Interventional Cardiology

Primary Angioplasty Versus Fibrinolysis in Acute Myocardial Infarction
Long-Term Follow-Up in the Danish Acute Myocardial Infarction 2 Trial

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Background—The Danish Acute Myocardial Infarction 2 (DANAMI-2) study found that primary angioplasty (primary percutaneous coronary intervention [pPCI]) compared with fibrinolysis reduced 30-day adverse events in patients with ST-segment elevation myocardial infarction. The present study investigated whether the benefit of pPCI was maintained at a long-term follow-up.

Methods and Results—We randomly assigned 1572 patients with ST-segment elevation myocardial infarction—1129 patients at referral hospitals and 443 patients at invasive hospitals—to pPCI or fibrinolysis. Median time from randomization to arrival in the catheterization laboratory for patients admitted to referral hospitals was 67 minutes, with 96% of patients arriving in the catheterization laboratory within 120 minutes. The primary study end point was a composite of death or reinfarction. Median follow-up time was 7.8 years. For the primary end point, 8-year cumulative incidence (1-Kaplan–Meier) was 34.8% in the pPCI group and 41.3% in the fibrinolysis group (hazard ratio, 0.78; 95% confidence interval, 0.66 to 0.92). Reinfarction rates were reduced in the pPCI group (11.7% versus 18.5%; hazard ratio, 0.60; 95% confidence interval, 0.46 to 0.77). Among patients randomized at referral hospitals, pPCI reduced reinfarction (13% versus 18.5%; hazard ratio, 0.66; 95% confidence interval, 0.49 to 0.89) and mortality (26.7% versus 33.3%; hazard ratio, 0.78; 95% confidence interval, 0.63 to 0.97).

Conclusions—The benefit of pPCI over fibrinolysis was maintained at a long-term follow-up. pPCI reduced the risk of reinfarction in the overall cohort and reduced reinfarction and mortality among patients randomized at referral hospitals. This result reinforces that pPCI should be offered to ST-segment elevation myocardial infarction patients when interhospital transport to an invasive hospital can be completed within 120 minutes. (Circulation. 2010;121:1484-1491.)

Key Words: angioplasty ■ fibrinolysis ■ mortality ■ myocardial infarction

Clinical Perspective on p 1491

Methods

Design of DANAMI-2
The DANAMI-2 trial design has been described previously; a diagram of the patient flow in the study is presented in Figure 1. In brief, we randomly assigned patients with STEMI to treatment with pPCI was superior to fibrinolysis when transport could be accomplished within 2 hours despite a transfer-related treatment delay of 55 minutes. Other minor studies have shown similar results. We have previously shown a persistence in the superiority of pPCI over fibrinolysis at a 3-year follow-up. The present study tested whether the benefit of pPCI could be extended to a median follow-up time of 7.8 years.
fibrinolysis or pPCI. The main inclusion criteria were the presence of symptoms for at least 30 minutes but <12 hours and cumulative ST-segment elevation ≥4 mm in at least 2 contiguous leads. Furthermore, a transfer time ≤3 hours from the time of randomization until arrival at a catheterization laboratory should be expected. The main exclusion criteria were cardiogenic shock, left bundle-branch block, and myocardial infarction treated with fibrinolysis within the previous 30 days.3,7 The patients were enrolled at 24 referral hospitals without pPCI facilities and at 5 pPCI centers with availability of pPCI on a 24-hour basis, 7 days a week. No patients were excluded from the trial because of unavailability of invasive facilities. The primary end point of DANAMI-2 was a composite of death, clinical reinfarction, or disabling stroke. The protocol called for randomization of 1100 patients at referral hospitals and 800 patients at invasive hospitals.7 Enrollment began in December 1997 and was terminated in accordance with the study protocol in October 2001 when the third interim analysis showed a significant benefit of pPCI in the referral hospital substudy. At that time, 1572 patients, including 1129 patients at referral hospitals and 443 patients at invasive hospitals, had been randomized. The present study followed up the patients to March 2008.

