Cerebral Small Vessel Disease and Kidney Function Predict Long-Term Survival in Patients With Acute Stroke

Niku K.J. Oksala, MD, PhD, DSc; Tapani Salonen, MD; Timo Strandberg, MD, PhD; Anni Oksala, MD; Tarja Pohjasaavaara, MD, PhD; Markku Kaste, MD, PhD; Pekka J. Karhunen, MD, PhD; Timo Erkinjuntti, MD, PhD

Background and Purpose—Cerebral small vessel disease reflected by white matter lesions (WMLs) in MRI and kidney function reflected by estimated glomerular filtration rate (eGFR) is closely associated in patients without stroke. We studied whether eGFR and WMLs predict long-term survival in patients with acute stroke.

Methods—After exclusion of patients with low eGFR (N=5 [1.3%]; <30 mL/min/1.73 m²), consecutive patients with acute stroke (N=378) subjected to MRI and serum creatinine determination were included in the study and prospectively followed-up up to 12 years.

Results—Of the patients, 71.2% had died during the follow-up, 152 (40.2%) had moderate (eGFR 60 mL/min/1.73 m²), and 226 (59.8%) had normal or mildly impaired eGFR (≥60 mL/min/1.73 m²). Of the patients, 108 (28.6%) had mild, 68 (18.0%) had moderate, and 202 (53.4%) had severe WMLs. In logistic regression analysis adjusted with age and sex, eGFR <60 mL/min/1.73 m² was associated with severe WMLs (relative risk 2.77, 95% CI 1.10 to 6.98, P=0.030). In Cox regression survival analysis adjusted with significant covariates, eGFR <60 mL/min/1.73 m² (1.30, 95% CI 1.02 to 1.71, P=0.033) were associated with poor survival, whereas they were not independent from each other. In further analyses, presence of either eGFR ≥60 mL/min/1.73 m² or only mild to moderate WMLs, or both, was associated with improved survival compared with all other combinations.

Conclusions—Cerebral small vessel disease is closely associated with kidney function in patients with acute stroke. Cerebral small vessel disease and kidney function are closely associated predictors of poor poststroke survival. (Stroke. 2010;41:1914-1920.)

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Key Words: cerebral n glomerular n small vessel disease n stroke n survival

Chronic kidney disease and cardiovascular disease are independent risk factors for poor cardiovascular outcome in the general population. Impaired renal function, whether determined by creatinine level, creatinine clearance, urea level, or estimated glomerular filtration rate (eGFR), is a predictor of stroke mortality in patients hospitalized for acute stroke. The intimate association of glomerular and cerebral small vessel disease has been demonstrated previously in cross-sectional studies in patients without a history of stroke and in patients with several stages of renal impairment. However, data on patients with acute stroke are lacking. Cognitive decline, a common phenomenon in the elderly, is closely associated with both WMLs and kidney function as determined by eGFR. WMLs are a marker of cerebral small vessel disease. Severe WMLs are an important predictor of cardiovascular and noncardiovascular survival in older people without a history of stroke. Increased frequency and extent of WMLs also occur in patients with ischemic stroke. In addition, severe WMLs predict long-term survival in patients with acute stroke. Previous studies addressing the effect of renal function on survival of patients with acute stroke did not report data on WMLs.

The intimate association of glomerular and cerebral small vessel disease has been subject to considerable debate. We hypothesized that kidney function as estimated by eGFR, potentially reflecting glomerular small vessel disease and cerebral small vessel disease as determined by MRI, might be associated with each other and could be used to predict long-term survival in patients hospitalized for acute stroke.
Methods

