REVIEW ARTICLE

Comparing risks of death and recurrent vascular events between lacunar and non-lacunar infarction

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Differences in prognosis of lacunar and non-lacunar infarction patients might support distinct arterial pathological processes underlying these two subtypes of ischaemic stroke. We performed a systematic review in which we identified cohort studies with ischaemic stroke subtype-specific follow-up data on death, recurrent stroke and/or myocardial infarction (MI). We calculated risks of death and recurrent stroke at 1 month, 1–12 months and 1–5 years, as well as risks of MI and cardiac death. We compared non-lacunar with lacunar infarction, using study-specific and summary odds ratios. We also compared the pattern of recurrent stroke subtypes after lacunar and non-lacunar infarction. One month odds of death and of recurrent stroke were significantly greater following non-lacunar than lacunar infarction, but the difference decreased thereafter (1 month mortality: OR 3.81, 95% CI 2.77–5.23; 1–12 month mortality: OR 2.32, 95% CI 1.74–3.08; 1–5 year mortality: OR 1.77, 95% CI 1.28–2.45; 1 month stroke recurrence: OR 2.11, 95% CI 1.20–3.69; 1–12 month stroke recurrence: OR 1.24, 95% CI 0.85–1.83; 1–5 year stroke recurrence: OR 1.61, 95% CI 0.96–2.70). Recurrent strokes were more likely to be lacunar if the index event was lacunar. Few studies reported on the risk of MI, but we found no significant difference in risk of cardiac death in non-lacunar versus lacunar infarction. Thus, although early mortality and stroke recurrence risks are higher among non-lacunar than lacunar infarct patients, the risks appear not to differ in the longer term and the risks of cardiac outcomes are similar, although data are limited. There is some evidence that recurrent ischaemic stroke subtypes breed true. These results provide limited support for a distinct arterial pathology underlying lacunar infarction.

Introduction

The precise arterial pathology underlying lacunar infarcts, which are presumed to result from the occlusion of single, small perforating arteries, remains undetermined (Wardlaw *et al.*, 2003). It is often assumed to differ from the athero-thromboembolic processes that occlude large intracranial and extracranial arteries and cause most other types of ischaemic stroke. However, evidence from direct pathological studies is limited because lacunar infarction has a low case fatality, autopsy rates are declining, and informative pathological studies are expensive, technically demanding and time-consuming.

Informative imaging studies are also scarce because of the difficulties in imaging small arteries. Alternative, less direct methods have therefore been used to study the pathology of lacunar infarction. These have included observational studies comparing the risk factor profiles and prognosis of patients with lacunar versus non-lacunar infarction, since differences might suggest distinct arterial pathologies. Our recent systematic review of studies comparing risk factor profiles in lacunar versus non-lacunar infarction found an excess of atrial fibrillation and severe carotid stenosis among non-lacunar infarction patients, but no clear difference in the frequency of any

other risk factors, including hypertension and diabetes (Jackson and Sudlow, 2005).

Lacunar infarction is often thought to have a more favourable outcome than other ischaemic stroke subtypes. Short term prognosis for death and disability is better among patients with lacunar infarction compared with non-lacunar infarction (Norrving, 2003), but this may reflect smaller infarct size and a low early recurrence rate rather than a fundamentally different arterial pathology. In the longer term, patients with lacunar infarction have a significantly higher risk of death compared with the general population, (Norrving, 2003) but less is known about the difference between lacunar and non-lacunar infarct patients.

Similarly, early recurrent stroke risk is lower in lacunar infarction compared with other ischaemic stroke subtypes (Lovett *et al.*, 2004). This early difference probably reflects different arterial occlusive mechanisms, with non-lacunar infarcts more likely to be caused by emboli from an active thrombotic source, such as the carotid bifurcation or the heart. However, it does not necessarily imply fundamentally different arterial pathologies, since atherothrombotic mechanisms could still cause most lacunar infarcts. Reports on recurrent stroke risk in the longer term are conflicting. Some studies have found that the risk of recurrence is greater among non-lacunar than lacunar patients while others suggest that stroke subtype is not a predictor of stroke recurrence (Norrving, 2003). These inconsistencies may arise from differences in study methodology and small study size (specifically small numbers of recurrent events). Furthermore, the definition of recurrent stroke differs markedly between studies, particularly with respect to the minimum time required between the index stroke and the recurrence. This makes comparing studies difficult, and may explain why estimates of the early recurrence risk differ so much between studies (Coull and Rothwell, 2004).

It is often assumed that ischaemic stroke subtypes 'breed true', in that the subtype of recurrent stroke is generally of the same subtype as the index event. If true, this may support the hypothesis of a distinct underlying arterial pathology in lacunar infarction.

If the arterial pathology underlying lacunar infarction is indeed different from the pathologies that cause other types of ischaemic stroke, we might also expect the risk of myocardial infarction (MI), a marker of atherothrombotic disease, to be lower among lacunar patients. However, little is known about the risk of MI following different subtypes of ischaemic stroke.

This paper reports the findings of a systematic review and series of meta-analyses of cohort studies that followed patients with lacunar and non-lacunar infarction for death, recurrent stroke and/or MI. It compares lacunar with non-lacunar infarct patients for short term and subsequent risks of death and recurrent stroke, recurrent stroke subtype patterns, and risks of MI and cardiac death. The separate assessment of the early and subsequent prognosis is an important feature of our study, since it is generally accepted that non-lacunar infarcts are associated with a higher early mortality and stroke

recurrence risk than lacunar infarcts, but there is uncertainty about the longer term.

