Long-term incidence of myocardial infarct, stroke, and mortality in patients operated on for abdominal aortic aneurysms

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Objective: **The risks of myocardial infarction (MI) and stroke after abdominal aortic aneurysm (AAA) resection are not known. Prophylaxis with aspirin and statins is not generally recommended, although patients with AAAs have an increased prevalence of cardiovascular atherosclerosis. We report the incidences of MI, stroke, and death in an unselected national cohort of patients operated on for AAAs, with the general population as the control group.**

Methods: **In a matched cohort study, 11,094 Danish patients who underwent acute or elective open AAA repair from January 1986 through June 2009 were compared with four randomly chosen age- and sex-matched individuals (controls) from the general population (n = 44,364). Data were collected retrospectively from the Danish Vascular Registry (Karbase), the National Population Registry, and the National Inpatient Registry. The groups were analyzed for the incidences of MI, stroke, and death, with up to 20 years of follow-up.**

Results: **AAA patients had an annual MI incidence of 2.5% (hazard ratio, 2.1; 95% confidence interval [CI], 1.9-2.2) compared with the general population. The annual incidence of stroke was 2.9% (hazard ratio, 1.8; 95% CI, 1.6-1.9), and there was a 2.4-fold (95% CI, 2.3-2.4) increase in the hazard of all-cause mortality compared with the general population.**

Conclusion: **AAA patients of both sexes have a high risk of atherosclerotic events (MI, stroke) and death, so lifelong prophylaxis must be considered from our epidemiologic data. Randomized trials investigating the potential benefit of aspirin and statin therapy in AAA patients are needed. (J Vasc Surg 2012;55:311-7.)**

The common form of abdominal aortic aneurysm (AAA), the nonspecific AAA, is a manifestation of a complex, multifactorial, and degenerative vascular disorder. The pathogenesis, which shares similarities with that of atherosclerosis, is only partially elucidated.[1,2] The overlap of risk factors, such as smoking, hypertension, and hypercholesterolemia, is well known.[3,4] AAA is also associated with the presence of coronary and cerebrovascular atherosclerosis: Only 6% of patients undergoing AAA repair have normal results on coronary angiograms[5]; whereas >55% of patients have signs of myocardial ischemia on stress-induced single-photon emission computed tomography analysis.[6] Up to 20% of these patients have atherosclerotic carotid arteries.[7,8]

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Competition of interest: none.

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The editors and reviewers of this article have no relevant financial relationships to disclose per the JVS policy that requires reviewers to decline review of any manuscript for which they may have a competition of interest.

0741-5214/$36.00

doi:10.1016/j.jvs.2011.08.046

The effect of this atherosclerotic burden on the risks for myocardial infarction (MI), stroke, and all-cause mortality in aneurysm patients is unknown. We undertook this study to establish the incidences of these events from the national databases.

METHODS

The Danish Vascular Registry (Karbase) includes all patients operated on for infrarenal AAA by open surgery since 1986. Registry data utilization has been systematically validated.[9,10] Karbase is crosslinked with the National Population Registry and the National Inpatient Registry, which is used for reimbursement. All citizens in Denmark have a unique, numeric identity code enabling complete follow-up.

Each aneurysm patient undergoing open surgery identified in Karbase from January 1986 through June 2009 was matched as of the day of operation with four individuals from the general population, with matching by age (born within the same month) and sex. All aneurysm patients in the national population registry were excluded before matching. Date of death was recorded for each deceased patient/matched control until end of June 2009. Diagnoses from patients and controls were extracted from the start of the Danish National Inpatient Registry in 1976 through June 2009. In this way, events of MI and stroke before

operation and inclusion in the Karbase material were identified.

The primary end point was the first MI or stroke, or death, each as an individual end point, from the day of operation for AAA repair or day of inclusion for controls. Perioperative events were defined as MI, stroke, or death occurring ≤30 days after operation.

An MI was defined according to the International Classification of Diseases, 8th edition (ICD-8) from 1976 through December 1993 as code 410, and from 1993 onward according to the ICD-10th edition as codes I21-I22. Stroke was defined by ICD-8 codes 430 to 436, excluding transient ischemic attack, and ICD-10 codes I60-I62. Patients who died or were lost due to emigration were censored at this date, except in the analysis for death. The controls for the excluded patients were retained in the analysis.

