Sex Differences in Long-Term Quality of Life Among Survivors After Stroke in the INSTRUCT

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Background and Purpose—Women are reported to have poorer health-related quality of life (HRQoL) after stroke than men, but the underlying reasons are uncertain. We investigated factors contributing to the sex differences.

Methods—Individual participant data on 4288 first-ever strokes (1996–2013) were obtained from 4 high-quality population-based incidence studies from Australasia and Europe. HRQoL utility scores among survivors after stroke (range from negative scores = worse than death to 1 = perfect health) were calculated from 3 scales including European Quality of Life-5 Dimensions, Short-Form 6-Dimension, and Assessment of Quality of Life at 1 year (3 studies; n=1210) and 5 years (3 studies; n=1057). Quantile regression was used to estimate the median differences in HRQoL for women compared to men with adjustment for covariates. Study factors included sociodemographics, prestroke dependency, stroke-related factors (eg, stroke severity), comorbidities, and poststroke depression. Study-specific median differences were combined into pooled estimates using random-effect meta-analysis.

Results—Women had lower pooled HRQoL than men (median difference unadjusted 1 year, −0.147; 95% CI, −0.258 to −0.036; 5 years, −0.090; 95% CI, −0.119 to −0.062). After adjustment for age, stroke severity, prestroke dependency, and depression, these pooled median differences were attenuated, more greatly at 1 year (−0.067; 95% CI, −0.111 to −0.022) than at 5 years (−0.085; 95% CI, −0.135 to −0.034).

Conclusions—Women consistently exhibited poorer HRQoL after stroke than men. This was partly attributable to women’s advanced age, more severe strokes, prestroke dependency, and poststroke depression, suggesting targets to reduce the differences. There was some evidence of residual differences in HRQoL between sexes but they were small and unlikely to be clinically significant. (Stroke. 2019;50:2299-2306. DOI: 10.1161/STROKEAHA.118.024437.)

Key Words: comorbidity ■ depression ■ incidence ■ quality of life ■ survivors

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The greater burden of stroke in women than in men has recently been recognized as a major concern worldwide.1 Women generally have a poorer health-related quality of life (HRQoL) than men, both in the short- and long-term after stroke.2,3 Despite the increased interest in sex differences, the reasons for worse HRQoL in women have been inadequately investigated.

Existing studies of sex differences in HRQoL after stroke have several limitations.2,3 Most only incorporate short-term outcomes (up to 6 months), as shown in a systematic review of sex differences in HRQoL following stroke.2 Many investigators also did not report sex-specific findings, used modeling that was not focused on the sex difference (ie, step-wise regression), or reported sex differences as incidental findings.2 Of a small number of studies specifically designed to examine sex differences, most were based in hospital or restricted to a specific type of stroke or to certain age groups.2 These limitations are problematic as selection bias may adversely affect the conclusions.4 Although population-based stroke incidence studies3 are the most generalizable and ideal study designs to examine sex differences,6 few incorporate assessment of...
HRQoL, or analysis of sex differences. In the most recent update on sex difference in outcome after stroke, only 2 out of 13 studies published since 2007 were designed to examine the sex difference in HRQoL, and neither of these were population-based studies. There are also inconsistent findings about the causes of the sex difference in HRQoL because of variation in outcome measurement and adjustment for different covariates.

The aim of this study was to quantify the sex differences in HRQoL among survivors up to 5 years after stroke and identify factors contributing to any observed sex differences, using individual participant data collected from ideal population-based incidence stroke studies conducted in different countries.

Methods

Qualified investigators can request access to patient-level data, analytic methods, and study materials after ethics clearance and approval by all authors.

The INSTRUCT (International Stroke Outcomes Study) is an international collaboration including individual participant data of n=16964 people with first-ever stroke from 13 different studies that adhered to the criteria for ideal population-based stroke incidence studies. The studies were conducted in Australasia, Europe, South America, and the Caribbean (1987–2014). This INSTRUCT was approved by the Tasmanian Health and Medical Human Research Ethics Committee (H0014861). All the participating studies had approval from their respective local Ethics Committees.