Methods
Study identification
We sought studies that had followed both lacunar and non-lacunar infarct patients, or lacunar infarct patients only, for at least one month for death, recurrent stroke and/or MI. We identified relevant studies published in English language journals between January 1966 and December 2004 by: a comprehensive electronic search strategy using Medline and Embase (*see* Appendix for details); perusing reference lists of all relevant primary and review articles identified; searching within books on cortical and subcortical stroke; and discussions with colleagues. We included inception cohort studies that were either community or hospital-based, but excluded studies among highly selected groups of patients (e.g. clinical trials). We also excluded studies with irresolvable data inconsistencies.

Data extraction
From each study identified, we extracted information on:

- The population studied (i.e. community or hospital-based, hospital admissions only or including outpatients, consecutive recruitment or not).
- The numbers of lacunar and non-lacunar patients (excluding those with infarction from unusual causes).
- Demographic characteristics of the study population.
- Definition of recurrent stroke.
- Stroke subtype classification method.
- Duration of follow-up.
- Proportion of patients with brain imaging following index and recurrent stroke.
- Numbers of lacunar and non-lacunar infarct patients who were dead or had a recurrent stroke at 1 month, from 1 to 12 months, and from 1 to 5 years after the index stroke.
- Numbers of lacunar and non-lacunar infarct patients who had an MI, or died from a cardiac cause.
- Numbers and subtypes of recurrences among lacunar and non-lacunar infarct patients.

We chose the 1 month, 1–12 month, and 1–5 year time points for death and recurrent stroke because this allowed us to assess separately the very early and longer term risks for these outcomes in the maximum number of studies. It also allowed us to eliminate the effects of varying definitions of early stroke recurrence in the assessment of longer term risk.

Statistical analysis
We calculated risks of death and recurrent stroke at 1 month, 1–12 months and 1–5 years and obtained 95% confidence intervals (CIs) using Confidence Interval Analysis software (Wilson method) (Bryant, 2000).

For studies with data on death, recurrent stroke, MI or cardiac death among both lacunar and non-lacunar infarct patients, we used Cochrane RevMan software (version 4.2) to calculate study-specific and summary Peto odds ratios (ORs, non-lacunar versus lacunar infarction) with 95% CIs for each of death and recurrent stroke at 1 month, 1–12 months and 1–5 years, and for cardiac death any time after index stroke. We used standard χ^2 tests to assess heterogeneity between studies or groups of studies. We analysed data on recurrent

stroke subtypes using three different methods: (i) we pooled data from all studies providing information on recurrent stroke subtypes, and compared the frequencies of stroke subtypes after each of lacunar and non-lacunar infarction; (ii) we calculated the ratio of the observed proportion of lacunar recurrences following a lacunar index event to the proportion expected from two community-based studies of first-ever stroke incidence (Bamford *et al.*, 1991; Hillen *et al.*, 2003) and the ratio of the observed to the expected proportion of non-lacunar recurrences following a non-lacunar index event; (iii) for studies reporting on both lacunar and non-lacunar patients, we calculated study-specific and summary relative risks (RRs) of having a lacunar recurrence (for lacunar versus non-lacunar infarction at baseline).

Results

Our search initially identified 3528 papers. From 154 papers relating to prognosis, we selected 31 relevant studies. Four studies were excluded (1328 patients); one study was not an inception cohort (Yamamoto and Bogousslavsky, 1998); one was conducted among a highly selected group of patients (Prencipe *et al.*, 1998); one followed only those patients that survived 3 months after the index event (Moroney *et al.*, 1997); and one had irresolvable data inconsistencies (Brainin *et al.*, 1992).

The data available on death, recurrent stroke and recurrent stroke subtypes from the remaining 27 studies are summarized in Fig. 1. We were unable to extract any analysable data