Patients
The Helsinki Stroke Aging Memory (SAM) cohort comprised a consecutive series of all Finnish (white) patients with suspected stroke admitted to Helsinki University Central Hospital (n=1622) between December 1, 1993, and March 30, 1995, as described in detail previously.23–24 According to predetermined exclusion criteria, patients without ischemic stroke (n = 175), with intracerebral hemorrhage (n = 229), or with subarachnoid hemorrhage (n = 69) were excluded. Of the 1149 patients with ischemic stroke, we further excluded those aged <55 years (n = 258) or >85 years (n = 88), those not living in Helsinki (n = 158), and those not speaking the Finnish language (n = 3). A total of 642 patients fulfilled the inclusion criteria and were invited to a follow-up visit 3 months later. Of these, 71 died (11.1%) before the 3-month follow-up, 82 refused (12.8%), and 3 were lost (0.5%) due to undefined causes. Four hundred eighty-six of the living patients were included in the cohort.25 Of these, 383 (78.9%) had data on both serum creatinine level and MRI. Of these, patients with low eGFR (N=5 [1.3%]; <30 mL/min/1.73 m²) were excluded from the analysis and the final cohort consisted of 378 patients. This final study population did not differ in demographic and medical parameters from the original cohort. A detailed medical and neurological history was taken and stroke subtypes were defined.24 Atrial fibrillation (AF) was defined by clinical criteria and cardiac arrhythmias other than AF were defined as other arrhythmias. Myocardial infarction (MI), heart failure (HF), and hypertension were based on clinical diagnosis. Diabetes mellitus was defined as previously documented diagnosis, current use of insulin or oral hypoglycemic medication, or fasting blood glucose >7.0 mmol/L. Peripheral artery disease (PAD) was considered if the patient had claudication, >2 peripheral pulses missing, or history of amputation or peripheral arterial surgery due to atherosclerosis. Smoking habits were scored at admission as nonsmokers and smokers (current or former). Laboratory analyses included total cholesterol and creatinine. Stroke severity was assessed using modified Rankin score.26

Standard Protocol Approvals
The study was approved by the ethics committee of the Department of Clinical Neurosciences, Helsinki University Central Hospital, Finland. The study was explained to the patients, and informed consent was obtained.

MRI Analysis
Patients were subjected to MRI at 3 months and constituted the final study population. MRI was performed with a 1.0-T imaging equipment (Siemens Magnetom)25 as detailed previously. The protocol included transaxial T2, proton density-, and T1-weighted 5-mm thick slices (conventional spin echo technique) and a 3-dimensional gradient-echo sequence yielding 64 3-mm thick coronal sections. WMLs were rated on proton density-weighted images in accordance with the Leukoaraiosis and Disability in the Elderly rating as no to mild, moderate, and severe degree. The rating atlas has been published.25 In no to mild degree of WMLs, periventricular lesions included no more than a small cap or thin lining and in other white matter areas no more than large focal lesions. In moderate degree of WMLs, the periventricular lesions included no more than a large cap and a smooth halo and the other white matter areas no more than focal confluent lesions. The severe degree of WMLs included cases with extending caps or irregular halo in the periventricular area and diffusely confluent lesions or extensive white matter change in other white matter areas. The intra- and interobserver reliabilities for rating basic WMLs in periventricular and other white matter areas were tested previously and were found to be good.25,28,29 However, we did not retest intra- and interobserver reliabilities using atlas-based assessment of the present follow-up study.27 Of the patients, 108 (28.6%) had mild, 68 (18.0%) had moderate, and 202 (53.7%) had severe WMLs. Because there were no differences in survival analyses between moderate and mild WML categories, these categories were combined.

Determination of eGFR
Renal function on admission was calculated using the abbreviated equation of the Modification Diet for Renal Disease,30 which estimates eGFR: eGFR (mL/min/1.73 m²) = 186.3×serum creatinine (exp[−1.154])×age (exp[0.203])×(0.742 if female). All the patients in our cohort were of white origin and therefore no correction had to be made for black race. eGFR was classified on the basis of internationally accepted classification.31 Patients with low (Stages 4 and 5) eGFR (N = 5 [1.3%]; <30 mL/min/1.73 m²) and very low survival rate were excluded from the analysis. Patients were divided into those with normal or mildly impaired (N = 226 [59.8%]; Stages 1 to 2; eGFR ≥60 mL/min/1.73 m²) eGFR and those with low to moderate (N = 152 [40.0%]; Stage 3; eGFR <60 mL/min/1.73 m²) eGFR.

