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Occurrence and Mortality of Vasospastic Angina Pectoris Hospitalizations. A Population based Register study

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Abstract

Objectives The occurrence and mortality of vasospastic angina pectoris (VAP) is largely unknown in Western countries. Our objective was to clarify the occurrence, gender-distribution and mortality of VAP in Finland using a population-based hospital registry.

Methods We studied consecutive patients aged ≥18 years hospitalized with vasospastic angina pectoris (VAP) as the primary cause of admission in Finland during 2004-2014. The data were collected from obligatory nationwide registries. During the study period 1762 admissions were recorded.

Results Majority of all VAP patients were male (59.7%) and mean age was 65.7±12.0 years. Annual admission rate for VAP was 2.29 / 100,000 person-years. Men were in higher risk for VAP than women (admission rate 3.00 / 100,000 vs. 1.68 / 100,000; RR 1.70; p<0.0001). Gender difference was not modified by age. Likelihood of VAP was highest in population aged 70-84 years. Admission rate for VAP decreased notably during the study period. One-year all-cause mortality was 8.0% and 3-year mortality was 15.5% (cardiac mortality 11.1%). Mortality was associated with increasing age, comorbidity burden and lack of detected coronary artery obstruction, but was similar between genders and during the study period.

Conclusions Men have higher risk for vasospastic angina caused admissions. Likelihood of vasospastic angina admission was highest in aged population. The 3-year all-cause mortality was 15.5%. Mortality was associated with increasing age, comorbidities and non-obstructive VAP diagnosis but was similar between genders.

An Article Summary

Strengths and limitation of this study

-This study gives new information about the vasospastic angina pectoris patients in a western country.

- Unique register data, which includes all medical hospitals admissions with the diagnoses of vasospastic amgima from all hospitals treating acute cardiac patients in mainland Finland.

-The study has a long follow-up period of 11 years

- As a limitation, this study is retrospective register data and the diagnoses were made by different doctors.

INTRODUCTION

Vasospastic angina pectoris (VAP), or Prinzmetal's angina originally described by Myron Prinzmetal et. al,[1] is defined as a sudden coronary vasocontraction leading to excessively reduced coronary blood flow causing myocardial ischemia[2]. 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, 3) demonstration of coronary artery spasm.[3,4] Coronary spasms occur mainly in large epicardial arteries but are known to occur also in coronary microvasculature of the myocardium. Coronary spasms are associated with sclerotic lesions in the arterial walls[3,5].

The prevalence of VAP seems to vary in different patient populations, but it has been reported that about 40% of the angina patients have vasospastic angina[3] and vasospasm have been detected in a third of non-ST-elevation myocardial infarction (MI) patients [6] In more detail, VAP is well studied in Japanese population and appears more common in Oriental countries in comparison to Western countries. Also, there seem to be substantial differences between Caucasian and Japanese VAP patients[3,7] with Japanese patients having more diffusely hypersensitive coronary arteries[8].

The 3-year MI mortality of VAP patients has been reported to be 3% in Japanese populations and 2% in Korean population[3,9,10]. Three-year MI mortality in Western VAP population has been 11%[3]. In Caucasian VAP patients with non-significant coronary obstructions, the all-cause mortality was 24% in a 140 months follow-up and the deaths were mostly age-related[11].

Several VAP patient series and registries originating mainly from Oriental populations have been reported whereas to our knowledge the occurrence of VAP at population level in Western countries is less well studied. We set out to clarify the occurrence, gender-distribution and mortality of VAP in Finland using a population-based hospital registry.

METHODS

Study population

We studied patients aged ≥18 years hospitalized with VAP (ICD-10 code I20.1X) as the primary cause of admission. Data of all medical hospitals admissions from all hospitals treating acute cardiac patients in mainland Finland between January 1st, 2004 and December 31st, 2014 were retrospectively collected from the Care Register for Health Care, a nationwide database containing all hospital discharge data from all admissions in Finland and maintained by the Finnish National Institute for Health and Welfare. VAP types were classified based on ICD-10 coding and the performed operations were identified based on operational codes (Nordic Classification of Surgical Procedures).

Finnish hospital system consists of three main levels: university hospitals (n=5) representing the highest level of hierarchy, followed by central hospitals (n=16) with coronary catherization laboratories and intensive care units, and then several smaller regional hospitals. Admissions due to VAP occurred in 38 hospitals during the study period. Mortality and cause of death data (follow-up ended in 31.12.2014) for the identified patients were obtained from nationwide and obligatory cause of death registry held by Statistics Finland. Annual admissions rates (one admission per year) were estimated by using age- and gender-matched population data of mainland Finland from the study period (46,642,940 person-years) obtained from Statistics Finland. The National Institute for Health and Welfare of Finland (permissions no: THL/143/5.05.00/2015 and THL/1569/5.05.00/2016) and Statistics Finland (TK53-1410-15) approved the study.

Statistical Analysis

Scale variables are presented as mean ± SD and categorical variables are presented as counts or percentages with 95% confidence intervals (CI) when applicable. Count data was analyzed by using negative binomial regression models. In the regression models of annual admission rate, the logarithm of population was used as an offset parameter. All-cause mortality from first VAP admission was studied using Kaplan-Maier method and Cox regression. Duration of hospital admission was calculated as beginning days. Results of regression analyses are given as rate ratios (RR) or hazard ratios (HR) as appropriate. CCI was calculated according to previously used algorithm[12]. Admission rates of admissions (one admission per year) were standardized to WHO 2010 standard population with the use of a direct method as appropriate. P-values <0.05 were considered statistically significant. Analyses were performed with the SAS system v. 9.4 (SAS Institute Inc, Cary, NC, USA).

Patient and public involvement

This is a retrospective register data. Data of all medical hospitals admissions from all hospitals treating acute cardiac patients in mainland Finland between January 1st, 2004 and December 31st, 2014 were retrospectively collected from the Care Register for Health Care. This is a nationwide database containing all hospital discharge data from all admissions in Finland and maintained by the Finnish National Institute for Health and Welfare and is a database to which all hospitals in Finland are obliged to report all ward discharges.

RESULTS

Patient Features

Vasospastic angina pectoris was the primary cause for 1762 hospital admissions (1570 individual patients, 59.7% male) during the study period. Mean age of all VAP patients was 65.7±12.0 years (range 18-98 years) (Figure 1A). Age distribution of VAP patients had similar patterns in both genders, although age-pattern was shifted towards older age in women (Figure 1B) with female patients being marginally older compared to men (66.8±13.0 vs. 64.2±11.3, p=0.002). Co-morbidity burden of patients was similar between genders (CCI-score 0 in 55.3%; 1 in 23.6% and ≥2 in 21.1% of patients). Coronary angiography was performed in 992 (56%) admissions. Angiography was more common for men (58.4%) than for women (53.2%) who were hospitalized for VAP (p=0.0334). Majority of VAP patients (45.0%) had no detected coronary obstruction while obstruction was present in 28.3%. Obstructive disease was more common in men than in women (32.9% vs. 21.4%; p<0.001). Admission for vasospastic angina lasted on average for 4.3±3.7 (range 1 - 44 days). There was no difference in duration of admission between genders.

Annual admission rate

During the whole study period, the total standardized annual admission rate for VAP was 2.29 (CI 2.15-2.43)/100,000 person-years (crude rate 3.45 (CI 3.29-3.63) / 100,000). Likelihood of VAP admission increased progressively from 40 to 70 years of age with highest rate (10.5 / 100,000) in patients aged 70-75 years (Figure 2). Among women, the standardized overall rate for VAP hospital admission was 1.68 (CI 1.52-1.86) / 100,000 person-years (crude rate 2.71 (CI 1.52-1.86) / 100,000), whereas for men the standardized rate was 3.00 (CI 2.77-3.22) / 100,000 (crude rate 4.25 (CI 3.98-4.53) / 100,000). In total

Finnish adult population, men were 70% more likely to be admitted to hospital due to VAP (RR for admission rate 1.70; CI 1.39-2.08; p<0.0001) than women. Gender difference was similar between age groups (interaction p=0.201) (Figure 3). Admission rate for VAP decreased notably during the study period (Figure 4).

Mortality

One-year all-cause mortality after VAP admission was 8.0% and 3-year mortality was 15.5% (Figure 5). One-year mortality was associated with increasing age, comorbidity burden and coronary artery status, but was similar between genders and study periods (Table 1). Comparably, 3-year mortality was associated with increasing age, CCI-score and lack of detected coronary artery obstruction but was similar between genders during study (Table 2). Majority (71.2%) of all the deaths were due to cardiac causes with cardiac mortality of 5.8% at 1-year and 11.1% at 3-year follow-up. Myocardial infarction and ischemic heart disease were most common underlying causes of death.

		Univariate			Multivariate		
Variable	**Mortality (%)**	**HR**	**95% CI**	**p value**	**HR**	**95% CI**	**p value**
Gender				0.79			0.31
Male	7.82	Ref.					
Female	8.19	1.05	0.73-1.50	0.79	0.83	0.57-1.19	0.31
Age (years)				<0.0001			<0.0001
<50	2.16	Ref.			Ref.		
50-59	0.85	0.4	0.08-2.00	0.27	0.40	0.08-1.97	0.26
60-69	5.46	2.62	0.79-8.71	0.12	2.25	0.67-7.53	0.19
70-79	10.26	5.03	1.56-16.19	0.007	4.15	1.28-13.45	0.02
80-	24.26	13.12	4.09-42.06	<0.0001	9.95	3.06-32.33	0.0001
CCI				<0.0001			<0.0001
0	4.18	Ref.			Ref.		
1	7.82	1.88	1.15-3.07	0.01	1.47	0.90-2.42	0.13
2	17.39	4.39	2.75-7.02	<0.0001	2.68	1.65-4.36	<0.0001
≥3	19.23	4.82	2.89-8.03	<0.0001	3.33	1.97-5.64	<0.0001
Coronary status				0.006			0.15
Obstruction	4.55	Ref.			Ref.		
No obstruction	8.36	1.87	1.12-3.14	0.02	1.69	0.99-2.87	0.05
NAS	10.67	2.41	1.41-4.12	0.001	1.51	0.87-2.65	0.16
Study year				0.20			
2004-2006	7.26	Ref.			Ref.		
2007-2010	7.62	1.05	0.70-1.56	0.82	0.99	0.66-1.49	0.97
2010-2014	10.79	1.44	0.90-2.31	0.09	1.26	0.78-2.07	0.34

Table 1. Factors associated with 1-year all-cause mortality. Univariate and multivariate analysis. CCI = Charlson co-morbidity index. HR = Hazard ratio.

		Univariate			Multivariate		
Variable	**Mortality (%)**	**HR**	**95% CI**	**p value**	**HR**	**95% CI**	**p value**
Gender				0.79			0.07
Male	15.78	Ref.					
Female	15.15	0.97	0.74-1.26	0.79	0.78	0.59-1.02	0.07
Age (years)				<0.0001			<0.0001
<50	4.60	Ref.			Ref.		
50-59	5.09	1.10	0.44-2.80	0.84	1.08	0.42-2.74	0.88
60-69	10.27	2.35	1.00-5.53	0.05	2.05	0.87-4.84	0.10
70-79	20.22	4.84	2.12-11.07	0.0002	4.13	1.80-9.48	0.008
80-	41.33	11.78	5.14-26.98	<0.0001	9.30	4.02-21.52	<0.0001
CCI				<0.0001			<0.0001
0	9.65	Ref.			Ref.		
1	14.57	1.57	1.11-2.23	0.01	1.25	0.88-1.78	0.21
2	28.87	3.42	2.43-4.82	<0.0001	2.29	1.61-3.27	<0.0001
≥3	36.65	4.36	3.03-6.27	<0.0001	3.26	2.17-4.59	<0.0001
Coronary status				<0.0001			0.04
Obstruction	10.08	Ref.			Ref.		
No obstruction	15.15	1.56	1.09-2.24	0.02	1.51	1.05-2.19	0.03
NAS	21.67	2.30	1.59-3.34	<0.0001	1.61	1.09-2.37	0.02
Study year				0.31			0.61
2004-2006	15.26	Ref.			Ref.		
2007-2010	14.76	0.96	0.73-1.28	0.96	0.80	0.68-1.21	0.51
2010-2014	17.81	1.29	0.89-1.87	0.19	1.10	0.75-1.6	0.64

Table 2. Factors associated with 3-year all-cause mortality. Univariate and multivariate analysis. CCI = Charlson co-morbidity index. HR = Hazard ratio.

DISCUSSION

This nationwide study describes the occurrence of VAP admissions in Finnish general population. Men were 70% more likely to be admitted for VAP compared with woman. All-cause mortality was 8% at one year and 16% at three years. Mortality was associated with older age, comorbidities and non-obstructive or non-specific coronary findings but similar between genders.

The diagnosis of vasospastic angina is characterized by spontaneous chest pains and drug or non-drug (i.e. hyperventilation) induced spasm. The golden standard of coronary artery spasm testing involves the administration of a provocative stimulus during coronary angiogram.[4] In our study population, the coronary angiogram was made for 58% of men and for 53% of women hospitalized for VAP. It is known from previous studies that coronary spasm develops in sclerotic lesions of varying severity[3,5]. Even if no stenotic lesions are visible on coronary angiography, IVUS commonly reveals arteriosclerotic lesions in locations consistent with regions of coronary spasm.[3] It has been shown that with OCT, thrombus was seen in one fourth of patients with vasospastic decease and luminal irregularity was observed in nearly two-thirds of the study patients[5]. In the present study, atherosclerotic changes in coronary arteries were diagnosed in 33% of men and 21% of women.

We found the overall annual admission rate for VAP to be 2.3 / 100,000. This compares to previously detected admission rates of 93 / 100,000 for unstable angina pectoris [13]105 / 100,000 for ST-elevation MI[14] and 206 / 100,000 for non-ST-elevation MI[15] in Finnish adult population. Volume of VAP admissions can thus be estimated to be approximately 1% of

the amount of acute coronary syndrome admissions. Decreasing VAP admissions are however likely to affect this ratio.

In Japan as well as in Western countries vasospastic angina is more prevalent in males. The gender-difference diminishes after menopause and disappears at the age of 80 in Japanese population[3]. We found VAP to be 70% more common among men while gender-difference was not modified by age. Vasospastic angina pectoris is known to cause significant morbidity to affected individuals[16]. In Korean population mortality was 2% at two years [5] with similar prognosis in both genders [17]. In a Japanese study population, the MI was 3% at 3-years[3]. In Western population the 3-year MI mortality has been reported to be 11%[3] comparably to our results.

In Caucasian study population of VAP without significant atherosclerotic stenosis, the mortality was 24% at 12-year follow-up with mostly non-cardiac deaths[11]. We found 3-year mortality to be 15.5% and to be mostly cardiogenic. In an earlier study, the risk of death and MI was similar in male ST-segment elevation MI patients and VAP patients while VAP patients with non-significant coronary stenosis seemed to have less complications and lower mortality[18].

Our results suggest that the vasospastic angina pectoris might not be as benign disease as often thought. We can assume, that most the of patients with a diagnostic code of narrowing or occlusive atherosclerosis had a visible occlusion in the coronary arteries have been taken care of by intervention or medication for coronary artery decease in the well-functioning Finnish health care system. For rest of the study population, coronary angiogram did not reveal atherosclerotic changes, or the angiography was not performed

during index admission. For comparison, in a Swedish register study, the 1-year mortality after admission for unstable angina pectoris was 10% in age group 65-105[19]. Interestingly, a Korean study found VAP patients presenting with acute coronary syndrome to have worse prognosis compared to VAP patients without presentation of ACS[9].

In North America, vasospastic angina has become less frequent for unknown reasons, possibly relating to more widespread use of calcium antagonists[20]. Up to 70% of patients with acute coronary syndrome (ACS) with typical ECG changes and/or elevation of cardiac markers had culprit lesions, whereas the remaining 30% of ACS patients had no obstructive coronary artery lesions. Cardiologists in the USA do not perform spasm provocation tests routinely in patients with non-obstructive coronary artery disease with chest pain/discomfort in the cardiac catheterization laboratory[20]. Similarly, in our study, the occurrence of VAP admissions decreased notably during the study period. In Finland, the spasm provocation test is rarely done. The use of high sensitive troponin initiated during the study period. This is likely to have increased the number of MI diagnoses towards the end of the study period.

The present study has some limitation. A major limitation is the retrospective nature of observational registry data. The diagnoses were made by the treating physician and this may have affected the selected study population and the accuracy of the comorbidity data. In addition, because our data included only hospitalized patients, the results underrepresents patients with low-risk features who may have been treated without being admitted to the hospital or who have not sought for help. Coronary angiography was performed only for 56% of VAP patients. Some of the coronary artery disease diagnoses might thus have been missed.