This analysis of INSTRUCT includes 4 studies: Oxford (United Kingdom), Perth (Australia), Melbourne (Australia), and Auckland (New Zealand). Of these, 2 had measures of HRQoL among survivors at both 1 and 5 years (Oxford, Melbourne) while the others had only 1-year (Perth) or 5-year measures (Auckland).

Outcome Measurements

Participants of the studies were followed-up with face-to-face interviews conducted at 1 and 5 years after stroke. Three instruments were used to assess HRQoL. In the Oxford study, HRQoL was assessed using the European Quality of Life-5 Dimensions (EQ5D) instrument which evaluates 5 dimensions: mobility, self-care, usual activities, depression/anxiety, and pain. In the Melbourne study, the Assessment of Quality of Life (AQoL) was used comprising 5 dimensions: illness, independent living, social relationships, physical senses, and psychological well-being. The Short Form-36 (SF36) was used in the Perth and Auckland studies. This instrument has 8 subdimensions: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health.

HRQoL utility scores were calculated from the 3 instruments among survivors by summing the component scores and adding value sets from relevant populations to generate the utility score. The utility score ranges from full health, with a value of one, to negative values indicating health states worse than death. The AQoL utility scores (Melbourne) were calculated based on the Australian population-based methods while the EQ5D scores (Oxford) were derived from patient data using the available value sets for the UK population.

The Short-Form 6-Dimension (SF6D) utility scores were derived from SF36 items (Perth, Auckland) using the published algorithm for the UK population given the lack of SF6D preference weights for Australia or New Zealand. The SF6D is developed for use in economic evaluation by reducing the SF36 to a 6-dimension classification and creating an overall index (utility) for health.

Study Factors

We included covariates that we hypothesized from our previous studies might explain sex differences in HRQoL outcomes. These included sociodemographics, prestroke health, treatment and management, and post-stroke factors. The availability and specification of individual variables for each study are provided in Supplement I in the online-only Data Supplement.

Statistical Analysis

Data were analyzed using Stata 12.1 (StataCorp Texas, 2011), with 2-tailed P≤0.05 considered statistically significant. Because of the skewed distribution of the outcome, quantile regression was used to estimate the median difference for women compared with men in utility scores from HRQoL measures among survivors at 1 and 5 years. We used a 2-stage analysis method. Study-specific models for the sex difference in HRQoL were built in the first stage. Within each study, the role of study factors as potential covariates of the association between sex and HRQoL were assessed. Variables were entered into the multivariable models if they met the following criteria: associated with sex, associated with stroke severity, and the inclusion of the covariate changed the magnitude of the sex coefficient by ≥10% (Supplement II in the online-only Data Supplement). Where possible, age, stroke severity, and pre-stroke dependency, variables that are common predictors of stroke outcome and associated with sex, were forced into the final multivariable models regardless of meeting the above criteria. Within each study, statistical interactions were assessed by a test of statistical significance of a sex × covariate product term. In the second stage of the analysis, the effect estimates from unadjusted and multivariable-adjusted models from the individual studies were combined to create pooled estimates using random-effects meta-analysis. Statistical heterogeneity between studies was evaluated using Q and F statistics. The potential sources of between-study heterogeneity were not assessed because the number of studies forming our pooled estimates was less than required (≥10).

We found substantial disparities in the definitions of the minimum clinically important difference across instruments. The comparability of the study populations with measured HRQoL was undertaken to see whether the sex differences in utility scores might be clinically meaningful. In these analyses, the clinically relevant thresholds were 0.06 for AQoL, 0.08 to 0.12 for EQ5D, and 0.03 to 0.08 for SF6D.

Sensitivity Analyses

HRQoL was highly correlated with poststroke functional outcome or activity limitation (correlation coefficient: r=0.5–0.8; Table I in the online-only Data Supplement) but not with mood disorder (r=0.1–0.3). To avoid over adjustment, the functional outcome, assessed using the Barthel Index (Melbourne) or modified Rankin Scale score (remaining studies; Supplement I in the online-only Data Supplement), was not included in the final models. We report further adjustment for this factor in separate models.

For the studies with >20% missing data on HRQoL, assuming that the data were missing at random, we performed multiple imputation combined with inverse probability weighting (Supplement II in the online-only Data Supplement). We compared these results to those from complete-case analyses.

