Cross vascular risk for first and recurrent hospitalised atherothrombosis determined retrospectively from linked data

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Title: Cross vascular risk for first and recurrent hospitalised atherothrombosis determined retrospectively from linked data

Short Title: Cross vascular disease risk

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Structured Abstract

Objectives – To determine sex and age-specific risk ratios for first-ever and recurrent hospitalisation for cerebrovascular, coronary and peripheral arterial disease in persons with versus without other vascular history in Western Australia from 2005-2007.

Design – Cross-sectional linkage study.

Setting – Hospitalised population in a representative Australian State.

Participants – All persons aged 34 to 85 years between 1 January 2005 and 31 December 2007 hospitalised with a principal diagnosis of atherothrombosis.

Data sources – Person-linked file of statutory collected administrative morbidity and mortality records.

Main outcome measures – Sex and age-specific risk ratios for first-ever and recurrent hospitalisations for symptomatic atherothrombosis of the brain, coronary and periphery using a 15-year lead-in to determine prior events.

Results – Over 3 years, 40,877 (66% men; 55% first-ever) were hospitalised for atherothrombosis. For each arterial territory, age-specific recurrent rates were higher than the corresponding first-ever rates, with the biggest difference seen in the youngest age groups. For all types of first-ever atherothrombosis, rates were higher in those with other vascular history and risk ratios declined with advancing age (trend: all $P<0.0001$) and remained significantly >1 even for 75-84 year-olds. Whereas, for recurrent events, rates were marginally higher in those with other vascular history and no risk ratio-age trend was apparent with several not significantly >1 (trend: all $P>0.13$).

Conclusions - This study of hospitalised atherothrombosis suggests first-events predominate and that the risk of further events in the same or other arterial territory is very high for all ages and both sexes, accentuating the necessity for early and sustained active prevention.

Article focus

- Stroke and heart attack dominate the vascular burden
- Vascular disease rates rise steeply with age
- Cross vascular risk is predictive of disease recurrence

Key messages

- First-ever atherothrombosis leads the vascular burden
- The risk of a new vascular event in same or another territory is universally very high
- Target primary and secondary prevention to reduce the population disease burden

Strengths and limitations of this study

- Quantification of new and recurrent vascular risk by disease subtype and prior history
- Excluding the very elderly, non-hospitalised events and underdiagnoses of other vascular disease likely overestimated the dominance of coronary events
- Including non-acute hospitalisations will have increased the absolute event rates but had negligible effect on relative comparisons.

Introduction

Few studies have reported population-based estimates of the rate and determinants of incident and recurrent vascular events of the brain (cerebrovascular disease), coronary (coronary heart disease) and periphery (peripheral arterial disease) collectively. The Oxford Vascular Study[1] indicated that 63% of all atherothrombosis subtypes were incident (first-ever) events, and 37% recurrent. Cerebrovascular events were most common, more than coronary, and all rates rose steeply with age. In contrast, the international REACH Registry[2] of atherothrombotic disease in primary-care suggested that coronary events were most common, and that history of symptomatic atheroma in more than one vascular bed was a strong predictor of higher rates of recurrence in the same and other vascular beds.

We aimed to explore the application of the results from the OXVASC and REACH studies[1,2] in a population-based study of hospitalisations for vascular disease among Western Australians aged 35-84 years between 2005 and 2007. Our specific aims were to determine: (1) the absolute age and sex-specific annual rates of first-ever and recurrent hospitalisations for symptomatic atherothrombosis of the brain, coronary and periphery; (2) the independent, significant contributions of atherothrombosis in a different vascular bed to first-ever and recurrent hospitalisations for symptomatic events of the brain, coronary and periphery.

Methods

Setting and data source

We conducted a cross-sectional data linkage study of statutory collected administrative data with no direct participant contact. The demographic profile and main health indices for WA are reflective of the Australian population.[3] Linked public and private hospital morbidity

and mortality data were extracted retrospectively from the WA Data Linkage System which is regularly audited for quality.[4] Person-based records are linked with >99% accuracy using probabilistic matching on standard criteria.[4] A linked file of all hospital admissions and deaths for all persons experiencing a cardiovascular event from 1 January 1990 to 31 December 2007 was available. As morbidity data in the very elderly are considered less reliable, event rates are calculated and reported for people aged 35-84 years. Atherothrombosis diagnoses were identified from discharge records according to the International Classification of Disease (ICD) versions 9-Clinical Modification and 10-Australian Modification.[5] The study was approved by research ethics committees at The University of WA (#RA/4/1/1491) and the Department of Health WA (#2009/18).

Definition and classification of atherothrombosis categories

Emergency and elective hospital admissions for brain, coronary and periphery ischaemia were identified from principal diagnoses on the discharge records and are described elsewhere.[6] Briefly, coronary included myocardial infarction, unstable angina, stable angina or other ischaemic heart disease; brain included cerebral infarction, transient ischaemic attack, precerebral or cerebral artery disease without infarction, unspecified stroke or intracerebral haemorrhage; and periphery comprised atherosclerosis of the aorta, renal arteries or arteries of the extremities, unspecified peripheral vascular disease, Buergers disease or stricture of arteries. Hospital morbidity codes for brain[7], coronary[8] and periphery[9] ischaemia have been previously validated, as have vascular deaths.[10] Hospital transfers were counted as one admission, as were readmissions for the same condition within 28 days for coronary, and within one day for each of brain and periphery episodes.

All atherothrombosis hospitalisations between 1 January 2005 and 31 December 2007 were classified by vascular bed (or disease subtype), and as first-ever or recurrent (or event type). First-ever events were defined as having no hospitalisation in the same vascular bed during a 15-year look-back period, otherwise the event was classified as recurrent. The same 15-year look back period was used to determine the binary variable of prior hospitalisation for other vascular manifestations. The 15-year look-back period was also used to identify the comorbidities of diabetes, hypertension, chronic kidney disease, atrial fibrillation, heart failure, chronic lung disease and cancer. There were <0.001% missing values for any of the variables used in this study.

Statistical analysis

Males and females were analysed separately. For each disease subtype, selected differences in patient characteristics (age by event type, and first-ever events by other vascular history) were evaluated using t-tests and χ^2 respectively. Overall proportions of first-ever and recurrent disease patients with hypertension, diabetes, chronic kidney disease, atrial fibrillation, heart failure, chronic lung disease and cancer were calculated. Age-specific first-ever and recurrent rates were calculated for each of brain, coronary and periphery stratified by other vascular history, using the number of events for that disease subtype over the three years (2005-2007) as the numerator and the corresponding disease-free (prevalent cases excluded) or disease-specific WA population as the denominator, respectively. Poisson regression was used to estimate risk ratios for first-ever and recurrent hospitalisations for each vascular bed for people with other vascular history compared with people without other vascular history. Models include sex, 5-year age group, and other vascular disease history. An interaction term of other vascular disease by 10-year age-group was added to the Poisson

model to test for trend in the risk ratio across age groups. Whilst technically we have estimated rate ratios these are interpreted as 1-year risk ratios as these two ratios are numerically very similar when the rates have small magnitude. Data analyses were performed using SAS (version 9.3),[11] and statistical significance was set at $p<0.05$.

Results

There were 27,156 hospitalisations (53% first-ever) for atherothrombosis in men and 13,721 (59% first-ever) in women aged 35 to 84 years between 2005 and 2007 (Table 1). Seventy-six percent of brain admissions were first-ever, whereas just over half were first-ever for coronary and periphery. Coronary patients were younger for both first-ever and recurrent admissions compared with their brain and periphery counterparts. The percentage of cases in the 75-84 year age group varied from a low of 17% in men for first-ever coronary event, to a high of 56% in women for recurrent brain events. Hypertension was the most common comorbidity followed by diabetes and chronic kidney disease. Periphery patients were less likely to be admitted acutely and more likely to undergo angiography and/or invasive intervention than brain or coronary patients.

Coronary admissions dominated first-ever (67% in men and 61% in women) and recurrent hospitalisations (80% in men and 77% in women) for atherothrombosis (Table 1). Only 6% of first-ever coronary events in men and women had a prior admission for other vascular disease, compared with first-ever brain (27% men, 18% women) and first-ever periphery (44% men, 30% women) hospitalisations. Recurrent events were more likely than first-ever events to have a history of vascular disease in another vascular bed.

Atherothrombosis event rates and risk ratios

Figure 1 shows sex and age-specific first-ever and recurrent hospitalisation rates for each disease subtype by history of other vascular disease. Age-specific rates ranged from about 3/1000 for first-ever brain event with no other vascular history to about 200/1000 for recurrent coronary event with other vascular history. For each vascular bed, age-specific recurrent rates in those with and without other vascular history were higher than the first-ever rates, with the biggest difference seen in the youngest age groups. For first-ever atherothrombosis, rates were generally higher in those with other vascular history compared with no other vascular history, particularly in the youngest age groups. There was little difference between those with and without other vascular history for recurrent rates, a trend seen across all age groups, although there were no recurrent hospitalisations for brain or periphery ischaemia involving another vascular territory in the 35-44 year age group in men.

Table 2 shows sex and age-specific risk ratios for first-ever and recurrent hospitalisation by disease subtype comparing persons with other vascular history to those without. The highest risk ratios were for first-ever brain hospitalisations in women 35-44 years (risk ratios 31.5, 95% CI 13.7 to 72.5) and for first-ever periphery event in men and women 35-44 years (risk ratios 21.7, 95% CI 6.3 to 75.1; risk ratios 19.2, 95% CI 2.5 to 145.9, respectively), although confidence intervals were wide. The risk of a first-ever event was greater for those with versus without other vascular history in all age groups, however risk ratios for all first-ever disease subtypes declined with advancing age (trend: all $P<0.0001$). Risk ratios for recurrent hospitalisations were smaller than for first-ever hospitalisations and several (including all risk ratios for recurrent periphery event) were not significant. Further, risk ratios for recurrent hospitalisations showed no trend with advancing age (trend: all $P>0.05$).

Discussion

This nationally representative population study of 40,877 first-ever and recurrent hospitalised atherothrombosis documents sex and age-specific risk ratios by vascular bed and history of other vascular disease. The majority of hospitalisations are first-ever, led by coronary, then brain and least for periphery; whilst first-ever rates without a history of other vascular disease rose steeply with age. Recurrent hospitalisation rates in men and women for any disease subtype are substantially higher than the corresponding first-ever rates, although narrowed with advancing age. A history of other vascular disease was associated with a high risk of a new event in another vascular bed in younger men and women. In contrast, a history of other vascular disease had little influence on recurrent events of any type and at any age. Greater sex and age-specific risk ratios occurred in first-ever brain and periphery hospitalisations compared with coronary events. There was less variance in risk ratios for recurrent events across disease subtypes. These findings suggest that once atherothrombosis is clinically manifest in any vascular bed, the risk of further events in the same or another vascular location is very high for all ages and both sexes. This reinforces the need for active secondary prevention in all patients with atherothrombotic disease of any type and regardless of age.

Strengths and limitations

Extensive and high-quality person-based linkage of all hospitalised atherothrombosis by other vascular history enabled determination of first-ever and recurrent rates and disease risk ratios.[4] Events were identified from the principal diagnosis at discharge and in-hospital death code where apparent, as previously validated by our group,[7-10] and others.[12] Sex and age-specific findings are largely consistent within and between disease subtypes, although the risk ratio's with wide CIs in 35-44 age groups should be interpreted with caution. Nonfatal brain/coronary attacks treated in the community were not included in the

analyses but are expected to be small in number.[6] Recognised underdiagnoses of peripheral arterial disease and cerebrovascular events may have resulted,[13] thus diluting their relative contribution to the total hospitalised atherothrombosis burden. Excluding the very elderly has likely overestimated the dominance of coronary events at the expense of brain events, as would the associated elective admissions for the diagnostic (e.g. stress testing, coronary angiography) and coronary revascularisation procedures. The inclusion of non-acute hospitalisations for greater coverage of elective procedures will have increased the absolute rates of events but had negligible effect on relative comparisons.

Comparisons with other studies

The age distribution and medical profile of each disease subtype in this representative Australian study are consistent with other hospitalised population studies for myocardial infarction [14,], stroke [15] and peripheral arterial disease.[16] We found little difference in recurrent rates by sex and age, which is entirely consistent with the non-uniform findings of others.[18, 17-20] Differences in methodology likely account for the variability, including: sample size, case definition, all hospitalisations, age restrictions, ethnicity, risk factor profile, duration of follow-up and adjustment for covariates.

The comprehensive population OXVASC study [1] confirms that the majority of atherothrombosis is incident (63% versus 57% in the present study), but led by stroke in that population, and that rates rise steeply with age. The large multinational REACH Registry suggests coronary events dominate the atherothrombosis burden and supports incremental higher rates with other arterial disease involvement.[21] In a separate REACH analysis[13], patients with peripheral disease experienced lower atherothrombosis rates than patients with

stroke or coronary disease, independent of other vascular history. There were no differences in atherothrombosis rates by gender, possibly due to low enrolment of women in that study.[22] Two smaller studies, the SIRO trial [23] and MITICO study [24] reported stroke patients with polyvascular disease had higher rates of recurrence. For co-morbidities, high proportions of first-ever or recurrent atherothrombosis with hypertension, diabetes and chronic kidney disease have been variously identified in population and cohort studies.[15, 21, 24-27]

Implication of results

These sex and age-specific rates and risk ratios for first-ever and recurrent hospitalised atherothrombosis by vascular bed and history of other vascular disease permit comparisons of secondary over primary prevention. To minimize the disease burden on the population and hospitals we should aim to prevent the 56% first-ever hospitalisations, in particular for the brain where it is 76%. The prevention of recurrent events is also very important (and not a mutually exclusive) priority, as they contribute a substantial volume of all hospitalisations, about 44%. The substantially higher risk ratios for recurrent events in persons with and without a history of other vascular disease magnify the scope for systematic secondary prevention across disease subtypes.

