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Risk of Further Acute Vascular Events Following an Initial Myocardial Infarction or Stroke

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EXECUTIVE SUMMARY

The prevalence of cardiovascular disease is increasing, as is the number of older people driving, and this will mean the number of drivers on the road who have had a myocardial infarction (MI) or stroke will increase. In order to help licensing authorities make fairer judgements in relation to a driver’s right to hold a licence, there is a need to examine the existing evidence quantifying the risk of a further vascular event or death for drivers following an MI or stroke.

We performed a systematic review of papers with follow-up data of people who have had at least one MI or stroke. We identified 572 English language papers (134 accepted for meta-analysis) related to survival following a primary MI event and 260 English language papers related to survival following a stroke (117 accepted for meta-analysis). An initial pilot meta-analysis showed that the year of patient recruitment into the study had a significant effect on survival, with more recent studies having improved survival compared to cohorts recruited in the late 1980s or early 1990s. Therefore, only studies conducted on patients from 1995 onwards were included.

Many of the studies published recently were on fewer than 500 patients and therefore because of small numbers would have a great deal of natural variation in survival rates. There were different selection criteria (i.e. studies had large differences in ratios of male/female, diabetes/non-diabetes, smokers/non-smokers, average age, treatments under investigation) and were in general too heterogeneous to be combined. There were few studies at each time point examined (6 months, 1 year, 2 years, 3 years, 4 years and 5 years) and many studies were based on selected groups of patients meeting specific criteria to enter clinical trials. In terms of MI, it appears that developments in treatment have been so rapid that estimates of survival based on the current published literature will be an underestimate of the true survival today. In terms of stroke, there have not been enough major trials with consistent selection criteria to reliably estimate survival following stroke. Patients who have a stroke have different survival rates based on their baseline characteristics and treatments, and stratification of patients would be needed to determine risk of adverse outcomes (i.e. death, stroke and MI) for individuals. However, meta-analysis of existing studies was not able to stratify patients as there were too few studies and too many variables (e.g. age, sex, type of stroke (ischemic, haemorrhagic, TIA, cerebral aneurysm, mixed cohort and acute stroke), diabetes, smoking history, treatments offered, year of stroke, country of study).

Very broad estimates of risk of further event would be: 2–10% for a re-infarction within 6–24 months after a primary MI, and 1% rate of stroke over a 12 month period after an MI. A risk of an MI following a stroke would be approximately 2–4% over 24 months and a risk of a further stroke (after a primary stroke) would be 6–10% over 12 months. Risk of death after an MI could be approximately 4%–6%
over 6–24 months and risk of death after a stroke could be 5%–13% over 6–24 months.

An alternative way to examine risk and stratify MI and stroke patients for their future risk of further events would be to use routine data such as the Myocardial Infarction National Audit Project (MINAP) and routine hospital admissions data such as HES (Hospital Episode Statistics) or PEDW (Patient Episode Database Wales). These databases could be used to examine survival in all the patients in England and Wales with an MI or stroke and would provide enough numbers of patients for reliable stratification of at-risk groups and for real-time follow-up of survival today and in the future as treatments improve.
1 BACKGROUND

In recent years, the Drivers’ Medical Group of the Driver and Vehicle Licensing Agency (DVLA) has seen an increased number of medical enquiries which require decisions to withdraw or maintain driving licences from people who have specific medical conditions that are thought to impair safe driving. At the same time, national and international researchers have been involved in improving the evidence base for identifying those drivers at higher road safety risk because of a specific medical condition.

Although some evidence is available at present, questions regarding the stratification of road safety risk in a specific condition and the factors that predict such risk categories (and therefore help licensing authorities make better, fairer judgements in relation to a driver’s entitlement to hold a licence) remain partially unanswered or have yet to take into account recent developments in diagnosis and treatment.

Acute vascular events are examples of medical conditions that come to the attention of the DVLA medical advisers, and it is possible that the road safety risk varies with the specific type and characteristics of the vascular event a person has suffered. Recent longitudinal studies of subsequent morbidity may be able to provide us with the risk of future acute vascular events of the same, or of another type, and the factors that predict this risk and enable us to improve licensing decisions.

Cardiovascular events are likely to become the number one world killer in the 21st century and it is the main cause of death in western Europe and the USA. As the prevalence of cardiovascular events increases, the number of drivers on the road who have had an event will increase. In order to improve decision-making in relation to driving safety risk in this group for drivers, there is a need to identify all the available evidence, appraise its quality and combine appropriate studies to properly support decision-making in terms of risk of a further vascular event in an individual with a diagnosis of vascular disease. This will involve both stratifying people with specific types of acute vascular events in terms of their risk of future events and reviewing the evidence on the value of various clinical tests in stratifying the risk of subsequent events.
2 METHODOLOGY

2.1 Objectives

The aim of this systematic review is to establish a resource of the probabilities of occurrence for a further vascular event over varying time periods after the initial MI or stroke, which can be used to assess an individual’s risk.

The primary question to be answered by this review of MI and stroke is therefore:

- What is the risk of a further vascular event (defined as: death, recurrence of a stroke, an MI, associated surgery) following a primary MI or stroke at time points: 6 months, 1 year, 2 years, 3 years, 4 years and 5 years and 10 years?

Secondary questions include:

- Is this a suitable means for stratifying drivers who have experienced an MI or stroke in terms of their risk of future events?

2.2 Method

A systematic review methodology was employed. A project advisory board including stakeholders from the Department for Transport, the DVLA and the Secretary of State for Transport’s Expert Advisory Panel on driving and disorders of the cardiovascular system has been set up at the beginning of the study. The group was consulted about the coverage of the literature review and the search terms to be used in the review.

2.2.1 Criteria for considering studies for this review

We included in our review studies that fulfil the following criteria:

Types of studies

(1) Prospective, longitudinal, cohort, incidence or follow-up.

(2) Controlled trial (randomised or quasi-randomised or Phase I, II, III or IV study, cross over trial, or blinded).

(3) Observational, non-experimental.

Types of participants

Adults (aged 18+), men and women who have had a previous MI or stroke.
Types of outcome measures

(1) Mortality
(2) MI (non-fatal and fatal)
(3) Stroke (non-fatal and fatal)
(4) Surgery
(5) Heart failure/ischemia (in the case of a primary MI)

2.2.2 Search strategy

The following electronic databases were searched for the years of 1990–2004: Cochrane Database of Systematic Reviews (complete reviews and protocols), Database of Abstracts of Reviews of Effects (DARE), the Cochrane Controlled Trials Register (CCTR/CENTRAL) on the Cochrane Library, NHS Economic Evaluation Database, HTAD (Health Technology Assessment Database), EMBASE, MEDLINE, National Research Register until 2000, SIGLE, CINAHL, Dissertation Abstracts, ISI Science Citation Index, PREMEDLINE, BIDS, British Nursing Index, Applied Social Sciences Index and Abstracts Database (ASSIA), Caredata abstracts, Social Services Abstracts, Web of Knowledge, HMIS.

MEDLINE was searched again between the dates of June 2004–March 2005 to obtain the most up-to-date manuscripts.

The reference list of identified relevant studies and reviews was checked to obtain any missing relevant manuscripts; no language restrictions were applied to the search strategy.