Statistical analysis. Data are presented as medians with interquartile ranges (IQR) or as counts and percentages. Differences in proportions are shown as odds ratios with 95% confidence intervals (CIs). Survival data were analyzed according to the Kaplan-Meier method, and the log-rank test was used to test for differences in survival from the time of operation. The Cox proportional hazards model was used to assess hazards ratios, unadjusted and stratified by age, sex, and year of operation for AAA and inclusion for controls and adjusted for infarct/stroke between 1976 and operation for AAA or inclusion for controls. Analyses of MI, stroke, and all-cause mortality were conducted separately to obtain the single defined end point, including death or survival. Thus, patients in each analysis were monitored to an event (MI, stroke, death) or were censored if no event had occurred.

Perioperative events were defined as events occurring ≤30 days after operation (patients) or inclusion (control). Survival analysis of patients and controls surviving >1 year was conducted by excluding all patients and controls with an event in the first year. To assess the validity of the proportional hazards assumption, we included AAA as a time-varying covariate in the Cox regression model; that is, we tested for a linear trend in the hazard ratio (HR) corresponding to AAA over time since the operation. Owing to the large number of observations, there was a significant linear trend in the HR in all analyses, and taking that into account only strengthened the conclusions (increased the HR corresponding to AAA). A two-sided $P < .05$ was considered significant. Changes in HRs over time were examined using the Wald χ^2 test. Analysis was performed with STATA 10SE software (StataCorp LP, College Station, Tex) and SPSS 17.0.3 software (SPSS Inc, Chicago, Ill).

RESULTS

The study included 11,094 patients who were matched to 44,376 individuals from the general population. Of these, 11 patients were excluded: three never underwent an operation, and eight emigrants were lost to follow-up, leaving 11,083 patients available for investigation. The respective 12 controls for the three excluded patients were also excluded, leaving 44,364 controls.

Table I. Basic characteristics

Variables[a]	*Patients (n = 11,094)*	*Controls (n = 44,364)*
Female	1940 (18)	7764 (18)
Age, years		
Male	71 (65-76)	
Female	71 (66-76)	
History of		
Myocardial infarction	2143 (19)	3524 (8)
Male	1836 (20)	3224 (9)
Female	307 (16)	300 (4)
Stroke	1134 (10)	2731 (6)
Male	945 (10)	2365 (7)
Female	189 (10)	366 (5)

[a]Categoric variables are presented as number (%); continuous variables as mean (interquartile range).

Operations were for asymptomatic AAAs in 4549 patients, symptomatic AAAs in 2031, ruptured AAAs in 3909, peripheral occlusive disease and AAAs in 351, and for other causes in 243. A total of 1940 patients (18%) were women and 9143 (82%) were men. The median age was 71 years for both sexes (IQR 65-76 years for men and 66-76 years for women; Table I).

MI. Before operation or inclusion, 5667 MIs had occurred since 1976 in 2143 of 11,083 patients (19%) and in 3524 of 44,364 controls (7.9%). This yielded an odds ratio of 2.8 (95% CI, 2.6-2.9; Table I). After operation or inclusion, 4506 MIs occurred: 1223 in patients (11.0%) and 3283 in controls (7.4%), corresponding to an average annual MI event rate of 2.5% in patients and 1.1% in controls. If those with an MI or stroke before operation or inclusion were excluded, the annual event rates of MI were 2.0% for patients and 0.9% for controls, corresponding to respective HRs of 2.3 (95% CI, 2.1-2.5) and 2.4 (95% CI, 2.2-2.6). Kaplan-Meier plots showed that presence of an AAA was associated with a significantly higher incidence of MI (log-rank test $P < .001$; Fig 1, *upper left panel*). The HR for MI was 2.2 (95% CI, 2.1-2.4) and 2.1 (95% CI, 1.9-2.2) after adjustment. Excluding perioperative MIs resulted in similar HRs of 2.0 (95% CI, 1.9-2.1) and 1.8 (95% CI, 1.7-2.0) after adjustment (Table II).

Kaplan-Meier plots stratified by sex showed a significantly higher incidence of MIs in patients with AAAs compared with controls, independent of sex (log-rank test $P < .001$; Fig 1, *lower left panel*). The incidence in female controls was significantly lower than in male controls (log-rank test $P < .001$). The difference in the incidence of MI between male and female patients was not significant (log-rank test $P = .41$). These findings remained unchanged after adjusting for events before inclusion, age, and year in a Cox regression analysis.

