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Persistence with dual antiplatelet therapy after percutaneous coronary intervention for ST-Segment-Elevation Acute Coronary Syndrome. A population-based cohort study

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Persistence with dual antiplatelet therapy after percutaneous coronary intervention for ST-Segment-Elevation Acute Coronary Syndrome. A population-based cohort study

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ABSTRACT

Objectives: International guidelines recommending dual antiplatelet therapy (DAPT) 12 months in patients with ST-elevation acute coronary syndrome (STEACS) undergoing percutaneous coronary intervention (PCI) were published in year 2012. The aims of the study were to describe trends in 12-month persistence with DAPT between 2010 and 2015 and to evaluate its relationship with variability in the recommended DAPT duration among PCI hospitals.

Design: Observational study based on region-wide registry data linked to pharmacy billing data for DAPT follow up.

Setting. All PCI hospitals (10) belonging to the AMI-Code network in Catalonia (Spain)

Participants: 10,711 STEACS patients undergoing PCI between 2010 and 2015 were followed up.

Primary and secondary outcome measures: Primary outcome was at least 12 month persistence with DAPT throughout the study period. 12-months recommendation of DAPT in the hospital discharge report and interhospital variability in the rate of 12-month recommendation were defined as secondary outcomes.

Results: The proportion of patients on-DAPT at 12 months increased from 58% (56-60) in 2010 to 73% (71-75) in 2015. Interhospital variability in the rate of 12-month recommendation decreased from ICC 69% (42-87) in 2010 to 37% (18-61) in 2015. Recommending 12 months DAPT at discharge from the PCI hospital was a major determinant of adherence to the 12-month schedule, OR=6.28 (5.28-7.47).

Conclusion: Adherence to 12-month DAPT has increased since publication of clinical guidelines. Even though most patients were discharged on DAPT, only 73% with potential indication were on-DAPT 12 months after PCI. A guideline-based

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recommendation at PCI hospital discharge had a substantial impact on persistence

with DAPT. Establishing evidence-based, common prescribing criteria across hospitals

in the AMI-network would favour adherence and reduce variability.

Strengths and limitations of this study

- The study describes the trends in persistence with DAPT during 2010-2015 in a

  region-wide unselected comprehensive cohort of patients using administrative

  data linked to a clinical registry

- It also evaluates the impact of the DAPT duration recommended at the PCI

  hospital discharge on 12-months persistence

- Limitations of using observational registry data include the possibility of coding

  errors and the inability to accurately identify specific contraindications for

  treatment or other patient characteristics that might be relevant for the study

  aims

- The use of pharmacy refill data as a proxy of patients adherence and

  persistence has also limitations which have been extensively described

Study funding

Competing interest statement

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Introduction

The need of dual antiplatelet therapy (DAPT) combining aspirin and an ADP-receptor blocker for at least 12 months in patients with ST-elevation acute coronary syndrome (STEACS) undergoing percutaneous coronary intervention (PCI) is well established and was incorporated into clinical guidelines in 2012[1,2].

Adherence of patients to this strategy is crucial to ensure its efficacy. Adherence to medication is usually defined[3] as the extent to which patients take medications as prescribed by their health care providers and persistence is defined as time from initiation to discontinuation of a therapy. Patients' persistence with DAPT may be influenced by several factors but will depend strongly on whether they ultimately receive a correct prescription from their physicians in the primary care setting. Patients may receive recommendations from various health providers at different stages of their process of care, from the interventionist cardiologist to their primary physician. It could be hypothesized that the last would tend to relay on the recommendation of the more specialized health professional. Thus, one potential determinant of patient's persistence with DAPT for at least 12 months is the instructions provided in the discharge report of the hospital where the patient was attended during the acute phase.

In Catalonia, an autonomous region of Spain, the acute care of STEACS is organized through a region-wide network, the Acute Myocardial Infarction (AMI) Code, to derive patients with suspected STEACS to one of the 10 reference hospitals with PCI capability. Performance of the AMI Code is prospectively and exhaustively registered[4,5], providing an appropriate tool for quality evaluation. The Catalan

Health Information System systematically registers, among other, data on pharmacy refills. Pharmacy billing data, although indirect, is an accepted method for evaluating persistence with treatment in large patient cohorts[3,6].

The aims of the present study were: first, to describe persistence with DAPT in patients with STEACS undergoing PCI from 2010 to 2015; second, to evaluate the impact of the DAPT duration recommended at the PCI hospital discharge on patients' persistence with treatment for at least 12 months as recommended in clinical guidelines. As a main determinant of persistence, determinants and variability of discharge recommendation patterns will be also analysed as a secondary objective.

Methods

Data sources

Data were obtained through the Public Data Analysis for Health Research and Innovation Program (PADRIS). The PADRIS allows access to information from different sources on public healthcare usage for the population of Catalonia linked at the patient level with warranted accomplishment of ethical principles. Specifically, for the present study we linked data of the pharmacy billing registry with the AMI Code Registry. The AMI Code registry was launched in 2010 to evaluate performance of the AMI Code [4,5]. Exhaustiveness and quality of data is assessed periodically (see supplemental methods for details). The database belongs to the Catalan Department of Health and includes demographic, clinical, and therapeutic data. It conforms to the ethical and legal requirements for research purposes. The study obtained ethics approval from the Vall d'Hebron Clinical Research Ethics Committee.

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The registry was completed for the purpose of the present analysis with retrospective collection of additional specific data: diseased vessels, responsible vessel, stent type, number of stents. The recommendation of antithrombotic drugs was also collected *ad hoc* for the study from the discharge report. The recommendation of DAPT was defined as the recommendation of Acetylsalisilic acid (ASA) and either clopidogrel, prasugrel or ticagrelor for specified periods. If the recommended duration of DAPT was not specified, the discharge recommendation pattern was classified as "unspecified". A local investigator at each center performed the specific retrospective data collection.

History of major haemorrhage, neoplasia, renal disease, heart failure, peripheral arterial disease and atrial fibrillation, were obtained from minimum basic data set (MBDS) diagnoses coded in hospitalization episodes occurring in the previous three months before index hospitalization. Major haemorrhage was defined as: a diagnosis of digestive bleeding in any diagnostic position (primary or secondary) together with a procedure code for endoscopic treatment or for transfusion of blood products, or a diagnosis of haemorrhagic stroke, or a diagnosis of intraocular haemorrhage, or a diagnosis of other types of haemorrhage together with a procedure code for transfusion of blood products. Major ischemic events (AMI or stroke) and major haemorrhage during the 12 months following the index episode were obtained in the same way. Mortality during the 12 months following the index episode was obtained from the insured registry status.

Drug treatment during the 12-month post-discharge follow up was obtained from the pharmacy billing registry. ICD9 and ATC codes used for the identification of study variables are listed in the supplemental tables.

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Study population

All consecutive patients who survived a STEACS between January 2010 and December 2015, received primary or post fibrinolysis PCI in one of the 10 reference hospitals of the AMI Code network and were discharged alive and/or survived at least one month after AMI with a discharge report providing instructions on treatment prescriptions were included. New episodes of STACS occurring to the same patients during the study period were only accounted as follow up events. Patients with likely contraindication for dual antiplatelet therapy (history of bleeding or neoplasm in the three months prior to the index episode and patients requiring anticoagulation) were excluded.

Persistence with treatment

DAPT was defined as the concomitant of ASA and a $P2Y_{12}$ antagonist. Persistence with DAPT was estimated by identification of consecutive months with pharmacy refills with one container of each agent in the 12-month period after hospital discharge. Because pharmacy billing is registered in a monthly basis and the exact day of dispensation is unknown, we considered that a monthly dispensation until at least month 11 after the index episode would approximate a 12-months treatment period. If more than one container were dispensed in one month, the excess containers were pulled along the following months. Non-persistence was defined as either discontinuation or a break in therapy of at least two months after pulling along the excess containers. To describe persistence over the whole study period we estimated the proportion of patients alive who were on treatment on each month[7].

The first primary outcome was a patients' persistence with DAPT for 12 months following discharge (or in other words, patients withdrawing both agents from the pharmacy until at least month 11).

Statistical analysis

To evaluate trends in 12 months persistence with DAPT we included the calendar year when the patient was discharged in logistic regression models. To evaluate the impact of the DAPT duration recommended in the discharge report, we included the recommendation pattern (≤1 month, 2 to 11 months, ≥ 12 months or unspecified) in a second step.

Additionally, we assessed the determinants (including calendar year of the episode) of a DAPT recommendation for at least 12 months with logistic regression models.

In both sets of analyses we took into account the clustered structure of data with patients being treated and, most importantly, with medications being recommended in different hospitals, by introducing random effects in the logistic regression models.

As recommendation is subject to interhospital variability we estimated variability measures for random effects. We tested whether models including random intercept for hospital and random slopes for each independent variable were significant using a deviance –based test of hypothesis.

Variable selection for multilevel modelling was based on the bivariate associations with the rate of each dependent variable. Candidate individual variables were those described in tables 1 and 3. Type of antiplatelet drug was not included in the multivariable analysis because it was highly correlated with the year of episode, as new antiplatelet agents (ticagrelor and prasugrel) were introduced later during the study

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period. We retained in the final model all variables with a p value<0.2 for the bivariate association with the dependent variable.

To measure the magnitude of hospital level variance in the odds of patients being recommended DAPT for at least 12 months we estimated the intraclass correlation (ICC) and the median odds ratio (MOR) for multilevel logistic models. The ICC can be interpreted as the proportion of total variance in the outcome that is attributable to the hospital level variability. The MOR is defined as the median value of the odds ratio between the hospital at higher risk and the hospital at lower risk when randomly picking out two hospitals. In the present study, the MOR estimates the extent to which the individual odds of being recommended DAPT for 12 months is determined by the hospital where the procedure is performed. If the MOR equals one, there would be no differences between hospitals. If the MOR is large, hospital differences are relevant to understand variations in individual probability of receiving a 12-month recommendation.

Multilevel logistic regression models were estimated assuming independent covariances using the xtmelogit procedure in STATA 14. Methods and formulas to compute indexes of interhospital variability and different measures of clustering were obtained from Merlo et al[8].

Sensitivity analyses

As a substantial proportion of patients were returned to their reference hospital and whether the DAPT duration recommendation was changed at discharge from the second hospital was unknown, we performed sensitivity analyses excluding these patients. Additionally, because ischemic and haemorrhagic events occurring during

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follow up would change the prescription pattern, sensitivity analyses were also performed by excluding patients suffering any vascular event during follow up.

Results

After excluding patients with likely contraindication for, we identified 10,711 STEACS patients undergoing PCI who were potential candidates to receive DAPT for at least 12 months and were discharged alive from the PCI hospitals or survived for at least one month (Figure 1). 631 (5.9%) patients experienced an ischemic major event (AMI or stroke) within 12 months after the index episode, 100 (0.9%) had a major haemorrhage and 280 (2.6%) died between one and 12 months after the index episode.

The rate of patients on-DAPT after discharge was 91% (95% CI: 90-91) without relevant differences between years (figure 2). Persistence with DAPT for 12 months significantly increased from 58% (56-61) in 2010 to 73% (71-75) in 2015. The larger increase in 12-month persistence was observed between 2014 (64% [62-66]) and 2015, two years after the publication of clinical guidelines. There was a growing rate of prasugrel and ticagrelor dispensation along the study period (figure 3).

Table 1 shows characteristics of study patients depending on persistence with DAPT for one month or less, 2 to 11 months or 12 months or more. The majority (76%) of patients (4740/6272) with an explicit recommendation of 12 months DAPT or more at PCI hospital discharge were on-DAPT at 12 months. This proportion was only 27% (462/1735) in the subgroup of patients with a shorter recommended duration. Among patients without a specified recommended time at discharge from the PCI hospital, 60% (1399/2332) were on-DAPT at 12 months. In multivariate analysis (Table 2),

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determinants of persistence with DAPT for at least 12 months were hypercholesterolemia, previous revascularization, having two or more diseased vessels and left anterior coronary disease, higher number of stents implanted and receiving drug eluting stents. An increased odd of persistence was observed in year 2015 but this association disappeared when including the prescription pattern. A longer hospital stay was related to a lower probability of 12 months persistence with DAPT. As expected, having an ischaemic event would increase DAPT duration, while suffering a haemorrhagic event would decrease it. Explicit instructions at the discharge report of DAPT for at least 12 months was one of the major determinants of 12-month persistence (OR=6.28; 95%CI: 5.28-7.47), and also patients with unspecified recommendation had an increased odds of persistence as compared with patients with a recommendation of less than 12 months.

Results of sensitivity analyses, excluding patients with ischemic or haemorrhagic events during follow up, or excluding patients that were transferred to another centre after PCI were similar to the main analysis.

The rate of explicit DAPT recommendation for at least 12 months in the hospital discharge reports was 51% (49-53) in 2010 and increased to 77% (75-79) in 2015 (supplemental figure). Interhospital variability in the rate of 12-month DAPT recommendation (figure 3) was 69% (42-87) in year 2010, indicating that half of the variability was due to variation between hospitals, and it decreased to 37% (18-61) in 2015, as indicated by the ICC calculated for each year.

Table 3 shows characteristics of study patients depending on the DAPT duration recommended at hospital discharge. In multivariate analysis (table 4) the strongest determinant of a higher rate of recommendation for ≥ 12 months was receiving a drug

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eluting stent. Other determinants were. There was also a strong increase in the rate of 12 months prescription in with year. For both random effect were significant, meaning that the association with drug eluting stent or with year vary between hospitals. When patients derived to their reference hospital were excluded results were similar.

Discussion

According to published guidelines, all STEACS patients undergoing PCI without contraindication should be on DAPT after 12 months unless an event occurs that precludes continuing with treatment. In this observational region-wide study we have found an increase in the proportion of patients on-DAPT at 12 months from 58 to 73% in the period from 2010 to 2015.

We also found a high variability between hospitals in the adherence to guidelines when recommending DAPT for at least 12 months which leads to differences between hospitals in the rate of patients persisting with the recommended DAPT one year time span. The progressive increase in the overall rate of adherence to guidelines was accompanied by a substantial reduction of interhospital variability.

Adherence of patients to 12-month DAPT assessed is strongly related to the instructions given at the PCI hospital discharge, as we observed a lower rate of 12-month persistence in patients receiving a discharge DAPT recommendation for less than 12 months. Although a causal direct relationship between the established recommendation in the more specialised setting and the final prescription at the primary care setting cannot be stated on the basis of observational data, this finding suggests that prescribing physicians strongly rely on the first recommendation specified at the discharge report in the PCI hospital. Therefore, hospital cardiologists

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should be kept aware of their impact and encouraged to be clear and specific enough when providing DAPT time recommendations in the discharge report form.

A number of factors have been described to contribute to underprescription[9]. The recommendation of DAPT for at least 12 months following STEACS[1,2] was based on the duration of follow up of randomised clinical trials designed for other purposes and[10–12], although a 12-month treatment seemed reasonable [13], no randomized studies have been performed to date aimed specifically at comparing 12 months DAPT with shorter in STEACS patients receiving PCI and thus this recommendation might well be seen as somehow arbitrary by some prescribers.

In 2015 the need for long term DAPT was reinforced by the recommendation of extended DAPT beyond 12 months in patients with ACS receiving drug eluting stents[14–16], but still safety concerns might induce some prescribers to be reluctant to prolong DAPT, especially in patients with higher complexity[17]. Safety concerns might also explain the high proportion of discharge reports with non-specified DAPT period, which deserved special attention in our analyses. Cardiologists might be reluctant to prescribe a specific duration of DAPT maybe fearing about the emergency of events that increase the haemorrhagic risk at some point after discharge, thus relaying on the follow up that will be made at the ambulatory setting. Our results showing a high degree of persistence for patients without a specification of DAPT time point out to the fact that this decision is not necessarily "incorrect", and that health providers coming later in the process of care are probably doing their job.

We might wonder whether the observed high variability between hospitals in the instructions provided about DAPT duration actually reflects suboptimal quality of care or confusion in the interpretation of international guidelines. In fact, although 2012

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ESC guidelines state that DAPT must be continued for 12 months after STEACS with a class of recommendation I, the level of evidence was established as C[1]. Thus, there was general agreement that a minimum of 12 months of DAPT is beneficial but based only on a consensus of experts or observational studies. Moreover, it is literally stated that the given recommendation on DAPT duration should be "with a strict minimum of 1 month for patients receiving BMS and 6 months for patients receiving DES", with Class IC and IIb respectively. This, which ultimately reflects the lack of clinical trials aimed to answer the specific question about DAPT duration, could have induced a perception of arbitrariness leading to variability in clinical practice.

Regardless the level of the evidence, one would expect that a Class I recommendation should be uniformly followed by clinicians. Moreover, as patient characteristics did not substantially differed across hospitals, we should expect a lower variability between hospitals. A large variation in individual country practices concerning the pattern of DAPT duration after ACS has been described, suggesting that local systems are strong drivers of DAPT duration[18]. These findings may imply that there is still room for improvement in the quality of care of STEACS patients and that quality improvement programs, whose efficacy and cost-effectiveness are still under evaluation, could be useful to reduce variability in clinical practice[19]. This is of prime importance in the context of the prescription of DAPT duration after ACS in which the clinician-driven variability in prescription patterns adds to the different levels patients' adherence[18].

Higher atherosclerotic burden and increased ischemic risk was associated to better persistence with DAPT. The need for 12-month DAPT schedules in patients treated with drug eluting stents is clearly perceived by physicians but the magnitude of this association varies largely between hospitals. This means that, even in clear indications,

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there are different levels of adoption of emerging clinical recommendations in hospitals belonging to the same AMI network.

It is also apparent from our data that the speed of adoption of clinical guidelines is different among hospitals and that an acceptable and generalised level of adherence is only reached after two years of implementation. Similar trends have been found in other contexts and earlier periods[20–25] reporting DAPT use between 60-80% at discharge and between 25-75 % at one year. In this sense, together with other quality improvement initiatives, the use of population-based registries to provide audit and feedback could be useful to promote quicker and smoother adoption of clinical practice guidelines[26].

