

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Antithrombotic management of patients with acute coronary syndromes and atrial fibrillation undergoing coronary stenting: a prospective, observational, nationwide study
<b>AUTHORS</b>	De Luca, Leonardo; Rubboli, Andrea; Bolognese, Leonardo; Gonzini, Lucio; Urbinati, Stefano; Murrone, Adriano; Scotto di Uccio, Fortunato; Ferrari, Fabio; Lucà, Fabiana; Caldarola, Pasquale; Lucci, Donata; Gabrielli, Domenico; Di Lenarda, Andrea; Gulizia, Michele

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Hideki Kawai Fujita Health University, Japan
<b>REVIEW RETURNED</b>	21-Jun-2020

<b>GENERAL COMMENTS</b>	<p>Dr. Luca et al examined 598 patients with AF and ACS after coronary stenting, specifically focusing on the antithrombotic prescription. I believe that an antithrombotic regimen just after PCI is very important for preventing bleeding events, so I am curious about this article.</p> <p>Q1. In Figure 4, the authors showed the independent predictors of “DAT” prescription at multivariate analysis. Probably they compared any factors between “DAT” and “others”. What is “others”? TAT only? TAT, DAPT, and SAPT? It is not written in statistical analysis in Methods. The authors need to clear it. Personally, I think that the analysis of “predictors of TAT prescription” is better.</p> <p>Q2. How many ACS patients died before discharge? How is the ratio of patients with AF?</p> <p>Q3. How many patients were given DC shock before discharge for new onset of AF?</p> <p>Q4. In Figure 2, what is the reason about the difference of antiplatelet prescription? The ratios of clopidogrel in patients with AF at admission and Prasugrel/Ticagrelor in those with New onset AF are so high. Why?</p>
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<b>REVIEWER</b>	Peter L Thompson Sir Charles Gairdner Hospital
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	University of Western Australia
<b>REVIEW RETURNED</b>	04-Sep-2020

<b>GENERAL COMMENTS</b>	<p>The study is well conducted with appropriate methods and analysis and has the strength of providing a national snapshot of anti thrombotic use for combinations of atrial fibrillation and acute coronary syndromes. There is some value in documenting the contemporary Italian physician practice.</p> <p>However, I also found the scope of the study rather limited. The authors quite rightly keep to the data in their interpretation, but make limited comment on the significance of the results obtained. In the opinion of this reviewer, the authors missed an opportunity to link the actual behaviour of the participating physicians/ hospitals to guideline recommendations.</p> <p>For instance the relatively small proportion of patients with new onset AF receiving VKA (8.6) or NOAC (50.5) is worthy of comments. Although some guidelines recommend anticoagulation for all AF patients, this is not universally accepted and this data confirms that. The topic is open for debate and some reference to the debate on the risk benefit of OAC for all AF even transient AF in the setting of acute illness would have been welcome.</p> <p>The relatively low use of DAT was also of some interest. There is increasing data confirming that this may be a valid and lower risk approach than TAT. This evidence has been accumulating rapidly in recent years and some comment on why this has not impacted o practice would be of value. The introduction refers to previous snapshots, and some comparisons with these re the decline in VKA, and increase in NOAC, and prescribing, and trends in DAT vs TAT would have been of some interest.</p> <p>Overall, despite the well conducted and well analysed registry, and the authors' discipline is interpreting it, this reviewer was left with a "So what" response to this data. It is of some interest as a snapshot of contemporary national Italian practice, but the aim of the exercise and how the data advances knowledge or practice is unclear.</p>
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### VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Dr. De Luca et al examined 598 patients with AF and ACS after coronary stenting, specifically focusing on the antithrombotic prescription. I believe that an antithrombotic regimen just after PCI is very important for preventing bleeding events, so I am curious about this article.

We thank the reviewer for his positive comment on our manuscript

Q1.

In Figure 4, the authors showed the independent predictors of “DAT” prescription at multivariate analysis. Probably they compared any factors between “DAT” and “others”. What is “others”? TAT only? TAT, DAPT, and SAPT? It is not written in statistical analysis in Methods. The authors need to clear it. Personally, I think that the analysis of “predictors of TAT prescription” is better.