Stroke. Before operation or inclusion, 3865 strokes had occurred: 1134 in 11,083 patients (10.2%) and 2731 in 44,364 controls (6.2%), rendering an odds ratio of 1.7 (95% CI, 1.6-1.9). After operation/inclusion, 6048 strokes occurred: 1396 in patients (12.6%) and 4652 in controls

Table III. Stroke after operation/inclusion divided on subtype

Event	*Frequency (%)*	*Event/no event*	*HR (95% CI) (unadjusted)*
All strokes			
AAA patients	12.60	1396/9687	1.9 (1.8-2.0)
Controls	10.50	4652/39,712	
Ischemic stroke			
AAA patients	4.20	466/10,617	1.9 (1.8-2.2)
Controls	3.40	1530/42,834	
Hemorrhagic stroke			
AAA patients	1.60	174/10,909	2.2 (1.9-2.7)
Controls	1.10	492/43,872	
Undefined stroke			
AAA patients	6.80	756/10,327	1.8 (1.6-1.9)
Controls	5.90	2630/41,734	

AAA, Abdominal aortic aneurysm; *CI,* confidence interval; *HR,* hazard ratio.

(10.5%), corresponding to an average annual event rate for stroke of 2.9% in patients vs 1.6% in controls. Excluding those with an MI or stroke before operation or inclusion resulted in an annual stroke event rate of 2.5% for patients and 1.4% for controls, corresponding to HRs of 1.9 (95% CI, 1.8-2.0) and 2.0 (95% CI, 1.8-2.1) after adjustment for age, sex, and year of inclusion. Kaplan-Meier plots showed that the presence of an AAA was associated with a significantly higher incidence of stroke (log-rank test $P < .001$; Fig 1, *upper right panel*). For patients with an AAA, the HR for stroke was 1.8 (95% CI, 1.7-1.9) and 1.8 (95% CI, 1.6-1.9) after adjustment, compared with controls. If perioperative stroke was excluded, the HR was 1.7 (95% CI, 1.6-1.8) and 1.8 (95% CI, 1.7-1.8) after adjustment (Table II). If stroke was divided into ischemic, hemorrhagic, or undefined, the unadjusted HRs between patients and controls consistently showed that aneurysm patients were at an increased risk (Table III).

When stratifying for sex, Kaplan-Meier plots showed that there was a significantly higher incidence of stroke in patients than in controls, independent of sex (log-rank test $P < .001$; Fig 1, *lower right panel*), but the incidence in female controls was significantly lower than in male controls (log-rank test $P < .001$). There was no significant difference in the incidence of stroke between male and female patients with AAAs (log-rank test $P = .86$). Adjusting for events before inclusion, age, and year in a Cox regression had no effect on these findings.

Survival. A total of 6904 patients (62.3%) and 17,437 controls (39.3%) died during follow-up. Kaplan-Meier plots showed that all-cause mortality is significantly increased in patients with AAAs compared with the general population (log-rank $P < .001$, Table IV). This was independent of time periods analyzed (ie, regardless of whether the perioperative 30 days or the first year after inclusion were excluded or not from analysis; Fig 2, *upper panel*).

For AAA patients compared with controls, the HR for all-cause mortality was 2.2 (95% CI, 2.1-2.2) and 2.4 (95% CI, 2.3-2.4) after adjustment. After exclusion of perioperative events, the HR was 1.7 (95% CI, 1.7-1.8) and 1.8 (95% CI, 1.7-1.8) after adjustment (Table II).

Kaplan-Meier plots of survival comparing aneurysm patients vs controls, and stratified for sex, show that the controls, independent of sex, lived significantly longer (log-rank $P < .001$). In patients with AAAs, there was no significant difference in survival between sexes (log-rank $P = .83$). For controls, women lived significantly longer than men (log-rank $P < .001$). These findings were unchanged after adjusting for events before inclusion, age, and year in a Cox regression analysis.

Changes in incidence over time: 1984 to 2009. The adjusted HRs of MI, stroke, and death are shown in Fig 3 and categorized into time periods. The HRs for MI (χ^2 $P = .05$) and all-cause mortality (χ^2 $P = .04$) changed significantly during the observation period, whereas the HRs for stroke (χ^2 $P = .32$) did not.