The following detailed strategy using a combination of MeSH terms and text words was used to search the databases:

heart attack OR angina pectoris OR coronary heart disease OR myocardial infarction OR post myocardial infarction OR acute coronary syndrome OR percutaneous coronary intervention OR coronary artery bypass grafting OR heart valve replacement OR atrial fibrillation OR cardiac dysrhythmia OR cardiac pacemaker OR implantable defibrillator OR cardiovascular disease OR heart failure OR cardiomyopathy OR myocarditis OR pulmonary heart disease OR prinzmetal angina OR unstable angina OR angina microvascular OR microvascular angina OR arrhythmia OR atrial flutter OR bradycardia OR cardiac complexes OR heart block

1 The start year of 1990 was set on the basis that, prior to this, the clinical management of stroke and MI was sufficiently different to that in more recent years to render any follow-up data irrelevant today.
OR long QT syndrome OR pre-excitation syndromes OR sick sinus syndrome OR tachycardia OR ventricular fibrillation OR heart arrest OR myocardial ischemia

OR

stroke OR transient ischemic attack (TIA) OR ischemic stroke OR carotid artery stenosis OR primary intracranial haemorrhage

OR

cardiac troponin OR exercise test OR ECG OR T-wave alternans OR heart rate variability OR ambulatory ECG OR echo cardiography OR myocardial perfusion scan OR coronary angiography OR electrophysiological study OR carotid ultrasound OR carotid intima medial thickness OR pulse wave velocity OR abdominal ultrasound OR barbel index OR ankle brachial pressure index OR aspirin OR warfarin or anticoagulants OR antiplatelet OR prosthetic heart valve OR antithrombotic OR calcium antagonists OR cardioselective beta-blockers OR cognitive rehabilitation OR dipyridamole OR electrical cardioversion OR endovascular stents OR exercise OR fibrinogen OR fibrinolytic OR heparin OR serum lipids OR prostacyclin OR diet OR smoking OR thrombolysis

OR

alagille syndrome OR aortic coarctation OR arrhythmogenic right ventricular dysplasia OR cor triatriatu OR coronary vessel anomalies OR crisscross heart OR dextrocardia OR ductus arteriosus OR ebstein anomaly OR eisenmenger complex OR heart septal defects OR hypoplastic left heart syndrome OR leopards syndrome OR levocardia OR marfan OR tetalogy of fallot OR transposition of great vessels OR tricuspid atresia OR truncus arteriosus OR aortic root replacement

AND

survival OR sudden death OR syncope OR road traffic accident OR cardiac arrest OR risk OR probability OR prognosis OR future event

AND

cohort OR prospective OR longitudinal OR controlled trial OR randomised OR quasi-randomised trial OR follow-up OR incidence OR longitudinal OR clinical trial OR therapeutic trial OR intervention OR phase I study OR phase II study OR phase III study OR phase IV study OR cointervention OR cross over trial OR double blind OR double masked OR triple blind OR triple masked OR economic analysis OR epidemiology OR observational OR non-experimental OR systematic review OR meta analysis
AND
recurrence OR relapse OR secondary event

NOT

Reynaud OR depression OR thalassemia OR renal failure OR asthma OR leptospirosis OR bladder OR rheumatoid arthritis OR osteoporosis OR parkinsons disease OR sleep apnoea OR malaria OR dementia OR kawasaki OR cancer OR migraine OR incontinence OR liver failure OR pulmonary fibrosis OR systemic lupus OR lymphoma OR common cold OR newborn infant OR syphilis OR pregnancy OR erectile dysfunction OR glaucoma OR fetal OR preterm OR neonates OR young infants OR neonatal OR varicose veins OR multiple sclerosis OR liver disease OR preterm

2.2.3 Methods of review

All citations identified by the search strategy were screened by title by one of the reviewers. Every 50th included citation and every 20th excluded citation was checked by another reviewer for validation. The criteria to screen titles had been developed by two independent reviewers. The titles were rejected if the reviewer could determine that:

– there was no primary vascular event
– there was no longterm follow-up lasting more than 30 days
– the article was a case report or case series
– the article dealt with animal subjects
– the article concerned children or infants (i.e. people below the age of 18) with no follow-up to adult years

When a title could not be rejected with certainty the abstract was obtained.

Abstracts were reviewed by two of the reviewers and every 50th included and 20th excluded was checked by another reviewer.

The exclusion criteria were:

• evaluations of efficacy and safety of treatment (without prognosis/recurrence data), no prior vascular event, predicting effect of a treatment or understanding mechanism of action of a treatment;
• carditis;
• subarachnoid haemorrhage;
- pulmonary embolism/vascular diseases;
- case reports;
- no longterm data;
- in-hospital follow-up only;

All selected citations were obtained in full manuscript form and were sorted into categories according to primary event (MI, stroke, angina, arrhythmia, TIA, intermittent claudication, carotid artery disease). All review articles were rejected to take to the next screening stage, but references were reviewed for identification of studies which may have been missed.

The remaining primary studies were reviewed in detail by three reviewers independently and data was collected using adapted versions of the Health Evidence Bulletins Wales data extraction forms.

**Data collected included:**

1. Follow-up from hospital following MI/stroke OR follow-up from hospital following surgery for the initial event. Excluded were trials recruiting patients following an MI/stroke, but not recruited in hospital directly following the event.

2. Raw figures available at specific time points OR averaged figures were used. For example variable follow-up results might be recorded as mortality rate X% at average follow-up of one year (+/− 5 months).

3. Study group name or database used (e.g. GUSTO trial or NOMASS trial or South London Community Stroke Register or OMID Database). The study group title was recorded in order to identify trials for which reports of the same patients might be made in multiple publications. In this way only one ‘copy’ of the follow-up of patients was used.

4. Patient characteristics (e.g. average age within the study, sex ratio within the study, percentage with diabetes within the study and (for stroke papers only) percentage smokers within the study population).

5. Country where patients were selected.

6. Year when patients were first recruited for study.

7. Time period of recruiting patients (e.g. 2001–2002 recruitment into study).

8. Treatments under evaluation within the study.

9. Numbers lost to follow-up.

10. Evidence of biased selection or follow-up of participants.
2.3 Data synthesis

Primary measures of interest were prognosis in terms of mortality, subsequent fatal and non-fatal MI and stroke or surgery following an MI/stroke. We extracted the numbers of participants experiencing an outcome at time points 6 months, 1 year, 2 years, 3 years, 4 years and 5 years and 10 years.

A meta-analysis using a random effects model was performed using log odds of event at a specific time point for unselected samples followed from MI/stroke. Meta-regression was used to control for sex, age, smoking history (in the case of stroke patients), year of recruitment and country of study.

2.3.1 Description of studies

Following the electronic searches, 15,328 titles were screened. Of these 9,691 appeared relevant to review as abstracts. The abstract selection identified 3,433 to order as full text papers and to be assessed for inclusion. 2,123 were included to continue to extraction of data (21 needing a second reviewer opinion). Of these there are 490 regarding MI, 361 regarding atrial fibulation or arrhythmia, 135 regarding angina, 535 a mixture of the above heart-related events, 250 other heart-related events not covered in above criteria, 12 aortic aneurysm, 243 stroke (both ischemic and haemorrhagic), 13 intermittent claudication, 28 syncope, 42 TIA, 5 carotid artery disease (see Figure 1).
The MI and stroke papers written in English have been taken to data extraction stage. There were 572 (490 MI papers and 82 mixed papers) relating to MI and 260 papers relating to stroke or TIA, which were taken to data extraction. Of these, 134 (23%) MI papers and 117 (45%) stroke papers were accepted for analysis. Reasons for rejection included recruitment period before 1990, sub study of a larger accepted paper or dealing with subarachnoid haemorrhage or carditis.

