Epidemiological Studies of the Effect of Stroke on Incident Dementia
A Systematic Review

George M. Savva, PhD; Blossom C.M. Stephan, PhD; the Alzheimer’s Society Vascular Dementia Systematic Review Group

Background and Purpose—Stroke is implicated in the incidence of dementia, and the risk of poststroke dementia is well characterized, but the excess risk of dementia in those with stroke compared with those without stroke is not well known.

Methods—We conducted a systematic review of the excess risk of incident dementia conferred by stroke. Studies of the risk of incident dementia in the population with stroke compared with the population without stroke were identified and compared.

Results—Sixteen studies were identified with all but one conducted in a community setting. A history of stroke doubles the risk of incident dementia in the older population. This increase is not explained by demographic or cardiovascular risk factors or by prestroke cognitive decline. The excess risk of incident dementia diminishes with time after stroke and may be higher in those without an APOE ε4 allele. There is no excess risk of incident dementia in those aged >85 years with a history of stroke compared to those aged >85 years without stroke.

Conclusions—The effect of stroke on dementia incidence in the population is not explained by common risk factors. At this time of population aging and increased stroke survival, more research is needed to determine to what extent efforts to reduce the incidence of stroke will affect the incidence of dementia. (Stroke. 2010;41:e41-e46.)

Key Words: dementia ■ epidemiology ■ review ■ stroke ■ systematic

Up to half of all cases of dementia are thought to be caused wholly or in part by vascular disease in the brain,1 and stroke has long been implicated in dementia.2 This is historically reflected by the diagnoses of “dementia with stroke” or “multi-infarct dementia,” although these terms have been replaced with the broader concepts of vascular dementia and vascular cognitive impairment3,4 recognizing the contribution to dementia of all vascular disease. Pathological findings have shown that much dementia cannot be attributed to a single underlying cause but arises from a combination of factors among which cerebrovascular disease, including infarct and hemorrhage, is an important contributor.4–7

There is a high incidence of stroke in the older population, and an increasing number of older people are stroke survivors.8 The absolute risk of incident dementia within the first few months of stroke (poststroke dementia) is well characterized,9 but it is less clear to what extent the risk of dementia poststroke is different from the risk in stroke-free but otherwise comparable individuals. Modifiable risk factors for stroke are known, making stroke an important target for dementia prevention. Many common risk factors have been identified for stroke and dementia.10 Cognitive decline and dementia are associated with an increased risk of incident stroke,11 and the Framingham study showed even in the absence of stroke or dementia, individuals with a raised stroke risk profile also have significantly higher cognitive deficits.12 As such, it is not clear to what extent stroke causes dementia as opposed to there being common underlying risk factors for both in certain cases. Estimating the excess risk of dementia after a stroke will provide an indication of the possible impact that strategies for reducing stroke would have on dementia prevalence.

Scope of the Current Review
We review studies of the effect of a symptomatic stroke on the incidence of all-cause dementia. First we determine the excess risk of incident dementia in individuals who have had a stroke. Second, we identify whether this increased risk is explained by other factors known to affect dementia incidence and consider the factors that might modify the effect.

Methods
Three databases were used: Medline, EMBASE, and Psycinfo. All searches were initially conducted on February 28, 2008 and later updated to December 31, 2008. The search terms applied were “stroke,” “dementia,” “prospective,” “risk factor,” “incidence,” and “post-stroke dementia,” with all terms expanded to include appropriate synonyms. All studies reporting the effect of stroke on incident dementia were included. Extracted from each study were the effect

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of stroke on dementia, both univariate and adjusted for whichever other covariates were included in the analysis, and any subgroup analyses. Both authors independently extracted the study design and findings.

Findings

The search identified 6578 publications. On inspection of titles, 1043 publications were retained as studies of the incidence of dementia, of the prognosis of patients with stroke, or concerning the relationship between dementia and stroke or the general epidemiology of either condition. Examination of the abstracts and, where necessary, the text of these articles revealed 96 concerning the risk factors for dementia incidence or cognition in people with stroke. Articles were finally selected if they included an estimate of the effect of symptomatic stroke on the incidence of all-cause dementia. Eighteen articles were selected. The results in 2 articles were subsequently included or reanalyzed in later studies. No articles were excluded on the grounds of quality. The updated search at the end of December 2008 revealed one additional study.