Survival
Long-term survival data and causes of death at September 21, 2006, were obtained from Statistics Finland. The mean (±SD) follow-up time was 7.5±4.0 years with a range between 0.3 and 12.8 years. Of the 378 patients with MRI data, 269 (72.1%) had died during the follow-up and data on survival were obtained in all the cases. Of all the dead subjects, the cause of death could not be verified for 8 cases (2.1%) with a death certificate. The outcome events were death from any cause and specific causes of death.

Statistical Analysis
SPSS/WIN (Version 12.0; SPSS Inc) software was used. The χ² test was used to test dichotomous variables and Student t test for independent samples to test continuous variables. Binary logistic regression analysis was used to study the association of different degrees of eGFR and WMLs. Kaplan–Meier log-rank test was used to analyze the effect of different factors on survival (sex, hypertension, diabetes mellitus, AF, HF, MI, PAD, smoking, modified Rankin score, WML degree, and eGFR). The cumulative hazard function was also used and according to these analyses, the proportional hazards assumption was met for each parameter included in further models. Three models were constructed, the first using covariates known to associate both with eGFR and WMLs (Model 1: age, sex, and stroke severity as assessed by modified Rankin score), another with classic factors associated with stroke (Model 2: age, sex, stroke severity, hypertension, diabetes mellitus, AF, HF, MI, PAD, smoking, and serum cholesterol), and the third using covariates proven to predict survival in univariate analyses with Kaplan–Meier log-rank test (Model 3: age, sex, modified Rankin score, AF, HF, PAD). All 4 different combinations of eGFR and WML were also tested in the models: (1) eGFR <60 mL/min/1.73 m²+mild to moderate WMLs; (2) eGFR <60 mL/min/1.73 m²+mild to severe WMLs; (3) eGFR ≥60 mL/min/1.73 m²+mild to moderate WMLs; and (4) eGFR ≥60 mL/min/1.73 m²+mild to severe WMLs. All the analyses were also performed including patients with first-ever stroke only (78.8%). Because the results were similar in both analyses, all the stroke cases were included in the study. Statistical significance was set at P<0.05 and borderline significance was considered at P<0.10.

Results

Patient Characteristics
Patients with eGFR <60 mL/min/1.73 m² (N=152 [40.2%]) were older (P<0.0001), were more often females (P<0.0001), had more seldom history of MI (P=0.013), had higher serum creatinine level on admission (P<0.0001), and had more often severe WMLs (P=0.003) compared with those with
Table 1. Demographics and Clinical and Laboratory Characteristics of 378 Patients With Acute Stroke

<table>
<thead>
<tr>
<th>Variable</th>
<th>All (N=378)</th>
<th>eGFR &lt;60 mL/min/1.73 m²</th>
<th>eGFR ≥60 mL/min/1.73 m²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD)</td>
<td>70.7 (7.6)</td>
<td>73.8 (6.4)</td>
<td>68.8 (7.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female sex, no. (%)</td>
<td>197 (52.1)</td>
<td>97 (63.8)</td>
<td>100 (44.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypertension, no. (%)</td>
<td>184 (48.7)</td>
<td>79 (52.0)</td>
<td>105 (46.5)</td>
<td>0.293</td>
</tr>
<tr>
<td>DM, no. (%)</td>
<td>91 (24.1)</td>
<td>30 (19.7)</td>
<td>61 (27.0)</td>
<td>0.106</td>
</tr>
<tr>
<td>AF, no. (%)</td>
<td>75 (19.8)</td>
<td>36 (23.7)</td>
<td>39 (17.3)</td>
<td>0.130</td>
</tr>
<tr>
<td>HF, no. (%)</td>
<td>80 (21.2)</td>
<td>38 (25.0)</td>
<td>42 (18.7)</td>
<td>0.140</td>
</tr>
<tr>
<td>MI, no. (%)</td>
<td>70 (18.5)</td>
<td>19 (12.5)</td>
<td>51 (22.6)</td>
<td>0.013</td>
</tr>
<tr>
<td>PAD, no. (%)</td>
<td>43 (11.4)</td>
<td>16 (10.5)</td>
<td>27 (11.9)</td>
<td>0.670</td>
</tr>
<tr>
<td>Smoking, no. (%)</td>
<td>185 (48.9)</td>
<td>66 (43.4)</td>
<td>119 (52.7)</td>
<td>0.071</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L (SD)</td>
<td>5.6 (1.2)</td>
<td>5.6 (1.3)</td>
<td>5.6 (1.1)</td>
<td>0.889</td>
</tr>
<tr>
<td>Creatinine on admission, μmol/L (SD)</td>
<td>90.5 (24.2)</td>
<td>106.6 (22.6)</td>
<td>79.7 (18.7)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Poor modified Rankin score, no. (%)</td>
<td>137 (36.2)</td>
<td>61 (40.1)</td>
<td>76 (33.6)</td>
<td>0.197</td>
</tr>
<tr>
<td>Severe WML</td>
<td>203 (53.7)</td>
<td>96 (63.2)</td>
<td>107 (47.3)</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