In conclusion, our results indicate that men have higher risk for vasospastic angina causing admissions compared with women. Likelihood of vasospastic angina admission was highest in population aged 70-84 years. The 3-year mortality was 15.5% and was predicted by patients age and comorbidities, but also by non-obstructive vasospastic angina diagnosis. The cause of death was mostly cardiac at 1- and 3-year follow-ups. These results may help characterize the inadequately known epidemiology of vasospastic angina pectoris in Western countries.

Funding Sources

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Footnote

Contributors: EP data interpretation, manuscript writing and editing, JB manuscript writing and editing, JS and PR proofreading and manuscript editing, VK study design, data collection/analysis/interpretation, manuscript writing and editing

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Competing interests: None to declare

Ethics approval: The National Institute for Health and Welfare of Finland (permissions no: THL/143/5.05.00/2015 and THL/1569/5.05.00/2016) and Statistics Finland (TK53-1410-15) approved the study.
Data sharing statement No additional data are available.

Patient consent for publication Not required.

Figure Legends:

Figure 1. Frequency of vasospastic angina pectoris admissions. Age-distribution of all patients (A) and by gender (from total number of patients) (B). Error bars represent upper limits of 95% confidence intervals

Figure 2. Annual rate of vasospastic angina pectoris admission in general adult population. Admission rates (per 100,000 person-years) by age. Error bars represent upper limits of 95% confidence intervals.

Figure 3. Gender-associated admission rate ratio of vasospastic angina pectoris by age in general population. Ratio is calculated as men vs. women and adjusted for background population and study year. Error bars represent 95% confidence intervals.

Figure 4. Trend for annual rate of VAP admissions in general adult population. Standardized to WHO standard population. Error bars represent 95% confidence intervals.

Figure 5. Cumulative all-cause mortality after VAP admission.

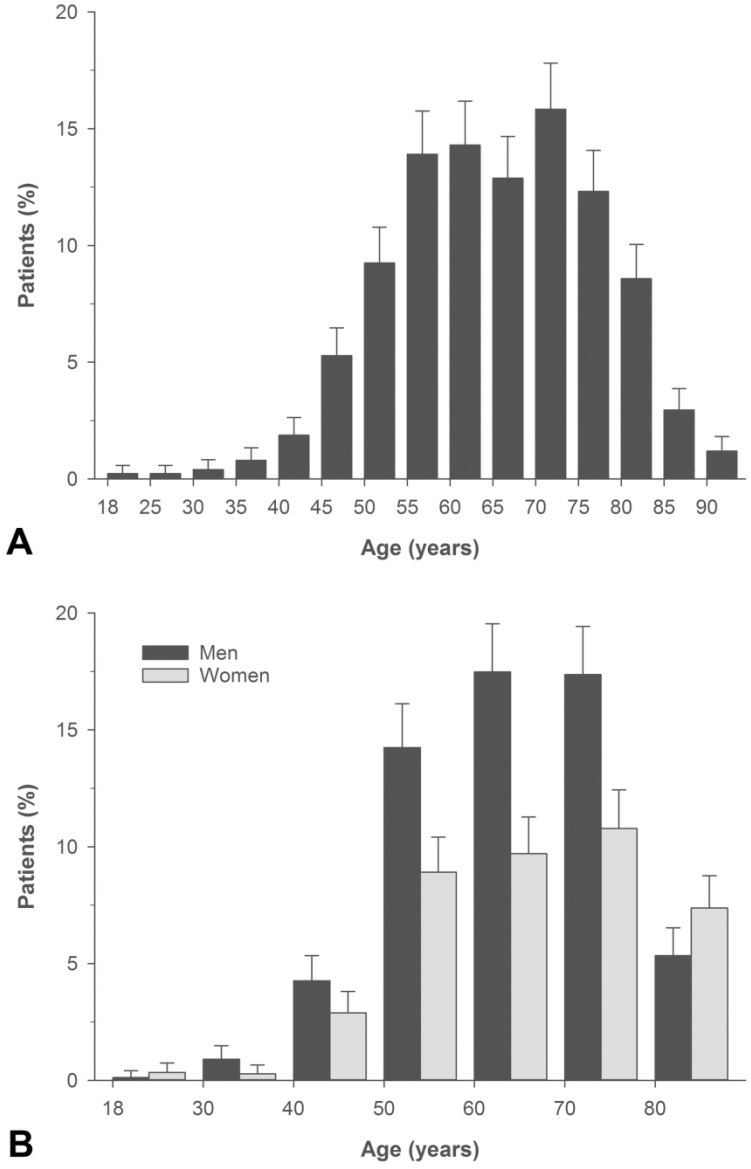

Figure 1. Frequency of vasospastic angina pectoris admissions. Age-distribution of all patients (A) and by gender (from total number of patients) (B). Error bars represent upper limits of 95% confidence intervals

144x230mm (300 x 300 DPI)

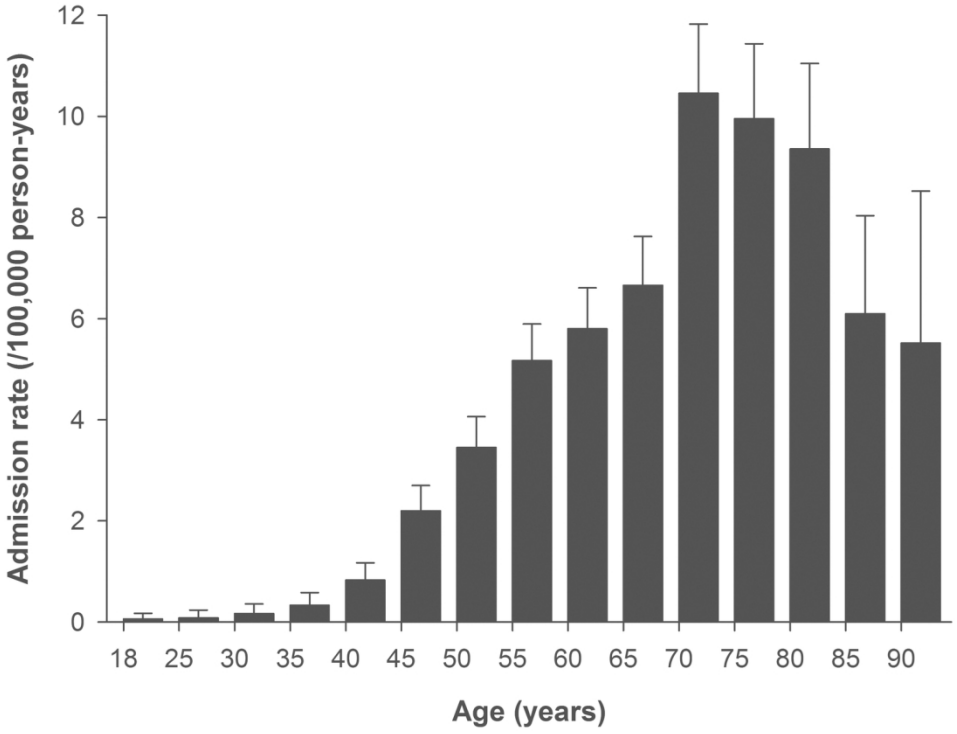

Figure 2. Annual rate of vasospastic angina pectoris admission in general adult population. Admission rates (per 100,000 person-years) by age. Error bars represent upper limits of 95% confidence intervals.

147x118mm (300 x 300 DPI)

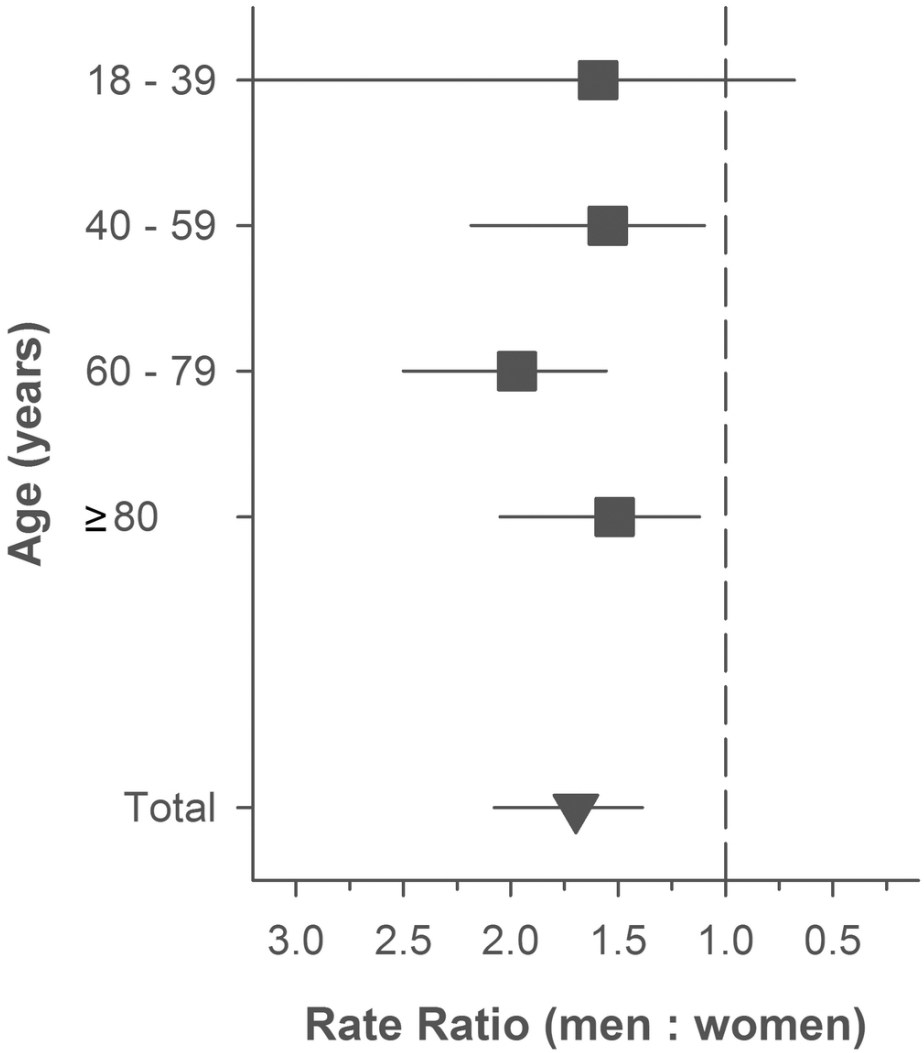

Figure 3. Gender-associated admission rate ratio of vasospastic angina pectoris by age in general population. Ratio is calculated as men vs. women and adjusted for background population and study year. Error bars represent 95% confidence intervals.

92x110mm (300 x 300 DPI)

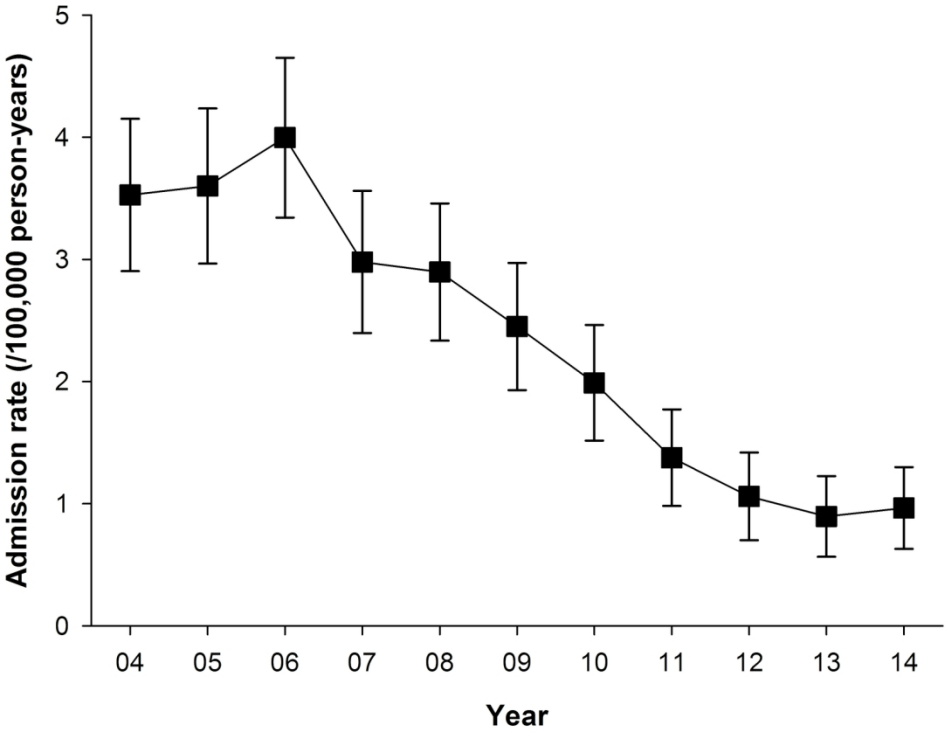

Figure 4. Trend for annual rate of VAP admissions in general adult population. Standardized to WHO standard population. Error bars represent 95% confidence intervals.

146x119mm (300 x 300 DPI)

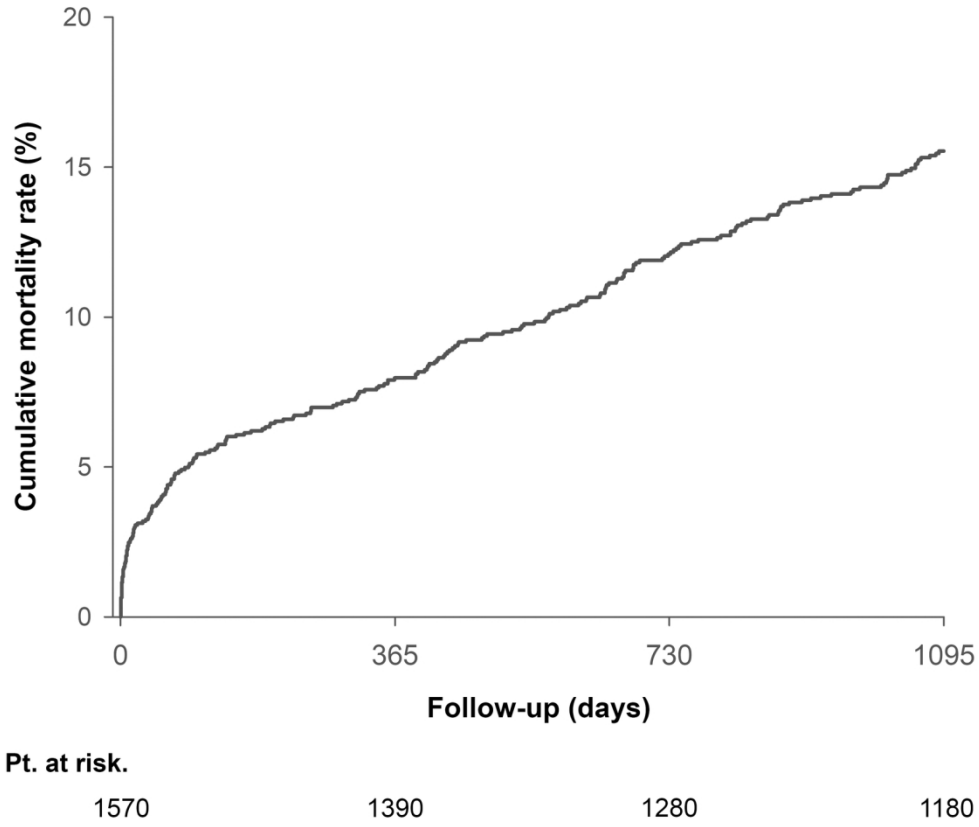

Figure 5. Cumulative all-cause mortality after VAP admission.

149x130mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*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	6
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	*6*
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
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	6
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	8
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	8
		(*b*) Report category boundaries when continuous variables were categorized	
		(*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	8-11
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14
Generalisability	21	Discuss the generalisability (external validity) of the study results	
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	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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 www.strobe-statement.org.

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Occurrence and Mortality of Vasospastic Angina Pectoris Hospitalized Patients in Finland.

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Occurrence and Mortality of Vasospastic Angina Pectoris Hospitalized Patients in Finland.

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Abstract

Objectives The occurrence and mortality of vasospastic angina pectoris (VAP) is largely unknown in Western countries. Our objective was to clarify the occurrence, gender-distribution and mortality of VAP in Finland using a population-based hospital registry.

Methods We studied consecutive patients aged ≥18 years hospitalized with vasospastic angina pectoris (VAP) as the primary cause of admission in Finland during 2004-2014. The data were collected from obligatory nationwide registries. During the study period 1762 admissions were recorded.