from 8 studies (2538 lacunar, 6967 non-lacunar patients) (Giroud *et al.*, 1991; Hier *et al.*, 1991; Kolominsky-Rabas *et al.*, 1998; Moroney *et al.*, 1998; Murat and Erturk, 2002; Soda *et al.*, 2004; Yokota *et al.*, 2004; Grau *et al.*, 2005). Characteristics of the 19 studies (2402 lacunar, 3462 non-lacunar patients) contributing to the analyses are shown in Table 1 (Gandolfo *et al.*, 1986; Bamford *et al.*, 1991; Norrving and Staaf, 1991; Sacco *et al.*, 1991, 1994; Landi *et al.*, 1992; Miyao *et al.*, 1992; Boiten and Lodder, 1993; Nadeau *et al.*, 1993; Anderson *et al.*, 1994; Clavier *et al.*, 1994; Samuelsson *et al.*, 1994, 1996; Toni *et al.*, 1995; Salgado *et al.*, 1996; Petty *et al.*, 2000; Eriksson and Olsson, 2001; Kazui *et al.*, 2001; Staaf *et al.*, 2001; De Jong *et al.*, 2002, 2003; Yamamoto *et al.*, 2002; Hillen *et al.*, 2003). In the majority of studies, the non-lacunar comparison group consisted of all non-lacunar ischaemic strokes. One study excluded patients with subtentorial infarction (Toni *et al.*, 1995), one excluded patients with cardioembolic infarction (Nadeau *et al.*, 1993), and a third study excluded both subtentorial and cardioembolic infarcts (Boiten and Lodder, 1993). The mean age (weighted by study size) of the lacunar infarct patients was 68 years (range 64–73) and of the non-lacunar infarct patients was 72 years (range 66–76). The majority of patients had a CT brain scan after their first stroke, but only a few studies used MR scanning. The few studies that mentioned the proportion of patients with recurrent stroke who had some form of brain imaging generally reported lower rates of scanning
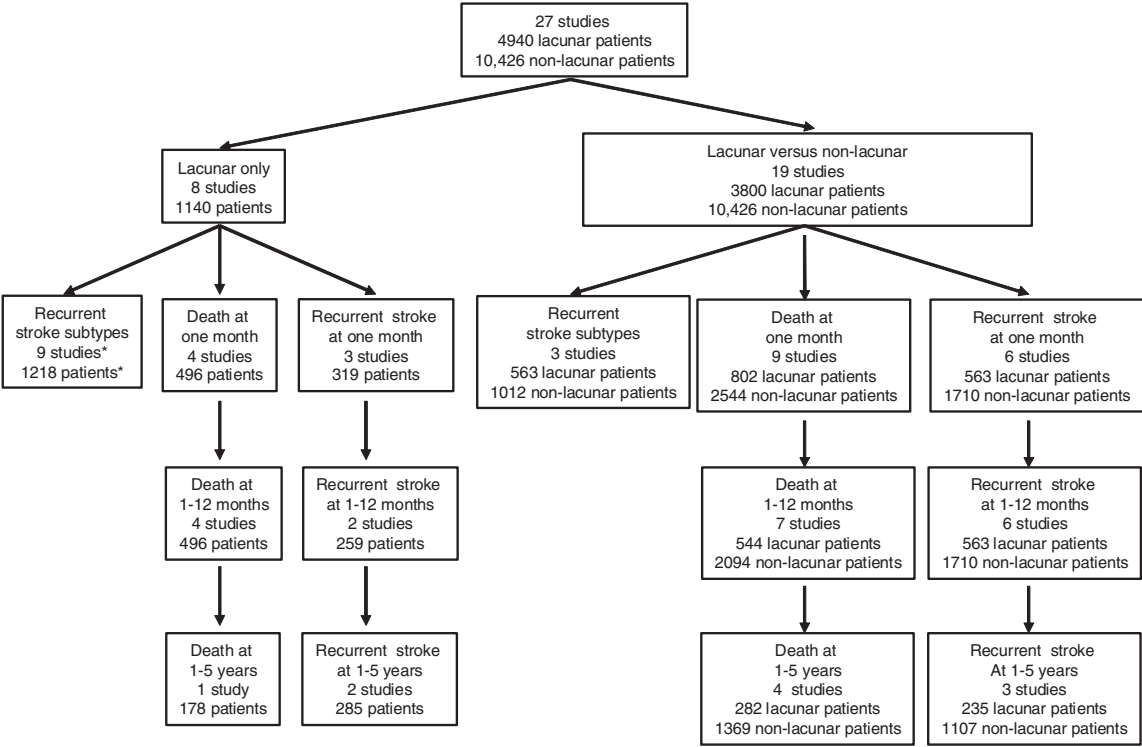
* One study reported on death and recurrent stroke among lacunar and non-lacunar patients, but reported on recurrent stroke subtypes among lacunar patients only

Fig. 1 Data available on death and recurrent stroke from 27 eligible studies.

Table 1 Characteristics of identified studies

Study	Stroke population recruited	Mean age		% male		Follow-up (months) (% loss)	% patients with CT/MRI brain scan		Total patients included (lacunar infarct patients)
		Lacunar	Non-lacunar	Lacunar	Non-lacunar		Index stroke	Recurrent stroke	
Studies including lacunar and non-lacunar patients									
London (Hillen et al., 2003)	Community-based (first-ever stroke)	NR	NR	NR	NR	14 (0)	87% had CT	65% had CT	1166 (401)
Maastricht (Boiten and Lodder, 1993; De Jong et al., 2002, 2003)	Admissions of first-ever stroke to hospital, excluding subtentorial infarcts	67	70	55	63	Max 29 (0)	93% had CT	56% had CT	197 (103)
Milan (Landi et al., 1992)	Patients seen in ER within 72 h of first-ever stroke and admitted to neurology department	64	66	63	61	Mean 28 (0)	100% had CT	NR	191 (88)
New York (Sacco et al., 1994)	Hospitalized first-ever strokes who were residents of Northern Manhattan	NR	NR	NR	NR	Mean 40 (6)	NR	NR	306 (85)
Oxford (Bamford et al., 1991)	Community-based (first-ever strokes)	72	73	40	54	12 (0)	93% had CT	NR	543 (137)
Perth (Anderson et al., 1994)	Community-based (first-ever strokes)	NR	NR	NR	NR	12 (0)	76% (of entire cohort) had CT	NR	247 (22)
Rochester (a) (Sacco et al., 1991)	Community-based (first-ever strokes; sensorimotor lacunar strokes excluded if no infarct on scan)	NR	NR	NR	NR	60 (NR)	NR	NR	594 (78)
Rochester (b) (Petty et al., 2000)	Community-based (first-ever strokes)	73	76	43	40	Mean 38 (0)	92% had CT, MRI (or autopsy)	NR	442 (72)
Sweden (Eriksson and Olsson, 2001)	Admissions to stroke unit	71	73	55	43	168 (0)	74% had CT	54% had CT	309 (47)
Rome (Toni et al., 1995)	Consecutive first-ever stroke patients admitted within 12 h of onset of event	67	68	65	55	1 (0)	100% had CT	NA	517 (170)
USA (b) (Nadeau et al., 1993)	Consecutive admissions to the Veterans Administration Medical Centre	NR	NR	100	100	Median 36 (7)	100% had CT	NR	212 (59)
Studies including lacunar patients only									
Australia (Kazui et al., 2001)	Consecutive admissions of first-ever strokes to stroke unit	65	NA	58	NA	Median 49 (0)	100% had CT or MRI	NR	60 (60)
France (Clavier et al., 1994)	Consecutive admissions of first-ever strokes to stroke unit	NR	NA	63	NA	Mean 35 (0.6)	100% had CT or MRI	81% had CT or MRI	177 (177)
Genoa (Gandolfo et al., 1986)	Consecutive admissions of first-ever strokes to neurology department	65	NA	79.4	NA	Mean 47 (0)	100% had CT	NR	107 (107)
Kyoto (Yamamoto et al., 2002)	Consecutive admissions of first-ever strokes to neurology department	69	NA	62	NA	Mean 107 (0)	100% had MRI	NR	177 (177)
Lund (Norrving and Staaf, 1991; Staaf et al., 2001)	Pure motor stroke (from presumed lacunar infarction) first-ever strokes patients admitted or seen in outpatient clinics	73	NA	60	NA	Mean 78 (0)	58% had CT	19% had CT	178 (178)
Nagoya (Miyao et al., 1992)	Admissions of first-ever strokes within 1 week of symptom onset	68	NA	64.7	NA	Mean 27 (0)	100% had CT	NR	215 (215)
Örebro (Samuelsson et al., 1994, 1996)	Consecutive admissions of first-ever strokes with lacunar syndromes	66	N/A	63	NA	Median 48 (0)	100% had MRI	100% had MRI	81 (81)
Portugal (Salgado et al., 1996)	Consecutive admissions and outpatients seen at hospital within 7 days after onset (first-ever strokes)	65	NA	64	NA	Median 39 (1)	100% had CT	93% had CT	145 (145)

