Quantifying the risk of heart disease following acute ischaemic stroke:   
a meta-analysis of over 50,000 subjects

Trishna Gunnoo, MBBS BSc1; Nazeeha Hasan, PhD1; Muhammad Saleem Khan, MSc1; Julia Slark, PhD2; Paul Bentley, MRCP PhD1; Pankaj Sharma, MD PhD FRCP3,4

(1) Department of Medicine, Imperial College London, UK

(2) Faculty of Medical & Health Sciences, University of Auckland, New Zealand

(3) Ashford & St Peters Hospital, Surrey, UK

(4) Institute of Cardiovascular Research Royal Holloway University of London (ICR2UL)

**Correspondence**:

[pankaj.sharma@rhul.ac.uk](mailto:pankaj.sharma@rhul.ac.uk)

Institute of Cardiovascular Research Royal Holloway University of London (ICR2UL)

Egham

London TW20 0EX

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Abstract

Objective: Following an acute stroke there is a high risk of recurrence. However, the leading cause of its mortality is due to coronary artery disease (CAD) and myocardial infarction (MI) but that risk has not been robustly quantified. We sought to reliably quantify the risk of ischaemic heart disease (IHD) in patients presenting with acute ischaemic stroke (AIS) in the absence of a known cardiac history.

Setting: A meta-analysis study. PubMed, MEDLINE, EMBASE and Google Scholar were searched for potential studies to October 2015. Included studies reported an acute cerebral ischaemic event and followed for CAD or MI within one year in patients without known IHD. Using arcsine transformed proportions for meta-analysis, studies were combined using a generic inverse variance random-effects model to calculate pooled standardised mean difference and 95% confidence intervals. These were interpreted as percentage prevalence of CAD or incidence of MI following AIS.

Results: Seventeen studies with 4869 AIS patients demonstrated a mean average of asymptomatic CAD in 52%. Anatomical methods of CAD detection revealed a prevalence of asymptomatic ≥50% coronary stenosis in 32% (95% CI 19-47%; p<0.00001). Eight studies with 47229 ischaemic stroke patients revealed an overall risk of MI in the year following stroke of 3% (95% CI 1-5%; p<0.00001) despite the absence of any cardiac history.

Conclusions: One-third of ischaemic stroke patients with no previous cardiac history have more than 50% coronary stenosis and 3% are at risk of developing MI within a year.Our findings provide a reliable quantitative measure of the risk of IHD following AIS in patients with no previous cardiac history.

Article summary

Strengths and limitations of this study

We study the risk of heart disease following a stroke in those patients with no previous cardiac history. This study is the largest of its kind and, by bringing together multiple datasets, robustly quantifies the risk of heart disease following stroke. As with all meta-analyses the main limitation of this work relates to publication bias.

* Most stroke patients die of heart disease
* One in three ischaemic stroke patients with no previous cardiac history have more than 50% coronary stenosis
* 3% are at risk of developing MI within a year of their stroke
* Stroke patients need to be screened for silent heart disease and appropriate and aggressive management of total cardiovascular risk factors is required

**Introduction**

Cardiovascular disease is the single leading cause of mortality worldwide,(1) costing the UK economy £19 billion every year, with The National Health Service in England spending around £6.8 billion on CVD in 2012/2013.(2) Given our ageing population and global increase in non-communicable diseases, the burden of heart disease and stroke are becoming an ever increasing public health issue.(3)

Atherosclerosis as a systemic disease process; common risk factors and pathophysiology exists between ischaemic stroke, coronary artery disease (CAD) and myocardial infarction (MI).(4) Any acute atherosclerotic event increases the risk for another in the same or different vascular bed(5). Following an acute ischaemic stroke (AIS) there is a high short-term risk of recurrence; however, the leading cause of mortality in these patients is MI.(4,6,7)

A number of studies have evaluated the relationship between stroke and MI yet show varying results on the rate of subsequent cardiovascular events(6,8,9) with wide discrepancy in the observed prevalence of asymptomatic CAD ranging 15-80% following AIS.(10,11) While it is probable that those with an established history of IHD will account for the majority of subsequent coronary events following AIS, the true risk of CAD and MI in stroke patients in the absence of previous cardiac history is unclear.