*Stroke Aging Memory (SAM) cohort according to eGFR. Poor modified Rankin score (ie, Rankin score 3–5), cerebral WMLs.

Factors Affecting Long-Term Survival

In Kaplan–Meier univariate analysis, history of AF (P<0.0001), HF (P<0.0001), PAD (P=0.004), and poor modified Rankin score (P<0.0001) were associated with poor survival, whereas sex (P=0.840), hypertension (P=0.824), diabetes (P=0.230), MI (P=0.182), and smoking (P=0.099) were not associated with survival.

Poor survival was predicted by eGFR <60 mL/min/1.73 m² (6.3, 95% CI 4.9 to 7.7 versus 9.0, 95% CI 7.9 to 10.0 years, P<0.0001; Figure A) and by severe WMLs (6.0, 95% CI 4.8 to 7.4 versus 9.3, 95% CI 8.0 to 10.6 years, P=0.0001; Figure B). Strikingly, these survival curves were almost superimposable.

In further analyses testing all the 4 possible combinations of eGFR and WML stages, presence of both eGFR ≥60 mL/min/1.73 m² and mild to moderate WMLs was associated with favorable outcome (11.3, 95% CI 9.6 to 13.1 years) compared with all other combinations of eGFR and WMLs (P<0.0001 to 0.004; Figure C).

To account for multiple factors, Cox regression survival analysis was performed. In analysis adjusted with age, sex, and stroke severity (Model 1), eGFR <60 mL/min/1.73 m² (hazard ratio [HR]1.30, 95% CI 1.00 to 1.67, P=0.047) and severe WMLs with a borderline significance (HR 1.27, 95%CI 0.99 to 1.63, P=0.067) were associated with impaired survival (Table 2). Inclusion of both of these predictors in the model resulted in lack of significant association with survival indicating a possible interaction of eGFR with WML stage (Table 2). To account for a possible residual confounding effect of associated comorbidities, in further analysis adjusted with classical risk factors (age, sex, stroke severity, hypertension, diabetes, AF, HF, MI, PAD, smoking, and serum cholesterol; Model 2), eGFR <60 mL/min/1.73 m² (HR 1.37, 95% CI 1.04 to 1.79, P=0.025) and severe WMLs (HR 1.34, 95% CI 1.03 to 1.74, P=0.028) remained associated with impaired survival (Table 2). Inclusion of both of these predictors in the model resulted in lack of significant association with survival as shown previously. In a third model (Model 3), the analyses were repeated adjusting with significant predictors from previous Kaplan–Meier univariate analyses (age, sex, stroke severity, AF, HF, PAD). In these analyses, eGFR <60 mL/min/1.73 m² (HR 1.30, 95% CI 1.00 to 1.68, P=0.047) and severe WMLs (HR 1.32, 95% CI 1.02 to 1.71, P=0.033) were associated with impaired survival, whereas inclusion of both of these predictors in the model resulted in lack of significant association with survival (Table 2).