NA = not applicable; ER = emergency room; NR = not reported.

than after first stroke. No study reported use of diffusion weighted MR scanning after first or recurrent strokes (Table 1).

Death

The death rate at 1 month among lacunar patients was ∼0–2%, and from 1 to 12 months ∼8%. Among non-lacunar patients, the 1 month death rate was higher, ranging from ∼10–20%, whilst the 1–12 month mortality rate was ∼20% (Fig. 2). Death rates among studies that included lacunar patients only were comparable to those obtained from lacunar patients in studies that also included non-lacunar patients (Fig. 2).

Of the nine studies reporting on death in lacunar and non-lacunar patients, all but one included first-ever strokes only,

and four were community-based. At 1 month the odds of death were almost four-fold greater in non-lacunar than lacunar patients (OR 3.81, 95% CI 2.77–5.23) (Fig. 3). This difference attenuated with time, with the odds of death at 1–12 months just 2-fold greater among non-lacunar patients (OR 2.32, 95% CI 1.74–3.08) and at 1–5 years <2-fold greater (OR 1.77, 95% CI 1.28–2.45; data not shown in the figure). However, there was significant heterogeneity between studies for the 1–5 year results [$\chi^2(3) = 7.91$, $P = 0.05$]. Data for this later time period are less reliable, since they were available for fewer studies in fewer patients (Fig. 1), and their extraction required us to make several assumptions about losses to follow-up and the statistical methods used in the original studies. The lacunar patients in these analyses were very slightly younger than the non-lacunar patients (weighted mean age 71 versus 74 years), but we were unable to assess the
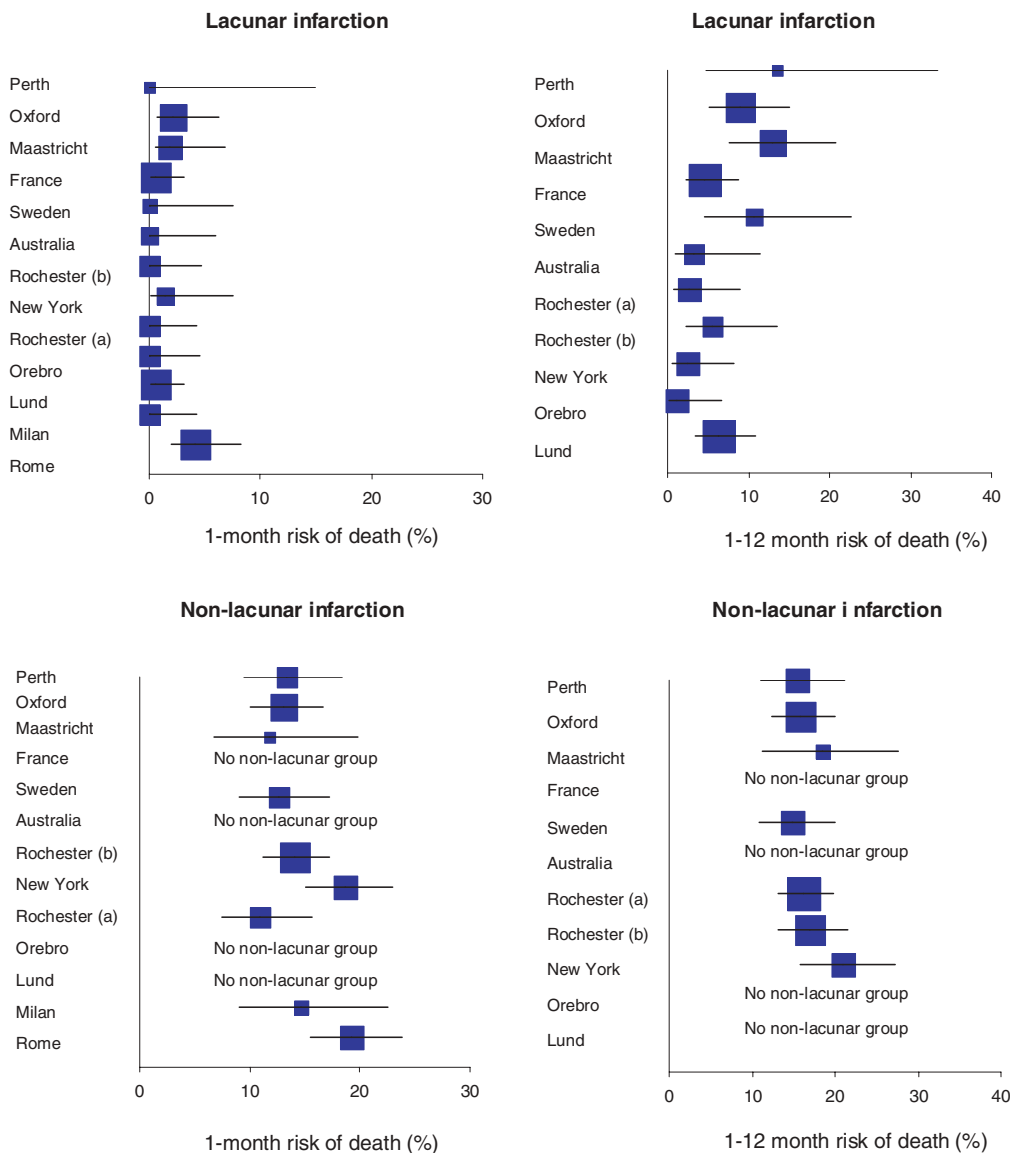