Treatment

Patients randomized to fibrinolysis received accelerated treatment with tissue plasminogen activator (alteplase). In patients randomized to pPCI, stenting of the culprit lesion was attempted in all patients unless the vessel had a diameter <2.0 mm. Only the culprit artery was treated at the index angioplasty. After stent implantation, ticlopidine 500 mg, without preceding bolus, was given daily for 1 month between 1997 and August 2001. After publication of the PCI subgroup in the Clopidogrel in Unstable angina to prevent Recurrent Events (PCI-CURE) study8 in August 2001, clopidogrel 300 mg bolus followed by 75 mg daily for 1 month gradually replaced ticlopidine for the last 2 months of the study period. Thus, the majority of patients were treated with ticlopidine; only a minority received clopidogrel. Platelet glycoprotein IIb/IIIa receptor inhibitors were administered at the discretion of the physician.

The study complied with the Declaration of Helsinki and was approved by the National Ethics Committee of Denmark. All patients provided written informed consent.

Study End Points and Follow-Up

The primary end point of this long-term follow-up was a composite of death or clinical reinfarction. This primary end-point definition differed from the previously published 30-day3 and 3-year6 reports in which the composite end point consisted of death, reinfarction, or disabling stroke. The rationale for the different primary end-point definition in the present study was that a clinical diagnosis of disabling stroke (severe handicap) could not be extracted from registries and was therefore removed from the present longer-term analysis. Secondary end points were all-cause mortality, cardiac mortality, noncardiac mortality, and reinfarction. As in the prior DANAMI-2 publications, the end points were subsequently analyzed separately in the referral hospital substudy and in the invasive hospital substudy. Furthermore, the primary end point was applied on a number of prespecified subgroups.

Follow-up until 3 years was performed at the hospital where the patient was randomized.3,7 An end-point committee blinded to treatment group continuously reviewed all end points.7,9 The longer-term follow-up data in the present study have been accrued by merging the DANAMI-2 database with Danish national registries on vital status, cause of death, and cause of hospital admissions. We identified death in the Danish Civil Registration System. Cause of death was obtained by using data from the Causes of Death Registry. Causes of death were classified according to the International Classification of Diseases and Related Health Problems, 10th revision (ICD-10). For the present analysis, death resulting from ischemic heart disease (ICD-10 codes I-20 to I-25), sudden cardiac death (ICD-10 code I-46), death caused by heart failure (ICD-10 code I-50), and sudden death undefined (ICD-10 code R-96) were considered to be cardiac. Data on reinfarction (ICD-10 code I-21) were obtained from the National Patient Registry.
Statistical Design and Analysis
Results were analyzed according to the intention-to-treat principle. For comparison of categorical variables, the Pearson χ² test was used. Continuous variables were reported as median and interquartile range (IQR). Mean and SD were also reported for time from onset of symptoms to randomization. Groups were compared by use of the U test. For the composite end point and the end point of death, cumulative incidence curves were estimated as 1-Kaplan–Meier curves. For the end points of reinfarction, cardiac death, and noncardiac death, competing-risks regression estimation was used.10 Specifically, estimates at the 8-year follow-up were computed. Event curves were compared by use of the log-rank test. Differences between groups were estimated with the Cox proportional-hazards model. We validated the proportionality by computing. Event curves were compared by use of the log-rank test. Differences between groups were estimated with the Cox proportional-hazards model. We validated the proportionality by

Results
Baseline Characteristics and Follow-Up
Baseline characteristics did not differ between patients randomized to pPCI or to fibrinolysis (Table 1). Time from randomization to censoring was from 6.5 to 10.2 years with a median follow-up of 7.8 years (IQR, 7.1 to 8.5 years).

Vital status at the study closing date was known for 1564 patients (99.5%); 8 patients emigrated during follow-up and were censored on the day of emigration. Information on cause of death in the registries was missing in 46 cases; we were able to determine the cause of death in 33 of these cases from hospital records. The cause of death could not be identified in 13 patients (pPCI, n=9; fibrinolysis, n=4); these patients were censored at the time of death in the analysis of cardiac and noncardiac death.