There are a number of assumptions that might be questionable: The complete process of care and the definite prescription at the ambulatory setting is poorly known for individual patients and has not been considered in this study. Changes in treatment prescription might be justified by the patients' varying conditions during follow up. We assume that hospital recommendation influences final prescription, and consequently, final adherence, but it can also be that both "prescribers" facing the same patient share the same criteria for prescription. I.e. the hospital cardiologist might have decided to recommend DAPT for a shorter period to an elderly patient with other comorbidities and suboptimal quality of life due to mild digestive symptoms, even if her objective bleeding risk is not high; similarly, the primary physician or the cardiologist at the primary care setting might have also decided to be less aggressive for the same reasons, even without being influenced by the recommendation of the first. This would probably explain a large amount of the strong relationship between

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hospital recommendation and pharmacy dispensation. Moreover, although effects were adjusted for patient characteristics and vascular events during follow up, there might be other unmeasured reasons for deciding upon a shorter DAPT period facing an individual patient.

In addition, the recommendation at PCI hospital discharge may not coincide with the final hospital prescription in patients derived to another reference hospital after PCI. However, results of sensitivity analyses excluding these patients did not differ substantially from the results of the main analyses.

The study was aimed to ascertain adherence to guidelines in hospital recommendation and its impact on patients' persistence with DAPT and thus, we did not measure the impact of adherence in terms of clinically relevant results which will be analysed further. Similarly, the study was not specifically aimed at a deep assessment of determinants of adherence. This requires a detailed examination of the social context and a detailed assessment of individual psychological factors[27].

Conclusion

From 2010 to 2015 there has been a substantial increase in the rate of STEACS patients persisting for at least 12 months has also increased but there is still a large variability between hospitals in prescription and a subtantial proportion of patients who discontinue DAPT before 12 months.

We have shown that instructions given at the PCI hospital discharge strongly influence persistence, thus establishing common and rational prescribing criteria between hospitals in the STEACS-network may favour patients adherence and persistence with scheduled prescriptions and also reduce variability in clinicians´ practices.

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Author contributions

IFG, AR, JRM conceived and designed the study; AR, JRM and MTF participated in the

acquisition and analysis of data; HTM, SR, CL, MC, SH, CTQ, JGP, JAGH and MM were

responsible for data acquisition in their respective hospitals; AR, IFG, JRM, GO, AR, JIP,

JM and DGD were involved in the interpretation of results; AR and IFG wrote the

manuscript and all other authors revised it critically and approved its final version

The AMI-Code Registry Investigators (listed below) contribute to the functioning of the

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Figure legends

Figure 1. Patients flow

Figure 2. Persistence with DAPT from discharge to 12 months by year of the episode.

Figure 3. Temporal trend of interhospital variability in 12 months DAPT

recommendation at the PCI hospital, measured as the percentage of variance

explained by the hospital level (intraclass correlation and 95 % CI). Vertical dashed line

indicates publication of guidelines.

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Table 1. Characteristics of study patients according to DAPT persistence during follow up in patients surviving for 12 months.

Patient Characteristics	No DAPT or ≤1 month (n=1692)	DAPT 2-11 months (n=2037)	DAPT ≥12 months (n=6610)	P for trend
Age, mean (SD)	61.2 (13.4)	61.2 (13.1)	61.2 (12.4)	0.693
Women	362 (21.4)	421 (20.7)	1325 (20.1)	0.202
Weight*(1154 missing)	77.5 (13.4)	78.5 (14.1)	78.5 (13.8)	0.023
Cardiovascular risk factors				
Current smoker	814 (48.1)	970 (47.6)	3057 (46.3)	0.077
Diabetes mellitus	295 (17.4)	360 (17.7)	1303 (19.7)	0.011
Hypercholesterolemia	589 (34.8)	713 (35)	2690 (40.7)	<0.001
Hypertension	724 (42.8)	912 (44.8)	3158 (47.8)	<0.001
History				
Chronic Hepatic Disease	23 (1.4)	25 (1.2)	56 (0.9)	0.025
Previous acute myocardial infarction	114 (6.7)	157 (7.7)	576 (8.7)	0.005

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Stroke or transient ischemic attack	50 (3)	51 (2.5)	172 (2.6)	0.526
Previous percutaneous revascularization	77 (4.6)	120 (5.9)	487 (7.4)	<0.001
Previous surgical revascularization	6 (0.4)	15 (0.7)	86 (1.3)	<0.001
Chronic renal impairment	77 (4.6)	110 (5.4)	320 (4.8)	0.913
Previous diagnosis of chronic heart failure	116 (6.9)	157 (7.7)	585 (8.9)	0.004
Previous diagnosis of peripheral arterial disease	65 (3.8)	88 (4.3)	276 (4.3)	0.913
Previous antiplatelet treatment	228 (13.5)	303 (14.9)	1034 (15.6)	0.026
Two or more diseased vessels	578 (34.2)	706 (34.7)	2742 (41.5)	<0.001
Vessel responsible				
Left anterior coronary artery	601 (35.5)	737 (36.2)	2882 (43.6)	<0.001
Right coronary artery	710 (42)	889 (43.6)	2513 (38)	<0.001

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Circumflex coronary artery	229 (13.5)	281 (13.8)	843 (12.8)	0.256
Left main Coronary artery	13 (0.8)	8 (0.4)	59 (0.9)	0.240
No. of treated vessels per patient, mean (SD)	1.01 (0.2)	1.04 (0.2)	1.06 (0.3)	<0.001
Stent	1458 (86.2)	1889 (92.7)	6208 (93.9)	<0.001
Bare metal	1255 (74.2)	1542 (75.7)	3651 (55.2)	<0.001
Drug-eluting	211 (12.5)	364 (17.9)	2716 (41.1)	<0.001
No. of stents per patient, mean (SD)	1.04 (0.6)	1.12 (0.6)	1.20 (0.7)	<0.001
Admission Features				
Admission days; mean (SD); (676 missing values)	8.2 (10.8)	6.9 (6)	6.7 (5.1)	0.004
Discharged home from the PCI* hospital	1128 (66.7)	1132 (55.6)	3686 (55.8)	<0.001
DAPT† duration prescribed at PCI hospital discharge				
No DAPT or ≤1 month	561 (33.2)	316 (15.5)	298 (4.5)	<0.001

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2-11 months	172 (10.2)	215 (10.6)	173 (2.6)
≥ 12 months	537 (31.7)	995 (48.9.9)	4740 (71.7)
Unspecified	422 (24.9)	511 (25.1)	1399 (21.2)

All numbers indicate n (column percentages) unless otherwise stated. *PCI: percutaneous coronary intervention; †DAPT: dual antiplatelet therapy

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Table 2. Determinants of 12 month persistence with DAPT in patients surviving for 12 months.

	Model 1	Model 2	Model 3	Model 4
	N=10,412	N= 10,412	N=9,740	N=5,947
	N centers = 10	N centers = 10	N centers = 10	N centers = 10
Obs per center: average (min-max)	**1041 (360-2290)**	**1041 (360-2290)**	**974, (330-2136)**	**595 (153-1076)**
Hypercholesterolemia	1.20 (1.10-1.32)	1.21 (1.10-1.33)	1.23 (1.12-1.36)	1.15 (1.01-1.31)
Previous revascularization	1.26 (1.05-1.51)	1.22 (1.02-1.46)	1.25 (1.04-1.52)	1.54 (1.19-2.00)
Two or more diseased vessels	1.21 (1.11-1.33)	1.19 (1.08-1.30)	1.17 (1.06-1.29)	1.15 (1.01-1.31)
Left anterior coronary artery	1.13 (1.03-1.24)	1.12 (1.02-1.23)	1.14 (1.04-1.26)	1.04 (0.92-1.19)
Drug eluting stent	3.21 (2.88-3.59)	2.17 (1.93-2.43)	2.21 (1.96-2.49)	2.11 (1.80-2.47)
Number of stents	1.19 (1.11-1.28)	1.24 (1.15-1.33)	1.26 (1.16-1.36)	1.37 (1.24-1.51)
Discharged home	0.86 (0.77-	0.95 (0.87-	0.93 (0.85-	N/A

	0.93)	1.05)	1.03)	
Hospital stay (for each day increase)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.98)
Ischaemic event in follow up	2.15 (1.74-2.66)	2.33 (1.87-2.90)	N/A	3.45 (2.47-4.80)
Hemorragic event in follow up	0.42 (0.26-0.67)	0.38 (0.24-0.62)	N/A	0.24 (0.17-0.34)
DAPT duration recommended				
No DAPT* or ≤ 1 month		1 (ref.)	1 (ref.)	1 (ref.)
1-11 months		1.24 (0.97-1.59)	1.26 (0.97-1.63)	1.81 (1.32-2.50)
≥12 months		6.28 (5.28-7.47)	6.54 (5.45-7.84)	8.41 (6.68-10.58)
unspecified		3.38 (2.84-4.02)	3.54 (2.95-4.24)	4.07 (3.20-5.17)
Year				
2010	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
2011	0.90 (0.77-1.04)	0.80 (0.68-0.94)	0.78 (0.67-0.92)	0.89 (0.72-1.10)

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2012	1.05 (0.90-1.21)	0.88 (0.76-1.03)	0.88 (0.75-1.04)	0.83 (0.67-1.02)
2013	1.03 (0.89-1.20)	0.81 (0.69-0.95)	0.82 (0.69-0.96)	0.80 (0.65-0.98)
2014	1.09 (0.94-1.27)	0.82 (0.70-0.96)	0.83 (0.71-0.98)	0.72 (0.58-0.90)
2015	1.54 (1.31-1.80)	1.07 (0.91-1.26)	1.11 (0.94-1.32)	1.09 (0.87-1.36)

All numbers indicate ORs and Confidence Intervals unless otherwise stated. *DAPT: dual antiplatelet therapy; Model 1: Without DAPT duration recommendation; Model 2: Final model; Model 3: Excluding patients with vascular events during follow up; Model 4: Excluding patients derived to another hospital

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Table 3. Characteristics of study patients according to DAPT duration recommended at the PCI hospital discharge.

	No DAPT* or ≤1 month (n=1212)	DAPT 2-11 months (n=581)	DAPT ≥12 months (n=6486)	Unspecified (n=2432)	P for trend (excluding unspecified)
Patient Characteristics					
Age, mean (SD)	62 (13.2)	61.2 (13.6)	61.3 (12.6)	61.6 (13.1)	0.221
Women	224 (18.5)	117 (20.1)	1333 (20.6)	539 (21.8)	0.107
Weight (1174 missing)	77.6 (13.7)	78.4 (13.8)	78.3 (13.6)	78.1 (14.4)	0.193
Cardiovascular risk factors					
Current smoker	601 (49.6)	303 (52.2)	2937 (45.3)	1142 (47)	0.001
Diabetes mellitus	243 (20.1)	93 (16)	1234 (19)	483 (19.9)	0.723

	467 (38.5)	171 (29.4)	2589 (39.9)	912 (37.5)	0.039
Hypercholesterolemia					
Hypertension	569 (47)	259 (44.6)	3075 (47.4)	1107 (45.5)	0.550

History

Chronic Hepatic Disease	22 (1.8)	7 (1.2)	61 (0.9)	22 (0.9)	0.007
Previous acute myocardial infarction	82 (6.8)	35 (6)	559 (8.6)	227 (9.3)	0.010
Stroke or transient ischemic attack	44 (3.6)	18 (3.1)	166 (2.6)	65 (2.7)	0.031
Previous percutaneous revascularization	59 (4.9)	28 (4.8)	455 (7)	182 (7.5)	0.002
Previous surgical revascularization	6 (0.5)	3 (0.5)	78 (1.2)	25 (1)	0.014
Chronic renal impairment	64 (5.3)	28 (4.8)	329 (5.1)	145 (6)	0.825
Previous diagnosis of chronic heart failure	98 (8.1)	36 (6.2)	539 (8.3)	249 (10.2)	0.495

Previous diagnosis of peripheral arterial disease	58 (4.8)	28 (4.8)	230 (3.6)	132 (5.4)	0.020
Previous Antiplatelet treatment	189 (15.6)	88 (15.2)	965 (14.9)	411 (16.9)	0.518
Two or more diseased vessels	457 (37.7)	187 (32.2)	2618 (40.4)	949 (39)	0.010
Vessel responsible					
Left anterior coronary artery	378 (31.2)	234 (40.3)	2800 (43.2)	973 (40)	<0.001
Right coronary artery	592 (48.8)	235 (40.5)	2475 (38.1)	944 (38.8)	<0.001
Circumflex coronary artery	182 (15)	71 (12.2)	869 (13.4)	279 (11.5)	0.218
Left main Coronary artery	3 (0.3)	0	65 (1)	19 (0.8)	0.002
No. of treated vessels per patient, mean (SD)	1.02 (0.1)	1.05 (0.2)	1.05 (0.3)	1.05 (0.3)	<0.001
Stent	1171 (96.6)	561 (96.6)	6057 (93.4)	2094 (86.1)	<0.001

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Bare metal	1154 (95.2)	536 (92.3)	3437 (53)	1571 (64.6)	<0.001
Drug-eluting	17 (1.4)	26 (4.5)	2756 (42.5)	578 (23.8)	<0.001
No. of stents per patient, mean (SD)	1.15 (0.5)	1.22 (0.6)	1.19 (0.7)	1.08 (0.7)	0.665
Admission Features					
Admission days; mean (SD); (662 missing values)	7 (4.7)	6.6 (5.8)	6.8 (5.8)	8.5 (11.2)	<0.001
Discharged home from the PCI hospital	904 (74.6)	438 (75.4)	3720 (57.4)	1095 (45)	<0.001

*DAPT: dual antiplatelet therapy

Table 4. Determinants of 12-month prescription and interhospital variability measures.

	Determinants of 12- month recommendation of DAPT*	Determinants of 12- month recommendation of DAPT excluding patients derived to another hospital
	N=8279	N=5062
	N centers = 10	N centers = 10
Obs per center: average (min-max)	828 (240-1750)	506 (122-986)
Previous heart failure	0.81 (0.59-1.11)	0.88 (0.57-1.37)
Drug eluting stent	28.75 (12.44-66.43)	36.52 (14.08-94.76)
Two or more treated vessels	1.50 (0.95-2.35)	2.00 (1.10-3.64)
Discharged home	0.40 (0.34-0.48)	N/A
Year		
2010	1 (ref.)	1 (ref.)

2011	2.60 (1.07-6.31)	2.40 (0.81-7.09)
2012	4.35 (1.77-10.65)	4.75 (1.57-14.43)
2013	9.88 (3.95-24.73)	9.28 (2.93-29.36)
2014	11.00 (4.31-28.08)	12.67 (3.86-41.62)
2015	14.23 (5.70-35.65)	29.40 (8.96-96.45)
Random effects		
Random intercept	4.46 (1.71-11.60)	6.05 (2.36-15.52)
Random slope (drug eluting stent)	1.10 (0.32-3.84)	1.00 (0.25-4.05)
Random slope (year)	0.69 (0.39-1.24)	0.99 (0.53-1.87)
Intraclass correlation (95% CI)	57.5 (34.2-77.9)	64.8 (41.7-82.5)
Median OR (95% CrI†)	7.49 (1.21-348)	10.44 (1.12-2428)

All numbers indicate ORs and Confidence Intervals unless otherwise stated

*DAPT: dual antiplatelet therapy; †CrI: credibility interval

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Figure 1

12,278 AMI/PCI patients discharged
alive or surviving 30 days after AMI
(2010 to 2015)

Previous history:
628 ACO at admission or at discharge
622 AF
77 haemorrhage in previous 3 months
240 neoplasia in previous 3 months

10,711 patients with
potential indication for
DAPT for at least 12 months

280 dyed between 30 days and 12
months after AMI
92 were lost to follow up

10,339 patients with
complete follow up
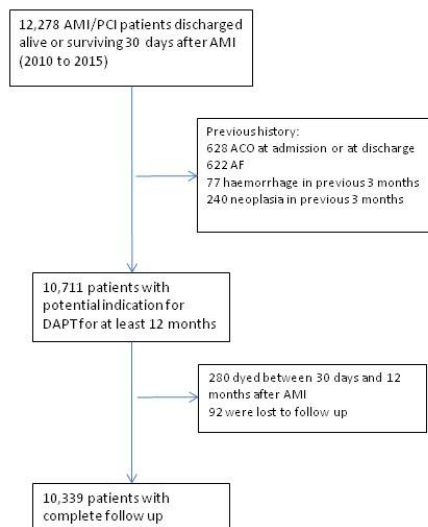
Figure 1

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Figure 2
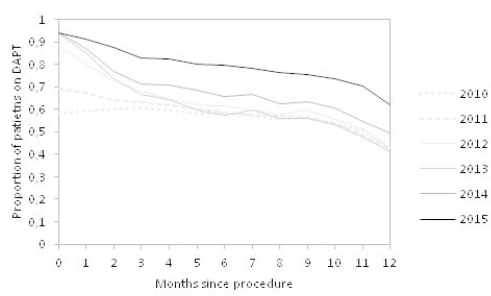
Patients alive	0	1	2	3	4	5	6	7	8	9	10	11	12
2010	1151	1148	1144	1141	1139	1138	1137	1135	1133	1132	1131	1131	1130
2011	1499	1497	1495	1494	1492	1489	1484	1480	1472	1468	1466	1463	1458
2012	1702	1698	1695	1693	1690	1689	1686	1685	1685	1680	1679	1679	1678
2013	1750	1741	1734	1731	1728	1724	1717	1713	1712	1711	1708	1701	1700
2014	1773	1765	1760	1757	1755	1753	1749	1745	1740	1737	1735	1729	1726
2015	1784	1779	1771	1766	1759	1754	1752	1750	1745	1742	1741	1741	1737

Figure 2

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Figure 4
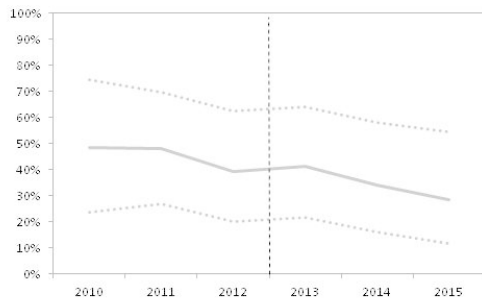
Figure 3

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Supplemental methods

Data validation processes in the AMI Code registry

1. Automatic data validation processes to identify and feed-back missing data and incongruities.

2. Periodic data validation process every 3-6 months:

   Since year 2011 this process was automated. The system automatically detects missing information in key variables and the identification of AMI codes that were activated by the emergency services (before admission) and were not included in the registry. Feed back for data validation is sent every 3-6 months for amendment or justification to the person responsible for data entry at each AMI Code Hospital.

