

Risk and Cumulative Risk of Stroke Recurrence

A Systematic Review and Meta-Analysis

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Background and Purpose—Estimates of risk of stroke recurrence are widely variable and focused on the short-term. A systematic review and meta-analysis was conducted to estimate the pooled cumulative risk of stroke recurrence.

Methods—Studies reporting cumulative risk of recurrence after first-ever stroke were identified using electronic databases and by manually searching relevant journals and conference abstracts. Overall cumulative risks of stroke recurrence at 30 days and 1, 5, and 10 years after first stroke were calculated, and analyses for heterogeneity were conducted. A Weibull model was fitted to the risk of stroke recurrence of the individual studies and pooled estimates were calculated with 95% CI.

Results—Sixteen studies were identified, of which 13 studies reported cumulative risk of stroke recurrence in 9115 survivors. The pooled cumulative risk was 3.1% (95% CI, 1.7–4.4) at 30 days, 11.1% (95% CI, 9.0–13.3) at 1 year, 26.4% (95% CI, 20.1–32.8) at 5 years, and 39.2% (95% CI, 27.2–51.2) at 10 years after initial stroke. Substantial heterogeneity was found at all time points. This study also demonstrates a temporal reduction in 5-year risk of stroke recurrence from 32% to 16.2% across the studies.

Conclusions—The cumulative risk of recurrence varies greatly up to 10 years. This may be explained by differences in case mix and changes in secondary prevention over time. However, methodological differences are likely to play an important role and consensus on definitions would improve future comparability of estimates and characterization of groups of stroke survivors at increased risk of recurrence. (*Stroke*. 2011;42:1489-1494.)

Key Words: frequency ■ predictors ■ recurrence ■ stroke

Patients surviving an initial stroke are known to be at significantly increased risk for further strokes compared to the general population.¹ However, studies show considerable variation in the estimation of risk of stroke recurrence in both the early years and in the long-term after first stroke.² For example, the cumulative risk of stroke recurrence up to 5 years after initial stroke has been reported in population-based studies as 19% in Manhattan, 29% in Rochester, 30% in Oxfordshire, and 32% in Perth.^{3–6}

Accurate identification of the time at which stroke survivors are at increased risk for stroke recurrence is important for modifiable risk factors to target and to help reduce the risk of recurrence occurring. The aim of this systematic review and meta-analysis is to estimate the pooled cumulative risk of stroke recurrence at time points ranging from 30 days to 10 years after first-ever stroke.

Materials and Methods

Search Strategy and Selection Criteria

This review included studies from hospital-based or community-based stroke registers reporting the risk of stroke recurrence at any time point after first-ever stroke irrespective of study design and setting or language. Ovid Medline (1950–November 2009), EMBASE (1950–November 2009), and the Web of Science were searched using both medical subject heading terms and free text, combining terms for stroke (stroke OR cerebrovascular disease OR cerebrovascular accident AND stroke recurrence [recurren*]).

The reference lists of all identified studies and contents pages of relevant peer-reviewed journals and abstracts from national and international conferences related to stroke were manually searched to identify further studies. All searches included studies published until the end of December 2009.

Studies reporting recurrence after ischemic strokes, primary intracerebral strokes, subarachnoid hemorrhages, and undefined strokes were included. A stroke “recurrence” was defined as a focal neurological deficit lasting >24 hours and occurring after an initial stroke. This broad definition was used to include all studies meeting

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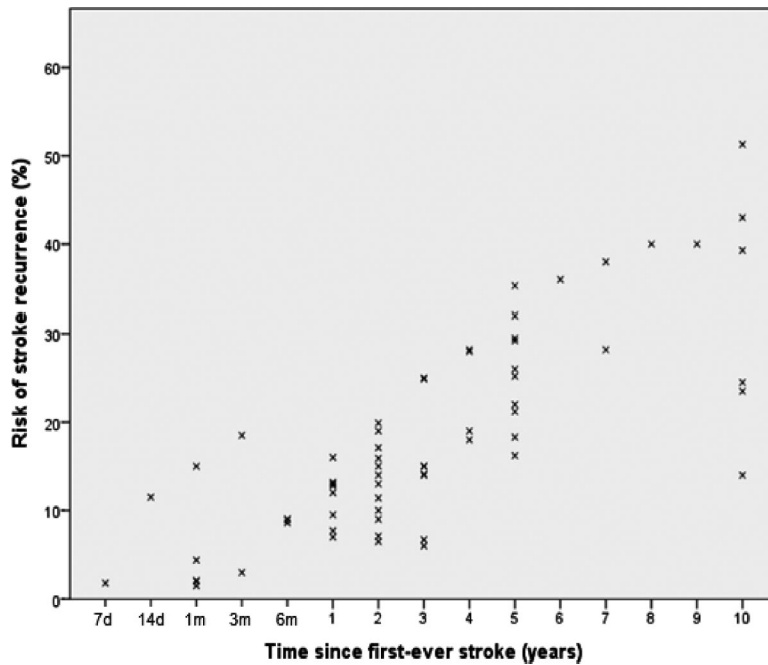