Details of each of the included studies are shown in Table 1. Nine studies reported an estimate of the effect of a history of stroke on the risk of dementia.13–24 Seven studies reported the effect of incident stroke on dementia risk in cohorts that were initially both stroke- and dementia-free.13,15,16,22–25 Rochester study investigators26 estimated standardized morbidity ratios for dementia by comparing dementia incidence rates in a population with incident stroke with those found in the general Rochester population and so this study is included despite no direct control comparison. There were 2 prospective, controlled studies of dementia incidence among patients with stroke.29 The results of the first study to quantify the excess risk of dementia in patients with stroke incorporated in a later study,27 which is included in this review.

Table 2 shows univariate effects and effects adjusted or stratified for demographic factors, cardiovascular risk factors, baseline or prestroke cognition, and APOE genotype.

Controlled Follow-Up of Patients With Stroke

Results from the 2 studies reporting controlled follow-up of patients with stroke differ markedly. The study conducted within the setting of the Columbia–Presbyterian Stroke Centre27 reports a high association between stroke and dementia over a 10-year follow-up (hazard ratio = 6.1, 95% CI = 3.6 to 10.5), whereas the community-based North East Melbourne Stroke Incidence Study (NEMESIS) study reports no excess risk of dementia during the first year (relative risk = 1.1, CI = 0.5 to 2.2)28 and only a slight increase in the second year.29 Both studies report similar rates of dementia incidence, approximately 10 per 100 person-years, among their patients with stroke, although the rates differed in the control groups, with a 1.37 per 100 person-years in the clinical control subjects compared with 14 of 91 control subjects at the first year of follow-up in the NEMESIS study. Dementia incidence is estimated to be approximately 2% per year in the elderly population,30 and so 14 of 91 is a high rate in the control population.

Effect of a History of Stroke

Univariate results from cohort studies of the effect of a history of stroke on the risk of incident dementia vary from no effect13,16 to a 4-fold increase17 in risk, although most report an effect consistent with a doubling of the risk of incident dementia in those with stroke compared with those without.14,15,18,20,21

Time Since Stroke

The delay between stroke and baseline assessment was found by both studies in which it was directly examined12,26 to affect the risk of dementia incidence with more recent strokes having a greater effect. Zhu et al13 report no excess risk of dementia incidence in participants whose stroke occurred >3 years before baseline, although this analysis was restricted to those without recurrent stroke in the follow-up period. Those with stroke within 3 years of baseline but no recurrent stroke had twice the risk of dementia.

Estimates of the effect of incident stroke were also variable,13,15,16,22–25 but the effect of an incident stroke on incident dementia is higher than the effect of a history of stroke, suggesting that the excess risk of stroke is greatest close to stroke occurrence.

Demographic Factors

None of the studies in which a univariate effect and an effect adjusted for demographics factors alone were presented found a significant difference after adjustment for demographic factors.22,23,27

The standardized morbidity ratio for dementia incidence from the Rochester study26 was significantly higher in the youngest age groups and was higher in men. Similar results were obtained by subgroup analysis of the results of the Framingham Study.27 The Cache County Study reported estimates for the risk of dementia subtypes by sex but found no significant differences.17 A slight inverse relationship between prevalent stroke and dementia incidence was discovered in the Vantaa study, whose participants were ≥85 years of age at baseline.13 Likewise, Leibetrau et al16 found no association between history of stroke and incident dementia in a population-based cohort of 85 year olds. This might be explained by survivor effects in very old cohorts; a survival analysis of incident stroke in the Vantaa study13 revealed a significant association with dementia (hazard ratio = 3.3, CI = 1.9 to 5.6) after adjusting for APOE genotype and other cardiovascular risk factors, and Leibetrau et al found a strong cross-sectional relationship between stroke and dementia (OR = 4.3: CI = 2.7 to 6.9). The effect of incident stroke on dementia incidence in older cohorts is similar to that in younger cohorts, so the lack of effect of history of stroke in older cohorts might also reflect a longer delay between stroke and baseline assessment.

