Bayesian probability analysis: a prospective demonstration of its clinical utility in diagnosing coronary disease

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ABSTRACT One hundred fifty-four patients referred for coronary arteriography were prospectively studied with stress electrocardiography, stress thallium scintigraphy, cine fluoroscopy (for coronary calcifications), and coronary angiography. Pretest probabilities of coronary disease were determined based on age, sex, and type of chest pain. These and pooled literature values for the conditional probabilities of test results based on disease state were used in Bayes' theorem to calculate posttest probabilities of disease. The results of the three noninvasive tests were compared for statistical independence, a necessary condition for their simultaneous use in Bayes' theorem. The test results were found to demonstrate pairwise independence in patients with and those without disease. Some dependencies that were observed between the test results and the clinical variables of age and sex were not sufficient to invalidate application of the theorem. Sixty-eight of the study patients had at least one major coronary artery obstruction of greater than 50%. When these patients were divided into low-, intermediate-, and high-probability subgroups according to their pretest probabilities, noninvasive test results analyzed by Bayesian probability analysis appropriately advanced 17 of them by at least one probability subgroup while only seven were moved backward. Of the 76 patients without disease, 34 were appropriately moved into a lower probability subgroup while 10 were incorrectly moved up. We conclude that posttest probabilities calculated from Bayes' theorem more accurately classified patients with and without disease than did pretest probabilities, thus demonstrating the utility of the theorem in this application.


BAYES' THEOREM can be used to calculate the probability of coronary artery disease based on clinical data and multiple noninvasive test results. Pretest probabilities of disease are assigned based on clinical data and the equation is used to calculate posttest probabilities after multiple sequential tests.

The validity of application of the theorem to multiple clinical and test variables depends on the mutual statistical independence of these variables in populations of patients with and without disease. The results of this investigation provide evidence that independence does in fact exist for the results of the following noninvasive tests: stress electrocardiography, thallium-201 stress scintigraphy, and cardiac cine fluoroscopy (for coronary calcifications). With some exceptions there is also evidence for the independence of these three test variables and the clinical variables of age, sex, and type of chest pain.

Diagnostic testing is useful if patients with disease who are initially judged to have a low probability of disease are finally judged to have a high probability because of the test results. Similarly, test utility is demonstrated if patients without disease are appropriately moved from a subgroup of high probability to one of low probability. Although previous reports have demonstrated that posttest probabilities are fairly closely associated with disease prevalence, there has been no prospective demonstration that they appropriately move patients from lower to higher probability groups or vice versa. This study demonstrates how a Bayesian analysis of clinical data and noninvasive test results can be useful in classifying patients with and without coronary disease.

Methods

Study sample. Between May 1981 and October 1982, 226 patients without histories or electrocardiographic evidence of
myocardial infarction were referred to a group of six participating cardiologists at our institution for the angiographic evaluation of suspected coronary disease. Sixty-seven of these were excluded from this study because they refused to undergo testing, had known or suspected valvular or cardiomyopathic disease, unstable angina, serious arrhythmia, left bundle branch block, extreme obesity, or orthopedic or neurologic conditions precluding performance of a symptom-limited treadmill exercise test. All 159 remaining subjects were informed and they and their angiographers agreed that test results would influence only postcatheterization medical or surgical management and not the decision of whether or not to perform an angiographic examination. Despite this, a breach in the research protocol resulted in five subjects not undergoing cardiac catheterization because they were considered to have a very low probability of significant coronary disease based on their exercise test results. Since the study subjects did not receive the full potential benefit of preangiography exercise testing, the cost of stress electrocardiography was absorbed by the institution. Of the 154 subjects undergoing angiography, there were 111 men and 43 women. Their mean age was 54 years.

**Clinical data.** Clinical histories were reviewed by an investigator unaware of any test or angiographic results. Patients were grouped according to age, sex, and type of chest pain. The latter was divided into the following four categories:

1. Typical angina pectoris. Pain that occurs in the anterior thorax, neck, shoulders, jaw, or arms is precipitated by exertion and relieved within 20 min by rest.
2. Atypical angina. Pain in one of the above locations and either not precipitated by exertion or not relieved by rest within 20 min.
3. Nonanginal pain. Pain not located in any of the above locations, or if so located not related to exertion, and lasting less than 10 sec or longer than 30 min.
4. No pain.