Results Majority of all VAP patients were male (59.7%) and mean age was 65.7±12.0 years. Annual admission rate for VAP was 2.29 / 100,000 person-years. Men were in higher risk for VAP than women (admission rate 3.00 / 100,000 vs. 1.68 / 100,000; RR 1.70; p<0.0001). Gender difference was not modified by age. Likelihood of VAP was highest in population aged 70-84 years. Admission rate for VAP decreased notably during the study period. One-year all-cause mortality was 8.0% and 3-year mortality was 15.5% (cardiac mortality 11.1%). Mortality was associated with increasing age, comorbidity burden and lack of detected coronary artery obstruction, but was similar between genders and during the study period.

Conclusions Men have higher risk for vasospastic angina caused admissions. Likelihood of vasospastic angina admission was highest in aged population. The 3-year all-cause mortality was 15.5%. Mortality was associated with increasing age, comorbidities and non-obstructive VAP diagnosis but was similar between genders.

An Article Summary

Strengths and limitation of this study

- New information about the vasospastic angina pectoris patients in a Western country.
- Unique registry data including all medical hospitals admissions with the diagnoses of vasospastic angina from all hospitals treating acute cardiac patients in mainland Finland.
- Follow-up period of 11 years
- Retrospective registry data and the diagnoses were made by different physicians.
- Coronary angiography was performed for 56% of the hospitalized patients limiting the accuracy of diagnoses

INTRODUCTION

Vasospastic angina pectoris (VAP), or Prinzmetal's angina, originally described by Myron Prinzmetal et. al,[1] is defined as a sudden coronary vasoconstriction leading to excessively reduced coronary blood flow causing myocardial ischemia[2]. 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, 3) demonstration of coronary artery spasm.[3,4] Coronary spasms occur mainly in large epicardial arteries but are known to occur also in coronary microvasculature of the myocardium. Coronary spasms are associated with sclerotic lesions in the arterial walls[3,5].

The prevalence of VAP seems to vary in different patient populations, but it has been reported that about 40% of the angina patients have vasospastic angina[3] and vasospasm have been detected in a third of non-ST-elevation myocardial infarction (MI) patients [6] In more detail, VAP is well studied in Japanese population and appears more common in Oriental countries in comparison to Western countries. Also, there seem to be substantial differences between Caucasian and Japanese VAP patients[3,7] with Japanese patients having more diffusely hypersensitive coronary arteries[8].

The 3-year MI mortality of VAP patients has been reported to be 3% in Japanese populations and 2% in Korean population[3,9,10]. Three-year MI mortality in Western VAP population has been 11%[3]. In Caucasian VAP patients with non-significant coronary obstructions, the all-cause mortality was 24% in a 140 months follow-up and the deaths were mostly age-related[11].

Several VAP patient series and registries originating mainly from Oriental populations have been reported whereas to our knowledge the occurrence of VAP at population level in Western countries is less well studied. We set out to clarify the occurrence, gender-distribution and mortality of VAP in Finland using a population-based hospital registry.

METHODS

Study population

We studied patients aged ≥18 years hospitalized with VAP (ICD-10 code I20.1X) as the primary cause of admission. Data of all medical hospitals admissions from all hospitals treating acute cardiac patients in mainland Finland between January 1st, 2004 and December 31st, 2014 were retrospectively collected from the Care Register for Health Care, a nationwide database containing all hospital discharge data from all admissions in Finland and maintained by the Finnish National Institute for Health and Welfare. VAP types were classified based on ICD-10 coding and the performed operations were identified based on operational codes (Nordic Classification of Surgical Procedures).

Finnish hospital system consists of three main levels: university hospitals (n=5) representing the highest level of hierarchy, followed by central hospitals (n=16) with coronary catherization laboratories and intensive care units, and then several smaller regional hospitals. Admissions due to VAP occurred in 38 hospitals during the study period. Mortality and cause of death data (follow-up ended in 31.12.2014) for the identified patients were obtained from nationwide and obligatory cause of death registry held by Statistics Finland. The co-morbidities of the patients were described by Charlson comorbidity index (CCI). Annual admissions rates (one admission per year) were estimated by using age- and gender-matched population data of mainland Finland from the study period (46,642,940 person-years) obtained from Statistics Finland. The National Institute for Health and Welfare of Finland (permissions no: THL/143/5.05.00/2015 and THL/1569/5.05.00/2016) and Statistics Finland (TK53-1410-15) approved the study.

Statistical Analysis

Scale variables are presented as mean ± SD and categorical variables are presented as counts or percentages with 95% confidence intervals (CI) when applicable. Gender differences in baseline features were analyzed using t-test or Chi-squared test. Count data was analyzed by using negative binomial regression models. In the regression models of annual admission rate, the logarithm of population was used as an offset parameter. All-cause mortality from first VAP admission was studied using Kaplan-Maier method and Cox regression. Duration of hospital admission was calculated as beginning days. Results of regression analyses are given as rate ratios (RR) or hazard ratios (HR) as appropriate. CCI was calculated according to previously used algorithm[12]. Admission rates of admissions (one admission per year) were standardized to WHO 2010 standard population with the use of a direct method as appropriate. P-values <0.05 were considered statistically significant. Analyses were performed with the SAS system v. 9.4 (SAS Institute Inc, Cary, NC, USA).

Patient and public involvement

This study is based on a retrospective registry data and does not have direct involvement of patients or the public.

RESULTS

Patient Features

Vasospastic angina pectoris was the primary cause for 1762 hospital admissions (1570 individual patients, 59.7% male) during the study period. Demographic baseline characteristics of the hospitalized patients are shown on Table 1. Mean age of all VAP patients was 65.7±12.0 years (range 18-98 years) (Figure 1A). Age distribution of VAP patients had similar patterns in both genders, although age-pattern was shifted towards older age in women (Figure 1B) with female patients being marginally older compared to men (Table 1). Co-morbidity burden of patients was similar between genders (Table 1). Coronary angiography was performed in 56% admissions and was more common for men than for women, who were hospitalized for VAP (Table 1). Majority of VAP patients had no detected coronary obstruction, but obstructive disease was more common in men than in women (Table 1). Admission for vasospastic angina lasted on average for 4.3±3.7 (range 1 - 44 days) with no difference in duration of admission between genders. Myocardial infarction (I21.X) was secondary or a tertiary diagnosis for 1.8% of VAP patients.

Variable	Total (n=1762)	Male (n=1052)	Female (n=710)	p-value*
Age (y, mean)	65.7±12.0	64.9±11.3	66.8±13.0	0.002
CCI score				0.178
0	975 (55.3%)	576 (54.8%)	399 (56.2%)	
1	415 (23.6%)	246 (23.4%)	169 (23.8%)	
2	224 (12.7%)	131 (12.5%)	93 (13.1%)	
≥3	148 (8.4%)	99 (9.4%)	49 (6.9%)	
Coronary angiography performed**	992 (56.3%)	614 (58.4%)	378 (53.2%)	0.033
Angiographical finding				<0.0001
No obstruction	793 (45.0%)	440 (41.8%)	353 (49.7%)	
Obstruction	498 (28.3%)	346 (32.9%)	152 (21.4%)	
NAS	471 (26.7%)	266 (25.3%)	205 (28.9%)	

Table 1. Patient characteristics of all hospital admission (n= 1762)

CCI= Charlson comorbidity index, ICD= International Classification of Diseases *Between genders. **During VAP admission.

Annual admission rate

During the whole study period, the total standardized annual admission rate for VAP was 2.29 (CI 2.15-2.43)/100,000 person-years (crude rate 3.45 (CI 3.29-3.63) / 100,000). Likelihood of VAP admission increased progressively from 40 to 70 years of age with highest rate (10.5 / 100,000) in patients aged 70-75 years (Figure 2). Among women, the standardized overall rate for VAP hospital admission was 1.68 (CI 1.52-1.86) / 100,000 person-years (crude rate 2.71 (CI 1.52-1.86) / 100,000), whereas for men the standardized rate was 3.00 (CI 2.77-3.22) / 100,000 (crude rate 4.25 (CI 3.98-4.53) / 100,000). In total Finnish adult population, men were 70% more likely to be admitted to hospital due to VAP (RR for admission rate 1.70; CI 1.39-2.08; p<0.0001) than women. Gender difference was similar between age groups (interaction p=0.201) (Figure 3). Admission rate for VAP decreased notably during the study period (Figure 4).

Mortality

Thirty-day all-cause mortality was 3.2%, one-year mortality was 8.0% and 3-year mortality was 15.5% after admission for VAP (Figure 5). One-year mortality was associated with increasing age, comorbidity burden and coronary artery status, but was similar between genders and study periods (Table 2). Comparably, 3-year mortality was associated with increasing age, CCI-score and lack of detected coronary artery obstruction but was similar between genders during study (Table 3). Majority (71.2%) of all the deaths were due to cardiac causes with cardiac mortality of 5.8% at 1-year and 11.1% at 3-year follow-up. Myocardial infarction and ischemic heart disease were most common underlying causes of death.

		Univariate			Multivariate		
Variable	**Mortality (%)**	**HR**	**95% CI**	**p value**	**HR**	**95% CI**	**p value**
Gender				0.795			0.311
Male	7.82	Ref.					
Female	8.19	1.05	0.73-1.50	0.795	0.83	0.57-1.19	0.311
Age (years)				<0.0001			<0.0001
<50	2.16	Ref.			Ref.		
50-59	0.85	0.4	0.08-2.00	0.267	0.40	0.08-1.97	0.259
60-69	5.46	2.62	0.79-8.71	0.117	2.25	0.67-7.53	0.189
70-79	10.26	5.03	1.56-16.19	0.007	4.15	1.28-13.45	0.018
80-	24.26	13.12	4.09-42.06	<0.0001	9.95	3.06-32.33	0.0001
CCI				<0.0001			<0.0001
0	4.18	Ref.			Ref.		
1	7.82	1.88	1.15-3.07	0.011	1.47	0.90-2.42	0.127
2	17.39	4.39	2.75-7.02	<0.0001	2.68	1.65-4.36	<0.0001
≥3	19.23	4.82	2.89-8.03	<0.0001	3.33	1.97-5.64	<0.0001
Coronary status				0.006			0.149
Obstruction	4.55	Ref.			Ref.		
No obstruction	8.36	1.87	1.12-3.14	0.017	1.69	0.99-2.87	0.050
NAS	10.67	2.41	1.41-4.12	0.001	1.51	0.87-2.65	0.155
Study year				0.198			0.564
2004-2006	7.26	Ref.			Ref.		
2007-2010	7.62	1.05	0.70-1.56	0.821	0.99	0.66-1.49	0.970
2010-2014	10.79	1.44	0.90-2.31	0.086	1.26	0.78-2.07	0.338

Table 2. Factors associated with 1-year all-cause mortality. Univariate and multivariate analysis. CCI = Charlson co-morbidity index. HR = Hazard ratio.

		Univariate			Multivariate		
Variable	**Mortality (%)**	**HR**	**95% CI**	**p value**	**HR**	**95% CI**	**p value**
Gender				0.788			0.065
Male	15.78	Ref.					
Female	15.15	0.97	0.74-1.26	0.788	0.78	0.59-1.02	0.065
Age (years)				<0.0001			<0.0001
<50	4.60	Ref.			Ref.		
50-59	5.09	1.10	0.44-2.80	0.835	1.08	0.42-2.74	0.876
60-69	10.27	2.35	1.00-5.53	0.050	2.05	0.87-4.84	0.102
70-79	20.22	4.84	2.12-11.07	0.0002	4.13	1.80-9.48	0.0008
80-	41.33	11.78	5.14-26.98	<0.0001	9.30	4.02-21.52	<0.0001
CCI				<0.0001			<0.0001
0	9.65	Ref.			Ref.		
1	14.57	1.57	1.11-2.23	0.010	1.25	0.88-1.78	0.208
2	28.87	3.42	2.43-4.82	<0.0001	2.29	1.61-3.27	<0.0001
≥3	36.65	4.36	3.03-6.27	<0.0001	3.26	2.17-4.59	<0.0001
Coronary status				<0.0001			0.045
Obstruction	10.08	Ref.			Ref.		
No obstruction	15.15	1.56	1.09-2.24	0.016	1.51	1.05-2.19	0.028
NAS	21.67	2.30	1.59-3.34	<0.0001	1.61	1.09-2.37	0.017
Study year				0.311			0.609
2004-2006	15.26	Ref.			Ref.		
2007-2010	14.76	0.96	0.73-1.28	0.796	0.80	0.68-1.21	0.511
2010-2014	17.81	1.29	0.89-1.87	0.188	1.10	0.75-1.6	0.640

Table 3. Factors associated with 3-year all-cause mortality. Univariate and multivariate analysis. CCI = Charlson co-morbidity index. HR = Hazard ratio.

DISCUSSION

This nationwide study describes the occurrence of VAP admissions in Finnish general population. Men were 70% more likely to be admitted for VAP compared with woman. All-cause mortality was 8.0% at one year and 15.5% at three years. Mortality was associated with older age, comorbidities and non-obstructive or non-specific coronary findings but it was similar between genders.

The diagnosis of vasospastic angina is characterized by spontaneous chest pains and drug or non-drug (i.e. hyperventilation) induced spasm. The golden standard of coronary artery spasm testing involves the administration of a provocative stimulus during coronary angiography.[4] In our study population, the coronary angiography was made for 58% of men and for 53% of women hospitalized for VAP.

It is known from previous studies that coronary spasm develops in sclerotic lesions of varying severity[3,5]. Even if no stenotic lesions are visible on coronary angiography, IVUS commonly reveals arteriosclerotic lesions in locations consistent with regions of coronary spasm.[3] It has been shown that with OCT, thrombus was seen in one fourth of patients with vasospastic decease and luminal irregularity was observed in nearly two-thirds of the study patients[5]. In the present study, atherosclerotic changes in coronary arteries were diagnosed in 33% of men and 21% of women.

We found the overall annual admission rate for VAP to be 2.3 / 100,000. This compares to previously detected admission rates of 93 / 100,000 for unstable angina pectoris [13], 105 / 100,000 for ST-elevation MI[14] and 206 / 100,000 for non-ST-elevation MI[15] in Finnish adult

population. Volume of VAP admissions can thus be estimated to be approximately 1% of the amount of acute coronary syndrome admissions. Decreasing VAP admissions are however likely to affect this ratio.

In Japan as well as in Western countries vasospastic angina is more prevalent in males. The gender-difference diminishes after menopause and disappears at the age of 80 in Japanese population[3]. We found VAP to be 70% more common among men while gender-difference was not modified by age. Vasospastic angina pectoris is known to cause significant morbidity to individuals affected[16]. In Korean population mortality was 2% at two years [5] with similar prognosis in both genders [17]. In a Japanese study population, the MI was 3% at 3-years[3]. In Western population the 3-year MI mortality has been reported to be 11%[3] comparably to our results.

In Caucasian study population of VAP without significant atherosclerotic stenosis, the mortality was 24% at 12-year follow-up with mostly non-cardiac deaths[11].

We found 3-year mortality to be 15.5% and to be mostly cardiogenic. In an earlier study, the risk of death and MI was similar in male ST-segment elevation MI patients and VAP patients while VAP patients with non-significant coronary stenosis seemed to have less complications and lower mortality[18].

Our results suggest that the vasospastic angina pectoris might not be as benign disease as often thought. We can assume, that most the of patients with a diagnostic code of narrowing or occlusive coronary artery findings, had a visible narrowing or occlusion in the coronary arteries and had been taken care of by intervention or medication for coronary

artery decease in the well-functioning Finnish health care system. For rest of the study population, coronary angiography did not reveal atherosclerotic changes, or the angiography was not performed during index admission. For comparison, in a Swedish register study, the 1-year mortality after admission for unstable angina pectoris was 10% in age group 65-105[19]. Interestingly, a Korean study found VAP patients presenting with acute coronary syndrome (ACS) to have worse prognosis compared to VAP patients without presentation of ACS [9]. One potential mechanism for VAP related mortality are vasospasm triggered arrythmias. In agreement, previous studies have shown VAP patients with aborted sudden cardiac death (ASCD) to have worse prognosis than those without[20,21].

In North America, vasospastic angina has become less frequent for unknown reasons, possibly relating to more widespread use of calcium antagonists[22]. Up to 70% of patients with ACS presenting with typical ECG changes and/or elevation of cardiac markers had culprit lesions, whereas the remaining 30% of ACS patients had no obstructive coronary artery lesions. Cardiologists in the USA do not perform spasm provocation tests routinely in patients with non-obstructive coronary artery disease with chest pain/discomfort in the cardiac catheterization laboratory[22]. Similarly, in our study, the occurrence of VAP admissions decreased notably during the study period. Underling reason for this change is unknown. In addition to true decrease in VAP, this finding may relate to increase in rates of Takotsubo cardiomyopathy diagnoses[23] and high-sensitive troponin assay usage increasing alternative diagnoses for VAP during the study period.