DISCUSSION

This is the first population-based study,[11] to our knowledge, to determine the risk of MI, stroke, or death in patients with AAAs compared with the general population, with up to 20 years of follow-up. The rate of MI and stroke before operation was greater for patients with AAAs than in an age-matched and sex-matched general population and independent of sex. Even after AAA repair, there was an increased risk of MI, stroke, or death. Previous studies have yielded similar rates of MI (10% to 40%) or stroke (5% to 15%) before AAA repair, just as this study confirms that AAA patients, in general, are at increased risk of death.[12-15]

We found an annual rate of 2.0% for MI and 2.5% for stroke in patients without a previous occurrence of either event. This corresponds well with the rates found in the prospective, international Reduction of Atherothrombosis for Continued Health (REACH) registry study,[16] where 1722 patients (of 68,236 out-patients enrolled) with an established AAA diagnosis had a 1.8% annual rate of MI and a 1.9% annual rate of stroke. This REACH material consisted of patients with established coronary artery disease, cerebrovascular disease, or peripheral arterial disease, or with at least three atherothrombotic risk factors. Our findings also confirmed equally poor survival for men and women with AAAs compared with the general population.[17-19] However, whether women with aneurysms have a higher risk for events than men is controversial. Our study showed no difference in the risk of MI, stroke, or death. Only data on mortality have been reported, whereas two other studies report an increased risk for women.[20,21] These studies were based on United States data and built on data purposed for administrative use. In both studies, where there is a time overlap, it seems that female patients are older and have a higher prevalence of comorbidity. In our study, we found that there was no difference in age at time of operation, but female patients had a lower prevalence of previous MI. This discrepancy between our data and previous reports could explain this previously shown sex difference.

Sanmuganathan et al[22] investigated the risk vs benefit of aspirin in a meta-analysis of four randomized controlled

Table IV. Life tables for crude mortality

Group	*Interval start time (year)*	*Entering interval (No.)*	*Exposed to risk (No.)*	*Terminal events (No.)*	*Cumulative proportion surviving at end of interval*
Controls	0	44,364	39,193	8649	.78
	5	25,372	21,364	5615	.57
	10	11,742	8729	2645	.40
	15	3071	1833	521	.29
	20	73	40	7	.24
Aneurysm patients	0	11,083	10,076	4726	.53
	5	4343	3692	1552	.31
	10	1488	1146	569	.15
	15	235	148	56	.10
	20	5	3	1	.06