Treatment and Treatment Delay
Ninety-nine percent of patients randomized to fibrinolysis received the assigned treatment; of these, 26 patients underwent repeated (rescue) fibrinolysis, and 15 patients underwent rescue PCI. Ninety-eight percent of patients randomized to pPCI underwent immediate coronary angiography. Balloon inflation was performed in 87% of patients randomized to pPCI, with bare metal stents implanted in 93% of patients undergoing pPCI.3

Detailed results on times from onset of symptoms to admission, randomization, transfer, and arrival in the catheterization laboratory have been published previously.3 Time from onset of symptoms to randomization was 135 minutes (IQR, 85 to 230 minutes) for the total study population, and there was no difference between randomization groups (Table 1). Median distance for interhospital transfer from referral hospitals to pPCI centers was 50 km, with limits of 3 to 150 km. Transfer time from randomization at referral hospitals to arrival at the catheterization laboratory was 67 minutes (IQR, 50 to 85 minutes), with 96% of patients arriving in the catheterization laboratory within 120 minutes. Median total interval from onset of symptoms to first balloon inflation was 224 minutes (IQR, 171 to 317 minutes) for patients transferred to pPCI compared with 169 minutes (IQR, 110 to 270 minutes) for patients randomized at referral hospitals to receive fibrinolysis. Thus, interhospital transfer for pPCI was associated with a median treatment delay of 55 minutes.

Study End Points
The results of major adverse cardiac end points are given in Table 2, and Kaplan–Meier curves detailing the occurrence of the primary composite end point of all-cause mortality, cardiac mortality, noncardiac mortality, and reinfarction are shown in Figure 2. The composite end point was reached in 37.2% of the patients, and 28.1% died during follow-up. pPCI was associated with significantly lower rates of the composite end point than fibrinolysis. This difference was driven mainly by an absolute 6.8% reduction in clinical reinfarction and, to a lesser degree, by a nonsignificant absolute 3.5% reduction in all-cause mortality.

In the referral hospital substudy, pPCI reduced the composite end point by an absolute 9.3%, all-cause mortality by 6.6%, and reinfarction by 5.5%, all of which reached statistical significance. In the smaller and prematurely terminated invasive hospital substudy, only reinfarction was significantly in favor of pPCI with an absolute risk reduction of 10.2%.

Figure 3 shows the odds ratios for the 8-year composite end point in a number of prespecified subgroups. pPCI was statistically superior to fibrinolysis in a number of subgroups, and all but 1 subgroup tended to favor pPCI over fibrinolysis.

Discussion
The present study examined long-term outcome after pPCI compared with fibrinolysis in the DANAMI-2 trial. It repre-
follow-up. We found that pPCI reduced the composite end point by an absolute 6.5% in the overall cohort, which concurs with the trend in studies reporting 5-year follow-up.11,12 The individual hazard ratios for each of the end points in the composite end point (death and reinfarction) were in favor of pPCI in the overall cohort and the referral hospital substudy. Reinfarction was significantly reduced in the overall cohort and the referral and invasive hospital substudies, and mortality was significantly reduced in the referral hospital substudy. In a meta-analysis by Dalby et al, each of these end points, as well as disabling stroke, significantly favored pPCI over fibrinolysis in patients who presented to a hospital for reperfusion therapy. Subsequently, the present data indicate that transport for pPCI should be offered to STEMI patients when transport to a hospital with interventional facilities can be completed within 2 hours after the diagnosis has been established. This conclusion differs from the current American and European guidelines. The American guidelines recommend fibrinolytic treatment if pPCI cannot be reliably performed by a hospital system within 90 minutes of first medical contact.14 The European guidelines differ slightly in that they recommend fibrinolytic treatment if pPCI cannot be reliably performed by a hospital system within 90 minutes of first medical contact when symptom duration is <2 hours but accept up to 120 minutes since first medical contact when symptom duration is >2 hours.15 A recent meta-analysis of the randomized trials comparing pPCI with fibrinolysis indicated a benefit of pPCI over fibrinolysis as long as the pPCI-related delay was <80 to 120 minutes.16 To meet these time limits, the current standard for STEMI patients in Denmark is a triage plan including prehospital 12-lead ECG, rerouting of ambulance transport directly to a hospital with 24/7 interventional facilities, and immediate angiography/PCI.

