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MEDIUM AND LONG TERM SAFETY, EFFECTIVENESS, COST-EFFECTIVENESS, OF ANTITHROMBOTIC THERAPY IN PATIENTS WITH ST-ELEVATION ACUTE CORONARY SYNDROME IN CLINICAL PRACTICE

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1. Summary

Duration of dual antiplatelet treatment (DAT: aspirin + thienopyridine) in patients after an acute coronary syndrome receiving percutaneous coronary revascularization is a matter of controversy. This is due to the coexistence of two opposite risks: the risk of an ischemic event (which the treatment prevents) and the risk of a hemorrhagic event (which the treatment might eventually cause). In most cases, except if the hemorrhagic risk is clear (i.e. in patients taking anticoagulants), the recommended duration of DAT is 12 months, although some studies have demonstrated that a 6 months regimen could be enough and that the benefit will depend on the type of stent received (drug eluting or conventional metallic). However, some clinical trials and observational studies suggest that for patients without hemorrhagic risk an extended duration beyond 12 months would be effective. In summary, there is confusion about the optimal, most effective and safest, duration of DAT.

In Catalonia we have sources of information at the population level that greatly facilitate the study of health care outcomes for patients suffering a heart attack: The AMI Code registry, which has been operating since 2010 and collects acute phase data from all AMI episodes occurring in Catalonia; and the PADRIS program, which allows linking health data from different sources for the entire population.

Using these two sources, the VESA project has made it possible to expand the information collected in the IAM Code registry and to link all the episodes between 2010 and 2017 with follow-up data of hospital episodes related to ischemic events (heart attack, stroke, new coronary artery bypass grafting) or hemorrhagic events (hemorrhagic stroke, digestive hemorrhage or other bleeding requiring hospital admission) and with the pharmacy dispensation of antiplatelet and anticoagulant drugs and other secondary prevention drugs for AMI.

Thus we have been able to answer two main research questions:

1. What is the effectiveness (outside the context of controlled clinical trials), in terms of incidence of cardiovascular events and the safety, in terms of incidence of hemorrhagic events, of different DAT duration regimens in a real clinical setting? We want to answer this question both globally and for specific patient subgroups:

depending on the type of stent (conventional drug and metal releasers), and whether, in addition to antiplatelet therapy, the patient needs chronic treatment with anticoagulants.

2. How patients' persistence with DAT has evolved over the years, and how it has changed after the publication of European clinical practice guidelines, which recommend a 12-month treatment duration.

Effectiveness and safety in real life of different DAT durations

We analyzed the data of 12,153 patients with DAT indication (excluding those who had contraindications due to high hemorrhagic risk and those who had an event in the first month after the index episode) treated in the 10 reference centers of the AMI Code network between 2010 and 2017.

Patients were classified and described based on DAT treatment duration (exposure): 0 to 3, 4 to 9, 10 to 14, and more than 14 months. The main outcome variable was defined as the onset of new myocardial infarction, ischemic stroke, or death from any cause.

The effect of exposure (DAT duration) on event rate was assessed using Cox regression-based marginal structural models. These models allow for time-dependent effects to be incorporated and adjusted using a propensity model for the baseline characteristics, time-varying characteristics and censorship probability. So, instead of considering DAT exposure as a constant variable (initially present by definition in 100% of cases), we can model exposure time because the unit of analysis is the patient-month with DAT treatment, thus each patient provides information in the "exposed" group while on DAT and in the comparison group when leaving the treatment.

Persistence with DAT after percutaneous revascularization in patients with ST-elevation acute coronary syndrome

We analyzed the data of 10,711 patients with ST-segment elevation acute coronary syndrome attended in the 10 reference hospitals of the AMI Code network in Catalonia between 2010 and 2015 and who received percutaneous coronary revascularization. We determined the antiplatelet treatment prescribed during the 12 months following the index episode and defined the main outcome as the dispensation of two antiplatelet

agents (aspirin + thienopyridine) until at least month 11, counting from the index episode. Non-persistence was considered when there was a gap in DAT dispensation of at least two months.

Patient characteristics were described based on whether or not they persisted in DAT for 12 months and based on the year of the index episode. The proportion of "persistent" patients was described based on the year of the episode.

This evolution of persistence was analyzed using a logistic regression-based interrupted time-series model, adjusting for patients' baseline characteristics. This model allows us to evaluate the factors associated with persistence and its evolution and to determine if an event occurring at a given time (publication of the European clinical guidelines in 2013) has influenced this evolution.

2. Results

Effectiveness and safety in real life of different DAT durations

The table shows the protective effect of DAT on the incidence of events (AMI or stroke or death from any cause) and how the magnitude of the effect is higher for a treatment period of 4 to 9 months (vs lower period), while it decreases for longer periods, until the beneficial effect of a DAT is no longer observed for a period of 14 months or more.
Table. Crude and adjusted effect of DAT duration on the occurrence of ischemic events (AMI or stroke) or death from any cause.

	Crude effect		**Adjusted effect**	
	HR (CI95%)	**p-value**	**HR (CI95%)**	**p-value**
Exposure (ref = ≤3m)				
4-9 m	0.50 (0.38 – 0.66)	<0.001	0.33 (0.25 – 0.44)	<0.001
10 – 14 m	0.77 (0.54 – 1.10)	0.146	0.56 (0.39 – 0.82)	0.003
> 14m	1.60 (1.25 – 2.05)	<0.001	1.22 (0.92 – 1.61)	0.162

A similar result is observed in the subgroup of patients with drug-eluting or conventional metallic stents.

