

Postoperative atrial fibrillation predicts long-term survival after aortic-valve surgery but not after mitral-valve surgery: a retrospective study

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ABSTRACT

Background: Postoperative atrial fibrillation (POAF) has been reported to be associated with reduced long-term survival after isolated coronary artery bypass grafting surgery. The objective of this study was to determine the impact of POAF on long-term survival after valvular surgery.

Methods: The authors retrospectively analysed the preoperative and operative data of 2986 consecutive patients with no preoperative history of atrial fibrillation undergoing first valvular surgery (aortic-valve replacement (AVR), mitral valve replacement or mitral valve repair (MVR/MVRp) with or without coronary artery bypass grafting surgery) in their institution between 1995 and 2008 (median follow-up 5.31 years, range 0.1–15.0). The authors investigated the impact of POAF on survival using multivariable Cox regression.

Results: Patients with POAF were older, and were more likely to have hypertension or renal failure when compared with patients without POAF. The 12-year survival in patients with POAF was 45.7±2.8% versus 61.4±2.1% in patients without POAF (p<0.001). On a multivariable analysis, when adjusting for age and other potential confounding factors, POAF tended to be associated with lower long-term survival (HR for all-cause death (HR)=1.17, 95% CI 1.00 to 1.38, p=0.051). The authors also analysed this association separately in patients with AVR and those with MVR/MVRp. In the multivariable analysis, POAF was a significant predictor of higher long-term mortality in patients with AVR (HR=1.22, CI 1.02 to 1.45, p=0.03) but not in patients with MVR/MVRp (HR=0.87, CI 0.58 to 1.29, p=0.48).

Conclusions: POAF is significantly associated with long-term mortality following AVR but not after MVR/MVRp. The underlying factors involved in the pathogenesis of POAF after MVR/MVRp may partially account for the lack of association between POAF and survival in these patients.

INTRODUCTION

Postoperative atrial fibrillation (POAF) is the most frequent complication following cardiac surgery. Indeed, POAF occurs in

ARTICLE SUMMARY

Article focus

- To investigate if postoperative atrial fibrillation (POAF) may affect long-term survival following heart-valve surgery.

Key messages

- POAF is significantly associated with long-term mortality following aortic-valve replacement (AVR).
- POAF is not associated with long-term mortality following mitral valve replacement/repair.

Strengths and limitations of this study

- This study indicates that POAF is a significant predictor of long-term survival after AVR.
- Hence, additional specific intervention, possibly a closer follow-up, should be considered in these patients.
- This is an observational study, hence causality between POAF and long-term survival following AVR cannot be ascertained.

20–50% of patients, depending on the type of surgical procedure.¹ POAF is associated with higher morbidity, prolonged hospitalisation and increased hospital costs following cardiac surgery.¹ However, conflicting results have been reported regarding the impact of POAF on early postoperative mortality.^{2–3} Moreover, recent studies have shown that POAF is associated with reduced long-term survival after isolated coronary artery bypass grafting surgery (CABG) in several large observational studies.^{4–8} Nonetheless, in the context of valvular surgery, few studies have examined the impact of POAF on long-term survival, and these studies have yielded conflicting results.^{6–9} Mariscalco and Engstrom⁶ reported that POAF is associated with lower survival after CABG but not after valvular surgery, whereas Filardo *et al*⁹ found that POAF is significantly associated with increased long-term risk of mortality after aortic-valve replacement (AVR).

The objective of this study was thus to examine the impact of POAF on long-term mortality after valvular surgery in a large cohort of patients. Further, we determined whether the impact of POAF on survival following valvular surgery was influenced by the treated valve (aortic or mitral) or the presence of concomitant coronary artery disease (CAD) requiring CABG.