A table summarising the studies included in the review is found in Appendix 1.
3 RESULTS

3.1 Myocardial infarction as primary event

3.1.1 Mortality

3.1.1.1 Pilot analysis – mortality at six month follow-up:

**UK only:**
There were three UK-only studies published, all of which began recruiting patients in 1988 (2–4). However, two of the studies were conducted by the same team in the same hospital with different aims but with an overlap of the same patients in both studies. Therefore, only one of these two papers was selected for inclusion in the analysis (2, 3).

The pooled estimate of odds of survival (i.e. numbers survival/numbers non-surviving) using the two studies carried out in the UK (2–3) was 5.389 (95% C.I: 3.17–9.15). That is the chance of surviving to six months after an MI is 84.3% (95% CI: 76.0%–90.1%) or 157 deaths per 1000. However, there was significant heterogeneity in these studies ($Q = 19.177 \ p < 0.0001$). Ninety-four per cent (94%) of the variability seen in the studies is due to between-study heterogeneity and not sampling error.

**Conclusion:** There is too much heterogeneity between the two studies carried out in the UK to enable a valid pooled estimate to be calculated. The two studies independently provided death rates of between 12% (i.e. 152 in 1225) [2] and 20% (i.e. 161 in 823 died) [3] at six months.

**EU countries with similar or better life expectancy as UK**

There are 19 published studies recruiting from the EU countries with a similar life expectancy as the UK (2–21). However, two of the studies from Italy were conducted by the same team and using the same patients. Therefore, only one has been selected to be included in the analysis (11).

The pooled estimate of odds of survival using the 18 studies was 16.9 (11.78–24.28) (Figure 2). This means that the chance of surviving to six months is 94.4% (95% CI: 92%–96%) or 56 deaths per 1000. However, there is again a great deal of heterogeneity in these studies ($Q = 521.23 \ p < 0.0001$). A meta regression analysis

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$Q = \text{Value of the amount of heterogeneity between each study. This is calculated using the sum of the weights given to each study based on its sample size times by [the study effect (i.e. odds of survival in the individual study) – pooled estimate] squared.}$

$Q = \Sigma \omega (y-\bar{y})^2$

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3 Ireland, Spain, France, Italy, Austria, Sweden, Norway, Finland, Sweden, the Netherlands, Denmark, Germany, Austria, Belgium, Switzerland, Greece. Ref: www.euro.who.int/document/ehr/e76907c.pdf
shows: the start year of recruitment to the study affects survival \( (p = 0.02) \), for every year later, odds of survival increase by 0.12 \( (95\% \text{ CI}: 0.02–0.2) \).

Factors not affecting outcome include: percentage of sample who are male, percentage with diabetes and average age.

**Conclusion:** There is too much heterogeneity seen in the EU studies for them to be combined. The survival at six months has improved with time, so that studies conducted some years ago will not reflect survival today.

**Figure 2:** Meta-analysis of six months’ survival (studies in EU countries with a similar life expectancy to the UK) Studies listed in order of year of recruitment (oldest to most recent)

**EU countries with similar life expectancy as UK and multicentered trials involving EU countries with similar life expectancy as UK**

There are 23 studies done in EU countries with a similar life expectance as the UK (three multi-centred trials with EU centres but also including centres in USA, Australia etc.) \( (2–24) \). The pooled estimate of odds of survival using the 21 (i.e. two Italian studies removed as above) studies was 16.567 \( (12.15–22.58) \). This means that the chance of surviving to six months is 94\% \( (92\%–96\%) \) and 60 in 1000 deaths occur before six months.
However there was again a great deal of heterogeneity in these studies ($Q = 657.579 \ p<0.0001$).

A meta regression analysis shows that the start year of recruitment to the study affects survival ($p = 0.017$), and that for every subsequent year the odds of survival increase by 0.0109 (95% CI: 0.02–0.2).

Factors not affecting outcome include the percentage of males, the percentage with diabetes in the sample and the average age.

**Conclusion:** There is too much heterogeneity seen in the EU studies for them to be combined. The survival has improved with time, so that studies conducted a few years ago will not reflect survival today.

**Summary of pilot analysis:** The main factor affecting survival is the year in which the study started recruitment. Survival has improved with time. There are very few recent studies conducted in the UK. However, studies conducted outside Europe show a large difference in survival. Therefore, future meta-analysis will focus on studies in the EU, countries which have a similar life expectancy to the UK recruiting from 1995 to date. Removing studies which recruited patients before 1995 leaves 28 papers selected for inclusion.
3.1.1.2 Survival

**Survival at six months (in studies conducted in 1995 or later in EU countries with similar life expectancy as the UK)**

There were 11 publications of studies conducted in the EU with six-month survival data. Of these four were conducted in Italy using the same patients. The most recent publication of these four was selected. The pooled estimate of odds in the remaining eight publications (7, 8, 10, 12–15,18) was 22.7 (95% CI: 14.4–35.6) or 95.8% survival to six months (95% CI: 93.5%–97.2%) (Figure 3). However there is still significant heterogeneity ($Q = 83.5 \ p<0.0001$) between studies.

The year of recruitment for the study is no longer a significant factor affecting survival in these studies ($p = 0.264$), and percentage of the sample who are male, or who have diabetes or are of average age does not account for the heterogeneity in these studies.

The studies were mainly double blind, multicenter trials examining different treatment methods, for example one study was examining aspirin vs Ticlopidine in different Italian centres. Therefore different treatment efficacy may contribute to genuine heterogeneity in findings of different studies.

**Summary**: The pooled survival at six months is 96% (93.6–97.5). However, a great deal of heterogeneity exists between studies. Some of this will be genuine biological variation in survival due to treatment methods and some due to methodological issues such as selection bias.

**Survival at 12 months (in studies recruiting in 1995 or later in EU countries with similar life expectancy as the UK)**

There are nine studies with 12 month follow-up data (13, 16, 25–26, 28–32). The pooled odds of survival are 16.2 (11.1–23.7) which is survival of 94.1% (95% CI: 91.7%–96.0%). That is 60 people in 1000 will have died within one year of their MI. However, there is again significant heterogeneity ($Q = 69.6 \ p<0.0001$). The percentage of the study population with diabetes had a significant effect on survival within these studies ($p = 0.008$) with odds of survival declining by $-0.10$ with each extra percentage of the population with diabetes. However, percentage male, average age and year of recruitment do not account for the variation in survival seen within these studies.
Figure 3b: Meta-analysis of survival at six months (in studies recruiting in 1995 onwards in EU countries with a similar life expectancy at the UK)

Figure 4: Meta-analysis of studies (listed by percentage with diabetes (lowest to highest percentage with diabetes as list descends))
Survival at 24 months (in studies conducted in 1995 or later in EU countries with similar life expectancy as the UK)

There were five studies with 24 month follow-up (27, 33–36). The pooled odds were 24.9 (95% CI : 10.9–56.2) giving a survival of 96.13% (95% CI: 91.6%–98.3%). That is 40 people in 1000 will have died within two years of their MI. There is significant heterogeneity in survival between studies ($Q = 27.4 \ p<0.0001$). The treatments under investigation within the studies differ and this will contribute to heterogeneity.

