PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Occurrence and Mortality of Vasospastic Angina Pectoris Hospitalized Patients in Finland -A Population Based Registry Cohort Study.
AUTHORS	Pikkarainen, Essi; Blomster, Juuso; Sipilä, Jussi; Rautava, Paivi; Kytö, Ville

VERSION 1 – REVIEW

REVIEWER	Fabien Picard Cochin Hospital - Paris - France
REVIEW RETURNED	29-Apr-2019

GENERAL COMMENTS	I read with interest the manuscript of Pikkarainen et al on the occurrence and mortality of vasospastic angina hospitalizations. They evaluated consecutive patients hospitalized for vasospastic angina in Finland during 10 years. During the study period 1762 admissions were recorded with predominance of male patients. Interestingly, one-year mortality was 8.0% at 1 year follow-up and 15.5% at 3-year follow-up The authors conclude that men have a higher risk for vasospastic angina caused admissions and that mortality was associated with increasing age, comorbidities and non-obstructive vasospastic angina diagnosis but was similar between genders. The authors have to congratulated for performing such study in this too often forgotten disease. Nevertheless, due to the retrospective nature of the study and the code-base diagnosis, this limits the impact of their study. I have minor comments: - The title could be changed “Occurrence and Mortality of Vasospastic angina pectoris hospitalized patients” - As highlighted in the introduction the definite VAP diagnosis involves three considerations: 1) classical clinical manifestations of VAP (spontaneous nitrate responsive angina episodes), 2) documentation of myocardial ischemia during spontaneous episodes, AND 3) demonstration of coronary artery spasm. How do the authors explain that coronary angiography was performed in only half of the patients. How can the authors can affirm that patients that did not have coronary angiography had indeed definite coronary vasospasm? This should be discussed and added as a limitation. - How do the authors explain that the admission rate for VAP decreased during the study period? This should be discussed - In the discussion, please use the same numbers than in the results for mortality, ie 15.5% - Do the authors have infos on medical therapies used in these patients? This could of interest to evaluate if medical treatment of vasospastic angina can reduce cardiac mortality? - There are few grammatical errors that should be corrected

REVIEWER	John F Beltrame University of Adelaide Central Adelaide Local Health Network Adelaide, Australia
REVIEW RETURNED	16-Jun-2019

GENERAL COMMENTS	This retrospective study utilises administrative datasets to identify the occurrence of vasospastic angina hospital admissions (ICD code I20.1) and the subsequent 1 & 3 year mortality in these Finish patients between 2004-14. Major findings include (1) an annual admission rate for vasospastic angina of 2.29/100,000 person-years, representing approximately 1% of acute syndrome admissions in Finland; (2) all-cause mortality of 8.0% and 15.5% for 1 & 3 years respectively, with 5.8% & 11.1% being cardiac mortality. The manuscript is well written and easy to follow. As stated by the authors, the major limitation is the treating physician-based diagnosis of vasospastic angina since provocative spasm testing is rarely performed in Finland. Accordingly, the diagnosis may be under-represented since potentially only spontaneous episodes would be identified. Moreover, what criteria the clinicians used to make the diagnosis is unclear (ie how many have transient ST changes or responded to nitrates). More insights may be gained by detailing the baseline features of the vasospastic angina cohort during their index admission (a) the presence of a concurrent diagnosis of acute myocardial infarction – were these infarct patients without obstructive coronary artery disease and thus attributable to coronary spasm, and (b) discharge medications – how many were discharged on calcium channel blockers, since these are considered the cornerstone therapy of vasospastic angina. The manuscript could be further improved by comparing the 1 & 3-year mortality (all-cause & non-cardiac) for the vasospastic angina cohort with those who had STEMI & NSTEMI.

