PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Persistence with dual antiplatelet therapy after percutaneous coronary intervention for ST-Segment-Elevation Acute Coronary Syndrome. A population-based cohort study in Catalonia (Spain)
AUTHORS	Ribera, Aida; Ferreira-Gonzalez, Ignacio; Marsal, Josep Ramon; Oristrell, Gerard; Faixedas, Maria Teresa; Rosas, Alba; Tizón-Marcos, Helena; Rojas, Sergio; Labata, Carlos; Cardenas, Merida; Homs, Silvia; Tomas-Querol, Carlos; Garcia-Picart, Joan; Gomez-Hospital, Joan; Pijoan, Jose; Masotti, Monica; Mauri, Josepa; Garcia Dorado, David

VERSION 1 – REVIEW

REVIEWER	Raffaele Bugiardini University of Bologna
REVIEW RETURNED	19-Dec-2018

GENERAL COMMENTS	Current guidelines recommend dual antiplatelet therapy (DAPT) of aspirin plus a P2Y12 inhibitor for at least 12 months after implantation of drug-eluting stents (DES) in patients with acute coronary syndrome. However, available data about the optimal duration of DAPT in patients with acute coronary syndrome undergoing percutaneous coronary intervention are scant. The current study aimed to investigate whether a12-month duration of DAPT would persist for 12-months in a population of consecutive patients who received primary or post fibrinolysis PCI and survived between January 2010 and December 2015 in one of the 10 reference hospitals of the Public Data Analysis for Health Research and Innovation Program (PADRIS). The authors conclude that a to 12-month DAPT has increased since publication of clinical guidelines. Comments (1) Recent work has shown that the increased risk of myocardial infarction with 6-month DAPT and the wide non-inferiority margin prevent us from concluding that short-term DAPT is safe in patients with acute coronary syndrome undergoing percutaneous coronary intervention with current-generation DES. Prolonged DAPT in patients with acute coronary syndrome without excessive risk of bleeding should remain the standard of care (Hahn JY1Lancet. 2018). This paper should be mentioned and its data should be discussed in the current study. (2) Do you have access to data that would provide reasons for shorter treatment length or treatment switch done by general practitioners?

(3) The authors defined persistence with DAPT as "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".

Recent work published in bmj open (ref. 21) defined persistence with DAPT as "having filled a prescription for the given drug within 90 days prior to the admission to 30 days after the admission" . "A participant was considered a current user of a given P2Y12 antagonist from the day of filling a prescription for that drug and for a number of days corresponding to either the number of tablets for clopidogrel and prasugrel (used once daily) or half the number of tablets for ticagrelor (used twice daily)". Finally, a 30-day grace period was added to the estimated duration to account for minor non-compliance and irregular prescription refills. A sensitivity analysis with a grace period of 60 days was also performed". An individual could be regarded as dropped out of treatment at one point in time and later be reclassified as a current user on filling a new prescription" The authors should explain differences between definitions. Even in comparable populations, it is difficult to standardize adherence in a multivariable model as underlying factors (such as tablet pack size and daily dosing patterns) may influence treatment length. Similarly, it is difficult to assess how these underlying factors influence the risk of having a calculated treatment break of 30 days.

(4) Currently available evidence suggests considering discontinuation of P2Y12 inhibitor therapy after 6 months, when the risk of bleeding is high. You comment and data (if available) is in order.

REVIEWER	C. Michael Gibson Harvard Medical School
REVIEW RETURNED	11-Jan-2019

| GENERAL COMMENTS | The manuscript entitled "Persistence with dual antiplatelet therapy after percutaneous coronary intervention for ST-Segment-Elevation Acute Coronary Syndrome" represents a population-based cohort study evaluating the persistence of dual antiplatelet therapy for at least 12 months among patients with STE-ACS.

My comments are as follows:
1. The present analysis appears to be descriptive. To assess the longitudinal impact of guideline implementation, a formal interrupted time-series analysis should be considered, with proper adjustments for covariates and considerations on clustering. It would also be of interest to investigate whether the observed increase in DAPT persistence could be translated into improved patient outcomes.

