared with 64.9% (287/442) and 41.0% (181/442) of NSTEMI-ACS patients at each time point.

Older patients ( $\geq 65$  years) were less likely to be discharged on DAPT compared with younger patients ( $<65$  vs  $\geq 65$  years: 92.3% [371/402] vs 80.0% [304/380],  $P<.01$ ). Conversely, continuation among those discharged on DAPT was significantly higher in older patients at 2 years ( $<65$  vs  $\geq 65$  years: 49.3% [169/343] vs 58.1% [155/267],  $P=.03$ ) (Table 1).

DAPT at discharge was comparable among nondiabetic and diabetic patients. However, patients with diabetes were significantly more likely to continue with DAPT at 1 year and 2 years compared with nondiabetic patients (nondiabetic vs diabetic: discharge, 87.0% [460/529] vs 84.2% [213/253],  $P=.30$ ; 1 year, 82.2% [361/439] vs 88.9% [176/198],  $P=.03$ ; 2 years, 50.5% [215/426] vs 59.3% [108/182];  $P=.04$ ) (Table 1).

Nearly all patients undergoing percutaneous coronary intervention (PCI) were discharged on DAPT, compared with less than two-thirds of patients who were medically managed (ie, no PCI or coronary artery bypass grafting [CABG]) (PCI vs medically managed: 95.0% [551/580] vs 64.5% [120/186];  $P<.01$ ). In contrast, DAPT continuation was higher among medically managed vs PCI patients at 2 years (63.6% [63/99] vs 51.1% [259/507];  $P=.02$ ) (Table 1). Of 14 patients (one with STEMI and 13 with NSTEMI-ACS) who underwent CABG, only three were on DAPT at discharge, all in the NSTEMI-ACS group, of whom two remained on DAPT at 1 year and one at 2 years.

### 3.3 | Postdischarge event rates by discharge therapy and index event diagnosis

We performed an exploratory analysis of cardiovascular and bleeding event rates according to antiplatelet treatment pattern and diagnosis (Table 2).

All-cause mortality and coronary event rates at 2 years post-discharge (regardless of management) were 5.8% and 6.6%, respectively (Table 2), indicating that increased risk of mortality and adverse coronary events persists beyond the first year following discharge. Although all-cause mortality and coronary event rates were numerically higher in NSTEMI-ACS versus STEMI patients (mortality, 7.5% vs 3.5%; coronary events, 7.9% vs 5.0%), this was not statistically significant (Table 2).

Mortality rates and coronary event rates at 2 years were numerically lower in patients managed with DAPT versus SAPT (mortality, 5.5% vs 6.8%; coronary events, 6.3% vs 10.2%), irrespective of index event diagnosis, but the difference was not statistically significant, with the exception of coronary events among STEMI patients managed with DAPT versus SAPT (4.8% vs 18.2%,  $P=.028$ ).

Across the total population, overall bleeding event rates were 2.7% at 1 year, and 4.4% at 2 years, and were similar among STEMI and NSTEMI-ACS patients (4.7% vs 4.1%, respectively). At 2 years, rate of bleeding that required hospitalization during follow-up were low (1.4%). Overall bleeding event rate did not differ significantly between DAPT and SAPT (4.0% [27/678] vs 3.4% [2/59], respectively;  $P=.88$ ) (Table 2).

## 4 | DISCUSSION

In this analysis of data from patients with ACS enrolled in EPICOR Spain, a high proportion of patients continued with DAPT beyond the recommended 12-month period following discharge from hospital, and remained on DAPT until the end of the 2-year follow-up period (53.1%). Moreover, nearly two-thirds of patients who experienced at least one bleeding event while on treatment (61.5%) remained on DAPT at the end of follow-up.

The most recent ESC guidelines for management of NSTEMI-ACS patients state that P2Y<sub>12</sub> inhibitor administration beyond 12 months may be considered, taking into account ischemic and bleeding risks.<sup>2</sup> Real-world studies of DAPT duration among ACS survivors are important for understanding physician-based decisions in accordance with guidelines, but are lacking in the literature, in particular those conducted in Spain. The PARIS (Patterns of nonadherence to Antiplatelet Regimens In Stented patients) registry investigated DAPT patterns in post-PCI patients and reported that 42.0% of patients were receiving DAPT at 2 years.<sup>16</sup> Similarly, the NHLBI (National Heart, Lung and Blood Institute) registry found that 53% of patients treated with drug-eluting stents remained on DAPT 2 years after PCI.<sup>17</sup> However, both studies limited analyses to PCI-treated patients and lacked information on DAPT duration and bleeding events during follow-up. We addressed these questions and have