REVIEWER	Amartya Kundu University of Massachusetts Medical School Worcester, MA, USA
REVIEW RETURNED	18-Jun-2019

GENERAL COMMENTS	The authors describe a retrospective study evaluating outcomes in patients hospitalized for vasospastic angina in Finland over a 10 year period. It is true that the vast majority of evidence on outcomes in patients with vasospastic angina is from eastern asian literature, so a population based study in western Europe provides useful insights on geographic differences in epidemiological factors and outcomes data in patients with variant angina. While the manuscript is well presented with rigorous statistical methods, further elaboration on the following pointers is warranted for further improvement: - Demographic baseline characteristics of the patients included in the study should be provided in a tabular format - Data on yearly trends in mortality associated with vasospastic angina will be useful, either in graphical or tabular format. Similarly data on short-term mortality should be reported. -Coronary angiography was performed in approximately 60 % of patients. How was the diagnosis of vasospastic angina made in the remaining cohort of patients? Also was a unified diagnostic criteria

	followed by all included hospitals to code someone as 'vasospastic angina' ? This needs to be clarified. - Discussion section should include further elaboration on the clinical impact of vasospastic angina, particularly its association with sudden cardiac death. Following articles can be used for reference: (a) Ahn JM, Lee KH, Yoo SY, Cho YR, Suh J, Shin ES, et al. Prognosis of Variant Angina Manifesting as Aborted Sudden Cardiac Death. J Am Coll Cardiol. 2016;68:137–45 (b) Kundu A, Vaze A, Sardar P, Nagy A, Aronow WS, Botkin NF. Variant Angina and Aborted Sudden Cardiac Death. Curr Cardiol Rep. 2018 Mar 8;20(4):26

VERSION 1 – AUTHOR RESPONSE

Reviewer 1
Fabien Picard

The title could be changed “Occurrence and Mortality of Vasospastic angina pectoris hospitalized patients”
Response: The title has been changed as suggested

How do the authors explain that coronary angiography was performed in only half of the patients. How can the authors can affirm that patients that did not have coronary angiography had indeed definite coronary vasospasm? This should be discussed and added as a limitation.

Response: We thank the Reviewer for the comment. This is a retrospective registry study and diagnoses were made by the treating doctor during each hospital stay. Angiogram and spasm provocation were not performed for all patients. This apparent limitation has now been further underlined in the limitation section of the discussion (p.15-16).

How do the authors explain that the admission rate for VAP decreased during the study period? This should be discussed

Response: We thank the Reviewer for the comment. Concurrently with previous US study (ref.22), we found occurrence rate of VAP admissions to decreased during study period. Reason for this change is unknown. In addition to true decrease in VAP, this finding may relate to increased rate of Takotsubo cardiomyopathy diagnoses and high-sensitive troponin assay usage. As suggested, this is now further discussed in the Discussion (p.15). Furthermore, a new reference (ref. no 23) has been added.

In the discussion, please use the same numbers than in the results for mortality, ie 15.5%

Response: Corrected as suggested (p.13). Furthermore, in order to make presentation of results uniform across the study, we have now given p-values with three decimals also in Tables 2 and 3.

Do the authors have infos on medical therapies used in these patients? This could of interest to evaluate if medical treatment of vasospastic angina can reduce cardiac mortality?
Response: Information of medicine usage in these patients would interesting. Unfortunately, however, we do not have this information available. We have now included this limitation in the limitations section of the Discussion (p.16).
There are few grammatical errors that should be corrected

Response: The grammatical errors have been corrected (pages 1, 3, 4, 14, 15, 16 and in the references)

Reviewer 2
John F Beltrame

More insights may be gained by detailing the baseline features of the vasospastic angina cohort during their index admission (a) the presence of a concurrent diagnosis of acute myocardial infarction – were these infarct patients without obstructive coronary artery disease and thus attributable to coronary spasm, and (b) discharge medications – how many were discharged on calcium channel blockers, since these are considered the cornerstone therapy of vasospastic angina.
Response:
We thank the Reviewer for comments.
a) Myocardial infarction (I21.X) was a second or a third additional diagnosis in 1.8% of admitted VAP patients. This information has now been added to the text (p.8).

b) Information of medicine usage in these patients would interesting. Unfortunately, however, we do not have this information available. We have now included this limitation in the limitations section of the Discussion (p.16).