2. It seems that the "determinants" of persistence with DAPT for at least 12 months were identified via multivariable analysis. In light of study design and statistical methods, these results at best indicate association rather than causality. Alternatively, physician surveys can be performed in order to identify the determinants or barriers for maintaining DAPT at hospital discharge. |

	3. Other well-established factors that may affect the duration of DAPT prescription (e.g., prior stent thrombosis, polyvascular disease, complex PCI) should be studied.
	4. The generalizability of the findings is questionable. The ischemic-bleeding risk profile of the study population is unknown. Risk scores (such as DAPT or PRECISE-DAPT score) should be reported.
	5. The sentence on Page 14 reads: "Other determinants were." Please correct.

REVIEWER	Kristen Tecson Baylor Heart and Vascular Institute, USA
REVIEW RETURNED	21-Feb-2019

GENERAL COMMENTS	Manuscript ID: bmjopen-2018-028114 Title: Persistence with dual antiplatelet therapy after percutaneous coronary intervention for ST-segment-elevation acute coronary syndrome. A population-based cohort study Summary: New guidelines were published in 2012 recommending the use of dual antiplatelet therapy for 12 or more months for patients who undergo a percutaneous coronary intervention for ST-elevated acute coronary syndrome. The authors utilized a database to examine 10,711 qualifying cases from 2010 to 2015 with regard to their providers' DAPT duration recommendation and their adherence/persistence with the recommendation. The authors conclude that the proportion of 12-month DAPT recommendation and persistence increased over time, particularly 2 years after the guidelines. The conclusions are generally supported by the data. Major Points: The presentation of results is very unclear and unexpected based on what is listed in the methods section. Please elaborate and name the models in the methods section prior to listing models 1-4 in Table 2. It doesn't make sense for Table 1 to be split based on 3 levels of DAPT duration when the analytic framework is based on a dichotomous variable. Often, Table 1 is meant to identify potential confounders to be considered in a multivariable model, providing adjustment for the primary factor of interest; however, having 3 levels in Table 1 does not adequately identify differences between groups. The point estimates and confidence intervals for drug eluting stents and years are highly alarming. Having confidence intervals that wide indicates problems with tractability and the ability to draw meaningful conclusions. What was the sample size (and outcome event count) for cases with DES? How was the variable 'year' coded in these analyses? If the years were truly entered as '2010, 2011,…,' that is probably why there are problems with the estimates' intervals. Instead, try dummy variables 1-6 or even a-f; they don't have to be numeric, just ordinal. The random slopes were non-significant (95% confidence intervals contained 1), so it is unclear why they are included in the final model(s). Many parts of this manuscript were difficult to read. I suggest the use of an English writing service for editing purposes – there are several non-sentences throughout, missing words, and incorrect uses of gerunds and grammar. Minor Points: There may be something wrong with the figures – one of the figures is named 'Figure 4,' but is referenced as Figure 3.

	It is nice to see the figure with the rates of DAPT use declining over time, but it is somewhat unclear as to why it is included when the analysis is logistic regression, not time-to-event.
	Some of the conclusions drawn in this manuscript are made too general for an analysis that utilized data only for 1 country. Please soften your language, putting into perspective for the reader that these findings have limitations.
	Please change "dyed" to "died" in Figure 1.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1
Reviewer Name: Raffaele Bugiardini
Institution and Country: University of Bologna
Please state any competing interests or state 'None declared': none

Please leave your comments for the authors below
Current guidelines recommend dual antiplatelet therapy (DAPT) of aspirin plus a P2Y12 inhibitor for at least 12 months after implantation of drug-eluting stents (DES) in patients with acute coronary syndrome. However, available data about the optimal duration of DAPT in patients with acute coronary syndrome undergoing percutaneous coronary intervention are scant. The current study aimed to investigate whether a12-month duration of DAPT would persist for 12-months in a population of consecutive patients who received primary or post fibrinolysis PCI and survived between January 2010 and December 2015 in one of the 10 reference hospitals of the Public Data Analysis for Health Research and Innovation Program (PADRIS). The authors conclude that a to 12-month DAPT has increased since publication of clinical guidelines.

Comments

(1) Recent work has shown that the increased risk of myocardial infarction with 6-month DAPT and the wide non-inferiority margin prevent us from concluding that short-term DAPT is safe in patients with acute coronary syndrome undergoing percutaneous coronary intervention with current-generation DES. Prolonged DAPT in patients with acute coronary syndrome without excessive risk of bleeding should remain the standard of care (Hahn JY1Lancet. 2018). This paper should be mentioned and its data should be discussed in the current study.