Survival at 36 months (in studies conducted in 1995 or later in EU countries with similar life expectancy as the UK)

There were four studies reporting three-year follow-up data (15, 26, 37, 38). The pooled odds of survival were 8.4 (4.5–15.4) which means 89% (95% CI: 81.8%–93.9%) survival. That is 110 people in 1000 will have died within three years of their MI. There is significant heterogeneity ($Q = 27.4 \ p<0.001$). The average age of the populations within the studies affects survival, with poorer survival with increasing age of the study sample ($p<0.0001$). However, year of recruitment, percentage male, percentage with diabetes do not affect the heterogeneity of the survival seen in these studies.
Survival at 48 months (in studies conducted in 1995 or later in EU countries with similar life expectancy as the UK)
There was one study with follow-up data at four years. This was a four-year follow-up of 130 consecutive patients in 1997 examining heart rate variability as a predictor of outcome. The odds of survival from this study were 31.5 (95% CI: 11.64–85.24) or a survival of 97% (95% CI: 92%–99%). That is 30 people in 1000 will have died within four years of their MI.

Survival at 60 months (in studies conducted in 1995 or later in EU countries with similar life expectancy as the UK)
There were three studies giving five-year follow-up data. One study (from Sweden) (40) studied unselected patients and classified them as having or not having diabetes. Patients with diabetes had odds of survival to five years of 0.64 (0.4–1.0) or 39.2% (95% CI: 28.6%–50.5%) compared to patients without diabetes who had odds of survival of 1.62 (1.2–2.1) or 61.9% (54%–67.7%). Combining these two survivals gives a rate of 56%. That is 440 people in 1000 will be dead within five years of their MI. A study from Germany (41) found 16% death rate (64/401) or 160 per 1000 deaths among patients who took part in a RCT using abciximab during stenting and a study from Sweden (42) found a 19% mortality rate (634/3300) among patients randomised to warfarin or aspirin.
Summary of survival following MI: Table 1 shows percentage of survival following MI. However, these results are based on studies conducted generally between 1995 and 1997, and it could be argued that survival has increased so much with time that these finding may not be a reliable reflection of the true rates of survival for a person having an MI today. The proportions of patients who are male, the average age and the proportions who have diabetes and the treatments and surgery all have a bearing on survival. The health systems are different in various European countries and it is likely that this may have an influence on survival in different countries. We have attempted to combine results from different studies but the heterogeneity suggests that the pooled result is not directly relevant to survival today in the UK and survival rates predicted are dependent on the mix of diabetes/non-diabetes, young/old and male/female within the studies examined. Subgroups and stratification of patients in the UK would be needed to understand true survival today. In addition, many of the people were elderly and they may have died from causes not related to their previous MI. A matched control sample of people who have not had an MI but are of similar age would be needed to see to what extent the death rate seen in the population is related to the MI as opposed to being elderly.

### Table 1: Summary of survival following an MI (see Appendix 2)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Time</th>
<th>Number of studies</th>
<th>Meta-analysis</th>
<th>Estimated mortality rate (EU studies only)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>6 m</td>
<td>11</td>
<td>No</td>
<td>0.8%–8.7%</td>
</tr>
<tr>
<td></td>
<td>12 m</td>
<td>10</td>
<td>No</td>
<td>2.3%–13.1%</td>
</tr>
<tr>
<td></td>
<td>24 m</td>
<td>4</td>
<td>No</td>
<td>1.5%–13.6%</td>
</tr>
<tr>
<td></td>
<td>36 m</td>
<td>4</td>
<td>No</td>
<td>6.8%–18.4%</td>
</tr>
<tr>
<td></td>
<td>48 m</td>
<td>1</td>
<td>No</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>60 m</td>
<td>3</td>
<td>No</td>
<td>16%–56%</td>
</tr>
<tr>
<td>MI</td>
<td>6 m</td>
<td>4</td>
<td>Yes</td>
<td>2.2%</td>
</tr>
<tr>
<td></td>
<td>12 m</td>
<td>4</td>
<td>Yes</td>
<td>3.6%</td>
</tr>
<tr>
<td></td>
<td>24 m</td>
<td>2</td>
<td>Yes</td>
<td>6.6%</td>
</tr>
<tr>
<td></td>
<td>36 m</td>
<td>2</td>
<td>Yes</td>
<td>6.3%</td>
</tr>
<tr>
<td>Stroke</td>
<td>6 m</td>
<td>2</td>
<td>Yes</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>12 m</td>
<td>2</td>
<td>Yes</td>
<td>0.5%</td>
</tr>
<tr>
<td></td>
<td>36 m</td>
<td>1</td>
<td>No</td>
<td>3.6%</td>
</tr>
<tr>
<td></td>
<td>60 m</td>
<td>2</td>
<td>No</td>
<td>7.8%–30%</td>
</tr>
</tbody>
</table>

### 3.1.2 Reinfarction

Reinfarction after MI at six months' follow-up (in studies conducted in 1995 or later in EU countries with similar life expectancy as the UK)

There were five studies with details of reinfarction at six months’ follow-up. (7, 12–15). The pooled odds estimate was 28.7 (12.7–65.1) or survival (non-reinfaction) of 96.6% (95% CI: 92.6%–98.5%). There is significant heterogeneity (Q = 42.49 p<0.001). There was one outlier study which had a higher proportion of women and a higher average age compared to the other studies (this study had a higher
reinfarction rate of 10.9% (survival = 89%). Removing this outlier gave odds of non-reinfarction of 43.45 (32.6–57.8) or survival (non-reinfarction) of 97.8% (95% CI: 97%–98%). That is 22 people in 1000 will have a second MI within six months. There was no significant heterogeneity ($Q = 2.6 \ p = 0.44$). Therefore, these four studies which recruited patients from 1995 to 2002 can be combined.

**Figure 7: Meta-analysis of odds of reinfarction at six months' follow-up after an MI**

Reinfarction after MI at 12 months’ follow-up (in studies conducted in 1995 or later in EU countries with similar life expectancy as the UK)

There were four studies reporting rate of reinfarction at one year post MI (13, 16, 29, 32). The pooled odds of survival (i.e. non-reinfarction) were 27.1 (20.09–36.7) or 96.4% (95%CI: 95.2%–97.3%). That is 36 people in 1000 will have a second MI within one year. There is no significant heterogeneity between studies ($Q = 5.6 \ p = 0.13$). Therefore, these four studies recruiting patients from 1995 to 2001 can be combined.
Reinfarction after MI at 24 months’ follow-up (in studies conducted in 1995 or later in EU countries with similar life expectancy as the UK)

There were two studies reporting on reinfarction at two years post MI (7, 27). The pooled odds of survival (i.e. no reinfarction) were 14.35 (11.04–18.6) or 93.4% (95% CI: 92%–94.9%). That is 66 people in 1000 will have an MI at two years. There was no significant heterogeneity ($Q = 0.1 \ p = 0.7$). Therefore, these two studies recruiting patients from 1995–1998 can be combined.

Reinfarction after MI at 36 months’ follow-up (in studies conducted in 1995 or later in EU countries with similar life expectancy as the UK)

There were two studies reporting on reinfarction at three years post MI (15, 38). The pooled odds of survival (i.e. no reinfarction) were 14.92 (11.24–19.8) or 93.7% (95% CI: 91.8%–95.1%). That is 63 people in 1000 will have an MI within three years. There was no significant heterogeneity ($Q = 0.07 \ p = 0.8$). Therefore, these two studies recruiting patients from 1995–1998 can be combined.

Reinfarction after MI at 48 follow-up (in studies conducted in 1995 or later in EU countries with similar life expectancy as the UK)

There were no studies reporting reinfarction at four years post MI.