In an attempt to provide clarity and quantification on this issue, we conducted a systematic review and meta-analysis to determine the prevalence of asymptomatic CAD and incidence of MI in AIS patients in the absence of previous cardiac disease. To the best of our knowledge, this is the largest such study conducted to-date.

Methods

Data Sources

A search was performed using electronic databases PubMed, MEDLINE, EMBASE and Google Scholar, to identify all relevant published studies up to October 2015. The search strategy included keywords with synonyms and MeSH terms: [stroke] OR [cerebrovascular accident] OR [CVA brain] OR [cerebral infarction] OR [transient ischaemic attack] OR [transient ischemic attack] OR [TIA] OR [Cerebral Infarction] OR [Stroke] OR [Brain Ischemia] OR [Ischemic Attack] OR [Transient], along with [asymptomatic coronary artery disease] OR [asymptomatic CAD]; [asymptomatic coronary heart disease] OR [asymptomatic CHD], along with [subclinical ischaemic heart disease] OR [silent myocardial infarction] OR [silent MI] OR [silent myocardial ischaemia]. Search criteria were limited to humans. All terms where then subjected to interaction with each other with Boolean operators *AND* or *OR*. Foreign language literature was included and papers translated where necessary. Manual searches identified additional studies from the references of electronically identified studies.

Study Selection

Studies were selected TG, NH and JS if they fulfilled the following inclusion criteria: 1) acute onset of stroke or TIA; 2) lesion confirmed by brain imaging (CT/MRI) or at autopsy; 3) investigations for CAD with acceptable levels of sensitivity and specificity;(12) 4) diagnosis of MI according to criteria of the third universal definition proposed by international expert consensus,(13) and; 5) follow-up data for CAD or MI up to one year from stroke onset.

Studies were excluded if: 1) age <18 years; 2) haemorrhagic stroke; and 3) previous history of IHD (CAD or MI), unless subgroup data was presented for extraction. Due to the low specificity of ECG to detect ischemia, investigations using ECG or exercise ECG alone were excluded, except when in conjunction with another modality of testing such as troponin.(14) Where duplicate studies were identified, data from the latest dataset was used. In an attempt to enhance the quality of our analyses only studies that recruited a minimum of 50 participants were included for final analysis. Studies with a higher minimum number of participants were more likely to be conducted in a systematic manner with a likely more reliable result. (15) We used the STROBE(16) checklist to assess for the inclusion of cohort studies, MOOSE(17) criteria for the reporting of observational studies and the PRISMA statement to guide our reporting of the meta-analyses.(18)

Data Extraction

Data extraction was undertaken independently by two investigators (TG and JS) and any disagreements were resolved by consensus or by the opinion of a third reviewer. For each selected study, the total population of ischaemic stroke patients without a history of IHD and the proportion with asymptomatic CAD or MI were extracted. Additional information on study design, method of CAD/MI diagnosis, as well as baseline characteristics such as mean age, sex, ethnicity and the presence of risk factors for cardiovascular disease was documented.

Statistical Analysis

As this was a one-sided investigation without a comparison group, a double arcsine transformation was used for proportion meta-analysis.(19,20) For each study, the proportion of stroke patients who were positive for asymptomatic CAD or silent MI from the total population of patients was recorded. The proportions P within the populations were calculated by dividing the number of positive events by the number of stroke patients without known heart disease.

The standardised mean difference (SMD) and standard error for each proportion was then calculated: Standardised Mean Difference (SMD) = 2 x arcsin (√P) and the Standard Error (SE) was generated by 1/√n. The results were combined using a generic inverse variance random-effects model (DerSimonian and Laird) to calculate weighted pooled SMD and 95% CIs using Review Manager SMD = (A).(21) The concluding result was interpreted as percentage prevalence of CAD or incidence of MI by transforming data back to original scale to give pooled percentage prevalence: % Prevalence = (Sin x (A/2)2) x 100.(22)