Figure 1. Risk of stroke recurrence across all studies.

our inclusion criteria, regardless of the length of period after initial stroke during which recurrences were excluded. Studies reporting data on only a subset of patients (eg, diabetic patients) were excluded. Multiple publications from the same study group were reviewed to avoid the use of data from overlapping cohorts. In instances when incomplete data were obtained, the authors were contacted in writing for permission to obtain further data. If no response was received within 2 weeks, then further correspondence contacts were sought and contacted if available. Data were extracted from all studies to estimate the pooled cumulative risk of stroke recurrence at 30 days and 1, 5, and 10 years after initial stroke.

Statistical Analyses

The risk of stroke recurrence ie, the probability of a stroke recurrence having occurred by a given time point, was obtained directly from the studies. The cumulative risk of stroke recurrence, defined as the probability that an individual will have a stroke recurrence at a given time point assuming they do not die from some other cause,⁷ and related 95% CI were calculated 30 days, and 1, 5, and 10 years after first stroke for individual studies and pooled estimates were derived. Pooled estimates and associated 95% CI were calculated using a random effects model,⁸ and Forrest plots were constructed for each time point. Analyses for heterogeneity were conducted using the χ^2 test. Sensitivity analyses were conducted to compare the pooled cumulative risk of recurrence 1 year after first stroke, for hospital and community-based stroke populations, and also to compare studies reporting the cumulative risk of recurrence after an ischemic stroke only, with studies including hemorrhagic strokes in their analyses.

A random effects meta-regression Weibull model was fit to the risk of stroke recurrence, estimated in the individual studies, to model cumulative risk as a function of time since first stroke. The Weibull is a generalization of the exponential distribution and was the simplest model providing an adequate fit to the meta-analytic estimates of stroke recurrence.⁹ This model allowed for the prediction of the cumulative risk at time points not directly analyzed in the meta-analysis. The model assumed that the cumulative risk followed a Weibull distribution with a bivariate random effect model for the study specific parameters. Analyses were conducted using SPSS version 17, PROC NL MIXED of SAS version 9.1, and Review Manager version 5.

Results

Two-thousand five-hundred seven studies were identified by the electronic database searches, of which 2483 did not meet the inclusion criteria for reasons such as not reporting risk of stroke recurrence after first-ever stroke only or reporting from only a subset of the population. Four studies were added by manually searching relevant journals and conference abstracts. Therefore, a total of 28 studies reporting the risk of stroke recurrence were included in this review. Of these, 13 studies reported the cumulative risk of stroke recurrence and were used in the meta-analysis.

Risk of Stroke Recurrence

The risk of stroke recurrence was reported to range from 1.1% in South London,¹⁰ UK, to 15% in Oxfordshire,¹¹ UK, by 1 month; from 7.0% in Lisbon, Portugal,¹² to 20.6% in Nanjing, China,¹³ by 1 year; from 16.2% in South London, UK,¹⁰ to 35.3% in Hisayama, Japan,¹⁴ by 5 years; and from 14% in Rome, Italy,¹⁵ to 51.3% in Hisayama, Japan,¹⁴ by 10 years after initial stroke. Figure 1 shows the estimates of risk of stroke recurrence across all the included studies.