Summary: The risk of re-infarction is low for patients recruited in 1995–2001 (Table 1). Therefore, it can be extrapolated that risk today would be lower than the risks seen almost a decade ago. Patients have a low risk of reinfarction (up to three years later) after an initial MI. However, some of the reinfarctions could have been missed in the records of some of the studies, and simply have been recorded as
deaths. In Genoni et al. 2000, 22/334 (6.6%) patients had a reinfarction and 50/334 (15%) died at a mean follow-up period of 3.1 ± 0.48 years. However, from these results it is not clear if the reinfarction rate refers only to non-fatal reinfarction or if it includes non-fatal and fatal reinfarction.

3.1.3 Stroke

Stroke after MI at six months’ follow-up (in studies conducted in 1995 or later in EU countries with similar life expectancy as the UK)
There were two studies that reported on stroke occurrence at six months’ follow-up post MI. (14, 18) The pooled odds were 99.0 (47.0–208.5) or survival (no stroke) of 99.0% (97.9%–99.5%). That is one person in 100 will have a stroke at six months. There was no significant heterogeneity between these studies (Q = 0.013 p = 0.9).

Stroke after MI at 12 months’ follow-up (in studies conducted in 1995 or later in EU countries with similar life expectancy as the UK)
There were two studies that reported on stroke occurrence at one year follow-up post MI (16, 29). The pooled odds were 183.79 (98.72–342.1) or survival (no stroke) of 99.5% (98.99–99.7). That is five people in 1000 have a stroke at six months. There was no significant heterogeneity between these studies (Q = 0.18 p = 0.669).

Stroke after MI at 24 months’ follow-up (in studies conducted in 1995 or later in EU countries with similar life expectancy as the UK)
There were no papers reporting stroke occurrence at 24 months.

Stroke after MI at 36 months’ follow-up (in studies conducted in 1995 or later in EU countries with similar life expectancy as the UK)
There was one study which reported on stroke occurrence at three years post MI. There were 6/168 people who had a stroke. These are odds of 27 (11.9–60.9), survival of 96.4% (95% CI: 92–98) or 36 people in 1000 have a stroke within three years of their MI.

Stroke after MI at 48 months’ follow-up (in studies conducted in 1995 or later in EU countries with similar life expectancy as the UK)
There were no papers reporting strokes at four years’ follow-up.

Stroke after MI at 60 months’ follow-up (in studies conducted in 1995 or later in EU countries with similar life expectancy as the UK)
There were two studies giving five-year follow-up data. One study from Sweden looked at unselected patients and classified them for diabetes. Patients with diabetes had odds of survival to five years of 8.25 (3.9–17.18) or 89.1% (95% CI: 79.6%–95.5%) compared to patients without diabetes who had odds of survival of 15.5 (9–26.6) or 93.9% (95% CI: 90–96.3). Combining these two survival rates gives a combined rate of 92.2%. That is 78 people in 1000 will have a stroke within five years of their MI. The other study from Sweden found a stroke rate of 5.9% after five years (194/3300) or 59 in 1000 having a stroke.
Summary of risk of stroke: The risk of stroke is low following an MI (Table 1). However, some fatal strokes could be missed in this data and recorded as deaths rather than strokes. Very few papers report on specific risk of stroke.

3.1.4 Heart failure and ischemia

Only one paper reported on heart failure or ischemia. From this paper the numbers suffering heart failure or ischemia were 31/540 (5.7%) at 12 months.

3.1.5 Surgery

Surgery after MI at six months’ follow-up (in studies conducted in 1995 or later in EU countries with similar life expectancy as the UK)

There were two studies conducted in Italy reporting need for surgery after six months (7, 15). The rates were 8% and 15% respectively. Pooled odds of survival were 7.67 (3.8–15.6) or 88.4% (95% CI: 79%–94%). However, there was significant heterogeneity between the studies (Q = 4.3 p = 0.038). Both papers selected patients who were having surgery (so were a selected sample from the beginning) and both recorded need for CABG (coronary artery bypass graft) and PTCA (percutaneous transluminal coronary angioplasty) at six months after discharge alive from hospital. The heterogeneity could be due to need for surgery being a clinical decision and therefore variable between clinicians. Therefore, the need for CABG or PTCA at six months after an MI is 8%–15% with an averaged survival of 88.4%.

Surgery after MI at 12 months’ follow-up (in studies conducted in 1995 or later in EU countries with similar life expectancy as the UK)

There was one paper reporting need for surgery at one year. There were 39/500 (7.8%) needing surgery at one year. This is a survival of non-surgery of 92.2%.

Surgery after MI at 24 months’ follow-up (in studies conducted in 1995 or later in EU countries with similar life expectancy as the UK)

There was one paper reporting need for surgery at two years. There were 22/88 (25%) needing surgery at two years. This is a survival of 75%.

Surgery after MI at 36 months’ follow-up (in studies conducted in 1995 or later in EU countries with similar life expectancy as the UK)

There were three studies reporting surgery at three-year follow-up (15, 26, 38). The pooled odds were 3.76 (2.0–7.0) or 79% (67%–87.5%) or 21 in 100 need surgery at three years. However, there was significant heterogeneity (Q = 28.7 p < 0.0001). The data for the individual studies was 9%–32% needing surgery. Some of this heterogeneity can be accounted for by percentage of the sample with diabetes (p = 0.011) (one study had 22% of the sample with diabetes compared to another study with 10% diabetes) and the year of recruitment for the study. The studies with the higher rate of surgery were conducted in 1995 compared to the study with the
lower rate conducted in 1998. However, clinical variation in treatment and selection for surgery may also play a part in the heterogeneity seen in these studies.

**Surgery after MI at 48 months follow-up (in studies conducted in 1995 or later in EU countries with similar life expectancy as the UK)**
There were no studies reporting survival at 48 months.

**Surgery after MI at 60 months follow-up (in studies conducted in 1995 or later in EU countries with similar life expectancy as the UK)**
There was one study reporting rate of surgery at five years. There were 64/399 (16%) operations carried out within the five-year period after an MI. This gives a survival of 84%.

**Summary of survival without need for surgery**: The need for surgery was so variable between studies that a reliable rate cannot be calculated. The survival is in the region of 90% within the first year and 75%–84% thereafter.

### 3.2 Stroke as primary event

#### 3.2.1 Mortality

**3.2.1.1 Pilot analysis**

_Pilot: Strokes and TIAs in all countries at three months_
Meta-analysis showed too much heterogeneity to be combined. Country of study and year of recruitment were significant factors affecting survival rates. Factors not impacting on the heterogeneity were percentage male and average age.

_Taking only the studies done in 1995 or after_ (41–47) showed there was still too much heterogeneity to combine the studies. One conducted in Germany in 1995 showed deaths at three months to be 10.6% (16/150) and one conducted in the UK in 1996 showed deaths at three months to be 25.8% (159/616). Both these studies examined ischemic stroke. Three studies conducted in the USA (1997–2002) examining ischemic stroke were also not combinable ($Q^4 = 46.9 \ p = 0.001$) as death rate varied between 3% and 23% in different studies. A meta-analysis of these three USA studies gives combined odds of survival which were 9.7 (1.8–52.4) or 90.7% (64%–98%) survival (nine deaths per 100). One study in the USA conducted in 2002 examining stroke/TIA found death rate at three months to be 3% (4/134).  

**Summary**: There is a great deal of variation between findings in different studies. Some of this variation could be due to treatment methods e.g. the study in Germany took patients treated with rtPA while the study in the UK took patients from the

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$Q = $ Value of the amount of heterogeneity between each study. This is calculated using the sum of the weights given to each study based on its sample size times by [the study effect (i.e. odds of survival in the individual study) – pooled estimate] squared.