**Test protocol.**

**Exercise tests.** All subjects underwent treadmill exercise according to the Bruce protocol. Exercise was terminated because of fatigue, dyspnea, progressive angina, ST depression greater than 2.5 mm, or when the subject reached his age-adjusted target heart rate. Modified 12-lead electrocardiograms were recorded in subjects at rest and at peak exercise. One minute before the completion of exercise, 2 mCi of thallium-201 were injected directly into an arm vein. Nuclear imaging was begun about 5 min after injection in the 45 degree and 70 degree left anterior oblique and anterior projections. All images were recorded for 10 min for each projection on a portable gamma camera with 1/4 inch crystal and a high-sensitivity low-energy collimator. All three projections were repeated approximately 4 hr after thallium injection to obtain redistribution images. Acquired data were stored in the VIP-550 microprocessor system for subsequent analysis.

**Coronary arteriography and cine fluoroscopy.** On the day after treadmill exercise all patients underwent selective coronary arteriographic examination by the Sones technique and multiple projections of each vessel were obtained. During this procedure cine fluoroscopic examination without contrast was done in the left and right anterior oblique projections. The x-ray exposure factors used for both cine angiography and cine fluoroscopy were 300 mA, 75 to 95 kV, and a 5 msec pulse width.

**Test analysis.** ST segment depressions at peak exercise were analyzed by an observer blinded to the clinical data, the noninvasive test results, and the results of angiographic examination. The vertical distance between the middle point of the PR segment and the ST segment 80 msec after the J point was measured to the nearest 0.2 mm for several complexes in leads I, II, V_2, V_4, and V_5. The resulting ST segment shifts were averaged for each lead and the corresponding resting ST shifts were subtracted. The five resulting ST segment depressions relative to rest were searched for a maximum and this number was assigned to the appropriate category from the following: ST < 0.5, 0.5 ≤ ST < 1.0, 1.0 ≤ ST < 1.5, 1.5 ≤ ST < 2.0, 2.0 ≤ ST < 2.5, 2.5 ≤ ST. The appropriate category became the test result for each subject’s stress electrocardiogram.

Computer-stored scintigraphic data were analyzed by an investigator unaware of the other test and angiographic results. Myocardial segments were evaluated by quantification of the decreased radioactivity in the poorly perfused area and comparison with the maximum pixel count in normal myocardium. Three results were possible: (1) normal, (2) fixed abnormality (defects observed during exercise that persisted at redistribution), and (3) reversible abnormality (defects present during exercise and significantly corrected during redistribution). Fluoroscopic films without contrast were reviewed by two investigators without knowledge of the clinical, exercise, or angiographic results. A result of one, two, three, or no calcified vessels was assigned to each subject. Coronary arteriograms were interpreted by an experienced angiographer not directly involved in the study. A stenosis of greater than 50% of the intraluminal diameter of one of the four main coronary arteries was considered sufficient to classify a subject as having coronary artery disease.

**Probability analysis.** Let the symbol D denote the event that a patient has coronary artery disease and let ND denote the alternative event that he does not have disease. P(D) will be the pretest probability of disease and will be, in fact, the prevalence of disease in a population of patients of a given sex and age (decade of life) and with one of the four possible types of chest discomfort, as defined above.

Let ST, Th, and Ca denote variables that can take on values determined by the results of the three noninvasive tests. For example, the stress electrocardiographic change, ST, can have the value ‘[1.5 ≤ ST < 2.0]‘ and the thallium scintigraphy reading Th can have the value ‘reversal perfusion defect.’ The number of calcified arteries, Ca, might take the value ‘2.’ P(ST|D), P(Th|D), and P(Ca|D) are the conditional probabilities of a particular test result given that an individual has coronary disease. If our tests had only two possible outcomes (positive or negative), these probabilities would be the test sensitivities. Similarly, P(ST|ND), P(Th|ND), and P(Ca|ND) are the conditional probabilities of the same test results given that a subject does not have disease. For tests with two outcomes, these would be the false-positive rates (1 − specificity).