Thank you very much for this comment. The reviewer is right and the general consensus in literature is to prolong DAPT in the ACS context. We have included the description and references of more contemporary clinical trials addressing this subject, (page 17)
"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]."

(2) Do you have access to data that would provide reasons for shorter treatment length or treatment switch done by general practitioners?

The analysis is based on the AMI Code data registry linked to administrative, hospitalization and pharmacy data. Unfortunately we do not have data obtained directly from patients follow up or from the primary care setting. The advantage of accessing to regional-wide data is exhaustiveness; however one main disadvantage is lack of precise clinical information. In any case, we can speculate that two reasons could have played a role. The first one is a possible unawareness of primary care physicians of the most recent version of specialized guidelines. In addition, it could represent a trend to restrict prolonged DAPT durations to those patients that are believed to receive a greater benefit and to avoid an increase in the rate of hemorrhagic complications in the case of a strict guidelines adherence. We have tried to give arguments for both possibilities in the discussion section (pages 16 and 17)

In sensitivity analyses we have included the haemorrhagic and ischemic events during follow up (identified from MBDS diagnostic codes) which would change the patient criteria for indication of double antiplatelet treatment, but we could not identify other reasons for changing the length or treatment switch during follow up.

(3) The authors defined persistence with DAPT as "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".
Recent work published in bmj open (ref. 21) defined persistence with DAPT as "having filled a prescription for the given drug within 90 days prior to the admission to 30 days after the admission" . "A participant was considered a current user of a given P2Y12 antagonist from the day of filling a prescription for that drug and for a number of days corresponding to either the number of tablets for clopidogrel and prasugrel (used once daily) or half the number of tablets for ticagrelor (used twice daily)". Finally, a 30-day grace period was added to the estimated duration to account for minor non-compliance and irregular prescription refills. A sensitivity analysis with a grace period of 60 days was also performed". An individual could be regarded as dropped out of treatment at one point in time and later be reclassified as a current user on filling a new prescription" The authors should explain differences between definitions. Even in comparable populations, it is difficult to standardize adherence in a multivariable model as underlying factors (such as tablet pack size and daily dosing patterns) may influence treatment length. Similarly, it is difficult to assess how these underlying factors influence the risk of having a calculated treatment break of 30 days.

The Danish National Prescription Registry12 contains data on all prescribed drugs dispensed from Danish community pharmacies. Prescription data include type of drug, date of dispensing and quantity and are categorised according to the Anatomic Therapeutic Chemical (ATC) index

We estimated dual antiplatelet treatment form the pharmacy billing registry which registers pharmacy refills in a monthly basis. Unfortunatelly we do not have the exact date when the container was dispensed, therefore we cannot establish the treatment period with precision or a grace period of either 30 or 60 days.

Similarly we allowed breaks of one month without billing information, which could correspond to a period between 30 and 60 days depending on the day of the month before and after the break when the container was dispensed.

Because our billing data are different from prescription data in the Danish Registry we cannot apply exacltly the same definition of persistence although we believe that the identification of persistence at 12 months from the index episode (i.e. the main outcome measure) should be similar using both approaches.

(4) Currently available evidence suggests considering discontinuation of P2Y12 inhibitor therapy after 6 months, when the risk of bleeding is high. You comment and data (if available) is in order.

Patients with high bleeding risk at baseline were excluded. We assume that all patients had an indication for at least 12 months DAPT. Unfortunately we cannot rule out the possibility of an acquired high risk of bleeding during follow up or the possibility of errors in risk assessment from administrative records. In any case, we do not believe that the possibility of errors in the classification of the risk bleeding during follow up could have changed substantially the main conclusions (it should have affected to an important part of the sample, which is unlikely).
In the new version of the manuscript we included the description of bleeding risk using the DAPT score (Tables 1 and 2)

Reviewer: 2
Reviewer Name: C. Michael Gibson
Institution and Country: Harvard Medical School
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
The manuscript entitled "Persistence with dual antiplatelet therapy after percutaneous coronary intervention for ST-Segment-Elevation Acute Coronary Syndrome" represents a population-based cohort study evaluating the persistence of dual antiplatelet therapy for at least 12 months among patients with STE-ACS.