$Q = \sum w_i(y_i - \Theta)^2$
South London Community Stroke Register regardless of treatment. However, all studies show a poor rate of survival at three months following a stroke with risk of death being 3%–26%.

3.2.1.2 Survival

Deaths at six months post stroke
There were four studies conducted in or after 1995 (49–52). Two were conducted in Turkey which showed a mortality rate of 7%–12% (10/137 and 34/266), one conducted in the UK showed a mortality rate of 5% (2/40) and one conducted in Demark showed a mortality of 20% (103/511). The design of the study will have a large selection bias on the survival rate: the UK study followed patients from carotid surgery and the Denmark study examined smoking cessation among first-ever stroke patients (38% were smokers in the Demark study and 68% were smokers in the UK study).

Summary: Rate of death is between 5% and 20% at six months depending on selection criteria.

Deaths at one year post stroke
There were five studies conducted in or after 1995 in an EU country (43, 53–56). Three of these studies examined ischemic stroke (two ischemic stroke and one TIA) but they could not be combined. They showed rates of death of between 2.4% (2/83) and 14.7% (22/150). However, it was the TIA study that had a rate of 2.4% and the two ischemic stroke studies had rates of 14.7% and 12.9% (61/473). One study examined stroke/TIA and showed a death rate of 14.3% (63/449) and one examined acute stroke and showed a rate of 33% (124/377). Among all these studies there was heterogeneity in the study designs (e.g. the percentage of the people in the study with diabetes differed between papers (range 18%–46%)), stroke studied and treatments given.

Deaths at two years post stroke
There were four studies conducted in the EU after the date of 1995 (53, 57–59) all evaluating survival after ischemic stroke. These studies were too heterogeneous to combine (Q = 57 p = 0.0001), but if meta-analysis is carried out the combined odds of survival are 11.1 (5.07–24.5) or 91.7% (83.5%–96.1%) or eight deaths per 100 over two years. Meta-regression analysis showed that the proportion of each study who were men (p = 0.016) and the average age (p<0.0001) of the participants in the studies were significant factors affecting the heterogeneity in survival. In these four studies, one recruited young people and showed a 4.9% death rate, one recruited people with ischemic stroke and atrial fibrillation and showed a death rate of 15%, one recruited people for a RCT of piracetam vs. acetylsalicylic acid and showed a rate of 3% deaths and one looked at ischemic stroke and markers of inflammation as predictors of risk and showed a 16.4% death rate. The section criteria and treatments offered mean that these studies are not comparable even
though they examine the same type of stroke (ischemic) in similar countries (EU only) in a similar time period (within the last ten years).

There were three studies (60–62) conducted in the USA which looked at acute stroke and were combinable ($Q = 5.3$ $p = 0.071$). The odds of survival at two years in the USA were 18.5 (14.4–23.69) or 94.9% (93.5%–95.9%) or five deaths per 100 over two years.

Figure 9: Meta-analysis of three studies examining two-year follow-up in studies in the USA

Summary: The survival at two years post stroke appears to be 92%–95%.

Deaths at three years post stroke
There were two studies conducted within the EU (after 1995) examining survival after stroke/TIA. One from Italy and one study from France which were combinable ($Q = 0.2$ $p = 0.6$) and the odds of survival were 88.96 (95% CI: 42–187) or 98.8% (95% CI: 97.6%–99.4%) or 1.5 % death rate.

Deaths at four years post stroke
There was one study conducted in the EU examining survival at four years. The study from Spain showed a 28% rate of death (94/333).

Deaths five years post stroke
There were no studies conducted in the EU (after 1995). However, one study conducted in Australia showed a 57% rate of death at five years (122/213) in a mixed cohort of patients (i.e. some with ischemic and some with haemorrhagic stroke).
Conclusion: Survival is affected by male sex (improved survival with more males in the study), average age (younger have improved survival), treatment options, year of study recruitment (recent years have improved survival), country of study, percentage of study population who have diabetes or who smoke (both decrease survival) and the type of stroke under investigation. There is too much heterogeneity in survival post stroke for meta-analysis to be used to evaluate death rates among stroke survivors. However, the majority of studies conducted in 1995+ and published in 2000+ show relatively poor survival (1.5%–30% rates of death, see Table 2). This will have improved for patients having strokes today and will depend on age, sex, diabetes, smoking status, type of stroke and treatment.

### 3.2.2 Recurrence of stroke

**Stroke at three months post primary stroke**

There were six studies reporting total recurrence of stroke (44, 48, 67–68) (both fatal and non-fatal) after an ischemic stroke (after 1995). The rate of stroke varied between 2% (UK Study) and 24% (USA study). The six studies could not be combined by meta-analysis (Q = 143 p = 0.0001) as there was too much heterogeneity. Taking only the two studies conducted in the UK looking at ischemic stroke (44, 67) showed a death rate of 2.7% (17/616) – 14.1% (93/657). Both these studies took patients from the community (one from a GP population in Oxford and one from the London Community Stroke Register) and were prospective studies looking at incidence. However, the definition of a recurrence of stroke will have contributed to heterogeneity with one study taking an event 21 days after the

### Table 2: Summary of survival following stroke

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Time</th>
<th>Stroke</th>
<th>Number of studies</th>
<th>Meta-analysis</th>
<th>Estimated mortality rate (EU studies only)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>3 m</td>
<td>ischemic</td>
<td>2</td>
<td>No</td>
<td>10.6% or 25.8%</td>
</tr>
<tr>
<td></td>
<td>6 m</td>
<td>ischemic</td>
<td>4</td>
<td>No</td>
<td>5% or 20%</td>
</tr>
<tr>
<td></td>
<td>12 m</td>
<td>ischemic</td>
<td>4</td>
<td>No</td>
<td>2% or 16%</td>
</tr>
<tr>
<td></td>
<td>24 m</td>
<td>ischemic</td>
<td>4</td>
<td>No</td>
<td>3% or 17%</td>
</tr>
<tr>
<td></td>
<td>36 m</td>
<td>ischemic</td>
<td>2</td>
<td>Yes</td>
<td>1.5%</td>
</tr>
<tr>
<td></td>
<td>48 m</td>
<td>ischemic</td>
<td>1</td>
<td>NA</td>
<td>28%</td>
</tr>
<tr>
<td>Stroke</td>
<td>3 m</td>
<td>ischemic</td>
<td>2</td>
<td>No</td>
<td>2.7% or 14.1%</td>
</tr>
<tr>
<td></td>
<td>6 m</td>
<td>ischemic</td>
<td>1</td>
<td>NA</td>
<td>22%</td>
</tr>
<tr>
<td></td>
<td>12 m</td>
<td>ischemic</td>
<td>2</td>
<td>No</td>
<td>7% or 19%</td>
</tr>
<tr>
<td></td>
<td>12 m</td>
<td>stroke/TIA</td>
<td>2</td>
<td>No</td>
<td>9.8% or 50%</td>
</tr>
<tr>
<td></td>
<td>24 m</td>
<td>ischemic</td>
<td>4</td>
<td>No</td>
<td>10% or 24%</td>
</tr>
<tr>
<td></td>
<td>24 m</td>
<td>stroke/TIA</td>
<td>2</td>
<td>Yes</td>
<td>21%</td>
</tr>
<tr>
<td></td>
<td>36 m</td>
<td>ischemic</td>
<td>2</td>
<td>No</td>
<td>8%</td>
</tr>
<tr>
<td></td>
<td>36 m</td>
<td>stroke/TIA</td>
<td>2</td>
<td>No</td>
<td>23% or 39%</td>
</tr>
<tr>
<td></td>
<td>48 m</td>
<td>ischemic</td>
<td>1</td>
<td>NA</td>
<td>18.9%</td>
</tr>
<tr>
<td>MI</td>
<td>12 m</td>
<td>ischemic</td>
<td>2</td>
<td>Yes</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>12 m</td>
<td>stroke/TIA</td>
<td>1</td>
<td>NA</td>
<td>5.6%</td>
</tr>
<tr>
<td></td>
<td>24 m</td>
<td>ischemic</td>
<td>1</td>
<td>NA</td>
<td>1.2%</td>
</tr>
<tr>
<td></td>
<td>24 m</td>
<td>stroke/TIA</td>
<td>1</td>
<td>NA</td>
<td>4.3%</td>
</tr>
<tr>
<td></td>
<td>36 m</td>
<td>stroke/TIA</td>
<td>1</td>
<td>NA</td>
<td>1.5%</td>
</tr>
</tbody>
</table>
primary stroke and one taking any stroke >24 hours after the primary event. Taking the two studies conducted in the USA (46, 68) showed a death rate of 7.4% (22/297) – 24.6% (327/1327).