To accurately determine the prevalence of asymptomatic CAD, meta-analysis was restricted to studies reporting more sensitive methods of CAD investigation and significant coronary artery occlusion (≥50% stenosis). Tests for heterogeneity and sensitivity analysis were performed by systematically and iteratively by removing one study at a time and re-running the model to determine the overall effect size. Based on the statistical method used, it was not possible or appropriate to assess for publication bias in this study.(20)

**Table 1:** Included studies and their characteristics

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **STUDY** | **Location** | **Male  (%)** | **Mean Age** | **Ischaemic Event** | **Method of Investigation** | **N** | **Asymptomatic CAD** | | | **MI** | |
| n | % | >50%  stenosis | n | % |
| **Gongora-Rivera  2007 MASS** (23) | France | 55 | 60 | fatal stroke | Autopsy: plaque, ischaemia, MI necrosis/fibrosis >1cm | **188** | 131 | 70 | 29% | 59 | 31 |
| **Amarenco 2011  AMISTAD** (24) | France | 72 | 62 | stroke | Coronary angiography | **315** | 195 | 62 | 26% | - | - |
| **Ahn 2013** (25) | Korea | 65 | 66 | stroke/TIA | CTCA | **314** | 145 | 46 | 46% |  |  |
| **Calvet 2010 PRECORIS** (5) | France | 70 | 63 | stroke/TIA | CTCA | **274** | 133 | 49 | 18% | - | - |
| **Cha 2013** (26) | Korea | 64 | 63 | stroke/TIA | CTCA | **1733** | 1220 | 70 | 33% |  |  |
| **Cho 2011** (27) | Korea | 60 | 68 | 1st stroke | CTCA | **274** | 158 | 58 | 22% | - | - |
| **Hoshino 2008** (28) | Japan | 72 | 66 | 1st stroke | CTCA | **100** | 36 | 36 | 36% | - | - |
| **Iwasaki 2015** (11) | Japan | 67 | 63 | stroke | CCS (calcium score) | **151** | 37 | 25 | 25% | - | - |
| **Kim 2011** (29) | Korea | 70 | 67 | stroke | CTCA | **200** | 161 | 81 | 36% | - | - |
| **Seo 2008** (30) | Korea | 63 | 68 | stroke | CTCA | **71** | 18 | 25 | 25% | - | - |
| **Yoon 2010** (31) | Korea | 50 | 71 | stroke/TIA | CTCA | **175** | 105 | 60 | 21% | - | - |
| **Arauz 2010** (32) | Mexico | 69 | 62 | 1st stroke | Stress SPECT | **125** | 40 | 32 | - | - | - |
| **Chimowitz  1997** (33) | USA | 64 | 61 | stroke/TIA | Stress thallium  myocardial scintigraphy | **65** | 23 | 35 | - | - | - |
| **Di Pasquale**  **1988** (34) | Italy | 73 | 56 | stroke/TIA of  carotid system | Exercise thallium  myocardial imaging | **140** | 33 | 24 | - | - | - |
| **Urbinati 1994** (35) | Italy | 71 | 64 | stroke/TIA of  carotid system | Exercise thallium  myocardial scintigraphy | **121** | 28 | 23 | - | - | - |
| **Nighoghossian**  **2006** (10) | France | 80 | 59 | stroke | Stress echo | **60** | 9 | 15 | - | - | - |
| **Leys 2006  DETECT** (36) | France | 74 | 69 | stroke | ECG + echo | **563** | 64 | 11 | - | - | - |
| **Gattringer  2014** (37) | Austria | 53 | 74 | stroke/TIA | Troponin + ECG | **37214** | - | - | - | 181 | **0.5** |
| **Jensen 2007** (38) | Denmark | 52 | 75 | stroke | Troponin + ECG | **244** | - | - | - | 7 | **3** |
| **Lee 2008** (39) | Korea | 56 | 67 | stroke | Troponin + ECG | **1247** | - | - | - | 8 | **1** |
| **Liao 2009** (40) | Canada | 52 | 72 | stroke | Troponin + ECG | **7199** | - | - | - | 129 | **2** |
| **Mathias 2014** (41) | USA | 52 | 64 | stroke | Troponin + ECG + echo | **323** | - | - | - | 7 | **2** |
| **Prosser 2007  VISTA** (42) | Canada Germany  Sweden  UK, US | 49 | 73 | stroke | Cardiac mortality &  serious cardiac adverse  events | **458** | - | - | - | 33 | **7** |
| **Song 2008** (43) | Korea | 56 | 72 | stroke | Troponin + ECG | **356** | - | - | - | 0 | **0** |