APOE Genotype

In 2 studies,15,20 the effects of stroke and APOE genotype were compared to yield effects for each combination of APOE genotype and stroke with the referent group of APOE e4-negative/stroke-negative. The effect of stroke was stratified by APOE genotype in another study22 and these effects are shown in Table 3. In the Canadian Study of Health and Ageing,20 there was only a small effect of stroke within APOE genotype groups, whereas there was a bigger effect across genotypes. This suggests that the effect of history of stroke on dementia incidence is partly explained by APOE genotype. Two studies13,22 found no effect of stroke on incident dementia in APOE e4-positive individuals but did find an effect without an e4 allele. The Cache County Study17 showed a slight attenuation after adjustment for APOE genotype, but statistical significance was not tested. In 3 studies of incident stroke and dementia, adjustment for APOE genotype had no effect on estimates.15,23,24

Cardiovascular Risk Factors

None of the studies that adjusted for cardiovascular risk factors discovered a significant attenuation of the effect. The NEMESIS study findings were stratified by recurrent stroke; those with recurrent stroke had a higher risk of dementia (relative risk = 4.5, CI = 1.9 to 10.6) when compared with the stroke-free group, whereas those without had a smaller risk (relative risk = 1.7, CI = 0.7 to 4.1).29 Zhu et al found no increased risk of dementia conferred by a stroke >3 years old when those with recurrent stroke were excluded.13 This suggests that the effect of a history of stroke on dementia might be mediated through the risk of recurrent stroke, although the Framingham study found no difference in the effect of incident stroke between those who did or did not have a second stroke during the follow-up period.22