In Australia, increased uptake and adherence to antiplatelet, blood pressure-lowering and lipid-lowering medication in persons with established atherothrombosis, and long-term anti-smoking campaigns are priority targets for improving cardiovascular outcomes.[28] Two Australian general practice studies suggest the application of these proven secondary prevention measures continues to be suboptimal.[29, 30] These findings are poignant given

the high rates of recurrent events and raised risk ratios in men and women across the age span in the present study. Further, the higher rates of a first-ever admission where there is a history of vascular disease in a different territory, particularly in the younger age groups, necessitates more aggressive treatment of risk factors. There was no clear gender difference which may be because of the similarly high levels of comorbidities in men and women, or because results were stratified by age, although there may be differences in the over 85 year age group which we have not investigated. Our findings have potential implications for the management of approximately 0.25 million (4.3% of the population) women and 0.5 million (8.6%) men in Australia hospitalised for atherothrombosis.[6]

Contributing to the high risk ratios of recurrent atherothrombosis in both sexes is that over half are hypertensive and around a quarter variously have diabetes, chronic kidney disease, atrial fibrillation and heart failure, consistent with other studies.[15, 17, 21, 26] Such comorbidities will likely complicate clinical treatment during rehospitalisation and subsequent chronic care.

Conclusions

We have shown in a population-based study of hospitalised atherothrombosis that first-ever events predominate and that once vascular disease clinically manifest, the risk of further events in the same or another vascular bed is very high, even for the young, supressing the usual demographic effects. These findings highlight the need for greater awareness among clinicians, patients and funders as to the level of risk related to recurrent events and detail the cross-risk associated with a prior hospitalisation in other vascular locations. These findings

have important implications for prevention strategies, and the prioritising of resources for service provision and research, and they signal an upward trajectory in absolute numbers of events as the population ages. Data on hospital incidence, recurrence, and event risk ratios across the vasculature will also permit modelling the effect of shared secondary preventive treatments, such as cardioprotective pharmacotherapy and lifestyle changes, on the total burden of hospitalised atherothrombosis.

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Declaration of Conflicting Interests

None Declared

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Contributors

TB, MK, GJH PEN and JH conceived and designed the study; LN, FS, SH, TB prepared the data files for analysis; TB, LN undertook the data analysis and drafted the paper; MK wrote the statistical plan and together with AB provided advanced statistical support; JH, GJH, PEN, PLT, FS provided clinical advice; all authors contributed to interpretation of data, reviewing article drafts, and approving the final manuscript. TB is guarantor.

Data sharing

The sharing of the linked data file is not permitted under the conditions under which ethics for the study was granted

References

1. Rothwell PM, Coull AJ, Silver LE, et al; Oxford Vascular Study. Population-based study of event-rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories. *Lancet*. 2005; 366:1773-1783.

2. Bhatt DL, Steg PG, Ohman M, et al; REACH Registry Investigators. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. *JAMA*. 2006; 295:180-189.

3. Clark A, Preen DB, Ng JQ, et al. Is Western Australia representative of other Australian States and Territories in terms of key socio-demographic and health economic indicators? *Aust Health Rev*. 2010; 34:210-215.

4. Holman CDJ, Bass AJ, Rouse IL, et al. Population-based linkage of health records in Western Australia: development of a health services research linked database. *Aust N Z J Public Health.* 1999; 23:453-459.

5. World Health Organization. *International Classification of Diseases: the international statistical classification of diseases, injuries, and causes of death.* http://www.who.int/classifications/icd/en/ (20 June 2013)

6. Nedkoff LJ, Briffa TG, Knuiman M, et al. Temporal trends in the incidence and recurrence of hospitalised atherothrombotic disease in an Australian population, 2000 - 2007. *Heart.* 2012;98:1449-1456.

7. Jamrozik K, Dobson A, Hobbs M, et al. Monitoring the incidence of cardiovascular disease in Australia. Report No. CVD Series 17. Canberra: AIHW; 2001.

8. Sanfilippo FM, Hobbs MST, Knuiman MW, et al. Can we monitor heart attack in the troponin era: evidence from a population-based cohort study. *BMC Cardiovasc Disord.* 2011; 11:35.

9. Mattes E, Norman PE, Jamrozik K. Falling incidence of amputations for peripheral occlusive arterial disease in Western Australia between 1980 and 1992. *Eur J Vasc Endovasc Surg.* 1997; 13:14-22.
10. Norman PE, Semmens JB, Lawrence-Brown MMD, et al. Long term relative survival after surgery for population based study abdominal aortic aneurysm in Western Australia. *BMJ.* 1998; 317:852-856.
11. SAS version 9.3 for Windows (Cary, North Carolina, USA).
12. Goldstein LB. Accuracy of ICD-9-CM coding for the identification of patients with acute ischemic stroke: effect of modifier codes. *Stroke.* 1998; 29:1602-1604.
13. Bhatt DL, Peterson ED, Harrington RA, et al. Prior polyvascular disease: risk factor for adverse ischaemic outcomes in acute coronary syndromes. *Eur Heart J.* 2009; 30:1195-1202.
14. Schmidt M, Jacobsen JB, Lash TL, et al. 25 year trends in first time hospitalisation for acute myocardial infarction, subsequent short and long term mortality, and the prognostic impact of sex and comorbidity: a Danish nationwide cohort study. *BMJ.* 2012 Jan 25;344:e356.
15. Rothwell PM, Coull AJ, Silver LE, et al; Oxford Vascular Study. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). *Lancet.* 2004; 363:1925–1933.
16. Van Kuijk J-P, Flu W-J, Welten GMJM, et al. Long-term prognosis of patients with peripheral arterial disease with or without polyvascular atherosclerotic disease. *Eur Heart J.* 2010; 31:992–999.
17. Bairey Merz CN, Shaw LJ, Reis SE, et al; WISE Investigators. Insights from the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) Study: Part II: gender differences in presentation, diagnosis, and outcome with regard to gender-based

pathophysiology of atherosclerosis and macrovascular and microvascular coronary disease. *J Am Coll Cardiol.* 2006;47:S21-29.

18. MacIntyre K, Stewart S, Capewell S, et al. Gender and survival: a population-based study of 201,114 men and women following a first acute myocardial infarction. *J Am Coll Cardiol.* 2001;38:729-935.
19. D'Ascenzo F, Gonella A, Quadri G, et al. Comparison of mortality rates in women versus men presenting with ST-segment elevation myocardial infarction. *Am J Cardiol.* 2011;107:651-654.
20. Roger VL, Jacobsen SJ, Weston SA, et al. Trends in the incidence and survival of patients with hospitalized myocardial infarction, Olmsted County, Minnesota, 1979 to 1994. *Ann Intern Med*. 2002;136:341–348.
21. Steg PG, Bhatt DL, Wilson PW, et al; REACH Registry Investigators. One-year cardiovascular event rates in outpatients with atherothrombosis. *JAMA*. 2007; 297:1197-1206.
22. Morrell J, Zeymer U, Baumgartner I, et al; REACH Registry Investigators. Differences in management and outcomes between male and female patients with atherothrombotic disease: results from the REACH Registry in Europe. *Eur J Cardiovasc Prev Rehabil.* 2011; 18:270-277.
23. Cimminiello C, Zaninelli A, Carolei A, et al. Atherothrombotic Burden and medium-term prognosis in patients with acute ischemic stroke: findings of the SIRIO Study. *Cerebrovasc Dis.* 2012; 33:341–347.
24. Blanco M, Sobrino T, Montaner J, et al; MÍTICO Study. Stroke with polyvascular atherothrombotic disease. *Atherosclerosis.* 2010; 208: 587–592

25. Feigin VL, Lawes CMM, Bennett DA, et al. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. *Lancet Neurol.* 2009; 8:355–369.

26. Yusuf S, Hawken S, Ôunpuu S, et al; INTERHEART investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries: case-control study. *Lancet.* 2004; 364:937–952.

27. O'Donnell MJ, Xavier D, Liu L, et al; INTERSTROKE investigators. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries:a case-control study. *Lancet.* 2010; 376:112-1 23.

28. Australian Institute of Health and Welfare 2011. *Cardiovascular disease: Australian facts 2011*. Cardiovascular disease series. Cat. no. CVD 53. Canberra: AIHW.

29. Ademi Z, Liew D, Chew D, et al; on behalf of the REACH registry investigators. Drug Treatment and Cost of Cardiovascular Disease in Australia. *Cardiovascular Therapeutics.* 2009; 27:164–172.

30. Heeley EL, Peiris DP, Patel AA, et al. Cardiovascular risk perception and evidence–practice gaps in Australian general practice (AusHEART Study). *Med J Aust.* 2010;192:254–259.

Figure 1 A-F. Age-specific rates for hospitalised coronary, brain and periphery ischaemia by other vascular history (OVH; yes/no) in men (A,C,E) and in women (B,D,F), respectively.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	p 1, 3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	p 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	p 5
Objectives	3	State specific objectives, including any prespecified hypotheses	p 5
Methods			
Study design	4	Present key elements of study design early in the paper	p 5.6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	p 5.6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	p 5-7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	p 6,7
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	p 6,7
Bias	9	Describe any efforts to address potential sources of bias	p 6, 10, 1
Study size	10	Explain how the study size was arrived at	N/A
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	p 7, 8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	p 7, 8
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	p 8
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*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	p 8, Table 1.
		(b) Give reasons for non-participation at each stage	N/A
		(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	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	
Outcome data	15*	Report numbers of outcome events or summary measures	Figure 1
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	Table 2
		(*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	

Discussion			
Key results	18	Summarise key results with reference to study objectives	p 9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	p 10,11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	p 11,12
Generalisability	21	Discuss the generalisability (external validity) of the study results	p 12
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	p 15

*Give information separately for exposed and unexposed groups.

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.

Table 1. Characteristics of atherothrombosis hospitalisations† 2005-2007, Western Australia

DISEASE SUBTYPE *cells in %, unless otherwise specified*	MEN		WOMEN	
	First-ever	**Recurrent**	**First-ever**	**Recurrent**
Coronary event, *n=29,048 (row %)*	9682 (33)	10105 (35)	4970 (17)	4291 (15)
Mean age□, (SD) *years*	62.2 (11.4)	66.3 (10.8)	66.0 (11.8)	69.7 (10.7)
Patients aged 75-84/35-54 years	17.2/26.0	26.9/15.5	29.2/18.9	40.9/10.7
Prior cerebrovascular disease	3.4	7.9	3.8	8.3
Prior peripheral arterial disease	1.9	4.7	1.7	4.2
Diabetes	20.7	33.7	23.9	39.7
Hypertension	50.7	78.1	59.9	85.4
Chronic Kidney Disease	7.7	18.5	9.3	20.8
Atrial Fibrillation	11.1	22.1	12.2	21.3
Heart Failure	8.9	20.7	12.3	27.1
Chronic Lung Disease	5.2	13.4	8.2	19.7
Cancer	8.2	13.9	9.9	17.5
Acute Admission†	51.2	36.9	52.1	42.7
Brain event, *n=7862 (row %)*	3556 (45)	1149 (15)	2465 (31)	692 (9)
Mean age□, (SD) *years*	68.3 (11.0)	71.2 (9.9)	70.6 (11.6)	72.7 (10.7)
Patients aged 75-84/35-54 years	36.1/12.9	47.2/8.0	48.7/12.2	56.1/7.5
Prior coronary heart disease	20.6	27.0	15.0[f]	22.4
Prior peripheral arterial disease	2.2	5.1	2.1	2.6
Diabetes	26.9	33.9	26.0	33.1

Hypertension	65.9	81.3	66.9	81.8
Chronic Kidney Disease	12.1	17.8	11.5	21.5
Atrial Fibrillation	20.3	26.0	21.3	33.5
Heart Failure	9.8	14.5	12.0	21.0
Chronic Lung Disease	8.3	14.5	10.2	15.3
Cancer	14.6	18.5	14.3	18.4
Acute Admission†	73.8	60.8	76.5	70.5
Periphery event, *n=3967 (row %)*	1276 (32)	1388 (35)	680 (17)	623 (16)
Mean age□, (SD) *years*	69.3 (10.1)	70.5 (9.6)	71.2 (11.0)	72.7 (10.0)
Patients aged 75-84/35-54 years	36.9/8.9	40.3/6.4	48.5/10.3	54.6/7.2
Prior coronary heart disease	27.5	30.4	18.1[f]	24.4
Prior cerebrovascular disease	6.4	8.1	6.3	8.0
Diabetes	11.5	8.6	11.5	7.5
Hypertension	47.7	56.8	52.5	64.0
Chronic Kidney Disease	14.4	16.7	12.8	14.3
Atrial Fibrillation	16.3	14.7	14.7	17.5
Heart Failure	13.2	13.0	11.0	17.2
Chronic Lung Disease	11.4	16.4	11.3	14.4
Cancer	12.6	16.4	11.6	14.1
Acute Admission†	12.2	13.0	14.6	11.4
All vascular events, *n* (40,877) *(row-%)*	14,514 (35)	12,642 (31)	8115 (20)	5606 (14)

† For coronary disease, cerebral infarction or transient ischaemic attack, or atherosclerosis of the periphery.

 For each disease subtype, mean age varied by sex and event type (incident versus recurrent) (All P<0.0001).