Bayes’ theorem states that if the variables ST, Th, and Ca are statistically independent in both the diseased and nondiseased populations, then the probability of coronary disease given the test results ST, Th, and Ca is defined by the equation

\[
P(D|ST, Th, Ca) = \frac{P(D)P(ST|D)P(Th|ND)P(Ca|ND)}{P(D)P(ST|D)P(Th|ND)P(Ca|ND) + P(ND)P(ST|ND)P(Th|ND)P(Ca|ND)}
\]

The left side of the equation, P(D|ST, Th, Ca), will be referred to as the posttest probability. The pretest probabilities used in this research, P(D), and the conditional probabilities P(ST|D), P(ST|ND), P(Th|D), P(Th|ND), P(Ca|D), and P(Ca|ND) were calculated by 'Diamond and Forrester' by pooling estimates of these quantities from the literature on the prevalence of coronary disease and the sensitivities and specificities of the noninvasive tests. The reference group that provided the data base for the pretest probabilities based on age, sex, and chest pain consisted of 4952 symptomatic individuals studied with coronary arteriography and 23,996 asymptomatic persons who died of disease other than cardiac disease and were not known to have coronary disease previous to their postmortem examinations. The conditional probabilities applied to our study group for the stress-
induced ST segment depression, thallium perfusion defects, and coronary calcifications were based on results in 4838, 1132, and 507 patients, respectively, studied with the respective noninvasive test and coronary arteriography. Three of our subjects’ stress electrocardiograms revealed rate dependent left bundle branch block. Since the conditional probabilities of this test result are unknown, we ignored their stress electrocardiograms in the probability calculations.

For each patient in the study a pretest probability was chosen from the pooled literature values based on age, sex, and type of chest pain. Conditional probabilities of the various noninvasive test results for subjects with and without disease were also assigned according to their performances on the tests. These quantities were then substituted into Bayes’ theorem to calculate posttest probability.

Both the pretest and posttest probabilities were divided into probability subgroups as follows: low (0 ≤ p < .2), intermediate (.2 ≤ p ≤ .8), and high (.8 ≤ p ≤ 1.0). A pretest and posttest subgroup was thus assigned to each subject and the number of subjects for whom probability either advanced or retreated by at least one subgroup as a result of testing was determined for subjects with and those without disease. The boundaries of these subgroups were chosen to obtain significant numbers of patients in each one and to retain symmetry between the first and third subgroup, and because we judged them to be clinically relevant to the decision of whether or not to perform angiography.

**Independence.** The validity of Bayes’ theorem depends on the mutual statistical independence of the test variables ST, Th, and Ca for subjects with and those without disease. It also depends on the statistical independence of these test variables and the clinical variables of age, sex, and type of chest pain, since the Bayes’ equation cannot be validly used if the conditional probabilities of certain test results in the patients with and without disease depend on the pretest probability determined by age, sex, and type of pain. There are thus three test variables for which mutual independence is required and independence between these and the three clinical variables should also be present. Because the number of patients with particular values for each clinical and test variable was small, it was necessary to dichotomize the variables as follows: age ≤ 55, age > 55; male, female; angina pectoris, other symptoms; ST depression < 1.0, ST depression ≥ 1.0; thallium normal, thallium abnormal; no calcified vessels, at least one calcified vessel. These six variables were then paired and tested for pairwise dependence with a chi-squared test and a 5% significance level without control over the type I error rate for multiple comparisons. True mutual independence was not tested because of the inadequate sample size.

**Results**

**Clinical data.** The numbers of men and women with each of the four chest pain syndromes are reported in table 1 for patients with and without significant coronary disease. The mean age of patients with and without significant disease was 57 and 52 years, respectively.