The present study has some limitation. A major limitation is the retrospective nature of observational registry data without access to more detailed clinical or therapeutic data. The

diagnoses were made by the treating physician and this may have affected the selected study population and the accuracy of the comorbidity data. In addition, because our data included only hospitalized patients, the results underrepresents patients with low-risk features who may have been treated without being admitted to the hospital or who have not sought for help. Coronary angiography was performed only for 56% of VAP patients. Some of the coronary artery disease diagnoses might thus have been missed. Furthermore, the spasm provocation tests are seldomly used in Finland limiting the accuracy of VAP diagnoses.

In conclusion, our results indicate that men have higher risk for vasospastic angina causing admissions compared with women. Likelihood of vasospastic angina admission was highest in population aged 70-84 years. The 3-year mortality was 15.5% and was predicted by patients age and comorbidities, but also by non-obstructive vasospastic angina diagnosis. The cause of death was mostly cardiac at 1- and 3-year follow-ups. These results may help characterize the inadequately known epidemiology of vasospastic angina pectoris in Western countries.

Funding Sources

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Footnote

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Data sharing statement No additional data are available.

Patient consent for publication Not required.

Figure Legends:

Figure 1. Frequency of vasospastic angina pectoris admissions. Age-distribution of all patients (A) and by gender (from total number of patients) (B). Error bars represent upper limits of 95% confidence intervals

Figure 2. Annual rate of vasospastic angina pectoris admission in general adult population. Admission rates (per 100,000 person-years) by age. Error bars represent upper limits of 95% confidence intervals.

Figure 3. Gender-associated admission rate ratio of vasospastic angina pectoris by age in general population. Ratio is calculated as men vs. women and adjusted for background population and study year. Error bars represent 95% confidence intervals.

Figure 4. Trend for annual rate of VAP admissions in general adult population. Standardized to WHO standard population. Error bars represent 95% confidence intervals.

Figure 5. Cumulative all-cause mortality after VAP admission.

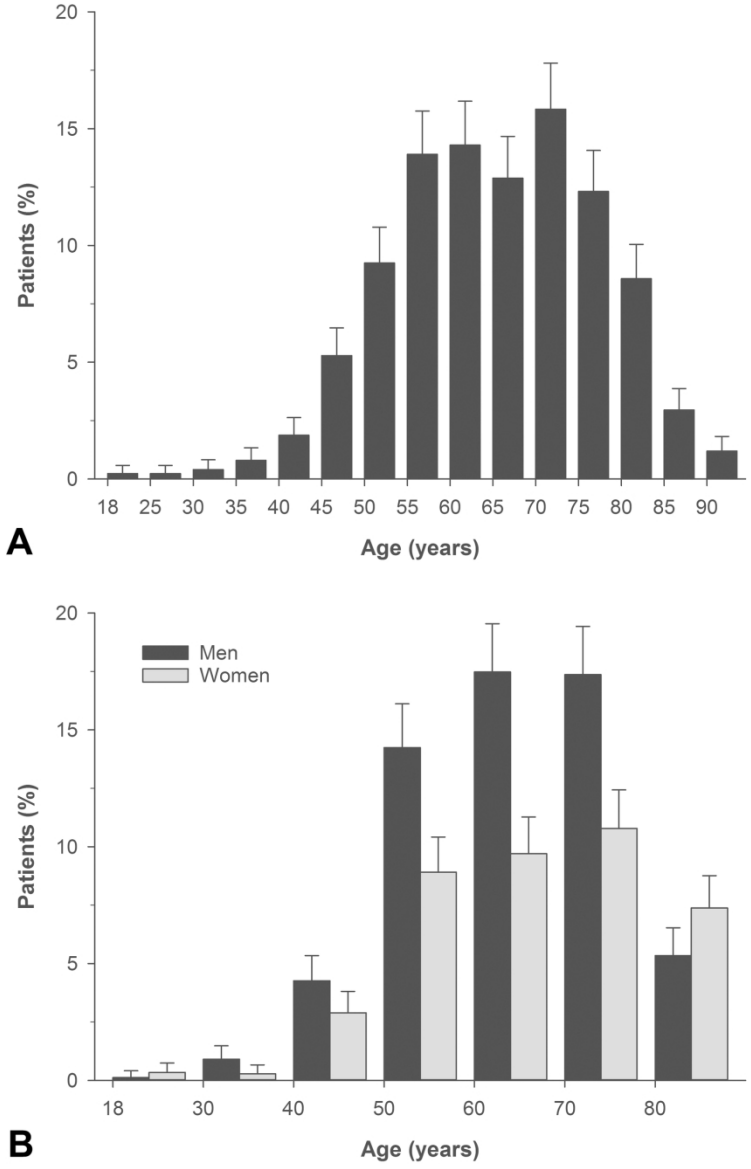

Figure 1. Frequency of vasospastic angina pectoris admissions. Age-distribution of all patients (A) and by gender (from total number of patients) (B). Error bars represent upper limits of 95% confidence intervals

144x230mm (300 x 300 DPI)

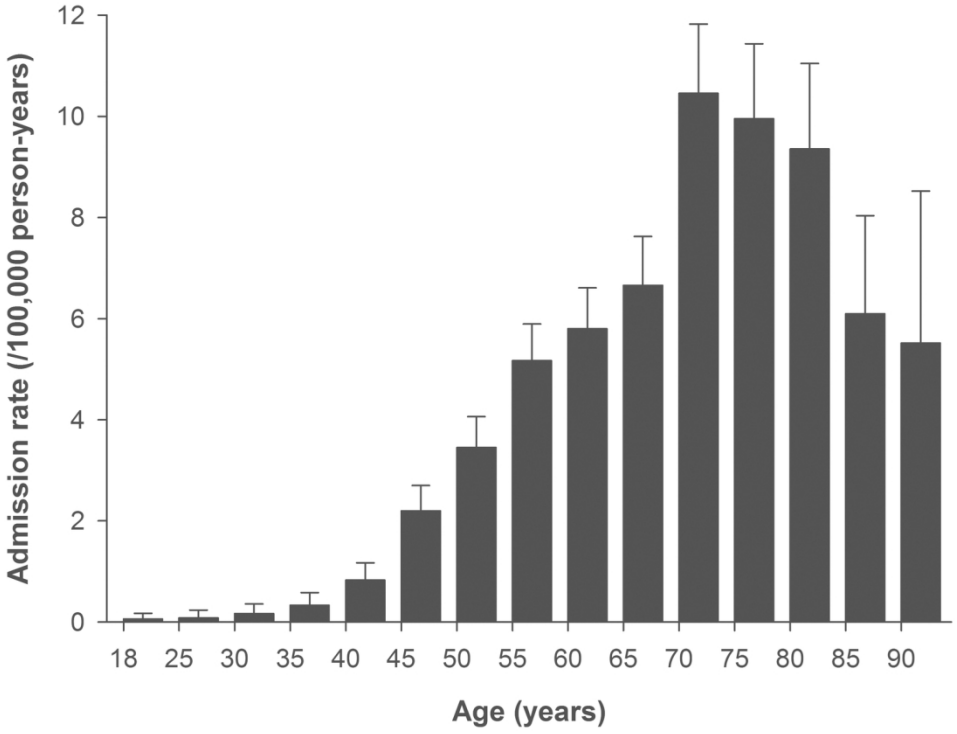

Figure 2. Annual rate of vasospastic angina pectoris admission in general adult population. Admission rates (per 100,000 person-years) by age. Error bars represent upper limits of 95% confidence intervals.

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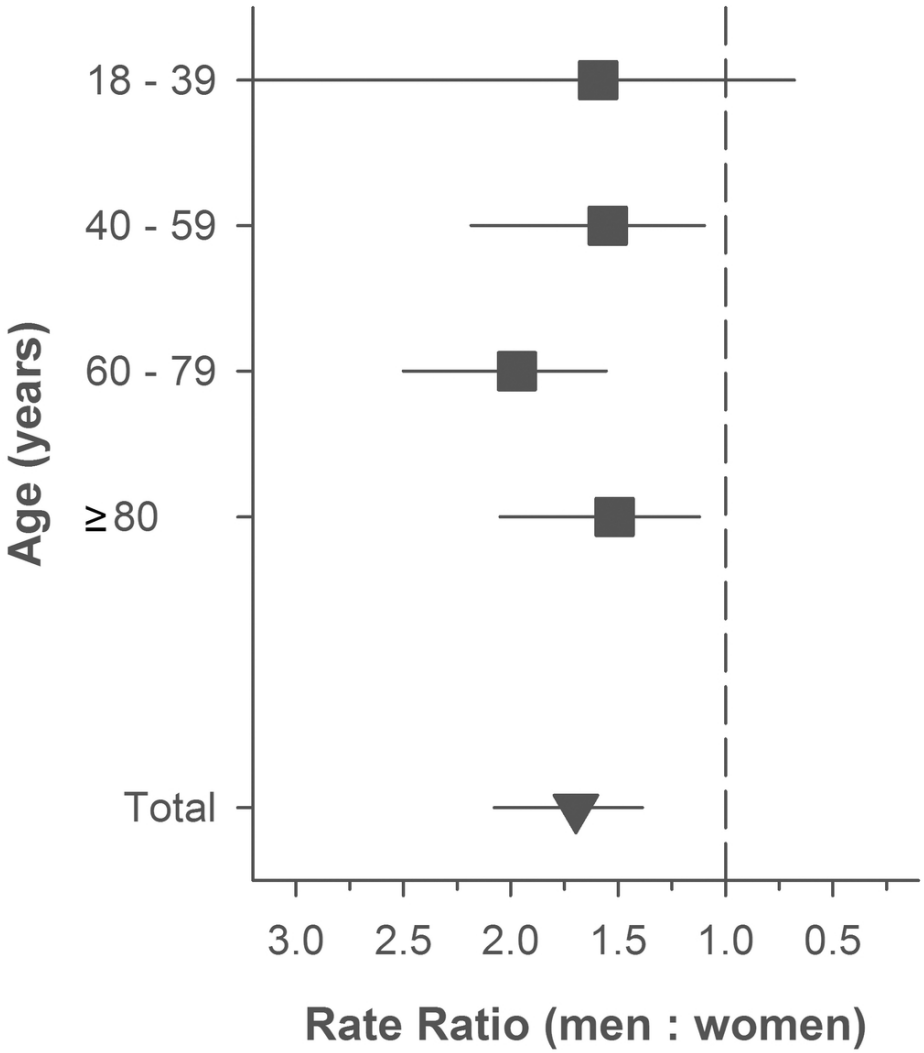

Figure 3. Gender-associated admission rate ratio of vasospastic angina pectoris by age in general population. Ratio is calculated as men vs. women and adjusted for background population and study year. Error bars represent 95% confidence intervals.

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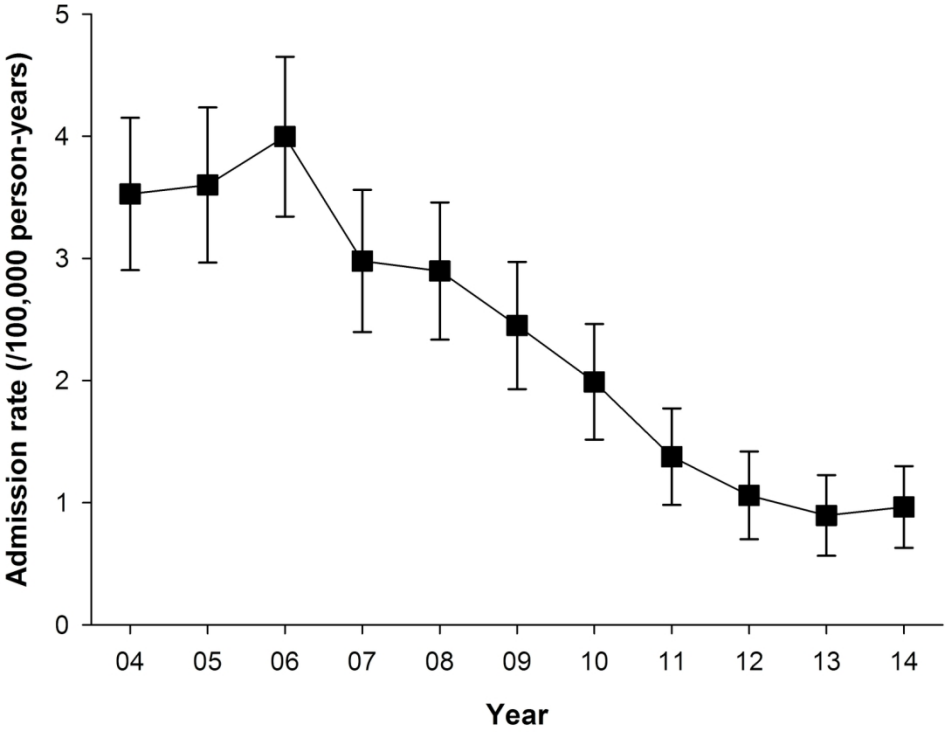

Figure 4. Trend for annual rate of VAP admissions in general adult population. Standardized to WHO standard population. Error bars represent 95% confidence intervals.

146x119mm (300 x 300 DPI)

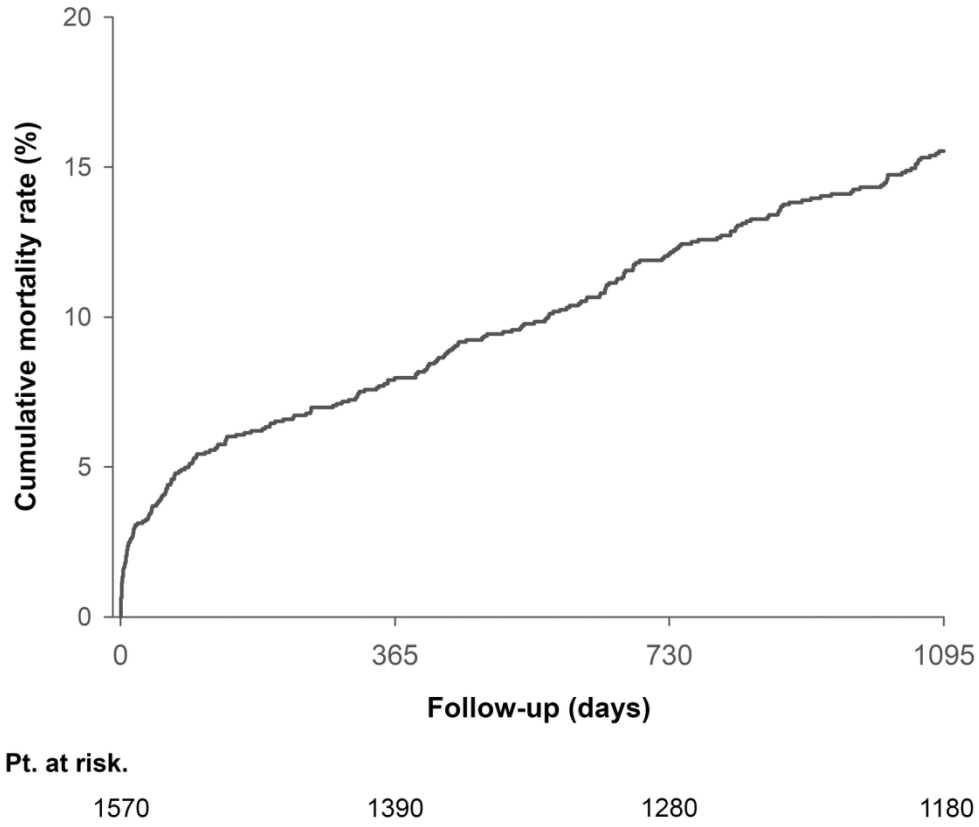

Figure 5. Cumulative all-cause mortality after VAP admission.

149x130mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*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	6
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	*6*
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
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	6
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	8
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	8
		(*b*) Report category boundaries when continuous variables were categorized	
		(*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	8-11
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14
Generalisability	21	Discuss the generalisability (external validity) of the study results	
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	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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 www.strobe-statement.org.

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Occurrence and Mortality of Vasospastic Angina Pectoris Hospitalized Patients in Finland -A Population Based Registry Cohort Study.

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Occurrence and Mortality of Vasospastic Angina Pectoris Hospitalized Patients in Finland -A Population Based Registry Cohort Study.

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Abstract

Objectives The occurrence and mortality of vasospastic angina pectoris (VAP) is largely unknown in Western countries. Our objective was to clarify the occurrence, gender-distribution and mortality of VAP in Finland using a population-based hospital registry.

Methods We studied consecutive patients aged ≥18 years hospitalized with vasospastic angina pectoris (VAP) as the primary cause of admission in Finland during 2004-2014. The data were collected from obligatory nationwide registries. During the study period 1762 admissions were recorded.