   Since year 2015 the automated process can be managed directly at any time by the person responsible for data entry in each hospital.

3. Specific studies:

   In 2012 data were evaluated for **exhaustiveness**: all AMI cases consecutively admitted in 43 hospitals in Catalonia (10 AMI Code hospitals and 32 no AMI Code hospitals) during a 3 months period were registered and compared with the episodes registered in the AMI Code registry. Between 88-92% of STEACS episodes were included in the AMI Code registry.

   In 2013 concordance of the information between the AMI Code registry and the information from clinical records was assessed. 330 cases were analyzed and concordance was good for all key variables and there were no differences between hospitals.

Supplemental tables

Table 1S. ICD9 codes used for the identification of conditions and diseases present at index admission and for the

identification of events during follow up.

Disease or condition	ICD9 diagnostic or procedure code
Heart failure	428.0, 428.1, 428.22, 428.23, 428.3, 428.32, 428.33, 428.41, 428.43
Renal disease	585*
Neoplasia	140-239
Anemia	280-285
Chronic obstructive pulmonary disease	491-492, 494*, 496*
Peripheral arterial disease	440.2, 440.3, 440.4
Atrial fibrillation	427.3*
Events during follow up	
Acute myocardial infarction	410*, except: 410.*2
Ischemic stroke	433*, 434*, except: 433.*0, 434.*0
Haemorrhagic stroke	430*, 431*, 432*
Intraocular bleeding	362.81, 363.6, 363.61, 363.62, 376.32, 377.42, 379.23
Digestive bleeding	530.21, 530.7, 530.82, 531.0, 531.2, 531.4, 531.6, 532.0, 532.2, 532.4, 532.6, 533.0, 533.2, 533.4, 534.4, 534.6, 535.01, 535.11,535.21, 535.31, 535.41, 535.51, 535.61, 535.71, 537.83, 562.02, 562.03, 562.12, 562.13, 569.3, 569.85, 578.1, 578.9
Other bleeding	246.3, 459.0, 602.1, 784.8, 596.7, 599.7, 852*, 997.02, 998.1,
Endoscopic treatment	444.3, 454.2, 454.3
Transfusion	990.4

Table 2S. ATC codes used for the identification of drug treatment

Drug treatment	**ATC code**
ASA	B01AC06, N02BA01, B01AC30
Ticlopidine	B01AC05
Clopidogrel	B01AC04
Prasugrel	B01AC22
Ticagrelor	B01AC24
Dabigatran etexilate	B01AE07
Rivaroxaban	B01AF01
Apixaban	B01AF02
Beta-blocker	C07
ACE inhibitor	C09
Statins	C10AA

Supplemental figure. DAPT duration recommended in each hospital by year of episode

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page num
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title and abstract page 3 (Design subheading)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 3. Abstract
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 6
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 6 (last paragraph)
Methods			
Study design	4	Present key elements of study design early in the paper	Pages 8-9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Pages 8-9
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Pages 8-9
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Pages 8-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Pages 8-9
Bias	9	Describe any efforts to address potential sources of bias	Page 11 (sensibility analyses)
Study size	10	Explain how the study size was arrived at	Page 9 (study population)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 9-11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Pages 10-11
		(*b*) Describe any methods used to examine subgroups and interactions	Pages10-11
		(*c*) Explain how missing data were addressed	Pages 10-11
		(*d*) If applicable, explain how loss to follow-up was addressed	Pages 10-11
		(*e*) Describe any sensitivity analyses	Page 11
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-	Page 12

		up, and analysed	
		(b) Give reasons for non-participation at each stage	Page 12
		(c) Consider use of a flow diagram	Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Tables 1, 3
		(b) Indicate number of participants with missing data for each variable of interest	Tables 1, 3
		(c) Summarise follow-up time (eg, average and total amount)	Page 9
Outcome data	15*	Report numbers of outcome events or summary measures over time	Fig 2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Tables 2, 4
		(*b*) Report category boundaries when continuous variables were categorized	Tables 2, 4
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Tables 2, 4
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Pages 5 and 17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Pages 14-18
Generalisability	21	Discuss the generalisability (external validity) of the study results	Pages 14-18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 5

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Persistence with dual antiplatelet therapy after percutaneous coronary intervention for ST-Segment-Elevation Acute Coronary Syndrome. A population-based cohort study in Catalonia (Spain)

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Persistence with dual antiplatelet therapy after percutaneous coronary intervention for ST-Segment-Elevation Acute Coronary Syndrome. A population-based cohort study in Catalonia (Spain)

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ABSTRACT

Objectives: Guidelines recommending 12 months dual antiplatelet therapy (DAPT) in patients with ST-elevation acute coronary syndrome (STEACS) undergoing percutaneous coronary intervention (PCI) were published in year 2012. We aimed to describe the influence of guidelines implementation on the trend in 12-month persistence with DAPT between 2010 and 2015 and to evaluate its relationship with DAPT duration regimens recommended at dischargefrom PCI hospitals.

Design: Observational study based on region-wide registry data linked to pharmacy billing data for DAPT follow up.

Setting. All PCI hospitals (10) belonging to the AMI-Code network in Catalonia (Spain)

Participants: 10,711 STEACS patients undergoing PCI between 2010 and 2015 were followed up.

Primary and secondary outcome measures: Primary outcome was 12 month persistence with DAPT. Calendar year quarter, publication of guidelines; DAPT duration regimen recommended in the hospital discharge report, baseline patient characteristics and significant interactions were included in mixed effects logistic regression based interrupted time-series models.**Results**: The proportion of patients on-DAPT at 12 months increased from 58% (56-60) in 2010 to 73% (71-75) in 2015. The rate of 12-months persistence with DAPT significantly increased after the publication of clinical guidelines with a time lag of one year (OR=1.20; 95% CI: 1.11-1.30). A higher risk profile, more extensive and complex coronary disease, use of drug-eluting stents (OR=2.02; 95% CI: 1.61-2.53) and a 12-months DAPT regimen recommendation at discharge from the PCI hospital (OR=5.92; 95% CI: 3.34-10.52) were associated with 12-months persistence. **Conclusion**: Persistence with 12-month DAPT has increased

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since publication of clinical guidelines. Even though most patients were discharged on DAPT, only 73% with potential indication were on-DAPT 12 months after PCI. A guideline-based recommendation at PCI hospital discharge was highly associated with full persistence with DAPT. Establishing evidence-based, common prescribing criteria across hospitals in the AMI-network would favour adherence and reduce variability.

Strengths and limitations of this study

- The study describes the trends in persistence with DAPT during 2010-2015 in a region-wide unselected comprehensive cohort of patients using administrative data linked to a clinical registry

- It also evaluates the impact of the DAPT duration recommended at the PCI hospital discharge on 12-months persistence

- Limitations of using observational registry data include the possibility of coding errors and the inability to accurately identify specific contraindications for treatment or other patient characteristics that might be relevant for the study aims

- The use of pharmacy refill data as a proxy of patients adherence and persistence has also limitations which have been extensively described

Study funding

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Competing interest statement

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work

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Introduction

The need of dual antiplatelet therapy (DAPT) combining aspirin and an ADP-receptor blocker for at least 12 months in patients with ST-elevation acute coronary syndrome (STEACS) undergoing percutaneous coronary intervention (PCI) is well established and was incorporated into clinical guidelines in 2012[1,2].

Adherence of patients to this strategy is crucial to ensure its efficacy. Adherence to medication is usually defined[3] as the extent to which patients take medications as prescribed by their health care providers and persistence is defined as time from initiation to discontinuation of a therapy. Patients' persistence with DAPT may be influenced by several factors but will depend strongly on whether they ultimately receive a correct prescription from their physicians in the primary care setting. Patients may receive recommendations from various health providers at different stages of their process of care, from the interventionist cardiologist to their primary physician. It could be hypothesized that the last would tend to relay on the recommendation of the more specialized health professional. Thus, one potential determinant of patient's persistence with DAPT for at least 12 months is the instructions provided in the discharge report of the hospital where the patient was attended during the acute phase.

In Catalonia, an autonomous region of Spain, the acute care of STEACS is organized through a region-wide network, the Acute Myocardial Infarction (AMI) Code, to derive patients with suspected STEACS to one of the 10 reference hospitals with PCI capability. Performance of the AMI Code is prospectively and exhaustively registered[4,5], providing an appropriate tool for quality evaluation. The Catalan

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Health Information System systematically registers, among other, data on pharmacy

refills. Pharmacy billing data, although indirect, is an accepted method for evaluating

persistence with treatment in large patient cohorts[3,6].

The aims of the present study were: first, to describe persistence with DAPT for at least

12 months in patients with STEACS undergoing PCI from 2010 to 2015; second, to

evaluate the influence of publication of guidelines incorporatins this specific

recommendation on increasing the rate of 12-monhts persistence along time; and

third, to evaluate the association of the DApT duration recommended at the PCI

hospital discharge with patients' persistence with treatment for at least 12 months.

Methods

Data sources

Data were obtained through the Public Data Analysis for Health Research and

Innovation Program (PADRIS). The PADRIS allows access to information from different

sources on public healthcare resources usage for the population of Catalonia linked at

the patient level with warranted accomplishment of ethical principles. Specifically, for

the present study we linked data of the pharmacy billing registry with the AMI Code

Registry. The AMI Code registry was launched in 2010 to evaluate performance of the

AMI Code [4,5]. Exhaustiveness and quality of data is assessed periodically (see

supplemental methods for details). The database belongs to the Catalan Department

of Health and includes demographic, clinical, and therapeutic data for each episode of

hospitalization for STEACS. It conforms to the ethical and legal requirements for

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research purposes. The study obtained ethics approval from the Vall d'Hebron Clinical

Research Ethics Committee.

The registry was completed for the purpose of the present analysis with retrospective

collection of additional specific data: diseased vessels, responsible vessel, stent type,

number of stents. The recommendation of antithrombotic drugs was also collected *ad*

hoc for the study from the discharge report. The recommendation of DAPT was

defined as the recommendation of Acetylsalisilic acid (ASA) and clopidogrel, prasugrel

or ticagrelor for specified periods. If the recommended duration of DAPT was not

specified, the discharge recommendation pattern was classified as "unspecified". A

local investigator at each center performed the specific retrospective data collection.

History of major haemorrhage, neoplasia, renal disease, heart failure, peripheral

arterial disease and atrial fibrillation, were obtained from minimum basic data set

(MBDS) diagnoses coded in hospitalization episodes occurring in the previous three

months before index hospitalization. Major haemorrhage was defined as: a diagnosis

of digestive bleeding in any diagnostic position (primary or secondary) together with a

procedure code for endoscopic treatment or for transfusion of blood products, or a

diagnosis of haemorrhagic stroke, or a diagnosis of intraocular haemorrhage, or a

diagnosis of other types of haemorrhage together with a procedure code for

transfusion of blood products. Major ischemic events (AMI or stroke) and major

haemorrhage during the 12 months following the index episode were obtained in the

same way. Mortality during the 12 months following the index episode was obtained

from the insured registry status.

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Drug treatment during the 12-month post-discharge follow up was obtained from the pharmacy billing registry. ICD9 and ATC codes used for the identification of study variables are listed in the supplemental tables 1 and 2.

Study population

We included all consecutive patients who survived a STEACS between January 2010 and December 2015, received primary or post fibrinolysis PCI in one of the 10 reference hospitals of the AMI Code network, were discharged home or transferred to another hospital and survived at least one month after AMI. New episodes of STACS occurring to the same patients during the study period were only accounted as follow up events. Patients with likely contraindication for DAPT (history of major bleeding or neoplasm in the three months prior to the index episode and patients requiring anticoagulation) were excluded.

Persistence with treatment

DAPT was defined as the concomitant use of ASA and a $P2Y_{12}$ antagonist. Persistence with DAPT was estimated by identification of consecutive months with pharmacy refills with one container of each agent in the 12-month period after hospital discharge. Because pharmacy billing is registered in a monthly basis and the exact day of dispensation is unknown, we considered that a monthly dispensation until at least month 11 after the index episode would approximate a 12-months treatment period. If more than one container were dispensed in one month, the excess containers were pulled along the following months. Non-persistence was defined as either

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discontinuation or a break in therapy of at least two months after pulling along the

excess containers. To describe persistence over the whole study period we estimated

the proportion of patients alive and within the 12 months after discharge window who

were on treatment on each month[7].

The primary outcome was a patients' persistence with DAPT for 12 months following

discharge (or in other words, patients withdrawing both agents from the pharmacy

until at least month 11).

Statistical analysis

We compared baseline characteristics between patients persisting with DAPT for at

least 12 months and patients withdrawing DAPT before 12 months with chi square test

or t test when appropriate. We tested for trends in patient's characteristics along

calendar year of discharge for the index procedure with Jonckheere-Terpstra test for

differences between ordered categories.

To evaluate the influence of time, guidelines publication and the DAPT duration

recommended in the PCI hospital discharge report we modelled logistic regression

based interrupted time-series analysis[8], adjusting for baseline characteristics. As a

first step, because it is expected that guidelines publication influences practice with a

time delay, we plotted the proportion of patients persisting on-DAPT for 12 months by

year quarter of discharge from the PCI hospital and we tested models with a slope

change (indicating the start of guidelines implementation) at different lag periods after

publication of the European clinical guidelines (last quarter of 2012). Once the lag

period between guidelines publication and implementation of recommendations was

estimated we included patient characteristics and second or third level interactions of

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each characteristic with year quarter and moment of implementation. We coded time (*T*) as the time elapsed since the publication of guidelines plus the lag period (in quarters) and a dummy variable (X_t) indicating the pre-implementation period (coded 0) or the post-implementation period (coded 1)[9].

The standard model specification was the following:

$$logit\ (Y_t) =\ \beta_0 + \beta_1 T + \beta_2 X_t + \beta_3 T X_t$$

Where β_0 represents the baseline level at T = 0, β_1 is interpreted as the change in outcome associated with a time unit (quarter) increase (representing the underlying pre-implementation trend), β_2 is the level change following the implementation and β_3 indicates the slope change following the implementation (using the interaction between time and implementation: TX_t). Additional terms can be added to model the effect of other covariables and their interactions with *T* and X_t and to include random effects. Note that we set T = 0 at the quarter where we observed a significant change in the slope at a lag time after guidelines publication.

We took into account the clustered structure of data with patients being treated and, most importantly, with recommendations on DAPT duration being provided in different hospitals, by introducing random effects in the logistic regression models.

. We tested whether models including random intercept for hospital and random slopes for each independent variable were significant using a deviance –based test of hypothesis.

Variable selection for multilevel modelling was based on the bivariate associations with the rate of each dependent variable. Candidate individual variables were those

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described in tables 1 and 2. Type of antiplatelet drug was not included in the multivariable analysis because it was highly correlated with the year of episode, as new antiplatelet agents (ticagrelor and prasugrel) were introduced later during the study period. We retained in the final model all variables with a p value<0.2.

Plots of predicted probability values were used to show marginal effects of variables of interest and variability between centres.

Sensitivity analyses

Because a substantial proportion of patients were returned to their reference hospital and because it was unknown whether the DAPT duration recommendation was changed at discharge from the second hospital, we performed sensitivity analyses excluding these patients. Additionally, because ischemic and haemorrhagic events occurring during follow up would change the treatment length, sensitivity analyses were also performed by excluding patients suffering any vascular event during follow up.

Patient and Public Involvement

The present study did not involve individual patients or public agencies.

Results

After excluding patients with likely contraindication for DAPT (figure 1), we identified 10,711 STEACS patients undergoing PCI who were potential candidates to receive DAPT for at least 12 months and survived for at least one month after discharge. 631 (5.9%) patients experienced an ischemic major event (AMI or stroke) within 12 months

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after the index episode, 100 (0.9%) had a major haemorrhage and 280 (2.6%) died between one and 12 months after the index episode. After excluding patients who died or were lost to follow up and patients with errors in quarter allocations, 10,262 patients remained for analysis.

Table 1 shows characteristics of study patients depending on persistence with DAPT. Patients persisting for at least 12 months had higher prevalence of cardiovascular risk factors (hypertension, diabetes and hypercholesterolemia), higher rate of a previous history of cardiovascular disease, more extended coronary disease, higher rate of drug eluting stents implantation and slightly higher ischemic risk (as measured with the DAPT score[10]). Persisting patients were more often transferred to their reference hospital and had had a prescription for a longer DAPT period at discharge from the PCI hospital.

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Table 1. Characteristics of study patients according to DAPT persistence during follow up.