**TABLE 1** DAPT duration by subgroup

Group	Patients discharged on DAPT		Continuation with DAPT after discharge, n/N (%)			
	n/Total (%)	P value	1 year	P value	2 years	P value
All	675/782 (86.3)		539/639 (84.4)		324/610 (53.1)	
Index event diagnosis						
STEMI	311/340 (91.5)		252/301 (83.7)		143/287 (49.8)	
NSTE-ACS	364/442 (82.4)	.0002	287/338 (84.9)	.6793	181/323 (56.0)	.1249
Age group						
<65 years	371/402 (92.3)		298/356 (83.7)		169/343 (49.3)	
≥65 years	304/380 (80.0)	<.0001	241/283 (85.2)	.6160	155/267 (58.1)	.0311
Diabetic status						
Diabetic	213/253 (84.2)		176/198 (88.9)		108/182 (59.3)	
Nondiabetic	460/529 (87.0)	.2960	361/439 (82.2)	.0326	215/426 (50.5)	.0447
Management						
Medical only	120/186 (64.5)		96/112 (85.7)		63/99 (63.6)	
PCI only	551/580 (95.0)	<.0001	440/523 (84.1)	.6749	259/507 (51.1)	.0221

DAPT, dual antiplatelet therapy; NSTE-ACS, non-ST-elevation acute coronary syndrome; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

n=number of patients on DAPT (aspirin and P2Y<sub>12</sub> inhibitor); Total=total number of patients enrolled; N=patients discharged on DAPT excluding those who died or were lost to follow-up. Across the total population, 21 patients had died and 15 were lost to follow-up at 1 year, and 35 patients had died and 30 were lost to follow-up at 2 years.

shown DAPT continuation beyond 1 year to be high among a broad range of patients with ACS in Spain, irrespective of management strategy and including those who experienced on-treatment bleeding. The proportion of patients in Spain remaining on uninterrupted DAPT at 2 years (53%) is comparable to the results shown for the total EPICOR cohort (57%).<sup>15</sup>

Between-country differences in the management of ACS have been described.<sup>18,19</sup> In addition, the rate of DAPT discontinuation in the total EPICOR population was found to differ significantly by country.<sup>15</sup> Thus, country-specific analyses are important to highlight a potential gap between regional guidelines and current practice. A decade ago, the DESCARTES (Descripción del Estado de los Síndromes Coronarios Agudos en un Registro Temporal ESpañol) study found that only 32.0% of NSTE-ACS patients were discharged on clopidogrel.<sup>20</sup> However, in-hospital DAPT and discharge on clopidogrel were strongly associated with improved 6-month survival. In EPICOR Spain, 86.3% of all patients with ACS were discharged on DAPT, highlighting an improvement in ACS management in Spain to align with current ESC guidelines.

A significant proportion of patients experience adverse coronary events beyond the first year following ACS.<sup>5,6,21</sup> While our analysis

was exploratory in nature, as dictated by the constraints of an observational study, we confirmed the persistence of ischemic risk post-ACS in EPICOR Spain patients: all-cause mortality continued to accumulate after the first year following discharge (1 year, 3.7%; 2 years, 5.8%). Mortality rates were similar to those reported by the GRACE (Global Registry of Acute Coronary Events) investigators at 2 years and were in line with overall EPICOR results and those reported in the recent DIOCLES (Descripción de la Cardiopatía Isquémica en el Territorio Español) registry in Spain.<sup>14,15,22–24</sup>

Increased bleeding is the primary risk associated with more potent or prolonged antiplatelet therapy and is an important consideration when deciding treatment.<sup>25</sup> Despite a high rate of DAPT continuation observed in this study, overall bleeding rates were low (1 year, 2.7%; 2 years, 4.4%) and in line with those reported in the recent CardioCHUS registry (3.2%).<sup>26</sup> Bleeding requiring hospitalization (1.4%) was several-fold lower than the rate of adverse coronary events (6.6%) at 2 years, in agreement with Rapsomaniki et al. (2016), who reported a country-dependent hospitalized bleeding risk of 2.7–4.0% versus a combined risk of death, myocardial infarction, or stroke of 24.4–28.9% in 1-year myocardial infarction survivors at 3 years.<sup>21</sup>

**TABLE 2** Event rates at 2 years by index event diagnosis and discharge medication

Event by AMP group <sup>a</sup>	Patients, n/N (%)					
	All	P value	STEMI	P value	NSTE-ACS	P value
Overall mortality at 2 years	45/782 (5.8)		12/340 (3.5)		33/442 (7.5)	
DAPT	37/678 (5.5)		9/313 (2.9)		28/365 (7.7)	
SAPT	4/59 (6.8)	.6220	1/11 (9.1)	.2088	3/48 (6.3)	.7398
Coronary events at 2 years	52/782 (6.6)		17/340 (5.0)		35/442 (7.9)	
DAPT	43/678 (6.3)		15/313 (4.8)		28/365 (7.7)	
SAPT	6/59 (10.2)	.2034	2/11 (18.2)	.0288	4/48 (8.3)	.8495
Overall bleeding events at 23 months	34/782 (4.4)		16/340 (4.7)		18/442 (4.1)	
DAPT	27/678 (4.0)		14/313 (4.5)		13/365 (3.6)	
SAPT	2/59 (3.4)	.8848	0/11 (0.0)	N/A	2/48 (4.2)	.8335

<sup>a</sup>Values exclude patients who were not managed on either DAPT or SAPT. DAPT includes patients managed on  $\geq 2$  antiplatelet agents.