Two studies (one in the UK and one in the USA) dealt with haemorrhagic stroke and showed a risk of recurrence of stroke as 12% (16/134) – 18% (31/174).

**Summary:** There is too much heterogeneity between studies to estimate a reliable rate of recurrence of stroke three months after the primary event.

**Stroke at six months post primary stroke**

There were four studies (one in the UK, two in Turkey and one in South Korea) (49–51, 69) that looked at recurrence of stroke at six months (conducted after 1995). These studies could not be combined using meta-analysis due to the heterogeneity. Taking only the study conducted in the UK it showed a recurrence rate of 22% (9/40). However, the patients in this study were included because they were undergoing carotid surgery and so they would have been a very select group with perhaps different outcome risks to other groups.

**Stroke at 12 months post primary stroke**

There were 13 studies (43, 55, 56, 66, 69–76) conducted after 1995 that looked at recurrence of stroke at 12 months. There were two (4, 54) in the EU which examined follow-up after ischemic stroke. The recurrence rate was 7% (10/150) and 19% (16/83). There was one (70) in the EU that examined follow-up after stroke/TIA and the recurrence rate was 9.8% (7/71). There were also two in the EU which examined follow-up in a mixed cohort (i.e. acute stroke) which had a recurrence rate of 8.7% (27/310) and 9.4% (153/1626). The studies in other parts of the world varied between 8.3% (Japan) and 17% (South Korea) for ischemic stroke and 6.5% (Australia) – 24% (Taiwan) for a mixed cohort (i.e. acute stroke).

**Summary:** There is a great deal of variation in recurrence of stroke one year after an initial stroke. Some of this variation could be due to type of primary stroke and treatments.

**Stroke at 24 months post primary stroke**

There were seven studies that looked at recurrence of ischemic stroke at 24 months (53, 57–59, 77–78). However, they could not be combined by meta-analysis (\(Q = 185, p = 0.0001\)). Taking only those studies conducted in the EU looking at ischemic stroke, there were four studies (53, 57–59) which could not be combined by meta-analysis (\(Q = 43, p = 0.0001\)). The rate of recurrence varied between 10% and 24%. However, there was a large difference in cohorts followed, for example the average age in the different studies varied between 36 years and 78 years, the percentage with diabetes varied between 2% and 46%, the percentage of the cohort males varied between 38% and 68% and the percentage of smokers varied between 13% and 46% and, as discussed previously, one looked at piracetam vs.
acetylsalicylic acid, one looked at younger people, one looked at stroke and atrial fibrillation.

There were two studies (54) looking at stroke/TIA which could be combined using meta-analysis \((Q = 0.113 \ (p = 0.7))\) and the combined survival was 79.3% (95% CI: 72.2–84.8) or 21 strokes per 100 over two years.

**Stroke at three years post primary stroke**
There were seven studies which could not be combined (60, 63, 64, 66, 79–81). Taking the three carried out in Europe (64, 79, 81) on ischemic stroke showed a recurrence of 6.3%, 10% and 22.6%. There was heterogeneity between these studies \((Q = 6.3 \ p = 0.012)\) which may be due to the different average ages included in the studies (37 years compared to 75 years). There was one carried out in Europe on a mixed stroke cohort of which 39% (23/59) had a stroke at three years.

**Stroke at four years post primary stroke**
There was one study conducted in an EU country after 1995 looking at ischemic stroke. The rate of recurrence of stroke was 18.9% (63/333). There was one study conducted in the USA on stroke/TIA and the rate of recurrence was 6.95% (13/187).

**Stroke at five years post primary stroke**
There were no studies conducted in the EU after 1995. One study in the USA looking at stroke/TIA showed a 7% recurrence rate (13/187).

**Summary:** The data from published papers do not give any real estimates of the rate of recurrence of stroke (see Table 2). Many of the studies are small (i.e. <500 patients) and so there will be a great deal of natural variation in rates among small samples, the selection criteria and treatments under investigation, which makes combining the studies difficult as the definition of a recurrent stroke is not uniform in all papers. In general, recurrence rate of stroke will depend on: year of study, country of study, smoking history, diabetes, age, sex, type of stroke and treatment given. Meta-analysis cannot currently be used to stratify people for stroke survival as there are more variables than papers (e.g. five variables and four papers). Even combining individual patient data from the published studies would be difficult as the selection criteria differed depending on the research question under investigation.

### 3.2.3 MI following stroke

**Occurrence of MI three months post stroke**
There were no EU studies but there were two studies carried out in the USA. The rate of MI in these studies was 1.5% (2/134) for stroke/TIA and 0.8% (11/1327) for TIA.

**Occurrence of MI six months post stroke**
There were no studies giving time to MI six months after a stroke.
Occurrence of MI 12 months post stroke
There were four studies conducted in the EU (after 1995) looking at risk of MI one year after a stroke (56, 70, 82, 83). Two of these studies looked at ischemic stroke and were combinable ($Q = 0.001 \ p = 0.9$) giving an odds of survival of 41.196 (16.9–100) or 98% (95% CI: 94–99%) or two people in 100 have an MI one year after an ischemic stroke. There was one study looking at stroke/TIA which found a rate of MI of 5.6% (4/71) and one study looking at a mixture of stroke types and the rate of MI was found to be 0.6% (1/157).

Occurrence of MI 24 months post stroke
There was one study carried out in Germany looking at ischemic stroke. The risk of MI after two years was 1.2% (7/563) in this study. There was one study carried out in the Netherlands looking at stroke/TIA. The risk of MI was 4.3% (5/115).

Occurrence of MI at three years post stroke
There was one study carried out in the Netherlands looking at stroke/TIA (after 1995), the rate was 1.5% (2/128).

Occurrence of MI at four or five years
There were no studies conducted after the date of 1995.

Summary: There was too much variation in the studies published to develop a reliable estimate of risk of myocardial infraction after a stroke (see Table 2).

3.2.4 Surgery following a stroke

Need for surgery at three months or six months
There were no studies conducted after the date of 1995 reporting surgery at three and six months.

Need for surgery at 12 months
There was one study (85) which was a multi-centred European study which showed 73% of people have surgery one year after their stroke (70/96).

Need for surgery at 24 months
There was one study which showed 33% (38/115) of people need surgery two years after their stroke.