Fig. 2 Risks of death at 1 month and 1–12 months among patients with lacunar and non-lacunar infarction. Risks are shown as squares, with size denoting the statistical weight of the study. Horizontal lines represent 95% CIs.
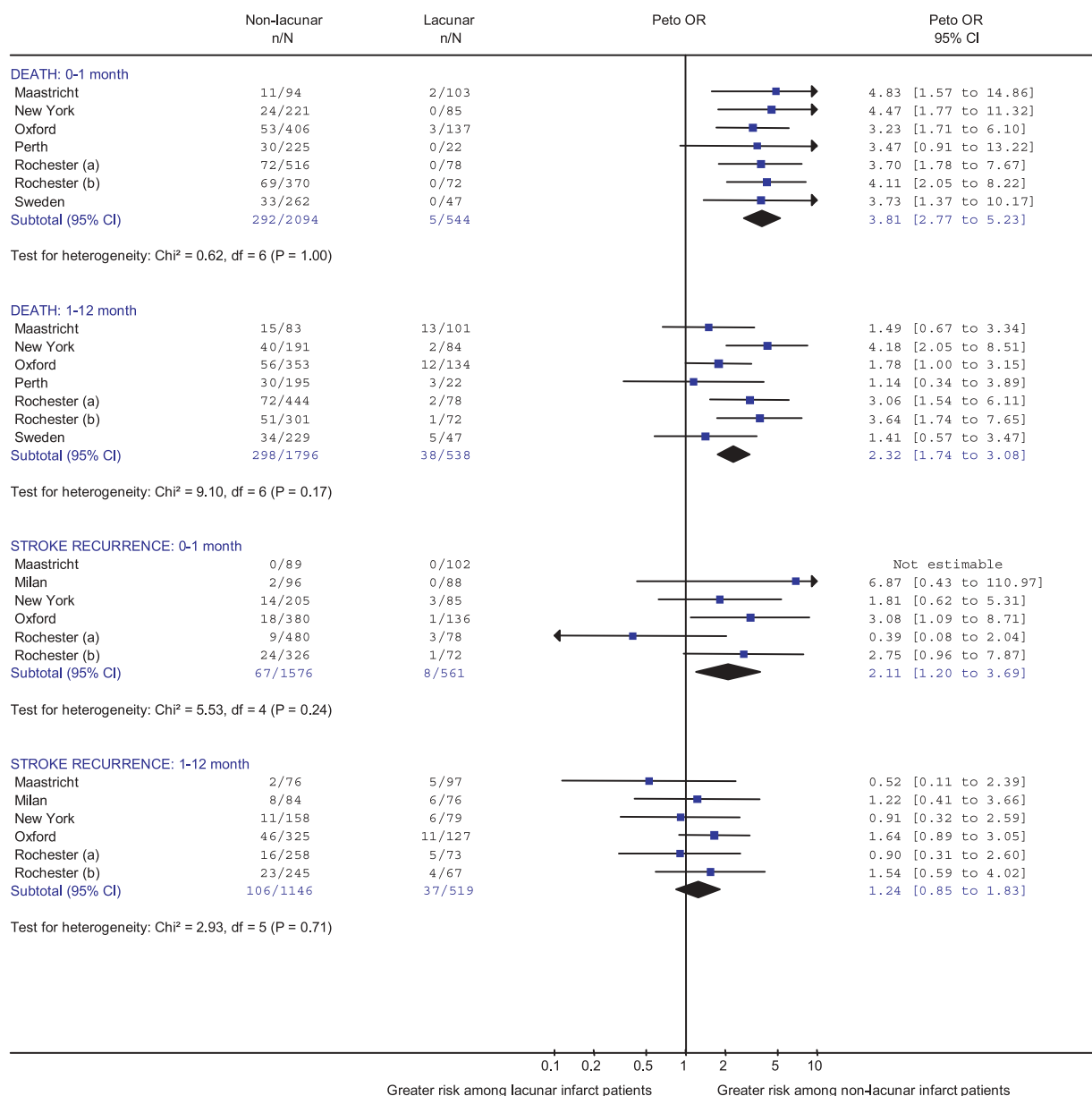
Fig. 3 Odds ratios (ORs) (non-lacunar versus lacunar infarction) for each of mortality and recurrence at 1 month and 1–12 months post-stroke. The OR for each study is shown as a square and horizontal lines represent 95% CIs. Diamonds represent pooled ORs, with 95% CIs represented by the width of the diamonds.

impact of this age difference, since mean age for lacunar and non-lacunar patients was not given in three of the included studies.

Recurrent stroke

Only 9 of the 19 studies reporting on recurrent stroke actually provided a definition of recurrent stroke, and no two studies used the same definition. In particular, the minimum necessary time interval between index event and recurrent stroke varied markedly, ranging from 3 to 21 days. If a stroke occurred during this time interval, it often had to be in a different vascular territory or anatomical site from the first

event, of a different stroke subtype, or result in a different neurological deficit, in order to be considered a recurrence.

The risk of recurrence among lacunar patients during the first month ranged from 0–4%, and from 1 to 12 months was ~5–8%. Among non-lacunar patients the 1 month recurrence risk was ~5%, and the 1–12 month risk was ~10% (Fig. 4). The recurrence risks among lacunar infarction patients in studies including lacunar patients only were similar to those reported in studies that also included non-lacunar patients (Fig. 4).