Subdomain Analyses

We examined sex differences in subdomain scores among the Auckland (SF36), Perth (SF36), and Melbourne (AQoL) studies using quantile regression.

Analyses of the Comparison With General Populations

We examined HRQoL between men and women with stroke and men and women in the general populations using linear regression (Supplement II in the online-only Data Supplement).
Results

There were 4228 first-ever stroke cases in the studies conducted between 1993 and 2013 (Table 1). HRQoL outcomes were assessed among 1210 (63%) of 1914 survivors at 1 year (3 studies) and 1057 (58%) of 1837 survivors at 5 years (3 studies; Table 1). Sex differences in baseline factors among survivors are provided in the online-only Data Supplement (Supplement III and Tables IIA and IIB in the online-only Data Supplement).

HRQoL at 1-Year

Among 3 studies with 1-year HRQoL, the sample for complete-case analysis was 1116 (8% of available cases were dropped because of missing data on covariates). In pooled unadjusted analyses, women had significantly lower median utility scores (median difference, MD_{unadjusted} = −0.147; 95% CI, −0.258 to −0.036; Figure 1, top). However, there was significant between-study heterogeneity (I^2=81.2%, Q=10.6, P=0.005). Study-specific unadjusted female:male MDs varied from −0.069 (Oxford), −0.197 (Melbourne), to −0.210 (Perth). These differences were statistically significant, but only in the Melbourne and Perth studies were they clinically significant based on minimum clinically important difference (MID) values of 0.06 for AQoL, 0.08 for SF6D, and 0.12 for EQ5D (Figure 1, top).

In the fully adjusted model, the sex differences were substantially attenuated (61.4%) after accounting for covariates (pooled MD_{adjusted} = −0.067; 95% CI, −0.111 to −0.022; Figure 1, bottom). We found no statistical evidence of heterogeneity in adjusted MD estimates (I^2=39.5%, Q=3.3, P=0.191). All the study-specific female:male MD were statistically significant (Figure 2). Clinical significance was only evident in the Melbourne and Auckland studies based on MID values of 0.06 for AQoL, 0.08 for SF6D, and 0.12 for EQ5D.

After adjustment, the sex differences were only slightly attenuated (5%; pooled MD_{adjusted} = −0.085; 95% CI, −0.135 to −0.034; Figure 2, bottom) without evidence of statistical heterogeneity (I^2=0%, Q=3.3, P=0.571). Study-specific MDs were statistically significant, but only in the Melbourne study was it clinically significant based on the MID values (Figure 2). Contributing factors to the 5-year sex differences were similar to those of 1-year analyses (Table V in the online-only Data Supplement).

Large loss to follow-up was observed in the Auckland study (61.6%), but few sex differences between those assessed and lost to follow-up in baseline characteristics were identified (Tables VI and VII in the online-only Data Supplement). Sensitivity analyses using the multiple imputation to account for missing data showed limited differences in the estimated pooled effects (MD_{adjusted} = −0.066; Table IV in the online-only Data Supplement) compared with complete-case analyses (MD_{adjusted} = −0.067).

HRQoL at 5-Year

Among 3 studies with 5-year HRQoL, the sample available for complete-case analysis was 927 (12% of cases were missing data on confounding factors). In unadjusted analyses, women had significantly lower utility scores (pooled MD_{adjusted} = −0.090; 95% CI, −0.119 to −0.062; Figure 2, top). There was no evidence of statistical heterogeneity (I^2=39.5%, Q=3.3, P=0.191). All the study-specific female:male MD were statistically significant (Figure 2). Clinical significance was only evident in the Melbourne and Auckland studies based on MID values of 0.06 for AQoL, 0.08 for SF6D, and 0.12 for EQ5D.

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Generally, compared with men, women had worse HRQoL in several subdomains. They included independent living, social relationships, and psychological well-being (Melbourne; Table VIIIA in the online-only Data Supplement); functioning and vitality (Perth; Table VIIIB in the online-only Data Supplement); physical functioning and mental health (Auckland; Table VIIIB in the online-only Data Supplement). Advanced age, more severe strokes, and prestroke dependency were main contributing factors to women’s poorer physical health and mental health (Table VIIIA and VIIIB in the online-only Data Supplement).