ƒ For first-ever brain and periphery events, proportions with prior coronary disease varied by sex (both P<0.0001);

SD=standard deviation

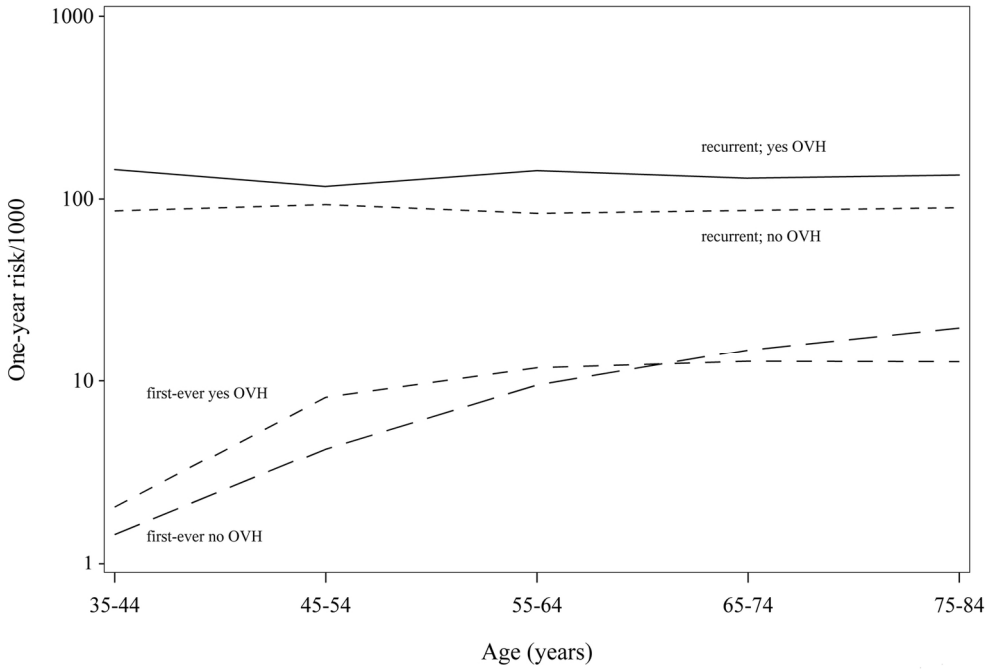
1

Table 2. Hospitalised atherothrombotic disease one-year risk ratios by sex and age-group comparing persons with other vascular history to those without: Western Australia 2005-2007

			Hospitalised disease one-year risk ratio (95% confidence intervals)					**Age group trend p value**
	Age-group *years*		**35-44**	**45-54**	**55-64**	**65-74**	**75-84**	
MEN	Coronary event	first-ever	2.5 (0.8 to 7.9)	3.5 (2.5 to 4.9)	2.3 (1.9 to 2.8)	1.6 (1.4 to 1.9)	1.2 (1.1 to 1.4)	<0.0001
		recurrent	1.6 (0.8 to 3.3)	1.3 (0.9 to 1.7)	1.7 (1.5 to 1.9)	1.5 (1.4 to 1.7)	1.5 (1.4 to 1.6)	0.6283
	Brain event	first-ever	5.4 (2.2 to 13.3)	5.0 (3.7 to 6.7)	2.2 (1.8 to 2.7)	1.6 (1.4 to 1.8)	1.2 (1.1 to 1.4)	<0.0001
		recurrent	_*	1.7 (1.0 to 2.9)	1.3 (0.9 to 1.9)	1.1 (0.9 to 1.3)	1.2 (1.0 to 1.4)	0.4721
	Periphery event	first-ever	21.7 (6.3 to 75.1)	5.1 (3.0 to 8.8)	4.9 (3.8 to 6.3)	2.8 (2.3 to 3.4)	1.7 (1.4 to 2.1)	<0.0001
		recurrent	_*	0.7 (0.4 to 1.3)	1.1 (0.8 to 1.4)	0.8 (0.7 to 1.0)	0.9 (0.7 to 1.0)	0.9696
WOME	Coronary event	first-ever	5.6 (1.4 to 22.5)	5.3 (3.0 to 9.1)	3.0 (2.1 to 4.3)	2.2 (1.8 to 2.8)	1.7 (1.5 to 2.0)	<0.0001
		recurrent	1.9 (0.9 to 4.1)	1.4 (0.9 to 2.1)	2.3 (1.8 to 2.9)	1.4 (1.2 to 1.7)	1.5 (1.3 to 1.7)	0.1357
	Brain event	first-ever	31.5 (13.7 to 72.5)	7.4 (4.4 to 12.3)	3.0 (2.1 to 4.4)	2.4 (1.9 to 2.9)	1.7 (1.5 to 1.9)	<0.0001
		recurrent	1.9 (0.4 to 8.0)	1.0 (0.3 to 3.3)	1.3 (0.7 to 2.3)	1.4 (1.0 to 2.0)	1.3 (1.0 to 1.6)	0.8530
	Periphery event	first-ever	19.2 (2.5 to 145.9)	11.1 (5.0 to 24.7)	6.7 (4.1 to 11.1)	3.7 (2.7 to 5.1)	2.0 (1.6 to 2.5)	<0.0001

N	recurrent	1.7 (0.2 to 13.7)	1.1 (0.5 to 2.4)	0.6 (0.4 to 1.2)	1.1 (0.8 to 1.5)	0.9 (0.7 to 1.1)	0.8577

*No events in these age-groups.



Age-specific rate for hospitalised coronary event by other vascular history (OVH; yes/no) in men
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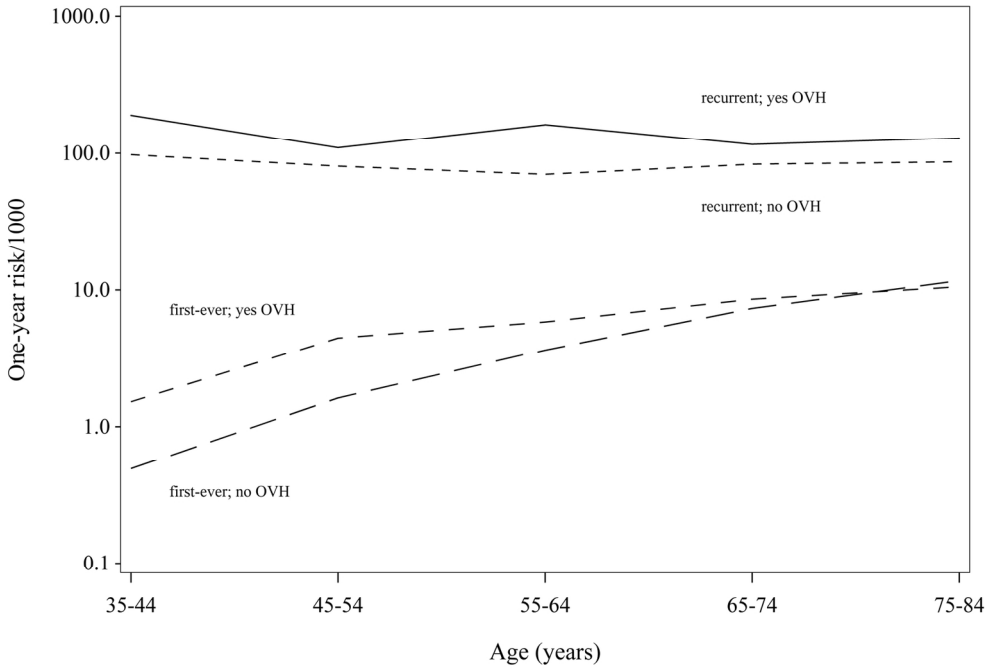

Age-specific rate for hospitalised coronary event by other vascular history (OVH; yes/no) in women
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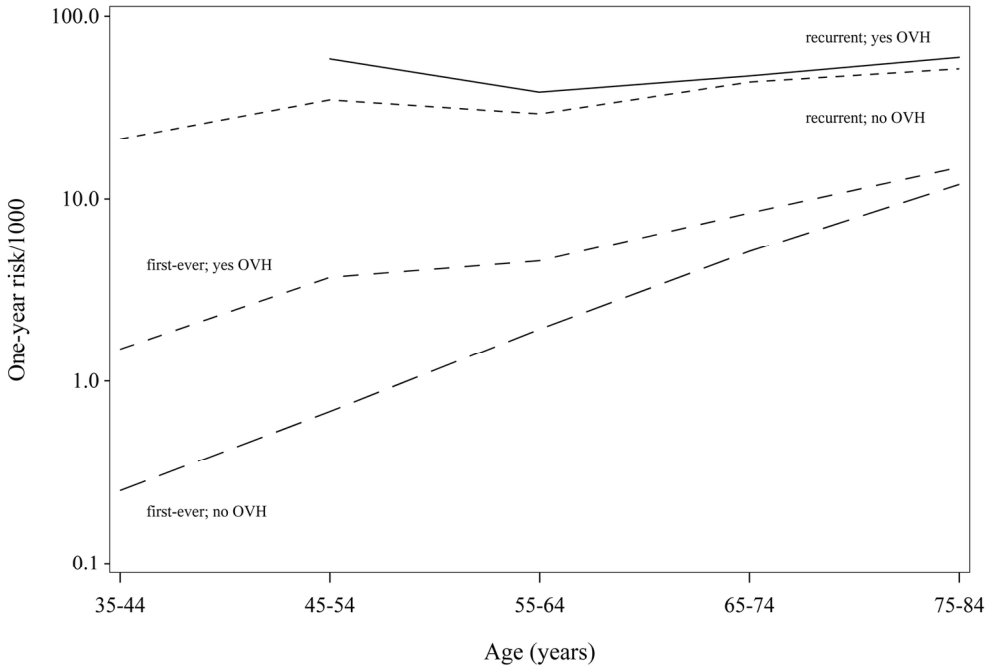
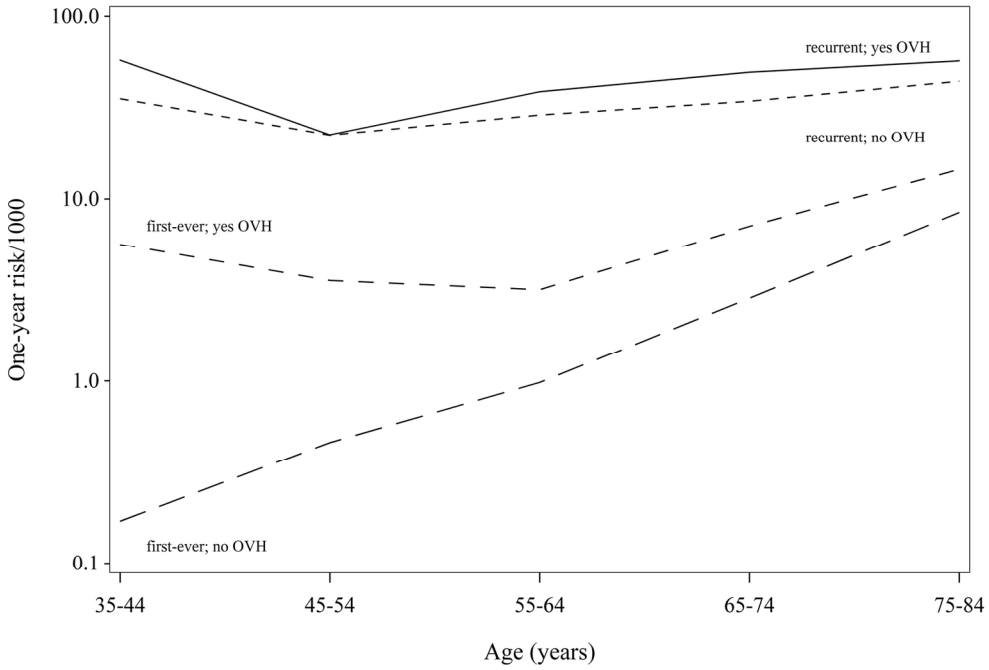


Age-specific rate for hospitalised brain event by other vascular history (OVH; yes/no) in men
76x57mm (600 x 600 DPI)