My comments are as follows:
1. The present analysis appears to be descriptive. To assess the longitudinal impact of guideline implementation, a formal interrupted time-series analysis should be considered, with proper adjustments for covariates and considerations on clustering. It would also be of interest to investigate whether the observed increase in DAPT persistence could be translated into improved patient outcomes.

The first objective of the study is purely descriptive, as it conveys the description of DAPT usage during a large period after the index episode in the specific context of STEACS.

In any case, we are grateful for the reviewer comments, since the suggestion of using formal interrupted time-series analysis led to change the main analytical approach of our work. By specifying an interrupted time series using mixed effects logistic regression we were able to answer our main questions regarding: time trends in adherence improvement, impact of guidelines implementation and association of adherence with individual patient and process characteristics and, specifically with the recommendation of DAPT duration at discharge from the PCI hospital.

Please note that the text in the statistical analysis subsection and the results section have been changed in accordance.

On the other hand, we agree with the reviewer that the impact of persistence with DAPT on outcomes is a really important issue. However, we believe that it is beyond the scope of the present manuscript. In fact, we are conducting a specific analysis to assess the impact of DAPT duration on outcomes.

2. It seems that the "determinants" of persistence with DAPT for at least 12 months were identified via multivariable analysis. In light of study design and statistical methods, these results at best indicate association rather than causality. Alternatively, physician surveys can be performed in order to identify the determinants or barriers for maintaining DAPT at hospital discharge.

The study did not intend to evaluate determinants or barriers for maintaining DAPT. In fact, this was assessed in our previous study (reference 30). Therefore we agree with the reviewer and thus we changed the word determinants by associated factors in accordance to the unknown nature of the association.

3. Other well-established factors that may affect the duration of DAPT prescription (e.g., prior stent thrombosis, polyvascular disease, complex PCI) should be studied.

We agree with the reviewer and we have tested the association of most of these factors with persistence, except for prior stent thrombosis which was unfortunately not available from administrative data as there is not a specific diagnostic code for stent thrombosis. An indicator variable for polyvascular disease has been defined as presence of previous AMI or PTCA or surgery and history of arteriopahty and/or previous stroke or TIA. We have also included an indicator of comorbidity (see tables 1 and 2). Number of treated vessels can be considered as an indicator of complex PCI.

4. The generalizability of the findings is questionable. The ischemic-bleeding risk profile of the study population is unknown. Risk scores (such as DAPT or PRECISE-DAPT score) should be reported.

This is a low bleeding risk population by design because we have excluded patients with potential contraindication for DAPT: patients with recent history of bleeding or neoplasia and needing anticoagulant treatment. Folowing the reviewer suggestion we have included the DAPT score description in tables 1 and 2, which is slightly higher (higher ischemic risk) in patients persisting for at least 12 months with DAPT.

5. The sentence on Page 14 reads: "Other determinants were." Please correct.

We have corrected the sentence in page 14

Reviewer: 3
Reviewer Name: Kristen Tecson
Institution and Country: Baylor Heart and Vascular Institute, USA
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
Manuscript ID: bmjopen-2018-028114
Title: Persistence with dual antiplatelet therapy after percutaneous coronary intervention for ST-segment-elevation acute coronary syndrome. A population-based cohort study
Summary: New guidelines were published in 2012 recommending the use of dual antiplatelet therapy for 12 or more months for patients who undergo a percutaneous coronary intervention for ST-elevated acute coronary syndrome. The authors utilized a database to examine 10,711 qualifying cases from 2010 to 2015 with regard to their providers' DAPT duration recommendation and their adherence/persistence with the recommendation. The authors conclude that the proportion of 12-month DAPT recommendation and persistence increased over time, particularly 2 years after the guidelines. The conclusions are generally supported by the data.
Major Points:

The presentation of results is very unclear and unexpected based on what is listed in the methods section. Please elaborate and name the models in the methods section prior to listing models 1-4 in Table 2.

According with one reviewer suggestion the analytic approach has completely changed in the new version of the manuscript, so models 1-4 have been removed.

It doesn't make sense for Table 1 to be split based on 3 levels of DAPT duration when the analytic framework is based on a dichotomous variable. Often, Table 1 is meant to identify potential confounders to be considered in a multivariable model, providing adjustment for the primary factor of interest; however, having 3 levels in Table 1 does not adequately identify differences between groups.