Cumulative Risk of Stroke Recurrence

Sixteen studies reporting cumulative risk of stroke recurrence were identified and data were obtained from 13 studies for the time points analyzed in the meta-analysis (Table). Data from 3 studies were unavailable despite multiple attempts to contact the authors. The pooled cumulative risk of stroke recurrence was: 3.1% (95% CI, 1.7–4.4) at 30 days (Figure 2A); 11.1% (95% CI, 9.0–13.3) at 1 year (Figure 2B); 26.4% (95% CI, 20.1–32.8) at 5 years (Figure 2C); and 39.2% (95% CI, 27.2–51.2) at 10 years after initial stroke (Figure 2D). Substantial heterogeneity was found between studies at all time points ($P < 0.0001$). No differences were observed when the cumulative risk of recurrence between hospital-based and community-based stroke populations were compared 1 year

Table. Cumulative Risk of Stroke Recurrence by Study

Authors	Population Studied	Initial Study Period	N in Study	Cumulative Risk of Stroke Recurrence (%)			
				30 d	1 y	5 y	10 y
Hata et al	Hisayama, Japan	1961–1993	410	...	12.8	35.3	51.3
Petty et al	Rochester, NY, USA	1975–1989	1111	4.4	12.0	29.2	39.3
Burn et al	Oxfordshire UK	1981–1986	675	...	13.2	29.5	...
Dhamoon et al	Northern Manhattan, NY, USA	1983–1988	655	1.5	7.7	18.3	...
Hardie et al	Perth, Australia	1989–1990	328	2.0	16.0	32.0	43.0
Salgado et al	Lisbon, Portugal	1990–1993	145	...	7.0
Rundek et al	Northern Manhattan, NY, USA	1990–1995	611	2.9	9.8
Kolominsky-Rabas et al	Erlangen, Germany	1994–1998	583	...	11.0
Mohan et al	South London, UK	1995–2004	2874	1.1	7.1	16.2	24.5
Modrego et al	Bajo Aragon, Spain	1997–2001	425	2.1	9.5	26.0	...
Appelros et al	Orebro, Sweden	1999–2000	377	...	9.0
Coull et al	Oxfordshire, UK	2002–2003	87	15.0
Xu et al	Nanjing, China	2003–2006	834	5.5	20.6

after stroke. Because significant heterogeneity remained between study estimates within the 2 groups, the results were not stratified. Similarly, no differences were noted between studies reporting the cumulative risk of recurrence after ischemic stroke only compared to studies including hemorrhagic strokes in their analyses.

A Weibull model was fitted to the risk of stroke recurrence of individual studies and pooled estimates of cumulative risk were calculated with 95% CI (Figure 3). It is notable that at each time point analyzed, the pooled estimates closely follow the Weibull model.

Discussion

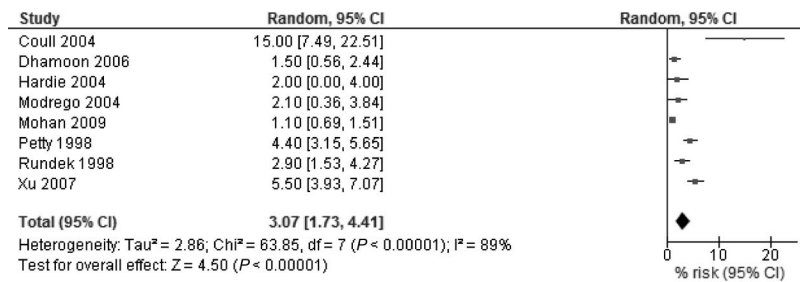
This systematic review and meta-analysis demonstrated wide variation in reported cumulative risk of stroke recurrence up to 10 years after first stroke and significant heterogeneity was observed at all time points. This degree of heterogeneity and its consistency throughout all time points suggest that the observed differences are unlikely to be attributable to chance.

Although case mix and differences in risk factors before stroke between the populations may be responsible for these observed variations, differences in case inclusion criteria also are likely to be contributory factors. One possible reason is that both hospital and population-based studies were included. Not all stroke patients present to hospital, either in the acute period or at all; therefore, hospital-based stroke registers cannot fully ascertain the incidence of initial or recurrent stroke within a population.²¹ Furthermore, it is impossible to predict which patients are more likely to present to hospital after a stroke, because patients with very mild and very severe strokes may not present to hospital for different reasons.²² In this meta-analysis, no significant differences were noted between hospital or community-based estimates 1 year after stroke, and stratification of results did not remove the observed heterogeneity. This indicates that other factors, such as differing definitions of recurrence, case mix, and changes in secondary prevention over time, are likely to be important in the differences observed in this review.

Variations in inclusion criteria may also have importance in differences between the study groups. Both the Northern Manhattan Stroke Study and the Hisayama study only included stroke patients aged older than 40 years.^{3,14,17} Furthermore Northern Manhattan Stroke Study patients were only included in analyses conducted by Dhamoon et al³ if they had a telephone, because a telephone follow-up in interview was conducted 6 months after first stroke. This may result in those from lower socioeconomic groups or older patients without access to a telephone being excluded from the study. Increasing age and lower socio-economic status have both been previously associated with increased incidence of stroke and stroke recurrence;^{10,23} therefore, these studies may be underestimating the true incidence of both stroke and stroke recurrence within the source population.