Results Majority of all VAP patients were male (59.7%) and mean age was 65.7±12.0 years. Annual admission rate for VAP was 2.29 / 100,000 person-years. Men were in higher risk for VAP than women (admission rate 3.00 / 100,000 vs. 1.68 / 100,000; RR 1.70; p<0.0001). Gender difference was not modified by age. Likelihood of VAP was highest in population aged 70-84 years. Admission rate for VAP decreased notably during the study period. One-year all-cause mortality was 8.0% and 3-year mortality was 15.5% (cardiac mortality 11.1%). Mortality was associated with increasing age, comorbidity burden and lack of detected coronary artery obstruction, but was similar between genders and during the study period.

Conclusions Men have higher risk for vasospastic angina caused admissions. Likelihood of vasospastic angina admission was highest in aged population. The 3-year all-cause mortality was 15.5%. Mortality was associated with increasing age, comorbidities and non-obstructive VAP diagnosis but was similar between genders.

An Article Summary

Strengths and limitation of this study

- New information about the vasospastic angina pectoris patients in a Western country.
- Unique registry data including all medical hospitals admissions with the diagnoses of vasospastic angina from all hospitals treating acute cardiac patients in mainland Finland.
- Follow-up period of 11 years
- Retrospective registry data and the diagnoses were made by different physicians.
- Coronary angiography was performed for 56% of the hospitalized patients limiting the accuracy of diagnoses

INTRODUCTION

Vasospastic angina pectoris (VAP), or Prinzmetal's angina, originally described by Myron Prinzmetal et. al,[1] is defined as a sudden coronary vasoconstriction leading to excessively reduced coronary blood flow causing myocardial ischemia[2]. 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, 3) demonstration of coronary artery spasm.[3,4] Coronary spasms occur mainly in large epicardial arteries but are known to occur also in coronary microvasculature of the myocardium. Coronary spasms are associated with sclerotic lesions in the arterial walls[3,5].

The prevalence of VAP seems to vary in different patient populations, but it has been reported that about 40% of the angina patients have vasospastic angina[3] and vasospasm have been detected in a third of non-ST-elevation myocardial infarction (MI) patients [6] In more detail, VAP is well studied in Japanese population and appears more common in Oriental countries in comparison to Western countries. Also, there seem to be substantial differences between Caucasian and Japanese VAP patients[3,7] with Japanese patients having more diffusely hypersensitive coronary arteries[8].

The 3-year MI mortality of VAP patients has been reported to be 3% in Japanese populations and 2% in Korean population[3,9,10]. Three-year MI mortality in Western VAP population has been 11%[3]. In Caucasian VAP patients with non-significant coronary obstructions, the all-cause mortality was 24% in a 140 months follow-up and the deaths were mostly age-related[11].

Several VAP patient series and registries originating mainly from Oriental populations have been reported whereas to our knowledge the occurrence of VAP at population level in Western countries is less well studied. We set out to clarify the occurrence, gender-distribution and mortality of VAP in Finland using a population-based hospital registry.

METHODS

Study population

We studied patients aged ≥18 years hospitalized with VAP (ICD-10 code I20.1X) as the primary cause of admission. Data of all medical hospitals admissions from all hospitals treating acute cardiac patients in mainland Finland between January 1st, 2004 and December 31st, 2014 were retrospectively collected from the Care Register for Health Care, a nationwide database containing all hospital discharge data from all admissions in Finland and maintained by the Finnish National Institute for Health and Welfare. VAP types were classified based on ICD-10 coding and the performed operations were identified based on operational codes (Nordic Classification of Surgical Procedures).

Finnish hospital system consists of three main levels: university hospitals (n=5) representing the highest level of hierarchy, followed by central hospitals (n=16) with coronary catherization laboratories and intensive care units, and then several smaller regional hospitals. Admissions due to VAP occurred in 38 hospitals during the study period (33% in university hospitals, 54% in central hospitals and 13% in regional hospitals). Mortality and cause of death data (follow-up ended in 31.12.2014) for the identified patients were obtained from nationwide and obligatory cause of death registry held by Statistics Finland. The co-morbidities of the patients were described by Charlson comorbidity index (CCI). Annual admissions rates (one admission per year) were estimated by using age- and gender-matched population data of mainland Finland from the study period (46,642,940 person-years) obtained from Statistics Finland. The National

Institute for Health and Welfare of Finland (permissions no: THL/143/5.05.00/2015 and THL/1569/5.05.00/2016) and Statistics Finland (TK53-1410-15) approved the study.

Statistical Analysis

Scale variables are presented as mean ± SD and categorical variables are presented as counts or percentages with 95% confidence intervals (CI) when applicable. Gender differences in baseline features were analyzed using t-test or Chi-squared test. Count data was analyzed by using negative binomial regression models. In the regression models of annual admission rate, the logarithm of population was used as an offset parameter. All-cause mortality from first VAP admission was studied using Kaplan-Maier method and Cox regression. Duration of hospital admission was calculated as beginning days. Results of regression analyses are given as rate ratios (RR) or hazard ratios (HR) as appropriate. CCI was calculated according to previously used algorithm[12]. Admission rates of admissions (one admission per year) were standardized to WHO 2010 standard population with the use of a direct method as appropriate. P-values <0.05 were considered statistically significant. Analyses were performed with the SAS system v. 9.4 (SAS Institute Inc, Cary, NC, USA).

Patient and public involvement

This study is based on a retrospective registry data and does not have direct involvement of patients or the public.

RESULTS

Patient Features

Vasospastic angina pectoris was the primary cause for 1762 hospital admissions (1570 individual patients, 59.7% male) during the study period. Demographic baseline characteristics of the hospitalized patients are shown on Table 1. Mean age of all VAP patients was 65.7±12.0 years (range 18-98 years) (Figure 1A). Age distribution of VAP patients had similar patterns in both genders, although age-pattern was shifted towards older age in women (Figure 1B) with female patients being marginally older compared to men (Table 1). Co-morbidity burden of patients was similar between genders (Table 1). Coronary angiography was performed in 56% admissions and was more common for men than for women, who were hospitalized for VAP (Table 1). Majority of VAP patients had no detected coronary obstruction, but obstructive disease was more common in men than in women (Table 1). Admission for vasospastic angina lasted on average for 4.3±3.7 (range 1 - 44 days) with no difference in duration of admission between genders. Myocardial infarction (I21.X) was secondary or a tertiary diagnosis for 1.8% of VAP patients.

Variable	Total (n=1762)	Male (n=1052)	Female (n=710)	p-value*
Age (y, mean)	65.7±12.0	64.9±11.3	66.8±13.0	0.002
CCI score				0.178
0	975 (55.3%)	576 (54.8%)	399 (56.2%)	
1	415 (23.6%)	246 (23.4%)	169 (23.8%)	
2	224 (12.7%)	131 (12.5%)	93 (13.1%)	
≥3	148 (8.4%)	99 (9.4%)	49 (6.9%)	
Coronary angiography performed**	992 (56.3%)	614 (58.4%)	378 (53.2%)	0.033
Angiographical finding				<0.0001
No obstruction	793 (45.0%)	440 (41.8%)	353 (49.7%)	
Obstruction	498 (28.3%)	346 (32.9%)	152 (21.4%)	
NAS	471 (26.7%)	266 (25.3%)	205 (28.9%)	

Table 1. Patient characteristics of all hospital admission (n= 1762)

CCI= Charlson comorbidity index, ICD= International Classification of Diseases *Between genders. **During VAP admission.

Annual admission rate

During the whole study period, the total standardized annual admission rate for VAP was 2.29 (CI 2.15-2.43)/100,000 person-years (crude rate 3.45 (CI 3.29-3.63) / 100,000). Likelihood of VAP admission increased progressively from 40 to 70 years of age with highest rate (10.5 / 100,000) in patients aged 70-75 years (Figure 2). Among women, the standardized overall rate for VAP hospital admission was 1.68 (CI 1.52-1.86) / 100,000 person-years (crude rate 2.71 (CI 1.52-1.86) / 100,000), whereas for men the standardized rate was 3.00 (CI 2.77-3.22) / 100,000 (crude rate 4.25 (CI 3.98-4.53) / 100,000). In total Finnish adult population, men were 70% more likely to be admitted to hospital due to VAP (RR for admission rate 1.70; CI 1.39-2.08; p<0.0001) than women. Gender difference was similar between age groups (interaction p=0.201) (Figure 3). Admission rate for VAP decreased notably during the study period (Figure 4).

Mortality

Thirty-day all-cause mortality was 3.2%, one-year mortality was 8.0% and 3-year mortality was 15.5% after admission for VAP (Figure 5). One-year mortality was associated with increasing age, comorbidity burden and coronary artery status, but was similar between genders and study periods (Table 2). Comparably, 3-year mortality was associated with increasing age, CCI-score and lack of detected coronary artery obstruction but was similar between genders during study (Table 3). Majority (71.2%) of all the deaths were due to cardiac causes with cardiac mortality of 5.8% at 1-year and 11.1% at 3-year follow-up. Myocardial infarction and ischemic heart disease were most common underlying causes of death.

		Univariate			Multivariate		
Variable	**Mortality (%)**	**HR**	**95% CI**	**p value**	**HR**	**95% CI**	**p value**
Gender				0.795			0.311
Male	7.82	Ref.					
Female	8.19	1.05	0.73-1.50	0.795	0.83	0.57-1.19	0.311
Age (years)				<0.0001			<0.0001
<50	2.16	Ref.			Ref.		
50-59	0.85	0.4	0.08-2.00	0.267	0.40	0.08-1.97	0.259
60-69	5.46	2.62	0.79-8.71	0.117	2.25	0.67-7.53	0.189
70-79	10.26	5.03	1.56-16.19	0.007	4.15	1.28-13.45	0.018
80-	24.26	13.12	4.09-42.06	<0.0001	9.95	3.06-32.33	0.0001
CCI				<0.0001			<0.0001
0	4.18	Ref.			Ref.		
1	7.82	1.88	1.15-3.07	0.011	1.47	0.90-2.42	0.127
2	17.39	4.39	2.75-7.02	<0.0001	2.68	1.65-4.36	<0.0001
≥3	19.23	4.82	2.89-8.03	<0.0001	3.33	1.97-5.64	<0.0001
Coronary status				0.006			0.149
Obstruction	4.55	Ref.			Ref.		
No obstruction	8.36	1.87	1.12-3.14	0.017	1.69	0.99-2.87	0.050
NAS	10.67	2.41	1.41-4.12	0.001	1.51	0.87-2.65	0.155
Study year				0.198			0.564
2004-2006	7.26	Ref.			Ref.		
2007-2010	7.62	1.05	0.70-1.56	0.821	0.99	0.66-1.49	0.970
2010-2014	10.79	1.44	0.90-2.31	0.086	1.26	0.78-2.07	0.338

Table 2. Factors associated with 1-year all-cause mortality. Univariate and multivariate analysis. CCI = Charlson co-morbidity index. HR = Hazard ratio.

		Univariate			Multivariate		
Variable	**Mortality (%)**	**HR**	**95% CI**	**p value**	**HR**	**95% CI**	**p value**
Gender				0.788			0.065
Male	15.78	Ref.					
Female	15.15	0.97	0.74-1.26	0.788	0.78	0.59-1.02	0.065
Age (years)				<0.0001			<0.0001
<50	4.60	Ref.			Ref.		
50-59	5.09	1.10	0.44-2.80	0.835	1.08	0.42-2.74	0.876
60-69	10.27	2.35	1.00-5.53	0.050	2.05	0.87-4.84	0.102
70-79	20.22	4.84	2.12-11.07	0.0002	4.13	1.80-9.48	0.0008
80-	41.33	11.78	5.14-26.98	<0.0001	9.30	4.02-21.52	<0.0001
CCI				<0.0001			<0.0001
0	9.65	Ref.			Ref.		
1	14.57	1.57	1.11-2.23	0.010	1.25	0.88-1.78	0.208
2	28.87	3.42	2.43-4.82	<0.0001	2.29	1.61-3.27	<0.0001
≥3	36.65	4.36	3.03-6.27	<0.0001	3.26	2.17-4.59	<0.0001
Coronary status				<0.0001			0.045
Obstruction	10.08	Ref.			Ref.		
No obstruction	15.15	1.56	1.09-2.24	0.016	1.51	1.05-2.19	0.028
NAS	21.67	2.30	1.59-3.34	<0.0001	1.61	1.09-2.37	0.017
Study year				0.311			0.609
2004-2006	15.26	Ref.			Ref.		
2007-2010	14.76	0.96	0.73-1.28	0.796	0.80	0.68-1.21	0.511
2010-2014	17.81	1.29	0.89-1.87	0.188	1.10	0.75-1.6	0.640

Table 3. Factors associated with 3-year all-cause mortality. Univariate and multivariate analysis. CCI = Charlson co-morbidity index. HR = Hazard ratio.

DISCUSSION

This nationwide study describes the occurrence of VAP admissions in Finnish general population. Men were 70% more likely to be admitted for VAP compared with woman. All-cause mortality was 8.0% at one year and 15.5% at three years. Mortality was associated with older age, comorbidities and non-obstructive or non-specific coronary findings but it was similar between genders.

The diagnosis of vasospastic angina is characterized by spontaneous chest pains and drug or non-drug (i.e. hyperventilation) induced spasm. The golden standard of coronary artery spasm testing involves the administration of a provocative stimulus during coronary angiography.[4] In our study population, the coronary angiography was made for 58% of men and for 53% of women hospitalized for VAP.

It is known from previous studies that coronary spasm develops in sclerotic lesions of varying severity[3,5]. Even if no stenotic lesions are visible on coronary angiography, IVUS commonly reveals arteriosclerotic lesions in locations consistent with regions of coronary spasm.[3] It has been shown that with OCT, thrombus was seen in one fourth of patients with vasospastic decease and luminal irregularity was observed in nearly two-thirds of the study patients[5]. In the present study, atherosclerotic changes in coronary arteries were diagnosed in 33% of men and 21% of women.

We found the overall annual admission rate for VAP to be 2.3 / 100,000. This compares to previously detected admission rates of 93 / 100,000 for unstable angina pectoris [13], 105 / 100,000 for ST-elevation MI[14] and 206 / 100,000 for non-ST-elevation MI[15] in Finnish adult

population. Volume of VAP admissions can thus be estimated to be approximately 1% of the amount of acute coronary syndrome admissions. Decreasing VAP admissions are however likely to affect this ratio.

In Japan as well as in Western countries vasospastic angina is more prevalent in males. The gender-difference diminishes after menopause and disappears at the age of 80 in Japanese population[3]. We found VAP to be 70% more common among men while gender-difference was not modified by age. Vasospastic angina pectoris is known to cause significant morbidity to individuals affected[16]. In Korean population mortality was 2% at two years [5] with similar prognosis in both genders [17]. In a Japanese study population, the MI was 3% at 3-years[3]. In Western population the 3-year MI mortality has been reported to be 11%[3] comparably to our results.

In Caucasian study population of VAP without significant atherosclerotic stenosis, the mortality was 24% at 12-year follow-up with mostly non-cardiac deaths[11].

We found 3-year mortality to be 15.5% and to be mostly cardiogenic. In an earlier study, the risk of death and MI was similar in male ST-segment elevation MI patients and VAP patients while VAP patients with non-significant coronary stenosis seemed to have less complications and lower mortality[18].

Our results suggest that the vasospastic angina pectoris might not be as benign disease as often thought. We can assume, that most the of patients with a diagnostic code of narrowing or occlusive coronary artery findings, had a visible narrowing or occlusion in the coronary arteries and had been taken care of by intervention or medication for coronary

artery decease in the well-functioning Finnish health care system. For rest of the study population, coronary angiography did not reveal atherosclerotic changes, or the angiography was not performed during index admission. For comparison, in a Swedish register study, the 1-year mortality after admission for unstable angina pectoris was 10% in age group 65-105[19]. Interestingly, a Korean study found VAP patients presenting with acute coronary syndrome (ACS) to have worse prognosis compared to VAP patients without presentation of ACS [9]. One potential mechanism for VAP related mortality are vasospasm triggered arrythmias. In agreement, previous studies have shown VAP patients with aborted sudden cardiac death (ASCD) to have worse prognosis than those without[20,21].

In North America, vasospastic angina has become less frequent for unknown reasons, possibly relating to more widespread use of calcium antagonists[22]. Up to 70% of patients with ACS presenting with typical ECG changes and/or elevation of cardiac markers had culprit lesions, whereas the remaining 30% of ACS patients had no obstructive coronary artery lesions. Cardiologists in the USA do not perform spasm provocation tests routinely in patients with non-obstructive coronary artery disease with chest pain/discomfort in the cardiac catheterization laboratory[22]. Similarly, in our study, the occurrence of VAP admissions decreased notably during the study period. Underling reason for this change is unknown. In addition to true decrease in VAP, this finding may relate to increase in rates of Takotsubo cardiomyopathy diagnoses[23] and high-sensitive troponin assay usage increasing alternative diagnoses for VAP during the study period.