We agree with the reviewer and we have described patient characteristics in two groups: patients persisting with DAPT for at least 12 months vs patients withdrawing treatment before 12 months, which is now coherent with the multivariable analysis performed later. .

The point estimates and confidence intervals for drug eluting stents and years are highly alarming. Having confidence intervals that wide indicates problems with tractability and the ability to draw meaningful conclusions. What was the sample size (and outcome event count) for cases with DES? How was the variable 'year' coded in these analyses? If the years were truly entered as '2010, 2011,…,' that is probably why there are problems with the estimates' intervals. Instead, try dummy variables 1-6 or even a-f; they don't have to be numeric, just ordinal.
The random slopes were non-significant (95% confidence intervals contained 1), so it is unclear why they are included in the final model(s).

Please note that, as suggested by another reviewer, we have completely changed the analytic approach of our work and removed the previous multivariable analysis.

Many parts of this manuscript were difficult to read. I suggest the use of an English writing service for editing purposes – there are several non-sentences throughout, missing words, and incorrect uses of gerunds and grammar.

We have tried to improve the English expression in the new version.

Minor Points:
There may be something wrong with the figures – one of the figures is named 'Figure 4,' but is referenced as Figure 3.

We apologise for this mistake which has been corrected in the new version

It is nice to see the figure with the rates of DAPT use declining over time, but it is somewhat unclear as to why it is included when the analysis is logistic regression, not time-to-event.

The aim of this figure is purely descriptive and it is to show the progression of persistence with DAPT along the whole follow up period which varies from 2010 to 2015 despite the rate of DAPT in the first month after the index procedure is identical. Although the this figure is not essential for the subsequent analyses which only account for the 12 months persistence we think that the description of the whole progression can be interesting for the reader and we have included it in the supplementary file.

Some of the conclusions drawn in this manuscript are made too general for an analysis that utilized data only for 1 country. Please soften your language, putting into perspective for the reader that these findings have limitations.

Following the reviewer suggestions we have changed the conclusions indicating that findings are driven from data of STACS patients attended in Catalonia (Spain)

Please change "dyed" to "died" in Figure 1.

VERSION 2 – REVIEW

REVIEWER	Raffaele Bugiardini University of Bologna
REVIEW RETURNED	13-Apr-2019

GENERAL COMMENTS	The study investigated dual antiplatelet therapy (DAPT) patterns over time and patient characteristics associated with the various treatments in a ST segment elevation myocardial infarction (STEMI) population. The authors conclude that from 2010 to 2015, there was an increase in the proportion of patients with STEMI receiving DAPT, and a longer duration of DAPT. Guideline-based recommendations at hospital discharge were associated with persistence with DAPT in the 12 month recommended period. Comments 1.How did you handle missing data? 2. Are those variables that you used in the logistic regression those indicated in table 2? You indicated in table 3 only the variables associated with a persistence of at least 12 months. What about diabetes? You may add in the supplementary material the entire logistic regression models of your analyses 3. How prasugrel and ticagrelor are used in contemporary clinical practice in Catalonia are not known. Could you disaggregate the data and give some insights? 4. The authors state, "The impact of persistence on clinically relevant results is beyond the objective of the present study and will be assessed in another article". The medical community needs information on the risk of subsequent cardiovascular events in patients discharged with DAPT after STEMI. Please provide data on clinically relevant outcomes in the current study. There are numerous nationwide registry studies describing patterns of prescription and drug use. You date are in overlap with other registries (ref 23–28). 5. One interesting issue was recently raised by the FAST-MI (Circulation: Cardiovascular Interventions. 2018). In the cohorts of ST-segment-elevation myocardial infarction patients considered for primary percutaneous coronary intervention, prehospital administration of DAPT was associated with higher 1-year survival and no increase in in-hospital bleeding complications. Do you have data to confirm that?