Prestroke Cognitive Impairment

Prestroke cognitive decline does not appear to account for the association between stroke and cognitive impairment; furthermore, there is no evidence for an interaction between stroke incidence and prestroke cognition on dementia incidence. Studies of series of stroke patients discovered an association between prestroke cognition and the risk of poststroke dementia.10,32
Table 1. Design and Characteristics of Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size</th>
<th>No. With Prevalent Stroke</th>
<th>No. With Incident Stroke</th>
<th>Age at Baseline</th>
<th>Study Design and Follow-Up Interviews</th>
<th>Classification of Dementia</th>
<th>Definition and Ascertainment of Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Srikanth et al, 2004/200618,29</td>
<td>118</td>
<td>99</td>
<td></td>
<td>Mean 69.9 (SD = 12.6)</td>
<td>Stroke patients who survived 3 months compared with age- and sex-matched community control subjects; 2 annual follow-up interviews</td>
<td>DSM-IV</td>
<td>WHO definition of stroke; multiple sources of ascertainment</td>
</tr>
<tr>
<td>Jin et al, 200620</td>
<td>740</td>
<td>Not given</td>
<td></td>
<td>65+</td>
<td>History of stroke assessed at baseline; single follow-up at 5 years</td>
<td>DSM-III-R</td>
<td>Self-report, informant report, and medical record linkage</td>
</tr>
<tr>
<td>Jin et al, 200625</td>
<td>725</td>
<td>Not given</td>
<td></td>
<td>65+</td>
<td>All stroke-free and not cognitively impaired at baseline; single follow-up at 5 years</td>
<td>DSM-III-R</td>
<td>Any incidence of stroke recorded during follow-up; self-report, informant report, and death certification</td>
</tr>
<tr>
<td>Reitz et al, 200824</td>
<td>6724</td>
<td>...</td>
<td>713</td>
<td>55+</td>
<td>Three follow-up examinations; continuous medical record linkage to ascertain incident stroke and dementia (mean = 7.3 years)</td>
<td>DSM-III-R</td>
<td>Ischemic or hemorrhagic stroke; self-report and clinical confirmation</td>
</tr>
<tr>
<td>Rastas et al, 200813</td>
<td>339</td>
<td>32</td>
<td>29</td>
<td>85+</td>
<td>Three follow-up interviews up to 9 years</td>
<td>DSM-III-R</td>
<td>TIA or stroke in medical records and clinical confirmation or neurological signs indicating stroke</td>
</tr>
<tr>
<td>Hayden et al, 200617</td>
<td>3264</td>
<td>109</td>
<td></td>
<td>65+</td>
<td>Single follow-up at 3 years</td>
<td>DSM-III-R</td>
<td>Self-report of clinician-diagnosed and treated stroke</td>
</tr>
<tr>
<td>Yip et al, 200619</td>
<td>2586*</td>
<td>218*</td>
<td></td>
<td>65+</td>
<td>Two follow-up interviews, 2 and 6 years after baseline</td>
<td>CAMDEX (ICD-10-equivalent)</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Simons et al, 200624</td>
<td>1489†</td>
<td>89†</td>
<td></td>
<td>68+</td>
<td>Biannual postal survey and medical record monitoring; 16 year follow-up</td>
<td>ICD-9-CM or ICD-10-AM (from medical records)</td>
<td></td>
</tr>
<tr>
<td>Gamaldo et al, 200623</td>
<td>335</td>
<td>...</td>
<td>36</td>
<td>70+</td>
<td>Annual assessment; (mean = 10.0 years)</td>
<td>DSM-III-R</td>
<td>Self-informant report (clinical confirmation)</td>
</tr>
<tr>
<td>Kuller et al, 200321</td>
<td>3375</td>
<td>151</td>
<td></td>
<td>65+</td>
<td>Annual assessment; (mean = 5.7 years)</td>
<td>DSM-III-R</td>
<td></td>
</tr>
<tr>
<td>Ivan et al, 200422</td>
<td>1272</td>
<td>...</td>
<td>212</td>
<td>Mean 79.2 (SD = 6.6)</td>
<td>Biennial assessment; 10-year follow-up</td>
<td>DSM-IV, CDR ≥1, impairment for at least 6 months</td>
<td>Focal neurological deficit lasting &gt;24 hours</td>
</tr>
<tr>
<td>Liebetrau et al, 200346</td>
<td>494</td>
<td>93</td>
<td>56</td>
<td>85</td>
<td>Single follow-up at 3 years and medical record linkage</td>
<td>DSM-III (baseline)</td>
<td>Self-report, informant report, and medical record linkage</td>
</tr>
<tr>
<td>Desmond et al, 200227</td>
<td>683</td>
<td>334</td>
<td></td>
<td>Mean 70.4 (SD = 7.5)</td>
<td>Annual follow-up, up to 10 years; median follow-up 21.1 months</td>
<td>Modified DSM-III-R (additional cognitive domains)</td>
<td>Ischemic stroke confirmed by imaging</td>
</tr>
<tr>
<td>Zhu et al, 200115</td>
<td>1301</td>
<td>92</td>
<td>91</td>
<td>75+</td>
<td>Single follow-up at 3 years</td>
<td>DSM-III-R</td>
<td>Medical record of ICD-8 codes 430–438 Informed report</td>
</tr>
<tr>
<td>Brayne et al, 199816</td>
<td>376</td>
<td>44</td>
<td></td>
<td>75+</td>
<td>Single follow-up at 2.4 years</td>
<td>CAMDEX (ICD-10-equivalent)</td>
<td></td>
</tr>
<tr>
<td>Kokmen et al, 199616</td>
<td>Community comparison</td>
<td>971</td>
<td>...</td>
<td>Age-stratified analysis</td>
<td>Comparison of rates in a cohort with a history of stroke to incident dementia rate estimated in the same community</td>
<td>History of normal functioning; irreversible intellectual or cognitive or social function; 2 domains affected; impaired age/sex social/occupational functioning</td>
<td>Dementia timing determined through medical record linkage</td>
</tr>
</tbody>
</table>

*Baseline to 2 years.
†Two years to 6 years.

although cognitive impairment is also a strong predictor of dementia incidence. In the NEMESIS study, all of the patients with stroke who developed dementia had been cognitively impaired prestroke. These findings confirm that prestroke impairment is an independent risk factor for poststroke cognitive decline but without comparing the effect of baseline cognitive impairment in the stroke-free control subjects. After comparison with a stroke-free cohort in the large Rotterdam study, no interaction between incident stroke and pre-existing cognitive impairment was seen. In the Baltimore Longitudinal Study of Ageing, this interaction was not examined; the incident stroke groups with and without cognitive impairment were compared with the whole of the stroke-free cohort. There was a significant effect of incident stroke on dementia incidence in the Canadian Study of Health and Ageing, in which those with baseline cognitive impairment had been excluded.