	DAPT <12 months (n=3684)		DAPT ≥ 12 months (n=6578)		Total (n=10262)		P value
	N	n (%)	N	n (%)	N	n (%)	
Age	3684	61.19 ± 13.21	6578	61.18 ± 12.38	10262	61.19 ± 12.69	0.578
Gender (Female)	3684	765 (20.8%)	6578	1319 (20.1%)	10262	2084 (20.3%)	0.399
Smoke (Y)	3684	1774 (48.2%)	6578	3042 (46.2%)	10262	4816 (46.9%)	0.064
Hypertension (Y)	3684	1622 (44%)	6578	3142 (47.8%)	10262	4764 (46.4%)	<0.001
Diabetes (Y)	3684	647 (17.6%)	6578	1298 (19.7%)	10262	1945 (19%)	0.008
Hypercholesterolaemia (Y)	3684	1291 (35%)	6578	2678 (40.7%)	10262	3969 (38.7%)	<0.001
Polyvascular disease (Y)*	3684	530 (14.4%)	6578	1048 (15.9%)	10262	1578 (15.4%)	0.038
Previous stroke or transient ischaemic attack (Y)	3684	101 (2.7%)	6578	172 (2.6%)	10262	273 (2.7%)	0.704
Previous acute myocardial infarction (Y)	3684	265 (7.2%)	6578	570 (8.7%)	10262	835 (8.1%)	0.010
Previous percutaneous coronary intervention (Y)	3684	194 (5.3%)	6578	482 (7.3%)	10262	676 (6.6%)	<0.001
Previous by-pass surgery (Y)	3684	20 (0.5%)	6578	85 (1.3%)	10262	105 (1%)	<0.001
History of peripheral arteriopathy (Y)	3684	153 (4.2%)	6578	276 (4.2%)	10262	429 (4.2%)	0.957
Comorbidity (Y)†	3684	462 (12.5%)	6578	885 (13.5%)	10262	1347 (13.1%)	0.191
Hepatopathy (Y)	3684	48 (1.3%)	6578	56 (0.9%)	10262	104 (1%)	0.030
History of Renal Impairment (Y)	3684	185 (5%)	6578	320 (4.9%)	10262	505 (4.9%)	0.741
History of Heart Failure (Y)	3684	272 (7.4%)	6578	583 (8.9%)	10262	855 (8.3%)	0.009
Affected number of vessels ≥2 (Y)	3684	1275 (34.6%)	6578	2731 (41.5%)	10262	4006 (39%)	<0.001
Number of treated vessels	3613	1.03 ± 0.21	6516	1.06 ± 0.26	10129	1.05 ± 0.25	<0.001
Drug eluting stent (Y)	3684	572 (15.5%)	6578	2704 (41.1%)	10262	3276 (31.9%)	<0.001
DAPT Score Points	3684	1.20 ± 1.20	6578	1.28 ± 1.17	10262	1.25 ± 1.18	<0.001
Discharged home (Y)	3684	2233 (60.6%)	6578	3672 (55.8%)	10262	5905 (57.5%)	<0.001
DAPT recommendation at discharge	3684		6578		10262		<0.001
1 month		875 (23.8%)		295 (4.5%)		1170 (11.4%)	
<12 months		385 (10.5%)		173 (2.6%)		558 (5.4%)	
≥12months		1522 (41.3%)		4732 (71.9%)		6254 (60.9%)	
unknown		902 (24.5%)		1378 (20.9%)		2280 (22.2%)	

*Polyvascular disease was defined as presence of at least two of the following conditions: previous myocardial infarction or percutaneous coronary or surgical revascularization; history of peripheral arteriophaty; history of stroke or transient ischaemic attack. †Comorbidity was defined as presence of one of the following conditions: hepatophaty, history of renal impairment, history of heart failure

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The rate of patients on-DAPT after discharge from the PCI hospital was 91% (95% CI: 90-91) without relevant differences between years (supplemental figure 1). The proportion of patients on-DAPT at 12 months significantly increased from 58% (56-61) in 2010 to 73% (71-75) in 2015. The larger increase in 12-month persistence was observed between 2014 (64% [62-66]) and 2015, two years after the publication of clinical guidelines.

Some baseline characteristics showed a temporal trend over the study period 2010-2015 (table 2). The prevalence of cardiovascular risk factors (smoking, hypertension and hypercholesterolemia) and comorbidities increased slightly. Likewise, the number of treated vessels, the rate of drug eluting stents implantation also increased with time.

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Table 2. Characteristics of study patients by year of discharge for the index admission.

	2010 (n=1537)	2011 (n=1628)	2012 (n=1760)	2013 (n=1779)	2014 (n=1779)	2015 (n=1779)	P value
Age	61 ± 12.92	61.01 ± 13.09	60.97 ± 12.52	61.27 ± 12.4	61.24 ± 12.72	61.58 ± 12.53	0.325
Gender	310 (20.2%)	311 (19.1%)	372 (21.1%)	359 (20.2%)	352 (19.8%)	380 (21.4%)	0.389
Smoke	686 (44.6%)	754 (46.3%)	811 (46.1%)	839 (47.2%)	840 (47.2%)	886 (49.8%)	0.004
Hypertension	674 (43.9%)	729 (44.8%)	808 (45.9%)	838 (47.1%)	844 (47.4%)	871 (49%)	0.001
Diabetes	296 (19.3%)	319 (19.6%)	340 (19.3%)	327 (18.4%)	325 (18.3%)	338 (19%)	0.438
Hypercholesterolaemia	541 (35.2%)	621 (38.1%)	648 (36.8%)	710 (39.9%)	742 (41.7%)	707 (39.7%)	<0.001
Polyvascular disease*	232 (15.1%)	253 (15.5%)	301 (17.1%)	259 (14.6%)	278 (15.6%)	255 (14.3%)	0.370
Previous stroke or transient ischaemic attack	42 (2.7%)	32 (2%)	45 (2.6%)	40 (2.2%)	65 (3.7%)	49 (2.8%)	0.126
Previous acute myocardial infarction	127 (8.3%)	142 (8.7%)	163 (9.3%)	151 (8.5%)	127 (7.1%)	125 (7%)	0.029
Previous percutaneous coronary intervention	94 (6.1%)	104 (6.4%)	123 (7%)	116 (6.5%)	118 (6.6%)	121 (6.8%)	0.485
Previous by-pass surgery	10 (0.7%)	16 (1%)	17 (1%)	19 (1.1%)	18 (1%)	25 (1.4%)	0.056
History of peripheral arteriopathy	51 (3.3%)	70 (4.3%)	93 (5.3%)	66 (3.7%)	86 (4.8%)	63 (3.5%)	0.876
Comorbidity†	155 (10.1%)	190 (11.7%)	233 (13.2%)	243 (13.7%)	266 (15%)	260 (14.6%)	<0.001
Hepatopathy	16 (1%)	12 (0.7%)	24 (1.4%)	24 (1.3%)	13 (0.7%)	15 (0.8%)	0.578
History of Renal Impairment	70 (4.6%)	75 (4.6%)	71 (4%)	86 (4.8%)	89 (5%)	114 (6.4%)	0.009
History of Heart Failure	80 (5.2%)	118 (7.2%)	154 (8.8%)	159 (8.9%)	187 (10.5%)	157 (8.8%)	<0.001
Affected number of vessels ≥2	594 (38.6%)	617 (37.9%)	679 (38.6%)	707 (39.7%)	688 (38.7%)	721 (40.5%)	0.188
Number of treated vessels	1.04 ± 0.25	1.03 ± 0.23	1.05 ± 0.26	1.05 ± 0.24	1.05 ± 0.26	1.06 ± 0.24	0.003
Drug eluting stent	462 (30.1%)	388 (23.8%)	472 (26.8%)	493 (27.7%)	652 (36.6%)	809 (45.5%)	<0.001
DAPT Score Points	1.24 ± 1.2	1.24 ± 1.19	1.26 ± 1.17	1.26 ± 1.17	1.22 ± 1.16	1.28 ± 1.19	0.435
Discharged home	961 (62.5%)	951 (58.4%)	933 (53%)	1042 (58.6%)	959 (53.9%)	1059 (59.5%)	0.041
DAPT recommendation at discharge							<0.001
1 month	281 (18.3%)	259 (15.9%)	243 (13.8%)	181 (10.2%)	135 (7.6%)	71 (4%)	
<12 months	150 (9.8%)	137 (8.4%)	100 (5.7%)	69 (3.9%)	65 (3.7%)	37 (2.1%)	
≥12 months	792 (51.5%)	871 (53.5%)	975 (55.4%)	1086 (61%)	1154 (64.9%)	1376 (77.3%)	

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	2010 (n=1537)	2011 (n=1628)	2012 (n=1760)	2013 (n=1779)	2014 (n=1779)	2015 (n=1779)	P value
unknown	314 (20.4%)	361 (22.2%)	442 (25.1%)	443 (24.9%)	425 (23.9%)	295 (16.6%)	

*Polyvascular disease was defined as presence of at least two of the following conditions: previous myocardial infarction or percutaneous coronary or surgical revascularization; history of peripheral arteriophaty; history of stroke or transient ischaemic attack. †Comorbidity was defined as presence of one of the following conditions: hepatophaty, history of renal impairment, history of heart failure

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The overall rate of explicit DAPT recommendation for at least 12 months in the hospital discharge reports was 51% (49-53) in 2010 and increased to 77% (75-79) in 2015 but it was highly variable between hospitals (supplemental figure 2).

Figure 2 shows the observed proportion of patients persisting with DAPT for at least 12 month at each time point and the interrupted time series model fitted after setting a one year lag period from publication to implementation of guidelines.

In interrupted time series logistic regression (Table 3), variables showing association with 12 months persistence on DAPT were two or more diseased vessels, higher number of stents implanted, receiving drug eluting stents, hypercholesterolemia, a previous surgical procedure and a recommendation of DAPT for a longer period at discharge from the PCI hospital. Guidelines implementation had a positive effect on persistence: a 20% increase in the odds of 12 months persistence each quarter after a lag of one year since publication. The effect of drug eluting stents was attenuated with time (OR for interaction: 0.97; 95%CI: 0.95-0.98)) while the effect of prescription was attenuated with time after guidelines implementation (OR for the interaction 0.87, 95%CI: 0.80-0.94 for a recommendation of ≥12 months and 0.89, 95%CI: 0.82-0.98 for an unknown recommendation). The effect of implantation of drug eluting stents and type of recommendation also varied between hospitals (significant random slopes).

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Table 3. Factors associated with a persistence of at least 12 months as assessed with interrupted time series logistic regression model

Fixed effects	OR	95% CI	P value
Drug eluting stent	2.02	1.61 - 2.53	<0.001
Number of stents	1.21	1.12 - 1.31	<0.001
Recommendation at PCI hospital discharge (Ref. 1 month)	1.00		
<12 months	1.67	0.88 - 3.17	0.120
>=12 months	5.92	3.34 - 10.52	<0.001
unknown	2.23	0.82 - 6.02	0.115
Hypercolesterolemia	1.19	1.08 - 1.31	<0.001
Previous by-pass surgery	1.81	1.06 - 3.07	0.029
Two or more treated vessels	1.20	1.09 - 1.32	<0.001
Drug eluting stent * Time (quarter)	0.97	0.95 - 0.98	<0.001
Guidelines implementation	1.20	1.11 - 1.3	<0.001
Recommendation at PCI hospital discharge (Ref. 1 month) * Time (quarter)*Guidelines implementation			
<12 months	0.91	0.8 - 1.05	0.191
≥ 10 months	0.87	0.8 - 0.94	0.001
unknown	0.89	0.82 - 0.98	0.013
Random effects	**Variance**	**95% CI**	
Random - Intercept	0.46	0.11 – 5.16	
Random - Slopes			
Recommendation at PCI hospital discharge (Ref. 1 month)			
<12 months	0.38	0.15 – 4.21	
≥12 months	0.39	0.15 – 4.29	
unknown	2.00	0.45 – 22.19	
Drug eluting stent	0.09	0.02 – 1.00	
Adjusted ICC	0.087		

Results of sensitivity analyses, excluding patients with ischemic or haemorrhagic events during follow up, or excluding patients that were transferred to another centre after PCI were similar to the main analysis (Supplemental table 3).

The interaction between drug eluting stents and time can be seen in figure 3A. Because 12-months persistence increased with time in patients without drug eluting stents, the effect of type of stent is attenuated with time. The interaction of the recommendation pattern with time and guidelines implementation can be seen in figure 3B: 12-months persistence increased with time mainly in the subgroups with

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shorter time specification in the discharge report and also in patients without a specific recommendation, but this increase started after guidelines implementation (one year after publication). Figure 3C shows a substantial reduction in the variability between centres mainly due to an increase in the proportion of 12-months persistence in patients attended in centres where the initial proportion was lower (significant random intercept and slopes).

Discussion

According to published guidelines, all STEACS patients undergoing PCI without contraindication should be kept on DAPT for at least 12 months unless an event occurs that precludes continuing with this treatment. In this observational region-wide study we have found an increase in the proportion of patients on-DAPT at 12 months from 58 to 73% in the period from 2010 to 2015, with an accelerated rate starting in the fourth quarter of 2013, one year after the publication of European guidelines.

We also found a high variability between hospitals in the adherence to guidelines when recommending DAPT for at least 12 months which leads to substantial differences between hospitals in the rate of patients persisting with the recommended DAPT. The progressive increase in the overall rate of 12-monhts persistence was accompanied by a substantial reduction of interhospital variability.

Likelihood of patients persisting with DAPT for one year is strongly related to the instructions given at the PCI hospital discharge, as we observed a lower rate of 12-month persistence in patients receiving a discharge DAPT recommendation for less than 12 months. Although a causal direct relationship between the established recommendation in the more specialised setting and the final prescription at the

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primary care setting cannot be stated on the basis of observational data, this finding suggests that prescribing physicians strongly rely on the first recommendation specified at the discharge report in the PCI hospital. Therefore, hospital cardiologists should be kept aware of their impact and encouraged to be clear and specific enough when providing DAPT time recommendations in the discharge report form.

The recommendation in clinical guidelines of DAPT for at least 12 months following STEACS[1,2] was based on the duration of follow up of randomised clinical trials designed for other purposes and[11–13], although a 12-month treatment seemed reasonable [14], no randomized studies had been performed within the study period aimed specifically at comparing 12 months DAPT with shorter periods in STEACS patients receiving PCI and thus this recommendation might well be seen as somehow arbitrary by some prescribers.

In 2015 the need for long term DAPT was reinforced by the recommendation of extended DAPT beyond 12 months in patients with ACS receiving drug eluting stents[15–17], but still safety concerns might induce some prescribers to be reluctant to prolong DAPT, especially in patients with higher complexity[18]. Safety concerns might also explain the high proportion of discharge reports with non-specified DAPT period, which deserved special attention in our analyses. Cardiologists might be reluctant to prescribe a specific duration of DAPT maybe fearing about the emergency of events that increase the haemorrhagic risk at some point after discharge, thus relaying on the follow up that will be made at the ambulatory setting. Our results showing a high degree of persistence for patients without a specification of DAPT time point out to the fact that this decision is not necessarily "incorrect", and that health providers coming later in the process of care are probably doing their job.

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We might wonder whether the observed high variability between hospitals in the instructions provided about DAPT duration actually reflects suboptimal quality of care or confusion in the interpretation of international guidelines. In fact, although 2012 ESC guidelines state that DAPT must be continued for 12 months after STEACS with a class of recommendation I, the level of evidence was established as C[1]. Thus, there was general agreement that a minimum of 12 months of DAPT is likely to be beneficial but based only on a consensus of experts or observational studies. Moreover, it is literally stated that the given recommendation on DAPT duration should be "with a strict minimum of 1 month for patients receiving BMS and 6 months for patients receiving DES", with Class IC and IIb respectively. These messages, which ultimately reflected the lack of clinical trials aimed to answer the specific question about DAPT duration, could have induced a perception of arbitrariness leading to variability in clinical practice.

In fact, the optimal duration of DAPT has not yet been totally established in more contemporary clinical trials. The most recent randomized clinical trial conducted in patients with STEACS aimed to assess the question of 12-month vs a 6-month DAPT duration, showed that 6-month DAPT duration after primary PCI was non-inferior to 12-month duration to prevent major cardiovascular events[19]. In another trial in the context of ACS, 12 months or longer DAPT duration versus 6 months was not associated with lower major cardiovascular events and total mortality[20].

Regardless the level of the evidence, one would expect that a Class I recommendation should be uniformly followed by clinicians. Moreover, as patient characteristics did not substantially differed across hospitals, we should expect a lower variability between hospitals. A large variation in individual country practices concerning the pattern of

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DAPT duration after ACS has been described, suggesting that local systems are strong drivers of DAPT duration[21]. These findings may imply that there is still room for improvement in the quality of care of STEACS patients and that quality improvement programs, whose efficacy and cost-effectiveness are still under evaluation, could be useful to reduce variability in clinical practice[22]. This is of prime importance in the context of the prescription of DAPT duration after ACS in which the clinician-driven variability in prescription patterns adds to the different levels patients' adherence[21]. Higher atherosclerotic burden and increased ischemic risk was associated to better persistence with DAPT. The need for 12-month DAPT schedules in patients treated with drug eluting stents is clearly perceived by physicians but the magnitude of this association varies largely between hospitals. This means that, even in clear indications, there are different levels of adoption of emerging clinical recommendations in hospitals belonging to the same AMI network.

It is also apparent from our data that the speed of adoption of clinical guidelines is different among hospitals and that an acceptable and generalised level of adherence is only reached after two years of implementation. Similar trends have been found in other contexts and earlier periods[23–28] reporting DAPT use between 60-80% at discharge and between 25-75 % at one year. In this sense, together with other quality improvement initiatives, the use of population-based registries to provide audit and feedback could be useful to promote quicker and smoother adoption of clinical practice guidelines[29].

There are a number of assumptions that might be questionable: A number of factors have been described to contribute to underprescription[30]. The complete process of

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care and the definite prescription at the ambulatory setting is poorly known for individual patients and has not been considered in this study. Changes in treatment prescription might be justified by the patients' varying conditions during follow up. We assume that hospital recommendation influences final prescription, and consequently, final adherence to guidelines, but it can also be that both "prescribers" facing the same patient share the same criteria for prescription. I.e. the hospital cardiologist might have decided to recommend DAPT for a shorter period to an elderly patient with other comorbidities and suboptimal quality of life due to mild digestive symptoms, even if her objective bleeding risk is not high; similarly, the primary physician or the cardiologist at the primary care setting might have also decided to be less aggressive for the same reasons, even without being influenced by the recommendation of the first prescriber. This would probably explain a large amount of the strong relationship between hospital recommendation and pharmacy dispensation. Moreover, although effects were adjusted for patient characteristics and vascular events during follow up, there might be other unmeasured reasons for deciding upon a shorter DAPT period facing an individual patient.

In addition, the recommendation at PCI hospital discharge may not coincide with the final hospital prescription in patients derived to another reference hospital after PCI. However, results of sensitivity analyses excluding these patients did not differ substantially from the results of the main analyses.

The study was aimed to ascertain influence of guidelines on hospital recommendation and its impact on patients' persistence with DAPT. The impact of persistence on clinically relevant results is beyond the objective of the present study andwill be assessed in another article. Similarly, the study was not specifically aimed at a deep

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assessment of determinants of adherence. This requires a detailed examination of the social context and a detailed assessment of individual psychological factors[31].

Conclusion

The study shows that 12-month DAPT persistence in revascularized patients with STEACS in Catalonia (Spain) has substantially increased between years 2010 to 2015 especially since one year after the publication of European guidelines in 2012. Guidelines implementation was also followed by a substantial decrease in variability between centres. We have shown that instructions given at the PCI hospital discharge are strongly associated with persistence. Thus establishing common and rational prescribing criteria between hospitals in the STEACS-network may favour patients persistence with scheduled prescriptions and also reduce variability in clinicians´ practices.