METHODS

Study population

Data on 2986 patients with no preoperative history of paroxysmal or chronic atrial fibrillation (AF) operated on for a first valvular surgery at the Quebec Heart & Lung Institute between 1995 and 2008 were prospectively collected in a computerised database and then retrospectively analysed. Patients with AVR, mitral valve replacement (MVR) and mitral valve repair (MVRp) were included. Previous or associated CABG was not considered as an exclusion criterion. Patients with at least one of the following criteria were excluded: (1) concomitant cardiac or vascular procedure (including tricuspid and pulmonary-valve surgery), (2) double-valve procedure (concomitant mitral and aortic-valve surgery), (3) previous valvular surgery and (4) short-term mortality (defined as death from any cause within 30 days after operation if the patient was discharged from hospital or within any interval if the patient was not discharged). The study was approved by the Institutional Review Board of Quebec Heart & Lung Institute.

Detection and treatment of AF

Detailed information regarding the detection and treatment of POAF in our institution was previously reported.^{10 11} Briefly, POAF was defined as any sustained episode recorded during the postoperative hospital stay and requiring medical and/or electrical cardioversion. No systematic prophylactic measures were used to prevent the development of POAF. However, as a general rule, unless contraindicated, β -blocker medication was introduced (or reintroduced) in all patients within the first 24 h after surgery. A constant ambulatory electrocardiographic (ECG) monitoring was performed in all patients during the first 48 h after surgery. Thereafter, a standard daily 12-lead ECG was recorded. In every patient suspected of an arrhythmic event, a standard 12-lead ECG was performed, and the patient was monitored with continuous ambulatory ECG until 48 h after the resolution of the arrhythmia. All patients with POAF were treated with intravenous amiodarone as a first-line therapy. When needed, electrical cardioversion was performed.

Outcome

Long-term survival data were obtained from the death certificates of the Registry Office of the Quebec government. All-cause mortality was analysed. Survival follow-up was closed on 31 December 2009.

Statistical analysis

Continuous variables were expressed as mean or median \pm SD and were compared using t tests for independent samples. Differences in proportion were compared using a χ^2 test. We used the Kaplan–Meier method to estimate survivals. Differences between survival curves were analysed using the logrank test. The association between POAF and risk of all-cause was examined using individual and multivariable Cox proportional hazard models. In the multivariable model, we adjusted for the following potential confounders: age, gender, diabetes, hypertension, renal failure, chronic obstructive pulmonary disease, previous myocardial infarction, previous stroke, current smoking status and left ventricular systolic dysfunction defined as left-ventricular ejection fraction <50%. The choice of the covariates was based on current available evidence in the field of cardiac surgery rather than data-driven. Multiplicative interaction with POAF was tested for the following predefined variables: type of surgical procedure, type of underlying valvular dysfunction (regurgitation vs stenosis), severity of CAD and mechanical-valve implantation. A probability value <0.05 was considered significant. All statistical analyses were performed with SPSS V.15.

RESULTS

Baseline characteristics of patients with and without POAF

Patients with POAF were older ($p<0.001$) and had a higher prevalence of hypertension ($p=0.03$) and renal failure ($p=0.001$) (table 1). Patients receiving mechanical valves or current smokers were less likely to have POAF ($p=0.004$ and <0.001 respectively).

Impact of POAF on long-term survival in the whole cohort

The median follow-up was 5.31 years (range: 0.1–15.0 years). Overall, 705 patients (23.6%) died. The 6- and 12-year survival in patients with and without POAF were $78.1\pm 1.3\%$ and $45.7\pm 2.8\%$ versus $83.6\pm 1.0\%$ and $61.4\pm 2.1\%$, respectively ($p<0.001$, figure 1).

On multivariable analysis, when adjusting for age and other potential confounding factors, POAF tended to be associated with long-term survival (HR=1.17, 95% CI 1.00 to 1.38, $p=0.051$) (table 2).