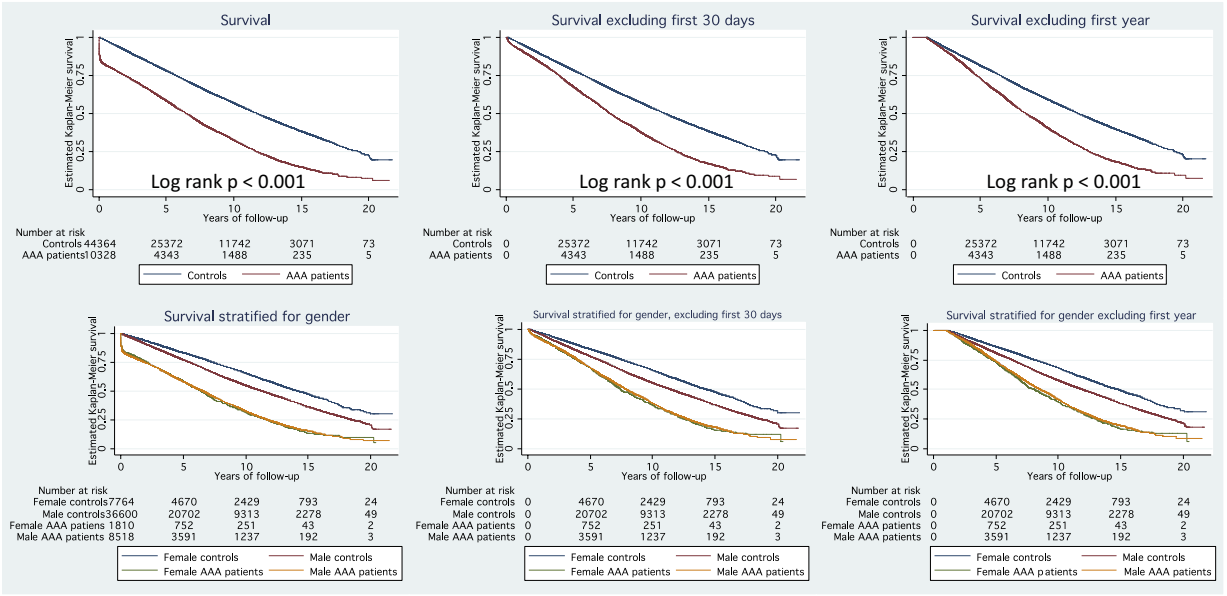

Fig 2. Comparisons of patients operated on for abdominal aortic aneurysm (*AAA*) and controls. **Upper panel,** Follow-up time is from date of operation/matching through June 2009: (*left*) all patients and controls included; (*middle*) excluding all patients and controls with an event ≤30 days of operation or inclusion; (*right*), excluding all patients and controls having an event within the first year. **Lower panel**, Kaplan-Meier plots for patients operated on for AAAs and controls for men and women: (*left*) all patients and controls included; (*middle*) excluding all patients and controls with an event within the first 30 days; and (*right*) excluding all patients and controls having an event within the first 1 year. Follow-up time is from the date of operation through June 2009.

trials of aspirin for primary prevention. They concluded that primary prevention was safe and worthwhile if the coronary risk >1.5% per year, thus rendering a number needed to treat of 44 for preventing one MI in 5 years. Under the current guidelines of the Society for Vascular Surgery (SVS),[23] aspirin is recommended only for AAA patients with pre-existing cardiovascular disease. Our epidemiologic data indicate that the initiation of lifelong aspirin therapy should be considered as soon as a diagnosis of AAA is made, in accordance with the recommendation from the European Society for Vascular Surgery,[24] but to date, no prospective randomized study on the use of aspirin in these patients has been conducted.

The SVS also recommended treatment with statins and angiotensin-converting enzyme (ACE) inhibitors, but evidence is weak and the recommendation is based on the observed inhibition of AAA expansion in small, open-label and retrospective studies.[23] Since the publication of these guidelines, a randomized study with fluvastatin has confirmed the efficacy of statin use in vascular surgical patients in reducing perioperative cardiovascular events,[25] but primary prevention trials indicate that statin treatment only reduces mortality marginally or not at all.[26,27] Nonfatal cardiovascular events are reduced by 15% to 30%,[26,28] but the increased risks of liver dysfunction, myopathy, and acute renal failure remain problematic. The number needed