Author contributions

IFG, ARi, JRM conceived and designed the study; ARi, JRM and MTF participated in the acquisition and analysis of data; HTM, SR, CL, MC, SH, CTQ, JGP, JAGH and MM were responsible for data acquisition in their respective hospitals; ARi, IFG, JRM, GO, ARo, JIP, JM and DGD were involved in the interpretation of results; ARi and IFG wrote the manuscript and all other authors revised it critically and approved its final version

The AMI-Code Registry Investigators (listed below) contribute to the functioning of the AMI code and to data acquisition for the AMI-Code Registry:

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Figure legends

Figure 1. Patients' flow chart

Figure 2. Observed 12-months persistence rate by quarter and interrupted time series model specification after setting a one year lag period for guidelines implementation

Figure 3. Predicted probabilities of 12-months persistence by (A) drug eluting stent, (B) recommendation pattern and (C) center, over time.

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12,278 AMI/PCI patients discharged alive or surviving 30 days after AMI (2010 to 2015)

Previous history:
628 ACO at admission or at discharge
622 Atrial fibrilation
77 haemorrhage in previous 3 months
240 neoplasia in previous 3 months

10,711 patients with potential indication for DAPT for at least 12 months

280 died between 30 days and 12 months after AMI
92 were lost to follow up
77 with date errors

10,262 patients with complete follow up

Figure 1. Patients flow

190x254mm (96 x 96 DPI)

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Figure 2. Observed 12-months persistence rate by quarter and interrupted time series model specification after setting a one year lag period for guidelines implementation

127x127mm (300 x 300 DPI)

Figure 3. Predicted probabilities of 12-months persistence by (A) drug eluting stent, (B) recommendation pattern and (C) center, over time

127x304mm (300 x 300 DPI)

Supplemental methods

Data validation processes in the AMI Code registry

1. Automatic data validation processes to identify and feed-back missing data and incongruities.

2. Periodic data validation process every 3-6 months:

   Since year 2011 this process was automated. The system automatically detects missing information in key variables and the identification of AMI codes that were activated by the emergency services (before admission) and were not included in the registry. Feed back for data validation is sent every 3-6 months for amendment or justification to the person responsible for data entry at each AMI Code Hospital.

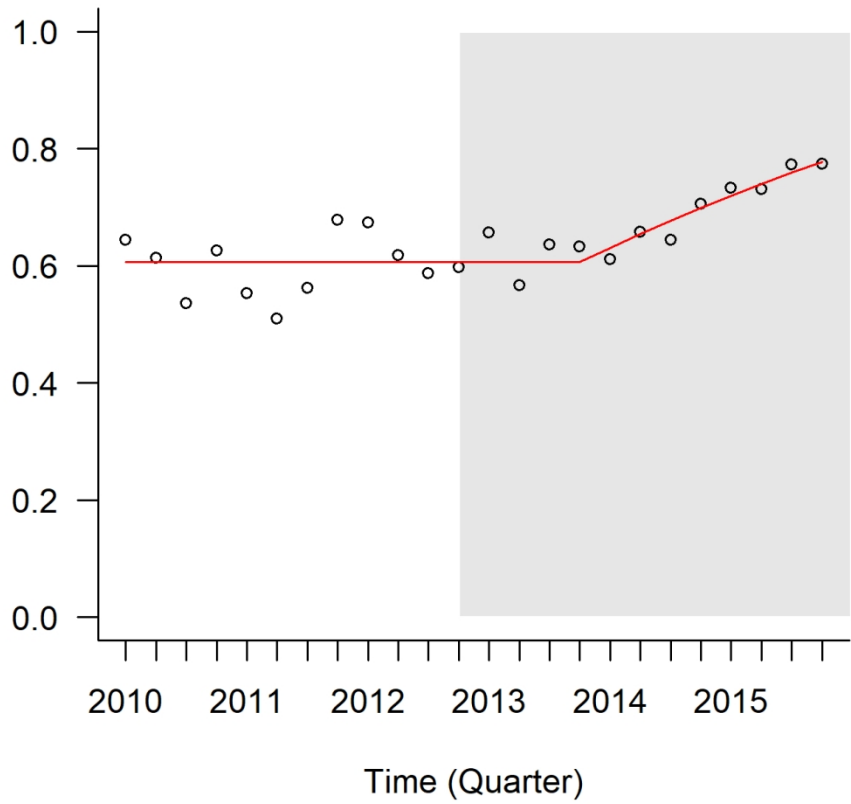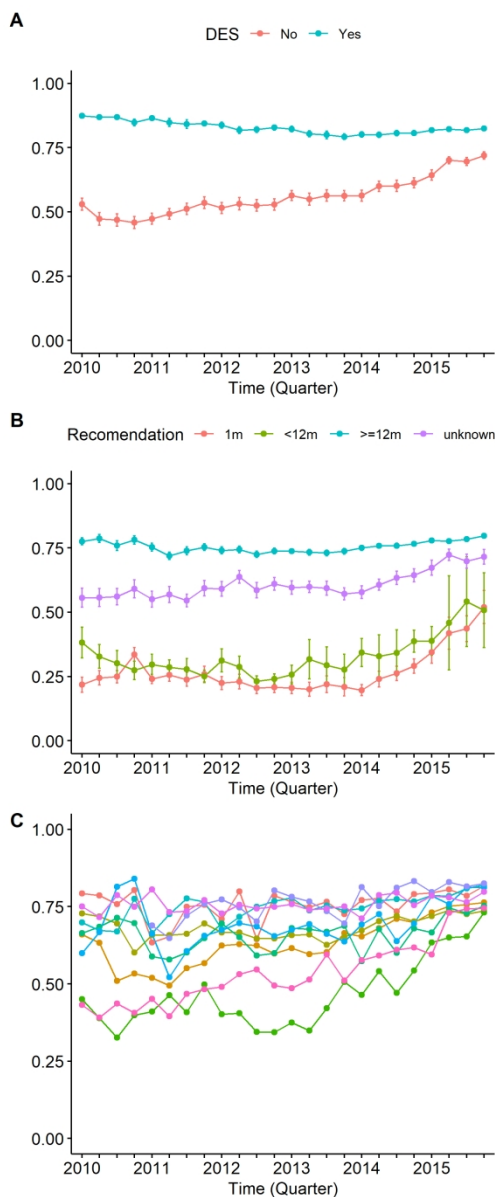   Since year 2015 the automated process can be managed directly at any time by the person responsible for data entry in each hospital.

3. Specific studies:

   In 2012 data were evaluated for **exhaustiveness**: all AMI cases consecutively admitted in 43 hospitals in Catalonia (10 AMI Code hospitals and 32 no AMI Code hospitals) during a 3 months period were registered and compared with the episodes registered in the AMI Code registry. Between 88-92% of STEACS episodes were included in the AMI Code registry.

   In 2013 concordance of the information between the AMI Code registry and the information from clinical records was assessed. 330 cases were analyzed and concordance was good for all key variables and there were no differences between hospitals.

Supplemental tables

Supplemental table 1. ICD9 codes used for the identification of conditions and diseases present at index admission and for the identification of events during follow up.

Disease or condition	ICD9 diagnostic or procedure code
Heart failure	428.0, 428.1, 428.22, 428.23, 428.3, 428.32, 428.33, 428.41, 428.43
Renal disease	585*
Neoplasia	140-239
Anemia	280-285
Chronic obstructive pulmonary disease	491-492, 494*, 496*
Peripheral arterial disease	440.2, 440.3, 440.4
Atrial fibrillation	427.3*
Events during follow up	
Acute myocardial infarction	410*, except: 410.*2
Ischemic stroke	433*, 434*, except: 433.*0, 434.*0
Haemorrhagic stroke	430*, 431*, 432*
Intraocular bleeding	362.81, 363.6, 363.61, 363.62, 376.32, 377.42, 379.23
Digestive bleeding	530.21, 530.7, 530.82, 531.0, 531.2, 531.4, 531.6, 532.0, 532.2, 532.4, 532.6, 533.0, 533.2, 533.4, 534.4, 534.6, 535.01, 535.11,535.21, 535.31, 535.41, 535.51, 535.61, 535.71, 537.83, 562.02, 562.03, 562.12, 562.13, 569.3, 569.85, 578.1, 578.9
Other bleeding	246.3, 459.0, 602.1, 784.8, 596.7, 599.7, 852*, 997.02, 998.1,
Endoscopic treatment	444.3, 454.2, 454.3
Transfusion	990.4

Supplemental table 2. ATC codes used for the identification of drug treatment

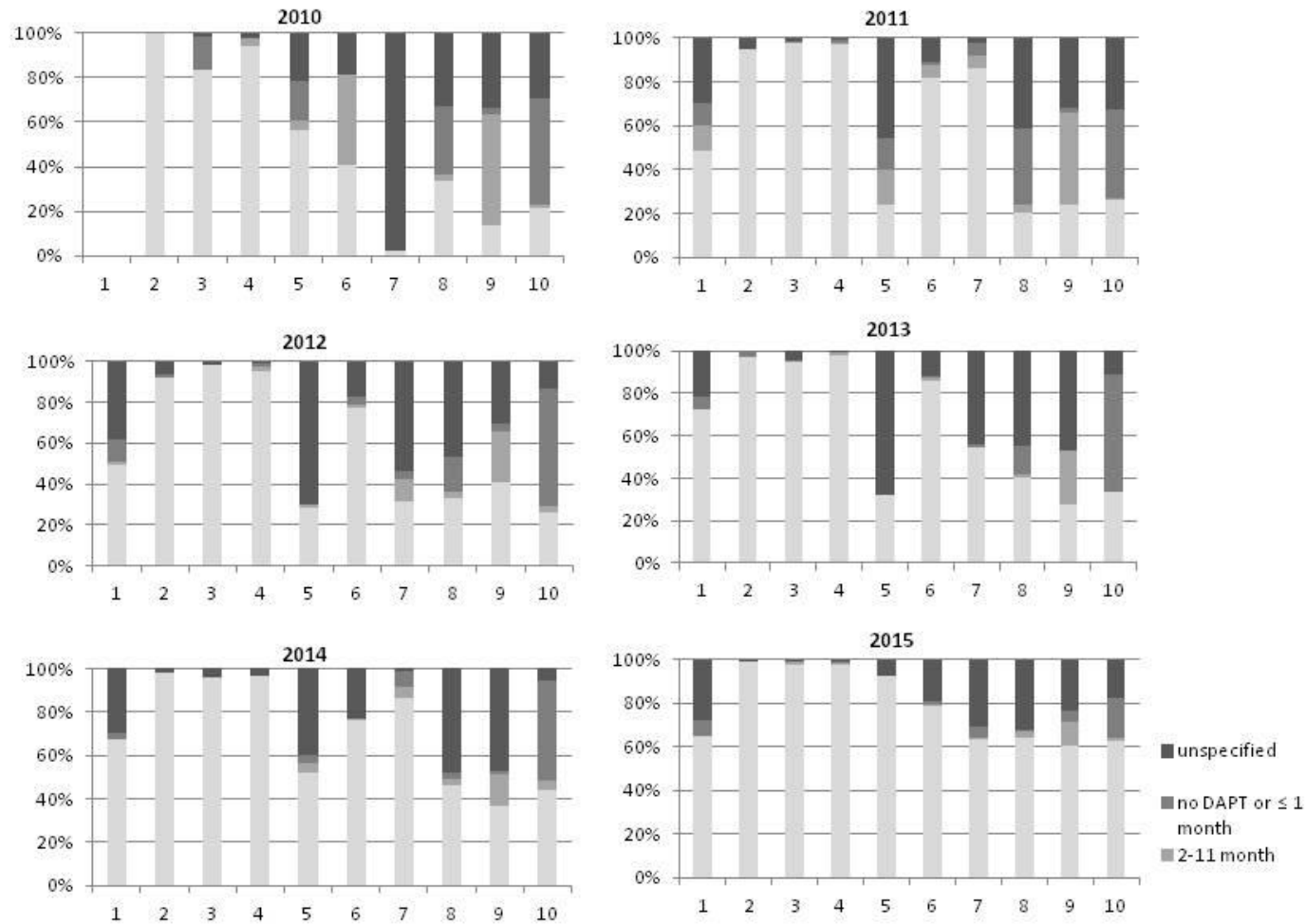| Drug treatment	ATC code
ASA	B01AC06, N02BA01, B01AC30
Ticlopidine	B01AC05
Clopidogrel	B01AC04
Prasugrel	B01AC22
Ticagrelor	B01AC24
Dabigatran etexilate	B01AE07
Rivaroxaban	B01AF01
Apixaban	B01AF02
Beta-blocker	C07
ACE inhibitor	C09
Statins	C10AA

Supplemental table 3. Factors associated with a persistence of at least 12 months as assessed with interrupted time series logistic regression model. Results of sensitivity analyses.

Fixed Effects	Original Model			Discharged home			Non-ischemic or haemorrhagic events		
	OR	CI95%	P value	OR	CI95%	P value	OR	CI95%	P value
Drug eluting stent	2.02	1.61 - 2.53	<0.001	1.93	1.46 - 2.54	<0.001	2.045	1.66 - 2.53	<0.001
Number of Stents	1.21	1.12 - 1.31	<0.001	1.31	1.18 - 1.44	<0.001	1.231	1.14 - 1.33	<0.001
Recommendation at PCI hospital discharge (Ref. 1 month)									
<12 months	1.67	0.88 - 3.17	0.120	3.26	1.71 - 6.2	<0.001	2.016	0.96 - 4.26	0.066
≥12 months	5.92	3.34 - 10.52	<0.001	6.97	3.97 - 12.26	<0.001	7.443	4.19 - 13.23	<0.001
unknown	2.23	0.82 - 6.02	0.115	2.50	0.88 - 7.08	0.086	2.594	0.93 - 7.25	0.069
Hyperlipidemia	1.19	1.08 - 1.31	<0.001	1.14	1 - 1.3	0.045	1.222	1.11 - 1.35	<0.001
Previous by-pass surgery	1.81	1.06 - 3.07	0.029	2.69	1.3 - 5.58	0.008	1.838	1.01 - 3.34	0.045
Two or more treated vessels	1.20	1.09 - 1.32	<0.001	1.18	1.04 - 1.34	0.012	1.116	1.01 - 1.24	0.033
Drug eluting stents * Time (quarter)	0.97	0.95 - 0.98	<0.001	0.96	0.94 - 0.98	<0.001	0.963	0.95 - 0.98	<0.001
Guidelines implementation	1.20	1.11 - 1.3	<0.001	1.24	1.12 - 1.36	<0.001	1.238	1.14 - 1.35	<0.001
Recommendation at PCI hospital discharge (Ref. 1 month) * Time (quarter)*Guidelines implementation									
<12 months	0.91	0.8 - 1.05	0.191	0.87	0.73 - 1.03	0.097	0.904	0.79 - 1.04	0.160
≥12 months	0.87	0.8 - 0.94	0.001	0.85	0.76 - 0.94	0.002	0.845	0.77 - 0.92	<0.001
unknown	0.89	0.82 - 0.98	0.013	0.86	0.77 - 0.97	0.012	0.865	0.79 - 0.95	0.003
Random Effects	Var.	SD		Var.	SD		Var.	SD	
Random - Intercept	0.46	0.68		0.62	0.78		0.40	0.63	
Random - Slopes									
Recommendation at PCI hospital discharge (Ref. 1 month)	0.38	0.62		0.11	0.33		0.66	0.81	
<12 months	0.39	0.62		0.39	0.63		0.40	0.63	
≥12 months	2.00	1.41		2.16	1.47		2.12	1.46	
Drug eluting stent	0.09	0.30		0.13	0.35		0.07	0.27	
ICC	0.087			0.099			0.100		

Supplemental figure 1. Persistence with DAPT from discharge to 12 monhts by year of episode.
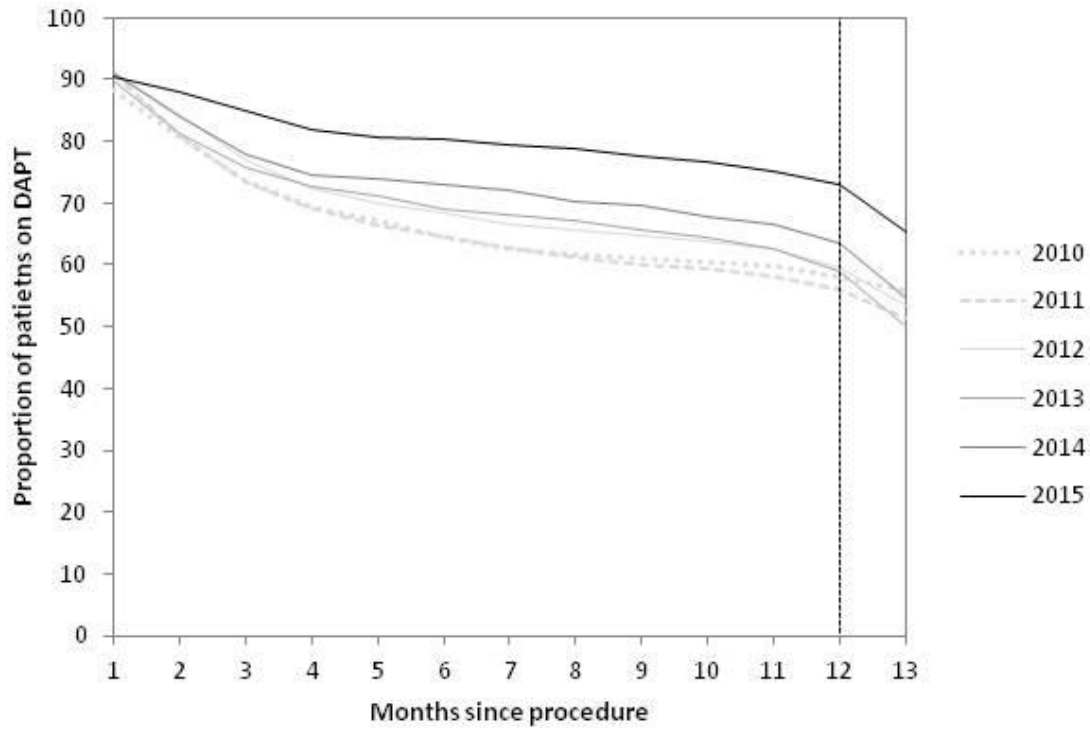
Supplemental figure 2. DAPT duration recommended in each hospital by year of episode

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page num
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3 (Design)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7-8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7-8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-8
Bias	9	Describe any efforts to address potential sources of bias	10-11
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10-11
		(*b*) Describe any methods used to examine subgroups and interactions	10-11
		(*c*) Explain how missing data were addressed	13
		(*d*) If applicable, explain how loss to follow-up was addressed	13
		(*e*) Describe any sensitivity analyses	12
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12
		(b) Give reasons for non-participation at each stage	12
		(c) Consider use of a flow diagram	Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Tables 1, 2
		(b) Indicate number of participants with missing data for each variable of interest	Tables 1, 2
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	Fig 1

			suppl
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 3
		(*b*) Report category boundaries when continuous variables were categorized	Table 3
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Table 3 suppl
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	19-20
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19-20
Generalisability	21	Discuss the generalisability (external validity) of the study results	20
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	5

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Persistence with dual antiplatelet therapy after percutaneous coronary intervention for ST-Segment-Elevation Acute Coronary Syndrome. A population-based cohort study in Catalonia (Spain)

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Persistence with dual antiplatelet therapy after percutaneous coronary intervention for ST-Segment-Elevation Acute Coronary Syndrome. A population-based cohort study in Catalonia (Spain)

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Keywords: dual antiplatelet therapy, persistence with treatment, ST-elevation myocardial infarction, percutaneous coronary intervention

2

ABSTRACT

Objectives: Guidelines recommending 12 months dual antiplatelet therapy (DAPT) in patients with ST-elevation acute coronary syndrome (STEACS) undergoing percutaneous coronary intervention (PCI) were published in year 2012. We aimed to describe the influence of guideline implementation on the trend in 12-month persistence with DAPT between 2010 and 2015 and to evaluate its relationship with DAPT duration regimens recommended at discharge from PCI hospitals.