There was no significant interaction with concomitant CABG, three-vessel disease or mechanical-valve implantation (all $p>0.20$). Of note, the interaction with the type of valvular procedure (aortic-valve surgery versus mitral-valve surgery) was of borderline statistical significance ($p=0.09$). Consequently, we also report results in subsets of patients with AVR or with MVR–MVRp.

Baseline characteristics of patients with and without POAF in patients with aortic-valve surgery and in patients with mitral-valve surgery

Patients with POAF were older and had a higher prevalence of renal failure regardless of the surgical procedure (table 1). Patients with hypertension and patients implanted with mechanical valves were more likely to

Table 1 Baseline characteristics in the whole cohort and in patients with aortic or mitral-valve surgery according to presence or absence of postoperative atrial fibrillation (POAF)

	Whole cohort, n = 2986		Patients undergoing aortic-valve replacement, n = 2287		Patients undergoing mitral-valve surgery, n = 699	
	POAF (%), n = 1282	No POAF (%), n = 1704	POAF (%), n = 951	No POAF (%), n = 1336	POAF (%), n = 331	No POAF (%), n = 368
Age (years)	70.4±9.3	66.1±11.0	71.8±8.3	67.7±10.1	66.2±10	60.0±12.0
Female gender	38.8%	36.7%	36.6%	37.3%	45.3%	34.5%
Diabetes mellitus	23.5%	22.3%	25.3%	24.0%	18.4%	16.0%
Hypertension	61.4%	57.4%	65.2%	60.5%	50.8%	46.0%
Renal failure	9.1%	5.8%	8.4%	5.4%	11.2%	7.3%
Chronic obstructive pulmonary disease	17.1%	15.0%	18.2%	15.1%	13.9%	14.4%
Previous myocardial infarction	23.9%	22.7%	20.8%	19.2%	32.9%	35.6%
Previous stroke	7.3%	6.1%	7.3%	6.7%	7.3%	3.8%
Current smoking status	10.5%	16.1%	10.0%	13.5%	11.8%	25.5%
Left-ventricular ejection fraction <50%	20.6%	18.0%	18.4%	14.6%	26.8%	29.7%
Mechanical valve implanted	18.2%	22.5%	10.0%	18.0%	41.7%	38.9%
Dominant valve dysfunction						
Aortic stenosis	64.0%	68.7%	86.3%	87.6%		
Aortic regurgitation	10.1%	9.7%	13.7%	12.4%		
Mitral stenosis	3.7%	2.2%			14.2%	10.3%
Mitral regurgitation	22.2%	19.4%			85.8%	89.7%
Coronary-artery disease						
Three-vessel disease	16.0%	17.7%	14.8%	15.9%	19.8%	24.1%
Previous coronary-artery bypass grafting	4.4%	5.6%	4.0%	6.1%	5.4%	3.8%
Concomitant coronary-artery bypass grafting	49.1%	47.6%	48.9%	48.4%	49.5%	44.6%

have POAF after aortic-valve surgery ($p=0.02$ and $p<0.001$ respectively), but not after mitral-valve surgery ($p=0.21$ and $p=0.45$ respectively). Current smokers were, in both groups, less likely to have POAF ($p<0.001$).

Impact of POAF on long-term survival in patients with aortic-valve surgery and in patients with mitral-valve surgery