REVIEWER	Kristen Tecson
	Baylor Heart and Vascular Institute, USA
REVIEW RETURNED	15-Apr-2019

GENERAL COMMENTS	Bmjopen-2018-028114.R1
	Major Points:
	Page 8- Please provide rationale for the choice of a 3 month retrospective review for medical history.
	Page 10 – Do patients regularly utilize insurance to obtain aspirin in Catalonia? If aspirin is available as an over the counter drug, I wonder whether the methods in this paper will exclude patients who obtained aspirin OTC.
	Please comment on autocorrelation in the ITS model.
	Table 3 – please comment on the confidence interval ranging from 0.45-22.19.
	Minor Points:
	Throughout – I think it should be "guideline implementation" (not guidelines)
	Abstract – please add a space between "discharge" and "from"
	First strength – I do not understand what you mean by 'unselected' cohort
	Last limitation- please update to "patients'"
	Throughout- please change "relay" and "relaying" to "rely" and "relying"
	Page 6 – please change "patient's" to "patients'"
	Page 7- The second aim is unclear. Please reword (please also correct "monhts" (page 20, too) and "incorporatins")
	Page 9 – Please change "STACS" to "STEACS"
	Page 10 – please change to "a patient's"
	Page 10- please change to "in patient characteristics"
	Page 11- please change to "random intercepts"
	Page 18 – please change to "least 12 months"
	Throughout – I think it should be "12 month persistence" (not months)
	Please mention IRB approval.

VERSION 2 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name
Raffaele Bugiardini

Institution and Country
University of Bologna

Please state any competing interests or state 'None declared':
none

Please leave your comments for the authors below
The study investigated dual antiplatelet therapy (DAPT) patterns over time and patient characteristics associated with the various treatments in a ST segment elevation myocardial infarction (STEMI) population. The authors conclude that from 2010 to 2015, there was an increase in the proportion of

patients with STEMI receiving DAPT, and a longer duration of DAPT. Guideline-based recommendations at hospital discharge were associated with persistence with DAPT in the 12 month recommended period.

Comments

1.How did you handle missing data?

The valid number of cases for each variable can be seen in table 1. The only variable with missing data included in the final model was 'Number of stents' with 18 cases missing. The logistic regression was performed with complete cases (n=10,244), so 18 cases were excluded.

This has been added in page 18: "Table 3 shows results of the complete cases analysis (n=10,244) using interrupted time series logistic regression"

2. Are those variables that you used in the logistic regression those indicated in table 2? You indicated in table 3 only the variables associated with a persistence of at least 12 months. What about diabetes? You may add in the supplementary material the entire logistic regression models of your analyses

The entire logistic regression is presented in table 3. We used the following criteria for variable selection, as explained in the methods section (pages 11 and 12): "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."

Diabetes did not show a significant association with persistence when added to the model.

3. How prasugrel and ticagrelor are used in contemporary clinical practice in Catalonia are not known. Could you disaggregate the data and give some insights?

We have added in tables 1 and 2 the description of the type of antiplatelet agent given at discharge. Overall, the rate of prasugrelor and ticagrelor is only 13.4% and 8%, and the proportion increases with time. We have added a new supplemental figure (figure 1) to show this trend. Although we were reluctant to include the antiplatelet agent in the final model because it was so strongly related with time, we have followed the reviewer suggestion and we have included it in the final model (table 3). Those patients receiving prasugrel have a higher odd of persisting at least 12 months on DAPT as compared with patients receiving clopidogrel. We thank the reviewer for this suggestion as, after including the antiplatelet agent, confidence intervals for the random effects became narrower and thus the model is more robust). For all other variables results are similar to the previous version.

Some changes in the text have been made to comment on this finding (page 18): "..., taking preasugrel instead of clopidogrel..."

4. The authors state, "The impact of persistence on clinically relevant results is beyond the objective of the present study and will be assessed in another article". The medical community needs information on the risk of subsequent cardiovascular events in patients discharged with DAPT after STEMI. Please provide data on clinically relevant outcomes in the current study. There are numerous nationwide registry studies describing patterns of prescription and drug use. You date are in overlap with other registries (ref 23–28).

We agree with the reviewer that the impact of dual antiplatelet treatment to subsequent cardiovascular events is of great interest to the medical community. In fact this is one of the main objectives of our study but was not the specific objective assessed in the present manuscript. Assessment of this association in an observational study is highly challenging due to the time varying nature of the exposure (switching different patterns of antithrombotic treatment and different agents along time), the high probability of inverse association (the outcome affects exposure) and the high probability of confounding. Because this assessment requires a sophisticated methodological approach we decided to answer two different questions in two different papers: 1) description of drug

persistence and the influence of guidelines implementation on persistence, and; 2) impact of persistence on clinical outcomes.