**Noninvasive test results.** One hundred fifteen subjects (75%) achieved 85% of their age-adjusted heart rates. Of those that did not, eight (21%) had less than 1.0 mm ST depression in all leads and nine (24%) had normal thallium-201 scintigrams. All of these patients were included in the final probability calculations. Test sensitivities and specificities based on the study sample were calculated for each of the three noninvasive tests. These are compared in table 2 with the pooled literature results reported by Diamond and Forrester and used in the Bayes theorem in this investigation. Sensitivities are the probabilities of test results at least as abnormal as the listed threshold values given that the disease is present, whereas specificities are probabilities of test results less abnormal than this threshold for subjects without disease. The conditional probabilities used in Bayes’ theorem can easily be derived from the pooled literature sensitivities and specificities in tables 2, 3, and 4.

**Coronary angiography.** A coronary artery was considered to be significantly diseased if there was more than a 50% reduction of its luminal diameter. By this criterion, 68 (44%) patients had at least one diseased artery, 27 (40%) of these had single-vessel disease, 16 (24%) had double-vessel disease, and 18 (26%) had triple-vessel disease. Patients with left main coronary artery disease (n = 7, 10%) were counted separately.

**Initial and final probability distributions.** Tables 5 and 6 give the number of patients who were initially placed in a low-, intermediate-, or high-probability subgroup on the basis of clinical data. They either did not move or were transferred to another subgroup when posttest probability of disease was calculated from their nonin-
vasive test results. Only data from patients with significant coronary disease are included in table 5, while table 6 contains those from subjects without disease. When the numbers in the boxes in table 5 are added, it is apparent that noninvasive testing appropriately advanced 17 diseased patients by at least one probability subgroup, while seven patients with disease were incorrectly moved backward. A similar analysis of table 6 reveals that 34 subjects without disease were appropriately moved into a lower subgroup after testing, while 10 were incorrectly moved up.

**Independence.** Only the two variable pairs sex-thallium scintigraphy and sex-coronary calcifications showed significant pairwise associations in the subjects without disease ($p < .001; p = .02$, respectively). Among the subjects with disease only age and calcification were related ($p = .009$). Table 7 illustrates these relationships. Care must be taken in interpreting these associations since by chance alone some correlations would be expected when making comparisons between a large number of variable pairs and when a significance level of .05 is used.

**Discussion**

The utility of diagnostic testing depends on its ability to refine the clinician’s capacity to distinguish individuals with disease from those without. Since any single noninvasive test can add only a limited amount of information for the clinical assessment of patients with suspected coronary artery disease, there have been attempts to combine tests in order to better predict the presence or absence of disease.$^6$-$^9$

Bayes’ theorem allows probabilistic revision of diagnostic assessments by incorporating new information made available by multiple noninvasive tests. The theorem has been applied in this way, but before this study its utility in improving clinical predictions of coronary disease had not been demonstrated. Diamond et al.,$^3$ using a method very similar to our own, attempted to document the applicability of the theorem but failed to verify that posttest probabilities were significantly better in correctly classifying patients than those based on clinical data. In their work angiograph-

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present study</td>
<td>Pooled literature$^2$</td>
<td>Present study</td>
</tr>
<tr>
<td>Fixed or reversible defect</td>
<td>82</td>
<td>85</td>
</tr>
<tr>
<td>Reversible defect</td>
<td>78</td>
<td>71</td>
</tr>
</tbody>
</table>

**TABLE 4**

Cine fluoroscopically detected coronary calcifications

<table>
<thead>
<tr>
<th>No. of calcified vessels</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present study</td>
<td>Pooled literature$^2$</td>
</tr>
<tr>
<td>3</td>
<td>65</td>
<td>58</td>
</tr>
<tr>
<td>5</td>
<td>29</td>
<td>34</td>
</tr>
<tr>
<td>8</td>
<td>12</td>
<td>14</td>
</tr>
</tbody>
</table>
less likely to have calcified vessels than were women.

The significant correlation between sex and results of thallium scintigraphic examination was most likely due to a tendency on the part of the investigator reading the test to overcompensate for the effect of breast absorption. It is significant that, despite rigorous efforts to avoid test-review bias by blinding the test readers to the other data, the nuclear cardiologist’s awareness of the patient’s sex contributed to the lack of independence for these two variables. It is possible that the finding of Melin et al. of a correlation between stress data and type of chest pain might also be due to test-review bias since there is no mention of any attempt to review tests blindly in their report.