Age-specific rate for hospitalised brain event by other vascular history (OVH; yes/no) in women
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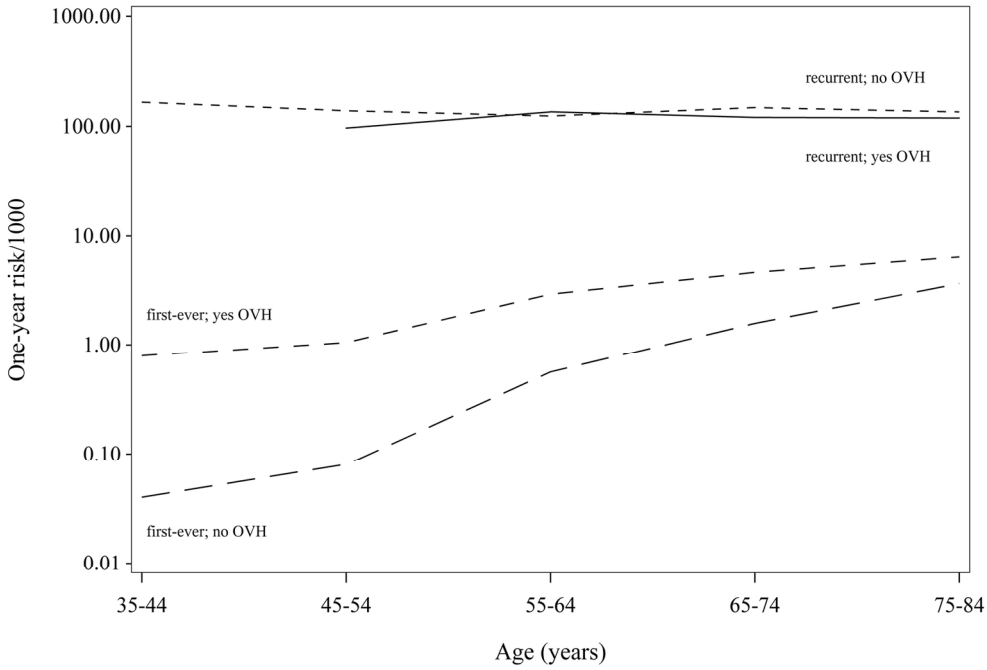
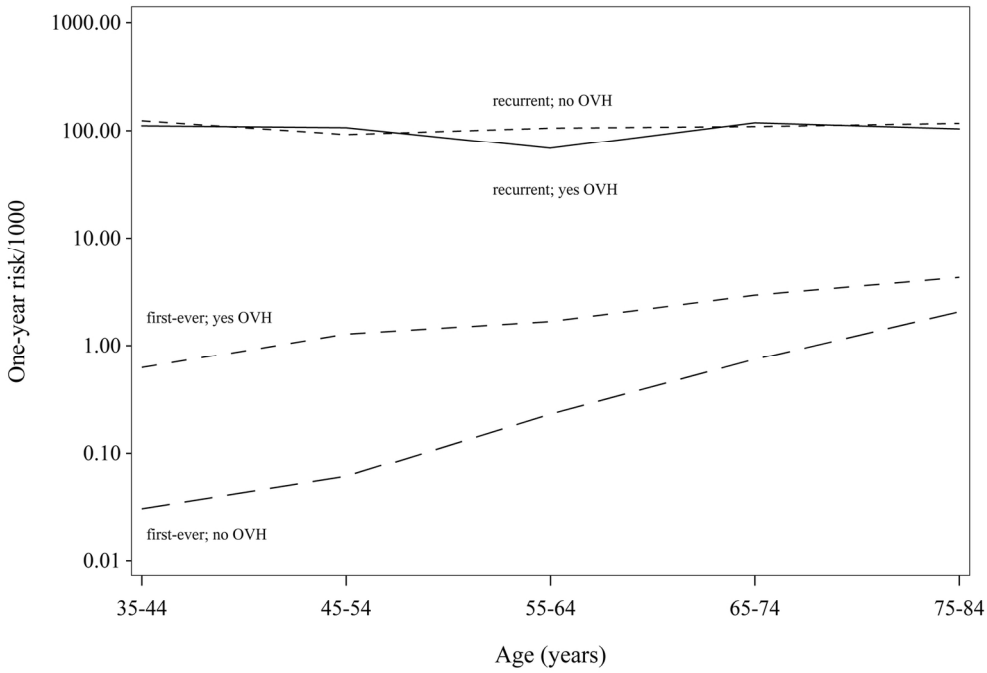


Age-specific rate for hospitalised periphery event by other vascular history (OVH; yes/no) in men
76x57mm (600 x 600 DPI)



Age-specific rate for hospitalised periphery event by other vascular history (OVH; yes/no) in women
76x57mm (600 x 600 DPI)

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Cross vascular risk for first and recurrent hospitalised atherothrombosis determined retrospectively from linked data

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Structured Abstract

Objectives – To determine sex and age-specific risk ratios for first-ever and recurrent hospitalisation for cerebrovascular, coronary and peripheral arterial disease in persons with versus without other vascular history in Western Australia from 2005-2007.

Design – Cross-sectional linkage study.

Setting – Hospitalised population in a representative Australian State.

Participants – All persons aged 34 to 85 years between 1 January 2005 and 31 December 2007 hospitalised with a principal diagnosis of atherothrombosis.

Data sources – Person-linked file of statutory collected administrative morbidity and mortality records.

Main outcome measures – Sex and age-specific risk ratios for first-ever and recurrent hospitalisations for symptomatic atherothrombosis of the brain, coronary and periphery using a 15-year lead-in to determine prior events.

Results – Over 3 years, 40,877 (66% men; 55% first-ever) were hospitalised for atherothrombosis. For each arterial territory, age-specific recurrent rates were higher than the corresponding first-ever rates, with the biggest difference seen in the youngest age groups. For all types of first-ever atherothrombosis, rates were higher in those with other vascular history and risk ratios declined with advancing age (trend: all $P<0.0001$) and remained significantly >1 even for 75-84 year-olds. Whereas, for recurrent events, rates were marginally higher in those with other vascular history and no risk ratio-age trend was apparent with several not significantly >1 (trend: all $P>0.13$).

Conclusions - This study of hospitalised atherothrombosis suggests first-events predominate and that the risk of further events in the same or other arterial territory is very high for all ages and both sexes, accentuating the necessity for early and sustained active prevention.

Article focus

- Stroke and heart attack dominate the vascular burden
- Vascular disease rates rise steeply with age
- Cross vascular risk is predictive of disease recurrence

Key messages

- First-ever atherothrombosis leads the vascular burden
- The risk of a new vascular event in same or another territory is universally very high
- Target primary and secondary prevention to reduce the population disease burden

Strengths and limitations of this study

- Quantification of new and recurrent vascular risk by disease subtype and prior history
- Excluding the very elderly, non-hospitalised events and underdiagnoses of other vascular disease likely overestimated the dominance of coronary events
- Including non-acute hospitalisations will have increased the absolute event rates but had negligible effect on relative comparisons.

Introduction

Few studies have reported population-based estimates of the rate and determinants of incident and recurrent vascular events of the brain (cerebrovascular disease), coronary (coronary heart disease) and periphery (peripheral arterial disease) collectively. The Oxford Vascular Study[1] indicated that 63% of all atherothrombosis subtypes were incident (first-ever) events, and 37% recurrent. Cerebrovascular events were most common, more than coronary, and all rates rose steeply with age. In contrast, the international REACH Registry[2] of atherothrombotic disease in primary-care suggested that coronary events were most common, and that history of symptomatic atheroma in more than one vascular bed was a strong predictor of higher rates of recurrence in the same and other vascular beds.

We aimed to explore the application of the results from the OXVASC and REACH studies[1,2] in a population-based study of hospitalisations for vascular disease among Western Australians aged 35-84 years between 2005 and 2007. Our specific aims were to determine: (1) the absolute age and sex-specific annual rates of first-ever and recurrent hospitalisations for symptomatic atherothrombosis of the brain, coronary and periphery; (2) the independent, significant contributions of atherothrombosis in a different vascular bed to first-ever and recurrent hospitalisations for symptomatic events of the brain, coronary and periphery.

Methods

Setting and data source

We conducted a cross-sectional data linkage study of statutory collected administrative data with no direct participant contact. The demographic profile and main health indices for WA are reflective of the Australian population.[3] Linked public and private hospital morbidity

and mortality data were extracted retrospectively from the WA Data Linkage System which is regularly audited for quality.[4] Person-based records are linked with >99% accuracy using probabilistic matching on standard criteria.[4] A linked file of all hospital admissions and deaths for all persons experiencing a cardiovascular event from 1 January 1990 to 31 December 2007 was available. As morbidity data in the very elderly are considered less reliable, event rates are calculated and reported for people aged 35-84 years. Atherothrombosis diagnoses were identified from discharge records according to the International Classification of Disease (ICD) versions 9-Clinical Modification and 10-Australian Modification.[5] The study was approved by research ethics committees at The University of WA (#RA/4/1/1491) and the Department of Health WA (#2009/18).

Definition and classification of atherothrombosis categories

Emergency and elective hospital admissions for brain, coronary and periphery ischaemia were identified from principal diagnoses on the discharge records and are described elsewhere.[6] Briefly, coronary included myocardial infarction, unstable angina, stable angina or other ischaemic heart disease; brain included cerebral infarction, transient ischaemic attack, precerebral or cerebral artery disease without infarction, unspecified stroke or intracerebral haemorrhage; and periphery comprised atherosclerosis of the aorta, renal arteries or arteries of the extremities, unspecified peripheral vascular disease, Buergers disease or stricture of arteries. Hospital morbidity codes for brain[7], coronary[8] and periphery[9] ischaemia have been previously validated, as have vascular deaths.[10] Hospital transfers were counted as one admission, as were readmissions for the same condition within 28 days for coronary, and within one day for each of brain and periphery episodes.

All atherothrombosis hospitalisations between 1 January 2005 and 31 December 2007 were classified by vascular bed (or disease subtype), and as first-ever or recurrent (or event type). First-ever events were defined as having no hospitalisation in the same vascular bed during a 15-year look-back period, otherwise the event was classified as recurrent. The same 15-year look back period was used to determine the binary variable of prior hospitalisation for other vascular manifestations. The 15-year look-back period was also used to identify the comorbidities of diabetes, hypertension, chronic kidney disease, atrial fibrillation, heart failure, chronic lung disease and cancer. There were <0.001% missing values for any of the variables used in this study.

Statistical analysis

Males and females were analysed separately. For each disease subtype, selected differences in patient characteristics (age by event type, and first-ever events by other vascular history) were evaluated using t-tests and χ^2 respectively. Overall proportions of first-ever and recurrent disease patients with hypertension, diabetes, chronic kidney disease, atrial fibrillation, heart failure, chronic lung disease and cancer were calculated. Age-specific first-ever and recurrent rates were calculated for each of brain, coronary and periphery stratified by other vascular history, using the number of events for that disease subtype over the three years (2005-2007) as the numerator and the corresponding disease-free (prevalent cases excluded) or disease-specific WA population as the denominator, respectively. Poisson regression was used to estimate risk ratios for first-ever and recurrent hospitalisations for each vascular bed for people with other vascular history compared with people without other vascular history. Models include sex, 5-year age group, and other vascular disease history. An interaction term of other vascular disease by 10-year age-group was added to the Poisson

model to test for trend in the risk ratio across age groups. Whilst technically we have estimated rate ratios these are interpreted as 1-year risk ratios as these two ratios are numerically very similar when the rates have small magnitude. Data analyses were performed using SAS (version 9.3),[11] and statistical significance was set at $p<0.05$.

Results

There were 27,156 hospitalisations (53% first-ever) for atherothrombosis in men and 13,721 (59% first-ever) in women aged 35 to 84 years between 2005 and 2007 (Table 1). Seventy-six percent of brain admissions were first-ever, whereas just over half were first-ever for coronary and periphery. Coronary patients were younger for both first-ever and recurrent admissions compared with their brain and periphery counterparts. The percentage of cases in the 75-84 year age group varied from a low of 17% in men for first-ever coronary event, to a high of 56% in women for recurrent brain events. Hypertension was the most common comorbidity followed by diabetes and chronic kidney disease. Periphery patients were less likely to be admitted acutely and more likely to undergo angiography and/or invasive intervention than brain or coronary patients.

Coronary admissions dominated first-ever (67% in men and 61% in women) and recurrent hospitalisations (80% in men and 77% in women) for atherothrombosis (Table 1). Only 6% of first-ever coronary events in men and women had a prior admission for other vascular disease, compared with first-ever brain (27% men, 18% women) and first-ever periphery (44% men, 30% women) hospitalisations. Recurrent events were more likely than first-ever events to have a history of vascular disease in another vascular bed.

Atherothrombosis event rates and risk ratios

Figure 1 shows sex and age-specific first-ever and recurrent hospitalisation rates for each disease subtype by history of other vascular disease. Age-specific rates ranged from about 3/1000 for first-ever brain event with no other vascular history to about 200/1000 for recurrent coronary event with other vascular history. For each vascular bed, age-specific recurrent rates in those with and without other vascular history were higher than the first-ever rates, with the biggest difference seen in the youngest age groups. For first-ever atherothrombosis, rates were generally higher in those with other vascular history compared with no other vascular history, particularly in the youngest age groups. There was little difference between those with and without other vascular history for recurrent rates, a trend seen across all age groups, although there were no recurrent hospitalisations for brain or periphery ischaemia involving another vascular territory in the 35-44 year age group in men.

Table 2 shows sex and age-specific risk ratios for first-ever and recurrent hospitalisation by disease subtype comparing persons with other vascular history to those without. The highest risk ratios were for first-ever brain hospitalisations in women 35-44 years (risk ratios 31.5, 95% CI 13.7 to 72.5) and for first-ever periphery event in men and women 35-44 years (risk ratios 21.7, 95% CI 6.3 to 75.1; risk ratios 19.2, 95% CI 2.5 to 145.9, respectively), although confidence intervals were wide. The risk of a first-ever event was greater for those with versus without other vascular history in all age groups, however risk ratios for all first-ever disease subtypes declined with advancing age (trend: all $P<0.0001$). Risk ratios for recurrent hospitalisations were smaller than for first-ever hospitalisations and several (including all risk ratios for recurrent periphery event) were not significant. Further, risk ratios for recurrent hospitalisations showed no trend with advancing age (trend: all $P>0.05$).

Discussion

This nationally representative population study of 40,877 first-ever and recurrent hospitalised atherothrombosis documents sex and age-specific risk ratios by vascular bed and history of other vascular disease. The majority of hospitalisations are first-ever, led by coronary, then brain and least for periphery; whilst first-ever rates without a history of other vascular disease rose steeply with age. Recurrent hospitalisation rates in men and women for any disease subtype are substantially higher than the corresponding first-ever rates, although narrowed with advancing age. A history of other vascular disease was associated with a high risk of a new event in another vascular bed in younger men and women. In contrast, a history of other vascular disease had little influence on recurrent events of any type and at any age. Greater sex and age-specific risk ratios occurred in first-ever brain and periphery hospitalisations compared with coronary events. There was less variance in risk ratios for recurrent events across disease subtypes. These findings suggest that once atherothrombosis is clinically manifest in any vascular bed, the risk of further events in the same or another vascular location is very high for all ages and both sexes. This reinforces the need for active secondary prevention in all patients with atherothrombotic disease of any type and regardless of age.