We have now performed a multivariate analysis on TAT prescription (Table 1 suppl). We have also specified in the methods section, statistical paragraph that ‘Clinically relevant variables which were significant at univariate analysis were included in a multivariable model (logistic regression) in order to identify the independent predictors of DAT and TAT prescription at discharge, compared to other

antithrombotic strategies. The variables included in the logistic model for DAT were: age (<65 reference group, 65-74, ≥75 years), gender, onset of AF (at admission vs during hospitalization), type of ACS (STEMI vs NSTEMI-ACS), diabetes mellitus, malignancy, major bleeding (history or occurred during hospitalization). Variables included in the logistic model for TAT were the following: age (<65 reference group, 65-74, ≥75 years), gender, onset of AF (at admission vs during hospitalization), type of ACS (STEMI vs NSTEMI-ACS), : hypertension, history of HF, previous revascularization, prior AMI, stroke/TIA, malignancy, major bleeding (history or occurred during hospitalization). When more than two categories were present, dummy variables were introduced to define a reference group.'

Q2.

How many ACS patients died before discharge? How is the ratio of patients with AF?

On page 9, third paragraph we have now specified that 'Ten (1.7%) patients died during the hospitalization (5 with AF at admission and 5 with new onset AF)'.

Q3.

How many patients were given DC shock before discharge for new onset of AF?

On page 9, third paragraph we have added that 'In patients with new onset AF (...) an electrical cardioversion was performed in 28 (9.2%)'.

Q4.

In Figure 2, what is the reason about the difference of antiplatelet prescription? The ratios of clopidogrel in patients with AF at admission and Prasugrel/Ticagrelor in those with New onset AF are so high. Why?

We thank the reviewer for his comment. On page 13, first paragraph, we have added the following sentence 'The high prescription of DAPT and the concomitant low use of OAT could justify the greater prescription of the potent oral P2Y12 inhibitors observed in our cohort of patients with new onset AF compared to those with AF at admission'.

Reviewer: 2

The study is well conducted with appropriate methods and analysis and has the strength of providing a national snapshot of anti thrombotic use for combinations of atrial fibrillation and acute coronary syndromes. There is some value in documenting the contemporary Italian physician practice.

We thank the reviewer for his positive comment.

However, I also found the scope of the study rather limited. The authors quite rightly keep to the data in their interpretation, but make limited comment on the significance of the results obtained.

In the opinion of this reviewer, the authors missed an opportunity to link the actual behaviour of the participating physicians/ hospitals to guideline recommendations. For instance the relatively small proportion of patients with new onset AF receiving VKA (8.6) or NOAC (50.5) is worthy of comments. Although some guidelines recommend anticoagulation for all AF patients, this is not universally accepted and this data confirms that. The topic is open for debate and some reference to the debate on the risk benefit of OAC for all AF even transient AF in the setting of acute illness would have been welcome.

On page 13 (first paragraph) there is a large discussion on the antithrombotic management of new onset AF. We have now added more data about the management of new onset AF in critically ill patients and quoted for additional references (26,27 and 38,39; 1 is from BMJ Open).

The relatively low use of DAT was also of some interest. There is increasing data confirming that this may be a valid and lower risk approach than TAT. This evidence has been accumulating rapidly in recent years and some comment on why this has not impacted on practice would be of value. The introduction refers to previous snapshots, and some comparisons with these re the decline in VKA, and increase in NOAC, and prescribing, and trends in DAT vs TAT would have been of some interest.

On page 12 (last paragraph) we have now added the following sentence 'These findings may be related to 2016 ESC guidelines recommendations that were available during the conduction of our registry and did not consider all the evidence coming from recent trials, to the lack of hospital protocols updating or to the issues in changing therapeutic habits, as confirmed by previous nationwide surveys conducted in Europe before the availability of newer evidence in this field'.

Overall, despite the well conducted and well analysed registry, and the authors' discipline is interpreting it, this reviewer was left with a "So what" response to this data. It is of some interest as a snapshot of contemporary national Italian practice, but the aim of the exercise and how the data advances knowledge or practice is unclear.

Thanks to reviewers's comments and suggestions, we tried to improve the discussion of our nationwide data.

#### VERSION 2 – REVIEW

<b>REVIEWER</b>	Hideki Kawai Department of Cardiology, Fujita Health University
<b>REVIEW RETURNED</b>	08-Oct-2020

<b>GENERAL COMMENTS</b>	The authors answered Reviewer's comment and revised the manuscript properly. In my opinion, the revised manuscript can be accepted to BMJ Open.
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<b>REVIEWER</b>	Peter L Thompson Heart and Vascular Research Institute Sir Charles Gairdner Hospital  Harry Perkins Institute of Medical Research  Medical School University of Western Australia
<b>REVIEW RETURNED</b>	10-Nov-2020

<b>GENERAL COMMENTS</b>	The authors have attended to the Reviewers' comments in particular with an excellent section on the multivariate determinants of Triple versus Double Antithrombotic Therapy and the debate on TAT versus DAT for recent onset AF. These and other changes make for a greatly improved paper and I would recommend Accept
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