Comparison Between Women and Men in Stroke and General Populations

Men and women who survived after stroke had worse utility scores than those in the general population across age groups (Tables IXA through XIB in the online-only Data Supplement). Statistically significant results were more often observed at 1-year compared to 5-year.

As compared with the general population, the reduction in HRQoL among stroke survivors was greater in women than in men. However, the magnitude of the sex difference varied among age groups and outcome instruments and was often below clinically relevant thresholds. For the AQoL, compared with the general population, the differences between women and men survivors of stroke (Melbourne) were greater for those aged <65 than for older people (Tables IXA and IXB in the online-only Data Supplement). The sex differences in SF6D utility scores among stroke survivors (Auckland), compared with the general population, were greatest in the youngest age group (<55; Table X in the online-only Data Supplement). By contrast, the sex differences in EQ5D utility scores between stroke survivors (Oxford) and the general population were greater among those aged 65+ (Table XIA and XIB in the online-only Data Supplement) than younger people.

Discussion

Women had poorer HRQoL at 1 and 5 years after stroke than men. Although the effect estimates varied by outcome measure (EQ5D, SF36, and AQoL), the direction of the sex difference was relatively consistent across studies. The greatest contributors to the worse HRQoL in women were advanced age, prestroke functional limitations, and stroke severity. These same factors also accounted for women’s worse survival and functional outcomes in the long-term following stroke.\(^5, 7\) The presence of poststroke mood disorders also accounted for some of the sex difference. In pooled analyses, the aforementioned covariates accounted for much (eg, 54% at 1-year), but not all,
of the sex differences in long-term HRQoL. In study-specific analyses, women still had worse HRQoL than men based on the fully adjusted models. These differences were generally below the clinically meaningful threshold.

Age played an important role in the association between sex and HRQoL after stroke, potentially because of frailty and comorbidities. A strategy to address this complexity may be better access to evidence-based therapies, such as poststroke rehabilitation to improve HRQoL in the long-term for the elderly. Another main determinant of poorer HRQoL in women was the presence of prestroke functional limitations. The poorer prestroke function in women reflects correlations between sex and age at stroke onset, again highlighting the importance of improving health for older people. In our sensitivity analyses, further adjustment for functional outcome removed the residual sex differences. This suggests that if we could improve function and maximize recovery from stroke for both sexes, the sex differences in HRQoL would be attenuated. More effective rehabilitation programs to increase participation, particularly for women after stroke, are needed to achieve this goal.

More severe strokes in women contributed to their worse HRQoL compared with men. An implication of this finding is that management of modifiable factors of stroke severity such as cardiovascular diseases, and cardioembolic strokes could help mitigate poorer outcomes in women. Increasing access to endovascular therapies in both sexes with ischemic stroke may be important as this clearly reduces stroke severity.

The presence of poststroke mood disorder (eg, anxiety and depression), assessed using the Irritability, Depression and Anxiety Scale (Melbourne) or depression subscore of the General Health Questionnaire (Auckland; Supplement I in the online-only Data Supplement), was a contributing factor to the sex differences for the Melbourne study, but not the Auckland study. This may be because of the variation in assessment scale between studies with both instruments having their own limitations. Whether there are sex differences in the diagnosis, response to treatment for poststroke depression and its association with HRQoL are uncertain. There are some sex differences in coping strategies that may affect self-reported poststroke depression. The presence of prestroke depression may be also relevant to assess in future work as it is generally more prevalent in women and depressed patients face poorer outcomes after stroke. This suggests that mood disorders should be assessed as part of a clinical diagnostic interview. Social and family participation in the prevention of poststroke depression in the elderly, many of whom are

| Table 2. Factors Contributing to the MD in 1-Year Utility Scores Between Sexes |