The manuscript could be further improved by comparing the 1 & 3-year mortality (all-cause & non-cardiac) for the vasospastic angina cohort with those who had STEMI & NSTEMI
Response:
We agree that comparing VAP with NSTEMI and STEMI would be interesting. Unfortunately, however, we don´t have data available for this comparison. We will however plan to look into the subject when planning acquisition of new data permissions and data collections.

Reviewer 3
Amartya Kundu

Demographic baseline characteristics of the patients included in the study should be provided in a tabular format.
Response: As suggested, demographic features are now presented in a new table (Table 1). In order to limit repetition in the text, results section of the text has been modified accordingly (p.8). Furthermore, statistical tests used for baseline comparisons are now added in Methods (p.7).

Data on yearly trends in mortality associated with vasospastic angina will be useful, either in graphical or tabular format. Similarly data on short-term mortality should be reported.
Response: We thank the Reviewer for comments.

In regression models for mortality (Tables 2 and 3) we divided study era into three sections (2004-2006, 2007-2010, 2010-2014). There were no differences in mortality between these eras (Tables 2 and 3). In addition, we looked into potential annual trends by inputting study year as continuous variable into regression models, but found no trends in yearly mortality as demonstrated by the following results:
Annual trend for mortality:
1-year mortality, in univariate model p=0.434 and in multivariate model p=0.851
3-year mortality, in univariate model p=0.818 and in multivariate model p= 0.609

The 30-day all-cause mortality was 3.2%. This has now been added to the text as suggested (p.10).

Coronary angiography was performed in approximately 60 % of patients. How was the diagnosis of vasospastic angina made in the remaining cohort of patients? Also was a unified diagnostic criteria followed by all included hospitals to code someone as 'vasospastic angina' ? This needs to be clarified.
Response:
We thank the Reviewer for comments. This is a retrospective register study and the diagnoses are made by the working doctor during each hospital stay. Angiogram and spasm provocation were not made for every patient. This apparent limitation has now been further underlined in the limitation section of the discussion (p.15-16). In clinical practice, VAP diagnosis without coronary angiography is made mainly for patients with previously normal angiography (with or without VAP) and clinical features corresponding to VAP.

Discussion section should include further elaboration on the clinical impact of vasospastic angina, particularly its association with sudden cardiac death. Following articles can be used for reference:
(a) Ahn JM, Lee KH, Yoo SY, Cho YR, Suh J, Shin ES, et al. Prognosis of Variant Angina Manifesting as Aborted Sudden Cardiac Death. J Am Coll Cardiol. 2016;68:137–45
(b) Kundu A, Vaze A, Sardar P, Nagy A, Aronow WS, Botkin NF. Variant Angina and Aborted Sudden Cardiac Death. Curr Cardiol Rep. 2018 Mar 8;20(4):26
Response:
We thank the Reviewer for the comment. This matter is now discussed in more detail (p.14-15). and these important references have been added to the reference list (ref no 20 and 21).

VERSION 2 – REVIEW

REVIEWER	Fabien Picard Hopital Cochin, Paris, France
REVIEW RETURNED	20-Jul-2019

GENERAL COMMENTS	All comments have been addressed

REVIEWER	John F Beltrame University of Adelaide Central Adelaide Local Health Network Adelaide, AUSTRALIA
REVIEW RETURNED	03-Aug-2019

GENERAL COMMENTS	The strength of this study is its patient inclusivity (covering consecutive hospital admissions in Finland) and availability of long-term follow-up (1 & 3 years all-cause mortality). Its weakness/limitation relates to the diagnosis of vasospastic angina, as this is dependent upon the treating-clinician perceptions rather than formal diagnostic criteria. The fact that less than 2/3 of the patients underwent angiography is disconcerting. Also the lack of available of discharge therapies, limits insights into the treating clinician's diagnostic mindset since vasospastic angina patients should be discharged on calcium channel blockers. Perhaps the distribution of patients admitted with a diagnosis of vasospastic angina amongst the participating hospitals could provide insights into the treating clinician's mindset. Were most of the vasospastic angina diagnoses made at 1 or 2 hospitals, potentially reflecting a diagnostic bias? Could this data be presented in the manuscript?