The present study has some limitation. A major limitation is the retrospective nature of observational registry data without access to more detailed clinical or therapeutic data. The

diagnoses were made by the treating physician and this may have affected the selected study population and the accuracy of the comorbidity data. In addition, because our data included only hospitalized patients, the results underrepresents patients with low-risk features who may have been treated without being admitted to the hospital or who have not sought for help. Coronary angiography was performed only for 56% of VAP patients. Some of the coronary artery disease diagnoses might thus have been missed. Furthermore, the spasm provocation tests are seldomly used in Finland limiting the accuracy of VAP diagnoses.

In conclusion, our results indicate that men have higher risk for vasospastic angina causing admissions compared with women. Likelihood of vasospastic angina admission was highest in population aged 70-84 years. The 3-year mortality was 15.5% and was predicted by patients age and comorbidities, but also by non-obstructive vasospastic angina diagnosis. The cause of death was mostly cardiac at 1- and 3-year follow-ups. These results may help characterize the inadequately known epidemiology of vasospastic angina pectoris in Western countries.

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Footnote

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Data sharing statement No additional data are available.

Patient consent for publication Not required.

Figure Legends:

Figure 1. Frequency of vasospastic angina pectoris admissions. Age-distribution of all patients (A) and by gender (from total number of patients) (B). Error bars represent upper limits of 95% confidence intervals

Figure 2. Annual rate of vasospastic angina pectoris admission in general adult population. Admission rates (per 100,000 person-years) by age. Error bars represent upper limits of 95% confidence intervals.

Figure 3. Gender-associated admission rate ratio of vasospastic angina pectoris by age in general population. Ratio is calculated as men vs. women and adjusted for background population and study year. Error bars represent 95% confidence intervals.

Figure 4. Trend for annual rate of VAP admissions in general adult population. Standardized to WHO standard population. Error bars represent 95% confidence intervals.

Figure 5. Cumulative all-cause mortality after VAP admission.

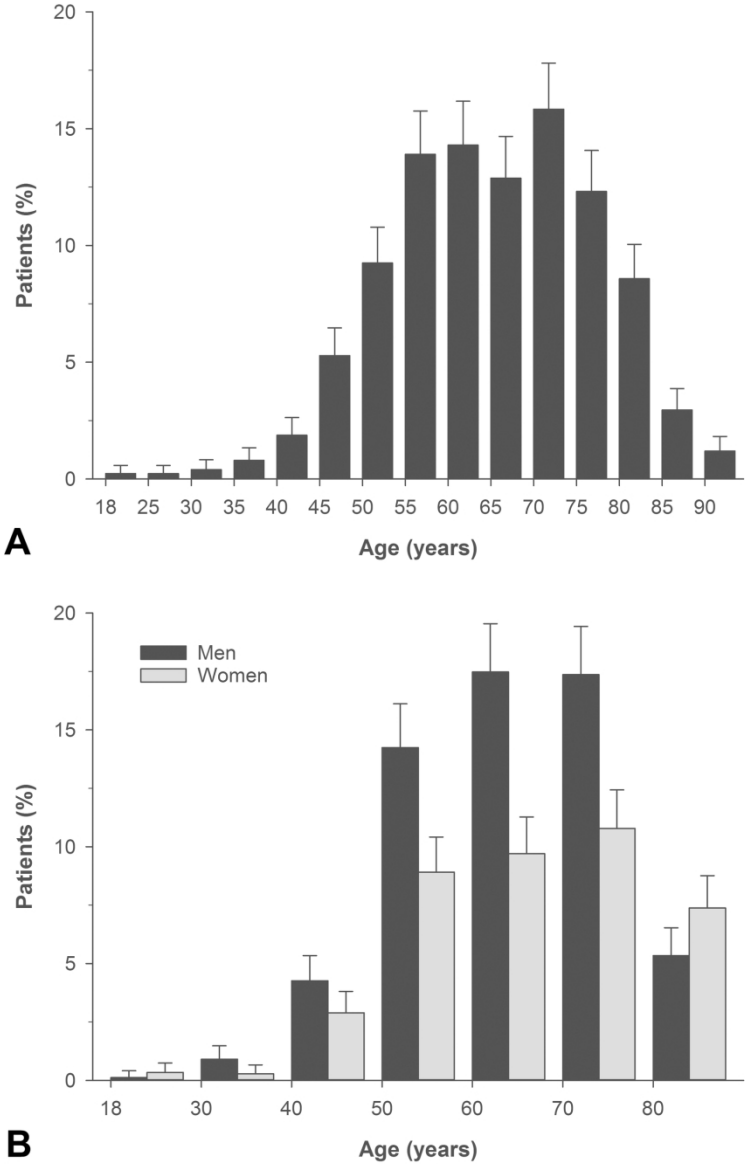

Figure 1. Frequency of vasospastic angina pectoris admissions. Age-distribution of all patients (A) and by gender (from total number of patients) (B). Error bars represent upper limits of 95% confidence intervals

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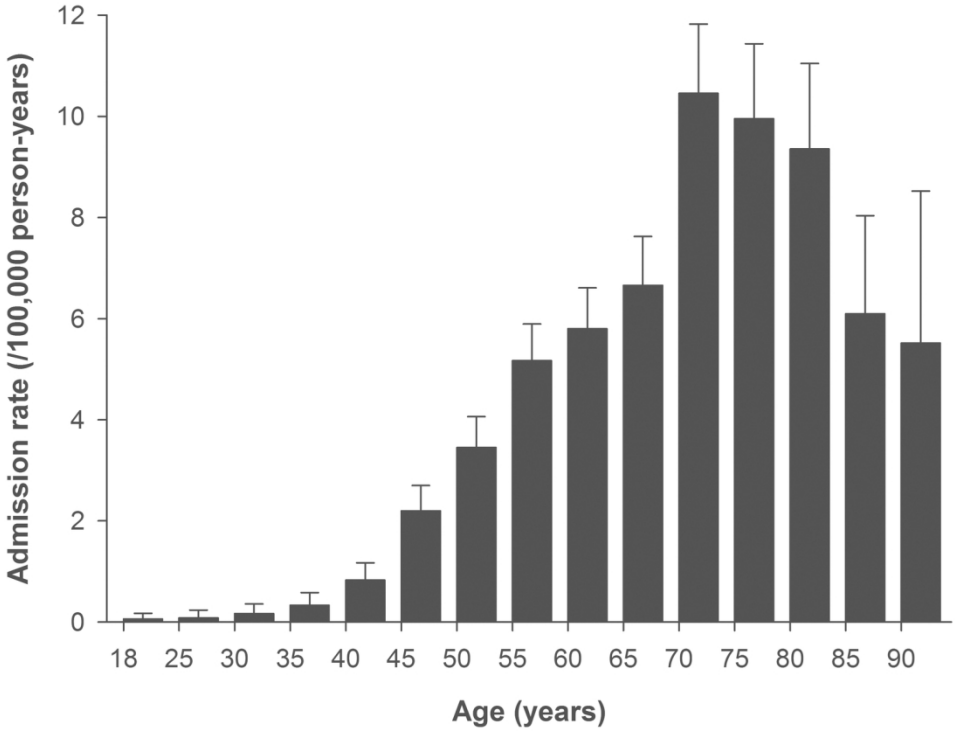

Figure 2. Annual rate of vasospastic angina pectoris admission in general adult population. Admission rates (per 100,000 person-years) by age. Error bars represent upper limits of 95% confidence intervals.

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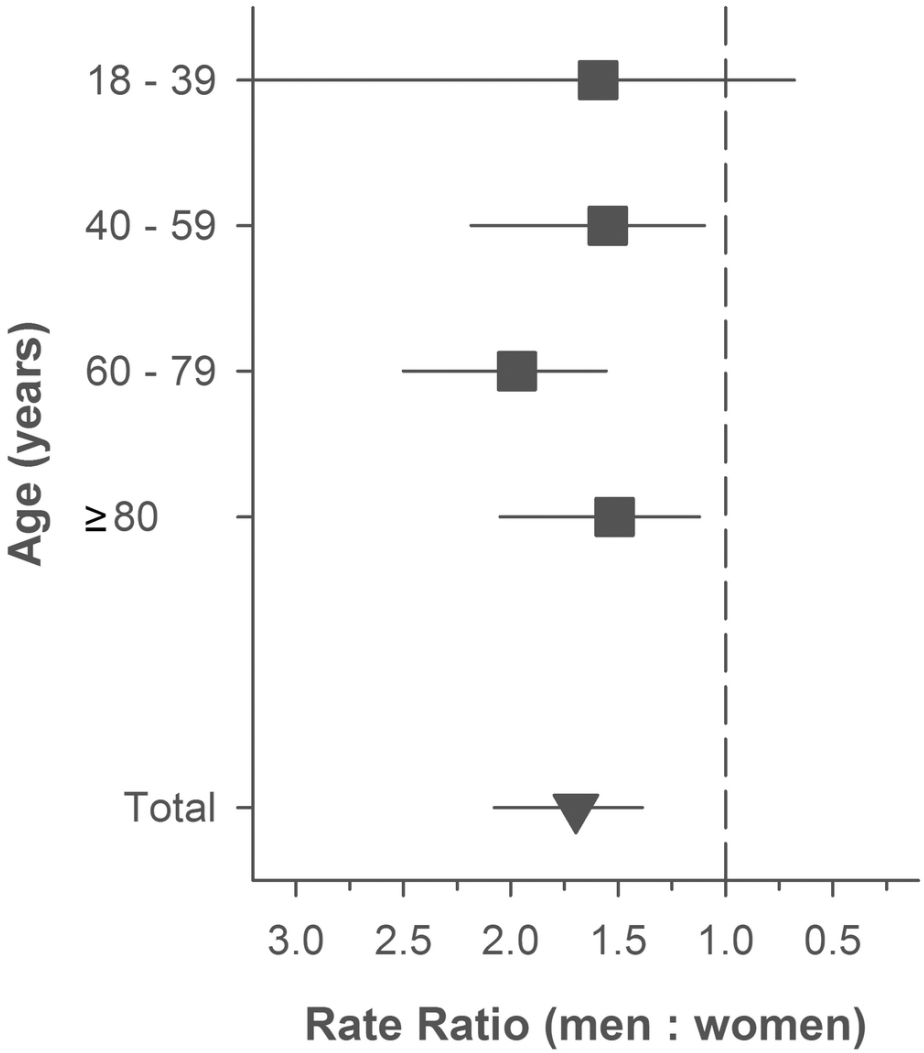

Figure 3. Gender-associated admission rate ratio of vasospastic angina pectoris by age in general population. Ratio is calculated as men vs. women and adjusted for background population and study year. Error bars represent 95% confidence intervals.

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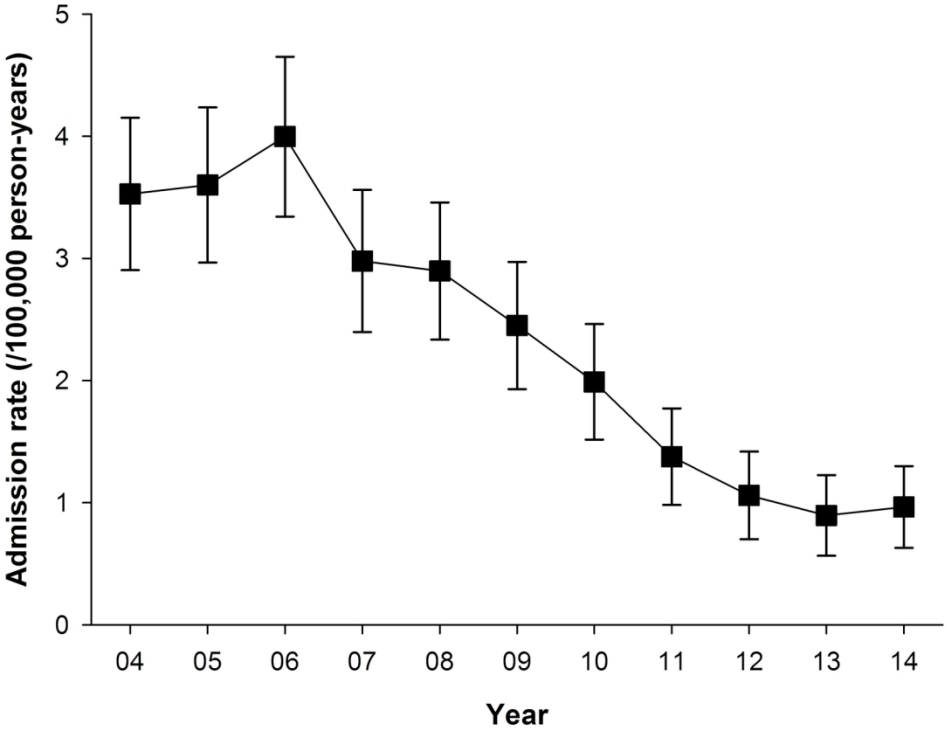

Figure 4. Trend for annual rate of VAP admissions in general adult population. Standardized to WHO standard population. Error bars represent 95% confidence intervals.

146x119mm (300 x 300 DPI)

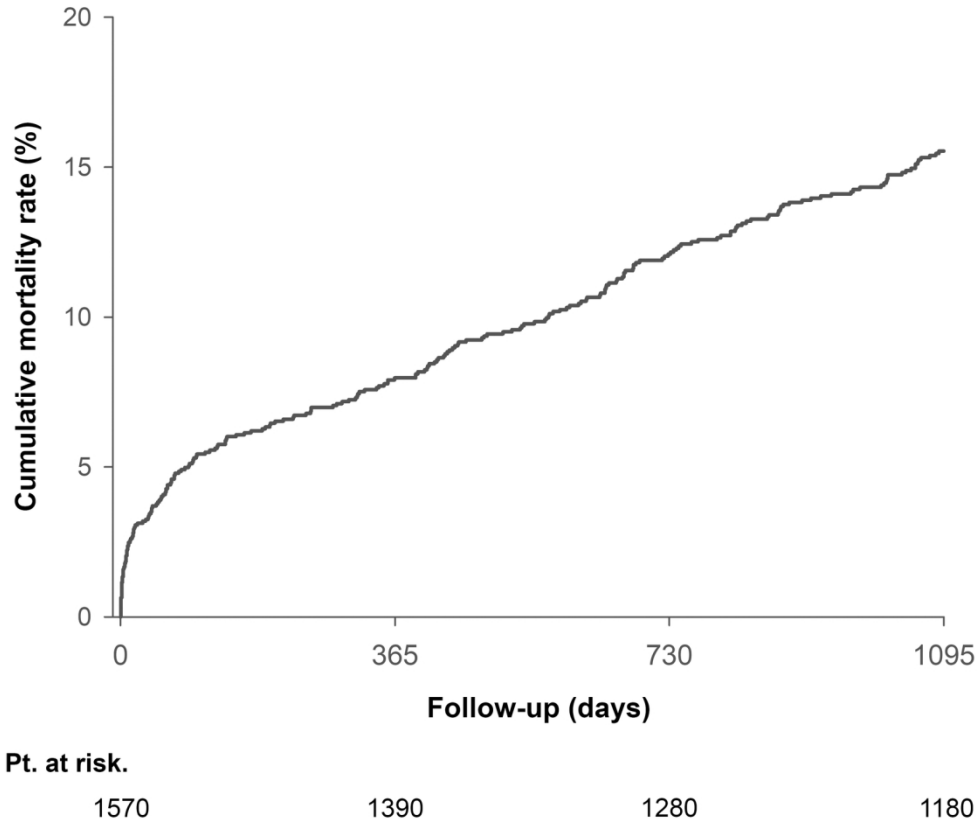

Figure 5. Cumulative all-cause mortality after VAP admission.

149x130mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*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	6
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	*6*
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
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	6
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	8
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	8
		(*b*) Report category boundaries when continuous variables were categorized	
		(*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	8-11
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14
Generalisability	21	Discuss the generalisability (external validity) of the study results	
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	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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 www.strobe-statement.org.

BMJ Open

Occurrence and Mortality of Vasospastic Angina Pectoris Hospitalized Patients in Finland -A Population Based Registry Cohort Study.

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Occurrence and Mortality of Vasospastic Angina Pectoris Hospitalized Patients in Finland -A Population Based Registry Cohort Study.

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Abstract

Objectives The occurrence and mortality of vasospastic angina pectoris (VAP) is largely unknown in Western countries. Our objective was to clarify the occurrence, gender-distribution and mortality of VAP in Finland using a population-based hospital registry.