### Table 2. Estimates of Effect of Stroke on the Risk of Incident Dementia*

<table>
<thead>
<tr>
<th>Reference</th>
<th>Univariable Effect</th>
<th>Multivariable or Stratified Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Age, Sex, and Demographic Data</td>
</tr>
<tr>
<td>Controlled follow-up of patients with stroke</td>
<td></td>
<td>6.1 (3.6–10.5)</td>
</tr>
<tr>
<td>Desmond, 2002</td>
<td>27</td>
<td>1.1 (0.5–2.2)</td>
</tr>
<tr>
<td>Srikanth, 2004/2006</td>
<td>28,29</td>
<td>...</td>
</tr>
<tr>
<td>Estimates of the association between a history of stroke and incident dementia</td>
<td>Jin, 2008</td>
<td>...</td>
</tr>
<tr>
<td>Zhu, 2000†‡</td>
<td>...</td>
<td>2.1 (1.4–4.2)</td>
</tr>
<tr>
<td>Brayne, 1998</td>
<td>18</td>
<td>...</td>
</tr>
<tr>
<td>Liebetrau, 2003</td>
<td>16</td>
<td>...</td>
</tr>
<tr>
<td>Yip, 2006†</td>
<td>19</td>
<td>...</td>
</tr>
<tr>
<td>Hayden, 2006</td>
<td>17</td>
<td>...</td>
</tr>
<tr>
<td>Simons, 2006</td>
<td>14</td>
<td>...</td>
</tr>
<tr>
<td>Rastas, 2008</td>
<td>13</td>
<td>...</td>
</tr>
<tr>
<td>Estimates of the association between incident stroke and incident dementia</td>
<td>Ivan, 2004</td>
<td>2.2 (1.5–3.1)</td>
</tr>
<tr>
<td>Kokmen, 1996</td>
<td>26</td>
<td>SMR=3.2 (2.8–3.7)</td>
</tr>
<tr>
<td>Zhu, 2000</td>
<td>15</td>
<td>...</td>
</tr>
<tr>
<td>Liebetrau, 2003</td>
<td>16</td>
<td>...</td>
</tr>
<tr>
<td>Reitz, 2008</td>
<td>24</td>
<td>...</td>
</tr>
<tr>
<td>Gamaldo, 2006</td>
<td>23</td>
<td>OR=5.5 (2.7–11.4)</td>
</tr>
<tr>
<td>Rastas, 2008</td>
<td>13</td>
<td>...</td>
</tr>
<tr>
<td>Jin, 2006</td>
<td>25</td>
<td>2.3 (1.3–4.1)§§</td>
</tr>
</tbody>
</table>

*Estimates are hazard ratio/relative risk unless specified.
†One-year follow-up.
‡Two-year follow-up of those with recurrent stroke.
§Two-year follow-up without recurrent stroke.
||Stroke within 3 years of baseline.
¶Stroke more than 3 years before baseline.
**Cognitive impairment at baseline in incident stroke group compared with total stroke-free population.
††No cognitive impairment at baseline in incident stroke group compared with total stroke-free population.
†††Incident stroke cases excluded from analysis.
§§Baseline cognitive impairment excluded from the analysis.
||| Also adjusted for neuropathological findings (including large infarcts) on MRI. SMR indicates standardized morbidity ratio.
Proportional hazards model used by many studies to estimate increased time after stroke. This suggests that the Cox baseline stroke-free cohorts.

history of stroke did not exclude incident cases of stroke from vascular risk factors but is greater in those with more recent stroke. APOE genotype and recurrent stroke may affect the relationship between a history of stroke and incident dementia risk. Prestroke cognitive impairment is a risk factor for dementia poststroke, although the increased dementia risk is not limited to those with prestroke cognitive impairment. Those with a history of stroke who survive without dementia to 85 years are at no increased risk of dementia incidence compared with their stroke-free contemporaries.