Of the six studies with data on risk of recurrence among lacunar and non-lacunar patients at 1 month and 1–12 months, only two provided a definition of recurrent
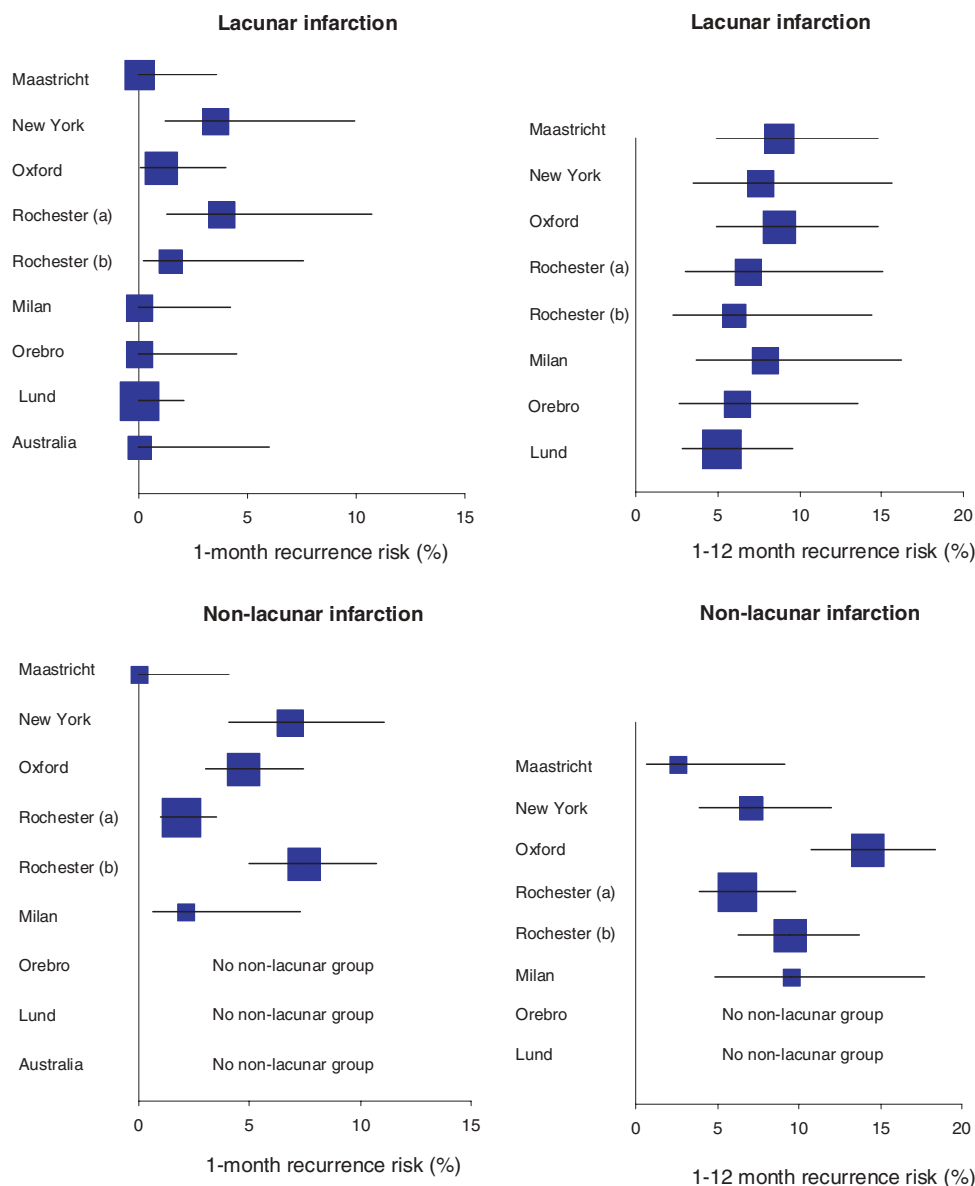
Fig. 4 Risks of recurrent stroke at 1 month and 1–12 months among patients with lacunar and non-lacunar infarction. Notation as for Fig. 2.

stroke, (Bamford *et al.*, 1991; Petty *et al.*, 2000) while one study reported no recurrent strokes in either group within the first month, suggesting that its definition of recurrent stroke excluded events within a month of the index event (Boiten and Lodder, 1993). Five studies included first-ever strokes only, and three were community-based (Table 1). In all studies, the proportion of index strokes with brain imaging (mostly CT scanning) was close to 100%, but the proportion of recurrent strokes with brain imaging was reported in only one study, in which 56% of recurrent stroke patients had a CT scan (Table 1) (Boiten and Lodder, 1993).

The odds of recurrent stroke in the first month were just over two times greater in non-lacunar compared with lacunar infarct patients (pooled OR 2.11, 95% CI 1.20–3.69) (Fig. 3). Thereafter, there was no statistically significant difference in

the risk of recurrent stroke between non-lacunar versus lacunar infarction either at 1–12 months (pooled OR 1.24, 95% CI 0.85–1.83) (Fig. 3) or at 1–5 years (OR 1.61, 95% CI 0.96–2.70; data not shown in the figure), although, as for mortality, the 1–5 year data are less reliable. The mean age for lacunar and non-lacunar patients was the same in the studies included in these analyses (weighted mean age 73), although stroke subtype-specific information on age was not provided in two studies.