When analyzing all the 4 possible combinations of eGFR and WMLs with adjusted Cox regression survival analysis, presence of both eGFR ≥60 mL/min/1.73 m² and mild to moderate WMLs was associated with favorable outcome in long-term follow-up compared with all other groups (Table 3). Different adjusted models (Models 1, 2, and 3; see “Statistical Analyses”) resulted in similar results.

Discussion

In the present study, for the first time to our knowledge, we demonstrated that cerebral small vessel disease is connected to kidney function as estimated by eGFR in patients hospitalized for acute stroke. Whether this association is due to coexisting glomerular small vessel disease remains to be elucidated in future studies. In addition, we demonstrated that...
small vessel disease and kidney function are closely associated predictors of poor poststroke survival.

We speculate that cerebral small vessel disease and glomerular small vessel disease might have a common soil of pathogenesis and therefore be closely connected with each other not only due to anatomic and vasoregulatory similarities. First, cerebral small vessel disease is reflected by WMLs and WMLs are directly related with risk of recurrent strokes and poor survival mostly due to cardiovascular causes. Second, the association of WMLs and glomerular small vessel disease has been demonstrated in several different stages of kidney disease involving predialysis patients and patients with end-stage kidney disease. Third, metabolic alterations and disturbances in cerebral blood flow have been demonstrated to be associated with degree of renal function. Our results are in accordance with these findings because in the present study, severe white matter lesions were more frequent (63.2% versus 47.3%) in patients with low to moderate eGFR compared with those with eGFR ≥60 mL/min/1.73 m². The association of low eGFR and severe WMLs was also demonstrated after adjusting for age and sex, the factors previously known to associate with renal function and WMLs, also labeled as age-related white matter changes. According to survival analysis, the survival curves for eGFR and WMLs were almost superimposable in line with the HRs for low eGFR and WMLs suggesting a possible associated cause of the small vessel disease in the brain and kidney, not unlikely.

Previous findings on the association of calculated creatinine clearance, creatinine level, high urea or ratio of urea to creatinine, and eGFR with long-term survival in patients hospitalized for acute stroke are in line with our findings. Using the same cohort, we have previously demonstrated the effect of WMLs and cognitive status on long-term survival after acute stroke. Interestingly, cognitive function, kidney function, and WMLs have been shown to be closely associated with each other most probably due to coexisting cerebral and glomerular small vessel disease. The intimate association of cerebral and glomerular small vessel disease is supported by the coexistence of lipohyalinosis and
endothelial dysfunction in both glomerular small vessel and cerebral small vessel disease. As a limitation, however, it must be emphasized that decreased eGFR is a measure of decreased renal function, but it does not necessarily show that the decreased renal function is due to small vessel disease.

In our cohort, the proportion of patients with eGFR <60 mL/min/1.73 m² was rather high, up to 40.2%, whereas in a previous study of patients with acute stroke, this proportion was 28.1%. However, similar prevalence was found in another study (36.0%). In line with a previous study, our patients with low eGFR were older and included more women. In another study, assessed by serum creatinine level, the proportion of patients with high values (≥124 μmol/L) was 26.0%. Acute renal failure has been reported to occur among 14.3% of patients with acute stroke, but we were not able to reliably exclude patients with acute renal failure in our cohort because we had a single determination of creatinine at admission. It must be emphasized that there are several causes of decreased eGFR; it could represent acute dehydration on admission, a concurrent infection, or renal artery stenosis as well as small vessel renovascular disease. Because acute renal failure itself is an independent prognostic factor for mortality after stroke, our results may underestimate the prognostic value of chronically lowered eGFR. To avoid bias from low eGFR (<30 mL/min/1.73 m²), 5 patients were excluded from the analysis. It must emphasized that Modification Diet for Renal Disease was the only feasible option to determine eGFR. Modification Diet for Renal Disease has not been validated in the very elderly or malnourished patients, which is a potential source of bias in the present study.