### Mortality
Meta-analyses of the randomized studies comparing pPCI and fibrinolysis have shown that the 30-day absolute mortality reduction is within the range of 2% to 3%,17–19 ie, a benefit similar to the use of fibrinolysis compared with placebo.20,21 In the present long-term follow-up study, a nonsignificant absolute mortality difference of 3.5% based on the 8-year Kaplan–Meier estimates was found in the overall cohort. In the referral hospital substudy, the absolute mortality difference of 6.6% reached statistical significance in favor of pPCI, whereas in the smaller and prematurely stopped invasive hospital substudy, there was no mortality difference. The curves for cardiac mortality in Figure 2, although not reaching statistical significance, seemed to diverge over time in favor of pPCI. None of the randomized studies comparing pPCI and fibrinolysis had sufficient power to show a difference on short-term mortality, but all studies showed a trend toward a mortality benefit of pPCI.1–5 Five-year follow-up in one of the first randomized trials showed a significant mortality reduction from 24% in the fibrinolysis arm to 13% in the pPCI arm,12 whereas 5-year data from the PRAGUE-2 study11 and 3-year data from the DANAMI-2 study6 showed nonsignificant absolute differences of 4.0% and 1.3%, respectively, in favor of pPCI.

### Table 2. Major Adverse Cardiac Events

<table>
<thead>
<tr>
<th>Overall cohort</th>
<th>pPCI</th>
<th>Fibrinolysis</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>790</td>
<td>782</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite end point, n (%)</td>
<td>267 (34.8)</td>
<td>317 (41.3)</td>
<td>0.78 (0.66–0.92)</td>
<td>0.003</td>
</tr>
<tr>
<td>Reinfarction, n (%)</td>
<td>91 (11.7)</td>
<td>142 (18.5)</td>
<td>0.60 (0.46–0.77)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death, n (%)</td>
<td>209 (27.3)</td>
<td>233 (30.8)</td>
<td>0.87 (0.72–1.05)</td>
<td>0.14</td>
</tr>
<tr>
<td>Cardiac death, n (%)</td>
<td>97 (12.4)</td>
<td>122 (15.6)</td>
<td>0.78 (0.59–1.01)</td>
<td>0.06</td>
</tr>
<tr>
<td>Noncardiac death, n (%)</td>
<td>103 (14.1)</td>
<td>107 (14.8)</td>
<td>0.93 (0.71–1.22)</td>
<td>0.60</td>
</tr>
<tr>
<td>Referral hospital substudy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>567</td>
<td>562</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite end point, n (%)</td>
<td>193 (35.0)</td>
<td>240 (44.3)</td>
<td>0.74 (0.61–0.90)</td>
<td>0.002</td>
</tr>
<tr>
<td>Reinfarction, n (%)</td>
<td>72 (13.0)</td>
<td>101 (18.5)</td>
<td>0.66 (0.49–0.89)</td>
<td>0.006</td>
</tr>
<tr>
<td>Death, n (%)</td>
<td>147 (26.7)</td>
<td>180 (33.3)</td>
<td>0.78 (0.63–0.97)</td>
<td>0.03</td>
</tr>
<tr>
<td>Cardiac death, n (%)</td>
<td>72 (12.8)</td>
<td>92 (16.4)</td>
<td>0.76 (0.56–1.03)</td>
<td>0.08</td>
</tr>
<tr>
<td>Noncardiac death, n (%)</td>
<td>69 (13.3)</td>
<td>84 (16.3)</td>
<td>0.78 (0.57–1.07)</td>
<td>0.13</td>
</tr>
<tr>
<td>Invasive hospital substudy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>223</td>
<td>220</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite end point, n (%)</td>
<td>74 (34.1)</td>
<td>77 (34.2)</td>
<td>0.91 (0.66–1.25)</td>
<td>0.54</td>
</tr>
<tr>
<td>Reinfarction, n (%)</td>
<td>19 (8.4)</td>
<td>41 (18.6)</td>
<td>0.43 (0.25–0.75)</td>
<td>0.002</td>
</tr>
<tr>
<td>Death, n (%)</td>
<td>62 (28.6)</td>
<td>53 (24.6)</td>
<td>1.17 (0.81–1.69)</td>
<td>0.40</td>
</tr>
<tr>
<td>Cardiac death, n (%)</td>
<td>25 (11.3)</td>
<td>30 (13.7)</td>
<td>0.83 (0.49–1.42)</td>
<td>0.50</td>
</tr>
<tr>
<td>Noncardiac death, n (%)</td>
<td>34 (16.0)</td>
<td>23 (11.0)</td>
<td>1.48 (0.87–2.52)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