We hope that this response convinces the reviewer about the difficulty of answering to both questions in a single article. Alternatively we present the rates of events in the study population in the last paragraph of page 12 but without trying to assess associations and confounding.

5. One interesting issue was recently raised by the FAST-MI (Circulation: Cardiovascular Interventions. 2018). In the cohorts of ST-segment-elevation myocardial infarction patients considered for primary percutaneous coronary intervention, prehospital administration of DAPT was associated with higher 1-year survival and no increase in in-hospital bleeding complications. Do you have data to confirm that?

We thank the reviewer for pointing out this interesting issue. Again this will help us at exploring the association between exposure and relevant outcomes in a further analysis.

Reviewer: 3

Reviewer Name
Kristen Tecson

Institution and Country
Baylor Heart and Vascular Institute, USA

Please state any competing interests or state 'None declared':
None declared

Please leave your comments for the authors below
Bmjopen-2018-028114.R1
Major Points:
Page 8- Please provide rationale for the choice of a 3 month retrospective review for medical history.

Medical history review is based on hospitalization episodes and the three months time window is conventional. We decided by clinical criteria that an episode of neoplasia within this time window would serve as a proxy of "active neoplasia" and that an episode of major haemorrhage within the same time window would imply a highly probable contraindication for dual antiplatelet treatment. In any case, should the reviewer consider that another window time is necessary we would proceed with additional analyses.

There might be other patients with contraindication for dual antiplatelet treatment that are being unnoticed in our study but this is, as already acknowledged in the limitations paragraph in page 24, a common limitation of using administrative data to answer clinical questions.

Page 10 – Do patients regularly utilize insurance to obtain aspirin in Catalonia? If aspirin is available as an over the counter drug, I wonder whether the methods in this paper will exclude patients who obtained aspirin OTC.

The reviewer is right. In Catalonia aspirin can be purchased without a prescription, however this is not the case for almost 100% of patients suffering a STEMI who will be discharged with a chronic prescription of aspirin along with other drugs. In fact, although while not 100% of the patients followed in this study are in DAPT, almost 100% are registered in the pharmacy billing data base for aspirin.

Please comment on autocorrelation in the ITS model.

We included an autocorrelation term into the model and it was not statistically significant. We have added this information in the methods section (page 11) and in the results section (page 18)

Table 3 – please comment on the confidence interval ranging from 0.45-22.19.

Confidence intervals for the random effects are narrower in the new version. CIs became narrower when we included the type of antiplatelet agent (presugrel, ticagrelor vs clopidogrel) as requested by another reviewer. A likely reason for this effect is the high variability between centers in the DAPT time recommendation which is also related with the variability in the type of antiplatelet agent prescribed at each center.

Minor Points:
Throughout – I think it should be "guideline implementation" (not guidelines)

We have corrected the mistake throughout the manuscript

Abstract – please add a space between "discharge" and "from"

We have corrected the sentence

First strength – I do not understand what you mean by 'unselected' cohort

We have deleted the word 'unselected' as we already use comprehensive meaning 'complete'

Last limitation- please update to "patients'"

We have corrected the mistake

Throughout- please change "relay" and "relaying" to "rely" and "relying"

We have corrected the mistake

Page 6 – please change "patient's" to "patients'"

We have corrected the mistake

Page 7- The second aim is unclear. Please reword (please also correct "monhts" (page 20, too) and "incorporatins")

We have reworded the second aim as follows: "second, to evaluate the influence of guidelines recommendation for a 12-months DAPT schedule on the rate of 12-months persistence along time"

We have corrected the mistakes

Page 9 – Please change "STACS" to "STEACS"

We have corrected the mistake

Page 10 – please change to "a patient's"

We have corrected the mistake

Page 10- please change to "in patient characteristics"

We have corrected the mistake

Page 11- please change to "random intercepts"

We have corrected the mistake

Page 18 – please change to "least 12 months"

We have corrected the mistake

Throughout – I think it should be "12 month persistence" (not months)

We have corrected the mistake

Please mention IRB approval.

Approval by the Vall d'Hebron Clincal Research Ethics Committee is mentioned in page 8 first paragraph