Significantly, studies differed in the way they defined both a stroke and a recurrence. Modrego et al¹⁹ demonstrated recurrence rates of 9.5% at 1 year and 26% at 5 years after initial stroke; however, this is an example of several studies that excluded patients with a subarachnoid hemorrhage or included ischemic stroke patients only. This review found no significant differences between studies reporting the cumulative risk of stroke recurrence after ischemic stroke only at 1 year after stroke compared to those studies including hemorrhagic strokes in their analyses. However, studies from the South London Stroke Register have found that subarachnoid hemorrhage confers an increased risk of recurrence in the first 6 months after initial stroke, after which there is no increase in risk of stroke recurrence reported up to 10 years of follow-up.¹⁰ By excluding this subgroup, artificially higher rates of recurrence may have been achieved in these studies.

The Oxfordshire Community Stroke Project followed up patients for 6.5 years and found a cumulative risk of recurrence of 30% at 5 years.⁶ The methodology used by Oxfordshire Community Stroke Project investigators included TIA as an initial stroke event. TIA are a known risk factor for strokes, particularly those of an atherosclerotic etiology,²⁴ and including these events as initial strokes may cause



A Cumulative risk of stroke recurrence 30 days after first-ever stroke

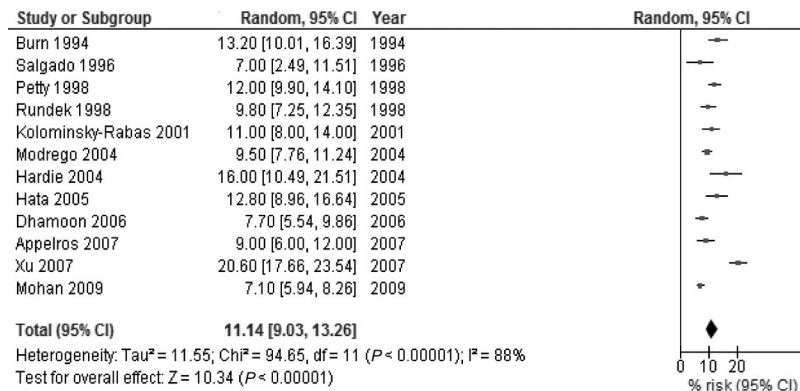
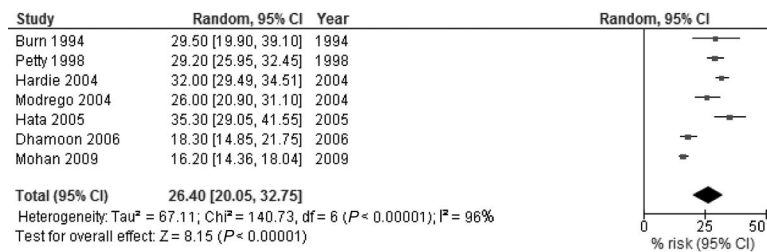
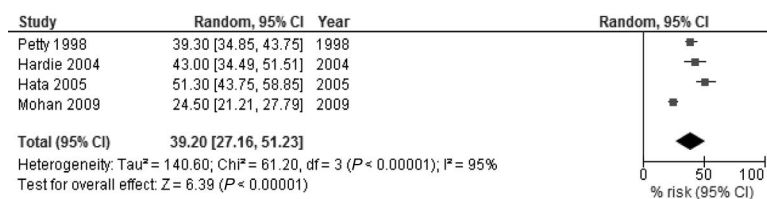


Figure 2. Cumulative risk of stroke recurrence (A) 30 days, (B) 1 year, (C) 5 years, and (D) 10 years, after first-ever stroke

B Cumulative risk of stroke recurrence 1 year after first-ever stroke



C Cumulative risk of stroke recurrence 5 years after first-ever stroke



D Cumulative risk of stroke recurrence 10 years after first-ever stroke

substantial overestimation of the reported risk of stroke recurrence. This is demonstrated in Figure 2A, in which the risk of stroke recurrence 30 days after first stroke was shown to be substantially higher in the study by Coull et al,¹¹ which included TIA, compared with the other studies which excluded TIA.