Despite the obvious shortcomings, our prospective study has several strengths. The cohort is a consecutive one and patients were reviewed by senior neurologists in the working group; also, the severity of stroke was quantitated according to the modified Rankin score. We consider it beneficial that our unit is responsible for primary stroke management of all inhabitants living in the Helsinki area. Also, the survival data are comprehensive with a small amount of unresolved deaths. We consider there is a possibility of selection bias due to formation of the cohort 3 months after the index stroke. This may limit generalization of the results. According to additional retrospectively obtained data in the Helsinki University Hospital district during the collection of the cohort from an independent organization (Statistics Finland), up to 64% of stroke-related deaths occurred in women. The proportion of women (52.1%) in the present study suggests that some women may have died before hospital assessment at 3 months. Due to exclusion of patients, the true survival rate may be underestimated. Another weakness is that we have no data on proteinuria, which has previously been associated with poor long-term survival in patients with acute stroke.

Table 2. Cox Regression Analysis on the Association of eGFR and Severe Cerebral WMLs as Determined by MRI With Poor Long-Term Survival in 378 Patients With Acute Stroke in the SAM Cohort

<table>
<thead>
<tr>
<th>Variable</th>
<th>eGFR Model</th>
<th>WML Model</th>
<th>eGFR + WML Model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR 95% CI</td>
<td>P</td>
<td>HR 95% CI</td>
</tr>
<tr>
<td>Model 1 (adjusted with age, sex, poor modified Rankin score)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR &lt;60 mL/min/1.73 m²</td>
<td>1.30</td>
<td>1.00–1.67</td>
<td>0.047</td>
</tr>
<tr>
<td>Severe WML</td>
<td>Not included</td>
<td>1.27</td>
<td>0.99–1.63</td>
</tr>
<tr>
<td>Model 2 (adjusted with age, sex, poor modified Rankin score, hypertension, diabetes, AF, HF, MI, PAD, smoking, serum cholesterol)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR &lt;60 mL/min/1.73 m²</td>
<td>1.37</td>
<td>1.04–1.79</td>
<td>0.025</td>
</tr>
<tr>
<td>Severe WML</td>
<td>Not included</td>
<td>1.34</td>
<td>1.03–1.74</td>
</tr>
<tr>
<td>Model 3 (adjusted with age, sex, poor modified Rankin score, AF, HF, PAD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR &lt;60 mL/min/1.73 m²</td>
<td>1.30</td>
<td>1.00–1.68</td>
<td>0.047</td>
</tr>
<tr>
<td>Severe WML</td>
<td>Not included</td>
<td>1.32</td>
<td>1.02–1.71</td>
</tr>
</tbody>
</table>

Poor modified Rankin score (ie, Rankin score 3–5). Reference eGFR ≥60 mL/min/1.73 m² or mild–moderate WMLs. Cox proportional hazards regression model.

Table 3. Cox Regression Analysis on the Association of Different Combinations of eGFR and cerebral WMLs as Determined by MRI With Poor Long-Term Survival in 378 Patients With Acute Stroke in the SAM Cohort

<table>
<thead>
<tr>
<th>Reference Group</th>
<th>12-Year Overall Mortality Relative to Reference Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR ≥60 mL/min/1.73 m² + WMLMM</td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>HR 95% CI</td>
</tr>
<tr>
<td>eGFR ≥60 mL/min/1.73 m² + WMLMM</td>
<td>1</td>
</tr>
<tr>
<td>eGFR ≥60 mL/min/1.73 m² + WMLMM</td>
<td>0.68</td>
</tr>
<tr>
<td>eGFR &lt;60 mL/min/1.73 m² + WMLMM</td>
<td>0.62</td>
</tr>
<tr>
<td>eGFR &lt;60 mL/min/1.73 m² + WMLMM</td>
<td>0.65</td>
</tr>
</tbody>
</table>

WMLMM indicates mild–moderate cerebral WMLs; WMLs, severe WMLs. Cox proportional hazards regression model with age, sex, and poor modified Rankin score as covariates.

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with vascular disease independent of glomerular filtration rate. Due to the homogenous population, the present results may not be applicable to other populations.

We demonstrated that kidney function is closely associated with cerebral small vessel disease in patients hospitalized for acute stroke. Furthermore, we demonstrated that kidney function and cerebral small vessel disease are closely associated predictors of poor poststroke survival.

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Disclosures

None.

References


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