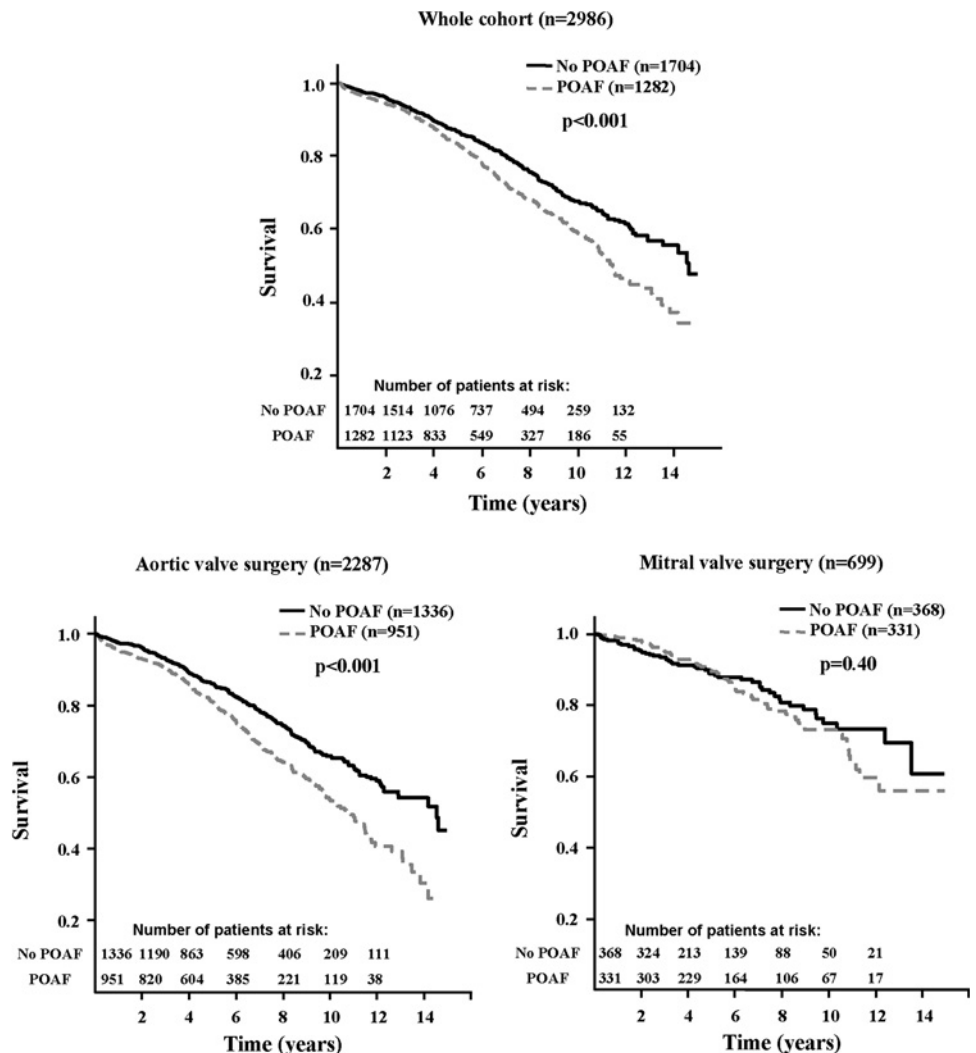
On individual analysis, POAF was associated with reduced long-term survival in patients who underwent AVR ($75.9\pm 1.6\%$ vs $82.6\pm 1.2\%$ at 6 years, $p<0.001$, figure 1), whereas no significant difference was observed in patients with MVR or MVRp ($84.4\pm 2.4\%$ vs $87.8\pm 2.0\%$, $p=0.40$).

In the multivariable analysis (table 2), POAF remained a significant predictor of long-term mortality in patients with AVR (HR=1.22, CI 1.02 to 1.45, $p=0.03$). POAF was not significantly associated with survival in patients with MVR or MVRp (HR=0.87, CI 0.58 to 1.29, $p=0.48$).

DISCUSSION

The major finding of this study is that POAF following valvular surgery is associated with long-term mortality in patients with AVR but not in those with MVR or MVRp.

Figure 1 Long-term survival in patients with or without postoperative atrial fibrillation (POAF) in the whole cohort and in subsets of patients defined according to the type of valvular procedure.