**Results**

1308 records were identified and following screening for exclusions a total of 24 studies met our inclusion criteria (Figure 1). Seventeen studies with 4869 acute ischaemic stroke/TIA patients investigated for asymptomatic CAD and eight studies with 47229 patients’ demonstrated risk of MI following ischaemic stroke in those without a prior cardiac history (Table). 23 studies recruited patients prospectively.

Prevalence of Asymptomatic CAD

There were a similar proportion of males to females in each of the included studies, with average of 55% male and mean age of 66 years. With the exception of a single autopsy study(23) where the median time between stroke and death was 12 days (interquartile range, 5-32 days), all studies recruited strokepatients within 10 days. Whilst most studies consisted of ischaemic stroke of atherosclerotic aetiology, three studies excluded cardio-embolic stroke(5,10,32) and only one study included those with suspected cardioembolism.29  Three studies looked exclusively at first ischaemic stroke.(28,32,44) There was limited data available for the risk factors present in patients found to have asymptomatic CAD; where evaluated, there were varying levels of all risk factors, except hypertension which coexisted in 42-67% of stroke patients and as high as 96% in one study.(24) Due to the variety of methods of investigation with varying levels of sensitivity, and wide range of results, it was not appropriate to perform meta-analysis on all 17 studies but the mean average of asymptomatic CAD was 52%.

Meta-analysis was performed on 11 studies using coronary angiography, CTCA (Computed Tomography Coronary Angiography), CCS (Coronary Calcium Score) and autopsy as more sensitive investigations for asymptomatic CAD in AIS patients. This revealed for any degree of coronary plaque a pooled SMD of 1.41 (95% 1.16-1.66; T2=0.27; I2=99%; p<0.00001) equivalent to a prevalence of 53% (95% CI 43-63%) (Figure 2). A pooled SMD of 1.20 (95% CI 0.89-1.51; T2=0.27; I2=99%; p<0.00001) was observed (Figure 3) equivalent to a prevalence for ≥50% asymptomatic coronary stenosis of 32% (95% CI 19-47%). Significant heterogeneity was observed, which was unchanged following iterative analysis, removal of patients with TIA(5,45) and a unique autopsy study conducted prior to the year 2000.(23) Prevalence of any degree of coronary artery stenosis was not statistically significant, most likely due to high variance in the studies analysed. However, removal of non-Caucasian populations (11,25-31,46) yielded a statistically significant pooled SMD of 1.03 (95% CI 0.88-1.17; p=0.01), equivalent to an asymptomatic CAD prevalence of 24% (95% CI 18-30%).

Incidence of Myocardial Infarction

With the exception of one study,(39) all eight studies prospectively recruited stroke patients. The majority of studies were based in predominately Caucasian populations from across Europe, Canada and the USA. The largest observational study included a total of 37 214 participants from multiple stroke centres across Austria.(37) For each study there were similar demographics including a balanced proportion of males to females, with an average of 53% males, and a mean age of 70 years old. There were limited data evaluating risk factors in those patients with MI which was diagnosed within three months of the acute ischaemic stroke and, in most studies in-hospital. A pooled SMD of 0.35 (95% CI 0.24-0.46; T2=0.02; I2=98%; p<0.00001) equivalent to a total MI incidence of 3% (95% CI 1-5%) in stroke patients with no previous cardiac history (Figure 4).

**Discussion**

This study which quantities the risk of IHD following ischaemic stroke revealed that over half of such stroke patients have evidence of asymptomatic coronary plaque and one in three patients has an occlusion of clinical significance (>50% stenosis). Given the strong evidence linking coronary artery stenosis >50% to the high risk of acute MI,(47,48) and our findings that 3% of ischaemic stroke patients suffer from MI within one year, it is clear that many more individuals with no prior history of IHD may be at risk of MI than previously appreciated.