Strengths and limitations

Extensive and high-quality person-based linkage of all hospitalised atherothrombosis by other vascular history enabled determination of first-ever and recurrent rates and disease risk ratios.[4] Events were identified from the principal diagnosis at discharge and in-hospital death code where apparent, as previously validated by our group,[7-10] and others.[12] Sex and age-specific findings are largely consistent within and between disease subtypes, although the risk ratio's with wide CIs in 35-44 age groups should be interpreted with caution. Nonfatal brain/coronary attacks treated in the community were not included in the analyses but are expected to be small in number.[6] Recognised underdiagnoses of peripheral

arterial disease and cerebrovascular events may have resulted,[13] thus diluting their relative contribution to the total hospitalised atherothrombosis burden. Excluding the very elderly has likely overestimated the dominance of coronary events at the expense of brain events, as would the associated elective admissions for the diagnostic (e.g. stress testing, coronary angiography) and coronary revascularisation procedures. The inclusion of non-acute hospitalisations for greater coverage of elective procedures will have increased the absolute rates of events but had negligible effect on relative comparisons.

Comparisons with other studies

The age distribution and medical profile of each disease subtype in this representative Australian study are consistent with other hospitalised population studies for myocardial infarction [14,], stroke [15] and peripheral arterial disease.[16] We found little difference in recurrent rates by sex and age, which is entirely consistent with the non-uniform findings of others.[18, 17-20] Differences in methodology likely account for the variability, including: sample size, case definition, all hospitalisations, age restrictions, ethnicity, risk factor profile, duration of follow-up and adjustment for covariates.

The comprehensive population OXVASC study [1] confirms that the majority of atherothrombosis is incident (63% versus 57% in the present study), but led by stroke in that population, and that rates rise steeply with age. The large multinational REACH Registry suggests coronary events dominate the atherothrombosis burden and supports incremental higher rates with other arterial disease involvement.[21] In a separate REACH analysis[13], patients with peripheral disease experienced lower atherothrombosis rates than patients with stroke or coronary disease, independent of other vascular history. There were no differences in atherothrombosis rates by gender, possibly due to low enrolment of women in that

study.[22] Two smaller studies, the SIRO trial [23] and MITICO study [24] reported stroke patients with polyvascular disease had higher rates of recurrence. For co-morbidities, high proportions of first-ever or recurrent atherothrombosis with hypertension, diabetes and chronic kidney disease have been variously identified in population and cohort studies.[15, 21, 24-27]

Implication of results

These sex and age-specific rates and risk ratios for first-ever and recurrent hospitalised atherothrombosis by vascular bed and history of other vascular disease permit comparisons of secondary over primary prevention. To minimize the disease burden on the population and hospitals we should aim to prevent the 56% first-ever hospitalisations, in particular for the brain where it is 76%. The prevention of recurrent events is also very important (and not a mutually exclusive) priority, as they contribute a substantial volume of all hospitalisations, about 44%. The substantially higher risk ratios for recurrent events in persons with and without a history of other vascular disease magnify the scope for systematic secondary prevention across disease subtypes.

In Australia, increased uptake and adherence to antiplatelet, blood pressure-lowering and lipid-lowering medication in persons with established atherothrombosis, and long-term anti-smoking campaigns are priority targets for improving cardiovascular outcomes.[28] Two Australian general practice studies suggest the application of these proven secondary prevention measures continues to be suboptimal.[29, 30] These findings are poignant given the high rates of recurrent events and raised risk ratios in men and women across the age span in the present study. Further, the higher rates of a first-ever admission where there is a history of vascular disease in a different territory, particularly in the younger age groups, necessitates

more aggressive treatment of risk factors. There was no clear gender difference which may be because of the similarly high levels of comorbidities in men and women, or because results were stratified by age, although there may be differences in the over 85 year age group which we have not investigated. Our findings have potential implications for the management of approximately 0.25 million (4.3% of the population) women and 0.5 million (8.6%) men in Australia hospitalised for atherothrombosis.[6]

Contributing to the high risk ratios of recurrent atherothrombosis in both sexes is that over half are hypertensive and around a quarter variously have diabetes, chronic kidney disease, atrial fibrillation and heart failure, consistent with other studies.[15, 17, 21, 26] Such comorbidities will likely complicate clinical treatment during rehospitalisation and subsequent chronic care.

Conclusions

We have shown in a population-based study of hospitalised atherothrombosis that first-ever events predominate and that once vascular disease clinically manifest, the risk of further events in the same or another vascular bed is very high, even for the young, supressing the usual demographic effects. These findings highlight the need for greater awareness among clinicians, patients and funders as to the level of risk related to recurrent events and detail the cross-risk associated with a prior hospitalisation in other vascular locations. These findings have important implications for prevention strategies, and the prioritising of resources for service provision and research, and they signal an upward trajectory in absolute numbers of events as the population ages. Data on hospital incidence, recurrence, and event risk ratios across the vasculature will also permit modelling the effect of shared secondary preventive

treatments, such as cardioprotective pharmacotherapy and lifestyle changes, on the total burden of hospitalised atherothrombosis.

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Declaration of Conflicting Interests

None Declared

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Contributors

TB, MK, GJH PEN and JH conceived and designed the study; LN, FS, SH, TB prepared the data files for analysis; TB, LN undertook the data analysis and drafted the paper; MK wrote the statistical plan and together with AB provided advanced statistical support; JH, GJH, PEN, PLT, FS provided clinical advice; all authors contributed to interpretation of data, reviewing article drafts, and approving the final manuscript. TB is guarantor.

Data sharing

The sharing of the linked data file is not permitted under the conditions under which ethics for the study was granted.

Table 1. Characteristics of atherothrombosis hospitalisations† 2005-2007, Western Australia

DISEASE SUBTYPE *cells in %, unless otherwise specified*	**MEN**		**WOMEN**	
	First-ever	**Recurrent**	**First-ever**	**Recurrent**
Coronary event, *n=29,048 (row %)*	9682 (33)	10105 (35)	4970 (17)	4291 (15)
Mean age□, (SD) *years*	62.2 (11.4)	66.3 (10.8)	66.0 (11.8)	69.7 (10.7)
Patients aged 75-84/35-54 years	17.2/26.0	26.9/15.5	29.2/18.9	40.9/10.7
Prior cerebrovascular disease	3.4	7.9	3.8	8.3
Prior peripheral arterial disease	1.9	4.7	1.7	4.2
Diabetes	20.7	33.7	23.9	39.7
Hypertension	50.7	78.1	59.9	85.4
Chronic Kidney Disease	7.7	18.5	9.3	20.8
Atrial Fibrillation	11.1	22.1	12.2	21.3
Heart Failure	8.9	20.7	12.3	27.1
Chronic Lung Disease	5.2	13.4	8.2	19.7
Cancer	8.2	13.9	9.9	17.5
Acute Admission†	51.2	36.9	52.1	42.7
Brain event, *n=7862 (row %)*	3556 (45)	1149 (15)	2465 (31)	692 (9)
Mean age□, (SD) *years*	68.3 (11.0)	71.2 (9.9)	70.6 (11.6)	72.7 (10.7)
Patients aged 75-84/35-54 years	36.1/12.9	47.2/8.0	48.7/12.2	56.1/7.5
Prior coronary heart disease	20.6	27.0	15.0[f]	22.4
Prior peripheral arterial disease	2.2	5.1	2.1	2.6
Diabetes	26.9	33.9	26.0	33.1

Hypertension	65.9	81.3	66.9	81.8
Chronic Kidney Disease	12.1	17.8	11.5	21.5
Atrial Fibrillation	20.3	26.0	21.3	33.5
Heart Failure	9.8	14.5	12.0	21.0
Chronic Lung Disease	8.3	14.5	10.2	15.3
Cancer	14.6	18.5	14.3	18.4
Acute Admission†	73.8	60.8	76.5	70.5
Periphery event, *n=3967 (row %)*	1276 (32)	1388 (35)	680 (17)	623 (16)
Mean age, (SD) *years*	69.3 (10.1)	70.5 (9.6)	71.2 (11.0)	72.7 (10.0)
Patients aged 75-84/35-54 years	36.9/8.9	40.3/6.4	48.5/10.3	54.6/7.2
Prior coronary heart disease	27.5	30.4	18.1[f]	24.4
Prior cerebrovascular disease	6.4	8.1	6.3	8.0
Diabetes	11.5	8.6	11.5	7.5
Hypertension	47.7	56.8	52.5	64.0
Chronic Kidney Disease	14.4	16.7	12.8	14.3
Atrial Fibrillation	16.3	14.7	14.7	17.5
Heart Failure	13.2	13.0	11.0	17.2
Chronic Lung Disease	11.4	16.4	11.3	14.4
Cancer	12.6	16.4	11.6	14.1
Acute Admission†	12.2	13.0	14.6	11.4
All vascular events, *n* (40,877) *(row-%)*	14,514 (35)	12,642 (31)	8115 (20)	5606 (14)

† For coronary disease, cerebral infarction or transient ischaemic attack, or atherosclerosis of the periphery.

 For each disease subtype, mean age varied by sex and event type (incident versus recurrent) (All P<0.0001).

ƒ For first-ever brain and periphery events, proportions with prior coronary disease varied by sex (both P<0.0001);

SD=standard deviation

Table 2. Hospitalised atherothrombotic disease one-year risk ratios by sex and age-group comparing persons with other vascular history to those without: Western Australia 2005-2007

			Hospitalised disease one-year risk ratio (95% confidence intervals)					**Age group trend p value**
	Age-group *years*		**35-44**	**45-54**	**55-64**	**65-74**	**75-84**	
MEN	Coronary event	first-ever	2.5 (0.8 to 7.9)	3.5 (2.5 to 4.9)	2.3 (1.9 to 2.8)	1.6 (1.4 to 1.9)	1.2 (1.1 to 1.4)	<0.0001
		recurrent	1.6 (0.8 to 3.3)	1.3 (0.9 to 1.7)	1.7 (1.5 to 1.9)	1.5 (1.4 to 1.7)	1.5 (1.4 to 1.6)	0.6283
	Brain event	first-ever	5.4 (2.2 to 13.3)	5.0 (3.7 to 6.7)	2.2 (1.8 to 2.7)	1.6 (1.4 to 1.8)	1.2 (1.1 to 1.4)	<0.0001
		recurrent	_*	1.7 (1.0 to 2.9)	1.3 (0.9 to 1.9)	1.1 (0.9 to 1.3)	1.2 (1.0 to 1.4)	0.4721
	Periphery event	first-ever	21.7 (6.3 to 75.1)	5.1 (3.0 to 8.8)	4.9 (3.8 to 6.3)	2.8 (2.3 to 3.4)	1.7 (1.4 to 2.1)	<0.0001
		recurrent	_*	0.7 (0.4 to 1.3)	1.1 (0.8 to 1.4)	0.8 (0.7 to 1.0)	0.9 (0.7 to 1.0)	0.9696
WOME	Coronary event	first-ever	5.6 (1.4 to 22.5)	5.3 (3.0 to 9.1)	3.0 (2.1 to 4.3)	2.2 (1.8 to 2.8)	1.7 (1.5 to 2.0)	<0.0001
		recurrent	1.9 (0.9 to 4.1)	1.4 (0.9 to 2.1)	2.3 (1.8 to 2.9)	1.4 (1.2 to 1.7)	1.5 (1.3 to 1.7)	0.1357
	Brain event	first-ever	31.5 (13.7 to 72.5)	7.4 (4.4 to 12.3)	3.0 (2.1 to 4.4)	2.4 (1.9 to 2.9)	1.7 (1.5 to 1.9)	<0.0001
		recurrent	1.9 (0.4 to 8.0)	1.0 (0.3 to 3.3)	1.3 (0.7 to 2.3)	1.4 (1.0 to 2.0)	1.3 (1.0 to 1.6)	0.8530
	Periphery event	first-ever	19.2 (2.5 to 145.9)	11.1 (5.0 to 24.7)	6.7 (4.1 to 11.1)	3.7 (2.7 to 5.1)	2.0 (1.6 to 2.5)	<0.0001

N	recurrent	1.7 (0.2 to 13.7)	1.1 (0.5 to 2.4)	0.6 (0.4 to 1.2)	1.1 (0.8 to 1.5)	0.9 (0.7 to 1.1)	0.8577

*No events in these age-groups.

References

1. Rothwell PM, Coull AJ, Silver LE, et al; Oxford Vascular Study. Population-based study of event-rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories. *Lancet*. 2005; 366:1773-1783.

2. Bhatt DL, Steg PG, Ohman M, et al; REACH Registry Investigators. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. *JAMA*. 2006; 295:180-189.

3. Clark A, Preen DB, Ng JQ, et al. Is Western Australia representative of other Australian States and Territories in terms of key socio-demographic and health economic indicators? *Aust Health Rev*. 2010; 34:210-215.

4. Holman CDJ, Bass AJ, Rouse IL, et al. Population-based linkage of health records in Western Australia: development of a health services research linked database. *Aust N Z J Public Health.* 1999; 23:453-459.

5. World Health Organization. *International Classification of Diseases: the international statistical classification of diseases, injuries, and causes of death.* http://www.who.int/classifications/icd/en/ (20 June 2013)

6. Nedkoff LJ, Briffa TG, Knuiman M, et al. Temporal trends in the incidence and recurrence of hospitalised atherothrombotic disease in an Australian population, 2000 - 2007. *Heart.* 2012;98:1449-1456.

7. Jamrozik K, Dobson A, Hobbs M, et al. Monitoring the incidence of cardiovascular disease in Australia. Report No. CVD Series 17. Canberra: AIHW; 2001.

8. Sanfilippo FM, Hobbs MST, Knuiman MW, et al. Can we monitor heart attack in the troponin era: evidence from a population-based cohort study. *BMC Cardiovasc Disord.* 2011; 11:35.