Studies of incident stroke record a higher excess risk of dementia incidence than do studies of prevalent stroke. This likely reflects both the higher risk of dementia as a consequence of stroke and the higher rate of mortality in individuals with stroke and dementia. Prestroke and poststroke dementia are risk factors for mortality in patients with stroke, and so participants of longitudinal studies with a history of stroke are likely to have been among those stroke survivors with a lower risk of dementia incidence.

### Strength and Limitations of this Review

The review was systematic, including double reading of study design and findings. Study characteristics and confounders were thoroughly examined. We did not include studies relating dementia incidence to findings obtained through neuroimaging or autopsy. Owing to the variations in study characteristics, we did not perform a quantitative analysis. We did not include studies of dementia subtypes, because the presence of stroke is central to the differential diagnosis of vascular dementia from Alzheimer disease.

Many studies rely on self- or informant report of stroke; others included a neurological examination, a report of treatment for stroke, or linkage with medical records. The Gothenburg study investigators compared self-report, informant report, and medical record linkage in a community cohort aged 85 years and discovered no single method to be sufficiently reliable. Many community-based studies of history of stroke did not exclude incident cases of stroke from the baseline stroke-free cohorts.

The effect of stroke on the risk of dementia is less with increased time after stroke. This suggests that the Cox proportional hazards model used by many studies to estimate the relative risk is not suitable, particularly when applied to studies of incident stroke and dementia with long follow-up periods. The timing of the onset of dementia is difficult to ascertain, and study diagnosis is usually made at assessments occurring at discrete times. Survival analyses were therefore either restricted to discrete time analysis or relied on assumptions regarding the time of dementia incidence.

### Implications

The increased risk of dementia in individuals with a history of stroke likely represents the effect of the stroke on the risk of and susceptibility of the brain to further pathological insults as opposed to an underlying effect of cardiovascular risk factors that led to stroke. Neuropathological findings from the Baltimore Longitudinal Study of Aging showed a relationship between the number of infarcts and dementia during life with no attenuation of the relationship after adjustment for cardiovascular risk factors (CVRFs). The Cardiovascular Health Study showed associations between vascular findings on MRI and subsequent incident dementia. Yet estimates of the effect on dementia incidence of interventions aimed at stroke prevention have been mixed despite consistent reductions in stroke incidence. Cohort studies have found that the use of statins decreases the risk of vascular dementia, whereas results from trials of antihypertensives have been mixed.

The increased risk of dementia in stroke survivors raises the question of how stroke and dementia are related. Longitudinal studies comparing cohorts with stroke with those without are informative, but their interpretation relies on the selection of both the stroke cohort and the stroke-free cohort and on how the incidence of stroke and dementia are analyzed. Further research is needed to determine the reciprocal relationship between stroke and dementia and to assess how efforts to reduce the incidence of stroke while improving stroke survival will affect dementia in the ageing population.

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### Table 3. Effect of Stroke and APOE e4 on the Risk of Incident Dementia Compared With the Population Without Stroke and Without APOE e4

<table>
<thead>
<tr>
<th>Study</th>
<th>e4-Negative/Stroke-Negative</th>
<th>e4-Negative/Stroke-Positive</th>
<th>e4-Positive/Stroke-Negative</th>
<th>e4-Positive/Stroke-Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jin, 2008</td>
<td>1*</td>
<td>1.3 (0.8–2.4)</td>
<td>2.1 (1.4–3.0)</td>
<td>2.6 (1.1–5.9)</td>
</tr>
<tr>
<td>Zhu, 2000</td>
<td>1*</td>
<td>1.7 (1.2–2.4)</td>
<td>2.7 (1.6–4.8)</td>
<td>2.7 (1.1–6.8)</td>
</tr>
<tr>
<td>Zhu, 2000</td>
<td>1*</td>
<td>2.3 (1.3–4.1)</td>
<td>1.7 (1.1–2.4)</td>
<td>4.6 (2.0–10.6)</td>
</tr>
<tr>
<td>Ivan, 2004</td>
<td>1*</td>
<td>3.4 (2.0–5.8)</td>
<td>1*</td>
<td>1.2 (0.4–4.1)†</td>
</tr>
</tbody>
</table>

*Reference group. †Compared with the e4-positive/stroke-negative group.
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Disclosures
None.

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