Methods We studied consecutive patients aged ≥18 years hospitalized with vasospastic angina pectoris (VAP) as the primary cause of admission in Finland during 2004-2014. The data were collected from obligatory nationwide registries. During the study period 1762 admissions were recorded.

Results Majority of all VAP patients were male (59.7%) and mean age was 65.7±12.0 years. Annual admission rate for VAP was 2.29 / 100,000 person-years. Men were in higher risk for VAP than women (admission rate 3.00 / 100,000 vs. 1.68 / 100,000; RR 1.70; p<0.0001). Gender difference was not modified by age. Likelihood of VAP was highest in population aged 70-84 years. Admission rate for VAP decreased notably during the study period. One-year all-cause mortality was 8.0% and 3-year mortality was 15.5% (cardiac mortality 11.1%). Mortality was associated with increasing age, comorbidity burden and lack of detected coronary artery obstruction, but was similar between genders and during the study period.

Conclusions Men have higher risk for vasospastic angina caused admissions. Likelihood of vasospastic angina admission was highest in aged population. The 3-year all-cause mortality was 15.5%. Mortality was associated with increasing age, comorbidities and non-obstructive VAP diagnosis but was similar between genders.

An Article Summary

Strengths and limitation of this study

- New information about the vasospastic angina pectoris patients in a Western country.
- Unique registry data including all medical hospitals admissions with the diagnoses of vasospastic angina from all hospitals treating acute cardiac patients in mainland Finland.
- Follow-up period of 11 years
- Retrospective registry data and the diagnoses were made by different physicians.
- Coronary angiography was performed for 56% of the hospitalized patients limiting the accuracy of diagnoses

INTRODUCTION

Vasospastic angina pectoris (VAP), or Prinzmetal's angina, originally described by Myron Prinzmetal et. al,[1] is defined as a sudden coronary vasoconstriction leading to excessively reduced coronary blood flow causing myocardial ischemia[2]. 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, 3) demonstration of coronary artery spasm.[3,4] Coronary spasms occur mainly in large epicardial arteries but are known to occur also in coronary microvasculature of the myocardium. Coronary spasms may be associated with sclerotic lesions in the arterial walls[3,5].

The prevalence of VAP seems to vary in different patient populations, but it has been reported that about 40% of the angina patients have vasospastic angina[3] and vasospasm have been detected in a third of non-ST-elevation myocardial infarction (MI) patients [6] In more detail, VAP is well studied in Japanese population and appears more common in Oriental countries in comparison to Western countries. Also, there seem to be substantial differences between Caucasian and Japanese VAP patients[3,7] with Japanese patients having more diffusely hypersensitive coronary arteries[8].

The 3-year MI mortality of VAP patients has been reported to be 3% in Japanese populations and 2% in Korean population[3,9,10]. Three-year MI mortality in Western VAP population has been 11%[3]. In Caucasian VAP patients with non-significant coronary obstructions, the all-cause mortality was 24% in a 140 months follow-up and the deaths were mostly age-related[11].

Several VAP patient series and registries originating mainly from Oriental populations have been reported whereas to our knowledge the occurrence of VAP at population level in Western countries is less well studied. We set out to clarify the occurrence, gender-distribution and mortality of VAP in Finland using a population-based hospital registry.

METHODS

Study population

We studied patients aged ≥18 years hospitalized with VAP (ICD-10 code I20.1X) as the primary cause of admission. Data of all medical hospitals admissions from all hospitals treating acute cardiac patients in mainland Finland between January 1st, 2004 and December 31st, 2014 were retrospectively collected from the Care Register for Health Care, a nationwide database containing all hospital discharge data from all admissions in Finland and maintained by the Finnish National Institute for Health and Welfare. VAP types were classified based on ICD-10 coding and the performed operations were identified based on operational codes (Nordic Classification of Surgical Procedures).

Finnish hospital system consists of three main levels: university hospitals (n=5) representing the highest level of hierarchy, followed by central hospitals (n=16) with coronary catherization laboratories and intensive care units, and then several smaller regional hospitals. Admissions due to VAP occurred in 38 hospitals during the study period (33% in university hospitals, 54% in central hospitals and 13% in regional hospitals). Mortality and cause of death data (follow-up ended in 31.12.2014) for the identified patients were obtained from nationwide and obligatory cause of death registry held by Statistics Finland. The co-morbidities of the patients were described by Charlson comorbidity index (CCI). Annual admissions rates (one admission per year) were estimated by using age- and gender-matched population data of mainland Finland from the study period (46,642,940 person-years) obtained from Statistics Finland. The National

Institute for Health and Welfare of Finland (permissions no: THL/143/5.05.00/2015 and THL/1569/5.05.00/2016) and Statistics Finland (TK53-1410-15) approved the study.

Statistical Analysis

Scale variables are presented as mean ± SD and categorical variables are presented as counts or percentages with 95% confidence intervals (CI) when applicable. Gender differences in baseline features were analyzed using t-test or Chi-squared test. Count data was analyzed by using negative binomial regression models. In the regression models of annual admission rate, the logarithm of population was used as an offset parameter. All-cause mortality from first VAP admission was studied using Kaplan-Maier method and Cox regression. Duration of hospital admission was calculated as beginning days. Results of regression analyses are given as rate ratios (RR) or hazard ratios (HR) as appropriate. CCI was calculated according to previously used algorithm[12]. Admission rates of admissions (one admission per year) were standardized to WHO 2010 standard population with the use of a direct method as appropriate. P-values <0.05 were considered statistically significant. Analyses were performed with the SAS system v. 9.4 (SAS Institute Inc, Cary, NC, USA).

Patient and public involvement

This study is based on a retrospective registry data and does not have direct involvement of patients or the public.

RESULTS

Patient Features

Vasospastic angina pectoris was the primary cause for 1762 hospital admissions (1570 individual patients, 59.7% male) during the study period. Demographic baseline characteristics of the hospitalized patients are shown on Table 1. Mean age of all VAP patients was 65.7±12.0 years (range 18-98 years) (Figure 1A). Age distribution of VAP patients had similar patterns in both genders, although age-pattern was shifted towards older age in women (Figure 1B) with female patients being marginally older compared to men (Table 1). Co-morbidity burden of patients was similar between genders (Table 1). Coronary angiography was performed in 56% admissions and was more common for men than for women, who were hospitalized for VAP (Table 1). Majority of VAP patients had no detected coronary obstruction, but obstructive disease was more common in men than in women (Table 1). Admission for vasospastic angina lasted on average for 4.3±3.7 (range 1 - 44 days) with no difference in duration of admission between genders. Myocardial infarction (I21.X) was secondary or a tertiary diagnosis for 1.8% of VAP patients.

Variable	Total (n=1762)	Male (n=1052)	Female (n=710)	p-value*
Age (y, mean)	65.7±12.0	64.9±11.3	66.8±13.0	0.002
CCI score				0.178
0	975 (55.3%)	576 (54.8%)	399 (56.2%)	
1	415 (23.6%)	246 (23.4%)	169 (23.8%)	
2	224 (12.7%)	131 (12.5%)	93 (13.1%)	
≥3	148 (8.4%)	99 (9.4%)	49 (6.9%)	
Coronary angiography performed**	992 (56.3%)	614 (58.4%)	378 (53.2%)	0.033
Angiographical finding				<0.0001
No obstruction	793 (45.0%)	440 (41.8%)	353 (49.7%)	
Obstruction	498 (28.3%)	346 (32.9%)	152 (21.4%)	
NAS	471 (26.7%)	266 (25.3%)	205 (28.9%)	

Table 1. Patient characteristics of all hospital admission (n= 1762)

CCI= Charlson comorbidity index, ICD= International Classification of Diseases *Between genders. **During VAP admission.

Annual admission rate

During the whole study period, the total standardized annual admission rate for VAP was 2.29 (CI 2.15-2.43)/100,000 person-years (crude rate 3.45 (CI 3.29-3.63) / 100,000). Likelihood of VAP admission increased progressively from 40 to 70 years of age with highest rate (10.5 / 100,000) in patients aged 70-75 years (Figure 2). Among women, the standardized overall rate for VAP hospital admission was 1.68 (CI 1.52-1.86) / 100,000 person-years (crude rate 2.71 (CI 1.52-1.86) / 100,000), whereas for men the standardized rate was 3.00 (CI 2.77-3.22) / 100,000 (crude rate 4.25 (CI 3.98-4.53) / 100,000). In total Finnish adult population, men were 70% more likely to be admitted to hospital due to VAP (RR for admission rate 1.70; CI 1.39-2.08; p<0.0001) than women. Gender difference was similar between age groups (interaction p=0.201) (Figure 3). Admission rate for VAP decreased notably during the study period (Figure 4).

Mortality

Thirty-day all-cause mortality was 3.2%, one-year mortality was 8.0% and 3-year mortality was 15.5% after admission for VAP (Figure 5). One-year mortality was associated with increasing age, comorbidity burden and coronary artery status, but was similar between genders and study periods (Table 2). Comparably, 3-year mortality was associated with increasing age, CCI-score and lack of detected coronary artery obstruction but was similar between genders during study (Table 3). Majority (71.2%) of all the deaths were due to cardiac causes with cardiac mortality of 5.8% at 1-year and 11.1% at 3-year follow-up. Myocardial infarction and ischemic heart disease were most common underlying causes of death.

		Univariate			Multivariate		
Variable	**Mortality (%)**	**HR**	**95% CI**	**p value**	**HR**	**95% CI**	**p value**
Gender				0.795			0.311
Male	7.82	Ref.					
Female	8.19	1.05	0.73-1.50	0.795	0.83	0.57-1.19	0.311
Age (years)				<0.0001			<0.0001
<50	2.16	Ref.			Ref.		
50-59	0.85	0.4	0.08-2.00	0.267	0.40	0.08-1.97	0.259
60-69	5.46	2.62	0.79-8.71	0.117	2.25	0.67-7.53	0.189
70-79	10.26	5.03	1.56-16.19	0.007	4.15	1.28-13.45	0.018
80-	24.26	13.12	4.09-42.06	<0.0001	9.95	3.06-32.33	0.0001
CCI				<0.0001			<0.0001
0	4.18	Ref.			Ref.		
1	7.82	1.88	1.15-3.07	0.011	1.47	0.90-2.42	0.127
2	17.39	4.39	2.75-7.02	<0.0001	2.68	1.65-4.36	<0.0001
≥3	19.23	4.82	2.89-8.03	<0.0001	3.33	1.97-5.64	<0.0001
Coronary status				0.006			0.149
Obstruction	4.55	Ref.			Ref.		
No obstruction	8.36	1.87	1.12-3.14	0.017	1.69	0.99-2.87	0.050
NAS	10.67	2.41	1.41-4.12	0.001	1.51	0.87-2.65	0.155
Study year				0.198			0.564
2004-2006	7.26	Ref.			Ref.		
2007-2010	7.62	1.05	0.70-1.56	0.821	0.99	0.66-1.49	0.970
2010-2014	10.79	1.44	0.90-2.31	0.086	1.26	0.78-2.07	0.338

Table 2. Factors associated with 1-year all-cause mortality. Univariate and multivariate analysis. CCI = Charlson co-morbidity index. HR = Hazard ratio.

		Univariate			Multivariate		
Variable	**Mortality (%)**	**HR**	**95% CI**	**p value**	**HR**	**95% CI**	**p value**
Gender				0.788			0.065
Male	15.78	Ref.					
Female	15.15	0.97	0.74-1.26	0.788	0.78	0.59-1.02	0.065
Age (years)				<0.0001			<0.0001
<50	4.60	Ref.			Ref.		
50-59	5.09	1.10	0.44-2.80	0.835	1.08	0.42-2.74	0.876
60-69	10.27	2.35	1.00-5.53	0.050	2.05	0.87-4.84	0.102
70-79	20.22	4.84	2.12-11.07	0.0002	4.13	1.80-9.48	0.0008
80-	41.33	11.78	5.14-26.98	<0.0001	9.30	4.02-21.52	<0.0001
CCI				<0.0001			<0.0001
0	9.65	Ref.			Ref.		
1	14.57	1.57	1.11-2.23	0.010	1.25	0.88-1.78	0.208
2	28.87	3.42	2.43-4.82	<0.0001	2.29	1.61-3.27	<0.0001
≥3	36.65	4.36	3.03-6.27	<0.0001	3.26	2.17-4.59	<0.0001
Coronary status				<0.0001			0.045
Obstruction	10.08	Ref.			Ref.		
No obstruction	15.15	1.56	1.09-2.24	0.016	1.51	1.05-2.19	0.028
NAS	21.67	2.30	1.59-3.34	<0.0001	1.61	1.09-2.37	0.017
Study year				0.311			0.609
2004-2006	15.26	Ref.			Ref.		
2007-2010	14.76	0.96	0.73-1.28	0.796	0.80	0.68-1.21	0.511
2010-2014	17.81	1.29	0.89-1.87	0.188	1.10	0.75-1.6	0.640

Table 3. Factors associated with 3-year all-cause mortality. Univariate and multivariate analysis. CCI = Charlson co-morbidity index. HR = Hazard ratio.

DISCUSSION

This nationwide study describes the occurrence of VAP admissions in Finnish general population. Men were 70% more likely to be admitted for VAP compared with woman. All-cause mortality was 8.0% at one year and 15.5% at three years. Mortality was associated with older age, comorbidities and non-obstructive or non-specific coronary findings but it was similar between genders.

The diagnosis of vasospastic angina is characterized by spontaneous chest pains and drug or non-drug (i.e. hyperventilation) induced spasm. The gold standard of coronary artery spasm testing involves the administration of a provocative stimulus during coronary angiography.[4] In our study population, coronary angiography was undertaken in 58% of men and in 53% of women hospitalized for VAP.

It is known from previous studies that coronary spasm may develop in sclerotic lesions of varying severity[3,5]. Even if no stenotic lesions are visible on coronary angiography, IVUS commonly reveals arteriosclerotic lesions in locations consistent with regions of coronary spasm.[3] It has been shown that with OCT, thrombus was seen in one fourth of patients with vasospastic angina and luminal irregularity was observed in nearly two-thirds of the study patients[5]. In the present study, atherosclerotic changes in coronary arteries were diagnosed in 33% of men and 21% of women.

We found the overall annual admission rate for VAP to be 2.3 / 100,000. This compares to previously detected admission rates of 93 / 100,000 for unstable angina pectoris [13], 105 / 100,000 for ST-elevation MI[14] and 206 / 100,000 for non-ST-elevation MI[15] in Finnish adult

population. Volume of VAP admissions can thus be estimated to be approximately 1% of the amount of acute coronary syndrome admissions. Decreasing VAP admissions are however likely to affect this ratio.

In Japan as well as in Western countries vasospastic angina is more prevalent in males. The gender-difference diminishes after menopause and disappears at the age of 80 in Japanese population[3]. We found VAP to be 70% more common among men while gender-difference was not modified by age. Vasospastic angina pectoris is known to cause significant morbidity to individuals affected[16]. In Korean population mortality was 2% at two years [5] with similar prognosis in both genders [17]. In a Japanese study population, the MI was 3% at 3-years[3]. In Western population the 3-year MI mortality has been reported to be 11%[3] comparably to our results.

In Caucasian study population of VAP without significant atherosclerotic stenosis, the mortality was 24% at 12-year follow-up with mostly non-cardiac deaths[11].

We found 3-year mortality to be 15.5% and to be mostly cardiogenic. In an earlier study, the risk of death and MI was similar in male ST-segment elevation MI patients and VAP patients while VAP patients with non-significant coronary stenosis seemed to have less complications and lower mortality[18].

Our results suggest that the vasospastic angina pectoris might not be as benign disease as often thought. We can assume, that most the of patients with a diagnostic code of narrowing or occlusive coronary artery findings, had a visible narrowing or occlusion in the coronary arteries and had been taken care of by intervention or medication for coronary

artery decease in the well-functioning Finnish health care system. For rest of the study population, coronary angiography did not reveal atherosclerotic changes, or the angiography was not performed during index admission. For comparison, in a Swedish register study, the 1-year mortality after admission for unstable angina pectoris was 10% in age group 65-105[19]. Interestingly, a Korean study found VAP patients presenting with acute coronary syndrome (ACS) to have worse prognosis compared to VAP patients without presentation of ACS [9]. One potential mechanism for VAP related mortality are vasospasm triggered arrythmias. In agreement, previous studies have shown VAP patients with aborted sudden cardiac death (ASCD) to have worse prognosis than those without[20,21].