9. Mattes E, Norman PE, Jamrozik K. Falling incidence of amputations for peripheral occlusive arterial disease in Western Australia between 1980 and 1992. *Eur J Vasc Endovasc Surg.* 1997; 13:14-22.
10. Norman PE, Semmens JB, Lawrence-Brown MMD, et al. Long term relative survival after surgery for population based study abdominal aortic aneurysm in Western Australia. *BMJ.* 1998; 317:852-856.
11. SAS version 9.3 for Windows (Cary, North Carolina, USA).
12. Goldstein LB. Accuracy of ICD-9-CM coding for the identification of patients with acute ischemic stroke: effect of modifier codes. *Stroke.* 1998; 29:1602-1604.
13. Bhatt DL, Peterson ED, Harrington RA, et al. Prior polyvascular disease: risk factor for adverse ischaemic outcomes in acute coronary syndromes. *Eur Heart J.* 2009; 30:1195-1202.
14. Schmidt M, Jacobsen JB, Lash TL, et al. 25 year trends in first time hospitalisation for acute myocardial infarction, subsequent short and long term mortality, and the prognostic impact of sex and comorbidity: a Danish nationwide cohort study. *BMJ.* 2012 Jan 25;344:e356.
15. Rothwell PM, Coull AJ, Silver LE, et al; Oxford Vascular Study. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). *Lancet.* 2004; 363:1925–1933.
16. Van Kuijk J-P, Flu W-J, Welten GMJM, et al. Long-term prognosis of patients with peripheral arterial disease with or without polyvascular atherosclerotic disease. *Eur Heart J.* 2010; 31:992–999.
17. Bairey Merz CN, Shaw LJ, Reis SE, et al; WISE Investigators. Insights from the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) Study: Part II: gender differences in presentation, diagnosis, and outcome with regard to gender-based

pathophysiology of atherosclerosis and macrovascular and microvascular coronary disease. *J Am Coll Cardiol.* 2006;47:S21-29.

18. MacIntyre K, Stewart S, Capewell S, et al. Gender and survival: a population-based study of 201,114 men and women following a first acute myocardial infarction. *J Am Coll Cardiol.* 2001;38:729-935.
19. D'Ascenzo F, Gonella A, Quadri G, et al. Comparison of mortality rates in women versus men presenting with ST-segment elevation myocardial infarction. *Am J Cardiol.* 2011;107:651-654.
20. Roger VL, Jacobsen SJ, Weston SA, et al. Trends in the incidence and survival of patients with hospitalized myocardial infarction, Olmsted County, Minnesota, 1979 to 1994. *Ann Intern Med*. 2002;136:341–348.
21. Steg PG, Bhatt DL, Wilson PW, et al; REACH Registry Investigators. One-year cardiovascular event rates in outpatients with atherothrombosis. *JAMA.* 2007; 297:1197-1206.
22. Morrell J, Zeymer U, Baumgartner I, et al; REACH Registry Investigators. Differences in management and outcomes between male and female patients with atherothrombotic disease: results from the REACH Registry in Europe. *Eur J Cardiovasc Prev Rehabil.* 2011; 18:270-277.
23. Cimminiello C, Zaninelli A, Carolei A, et al. Atherothrombotic Burden and medium-term prognosis in patients with acute ischemic stroke: findings of the SIRIO Study. *Cerebrovasc Dis.* 2012; 33:341–347.
24. Blanco M, Sobrino T, Montaner J, et al; MÍTICO Study. Stroke with polyvascular atherothrombotic disease. *Atherosclerosis.* 2010; 208: 587–592
25. Feigin VL, Lawes CMM, Bennett DA, et al. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. *Lancet Neurol.* 2009; 8:355–369.

26. Yusuf S, Hawken S, Ôunpuu S, et al; INTERHEART investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries: case-control study. *Lancet.* 2004; 364:937–952.

27. O'Donnell MJ, Xavier D, Liu L, et al; INTERSTROKE investigators. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries:a case-control study. *Lancet.* 2010; 376:112-1 23.

28. Australian Institute of Health and Welfare 2011. *Cardiovascular disease: Australian facts 2011*. Cardiovascular disease series. Cat. no. CVD 53. Canberra: AIHW.

29. Ademi Z, Liew D, Chew D, et al; on behalf of the REACH registry investigators. Drug Treatment and Cost of Cardiovascular Disease in Australia. *Cardiovascular Therapeutics.* 2009; 27:164–172.

30. Heeley EL, Peiris DP, Patel AA, et al. Cardiovascular risk perception and evidence–practice gaps in Australian general practice (AusHEART Study). *Med J Aust.* 2010;192:254–259.

Figure 1 A-F. Age-specific rates for hospitalised coronary, brain and periphery ischaemia by other vascular history (OVH; yes/no) in men (A,C,E) and in women (B,D,F), respectively.

Title: Cross vascular risk for first and recurrent hospitalised atherothrombosis determined retrospectively from linked data

Short Title: Cross vascular disease risk

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Structured Abstract

Objectives – To determine sex and age-specific risk ratios for first-ever and recurrent hospitalisation for cerebrovascular, coronary and peripheral arterial disease in persons with versus without other vascular history in Western Australia from 2005-2007.

Design – Cross-sectional linkage study.

Setting – Hospitalised population in a representative Australian State.

Participants – All persons aged 34 to 85 years between 1 January 2005 and 31 December 2007 hospitalised with a principal diagnosis of atherothrombosis.

Data sources – Person-linked file of statutory collected administrative morbidity and mortality records.

Main outcome measures – Sex and age-specific risk ratios for first-ever and recurrent hospitalisations for symptomatic atherothrombosis of the brain, coronary and periphery using a 15-year lead-in to determine prior events.

Results – Over 3 years, 40,877 (66% men; 55% first-ever) were hospitalised for atherothrombosis. For each arterial territory, age-specific recurrent rates were higher than the corresponding first-ever rates, with the biggest difference seen in the youngest age groups. For all types of first-ever atherothrombosis, rates were higher in those with other vascular history and risk ratios declined with advancing age (trend: all $P<0.0001$) and remained significantly >1 even for 75-84 year-olds. Whereas, for recurrent events, rates were marginally higher in those with other vascular history and no risk ratio-age trend was apparent with several not significantly >1 (trend: all $P>0.13$).

Conclusions - This population study of hospitalised atherothrombosis suggests that rates of recurrence are substantially higher than first-events independent of vascular territory, age and sex. These findings accentuate the necessity for early and sustained active prevention.

Article focus

- Stroke and heart attack dominate the vascular burden
- Vascular disease rates rise steeply with age
- Cross vascular risk is predictive of disease recurrence

Key messages

- First-ever atherothrombosis leads the vascular burden
- The risk of a new vascular event in same or another territory is universally very high
- Target primary and secondary prevention to reduce the population disease burden

Strengths and limitations of this study

- Quantification of new and recurrent vascular risk by disease subtype and prior history
- Excluding the very elderly, non-hospitalised events and underdiagnoses of other vascular disease likely overestimated the dominance of coronary events
- Including non-acute hospitalisations will have increased the absolute event rates but had negligible effect on relative comparisons.

Introduction

Few studies have reported population-based estimates of the rate and determinants of incident and recurrent vascular events of the brain (cerebrovascular disease), coronary (coronary heart disease) and periphery (peripheral arterial disease) collectively. The Oxford Vascular Study[1] indicated that 63% of all atherothrombosis subtypes were incident (first-ever) events, and 37% recurrent. Cerebrovascular events were most common, more than coronary, and all rates rose steeply with age. In contrast, the international REACH Registry[2] of atherothrombotic disease in primary-care suggested that coronary events were most common, and that history of symptomatic atheroma in more than one vascular bed was a strong predictor of higher rates of recurrence in the same and other vascular beds.

We aimed to explore the application of the results from the OXVASC and REACH studies[1,2] in a population-based study of hospitalisations for vascular disease among Western Australians aged 35-84 years between 2005 and 2007. Our specific aims were to determine: (1) the absolute age and sex-specific annual rates of first-ever and recurrent hospitalisations for symptomatic atherothrombosis of the brain, coronary and periphery; (2) the independent, significant contributions of atherothrombosis in a different vascular bed to first-ever and recurrent hospitalisations for symptomatic events of the brain, coronary and periphery.

Methods

Setting and data source

We conducted a cross-sectional data linkage study of statutory collected administrative data with no direct participant contact. The demographic profile and main health indices for WA are reflective of the Australian population.[3] Linked public and private hospital morbidity

and mortality data were extracted retrospectively from the WA Data Linkage System which is regularly audited for quality.[4] Person-based records are linked with >99% accuracy using probabilistic matching on standard criteria.[4] A linked file of all hospital admissions and deaths for all persons experiencing a cardiovascular event from 1 January 1990 to 31 December 2007 was available. As morbidity data in the very elderly are considered less reliable, event rates are calculated and reported for people aged 35-84 years. Atherothrombosis diagnoses were identified from discharge records according to the International Classification of Disease (ICD) versions 9-Clinical Modification and 10-Australian Modification.[5] The study was approved by research ethics committees at The University of WA (#RA/4/1/1491) and the Department of Health WA (#2009/18).

Definition and classification of atherothrombosis categories

Emergency and elective hospital admissions for brain, coronary and periphery ischaemia were identified from principal diagnoses on the discharge records and are described elsewhere.[6] Briefly, coronary included myocardial infarction, unstable angina, stable angina or other ischaemic heart disease; brain included cerebral infarction, transient ischaemic attack, precerebral or cerebral artery disease without infarction, unspecified stroke or intracerebral haemorrhage; and periphery comprised atherosclerosis of the aorta, renal arteries or arteries of the extremities, unspecified peripheral vascular disease, Buergers disease or stricture of arteries. Hospital morbidity codes for brain[7], coronary[8] and periphery[9] ischaemia have been previously validated, as have vascular deaths.[10] Hospital transfers were counted as one admission, as were readmissions for the same condition within 28 days for coronary, and within one day for each of brain and periphery episodes.

All atherothrombosis hospitalisations between 1 January 2005 and 31 December 2007 were classified by vascular bed (or disease subtype), and as first-ever or recurrent (or event type). First-ever events were defined as having no hospitalisation in the same vascular bed during a 15-year look-back period, otherwise the event was classified as recurrent. The same 15-year look back period was used to determine the binary variable of prior hospitalisation for other vascular manifestations. The 15-year look-back period was also used to identify the comorbidities of diabetes, hypertension, chronic kidney disease, atrial fibrillation, heart failure, chronic lung disease and cancer. There were <0.001% missing values for any of the variables used in this study.

Statistical analysis

Males and females were analysed separately. For each disease subtype, selected differences in patient characteristics (age by event type, and first-ever events by other vascular history) were evaluated using t-tests and χ^2 respectively. Overall proportions of first-ever and recurrent disease patients with hypertension, diabetes, chronic kidney disease, atrial fibrillation, heart failure, chronic lung disease and cancer were calculated. Age-specific first-ever and recurrent rates were calculated for each of brain, coronary and periphery stratified by other vascular history, using the number of events for that disease subtype over the three years (2005-2007) as the numerator and the corresponding disease-free (prevalent cases excluded) or disease-specific WA population as the denominator, respectively. Poisson regression was used to estimate risk ratios for first-ever and recurrent hospitalisations for each vascular bed for people with other vascular history compared with people without other vascular history. Models include sex, 5-year age group, and other vascular disease history. An interaction term of other vascular disease by 10-year age-group was added to the Poisson

model to test for trend in the risk ratio across age groups. Whilst technically we have estimated rate ratios these are interpreted as 1-year risk ratios as these two ratios are numerically very similar when the rates have small magnitude. Data analyses were performed using SAS (version 9.3),[11] and statistical significance was set at $p<0.05$.

Results

There were 27,156 hospitalisations (53% first-ever) for atherothrombosis in men and 13,721 (59% first-ever) in women aged 35 to 84 years between 2005 and 2007 (Table 1). Seventy-six percent of brain admissions were first-ever, whereas just over half were first-ever for coronary and periphery. Coronary patients were younger for both first-ever and recurrent admissions compared with their brain and periphery counterparts. The percentage of cases in the 75-84 year age group varied from a low of 17% in men for first-ever coronary event, to a high of 56% in women for recurrent brain events. Hypertension was the most common comorbidity followed by diabetes and chronic kidney disease. Periphery patients were less likely to be admitted acutely and more likely to undergo angiography and/or invasive intervention than brain or coronary patients.

Coronary admissions dominated first-ever (67% in men and 61% in women) and recurrent hospitalisations (80% in men and 77% in women) for atherothrombosis (Table 1). Only 6% of first-ever coronary events in men and women had a prior admission for other vascular disease, compared with first-ever brain (27% men, 18% women) and first-ever periphery (44% men, 30% women) hospitalisations. Recurrent events were more likely than first-ever events to have a history of vascular disease in another vascular bed.

Atherothrombosis event rates and risk ratios

Figure 1 shows sex and age-specific first-ever and recurrent hospitalisation rates for each disease subtype by history of other vascular disease. Age-specific rates ranged from about 3/1000 for first-ever brain event with no other vascular history to about 200/1000 for recurrent coronary event with other vascular history. For each vascular bed, age-specific recurrent rates in those with and without other vascular history were higher than the first-ever rates, with the biggest difference seen in the youngest age groups. For first-ever atherothrombosis, rates were generally higher in those with other vascular history compared with no other vascular history, particularly in the youngest age groups. There was little difference between those with and without other vascular history for recurrent rates, a trend seen across all age groups, although there were no recurrent hospitalisations for brain or periphery ischaemia involving another vascular territory in the 35-44 year age group in men.

Table 2 shows sex and age-specific risk ratios for first-ever and recurrent hospitalisation by disease subtype comparing persons with other vascular history to those without. The highest risk ratios were for first-ever brain hospitalisations in women 35-44 years (risk ratios 31.5, 95% CI 13.7 to 72.5) and for first-ever periphery event in men and women 35-44 years (risk ratios 21.7, 95% CI 6.3 to 75.1; risk ratios 19.2, 95% CI 2.5 to 145.9, respectively), although confidence intervals were wide. The risk of a first-ever event was greater for those with versus without other vascular history in all age groups, however risk ratios for all first-ever disease subtypes declined with advancing age (trend: all $P<0.0001$). Risk ratios for recurrent hospitalisations were smaller than for first-ever hospitalisations and several (including all risk ratios for recurrent periphery event) were not significant. Further, risk ratios for recurrent hospitalisations showed no trend with advancing age (trend: all $P>0.05$).