HR indicates hazard ratio; CI, confidence interval.

sent both the longest follow-up and the largest randomized study on this issue performed to date. We found that pPCI compared with fibrinolysis carried a sustained reduction in the primary composite end point of death or reinfarction in the overall cohort. In the referral hospital substudy, pPCI significantly reduced the composite end point by an absolute 9.3%, all-cause mortality by 6.6%, and reinfarction by 6.4%. Our long-term data thus reinforce that pPCI should be offered to STEMI patients, not only those admitted to an invasive hospital1,2 but also those patients for whom transport from a referral to an invasive hospital can be completed within 2 hours.

### Composite End Point
The present study found that the benefit of pPCI over fibrinolysis was maintained after a median of 7.8 years’ follow-up. We found that pPCI reduced the composite end point by an absolute 6.5% in the overall cohort, which concurs with the trend in studies reporting 5-year follow-up.11,12 The individual hazard ratios for each of the end points in the composite end point (death and reinfarction) were in favor of pPCI in the overall cohort and the referral hospital substudy. Reinfarction was significantly reduced in the overall cohort and the referral and invasive hospital substudies, and mortality was significantly reduced in the referral hospital substudy. In a meta-analysis by Dalby et al, each of these end points, as well as disabling stroke, significantly favored pPCI over fibrinolysis in patients who presented to a hospital for reperfusion therapy. Subsequently, the present data indicate that transport for pPCI should be offered to STEMI patients when transport to a hospital with interventional facilities can be completed within 2 hours after the diagnosis has been established. This conclusion differs from the current American and European guidelines. The American guidelines recommend fibrinolytic treatment if pPCI cannot be reliably performed by a hospital system within 90 minutes of first medical contact.14 The European guidelines differ slightly in that they recommend fibrinolytic treatment if pPCI cannot be reliably performed by a hospital system within 90 minutes of first medical contact when symptom duration is <2 hours but accept up to 120 minutes since first medical contact when symptom duration is >2 hours.15 A recent meta-analysis of the randomized trials comparing pPCI with fibrinolysis indicated a benefit of pPCI over fibrinolysis as long as the pPCI-related delay was <80 to 120 minutes.16 To meet these time limits, the current standard for STEMI patients in Denmark is a triage plan including prehospital 12-lead ECG, rerouting of ambulance transport directly to a hospital with 24/7 interventional facilities, and immediate angiography/PCI.

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The fibrinolysis group was treated according to the documented optimal standards in 1997 to 2001. The DANAMI-2 study had a very low rate of crossover between the 2 groups, and <50% of patients in the fibrinolysis arm had PCI performed within the first 3 years of follow-up. A recent French registry study found that a strategy with liberal use of early angiography/PCI (96% coronary angiography, 84% PCI) after fibrinolysis yielded 1-year survival rates that were comparable to rates for pPCI. It is thus possible that a strategy of fibrinolysis combined with invasive treatment within 24 hours will be comparable to a strategy of referral for pPCI, especially if transport to a hospital with interventional facilities cannot be completed within ≈1 to 2 hours. However, the French registry data still need confirmation in a randomized design. Until such data exist, interhospital transfer for pPCI should be the standard treatment, when it can be completed within 120 minutes.
Data from the American National Registry of Myocardial Infarction showed that among 4278 patients transferred for pPCI, only 16% had a referral hospital door-to-pPCI time <2 hours. The time limits recommended by the guidelines is thus difficult to achieve in some regions because of logistical issues, which opens up for a pharmacoinvasive strategy when pPCI cannot be performed appropriately.