Sensitivity analysis

When we repeated our analyses for death and recurrent stroke including only community-based studies, we found very similar results.
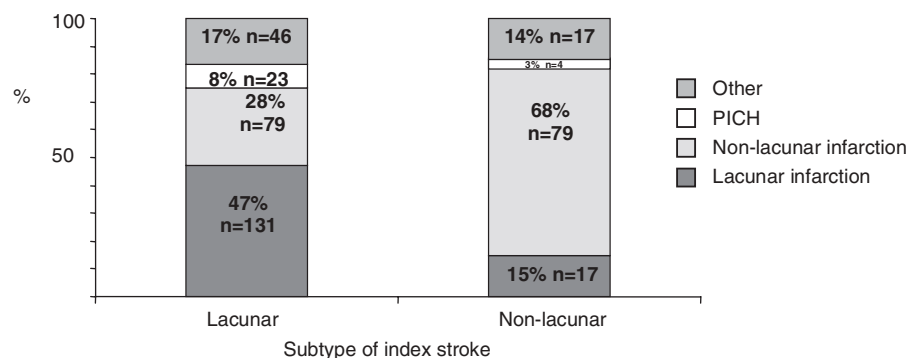
Fig. 5 Recurrent stroke subtypes following lacunar and non-lacunar infarction at baseline. Total number of lacunar patients = 279; total number of non-lacunar patients = 117; Other = unclassified ischaemic recurrences; PICH = primary intracerebral haemorrhage.

Recurrent stroke subtypes

Only 6 of the 12 studies reporting on recurrent stroke subtypes provided information on the proportion of recurrences having brain imaging (ranging from 19 to 100%) (Boiten and Lodder, 1993; Clavier *et al.*, 1994; Salgado *et al.*, 1996; Samuelsson *et al.*, 1996; Staaf *et al.*, 2001; Hillen *et al.*, 2003). Just two of these studies used MRI (Clavier *et al.*, 1994; Samuelsson *et al.*, 1996), and neither used diffusion weighted imaging (DWI) (Table 1). When we pooled data from these 12 studies, we found that following lacunar infarction just under half the recurrences were lacunar again, and almost one-third were non-lacunar (Fig. 5). Following non-lacunar infarction, two thirds of the recurrences were non-lacunar again. In a second analysis of recurrent stroke subtypes, the proportion of recurrences that were lacunar following a lacunar index event was greater than expected, based on the 25% reported proportion of first-ever strokes attributed to lacunar infarction in two community-based studies (RR observed to expected 1.90, 95% CI 1.49–2.41). There was no statistically significant difference between the 68% observed and the 57% expected proportion of recurrences that were non-lacunar following a non-lacunar index event (RR observed to expected 1.19, 95% CI 0.94–1.48). In a third analysis of recurrent stroke subtypes, in which we pooled studies that included both lacunar and non-lacunar patients, the risk of a lacunar recurrence following a lacunar event at baseline was two times greater than the risk of a lacunar recurrence following a non-lacunar event at baseline (RR lacunar versus non-lacunar at baseline 2.24, 95% CI 1.30–3.85). However, there was significant heterogeneity between these studies [$\chi^2(2) = 7.22$, $P = 0.03$] and the numbers of events were small (54 recurrences following a lacunar event at baseline, and 117 recurrences following a non-lacunar event at baseline).

Myocardial infarction

Only three studies reported on non-fatal MI (14 MIs among 513 patients) (Landi *et al.*, 1992; Salgado *et al.*, 1996; Yamamoto *et al.*, 2002). Five studies (four of which included lacunar patients only) reported on fatal MI (16 MIs among 484 patients) (Gandolfo *et al.*, 1986; Landi *et al.*, 1992; Salgado *et al.*, 1996; Samuelsson *et al.*, 1996; Kazui *et al.*, 2001). A further six studies (two of which included lacunar patients only) reported on death from a cardiac cause (Bamford *et al.*, 1991; Miyao *et al.*, 1992; Anderson *et al.*, 1994; Toni *et al.*, 1995; Staaf *et al.*, 2001; De Jong *et al.*, 2003). There was no significant difference in odds of cardiac death among non-lacunar compared with lacunar patients (OR non-lacunar versus lacunar 0.96, 95% CI 0.63–1.46), but this was based on a relatively small number of outcome events (85 cardiac deaths among 1966 non-lacunar patients versus 33 cardiac deaths among 668 lacunar patients).

Discussion

Our systematic review found that the early risk of death was greater among non-lacunar than lacunar infarct patients. However, when the early period was excluded, the difference in risk attenuated, suggesting that much of the difference in 1 month death rates between lacunar and non-lacunar patients may be accounted for by the early effects of infarct size, and early risk of recurrent stroke.

After 1 month, we found no statistically significant difference in the risk of recurrent stroke between lacunar and non-lacunar infarction. The higher early recurrence risk among non-lacunar infarct patients confirms previous work (Lovett *et al.*, 2004) and supports other lines of evidence for a greater prevalence of active sources of thrombotic emboli among these patients (Jackson and Sudlow, 2005). However, it does not rule out similar atherothrombotic mechanisms, albeit with a different anatomical distribution, accounting for most lacunar infarcts.

A number of methodological limitations affect our death and recurrent stroke analyses. Firstly, relevant studies identified in our search reported on risks of outcome events at varying time points, making it impossible to include data in pooled analyses from every potentially relevant study identified. Secondly, the total number of outcome events, particularly recurrent strokes, was relatively small. Thirdly, we were

only able to perform univariate analyses, and thus were unable to control for potential confounding factors such as age, sex and co-morbidity. These limitations highlight the need for pooled multivariate analyses of prognosis among different stroke subtypes using individual patient data from large stroke cohort studies, to increase numbers of patients and outcome events and allow for control of confounding factors. Other potential confounders include interventions such as carotid endarterectomy and anticoagulation, which are usually tailored to stroke subtype. Both interventions are generally used more often following non-lacunar stroke than lacunar ischaemic stroke, and indeed oral anticoagulants have only been shown to be of benefit in patients with atrial fibrillation, whose ischaemic stroke is likely to have been cardioembolic. Furthermore, there are also likely to be differential effects on recurrent stroke subtypes, since available evidence from randomized trials and observational studies of oral anticoagulation suggests that this treatment is more effective in the prevention of cardioembolic than other types of ischaemic stroke (Evans *et al.*, 2000; Hart *et al.*, 2000). However, available data do not suggest a definite difference in the effectiveness of carotid endarterectomy between symptomatic patients presenting with non-lacunar versus lacunar ischaemic stroke (Inzitari *et al.*, 2000). Neither is there clear evidence to suggest that carotid endarterectomy prevents a greater proportion of subsequent non-lacunar than lacunar ischaemic strokes (Barnett *et al.*, 2000).