In North America, vasospastic angina has become less frequent for unknown reasons, possibly relating to more widespread use of calcium antagonists[22]. Up to 70% of patients with ACS presenting with typical ECG changes and/or elevation of cardiac markers had culprit lesions, whereas the remaining 30% of ACS patients had no obstructive coronary artery lesions. Cardiologists in the USA do not perform spasm provocation tests routinely in patients with non-obstructive coronary artery disease with chest pain/discomfort in the cardiac catheterization laboratory[22]. Similarly, in our study, the occurrence of VAP admissions decreased notably during the study period. Underling reason for this change is unknown. In addition to true decrease in VAP, this finding may relate to increase in rates of Takotsubo cardiomyopathy diagnoses[23] and high-sensitive troponin assay usage increasing alternative diagnoses for VAP during the study period.

The present study has some limitation. A major limitation is the retrospective nature of observational registry data without access to more detailed clinical or therapeutic data.

Diagnoses were based upon the treating physician's clinical impression and this may not have fulfilled published diagnostic criteria. This may have affected the selected study population and the accuracy of the comorbidity data. In addition, because our data included only hospitalized patients, the results underrepresents patients with low-risk features who may have been treated without being admitted to the hospital or who have not sought for help. Coronary angiography was performed only for 56% of VAP patients. Some of the coronary artery disease diagnoses might thus have been missed. Furthermore, the spasm provocation tests are seldomly used in Finland limiting the accuracy of VAP diagnoses.

In conclusion, our results suggest that men have higher risk for vasospastic angina causing admissions compared with women. Likelihood of vasospastic angina admission was highest in population aged 70-84 years. The 3-year mortality was 15.5% and was predicted by patients age and comorbidities, but also by non-obstructive vasospastic angina diagnosis. The cause of death was mostly cardiac at 1- and 3-year follow-ups. These results may help characterize the inadequately known epidemiology of vasospastic angina pectoris in Western countries.

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Footnote

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Competing interests: None to declare

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Data sharing statement: All data relevant to the study are included in the article.

Patient consent for publication Not required.

Figure Legends:

Figure 1. Frequency of vasospastic angina pectoris admissions. Age-distribution of all patients (A) and by gender (from total number of patients) (B). Error bars represent upper limits of 95% confidence intervals

Figure 2. Annual rate of vasospastic angina pectoris admission in general adult population. Admission rates (per 100,000 person-years) by age. Error bars represent upper limits of 95% confidence intervals.

Figure 3. Gender-associated admission rate ratio of vasospastic angina pectoris by age in general population. Ratio is calculated as men vs. women and adjusted for background population and study year. Error bars represent 95% confidence intervals.

Figure 4. Trend for annual rate of VAP admissions in general adult population. Standardized to WHO standard population. Error bars represent 95% confidence intervals.

Figure 5. Cumulative all-cause mortality after VAP admission.

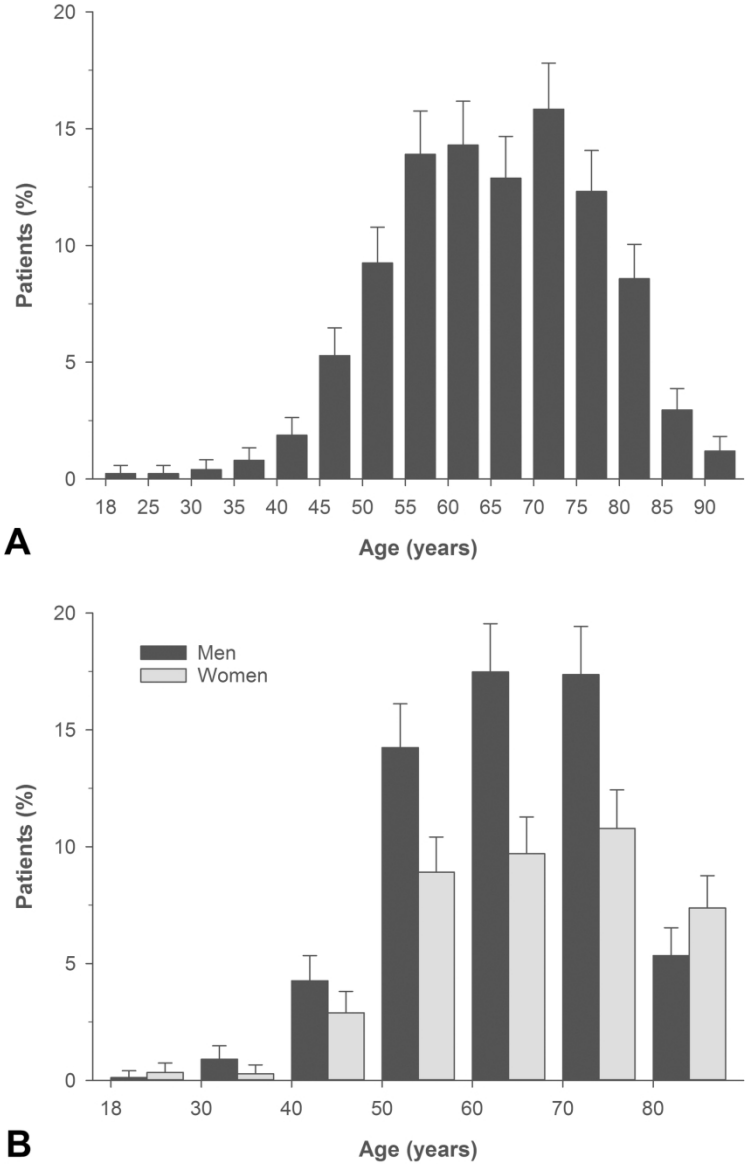

Figure 1. Frequency of vasospastic angina pectoris admissions. Age-distribution of all patients (A) and by gender (from total number of patients) (B). Error bars represent upper limits of 95% confidence intervals

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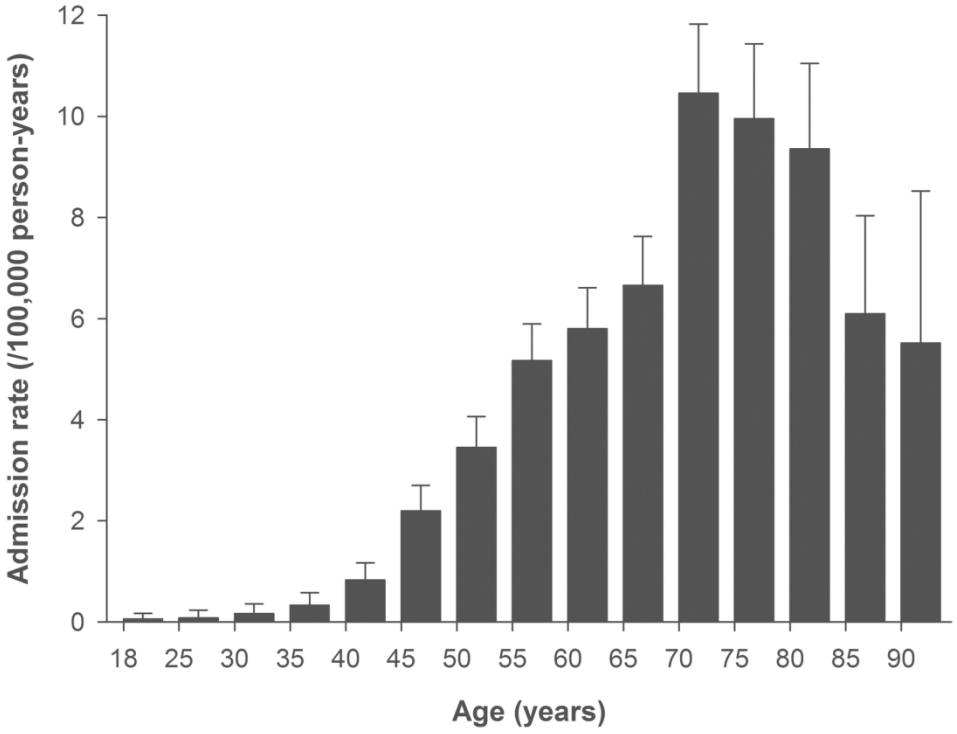

Figure 2. Annual rate of vasospastic angina pectoris admission in general adult population. Admission rates (per 100,000 person-years) by age. Error bars represent upper limits of 95% confidence intervals.

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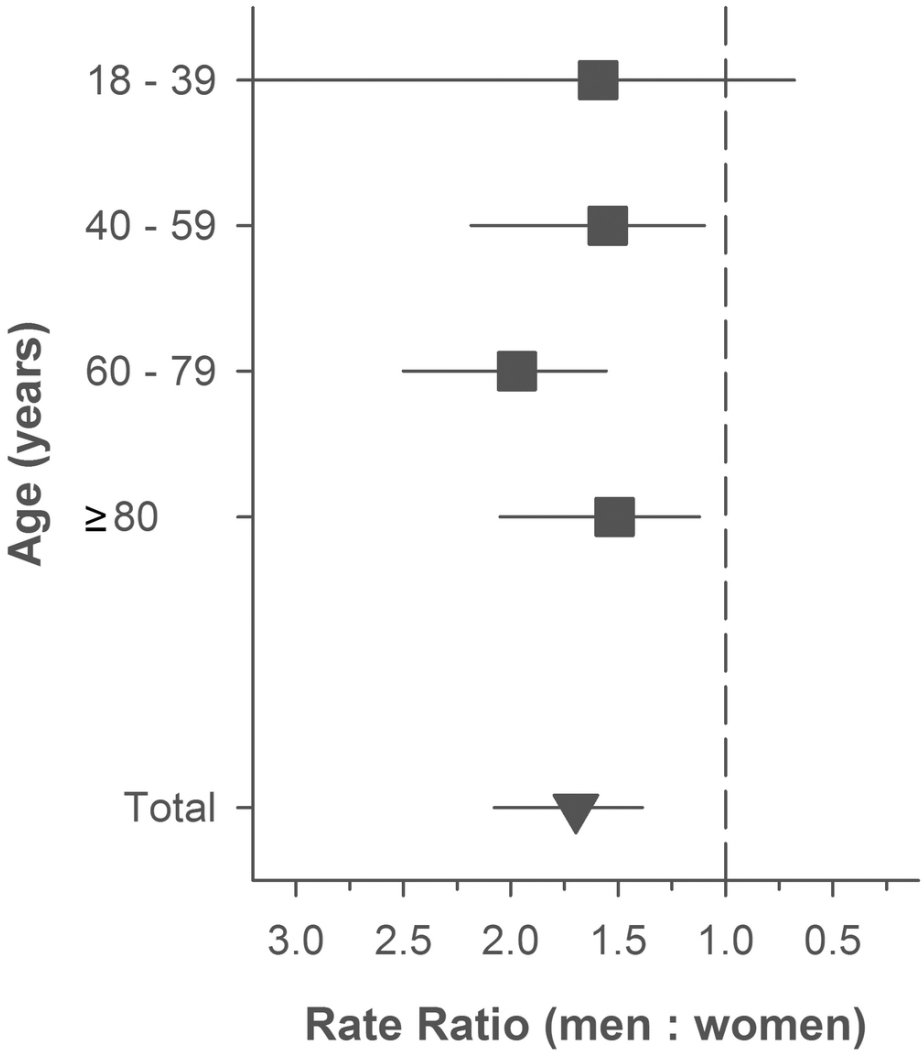

Figure 3. Gender-associated admission rate ratio of vasospastic angina pectoris by age in general population. Ratio is calculated as men vs. women and adjusted for background population and study year. Error bars represent 95% confidence intervals.

92x110mm (300 x 300 DPI)

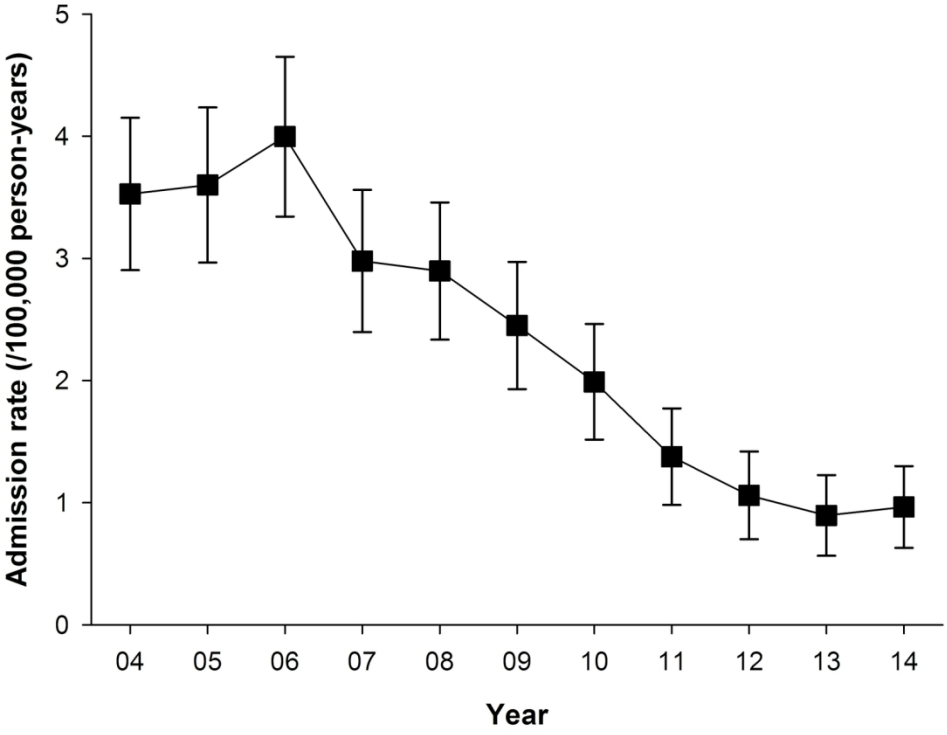

Figure 4. Trend for annual rate of VAP admissions in general adult population. Standardized to WHO standard population. Error bars represent 95% confidence intervals.

146x119mm (300 x 300 DPI)

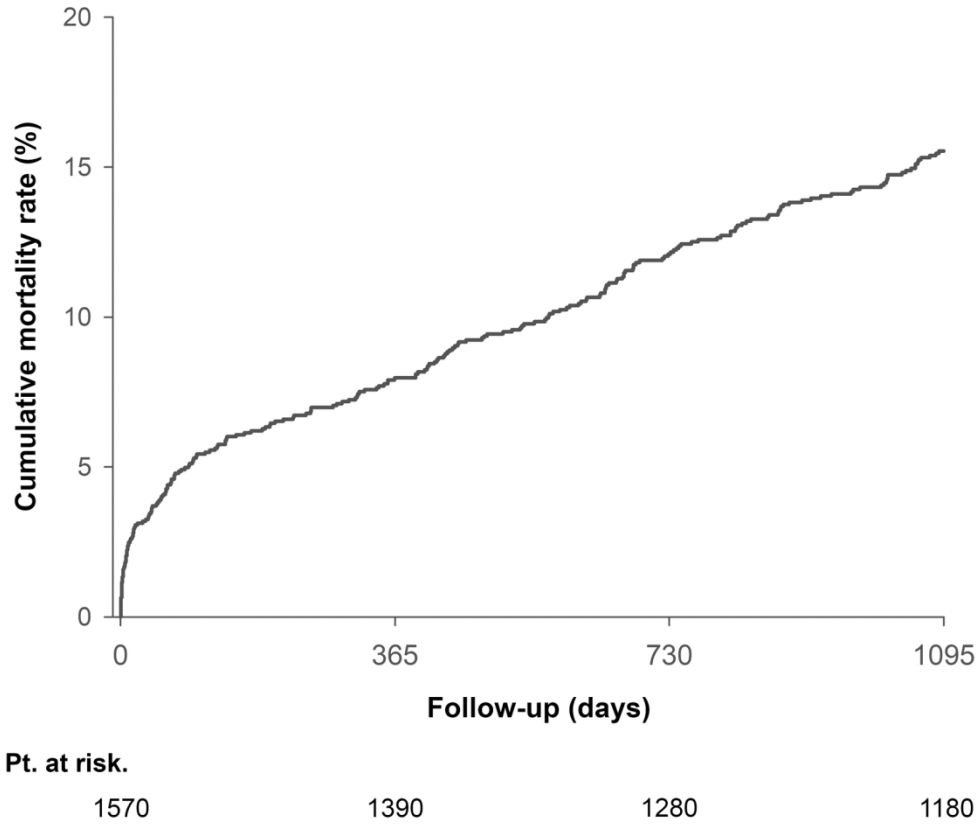

Figure 5. Cumulative all-cause mortality after VAP admission.

149x130mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*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	6
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	*6*
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
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	6
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	8
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	8
		(*b*) Report category boundaries when continuous variables were categorized	
		(*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	8-11
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14
Generalisability	21	Discuss the generalisability (external validity) of the study results	
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	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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 www.strobe-statement.org.