REVIEWER	Amartya Kundu University of Massachusetts Medical School
REVIEW RETURNED	16-Jul-2019

GENERAL COMMENTS	Revised version of the manuscript appears significantly improved. No further specific comments.

VERSION 2 – AUTHOR RESPONSE

Reviewer 2

"Perhaps the distribution of patients admitted with a diagnosis of vasospastic angina amongst the participating hospitals could provide insights into the treating clinician's mindset. Were most of the vasospastic angina diagnoses made at 1 or 2 hospitals, potentially reflecting a diagnostic bias? Could this data be presented in the manuscript?"

Response: We thank the Reviewer for the comment. Diagnoses were made in all 38 hospitals included in the study (based on nationwide data search). Of VAP diagnoses 33% were made in 5 university hospital (representing highest level of hospital hierarchy), 54% in central hospitals (middle level of hospital hierarchy) and 13% in regional hospitals (lowest level of hospital hierarchy). Unfortunately, the research permission does not allow us to present the numbers of VAP diagnosis on individual hospitals basis.

As suggested, information on locations of diagnosis is now added to the manuscript (Methods, p.6).

VERSION 3 – REVIEW

REVIEWER	John Beltrame University of Adelaide Central Adelaide Local Health Network
REVIEW RETURNED	06-Sep-2019

GENERAL COMMENTS	The revised manuscript requires grammatical edits, particularly to clarify the limitations. These are summarised below, with reference to the marked-up version of the manuscript (changes in italics): Pg 35, L24 – should read as 'coronary spasm may be associated with sclerotic lesions in the arterial walls'. Pg 43, L24 - should read as 'The gold standard of coronary artery spasm testing…' Pg 44, L29 - should read as 'In our study population, coronary angiography was undertaken in 58% of men…' Pg 44, L36 - should read as 'It is known from previous studies that coronary spasm may develop in… Pg 44, L45 - should read as 'with vasospastic angina and luminal irregularity…

	Pg46, L3 – should read as '…diagnoses were based upon the treating physician's clinical impression and this may not have fulfilled published diagnostic criteria. Pg 47, L24 - should read as 'In conclusion, our results suggest that men…' Also, from my comments on the previous version – is data available concerning the discharge therapies in these patients with vasospastic angina?

VERSION 3 – AUTHOR RESPONSE

Reviewer 2
Thank you for the grammatical corrections, all correctios have been made:
Pg 35, L24 – should read as 'coronary spasm may be associated with sclerotic lesions in the arterial walls'.
Page 4

Pg 43, L24 - should read as 'The gold standard of coronary artery spasm testing…'
Page 13

Pg 44, L29 - should read as 'In our study population, coronary angiography was undertaken in 58% of men…'
Page 13

Pg 44, L36 - should read as 'It is known from previous studies that coronary spasm may develop in…
Page 13

Pg 44, L45 - should read as 'with vasospastic angina and luminal irregularity…
Page 13

Pg46, L3 – should read as '…diagnoses were based upon the treating physician's clinical impression and this may not have fulfilled published diagnostic criteria.
Page 16

Pg 47, L24 - should read as 'In conclusion, our results suggest that men…'
Page 16

Also, from my comments on the previous version – is data available concerning the discharge therapies in these patients with vasospastic angina?
Response: Information of medicine usage in these patients would interesting. Unfortunately, however, we do not have this information available. After the reviewers previous comment, this was added to the limitations section of the Discussion (p.15).