Fourthly, the clinical distinction between lacunar and non-lacunar infarction is not perfect. Ten to twenty per cent of patients with a clinical lacunar syndrome actually have a recent relevant cortical infarct on brain imaging, and 10–20% of patients with a clinical cortical syndrome have a relevant subcortical lesion on brain imaging (Mead *et al.*, 1999). When there is no lesion present on imaging (and stroke subtype is therefore determined by clinical syndrome), around one-fifth of lacunar and small cortical ischaemic strokes may therefore be misclassified. This proportion could be reduced in future studies by the more frequent use of advanced MR imaging, especially when the CT scan does not show a relevant infarct. The effect of this misclassification would be to reduce the apparent size of any real epidemiological differences between infarct subtypes.

Finally, the data on very early risk of stroke should be interpreted with caution because of widely varying stroke recurrence definitions. In some studies, the risk of recurrence within the first month would have been underestimated since early recurrences involving the same arterial territory, or resulting in similar symptoms to the index event, were not always considered as recurrent strokes. There is also some overlap between the definition of recurrent stroke and stroke-in-progression. Stroke-in-progression is thought to be particularly common in lacunar stroke (Nakamura *et al.*, 1999); therefore, very early recurrences among lacunar patients may not be counted as such and may instead be considered part of the evolution of the initial stroke. Stroke-in-progression has been defined recently by the European Stroke Database collaboration as 'neurological progression occurring within the first 3 days' (Birschel *et al.*, 2004). In agreement with others (Coull and Rothwell, 2004), we recommend that neurological worsening occurring at any time after the index event, following a period of stability of ≥ 24 h should be considered a potential recurrent stroke. Otherwise the very early recurrence risk will be underestimated (Coull and Rothwell, 2004). A standard definition of recurrent stroke is needed if reliable and unbiased conclusions are to be drawn from individual studies and pooled analyses.

Notwithstanding the methodological limitations outlined above, our findings on the longer term risks of recurrent stroke (which are less likely to be subject to stroke recurrence definition bias) and death do not provide support for fundamentally different arterial pathologies in lacunar and non-lacunar infarction.

Our three different analyses on recurrent stroke subtypes do, however, provide some evidence that recurrent stroke subtypes 'breed true', lending some support to the hypothesis of a different arterial pathology underlying lacunar infarction. However, as mentioned above, there will have been some misclassification of ischaemic stroke subtypes, both at baseline and following recurrent events. Recurrent stroke subtypes in particular may not have been very accurately classified since very few studies reported using MR brain imaging for recurrences, and none reported use of MR DWI, which is particularly useful in differentiating between old and recent infarcts and in establishing the infarct subtype. In patients with residual deficits from their first stroke, suspected recurrences in the same arterial territory as the index event can be particularly difficult to diagnose and classify without the help of advanced MRI. It is difficult to predict the effect of such misclassification on the results, but it is possible that, in the face of uncertainty, the infarct subtype assigned is more likely to be the same as that of the first stroke. In addition, our analyses of recurrent stroke subtypes could not control for the differential use or effects of secondary preventive interventions such as anticoagulation and carotid endarterectomy in different subtypes of ischaemic stroke. There were very few available data on the risk of MI following different ischaemic stroke subtypes. We found no significant difference in the risk of cardiac death among non-lacunar versus lacunar infarct patients. However, this was based on a relatively small number of outcome events, and further study of the long-term risks of fatal and non-fatal MI after different stroke subtypes is needed before reliable conclusions can be drawn.

In conclusion, while differences between lacunar and non-lacunar infarct patients in early risks of death and recurrent stroke suggest different predominant mechanisms in terms of the arterial occlusive source, available data on the longer-term risks of death and recurrent stroke do not provide convincing support for fundamentally different arterial pathologies. Recurrent stroke subtype patterns provide some evidence for different arterial pathologies, but the studies had methodological limitations. Data on long term risks of MI after lacunar versus non-lacunar infarction are very sparse.

Pooled analyses of individual patient data from existing studies, as well as further, methodologically rigorous, long term follow-up studies that include both lacunar and non-lacunar infarct patients, with advanced MRI (including DWI) of recurrent strokes and collection of data on cardiac as well as stroke outcomes, are needed if meaningful conclusions about the arterial pathology of lacunar infarction are to be drawn from follow-up studies.

Acknowledgements

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Appendix
Medline search*

(i) Cerebrovascular disorders/or exp basal ganglia cerebrovascular disease/or exp brain ischemia/or exp carotid artery diseases/or exp cerebrovascular accident/or exp dementia, vascular/or exp hypoxia-ischemia, brain/or exp intracranial arterial diseases/or exp 'intracranial embolism and thrombosis'/or exp intracranial hemorrhages/or exp vasospasm, intracranial/

(ii) (Stroke$ or cerebrovasc$ or cerebral vasc$).tw.

(iii) 1 or 2

(iv) lacun$.tw.

(v) ((lacunar or small or subcortical or silent) adj5 (infarct$ or stroke)).tw.

(vi) (small vessel adj5 (stroke$ or occlusion or disease)).tw.

(vii) 4 or 5 or 6

(viii) 3 and 7

(ix) Limit 8 to human.

*A similar, appropriately adapted search was used for Embase.