<table>
<thead>
<tr>
<th></th>
<th>Oxford (EQ5D; n=700)</th>
<th>Melbourne (AQoL; n=385)</th>
<th>Perth (SF36; n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MD</td>
<td>95% CI</td>
<td>Δ*</td>
</tr>
<tr>
<td>Age</td>
<td>−0.069</td>
<td>−0.089</td>
<td>−0.049</td>
</tr>
<tr>
<td>Adjusted for</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>−0.060†</td>
<td>−0.096</td>
<td>−0.025</td>
</tr>
<tr>
<td>NIHSS</td>
<td>−0.067†‡</td>
<td>−0.107</td>
<td>−0.028</td>
</tr>
<tr>
<td>Prestroke mRS</td>
<td>−0.061†</td>
<td>−0.087</td>
<td>−0.034</td>
</tr>
<tr>
<td>Prestroke BI</td>
<td>...</td>
<td>−0.187†‡</td>
<td>−0.295</td>
</tr>
<tr>
<td>Marital status</td>
<td>−0.052</td>
<td>−0.087</td>
<td>−0.017</td>
</tr>
<tr>
<td>Prestroke dementia</td>
<td>...</td>
<td>−0.173</td>
<td>−0.278</td>
</tr>
<tr>
<td>1-year mood disorder (IDA)</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>1-year BI</td>
<td>...</td>
<td>−0.116†</td>
<td>−0.206</td>
</tr>
<tr>
<td>1-year mRS</td>
<td>−0.014</td>
<td>−0.015</td>
<td>0.012</td>
</tr>
<tr>
<td>Full model§</td>
<td>−0.049</td>
<td>−0.093</td>
<td>−0.004</td>
</tr>
<tr>
<td>Full+functional outcome (mRS/BI)</td>
<td>−0.018</td>
<td>−0.058</td>
<td>0.022</td>
</tr>
</tbody>
</table>

Negative scores indicate worse outcome in women. AQoL indicates Assessment of Quality of Life; BI, Barthel index; EQ5D, European Quality of Life-5 Dimensions; IDA, irritability, depression, and anxiety scale (continuous); MD, mean difference; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and SF36, Short form-36 questions.

*% Change of coefficient of sex difference between unadjusted and adjusted models: (unadjusted β−adjusted β)/unadjusted β×100.
†Covariates which remained in the full models.
‡Not meeting criteria of being a confounder but being forced into the fully adjusted multivariable model (see Methods for further details). Other nonsignificant factors included health behaviors/comorbidities, stroke treatment, and management (Supplement III in the online-only Data Supplement, nonsignificant factors for the full list).
§Best-fit multivariable models.
women, may provide opportunities to address the sex differences in HRQoL. Better detection and treatment of poststroke depression, particularly early after stroke, are likely to improve HRQoL for both sexes.

In subdomain analyses, the impacts of stroke were greater in women compared with men in physical functioning, independence living, social relationships, and psychological well-being. These were mainly explained by prestroke factors or stroke severity. The domains that showed no difference between sexes included illness, physical senses (AQoL), or bodily pain, general health, and role emotional (SF36). A potential limitation of these analyses is that the available instruments are generic scales. In a study of sex differences using a stroke-specific instrument, women had poorer HRQoL in some other domains (ie, language, thinking, and energy) and these differences existed after adjustment for confounding factors.28 The residual sex differences may be further accounted for by unmeasured or poorly measured factors, such as psychosocial functioning or mood disorders.

Authors of previous research have reported sex differences in utility scores, but less often considered whether the differences are clinically meaningful.23,24 This is important as women in the general population may also have poorer HRQoL than men, particularly in older age groups.16,20 However, there is a lack of comparison of sex difference in HRQoL between people with stroke and the general population. In our analyses, sex differences in utility scores between stroke and general populations existed in some age groups but varied between studies. The variation may be attributable to the specific utility scores used, with opposing results by age for the EQ5D and the other instruments. This possibly relates to the scale discrepancy whereby some social aspects of HRQoL measured in the SF36 or AQoL (eg, social functioning, family role; Table XII in the online-only Data Supplement) that may contribute to the greater health loss for younger women than younger men, were not captured by the EQ5D. Another possibility is the impact of variability in self-reported HRQoL because of different demographic, economic, cultural, and social factors across populations.30 Future studies of sex differences in HRQoL should consider these cultural and contextual factors by comparing findings in patients with stroke to population norms, and determining whether the differences are clinically meaningful. We found that stroke caused a substantial HRQoL loss for both men and women, consistent with a previous report.31 Addressing this impaired HRQoL should be a priority with targets including access to evidence-based care, these being associated with better HRQoL.32

Our research has several strengths. We used individual long-term outcome data from high-quality population-based studies across countries. To our knowledge, this is the largest study ever performed to comprehensively examine the contributing factors to the sex difference in HRQoL using a common metric of utility scores. The use of 2-stage meta-analysis overcame the variability in HRQoL measures and covariates between studies. 