It is not surprising that older individuals with significant coronary disease were more likely to exhibit coronary calcifications since calcium deposition in atherosclerotic plaque is a late pathophysiologic development. There has been a report of a positive correlation between female sex and coronary calcification at autopsy in an asymptomatic population in which cause of death was not cardiac. This is consistent with our finding of an association between sex and calcification in individuals without significant coronary disease. These relationships between coronary calcification and the variables of age and sex may therefore represent a true physiologic dependence.

Aside from bias and physiology, disease severity presents a third possible source of dependence. This would arise from the tendency of severe disease (multivessel or left main) to produce a higher proportion of positive tests. For example, if we had a study sample in which one-third of the subjects did not have any angiographically apparent lesions, one-third had exactly one 51% lesion, and the remaining third had multivessel disease, we would expect a significant correlation between noninvasive test results in the diseased subgroup since these tests have been shown to be more sensitive in multivessel than single-vessel disease. This would reflect neither study bias nor physiologic dependence, but rather the unrealistically discrete separation of individuals into diseased and nondiseased subgroups by the arbitrary angiographic criterion of a single 50% obstructive lesion. Despite the fact that

| TABLE 5 |
| Distribution of probabilities before and after noninvasive testing in study subjects with significant coronary obstructions |
| Final subgroup (posttest probability) |
| Probability | $0 \leq p < .2$ | $.2 \leq p \leq .8$ | $.8 \leq p \leq 1.0$ | Total |
| Initial subgroup | 3 |
| (pretest probability) | 20 |
| Total | 68 |

Initial subgroup: based on clinical data; final subgroup: based on clinical data and noninvasive tests.

| TABLE 6 |
| Distribution of probabilities before and after noninvasive testing in study subjects without significant coronary obstructions |
| Final subgroup (posttest probability) |
| Probability | $0 \leq p < .2$ | $.2 \leq p \leq .8$ | $.8 \leq p \leq 1.0$ | Total |
| Initial subgroup | 29 |
| (pretest probability) | 45 |
| Total | 86 |

Initial subgroup: based on clinical data; final subgroup: based on clinical data and noninvasive tests.
TABLE 7
Variables demonstrating dependence

<table>
<thead>
<tr>
<th></th>
<th>Abnormal scintigram</th>
<th>Normal scintigram</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No coronary disease — sex-thallium</td>
<td>16 (30%)</td>
<td>38 (70%)</td>
<td>54</td>
</tr>
<tr>
<td>Female</td>
<td>0 (0%)</td>
<td>31 (100%)</td>
<td>31</td>
</tr>
<tr>
<td><strong>p</strong> &lt; .001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No coronary disease — sex-calcifications</td>
<td>8 (25%)</td>
<td>5 (9%)</td>
<td>32</td>
</tr>
<tr>
<td>Female</td>
<td>24 (75%)</td>
<td>49 (91%)</td>
<td>54</td>
</tr>
<tr>
<td><strong>p</strong> = .02</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary disease — age-calcification</td>
<td>34 (76%)</td>
<td>10 (43%)</td>
<td>45</td>
</tr>
<tr>
<td>Male</td>
<td>11 (24%)</td>
<td>13 (57%)</td>
<td>23</td>
</tr>
<tr>
<td>Female</td>
<td>0 (0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>p</strong> = .009</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

60% of our patients with disease had multivessel or left main disease, this type of dependence was not evident, giving further support to the validity of the Bayesian method.

In the comparison of 30 pairs of variables, chance alone should lead to finding an association in at least one pair at the 5% significance level. It is therefore quite possible that one or both associations with calcification is spurious.

We feel confident in concluding that despite some deviation from statistical independence, the application of Bayesian probability analysis to the three clinical and three test variables studied here has at least an approximate validity. We stop short, however, of assuming that the independence assumption can be extrapolated to larger numbers of variables without experimental verification. Fryback has elegantly shown that the size of the error will increase with the number of variables falsely assumed to be independent. Caution is therefore necessary when including other clinical data (risk factors) and other test results (stress ventriculography, etc.) when Bayes’ theorem is used.