Our results are supported by previously published data that demonstrate a high burden of coronary plaque even when there is no previous evidence of systemic disease. The Asymptomatic Myocardial Ischemia in Stroke and Atherosclerotic Disease (AMISTAD) study set out to determine whether asymptomatic coronary atherosclerosis predicts a higher risk of major vascular event on stroke patients, and found that from baseline diagnosis of asymptomatic CAD, the two year Hazard Ratio of stroke patients developing ≥1 vessel disease (coronary stenosis >50%) was 3.43 (95% CI 1.48-7.93).(24) In the Multiple Atherosclerosis Site in Stroke (MASS) study, stroke patients with no atherosclerotic plaque in the cerebral arteries demonstrated prevalence of coronary plaque as high as 51%.(23) Thus, despite the limitations in predicting the presence of asymptomatic CAD based on the detection of extra-cardiac atherosclerosis, an association exists and there is a significant global vascular burden in patients with stroke.

There is limited data to compare our results with the prevalence of subclinical atherosclerosis in an asymptomatic population of similar age. A Norwegian study in 1852 asymptomatic male office workers found 2.7% had at least one coronary stenosed artery ≥50% by coronary angiography.(49) A more recent European study with 244 asymptomatic patients undergoing CTCA found a 5% prevalence of obstructive CAD requiring further investigation.(50) One larger Korean study with 6311 asymptomatic patients found a prevalence of coronary atherosclerosis >50% stenosis in 9% by CTCA.(51) Thus, there is considerable difference in cardiac risk between the asymptomatic population and stroke patients, with a prevalence gap, from these few studies, between 23-29%.

Following stroke/TIA patients with no known IHD history the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial demonstrated not only the high risk of cardiac events but also supports the benefits of statin therapy in the treatment of stroke when considering this ischaemic event as a coronary risk equivalent.(52) In determining the beneficial effects of blood pressure reduction, the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) found that 1.2% of ischemic stroke patients went on to have non-fatal MI or death accountable to CHD, concluding that secondary prevention should target not only the cause of the original event but also mixed vascular risk factors.(53) The results from an older meta-analysis, (6) calculated a 2.2% annual risk of MI after ischaemic stroke/TIA, although it failed to estimate the risk of MI according to previous cardiac history. Our results support proposals of the American Heart Association and American Stroke Association in recommending that stroke patients be considered for further cardiac evaluation based on their individual cardiovascular risk factor profile.(53,54)

Despite our efforts, no meta-analysis is free from publication bias. A considerable level of heterogeneity in our analyses reflects clinical differences between the studies with inclusion of different subtypes of ischaemic event partly accounting for some of the observed variation. In particular, the different investigations to determine extent and severity of coronary stenosis (e.g. formal coronary angiography, CT angiogram, coronary calcium scores) may not be equally comparable in terms of their assessment of stenosis. Although we categorise the data by cardiac investigation in our Table, the overall pooled result is subject to this limitation. To limit the effect of major differences occurring in clinical cardiovascular care, studies prior to year 2000 were removed. We attempted to improve quality control by incorporating studies with at least 50 subjects. These larger studies tend to be better conducted. Study populations located worldwide demonstrated the global burden of asymptomatic disease; however, our results should be extrapolated to other ancestral populations with caution.

We demonstrate up to a third of ischaemic stroke patients with no previous cardiac history have more than 50% coronary stenosis and 3% are at risk of developing MI within one year following their stroke even in the absence of any previous cardiac symptoms. The cardiac risk posed to ischaemic stroke patients is substantial even in the absence of a prior IHD history.

**Author contributions:**

PS conceived the idea and designed the overall strategy. He critically revised the first and all subsequent drafts and gave final approval to submit. He agrees to be accountable for all aspects of this work.

TG, NH and JS undertook the preliminary searches and designed the search criteria. TG wrote the first draft and gave final approval to submit. They both agree to be accountable for all aspects of this work.

NH, PB and MS undertook independent statistical analysis of the data with each providing their expert statistical advice. They critically reviewed and revised all manuscript drafts, particularly in relation to the statistical aspects, and all agree to be accountable for all aspects of this work.

**Competing interests:** None.

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