Figure 2. Median difference in 5-y utility scores between sexes after stroke in unadjusted (top) and adjusted (bottom) models. Negative values to the left of 0 indicate worse outcome in women. AQoL indicates Assessment of Quality of Life; EQ5D, European Quality of Life-5 Dimensions; and SF36, Short form-36 questions.
We also compared the net mean differences in HRQoL between people with stroke and the general population to determine how stroke impacts on men and women’s health.

We acknowledge several limitations in this study. We performed multiple imputation with available baseline covariates to replace missing data in the studies with large proportions of loss-to-follow-up. However, the possibility of selection bias cannot be eliminated due to the potential differences developing after discharge, and the likelihood that the data are not missing at random. We found that the direction of sex differences in baseline characteristics and clinical factors were similar between people with and without HRQoL assessment (Tables III and VI in the online-only Data Supplement). However, those lost-to-follow-up, compared to those assessed (Table VII in the online-only Data Supplement), were generally more likely to be women, (except for Melbourne) older, dependent before stroke, and had more severe strokes. Thus, they may face poorer HRQoL. The sex differences in HRQoL among all stroke survivors may, therefore, be different to our estimates. The HRQoL assessment was only available in 3 studies at each time point (1- and 5-year). The included cohorts were mostly conducted in high-income countries so the results might not be generalizable to low- and middle-income countries. We identified some other stroke incidence studies that we did not include without sex-specific results or HRQoL assessment. We advocate the inclusion of longer-term patient-reported outcome measures in such studies to assess sex differences in HRQoL, particularly in low- and middle-income countries. We did not have measures of all potentially important covariates. For example, hormonal factors and cognitive status could also impact sex differences in HRQoL, but we lacked these details across our various studies. Stroke care and poststroke factors (e.g., mood disorders) were not measured in all studies and so there is a risk of residual confounding. We found that stroke care did not affect the sex difference in HRQoL, but the investigated studies were conducted a long time ago. Further work should confirm whether the difference in contemporary processes of hospital care could have an impact on sex differences in HRQoL and associated factors.

Conclusions

Women generally have poorer long-term HRQoL after stroke in several dimensions of physical and mental health. The sex differences were partly explained by women’s advanced age, poststroke function, and stroke severity with some evidence that poststroke depression was also important. Targeting potentially modifiable factors including stroke severity and mood disorders will provide more opportunities to reduce the sex differences in stroke outcomes. Men and women with stroke, compared to the general population, have reasonably similar loss of HRQoL. Therefore, strategies to improve HRQoL following stroke should be focused on all stroke survivors.

Sources of Funding

The Chief investigators for each of the studies provided their data at no cost. Dr Phan was supported by a Merle Weaver Postgraduate Scholarship (Australia). Dr Gall is supported by a National Heart Foundation of Australia Future Leader Fellowship (100446). Dr Reeves was supported by a Menzies Institute Visiting scholars program (Tasmania, Australia). The following authors received research fellowship funding from the National Health and Medical Research Council (NHMRC) of Australia: Dr Thrift (1042600), Dr Cadilhac (co-funded Heart Foundation: 1063761). Dr Anderson received grants from the NHMRC and Takeda paid to his institution, and Advisory Board fees from Amgen and Boehringer Ingelheim. The NHMRC also provided support for the Melbourne study (154600 and 307590), as did VicHealth and the Stroke Foundation (Australia). The Health Research Council of New Zealand funded the Auckland study. The Oxford Vascular Study is funded by the Wellcome Trust, Stroke Association, and the National Institute of Health Research Biomedical Research Centre, Oxford.

Disclosures

None.

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