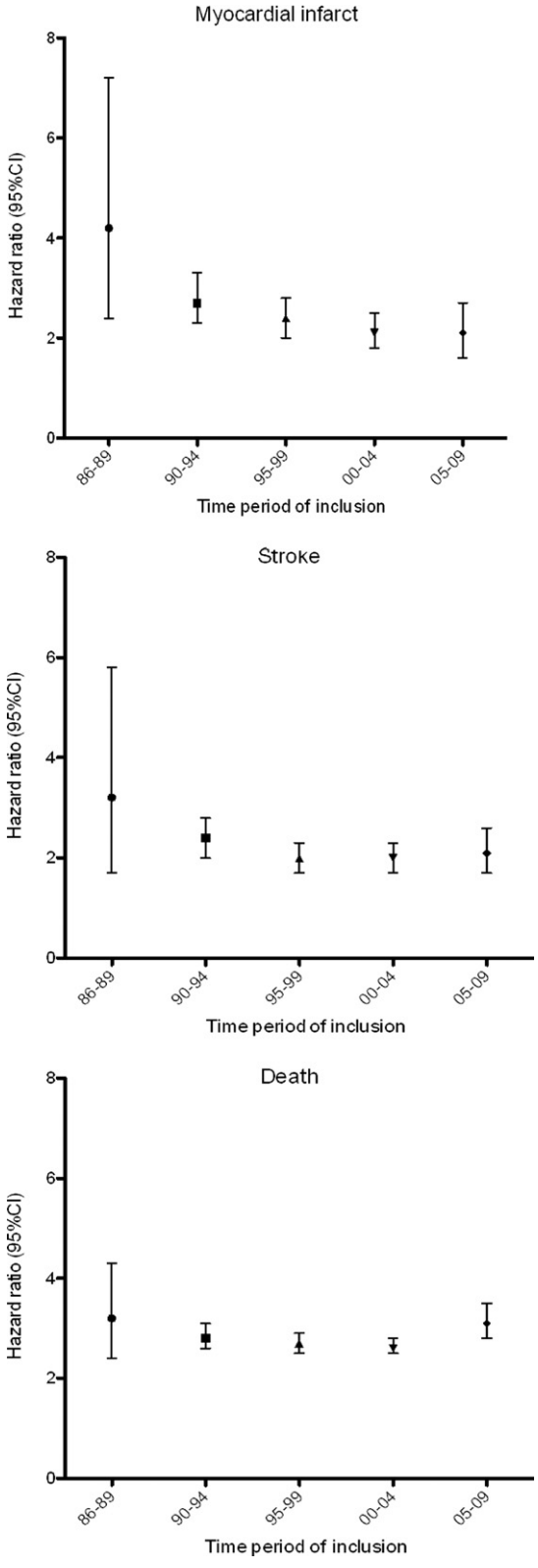

Fig 3. Variation in adjusted hazard ratios during the study period in 5-year intervals: **(top)** myocardial infarction; **(middle)** stroke; **(bottom)**, death.

to treat to avoid one cardiovascular event in 5 years is 37, whereas the number needed to harm is 434 for one acute renal failure in patients with a 20% cardiovascular event risk over 10 years.[29] From these considerations, we conclude that statin therapy should be initiated the day an AAA is diagnosed and maintained lifelong thereafter. This contrasts with the European guidelines,[24] which recommend statin therapy 30 days before aneurysm repair.

ACE inhibitors have also been linked to a reduced growth rate of AAAs[30] and in a retrospective registry study, were associated with a reduction in the risk of rupture.[31] A recent secondary analysis of the United Kingdom Small Aneurysm Trial notes that ACE inhibitors may actually be associated with increased growth of aneurysms.[32] On this basis, ACE inhibitors given for growth reduction cannot be recommended. If, as is often the case, hypertension is present, an ACE inhibitor should certainly be considered and used, given the drug's potential benefits beyond lowering blood pressure.[33]

Our study has a few limitations. Because patients were identified from a registry, missing data entry or failure of data registration could have led to a lack of inclusion of some patients. However, the Danish National Inpatient Registry has been validated, and the accuracy of diagnosis regarding diseases of the circulation is reported to be >75%.[9] On the other hand, this nationwide Karbase database provides an unselected national cohort of all aneurysm patients seen in clinical practice. A strength of our data was the length of follow-up of up to 20 years: follow-up data were lacking for only eight of 11,094 patients.

By only including into our analysis patients who underwent open surgery, the incidence of MI, stroke, and death may be underestimated, but patients with small aneurysms, those not requiring intervention, will theoretically counterbalance this effect. However, because matching was conducted at the day of operation, a bias toward healthier controls was introduced, potentially underestimating the frequency of disease in the healthy controls. Because the patients had a higher frequency of MI and stroke before operation or inclusion, it could be speculated that this explained the observed difference between the groups after operation or inclusion. This is not the case, as seen when excluding all patients and controls with a prior event in the Cox analysis, yielding an HR of 2.4 for MI and 2.0 for stroke after adjustment for age, sex, and year of inclusion.

The data are also limited because the status of comorbidities or use of aspirin and statins for both patients and controls was unknown. This included whether previous cardiac interventions had been performed.

CONCLUSIONS

Men and women with AAAs have an HR of 2 for MI and stroke compared with the general population. These patients also have a significant reduction in life expectancy, despite aneurysm repair. Randomized trials testing the potential benefit of aspirin and statins are needed. Until then, we suggest that aspirin and statin therapy should be

instituted for all patients identified with an AAA in clinical practice as well as in population screening programs.

AUTHOR CONTRIBUTIONS

Conception and design: NE, JL, WP
Analysis and interpretation: NE, JB, JL, BB, WP
Data collection: NE
Writing the article: NE
Critical revision of the article: NE, JB, JL, BB, WP
Final approval of the article: NE, JB, JL, BB, WP
Statistical analysis: NE, BB
Obtained funding: Not applicable
Overall responsibility: NE

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Submitted Jun 23, 2011; accepted Aug 26, 2011.