Persistence on DAT after percutaneous revascularization in patients with ST-segment elevation acute coronary syndrome

The proportion of patients on DAT at 12 months after the index episode increased significantly from 58% in 2010 to 73% in 2015. The highest growth was observed between 2014 and 2015, two years after the publication of the European clinical guidelines (figure).

On the other hand, we observed that, apart from the temporary trend beginning in 2014, there were other factors related to greater persistence: drug-eluting stent vs conventional stent (OR = 1.90, CI95%: 1.50-2.40), more than one stent (1.22; 1.13-1.32), receiving a prescription at discharge of prasugrel instead of clopidogrel (1.59; 1, 36-1.86), receiving an explicit recommendation of a 12 months DAT regimen at discharge from the acute phase (5.76; 3.26-10.2), hypercholesterolemia (1.19; 1.08 - 1,31), history of by-pass (1,85; 1,09-3,14) and two or more treated vessels (1,21; 1,10-1,33). There was a high variability in persistence between the AMI Code network referral centers, which also decreased over time after the publication of guidelines.

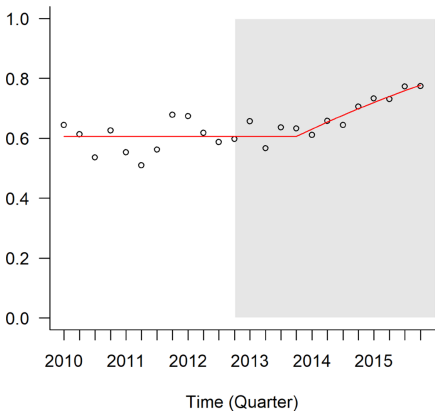

Figure. Observed proportion of patients persisting with DAT for 12 months in each quarter and the estimated rate using interrupted time series modeling defining a one-year latency period from 2013 (publication of the European Guidelines).

3. Relevance and potential future implications

The main finding of the study is that in real life, in patients who have had an ST-elevation acute coronary syndrome and have undergone a percutaneous coronary syndrome, no beneficial effect of DAT is observed for a period of 14 months or more

and this will reinforce the idea that prolonging therapy beyond one year does not imply a benefit and is only associated with the inherent risk of bleeding. This result, observed in a comprehensive, non-selected cohort of more than 10,000 patients without significant hemorrhage risk, provides relevant information that should be used to clarify some of the recommendations in the clinical practice and consensus guidelines that advocate prolongation of DAT beyond 1 year. We believe that this strategy, based on the results of this study, should be considered carefully and only for selected patients. Thus, the results of this study may contribute to the reduction of effective DAT time. This will have two notable impacts:

1. On safety. The 2017 Guidelines recommend prolonging DAT in patients with low hemorrhagic and high ischemic risk (about 950 patients would be in this category each year in Catalonia). In a conservative scenario, if the expected hemorrhage rate in this population attributable to DAT is 3.6 per 1000 patients per year, an average of 6-month reduction of DAT could lead to a saving of 1.8 major bleeding events every year.

2. Economical. Using the same scenario, and considering that the price of ticagrelor is € 89.61 / month, an average 6-month reduction of DAT would result in a saving for the health system and / or the patient (depending on the pharmacy co-payment level) of €500,000 per year.

We plan to analyze in the future the economic and health impact of different DAT regimens in the context of the Catalan public health system.

Despite the demonstrated beneficial effect of a 12 months DAT duration we have estimated a DAT persistence rate that is far from optimal (73% in 2015). This indicates that there is a latency period before a reaction to this type of recommendation is observed in real practice, and an even longer period is needed to reach reasonable levels of compliance. In our study, we found that a simple action that improves persistence is to recommend an appropriate treatment regimen at discharge from the acute care hospital. These results indicate that prescribing physicians strongly rely on the recommendation made by the specialist.

An operational objective of the project, beyond its relevance for clinical knowledge and practice, was to promote the use of population-based clinical and administrative data for research in cardiovascular and pharmacological therapy. The project has contributed through the following activities:

- The presentation of the study at a scientific meeting of the Spanish Society of Cardiology, aimed at optimizing real-world research on acute coronary syndrome, led to the incorporation of our data in a meta-regression to merge and analyze data from different registries.

- The participation in the VESA project of people involved in the management of the health system and those responsible for the AMI Code registry has facilitated the use of the VESA study processes to the improve the registry. The AMI Code Registry is one of the fundamental tools for continuous evaluation and improvement of the AMI process of care. Specifically, during the course of the study, the need emerged to incorporate new variables in the AMI Code Registry, variables related to the clinical history of patients and the type of treatment received, because they had an impact on the pharmacological regimen in the post-AMI period and on patients' prognosis.

- Additionally, the experience acquired with the VESA Project allowed us to design a new project that will also use data from AMI Code Registry and the PADRIS program: analysis of the impact of the socio-economic level on acute and post-acute care, therapeutic compliance and clinical outcome of AMI. With this new study we will continue to evaluate the quality and outcome of AMI care in Catalonia. The project was selected in the 2019 competitive call for research projects of the AMI Code Scientific Committee.

4. References generated by the study

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syndrome: a population-based cohort study in Catalonia (Spain). BMJ Open 2019; 9 e028114. doi:10.1136/bmjopen-2018-028114

Two articles in the process of writing the manuscript

Effectiveness of different dual antiplatelet duration regimens after percutaneous coronary intervention in patients with ST-segment-elevation acute myocardial infarction

Validity of DAPT score to predict late ischemic and hemorrhagic events in patients with ST-segment-elevation acute coronary syndrome