Discussion

This nationally representative population study of 40,877 first-ever and recurrent hospitalised atherothrombosis documents sex and age-specific risk ratios by vascular bed and history of other vascular disease. The majority of hospitalisations are first-ever, led by coronary, then brain and least for periphery; whilst first-ever rates without a history of other vascular disease rose steeply with age. Recurrent hospitalisation rates in men and women for any disease subtype are substantially higher than the corresponding first-ever rates, although narrowed with advancing age. A history of other vascular disease was associated with a high risk of a new event in another vascular bed in younger men and women. In contrast, a history of other vascular disease had little influence on recurrent events of any type and at any age. Greater sex and age-specific risk ratios occurred in first-ever brain and periphery hospitalisations compared with coronary events. There was less variance in risk ratios for recurrent events across disease subtypes. These findings suggest that once atherothrombosis is clinically manifest in any vascular bed, the risk of further events in the same or another vascular location is very high for all ages and both sexes. This reinforces the need for active secondary prevention in all patients with atherothrombotic disease of any type and regardless of age.

Strengths and limitations

Extensive and high-quality person-based linkage of all hospitalised atherothrombosis by other vascular history enabled determination of first-ever and recurrent rates and disease risk ratios.[4] Events were identified from the principal diagnosis at discharge and in-hospital death code where apparent, as previously validated by our group,[7-10] and others.[12] A weakness is that the analysis is limited to hospitalisation data and does not control for out-of-hospital deaths. Sex and age-specific findings are largely consistent within and between disease subtypes, although the risk ratio's with wide CIs in 35-44 age groups should be

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interpreted with caution. Nonfatal brain/coronary attacks treated in the community were not included in the analyses but are expected to be small in number.[6] Recognised underdiagnoses of peripheral arterial disease and cerebrovascular events may have resulted,[13] thus diluting their relative contribution to the total hospitalised atherothrombosis burden. Excluding the very elderly has likely overestimated the dominance of coronary events at the expense of brain events, as would the associated elective admissions for the diagnostic (e.g. stress testing, coronary angiography) and coronary revascularisation procedures. The inclusion of non-acute hospitalisations for greater coverage of elective procedures will have increased the absolute rates of events but had negligible effect on relative comparisons.

Comparisons with other studies

The age distribution and medical profile of each disease subtype in this representative Australian study are consistent with other hospitalised population studies for myocardial infarction [14,], stroke [15] and peripheral arterial disease.[16] We found little difference in recurrent rates by sex and age, which is entirely consistent with the non-uniform findings of others.[18, 17-20] Differences in methodology likely account for the variability, including: sample size, case definition, all hospitalisations, age restrictions, ethnicity, risk factor profile, duration of follow-up and adjustment for covariates.

The comprehensive population OXVASC study [1] confirms that the majority of atherothrombosis is incident (63% versus 57% in the present study), but led by stroke in that population, and that rates rise steeply with age. The large multinational REACH Registry suggests coronary events dominate the atherothrombosis burden and supports incremental

higher rates with other arterial disease involvement.[21] In a separate REACH analysis[13], patients with peripheral disease experienced lower atherothrombosis rates than patients with stroke or coronary disease, independent of other vascular history. There were no differences in atherothrombosis rates by gender, possibly due to low enrolment of women in that study.[22] Two smaller studies, the SIRO trial [23] and MITICO study [24] reported stroke patients with polyvascular disease had higher rates of recurrence. For co-morbidities, high proportions of first-ever or recurrent atherothrombosis with hypertension, diabetes and chronic kidney disease have been variously identified in population and cohort studies.[15, 21, 24-27]

Implication of results

These sex and age-specific rates and risk ratios for first-ever and recurrent hospitalised atherothrombosis by vascular bed and history of other vascular disease permit comparisons of secondary over primary prevention. To minimize the disease burden on the population and hospitals we should aim to prevent the 56% first-ever hospitalisations, in particular for the brain where it is 76%. The prevention of recurrent events is also very important (and not a mutually exclusive) priority, as they contribute a substantial volume of all hospitalisations, about 44%. The substantially higher risk ratios for recurrent events in persons with and without a history of other vascular disease magnify the scope for systematic secondary prevention across disease subtypes.

In Australia, increased uptake and adherence to antiplatelet, blood pressure-lowering and lipid-lowering medication in persons with established atherothrombosis, and long-term anti-smoking campaigns are priority targets for improving cardiovascular outcomes.[28] Two

Australian general practice studies suggest the application of these proven secondary prevention measures continues to be suboptimal.[29, 30] These findings are poignant given the high rates of recurrent events and raised risk ratios in men and women across the age span in the present study. Further, the higher rates of a first-ever admission where there is a history of vascular disease in a different territory, particularly in the younger age groups, necessitates more aggressive treatment of risk factors. The nationally funded health checks in general practice for 45-49 year olds are an ideal opportunity to effect comprehensive risk assessment and more active primary and secondary prevention in this group. There was no clear gender difference which may be because of the similarly high levels of comorbidities in men and women, or because results were stratified by age, although there may be differences in the over 85 year age group which we have not investigated. Further, ~~O~~our findings have potential implications for the management of approximately 0.25 million (4.3% of the population) women and 0.5 million (8.6%) men in Australia hospitalised for atherothrombosis.[6]

Contributing to the high risk ratios of recurrent atherothrombosis in both sexes is that over half are hypertensive and around a quarter variously have diabetes, chronic kidney disease, atrial fibrillation and heart failure, consistent with other studies.[15, 17, 21, 26] Such comorbidities will likely complicate clinical treatment during rehospitalisation and subsequent chronic care.

Conclusions

We have shown in a population-based study of hospitalised atherothrombosis that first-ever events predominate and that once vascular disease clinically manifests, the risk of further

events in the same or another vascular bed is very high, even for the young, supressing the usual demographic effects. These findings highlight the need for greater awareness among clinicians, patients and funders as to the level of risk related to recurrent events and detail the cross-risk associated with a prior hospitalisation in other vascular locations. These findings have important implications for prevention strategies, and the prioritising of resources for service provision and research, and they signal an upward trajectory in absolute numbers of events as the population ages. Data on hospital incidence, recurrence, and event risk ratios across the vasculature will also permit modelling the effect of shared secondary preventive treatments, such as cardioprotective pharmacotherapy and lifestyle changes, on the total burden of hospitalised atherothrombosis.

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Declaration of Conflicting Interests

None Declared

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Contributors

TB, MK, GJH PEN and JH conceived and designed the study; LN, FS, SH, TB prepared the data files for analysis; TB, LN undertook the data analysis and drafted the paper; MK wrote the statistical plan and together with AB provided advanced statistical support; JH, GJH, PEN, PLT, FS provided clinical advice; all authors contributed to interpretation of data, reviewing article drafts, and approving the final manuscript. TB is guarantor.

References

1. Rothwell PM, Coull AJ, Silver LE, et al; Oxford Vascular Study. Population-based study of event-rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories. *Lancet*. 2005; 366:1773-1783.
2. Bhatt DL, Steg PG, Ohman M, et al; REACH Registry Investigators. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. *JAMA*. 2006; 295:180-189.
3. Clark A, Preen DB, Ng JQ, et al. Is Western Australia representative of other Australian States and Territories in terms of key socio-demographic and health economic indicators? *Aust Health Rev*. 2010; 34:210-215.
4. Holman CDJ, Bass AJ, Rouse IL, et al. Population-based linkage of health records in Western Australia: development of a health services research linked database. *Aust N Z J Public Health*. 1999; 23:453-459.
5. World Health Organization. *International Classification of Diseases: the international statistical classification of diseases, injuries, and causes of death.* http://www.who.int/classifications/icd/en/ (20 June 2013)
6. Nedkoff LJ, Briffa TG, Knuiman M, et al. Temporal trends in the incidence and recurrence of hospitalised atherothrombotic disease in an Australian population, 2000 - 2007. *Heart*. 2012;98:1449-1456.
7. Jamrozik K, Dobson A, Hobbs M, et al. Monitoring the incidence of cardiovascular disease in Australia. Report No. CVD Series 17. Canberra: AIHW; 2001.
8. Sanfilippo FM, Hobbs MST, Knuiman MW, et al. Can we monitor heart attack in the troponin era: evidence from a population-based cohort study. *BMC Cardiovasc Disord*. 2011; 11:35.

9. Mattes E, Norman PE, Jamrozik K. Falling incidence of amputations for peripheral occlusive arterial disease in Western Australia between 1980 and 1992. *Eur J Vasc Endovasc Surg.* 1997; 13:14-22.

10. Norman PE, Semmens JB, Lawrence-Brown MMD, et al. Long term relative survival after surgery for population based study abdominal aortic aneurysm in Western Australia. *BMJ.* 1998; 317:852-856.

11. SAS version 9.3 for Windows (Cary, North Carolina, USA).

12. Goldstein LB. Accuracy of ICD-9-CM coding for the identification of patients with acute ischemic stroke: effect of modifier codes. *Stroke.* 1998; 29:1602-1604.

13. Bhatt DL, Peterson ED, Harrington RA, et al. Prior polyvascular disease: risk factor for adverse ischaemic outcomes in acute coronary syndromes. *Eur Heart J.* 2009; 30:1195-1202.

14. Schmidt M, Jacobsen JB, Lash TL, et al. 25 year trends in first time hospitalisation for acute myocardial infarction, subsequent short and long term mortality, and the prognostic impact of sex and comorbidity: a Danish nationwide cohort study. *BMJ.* 2012 Jan 25;344:e356.

15. Rothwell PM, Coull AJ, Silver LE, et al; Oxford Vascular Study. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). *Lancet.* 2004; 363:1925–1933.

16. Van Kuijk J-P, Flu W-J, Welten GMJM, et al. Long-term prognosis of patients with peripheral arterial disease with or without polyvascular atherosclerotic disease. *Eur Heart J.* 2010; 31:992–999.

17. Bairey Merz CN, Shaw LJ, Reis SE, et al; WISE Investigators. Insights from the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) Study: Part II: gender differences in presentation, diagnosis, and outcome with regard to gender-based

pathophysiology of atherosclerosis and macrovascular and microvascular coronary disease. *J Am Coll Cardiol.* 2006;47:S21-29.

18. MacIntyre K, Stewart S, Capewell S, et al. Gender and survival: a population-based study of 201,114 men and women following a first acute myocardial infarction. *J Am Coll Cardiol.* 2001;38:729-935.
19. D'Ascenzo F, Gonella A, Quadri G, et al. Comparison of mortality rates in women versus men presenting with ST-segment elevation myocardial infarction. *Am J Cardiol.* 2011;107:651-654.
20. Roger VL, Jacobsen SJ, Weston SA, et al. Trends in the incidence and survival of patients with hospitalized myocardial infarction, Olmsted County, Minnesota, 1979 to 1994. *Ann Intern Med*. 2002;136:341–348.
21. Steg PG, Bhatt DL, Wilson PW, et al; REACH Registry Investigators. One-year cardiovascular event rates in outpatients with atherothrombosis. *JAMA.* 2007; 297:1197-1206.
22. Morrell J, Zeymer U, Baumgartner I, et al; REACH Registry Investigators. Differences in management and outcomes between male and female patients with atherothrombotic disease: results from the REACH Registry in Europe. *Eur J Cardiovasc Prev Rehabil.* 2011; 18:270-277.
23. Cimminiello C, Zaninelli A, Carolei A, et al. Atherothrombotic Burden and medium-term prognosis in patients with acute ischemic stroke: findings of the SIRIO Study. *Cerebrovasc Dis.* 2012; 33:341–347.
24. Blanco M, Sobrino T, Montaner J, et al; MÍTICO Study. Stroke with polyvascular atherothrombotic disease. *Atherosclerosis.* 2010; 208: 587–592

25. Feigin VL, Lawes CMM, Bennett DA, et al. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. *Lancet Neurol.* 2009; 8:355–369.

26. Yusuf S, Hawken S, Ôunpuu S, et al; INTERHEART investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries: case-control study. *Lancet.* 2004; 364:937–952.

27. O'Donnell MJ, Xavier D, Liu L, et al; INTERSTROKE investigators. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries:a case-control study. *Lancet.* 2010; 376:112-1 23.

28. Australian Institute of Health and Welfare 2011. *Cardiovascular disease: Australian facts 2011*. Cardiovascular disease series. Cat. no. CVD 53. Canberra: AIHW.

29. Ademi Z, Liew D, Chew D, et al; on behalf of the REACH registry investigators. Drug Treatment and Cost of Cardiovascular Disease in Australia. *Cardiovascular Therapeutics.* 2009; 27:164–172.

30. Heeley EL, Peiris DP, Patel AA, et al. Cardiovascular risk perception and evidence–practice gaps in Australian general practice (AusHEART Study). *Med J Aust.* 2010;192:254–259.

Figure 1 A-F. Age-specific rates for hospitalised coronary, brain and periphery ischaemia by other vascular history (OVH; yes/no) in men (A,C,E) and in women (B,D,F), respectively.