Design: Observational study based on region-wide registry data linked to pharmacy billing data for DAPT follow up.

Setting. All PCI hospitals (10) belonging to the AMI-Code network in Catalonia (Spain)

Participants: 10,711 STEACS patients undergoing PCI between 2010 and 2015 were followed up.

Primary and secondary outcome measures: Primary outcome was 12 month persistence with DAPT. Calendar year quarter, publication of guidelines; DAPT duration regimen recommended in the hospital discharge report, baseline patient characteristics and significant interactions were included in mixed effects logistic regression based interrupted time-series models. **Results**: The proportion of patients on-DAPT at 12 months increased from 58% (56-60) in 2010 to 73% (71-75) in 2015. The rate of 12-months persistence with DAPT significantly increased after the publication of clinical guidelines with a time lag of one year (OR=1.20; 95% CI: 1.11-1.30). A higher risk profile, more extensive and complex coronary disease, use of drug-eluting stents (OR=1.90; 95% CI: 1.50-2.40) and a 12-months DAPT regimen recommendation at discharge from the PCI hospital (OR=5.76; 95% CI: 3.26-10.2) were associated with 12-months persistence.

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Conclusion: Persistence with 12-month DAPT has increased since publication of clinical guidelines. Even though most patients were discharged on DAPT, only 73% with potential indication were on-DAPT 12 months after PCI. A guideline-based recommendation at PCI hospital discharge was highly associated with full persistence with DAPT. Establishing evidence-based, common prescribing criteria across hospitals in the AMI-network would favour adherence and reduce variability.

Strengths and limitations of this study

- The study describes the trends in persistence with DAPT during 2010-2015 in a region-wide comprehensive cohort of patients using administrative data linked to a clinical registry

- It also evaluates the impact of the DAPT duration recommended at the PCI hospital discharge on 12-months persistence

- Limitations of using observational registry data include the possibility of coding errors and the inability to accurately identify specific contraindications for treatment or other patient characteristics that might be relevant for the study aims

- The use of pharmacy refill data as a proxy of patients' adherence and persistence has also limitations which have been extensively described

Study funding

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Competing interest statement

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work

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Introduction

The need of dual antiplatelet therapy (DAPT) combining aspirin and an ADP-receptor blocker for at least 12 months in patients with ST-elevation acute coronary syndrome (STEACS) undergoing percutaneous coronary intervention (PCI) is well established and was incorporated into clinical guidelines in 2012[1,2].

Adherence of patients to this strategy is crucial to ensure its efficacy. Adherence to medication is usually defined[3] as the extent to which patients take medications as prescribed by their health care providers and persistence is defined as time from initiation to discontinuation of a therapy. Patients' persistence with DAPT may be influenced by several factors but will depend strongly on whether they ultimately receive a correct prescription from their physicians in the primary care setting. Patients may receive recommendations from various health providers at different stages of their process of care, from the interventionist cardiologist to their primary physician. It could be hypothesized that the last would tend to rely on the recommendation of the more specialized health professional. Thus, one potential determinant of patients' persistence with DAPT for at least 12 months is the instructions provided in the discharge report of the hospital where the patient was attended during the acute phase.

In Catalonia, an autonomous region of Spain, the acute care of STEACS is organized through a region-wide network, the Acute Myocardial Infarction (AMI) Code, to derive patients with suspected STEACS to one of the 10 reference hospitals with PCI

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capability. Performance of the AMI Code is prospectively and exhaustively registered[4,5], providing an appropriate tool for quality evaluation. The Catalan Health Information System systematically registers, among other, data on pharmacy refills. Pharmacy billing data, although indirect, is an accepted method for evaluating persistence with treatment in large patient cohorts[3,6].

The aims of the present study were: first, to describe persistence with DAPT for at least 12 months in patients with STEACS undergoing PCI from 2010 to 2015; second, to evaluate the influence guidelines recommendation for a 12-months DAPT schedule on the rate of 12-months persistence along time; and third, to evaluate the association of the DAPT duration recommended at the PCI hospital discharge with patients' persistence with treatment for at least 12 months.

Methods

Data sources

Data were obtained through the Public Data Analysis for Health Research and Innovation Program (PADRIS). The PADRIS allows access to information from different sources on public healthcare resources usage for the population of Catalonia linked at the patient level with warranted accomplishment of ethical principles. Specifically, for the present study we linked data of the pharmacy billing registry with the AMI Code Registry. The AMI Code registry was launched in 2010 to evaluate performance of the AMI Code [4,5]. Exhaustiveness and quality of data is assessed periodically (see supplemental methods for details). The database belongs to the Catalan Department

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of Health and includes demographic, clinical, and therapeutic data for each episode of

hospitalization for STEACS. It conforms to the ethical and legal requirements for

research purposes. The study obtained ethics approval from the Vall d'Hebron Clinical

Research Ethics Committee (EPA(AG)7/2014(3989)).

The registry was completed for the purpose of the present analysis with retrospective

collection of additional specific data: diseased vessels, responsible vessel, stent type,

number of stents. The recommendation of antithrombotic drugs was also collected *ad*

hoc for the study from the discharge report. The recommendation of DAPT was

defined as the recommendation of Acetylsalisilic acid (ASA) and clopidogrel, prasugrel

or ticagrelor for specified periods. If the recommended duration of DAPT was not

specified, the discharge recommendation pattern was classified as "unspecified". A

local investigator at each center performed the specific retrospective data collection.

History of major haemorrhage, neoplasia, renal disease, heart failure, peripheral

arterial disease and atrial fibrillation, were obtained from minimum basic data set

(MBDS) diagnoses coded in hospitalization episodes occurring in the previous three

months before index hospitalization. Major haemorrhage was defined as: a diagnosis

of digestive bleeding in any diagnostic position (primary or secondary) together with a

procedure code for endoscopic treatment or for transfusion of blood products, or a

diagnosis of haemorrhagic stroke, or a diagnosis of intraocular haemorrhage, or a

diagnosis of other types of haemorrhage together with a procedure code for

transfusion of blood products. Major ischemic events (AMI or stroke) and major

haemorrhage during the 12 months following the index episode were obtained in the

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same way. Mortality during the 12 months following the index episode was obtained

from the insured registry status.

Drug treatment during the 12-month post-discharge follow up was obtained from the

pharmacy billing registry. ICD9 and ATC codes used for the identification of study

variables are listed in the supplemental tables 1 and 2.

Data Availability Statement

Additional data is not available due to ethical requirements of the PADRIS Program

Study population

We included all consecutive patients who survived a STEACS between January 2010

and December 2015, received primary or post fibrinolysis PCI in one of the 10

reference hospitals of the AMI Code network, were discharged home or transferred to

another hospital and survived at least one month after AMI. New episodes of STACS

occurring to the same patients during the study period were only accounted as follow

up events. Patients with likely contraindication for DAPT (history of major bleeding or

neoplasm in the three months prior to the index episode and patients requiring

anticoagulation) were excluded.

Persistence with treatment

DAPT was defined as the concomitant use of ASA and a $P2Y_{12}$ antagonist. Persistence

with DAPT was estimated by identification of consecutive months with pharmacy refills

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with one container of each agent in the 12-month period after hospital discharge. Because pharmacy billing is registered in a monthly basis and the exact day of dispensation is unknown, we considered that a monthly dispensation until at least month 11 after the index episode would approximate a 12-months treatment period. If more than one container were dispensed in one month, the excess containers were pulled along the following months. Non-persistence was defined as either discontinuation or a break in therapy of at least two months after pulling along the excess containers. To describe persistence over the whole study period we estimated the proportion of patients alive and within the 12 months after discharge window who were on treatment on each month[7].

The primary outcome was a patient's persistence with DAPT for 12 months following discharge (or in other words, patients withdrawing both agents from the pharmacy until at least month 11).

Statistical analysis

We compared baseline characteristics between patients persisting with DAPT for at least 12 months and patients withdrawing DAPT before 12 months with chi square test or t test when appropriate. We tested for trends in patients' characteristics along calendar year of discharge for the index procedure with Jonckheere-Terpstra test for differences between ordered categories.

To evaluate the influence of time, guidelines publication and the DAPT duration recommended in the PCI hospital discharge report we modelled logistic regression based interrupted time-series analysis[8], adjusting for baseline characteristics. As a

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first step, because it is expected that guidelines publication influences practice with a time delay, we plotted the proportion of patients persisting on-DAPT for 12 months by year quarter of discharge from the PCI hospital and we tested models with a slope change (indicating the start of guideline implementation) at different lag periods after publication of the European clinical guidelines (last quarter of 2012). Once the lag period between guidelines publication and implementation of recommendations was estimated we included patient characteristics and second or third level interactions of each characteristic with year quarter and moment of implementation. We also included an autocorrelation term. We coded time (T) as the time elapsed since the publication of guidelines plus the lag period (in quarters) and a dummy variable (X_t) indicating the pre-implementation period (coded 0) or the post-implementation period (coded 1)[9].

The standard model specification was the following:

$$logit\ (Y_t) = \ \beta_0 + \beta_1 T + \beta_2 X_t + \beta_3 TX_t$$

Where β_0 represents the baseline level at T = 0, β_1 is interpreted as the change in outcome associated with a time unit (quarter) increase (representing the underlying pre-implementation trend), β_2 is the level change following the implementation and β_3 indicates the slope change following the implementation (using the interaction between time and implementation: TX_t). Additional terms can be added to model the effect of other covariables and their interactions with T and X_t and to include random effects. Note that we set T = 0 at the quarter where we observed a significant change in the slope at a lag time after guidelines publication.

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We took into account the clustered structure of data with patients being treated and, most importantly, with recommendations on DAPT duration being provided in different hospitals, by introducing random effects in the logistic regression models.

We tested whether models including random intercepts for hospital and random slopes for each independent variable were significant using a deviance–based test of hypothesis.

Variable selection for multilevel modelling was based on the bivariate associations with the rate of each dependent variable. Candidate individual variables were those described in tables 1 and 2. We retained in the final model all variables with a p value<0.2.

Plots of predicted probability values were used to show marginal effects of variables of interest and variability between centres.

Sensitivity analyses

Because a substantial proportion of patients were returned to their reference hospital and because it was unknown whether the DAPT duration recommendation was changed at discharge from the second hospital, we performed sensitivity analyses excluding these patients. Additionally, because ischemic and haemorrhagic events occurring during follow up would change the treatment length, sensitivity analyses were also performed by excluding patients suffering any vascular event during follow up.

Patient and Public Involvement

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Neither patients nor public were directly involved in the study.

Results

After excluding patients with likely contraindication for DAPT (figure 1), we identified 10,711 STEACS patients undergoing PCI who were potential candidates to receive DAPT for at least 12 months and survived for at least one month after discharge. 631 (5.9%) patients experienced an ischemic major event (AMI or stroke) within 12 months after the index episode, 100 (0.9%) had a major haemorrhage and 280 (2.6%) died between one and 12 months after the index episode. After excluding patients who died or were lost to follow up and patients with errors in quarter allocations, 10,262 patients remained for analysis.

Table 1 shows characteristics of study patients depending on persistence with DAPT. Patients persisting for at least 12 months had higher prevalence of cardiovascular risk factors (hypertension, diabetes and hypercholesterolemia), higher rate of a previous history of cardiovascular disease, more extended coronary disease, higher rate of drug eluting stents implantation and slightly higher ischemic risk (as measured with the DAPT score[10]). Persisting patients were more often transferred to their reference hospital and had had a prescription for a longer DAPT period at discharge from the PCI hospital.

Table 1. Characteristics of study patients according to DAPT persistence during follow up.

	DAPT <12 months (n=3684)		DAPT ≥ 12 months (n=6578)		Total (n=10262)		P value
	N	n (%)	N	n (%)	N	n (%)	
Age	3684	61.19 ± 13.21	6578	61.18 ± 12.38	10262	61.19 ± 12.69	0.578

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Gender (Female)	3684	765 (20.8%)	6578	1319 (20.1%)	10262	2084 (20.3%)	0.399
Smoke (Y)	3684	1774 (48.2%)	6578	3042 (46.2%)	10262	4816 (46.9%)	0.064
Hypertension (Y)	3684	1622 (44%)	6578	3142 (47.8%)	10262	4764 (46.4%)	<0.001
Diabetes (Y)	3684	647 (17.6%)	6578	1298 (19.7%)	10262	1945 (19%)	0.008
Hypercholesterolaemia (Y)	3684	1291 (35%)	6578	2678 (40.7%)	10262	3969 (38.7%)	<0.001
Polyvascular disease (Y)*	3684	530 (14.4%)	6578	1048 (15.9%)	10262	1578 (15.4%)	0.038
Previous stroke or transient ischaemic attack (Y)	3684	101 (2.7%)	6578	172 (2.6%)	10262	273 (2.7%)	0.704
Previous acute myocardial infarction (Y)	3684	265 (7.2%)	6578	570 (8.7%)	10262	835 (8.1%)	0.010
Previous percutaneous coronary intervention (Y)	3684	194 (5.3%)	6578	482 (7.3%)	10262	676 (6.6%)	<0.001
Previous by-pass surgery (Y)	3684	20 (0.5%)	6578	85 (1.3%)	10262	105 (1%)	<0.001
History of peripheral arteriopathy (Y)	3684	153 (4.2%)	6578	276 (4.2%)	10262	429 (4.2%)	0.957
Comorbidity (Y)†	3684	462 (12.5%)	6578	885 (13.5%)	10262	1347 (13.1%)	0.191
Hepatopathy (Y)	3684	48 (1.3%)	6578	56 (0.9%)	10262	104 (1%)	0.030
History of Renal Impairment (Y)	3684	185 (5%)	6578	320 (4.9%)	10262	505 (4.9%)	0.741
History of Heart Failure (Y)	3684	272 (7.4%)	6578	583 (8.9%)	10262	855 (8.3%)	0.009
Affected number of vessels ≥2 (Y)	3684	1275 (34.6%)	6578	2731 (41.5%)	10262	4006 (39%)	<0.001
Number of treated vessels	3613	1.03 ± 0.21	6516	1.06 ± 0.26	10129	1.05 ± 0.25	<0.001
Number of stents	3681	1.09±0.6	6563	1.21±0.68	10244	1.16±0.65	<0.001
Drug eluting stent (Y)	3684	572 (15.5%)	6578	2704 (41.1%)	10262	3276 (31.9%)	<0.001
DAPT Score Points	3684	1.20 ± 1.20	6578	1.28 ± 1.17	10262	1.25 ± 1.18	<0.001
Discharged home (Y)	3684	2233 (60.6%)	6578	3672 (55.8%)	10262	5905 (57.5%)	<0.001
Antiplatelet agent at discharge	3684		6578		10262		<0.001
Clopidogrel		3184 (86.4%)		4872 (74.1%)		8056 (78.5%)	
Prasugrel		278 (7.5%)		1102 (16.8%)		1380 (13.4%)	
Ticagrelor		222 (6%)		604 (9.2%)		826 (8%)	
DAPT recommendation at discharge	3684		6578		10262		<0.001
1 month		875 (23.8%)		295 (4.5%)		1170 (11.4%)	
<12 months		385 (10.5%)		173 (2.6%)		558 (5.4%)	
≥12months		1522 (41.3%)		4732 (71.9%)		6254 (60.9%)	
unknown		902 (24.5%)		1378 (20.9%)		2280 (22.2%)	

*Polyvascular disease was defined as presence of at least two of the following conditions: previous myocardial infarction or percutaneous coronary or surgical revascularization; history of peripheral arteriophaty; history of stroke or transient ischaemic attack. †Comorbidity was defined as presence of one of the following conditions: hepatophaty, history of renal impairment, history of heart failure

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The rate of patients on-DAPT after discharge from the PCI hospital was 91% (95% CI: 90-91) without relevant differences between years (supplemental figure 1). The proportion of patients on-DAPT at 12 months significantly increased from 58% (56-61) in 2010 to 73% (71-75) in 2015. The larger increase in 12-month persistence was observed between 2014 (64% [62-66]) and 2015, two years after the publication of clinical guidelines. The proportion of patients with prasugrel or ticagrelor instead of clopidogrel started increasing after 2012 (supplemental figure 2).

Some baseline characteristics showed a temporal trend over the study period 2010-2015 (table 2). The prevalence of cardiovascular risk factors (smoking, hypertension and hypercholesterolemia) and comorbidities increased slightly. Likewise, the number of treated vessels the rate of drug eluting stents implantation and the rate of prasugrel or ticagrelor also increased with time.