AMP, antithrombotic management pattern; DAPT, dual antiplatelet therapy; NSTE-ACS, non-ST-elevation acute coronary syndrome; PCI, percutaneous coronary intervention; SAPT, single antiplatelet therapy; STEMI, ST-elevation myocardial infarction.

n=number of patients experiencing event; N=total number of patients within each respective subgroup.

A numerically lower incidence of coronary events over a 2-year period was observed with DAPT compared with SAPT. This was largely driven by a decrease in the rate of coronary events in STEMI patients treated with DAPT, but it should be noted that event rates with SAPT in this study were low. A number of randomized trials and meta-analyses have established a benefit in extending the duration of DAPT beyond 1 year in patients with coronary artery disease.<sup>8,27</sup> The DAPT (dual antiplatelet therapy) trial showed a benefit of 30 months versus 12 months of combined aspirin and P2Y<sub>12</sub> inhibition for reducing major adverse cardiovascular events in patients undergoing PCI, at the expense of increased moderate or severe bleeding and an increase in total mortality.<sup>7</sup> Similarly, PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin—Thrombolysis in Myocardial Infarction 54) showed that extended ticagrelor therapy (on background aspirin) in patients with myocardial infarction 1–3 years prior reduced major adverse cardiovascular events by 16% at 3 years, with a concurrent increase in TIMI (Thrombolysis in Myocardial Infarction) major bleeding.<sup>9</sup> Ticagrelor is now approved by the US Food and Drug Administration Agency and the European Medicines Agency for the treatment of postmyocardial infarction patients beyond the first year.<sup>28</sup> Moreover, a recent statement released by the American College of Cardiology/American Heart Association now supports continued DAPT beyond 1 year in STEMI and NSTE-ACS patients treated with PCI or medical therapy, without a high risk of bleeding.<sup>29</sup>

In PEGASUS-TIMI 54, patients with additional ischemic risk factors, such as those with renal dysfunction, peripheral artery disease, diabetes, or multivessel disease, experienced a greater absolute risk reduction with prolonged versus standard DAPT, compared with patients without additional risk factors.<sup>10,30–32</sup> Similarly, Yeh et al. showed that the benefit gained from prolonged DAPT is greater among PCI patients with additional ischemic risk factors.<sup>12</sup> Few studies, however, have investigated the relationship between patient's risk profile and DAPT duration in an unselected population. We showed here that patients with additional ischemic risk factors (age >65 years, diabetic status, or medically managed) were significantly more likely to remain on DAPT at 2 years postdischarge. This suggests a move toward a more individualized antiplatelet regimen for patients with ACS in Spain, based on risk stratification. Further analyses to align DAPT management patterns with cardiovascular and bleeding event rates will aid in this approach.

#### 4.1 | Limitations

As with all observational studies, the potential for bias and confounding precludes the establishment of a causal relationship between prolonged DAPT and improvement in cardiovascular outcomes. Additionally, there may be confounding factors in the distribution of baseline characteristics.



We consider the analysis of cardiovascular and bleeding events to be exploratory due to the low number of overall events. Further analysis with a larger patient population is needed to confirm conclusions.

Bleeding and coronary events were not classified according to standard definitions, which limits comparability to other studies. Only events confirmed by physicians with full event report were included in the analysis, which may underestimate the total number of coronary events. Conversely, telephone call follow-up may have led to an overestimation of the proportion of patients on remaining DAPT after discharge. Calls may have prompted patients to continue their medication longer than they would of their own accord, or alternatively, patient responses may not have aligned with actual medication taken.

## 5 | CONCLUSIONS

The EPICOR Spain study results support the guideline recommendations for patients with ACS to be discharged on DAPT, regardless of initial management strategy. Physicians participating in EPICOR Spain prioritized ischemic risk over bleeding risk when deciding DAPT duration, taking into account the patient's risk profile. A lower rate of adverse coronary events was observed with DAPT compared with SAPT treatment, without a concurrent increase in the risk of bleeding. This confirms recent studies that show patients at high ischemic risk and without high bleeding-risk benefit from DAPT beyond the first year following ACS.

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## CONFLICT OF INTEREST

Alfredo Bardají has received honoraria for advisory boards from AstraZeneca. Manuel Leal is an employee of AstraZeneca. Vicente Arrarte has received advisory/consulting fees from AstraZeneca, Boehringer, and MSD. Xavier Garcia-Moll has received advisory/consulting fees from Amgen, AstraZeneca, Bayer, Böehringer, Daichii-Sankyo, Ferrer, Menarini, MSD, Rovi, Sanofi, and Servier. Leopoldo Pérez de Isla has received honoraria for advisory boards from AstraZeneca. Héctor Bueno has received advisory/consulting fees from Abbott, AstraZeneca, Bayer, BMS-Pfizer, Daichii-Sankyo, Eli-Lilly, Ferrer, Menarini, Novartis, Sanofi, and Servier and research grants from AstraZeneca.

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