The reported differences in risk of recurrence may also be explained by differing definitions of “stroke recurrence.” There was wide variation in definition of stroke recurrence used, ranging from any focal neurological deficit lasting for >24 hours occurring after an initial stroke^{3,5,14,19} to an exclusion period of 28 days, only after which further strokes were considered a recurrence.^{25,26} Coull and Rothwell previously demonstrated the effect of different definitions of

stroke recurrence on estimates of risk of recurrence 90 days after first stroke in the Oxford Vascular Study and Oxford Community Stroke Project cohorts.²⁷ They found that the risk of recurrence in Oxford Vascular Study and Oxfordshire Community Stroke Project, respectively, ranged from 18.3% to 14.5% when including all stroke recurrences occurring 24 hours after initial stroke, and from 5.9% to 4.8% using the definition used in the Monitoring Trends and Determinants in Cardiovascular Disease study and other population-based studies.²⁷

This is particularly important when considering the risk of stroke recurrence at 30 days, when an exclusion period of 21 or 28 days imposed in some studies may substantially impact the reported risk.^{10,16,17} In this review, studies excluding

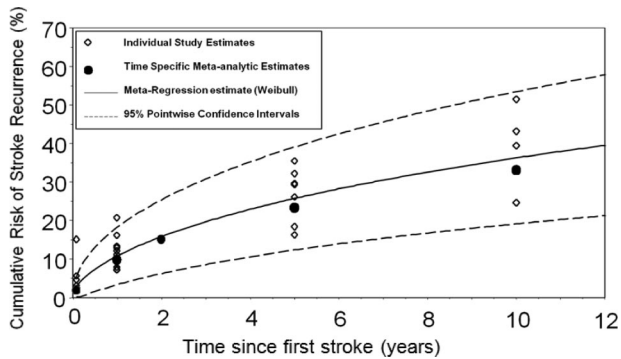


Figure 3. Weibull distribution modeling the cumulative risk of stroke recurrence after first-ever stroke.

recurrences occurring in the first 21 days after initial stroke were at the lower end of estimates of risk of recurrence reported at 30 days.^{10,16} However, the effect of excluding recurrent strokes in the first weeks after initial stroke may be seen well into the long-term period. It is known that strokes with an atherosclerotic origin recur earlier than other stroke subtypes; therefore, by excluding recurrent strokes occurring in the first weeks after initial stroke, artificially lower risk of stroke recurrence may be reported.²⁵

The studies included in this review have a combined study period encompassing 50 years (Table). Temporal trends in stroke management and, in particular, the advent and increasing importance given to secondary prevention after initial stroke may be another important contributory factor of variation in risk of recurrence during this period. Figure 2C largely demonstrates a temporal reduction in risk of stroke recurrence across the different study populations, with smaller recurrence risk reported in later studies. Statistical modeling was used to demonstrate time trends in risk of stroke recurrence and to predict future trends. The cumulative risks of stroke recurrence both at 1 year and 5 years after first stroke was shown to reduce over time, with cumulative risk of 6.49% and 14.3%, respectively, predicted for studies conducted in 2010.

This study provides a comprehensive systematic review of the risk of stroke recurrence demonstrating a temporal reduction across different study populations, with smaller recurrence risk reported in later studies. Our results include patients of all ages, from both hospital-based and population-based studies; however, these criteria also may contribute to the substantial heterogeneity observed and therefore may be a limitation of the study design. Stratification of results according to etiologic subtype may reduce heterogeneity and provide important information regarding the risk of early stroke recurrence. However, because this was not consistently reported in the included studies, this could not be performed.

To identify true populations at high risk for stroke recurrence, good-quality population-based studies using consistent criteria to define a stroke and a recurrence are needed. In particular, for studies reporting the cumulative risk of stroke recurrence in the first weeks and months after initial stroke, notification and analysis of all stroke recurrences without a defined exclusion period are important to understand fully the risk of recurrence during this period.

Although many methodological factors may play a part, this study has demonstrated that genuine differences between populations and temporal changes in stroke management and secondary prevention also may be important in explaining these results. Further research therefore is needed to investigate the effect of acute stroke management and secondary prevention measures on the risk of stroke recurrence from the first weeks to beyond 10 years after first stroke.

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Disclosures

A.P.G. has consultancy agreements with Pfizer Global R&D, Takeda Global R&D (Europe), Schwarz Biosciences, Solace Pharmaceuticals, Cytel Novartis, and Organon. C.W. is an NIHR Senior Investigator. The remaining authors report no conflicts.

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