Need for surgery at 36, 48 or 60 months
There were no studies conducted in or after 1995 that reported on surgery at these time periods.

Summary: There were too few studies reporting on surgery after a stroke to draw any reliable estimates of the need for surgery after a stroke.
4 CONCLUSIONS

A systematic review of studies published in stroke or MI does not give a reliable estimate of survival for a person who survives an MI/stroke. A person’s risk of further events varies greatly with different baseline characteristics (age, sex, type of primary stroke, diabetes, smoking, year of stroke/MI, country of study, treatment) and with the selection criteria of the studies examined. In terms of stroke there are few studies that are large enough to give a reliable estimate alone of survival and for both MI and stroke, many of the smaller studies cannot be combined because the patients selected vary greatly.

There were over 500 studies on MI and 260 on stroke/TIA. However, few were included in the meta-analysis because they are:

1. Based on study populations that were pre-1995. Survival more than a decade ago does not appear to reflect survival in more recent years. Many studies which have influenced clinical practice are now out of date and are probably not appropriate for studying survival today. For example MONICA and ISIS trials conducted in the 1980s are now 20 years out of date.

2. Sub-sets or reanalyses of previous studies. For example, there were 12 papers of the CARE trial (86–97) using subsets of the same patients. Only one paper was included from this group. There are more than 12 GISSI papers (GISSI-I – GISSI-V) (22, 99–107) which, in some cases, related to the same patient population and in others described a new cohort of patients.

3. Based on selected patient populations. Most of the published studies were randomised clinical trials and have inclusion and exclusion criteria that meant the cohort followed a highly selected group with distinct characteristics that would influence survival.

4. Based on patients who had an MI or stroke within six months of the onset of study. Many of the studies were RCTs that recruited patients who had an MI or stroke in the past but did not recruit them at the hospital following their MI. Therefore, the definition of the follow-up period was unreliable for use in this survival analysis.

The main problem with conducting the systematic review was that many studies published recently are based on cohorts of patients recruited in the 1990s. Developments in the management of stroke and MI are so rapid that it is likely that survival of patients in the 1990s is an underestimate of survival today. In terms of stroke the definitions of a further stroke are not always consistent across studies and the type of stroke examined varies from ischemic, haemorrhagic, TIA, mixed, acute or cerebral aneurysm, each with different survival characteristics.
Best estimate of risk of further events following a vascular event

Risk of further MI after primary MI
A meta-analysis of four studies showed that the best estimate of risk of re-infarction at six months is approximately 2%.

A meta-analysis of four studies showed that the best estimate of the risk of re-infarction at 12 months is approximately 3–4%.

A meta-analysis of two studies showed that the best estimate of risk of re-infarction at 24 months was 6–7%.

Risk of stroke after primary MI
A meta-analysis of two studies showed that the best estimate of risk of stroke at six months is approximately 1%.

A meta-analysis of two studies showed that the best estimate of risk of stroke at 12 months is less than 0.5%.

There is no reliable estimate of stroke risk 24 months after a primary MI.

Risk of MI after a primary stroke
There is no reliable estimate at six months.

A meta-analysis of two studies found the best estimate of MI 12 months after a stroke is 2%.

The only prospective cohort study carried out in the EU gives a best estimate of MI 24 months after a stroke of approximately 4%.

Risk of further stroke after a primary stroke
At six months the largest study (which was from Turkey [51]) found a rate of 6.4% (17/266). Therefore the best estimate is approximately 6%.

At 12 months the largest cohort study (carried out in the UK [76]) found a rate of 9.4% (153/1626). Therefore the best estimate is approximately 9%.

At 24 months the largest study (an RCT [62]) found a rate of 8% (300/3680). However, an RCT is likely to give a lower estimate than a cohort study. Therefore the best estimate is approximately 8%–10%.
5 FURTHER STUDIES

To gain a reliable estimate of MI/stroke survival, studies large enough to stratify people are needed or alternatively routine data (such as hospital admissions data) could be used to examine survival. For MI, the Myocardial Infarction National Audit Project (MINAP) (106) which started in 2000, collects data from all patients with an MI or suspected MI in England and Wales. The HES [Hospital Episode Statistics] and PEDW [Patient Episode Database Wales]) databases collect all episodes of in-patient admissions to hospitals in England and Wales. These databases can be used to follow patients from first MI/stroke and can examine survival or time to death, recurrent MI or stroke with specific characteristics of individual patients known and recorded. Deaths can be followed up using links to the Office for National Statistics Mortality data (MINAP already has a link with ONS). From MINAP we can record medication (pre event medication such as aspirin for example, and in hospital records and management with agents such as aspirin, thrombolytic therapy, heparin, clopidogrel, glycoprotein receptor blocker, nitrate, warfarin, diuretic, calcium channel blocker, ACE inhibitors, beta blockers; discharge medication such as statins, beta blockers, ACE inhibitor and aspirin) and co-disorders (whether diagnosed hypertension or diabetes (and drugs prescribed)). These can be linked with routine hospital data which will record surgery (such as stents, angioplasty, coils or bypass). A matched control cohort of people who have not had an MI (in the MI survival analysis) or not had a stroke (in the stroke survival analysis) can be identified in Wales using the NHS Administration Register (i.e. people matched for sex, age and socio-economic area) and could also be followed up to give survival of controls. For example, survival post stroke (from the published data) looks poor but this could be to do with the age of people having strokes rather than the influence of the stroke itself.

Multi-level modelling can be used to examine the survival of people taking into account co-variables such as specific medication and specific surgical interventions given individual characteristics (e.g. age, sex, co-disorders, previous vascular events) and socio-economic deprivation (as defined by Townsend Deprivation Score of place of residence).

Research examining survival following MI/stroke in the UK using routine data is now feasible. This approach will mean that the data is up to date and changes in survival are reflected in the data collected. Using all the patients in England and Wales with an MI or stroke would mean there is a big enough number of patients to design tables to stratified people by risk factors and treatment.
6 RECOMMENDATIONS

Treatment and management after a vascular event is such a fast-moving field that cohort studies are out of date before they are finished and often involve selected groups of patients with specific characteristics. Currently the only relevant survival information would come from the latest research study carried out in the country of interest and not from systematic reviews of existing data. Future work could use existing data such as MINAP to keep up to date with changes in survival and to have enough people in order to be able to stratify by age, sex, treatment, co-disorders (such as diabetes, hypertension) and environmental factors (such as smoking). The results of this review meta-analysis would therefore give a worst case evaluation of survival and this is not likely to reflect the survival today.
REFERENCES

1. http://hebw.uwcm.ac.uk/projectmethod/appendix5.htm#top


levels: Subgroup Analyses in the Cholesterol and Recurrent Events (CARE) trial. Circulation, 98(23), 8.


APPENDIX 1: SUMMARY OF STUDIES INCLUDED IN THE REVIEW
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APPENDIX 2: VARIATION IN RISK OF DEATH FROM INDIVIDUAL STUDIES

Risk of death at 6 months post MI

- 14 (N = 611)
- 7 (N = 1164)
- 18 (N = 90)
- 12 (N = 300)
- 15 (N = 121)
- 10 (N = 765)
- 13 (N = 316)
- 8 (N = 1470)

Risk of death 12 months after MI

- 31 (n = 380)
- 32 (n = 519)
- 30 (n = 369)
- 26 (n = 318)
- 28 (n = 500)
- 16 (n = 872)
- 13 (n = 216)
- 25 (n = 540)
- 29 (n = 999)
Risk of further acute vascular events following an initial myocardial infarction or stroke