Impact of POAF on long-term survival in patients with valvular surgery

Mariscalco and Engstrom⁶ found no significant association between POAF and long-term survival following valvular surgery, whereas Filardo *et al*⁹ reported that POAF after AVR is significantly associated with long-term mortality independently of the preoperative disease severity. Our results are highly consistent with both studies. Indeed, the association between POAF and survival was only borderline in the whole cohort, largely driven by the significant association with survival in patients with AVR. In patients who underwent mitral-valve surgery, we did not find a significant impact of POAF on long-term survival. Our results thus suggest that the lack of association between POAF and survival reported in the study of Mariscalco and Engstrom might be due to the inclusion of a mixed group of patients who underwent AVR and/or mitral surgery. Furthermore, our study has more statistical power than the two reports previously published. The association reported in the study of Mariscalco and Engstrom (HR=1.21, CI 0.92 to 1.58) which included 995 patients with isolated valvular surgery would probably have been statistically significant in a sample of patients as large as ours.

Table 2 Individual and multivariable analysis of the impact of postoperative atrial fibrillation on survival in the whole cohort and in patients with aortic or mitral-valve surgery

	Whole cohort, n=2986		Patients undergoing aortic-valve replacement, n=2287		Patients undergoing mitral-valve surgery, n=699	
	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
Individual analysis	1.41 (1.21 to 1.63)	<0.001	1.53 (1.30 to 1.80)	<0.001	1.17 (0.81 to 1.68)	0.40
Model 1: adjusted on age, gender and the type of surgical procedure	1.18 (1.01 to 1.37)	0.04	1.23 (1.05 to 1.46)	0.01	0.86 (0.59 to 1.25)	0.43
Model 2: adjusted on age, gender, comorbidities and the type of surgical procedure*	1.17 (1.00 to 1.38)	0.05	1.22 (1.02 to 1.45)	0.03	0.87 (0.58 to 1.29)	0.48

*The Cox model analysis was adjusted for age, sex, diabetes, hypertension, renal failure, chronic obstructive pulmonary disease, previous myocardial infarction, previous stroke, current smoking status, left-ventricular ejection fraction <50% and the type of surgical procedure (concomitant coronary artery bypass grafting, aortic-valve replacement, mitral surgery when applicable).

It remains unclear why the significance of the association between POAF and survival differs markedly according to the type of valvular procedure. In our population, patients with AVR were mainly patients with severe aortic stenosis. As aortic stenosis shares some pathophysiology similarities with CAD, the association of POAF with long-term survival in patients with AVR appears consistent with the significant association between POAF and long-term survival after isolated CABG.^{4–8} The lack of significant association between POAF and long-term survival after MVR or MVRp may be explained, at least in part, by differences in the factors and mechanisms involved in the pathogenesis of POAF in patients with mitral surgery versus patients with AVR and/or CABG. The determinants of POAF in patients with mitral-valve surgery are largely unknown. To the best of our knowledge, there is no specific study focusing on the prediction of the risk for POAF after mitral-valve surgery. On the other hand, inflammation appears to be the key determinant of POAF following CABG.^{11–14} Consistently, pharmacological interventions targeting postoperative inflammation such as glucocorticoids have been shown to reduce the incidence of POAF after CABG.¹⁵ Hence, POAF after isolated CABG and AVR could be a marker of exaggerated inflammatory response to stress, which would in turn translate into a higher incidence of perioperative morbidity and long-term mortality. In contrast, POAF after mitral-valve surgery might be linked to the preoperative features of mitral valve disease (left atrial dilation and hypertension, etc), which are, at least in part, corrected by surgery. This hypothesis has to be tested in future studies. In particular, mechanistic studies specifically focusing on the pathogenesis of POAF after aortic and mitral-valve surgery are needed.