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Table 2. Characteristics of study patients by year of discharge for the index admission.

	2010 (n=1537)	2011 (n=1628)	2012 (n=1760)	2013 (n=1779)	2014 (n=1779)	2015 (n=1779)	P value
Age	61 ± 12.92	61.01 ± 13.09	60.97 ± 12.52	61.27 ± 12.4	61.24 ± 12.72	61.58 ± 12.53	0.325
Gender	310 (20.2%)	311 (19.1%)	372 (21.1%)	359 (20.2%)	352 (19.8%)	380 (21.4%)	0.389
Smoke	686 (44.6%)	754 (46.3%)	811 (46.1%)	839 (47.2%)	840 (47.2%)	886 (49.8%)	0.004
Hypertension	674 (43.9%)	729 (44.8%)	808 (45.9%)	838 (47.1%)	844 (47.4%)	871 (49%)	0.001
Diabetes	296 (19.3%)	319 (19.6%)	340 (19.3%)	327 (18.4%)	325 (18.3%)	338 (19%)	0.438
Hypercholesterolaemia	541 (35.2%)	621 (38.1%)	648 (36.8%)	710 (39.9%)	742 (41.7%)	707 (39.7%)	<0.001
Polyvascular disease*	232 (15.1%)	253 (15.5%)	301 (17.1%)	259 (14.6%)	278 (15.6%)	255 (14.3%)	0.370
Previous stroke or transient ischaemic attack	42 (2.7%)	32 (2%)	45 (2.6%)	40 (2.2%)	65 (3.7%)	49 (2.8%)	0.126
Previous acute myocardial infarction	127 (8.3%)	142 (8.7%)	163 (9.3%)	151 (8.5%)	127 (7.1%)	125 (7%)	0.029
Previous percutaneous coronary intervention	94 (6.1%)	104 (6.4%)	123 (7%)	116 (6.5%)	118 (6.6%)	121 (6.8%)	0.485
Previous by-pass surgery	10 (0.7%)	16 (1%)	17 (1%)	19 (1.1%)	18 (1%)	25 (1.4%)	0.056
History of peripheral arteriopathy	51 (3.3%)	70 (4.3%)	93 (5.3%)	66 (3.7%)	86 (4.8%)	63 (3.5%)	0.876
Comorbidity†	155 (10.1%)	190 (11.7%)	233 (13.2%)	243 (13.7%)	266 (15%)	260 (14.6%)	<0.001
Hepatopathy	16 (1%)	12 (0.7%)	24 (1.4%)	24 (1.3%)	13 (0.7%)	15 (0.8%)	0.578
History of Renal Impairment	70 (4.6%)	75 (4.6%)	71 (4%)	86 (4.8%)	89 (5%)	114 (6.4%)	0.009
History of Heart Failure	80 (5.2%)	118 (7.2%)	154 (8.8%)	159 (8.9%)	187 (10.5%)	157 (8.8%)	<0.001
Affected number of vessels ≥2	594 (38.6%)	617 (37.9%)	679 (38.6%)	707 (39.7%)	688 (38.7%)	721 (40.5%)	0.188
Number of treated vessels	1.04 ± 0.25	1.03 ± 0.23	1.05 ± 0.26	1.05 ± 0.24	1.05 ± 0.26	1.06 ± 0.24	0.003
Number of stents	1.23 ± 0.69	1.17 ± 0.60	1.18 ± 0.63	1.14 ± 0.66	1.12 ± 0.67	1.16 ± 0.66	<0.001
Drug eluting stent	462 (30.1%)	388 (23.8%)	472 (26.8%)	493 (27.7%)	652 (36.6%)	809 (45.5%)	<0.001
DAPT Score Points	1.24 ± 1.2	1.24 ± 1.19	1.26 ± 1.17	1.26 ± 1.17	1.22 ± 1.16	1.28 ± 1.19	0.435
Discharged home	961 (62.5%)	951 (58.4%)	933 (53%)	1042 (58.6%)	959 (53.9%)	1059 (59.5%)	0.041
Antiplatelet agent at discharge							<0.001
Clopidogrel	1528 (99.4%)	1587 (97.5%)	1582 (89.9%)	1384 (77.8%)	1114 (62.6%)	861 (48.4%)	
Prasugrel	9 (0.6%)	38 (2.3%)	135 (7.7%)	244 (13.7%)	416 (23.4%)	538 (30.2%)	

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	2010 (n=1537)	2011 (n=1628)	2012 (n=1760)	2013 (n=1779)	2014 (n=1779)	2015 (n=1779)	P value
Ticagrelor	0 (0%)	3 (0.2%)	43 (2.4%)	151 (8.5%)	249 (14%)	380 (21.4%)	
DAPT recommendation at discharge							<0.001
1 month	281 (18.3%)	259 (15.9%)	243 (13.8%)	181 (10.2%)	135 (7.6%)	71 (4%)	
<12 months	150 (9.8%)	137 (8.4%)	100 (5.7%)	69 (3.9%)	65 (3.7%)	37 (2.1%)	
≥12 months	792 (51.5%)	871 (53.5%)	975 (55.4%)	1086 (61%)	1154 (64.9%)	1376 (77.3%)	
unknown	314 (20.4%)	361 (22.2%)	442 (25.1%)	443 (24.9%)	425 (23.9%)	295 (16.6%)	

*Polyvascular disease was defined as presence of at least two of the following conditions: previous myocardial infarction or percutaneous coronary or surgical revascularization; history of peripheral arteriophaty; history of stroke or transient ischaemic attack. †Comorbidity was defined as presence of one of the following conditions: hepatophaty, history of renal impairment, history of heart failure

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The overall rate of explicit DAPT recommendation for at least 12 months in the hospital discharge reports was 51% (49-53) in 2010 and increased to 77% (75-79) in 2015 but it was highly variable between hospitals (supplemental figure 3).

Figure 2 shows the observed proportion of patients persisting with DAPT for at least 12 months at each time point and the interrupted time series model fitted after setting a one year lag period from publication to implementation of guidelines.

Table 3 shows results of the complete cases analysis (n=10,244) using interrupted time series logistic regression. Variables showing association with 12 month persistence on DAPT were two or more diseased vessels, higher number of stents implanted, receiving drug eluting stents, hypercholesterolemia, a previous surgical procedure, taking prasugrel instead of clopidogrel and a recommendation of DAPT for a longer period at discharge from the PCI hospital. Autocorrelation was not significant. Guideline implementation had a positive effect on persistence: a 20% increase in the odds of 12 month persistence each quarter after a lag of one year since publication. The effect of drug eluting stents was attenuated with time (OR for interaction: 0.96; 95%CI: 0.94-0.97) while the effect of prescription was attenuated with time after guideline implementation (OR for the interaction 0.86, 95%CI: 0.79-0.94 for a recommendation of ≥12 months and 0.88, 95%CI: 0.81-0.97 for an unknown recommendation). The effect of implantation of drug eluting stents and type of recommendation also varied between hospitals (significant random slopes).

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Table 3. Factors associated with a persistence of at least 12 months as assessed with interrupted time series logistic regression model

Fixed effects	OR	95% CI	P value
Drug eluting stent	1.90	1.50 - 2.40	<0.001
Number of stents	1.22	1.13 - 1.32	<0.001
Antiplatelet agent at discharge (Ref. Clopidogrel)			
Prasugrel	1.59	0.88 – 1.26	<0.001
Ticagrelor	1.05	1.36 – 1.86	0.575
Recommendation at PCI hospital discharge (Ref. 1 month)			
<12 months	1.67	0.89 - 3.14	0.110
>=12 months	5.76	3.26 - 10.2	<0.001
unknown	2.25	0.84 - 6.01	0.107
Hypercolesterolemia	1.19	1.08 - 1.31	<0.001
Previous by-pass surgery	1.85	1.09 - 3.14	0.023
Two or more treated vessels	1.21	1.10 - 1.33	<0.001
Drug eluting stent * Time (quarter)	0.96	0.94 - 0.97	<0.001
Guideline implementation	1.20	1.11 - 1.30	<0.001
Recommendation at PCI hospital discharge (Ref. 1 month) * Time (quarter)*Guideline implementation			
<12 months	0.90	0.79 - 1.04	0.144
≥ 12 months	0.86	0.79 - 0.94	<0.001
unknown	0.88	0.81 - 0.97	0.007
Random effects	**Variance**	**95% CI**	
Random - Intercept	0.46	0.22 – 1.53	
Random - Slopes			
Recommendation at PCI hospital discharge (Ref. 1 month)			
<12 months	0.37	0.17 – 1.23	
≥12 months	0.39	0.19 – 1.31	
unknown	1.97	0.93 – 6.58	
Drug eluting stent	0.10	0.05 – 0.33	
Adjusted ICC	0.085		

Results of sensitivity analyses, excluding patients with ischemic or haemorrhagic events during follow up, or excluding patients that were transferred to another centre after PCI were similar to the main analysis (Supplemental table 3S).

The interaction between drug eluting stents and time can be seen in figure 3A. Because 12-months persistence increased with time in patients without drug eluting

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stents, the effect of type of stent is attenuated with time. The interaction of the recommendation pattern with time and guideline implementation can be seen in figure 3B: 12-months persistence increased with time mainly in the subgroups with shorter time specification in the discharge report and also in patients without a specific recommendation, but this increase started after guideline implementation (one year after publication). Figure 3C shows a substantial reduction in the variability between centres mainly due to an increase in the proportion of 12-months persistence in patients attended in centres where the initial proportion was lower (significant random intercept and slopes).

Discussion

According to published guidelines, all STEACS patients undergoing PCI without contraindication should be kept on DAPT for at least 12 months unless an event occurs that precludes continuing with this treatment. In this observational region-wide study we have found an increase in the proportion of patients on-DAPT at 12 months from 58 to 73% in the period from 2010 to 2015, with an accelerated rate starting in the fourth quarter of 2013, one year after the publication of European guidelines.

We also found a high variability between hospitals in the adherence to guidelines when recommending DAPT for at least 12 months which leads to substantial differences between hospitals in the rate of patients persisting with the recommended DAPT. The progressive increase in the overall rate of 12-months persistence was accompanied by a substantial reduction of interhospital variability.

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Likelihood of patients persisting with DAPT for one year is strongly related to the instructions given at the PCI hospital discharge, as we observed a lower rate of 12-month persistence in patients receiving a discharge DAPT recommendation for less than 12 months. Although a causal direct relationship between the established recommendation in the more specialised setting and the final prescription at the primary care setting cannot be stated on the basis of observational data, this finding suggests that prescribing physicians strongly rely on the first recommendation specified at the discharge report in the PCI hospital. Therefore, hospital cardiologists should be kept aware of their impact and encouraged to be clear and specific enough when providing DAPT time recommendations in the discharge report form.

The recommendation in clinical guidelines of DAPT for at least 12 months following STEACS[1,2] was based on the duration of follow up of randomised clinical trials designed for other purposes[11–13] and, although a 12-month treatment seemed reasonable [14], no randomized studies had been performed within the study period aimed specifically at comparing 12 months DAPT with shorter periods in STEACS patients receiving PCI and thus this recommendation might well be seen as somehow arbitrary by some prescribers.

In 2015 the need for long term DAPT was reinforced by the recommendation of extended DAPT beyond 12 months in patients with ACS receiving drug eluting stents[15–17], but still safety concerns might induce some prescribers to be reluctant to prolong DAPT, especially in patients with higher complexity[18]. Safety concerns might also explain the high proportion of discharge reports with non-specified DAPT

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period, which deserved special attention in our analyses. Cardiologists might be reluctant to prescribe a specific duration of DAPT maybe fearing about the emergency of events that increase the haemorrhagic risk at some point after discharge, thus relying on the follow up that will be made at the ambulatory setting. Our results showing a high degree of persistence for patients without a specification of DAPT time point out to the fact that this decision is not necessarily "incorrect", and that health providers coming later in the process of care are probably doing their job.

We might wonder whether the observed high variability between hospitals in the instructions provided about DAPT duration actually reflects suboptimal quality of care or confusion in the interpretation of international guidelines. In fact, although 2012 ESC guidelines state that DAPT must be continued for 12 months after STEACS with a class of recommendation I, the level of evidence was established as C[1]. Thus, there was general agreement that a minimum of 12 months of DAPT is likely to be beneficial but based only on a consensus of experts or observational studies. Moreover, it is literally stated that the given recommendation on DAPT duration should be "with a strict minimum of 1 month for patients receiving BMS and 6 months for patients receiving DES", with Class IC and IIb respectively. These messages, which ultimately reflected the lack of clinical trials aimed to answer the specific question about DAPT duration, could have induced a perception of arbitrariness leading to variability in clinical practice.

In fact, the optimal duration of DAPT has not yet been totally established in more contemporary clinical trials. The most recent randomized clinical trial conducted in

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patients with STEACS aimed to assess the question of 12-month vs a 6-month DAPT duration, showed that 6-month DAPT duration after primary PCI was non-inferior to 12-month duration to prevent major cardiovascular events[19]. In another trial in the context of ACS, 12 months or longer DAPT duration versus 6 months was not associated with lower major cardiovascular events and total mortality[20].

Regardless the level of the evidence, one would expect that a Class I recommendation should be uniformly followed by clinicians. Moreover, as patient characteristics did not substantially differed across hospitals, we should expect a lower variability between hospitals. A large variation in individual country practices concerning the pattern of DAPT duration after ACS has been described, suggesting that local systems are strong drivers of DAPT duration[21]. These findings may imply that there is still room for improvement in the quality of care of STEACS patients and that quality improvement programs, whose efficacy and cost-effectiveness are still under evaluation, could be useful to reduce variability in clinical practice[22]. This is of prime importance in the context of the prescription of DAPT duration after ACS in which the clinician-driven variability in prescription patterns adds to the different levels patients' adherence[21]. Higher atherosclerotic burden and increased ischemic risk was associated to better persistence with DAPT. The need for 12-month DAPT schedules in patients treated with drug eluting stents is clearly perceived by physicians but the magnitude of this association varies largely between hospitals. This means that, even in clear indications, there are different levels of adoption of emerging clinical recommendations in hospitals belonging to the same AMI network.

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It is also apparent from our data that the speed of adoption of clinical guidelines is different among hospitals and that an acceptable and generalised level of adherence is only reached after two years of implementation. Similar trends have been found in other contexts and earlier periods[23–28] reporting DAPT use between 60-80% at discharge and between 25-75 % at one year. In this sense, together with other quality improvement initiatives, the use of population-based registries to provide audit and feedback could be useful to promote quicker and smoother adoption of clinical practice guidelines[29].

There are a number of assumptions that might be questionable: A number of factors have been described to contribute to underprescription[30]. The complete process of care and the definite prescription at the ambulatory setting is poorly known for individual patients and has not been considered in this study. Changes in treatment prescription might be justified by the patients' varying conditions during follow up. We assume that hospital recommendation influences final prescription, and consequently, final adherence to guidelines, but it can also be that both "prescribers" facing the same patient share the same criteria for prescription. I.e. the hospital cardiologist might have decided to recommend DAPT for a shorter period to an elderly patient with other comorbidities and suboptimal quality of life due to mild digestive symptoms, even if her objective bleeding risk is not high; similarly, the primary physician or the cardiologist at the primary care setting might have also decided to be less aggressive for the same reasons, even without being influenced by the recommendation of the first prescriber. This would probably explain a large amount of the strong relationship between hospital recommendation and pharmacy dispensation. Moreover, although

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effects were adjusted for patient characteristics and vascular events during follow up, there might be other unmeasured reasons for deciding upon a shorter DAPT period facing an individual patient.

In addition, the recommendation at PCI hospital discharge may not coincide with the final hospital prescription in patients derived to another reference hospital after PCI. However, results of sensitivity analyses excluding these patients did not differ substantially from the results of the main analyses.

The study was aimed to ascertain influence of guidelines on hospital recommendation and its impact on patients' persistence with DAPT. The impact of persistence on clinically relevant results will be assessed in another article. Similarly, the study was not specifically aimed at a deep assessment of determinants of adherence. This requires a detailed examination of the social context and a detailed assessment of individual psychological factors[31].

Conclusion

The study shows that 12-month DAPT persistence in revascularized patients with STEACS in Catalonia (Spain) has substantially increased between years 2010 to 2015 especially since one year after the publication of European guidelines in 2012. Guideline implementation was also followed by a substantial decrease in variability between centres. We have shown that instructions given at the PCI hospital discharge are strongly associated with persistence. Thus establishing common and rational prescribing criteria between hospitals in the STEACS-network may favour patients

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persistence with scheduled prescriptions and also reduce variability in clinicians´ practices.

Author contributions

IFG, AR, JRM conceived and designed the study; AR, JRM and MTF participated in the acquisition and analysis of data; HTM, SR, CL, MC, SH, CTQ, JGP, JAGH and MM were responsible for data acquisition in their respective hospitals; AR, IFG, JRM, GO, AR, JIP, JM and DGD were involved in the interpretation of results; AR and IFG wrote the manuscript and all other authors revised it critically and approved its final version

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Figure legends

Figure 1. Patients flow

Figure 2. Observed proportion of patients persisting with DAPT for at least 12 months at each quarter and the interrupted time series model fitted after setting a one year lag period from publication to implementation of guidelines.

Figure 3. Temporal trend of interhospital variability in 12 months DAPT recommendation at the PCI hospital, measured as the percentage of variance explained by the hospital level (intraclass correlation and 95 % CI). Vertical dashed line indicates publication of guidelines.