Decision algorithms. Tables 5 and 6 indicate that information from noninvasive tests is useful in reassessing patients’ probabilities of disease appropriately so that they can be more accurately classified with the use of a decision rule or algorithm. Two possible algorithms follow.

First, consider the rule that all subjects with a disease probability of at least 0.2 will undergo coronary arteriography. Execution of this rule without noninvasive testing would result in 57 angiographic diagnoses of normal coronary arteries and three patients with undiagnosed disease. Execution of the rule after noninvasive testing would lead to only 32 normal angiograms and six undiagnosed cases of coronary disease. We reviewed the angiograms of the latter six patients and found that five of them had only a single occlusion of between 50% and 75%. The sixth had a 90% stenosis of the terminal portion of the left anterior descending coronary artery. None of these six individuals required coronary artery bypass surgery.

One might argue that the above algorithm is too expensive since it involves three noninvasive tests on 154 individuals and cardiac catheterization in 94 of these. A less costly algorithm follows:

1. All subjects with pretest disease probability of at least 0.8 will undergo coronary angiography without noninvasive testing.

2. All subjects with pretest disease probability of less than 0.2 will undergo coronary angiography.

3. Subjects with pretest disease probabilities between 0.2 and 0.8 will be tested noninvasively and coronary angiograms will be done only if their posttest probabilities are greater than or equal to 0.2.

This algorithm resulted in 32 normal angiograms and seven undiagnosed cases of coronary disease. Six of the latter had only one single-vessel obstruction of less than 75% that did not require bypass surgery, while one had an 85% stenosis of a single vessel that was corrected surgically. The cost of executing this strategy would be lower since only 65 of the 154 subjects were to be submitted to the three noninvasive tests.

The actual decision to submit a patient to coronary arteriography will be based on a physician’s skill and experience, and the logical mechanism that leads to that decision must depend not only on costs and probabilities but also on the quality and safety of stress testing and angiography and the general health, quality of life, and mental attitude of the patient. Probability analysis will never replace clinical judgment in this decision, but can only aid the clinician in interpreting complex data such as discordant test results and weakly positive stress electrocardiograms.

Limitations of the study. Ethical considerations prohibit performing angiography without at least a fair suspicion that coronary disease is present and clinically significant. The fact that many patients who are referred for invasive evaluation have already been submitted to a noninvasive work-up introduces an un-
avoidable selection bias. The degree of this bias will be reflected in the number of abnormal angiograms. Since only 44% of our study sample had significantly abnormal coronary arteries by angiography, we are confident that we have decreased this bias.

We conclude from our results that pairwise if not mutual statistical independence, although imperfect, is at least an approximately valid assumption. The limited size of our study sample may hide subtle associations that could only be revealed by studying a larger group of patients.

The conditional probabilities on the right side of Bayes’ theorem were calculated by Diamond and Forrester as weighted averages of several results from the literature for the corresponding noninvasive tests. The electrocardiographic stress test literature in particular is notorious for the wide range of values for the sensitivity and specificity of ST segment depressions. Philbrick et al. reviewed this subject and concluded that this variability was as much due to methodologic bias as it was to inconsistencies in the criteria for abnormal tests and difference in leads and stress protocol. Our own review of the publications selected by Diamond and Forrester revealed similar biases, inconsistencies, and differences.

Although the sensitivities and specificities of exercise thallium imaging and fluoroscopy for diagnosing coronary calcifications are less variable than those of stress electrocardiography, inconsistencies in the methods of performance and analysis that were present in the reports of the studies reviewed by Diamond and Forrester and differences between these and our own methods of performance and analysis also limit the validity of our application of the pooled values of conditional probabilities to our study group’s test results.

Not surprisingly, the test sensitivities and specificities derived from our study sample for various threshold test criteria were different from those of the pooled literature that we used in Bayes’ theorem (tables 2 through 4). Despite these differences, Bayes’ theorem performed remarkably well in separating subjects with disease from those without it.

We conclude that, despite some limitations, this application of Bayes’ theorem has approximate validity and is clinically useful in the noninvasive diagnosis of coronary artery disease.

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