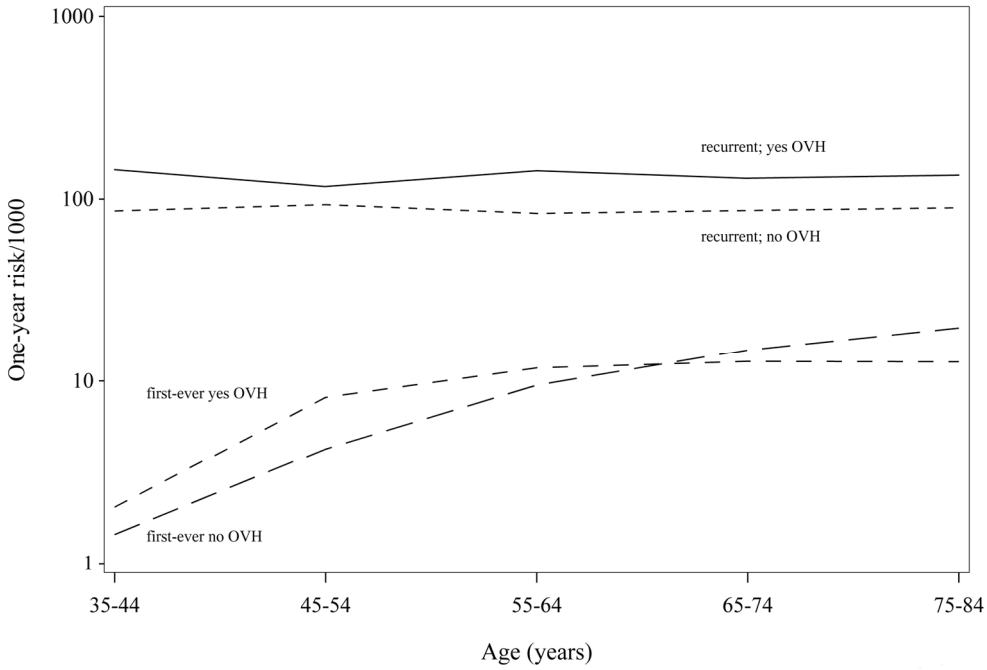
STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	p 1, 3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	p 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	p 5
Objectives	3	State specific objectives, including any prespecified hypotheses	p 5
Methods			
Study design	4	Present key elements of study design early in the paper	p 5.6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	p 5.6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	p 5-7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	p 6,7
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	p 6,7
Bias	9	Describe any efforts to address potential sources of bias	p 6, 10, 1
Study size	10	Explain how the study size was arrived at	N/A
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	p 7, 8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	p 7, 8
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	p 7
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*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	p 8, Table 1.
		(b) Give reasons for non-participation at each stage	N/A
		(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	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	
Outcome data	15*	Report numbers of outcome events or summary measures	Figure 1
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	Table 2
		(*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	

Discussion			
Key results	18	Summarise key results with reference to study objectives	p 9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	p 10,11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	p 11,12
Generalisability	21	Discuss the generalisability (external validity) of the study results	p 12
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	p 15

*Give information separately for exposed and unexposed groups.

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.



Age-specific rate for hospitalised coronary event by other vascular history (OVH; yes/no) in men
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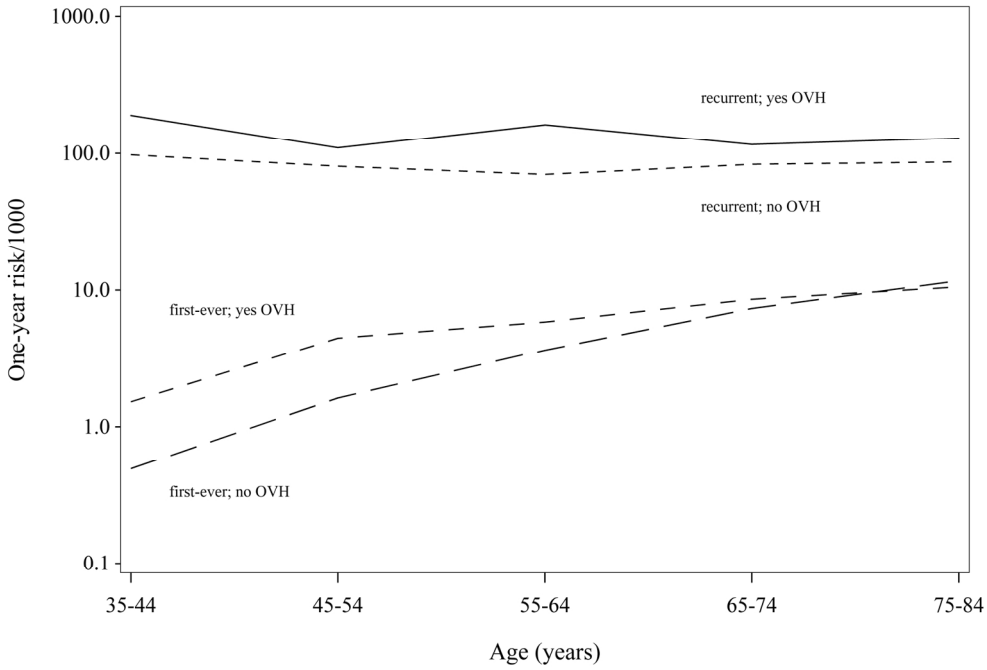

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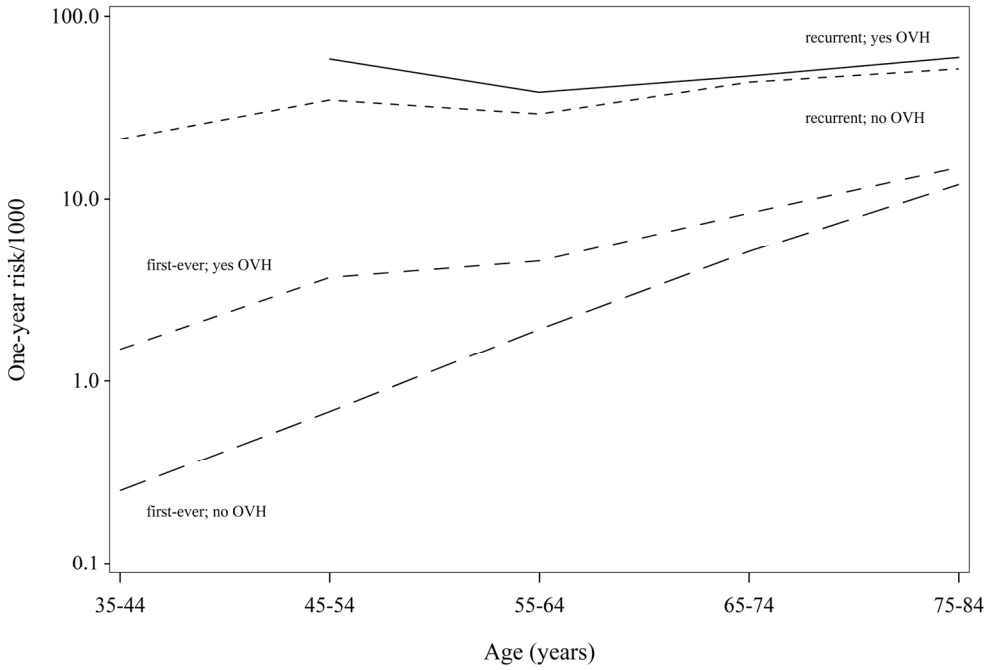

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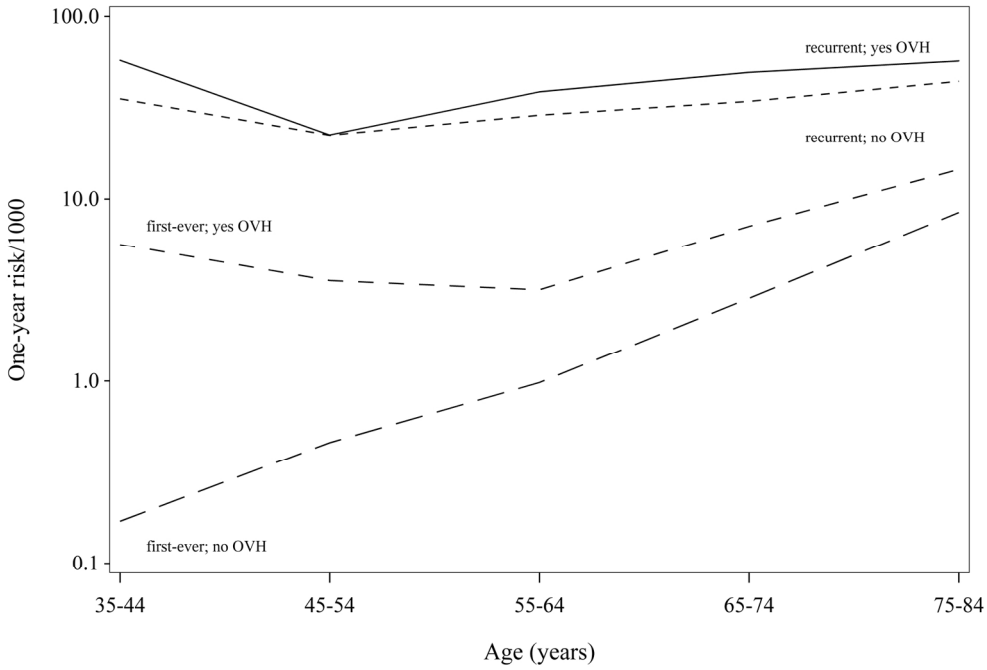

Age-specific rate for hospitalised brain event by other vascular history (OVH; yes/no) in women
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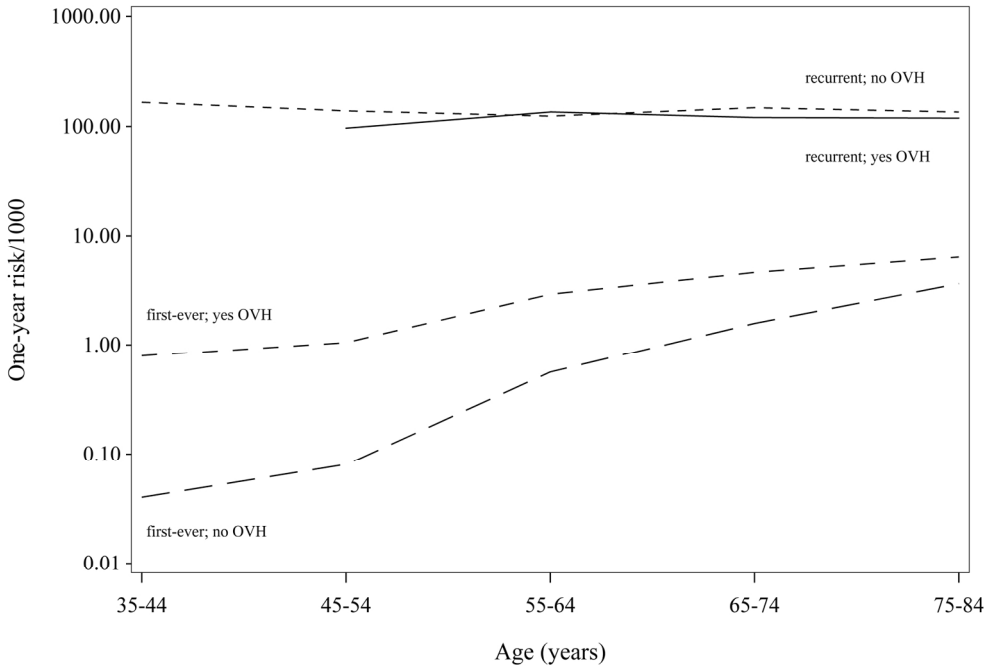

Age-specific rate for hospitalised periphery event by other vascular history (OVH; yes/no) in men
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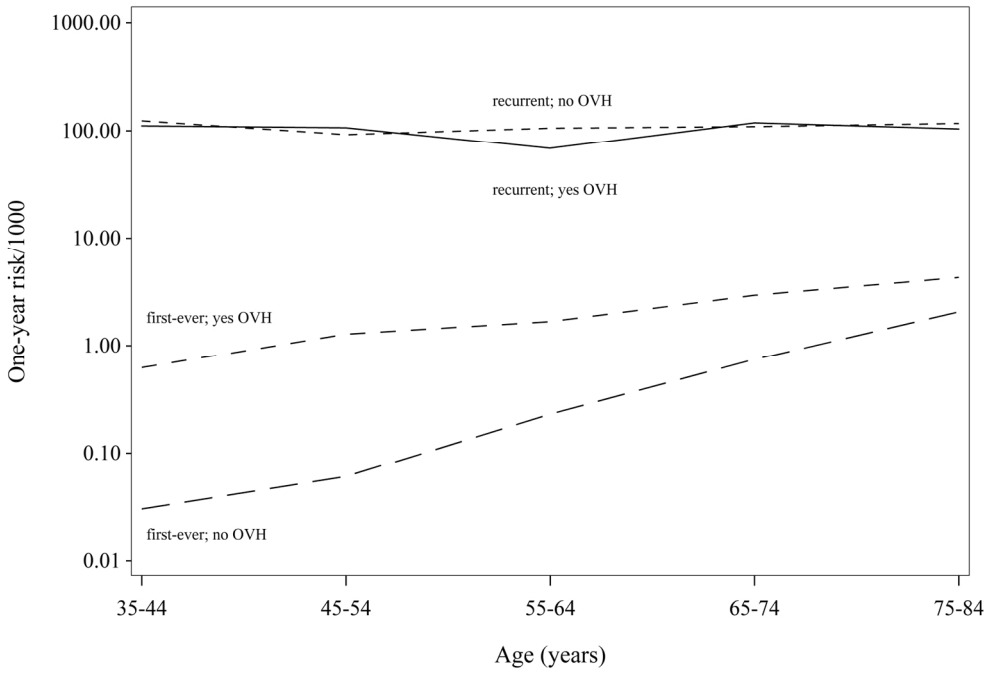

Age-specific rate for hospitalised periphery event by other vascular history (OVH; yes/no) in women
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