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Figure 1. Patients flow

190x254mm (96 x 96 DPI)

Figure 2. Observed 12-months persistence rate by quarter and interrupted time series model specification after setting a one year lag period for guidelines implementation

127x127mm (300 x 300 DPI)

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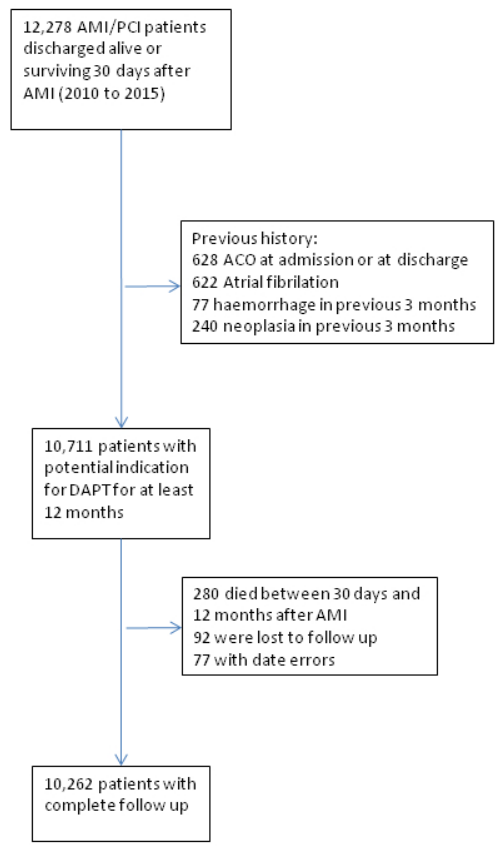45
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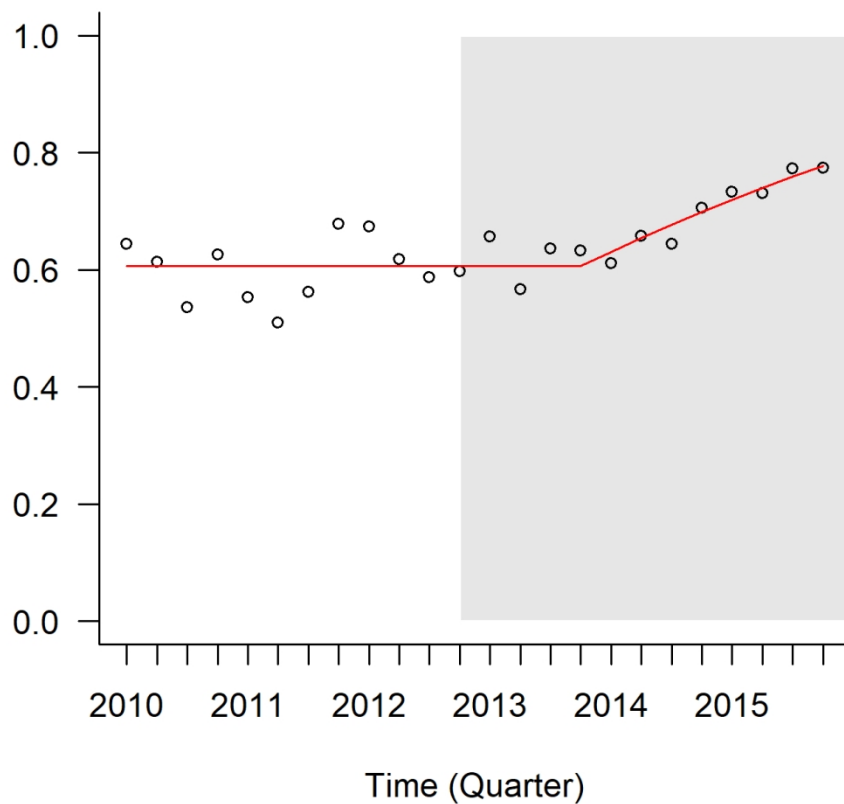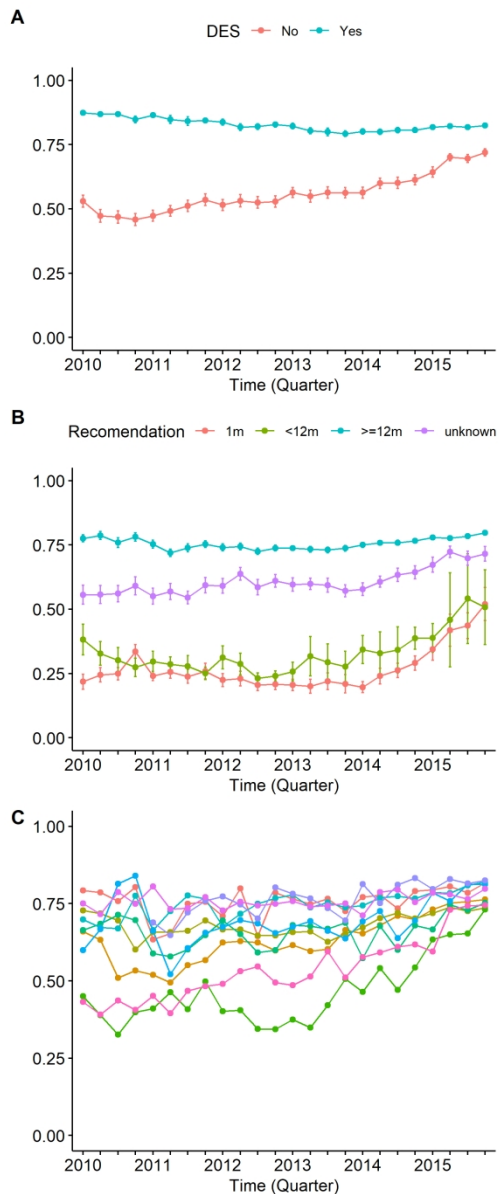47
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Figure 3. Predicted probabilities of 12-months persistence by (A) drug eluting stent, (B) recommendation pattern and (C) center, over time

127x304mm (300 x 300 DPI)

Supplemental methods

Data validation processes in the AMI Code registry

1. Automatic data validation processes to identify and feed-back missing data and incongruities.

2. Periodic data validation process every 3-6 months:

   Since year 2011 this process was automated. The system automatically detects missing information in key variables and the identification of AMI codes that were activated by the emergency services (before admission) and were not included in the registry. Feed back for data validation is sent every 3-6 months for amendment or justification to the person responsible for data entry at each AMI Code Hospital.

   Since year 2015 the automated process can be managed directly at any time by the person responsible for data entry in each hospital.

3. Specific studies:

   In 2012 data were evaluated for **exhaustiveness**: all AMI cases consecutively admitted in 43 hospitals in Catalonia (10 AMI Code hospitals and 32 no AMI Code hospitals) during a 3 months period were registered and compared with the episodes registered in the AMI Code registry. Between 88-92% of STEACS episodes were included in the AMI Code registry.

   In 2013 concordance of the information between the AMI Code registry and the information from clinical records was assessed. 330 cases were analyzed and concordance was good for all key variables and there were no differences between hospitals.

Supplemental tables

Supplemental table 1. ICD9 codes used for the identification of conditions and diseases present at index

admission and for the identification of events during follow up.

Disease or condition	ICD9 diagnostic or procedure code
Heart failure	428.0, 428.1, 428.22, 428.23, 428.3, 428.32, 428.33, 428.41, 428.43
Renal disease	585*
Neoplasia	140-239
Anemia	280-285
Chronic obstructive pulmonary disease	491-492, 494*, 496*
Peripheral arterial disease	440.2, 440.3, 440.4
Atrial fibrillation	427.3*
Events during follow up	
Acute myocardial infarction	410*, except: 410.*2
Ischemic stroke	433*, 434*, except: 433.*0, 434.*0
Haemorrhagic stroke	430*, 431*, 432*
Intraocular bleeding	362.81, 363.6, 363.61, 363.62, 376.32, 377.42, 379.23
Digestive bleeding	530.21, 530.7, 530.82, 531.0, 531.2, 531.4, 531.6, 532.0, 532.2, 532.4, 532.6, 533.0, 533.2, 533.4, 534.4, 534.6, 535.01, 535.11,535.21, 535.31, 535.41, 535.51, 535.61, 535.71, 537.83, 562.02, 562.03, 562.12, 562.13, 569.3, 569.85, 578.1, 578.9
Other bleeding	246.3, 459.0, 602.1, 784.8, 596.7, 599.7, 852*, 997.02, 998.1,
Endoscopic treatment	444.3, 454.2, 454.3
Transfusion	990.4

Supplemental table 2. ATC codes used for the identification of drug treatment

| Drug treatment	ATC code
ASA	B01AC06, N02BA01, B01AC30
Ticlopidine	B01AC05
Clopidogrel	B01AC04
Prasugrel	B01AC22
Ticagrelor	B01AC24
Dabigatran etexilate	B01AE07
Rivaroxaban	B01AF01
Apixaban	B01AF02
Beta-blocker	C07
ACE inhibitor	C09
Statins	C10AA

Supplemental table 3. Factors associated with a persistence of at least 12 months as assessed with interrupted time series logistic regression model. Results of sensitivity analyses.

Fixed Effects	Original Model			Discharged home			Non-ischemic or haemorrhagic events		
	OR	CI95%	P value	OR	CI95%	P value	OR	CI95%	P value
Drug eluting stent	1.90	1.50 - 2.40	<0.001	2.00	1.43 - 2.81	<0.001	1.92	1.54 – 2.39	<0.001
Number of Stents	1.22	1.13 - 1.32	<0.001	1.10	0.98 – 1.24	0.117	1.24	1.15 – 1.35	<0.001
Antiplatelet agent at discharge (Ref. Clopidogrel)									
Prasugrelor	1.59	0.88 – 1.26	<0.001	1.72	1.34 – 2.20	<0.001	1.63	1.38 – 1.91	<0.001
Ticagrelor	1.05	1.36 – 1.86	0.575	1.06	0.81 – 1.38	0.665	1.05	0.87 – 1.27	0.614
Recommendation at PCI hospital discharge (Ref. 1 month)									
<12 months	1.67	0.89 - 3.14	0.110	0.98	0.51 – 1.88	0.957	2.03	0.97 – 4.24	0.059
≥ 12 months	5.76	3.26 - 10.2	<0.001	4.29	2.45 – 7.51	<0.001	7.22	4.09 – 12.8	<0.001
unknown	2.25	0.84 - 6.01	0.107	2.81	1.33 – 5.93	0.007	2.62	0.95 – 7.24	0.064
Hyperlipidemia	1.19	1.08 - 1.31	<0.001	1.25	1.09 - 1.44	0.002	1.22	1.11 – 1.35	<0.001
Previous by-pass surgery	1.85	1.09 - 3.14	0.023	1.11	0.51 – 2.41	0.795	1.91	1.05 – 3.46	0.033
Two or more treated vessels	1.21	1.10 - 1.33	<0.001	1.27	1.10 - 1.46	0.001	1.12	1.01 – 1.24	0.026
Drug eluting stents * Time (quarter)	0.96	0.94 - 0.97	<0.001	0.97	0.94 - 0.99	0.006	0.96	0.94 – 0.97	<0.001
Guidelines implementation	1.20	1.11 - 1.30	<0.001	1.10	0.96 - 1.26	0.161	1.23	1.14 – 1.34	<0.001
Recommendation at PCI hospital discharge (Ref. 1 month) * Time (quarter)*Guidelines implementation									
<12 months	0.90	0.79 - 1.04	0.144	1.03	0.82 - 1.28	0.806	0.89	0.78 – 1.03	0.118
≥12 months	0.86	0.79 - 0.94	<0.001	0.93	0.81 – 1.08	0.349	0.84	0.77 – 0.92	<0.001
unknown	0.88	0.81 - 0.97	0.007	0.97	0.84 – 1.12	0.678	0.86	0.78 – 0.94	0.001
Random Effects	Var.	95% CI		Var.	95% CI		Var.	95% CI	
Random - Intercept	0.46	0.22 – 1.53		0.26	0.12 – 0.88		0.40	0.19 – 1.32	
Random - Slopes									
Recommendation at PCI hospital discharge (Ref. 1 month)									
<12 months	0.37	0.17 – 1.23		0.15	0.07 – 0.49		0.64	0.31 – 2.15	
≥12 months	0.39	0.19 – 1.31		0.30	0.14 – 0.99		0.40	0.19 – 1.33	
unknown	1.97	0.93 – 6.58		0.66	0.31 – 2.18		2.09	0.99 – 6.97	
Drug eluting stent	0.10	0.05 – 0.33		0.17	0.08 – 0.57		0.08	0.04 – 0.26	
ICC	0.085			0.043			0.098		

Supplemental figure 1. Persistence with DAPT from discharge to 12 monhts by year of episode.
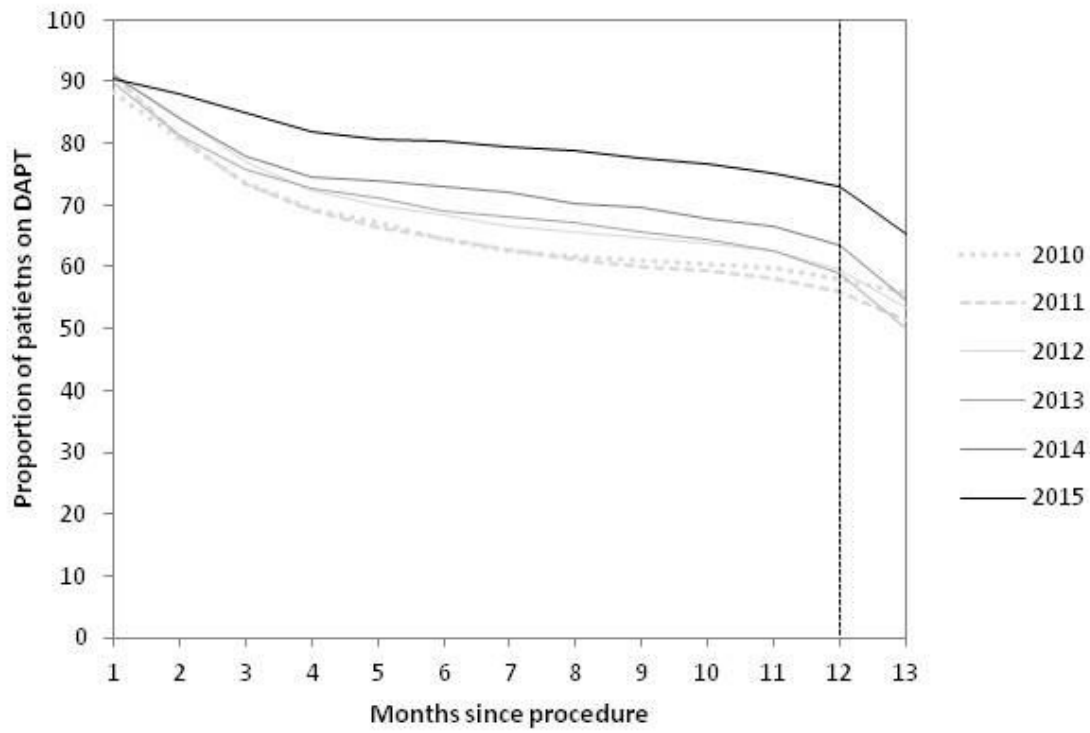
1 Supplemental figure 2. Antiplatelet agent taken at discharge by quarter of the index episode.

ANTIAGREGANT DISTRIBUTION IN EACH QUARTER

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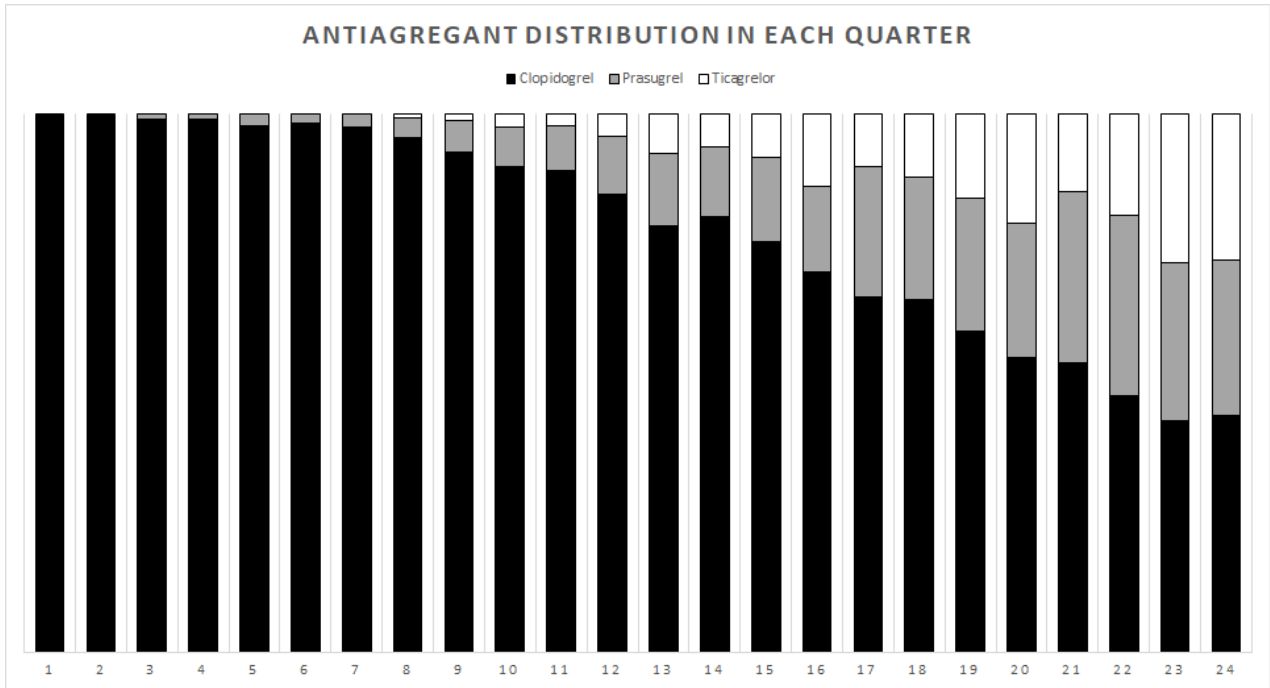
Supplemental figure 3. DAPT duration recommended in each hospital by year of episode

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page num
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3 (Design)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7-8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7-8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-8
Bias	9	Describe any efforts to address potential sources of bias	10-11
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10-11
		(*b*) Describe any methods used to examine subgroups and interactions	10-11
		(*c*) Explain how missing data were addressed	13
		(*d*) If applicable, explain how loss to follow-up was addressed	13
		(*e*) Describe any sensitivity analyses	12
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12
		(b) Give reasons for non-participation at each stage	12
		(c) Consider use of a flow diagram	Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Tables 1, 2
		(b) Indicate number of participants with missing data for each variable of interest	Tables 1, 2
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	Fig 1

				suppl
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 3
		(*b*) Report category boundaries when continuous variables were categorized	Table 3
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Table 3 suppl
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	19-20
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19-20
Generalisability	21	Discuss the generalisability (external validity) of the study results	20
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	5

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.