Limitations
The use of thienopyridine in pPCI patients but not fibrinolysis patients may have affected the frequency of myocardial infarction and the composite end-point rates in the 2 groups, although a similar short-term benefit was reported in the initial randomized studies with balloon angioplasty and no subsequent thienopyridine treatment. Furthermore, in the PRAQUE-2 study, which reached a conclusion similar to the DANAMI-2 study, thienopyridine was given for 1 month to both the pPCI and fibrinolysis groups. Moreover, the benefit of long-term treatment with clopidogrel as an adjunct to both angioplasty and fibrinolysis had not been shown when the DANAMI 2 trial was planned. Second, DANAMI-2 enrolled patients in the early era of pPCI, with invasive hospitals allowed to include patients after having performed only 25 pPCIs per center and referral hospitals allowed to randomize and transfer patients after having organized only 3 transports of STEMI patients. Thus, in the DANAMI-2 study, the strategy of pPCI including interhospital transfer of patients was initially performed by hospitals with limited experience. In contrast, fibrinolysis was a long-established treatment in all participating hospitals. Furthermore, the mortality benefit of thrombus aspiration and adjunct therapy with bivalirudin had not been documented. The present DANAMI-2 analysis may thus underestimate the mortality benefit of current state-of-the-art pPCI. Similarly, an up-to-date pharmacoinvasive strategy of fibrinolysis with the addition of clopidogrel, enoxaparin, and cardiac catheterization within 24 hours may compare favorably with the DANAMI-2 fibrinolysis strategy.

Conclusions
The benefit of pPCI over fibrinolysis was maintained at a long-term follow-up. pPCI reduced the risk of reinfarction in the overall cohort and in the referral and invasive hospital substudies and reduced mortality in the referral hospital substudy. This result reinforces that pPCI should be offered to STEMI patients when interhospital transport to a PCI center can be completed within 2 hours.

Sources of Funding
The DANAMI-2 trial was supported by grants from the Danish Heart Foundation, the Danish Medical Research Council, AstraZeneca,
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Bristol-Myers Squibb, Cordis, Pfizer, Pharmacia-Upjohn, Boehringer-er Ingelheim, and Guerbet (all in Denmark). The Danish Council for Independent Research supported the present analysis.

Disclosures

None.

References


CLINICAL PERSPECTIVE

The Danish Acute Myocardial Infarction 2 (DANAMI-2) study was a randomized multicenter investigation comparing fibrinolytic treatment and primary percutaneous coronary intervention (pPCI) in patients with ST-segment elevation myocardial infarction. It consisted of 2 substudies: a substudy of patients randomized at noninvasive referral hospitals where the pPCI arm included transfer for pPCI and a substudy of patients randomized at hospitals with interventional facilities. The study was terminated prematurely when the third interim analysis showed a significant benefit of pPCI in the referral hospital substudy. The present study investigated the long-term outcome. The primary end point consisted of death and reinfarction with a median follow-up of 7.8-years. In the overall cohort, pPCI reduced the composite end point from 41.3% in the fibrinolysis arm to 34.8% (P=0.003), reduced reinfarction by an absolute 6.8% (P<0.001), and reduced death by an absolute 3.5% (P=0.14). In the referral hospital substudy, pPCI reduced reinfarction by 5.5% (P=0.006) and mortality by 6.6% (P=0.03). In the smaller invasive hospital substudy, which was terminated after inclusion of only half of the planned number of patients, reinfarction was reduced by 10.2% (P=0.002). The results indicate that transfer from noninvasive referral hospitals to invasive hospitals is associated with a significant improvement in long-term clinical outcome.

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Circulation. 2010;121:1484-1491; originally published online March 22, 2010; doi: 10.1161/CIRCULATIONAHA.109.873224

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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