Lack of association even in patients without long-term indication for warfarin

It has been previously hypothesised that POAF might have a weaker effect after valvular surgery because of the indication of lifelong warfarin therapy after mechanical-valve

implantation.⁶ In line with this hypothesis, the long-term anticoagulation instituted at the time of mechanical-valve AVR would prevent embolism related to atrial fibrillation recurrence, thus reducing the impact of POAF on survival. The results of a large observational study recently supported this hypothesis.⁸ In this study, anticoagulant treatment at discharge was associated with decreased long-term mortality in patients who experience POAF after isolated CABG. However, in our cohort, there was no significant interaction between the association of POAF with survival and an indication for long-term warfarin treatment (ie, patients with mechanical valves). This lack of modifying effect of lifetime warfarin treatment would argue against the hypothesis that the lack of impact of POAF after mitral valvular surgery is due to the anticoagulation needed for mechanical valves.

Clinical implications

According to our results, POAF is a significant predictor of long-term survival after isolated or combined AVR. Consequently, patients with POAF after AVR should be considered at increased risk for longer-term events. Hence, additional specific intervention, possibly a closer follow-up, should be considered in these patients.

Limitations

This is a large retrospective monocentre observational study. As in any observational study, causality between POAF after AVR and mortality cannot be ascertained. POAF might be a marker of underlying myocardial disease, or other conditions, which are associated with poorer outcome. Besides, the mechanisms involved in the poorer survival of patients with POAF remain uncertain. Postdischarge atrial fibrillation recurrence could be implicated in this excess of mortality. We unfortunately do not have the data regarding post-discharge arrhythmia recurrences. Because of these limitations, the mechanisms by which mortality is explained by postoperative AF remain speculative, and

the causative link between POAF and survival is still uncertain.

We had no precise information regarding the post-discharge management of POAF. Medications introduced after the episode of POAF may have influenced our analysis. However, as a general rule, only recurrent or sustained episodes of AF after the postoperative period are treated by long-term anticoagulant therapy or antiarrhythmic drugs. Considering the relatively low proportion of patients with persistent AF after the early postoperative period, this residual confounding probably has a minimal impact on the results.

Constant ECG monitoring was performed only during the first 48 h after surgery. Asymptomatic episodes or transient episodes of POAF after the first 48 h after surgery might consequently have been underdiagnosed. This misclassification might have biased the results. Besides, no conclusions can be drawn from our results regarding the significance of asymptomatic POAF.

Conclusion

This study demonstrates that POAF is associated with long-term mortality in patients with AVR but not in those with mitral-valve surgery. The underlying factors involved in the pathogenesis of POAF after mitral-valve surgery may account for this lack of impact of POAF on survival in these patients.

Correction notice The “To cite: ...” information and running footer in this article have been updated with the correct volume number (volume 1).

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Competing interests None.

Ethics approval Ethics approval was provided by the Institutional Review Board of Quebec Heart & Lung Institute.

Contributors NG performed the statistical analyses and drafted the manuscript; JM participated in the interpretation of the data and critically reviewed the manuscript; PP, PV and FD critically reviewed the manuscript and participated in the interpretation of the data; PM participated in the design of the study, interpretation of the data and critical review of the manuscript.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data available.

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

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	P2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	P2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	P3
Objectives	3	State specific objectives, including any prespecified hypotheses	P3
Methods			
Study design	4	Present key elements of study design early in the paper	P3-4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	P3
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	P3-4
		(b) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	P4
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	P3-4
Bias	9	Describe any efforts to address potential sources of bias	P4
Study size	10	Explain how the study size was arrived at	P3
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	P4
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	P4
		(b) Describe any methods used to examine subgroups and interactions	P4
		(c) Explain how missing data were addressed	-
		(d) If applicable, explain how loss to follow-up was addressed	-
		(e) Describe any sensitivity analyses	-
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	P5-16
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	P14
		(b) Indicate number of participants with missing data for each variable of interest	-
		(c) Summarise follow-up time (eg, average and total amount)	P5-16
Outcome data	15*	Report numbers of outcome events or summary measures over time	P16
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	P6
		(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	P6
Discussion			
Key results	18	Summarise key results with reference to study objectives	P7
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	P7-9
Generalisability	21	Discuss the generalisability (external validity) of the study results	P9
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	P9

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

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.