

The Influence of Rheumatoid Arthritis Disease Characteristics on Heart Failure

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ABSTRACT. *Objective.* To examine the influence of rheumatoid arthritis (RA) characteristics and antirheumatic medications on the risk of heart failure (HF) in patients with RA.

Methods. A population-based incidence cohort of RA patients aged ≥ 18 years (1987 American College of Rheumatology criteria first met between January 1, 1980, and January 1, 2008) with no history of HF was followed until onset of HF (defined by Framingham criteria), death, or January 1, 2008. We collected data on RA characteristics, antirheumatic medications, and cardiovascular (CV) risk factors. Cox models adjusting for age, sex, and calendar year were used to analyze the data.

Results. The study included 795 RA patients [mean age 55.3 yrs, 69% women, 66% rheumatoid factor (RF)-positive]. During the mean followup of 9.7 years, 92 patients developed HF. The risk of HF was associated with RF positivity (HR 1.6, 95% CI 1.0, 2.5), erythrocyte sedimentation rate (ESR) at RA incidence (HR 1.6, 95% CI 1.2, 2.0), repeatedly high ESR (HR 2.1, 95% CI 1.2, 3.5), severe extra-articular manifestations (HR 3.1, 95% CI 1.9, 5.1), and corticosteroid use (HR 2.0, 95% CI 1.3, 3.2), adjusting for CV risk factors and coronary heart disease (CHD). Methotrexate users were half as likely to have HF as nonusers (HR 0.5, 95% CI 0.3, 0.9).

Conclusion. Several RA characteristics and the use of corticosteroids were associated with HF, with adjustment for CV risk factors and CHD. Methotrexate use appeared to be protective against HF. These findings suggest an independent effect of RA on HF that may be further modified by antirheumatic treatment. (First Release May 15 2011; J Rheumatol 2011;38:1601–6; doi:10.3899/jrheum.100979)

Key Indexing Terms:

RHEUMATOID ARTHRITIS

HEART FAILURE

DETERMINANTS

Heart failure (HF) is a multifactorial clinical syndrome with poor prognosis representing a universal final stage of nearly every form of heart disease^{1,2}. Patients with rheumatoid arthritis (RA) are at approximately 2-fold increased risk of HF compared with persons without RA, and this increased risk is not fully explained by traditional cardiovascular (CV) risk factors^{3,4,5}. Further, patients with RA appear to have more subtle HF presentation, yet significantly higher early mortality following HF compared with non-RA subjects⁶. These findings suggest a potential role for RA-specific mechanisms in HF development and emphasize the need for understanding the determinants of HF in RA. RA disease activity and sever-

ity have been linked to HF development in RA^{5,7,8,9,10}. Further, antirheumatic medications, particularly methotrexate (MTX) and more recently biologic response modifiers, but not corticosteroids, appear to have a beneficial effect on risk of HF in RA^{11,12,13}. However, the nature of these associations is unclear and longitudinal population-based studies analyzing the relative effects of the major potential contributors (CV risk factors, RA disease characteristics, and antirheumatic medications) for development of HF in RA are lacking. We examined the influence of RA disease characteristics and antirheumatic medications on the risk of HF in RA.

MATERIALS AND METHODS

Study setting and design. This study was conducted using the population-based resources of the Rochester Epidemiology Project (REP) medical records linkage system¹⁴. This system facilitates access to the complete inpatient and outpatient medical records of residents of Olmsted County, Minnesota, from all community medical providers including the Mayo Clinic, its affiliated hospitals, and the Olmsted Medical Center. REP resources ensure virtually complete ascertainment of all clinically recognized cases of RA and associated complications among the residents of Olmsted County^{14,15}.

The study included a retrospectively identified incidence cohort of RA patients who were Olmsted County residents ≥ 18 years of age and first met the 1987 American College of Rheumatology (ACR) criteria¹⁶ between January 1, 1980, and January 1, 2008. RA incidence date was defined as the earliest date at which each patient fulfilled ≥ 4 ACR criteria for RA. The original and complete medical records of all RA patients were screened longitudinally until HF incidence, death, migration, or last date of followup (January

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1, 2008) by trained nurse abstractors blinded to the study hypothesis. HF was defined based on the Framingham criteria^{17,18}. HF diagnosis requires ≥ 2 of the major criteria [i.e., paroxysmal nocturnal dyspnea or orthopnea, neck vein distention, rales, radiographic cardiomegaly (i.e., increasing heart size on chest radiograph), acute pulmonary edema, S3 gallop, increased central venous pressure ≥ 16 cm of water at the right atrium, circulation time ≥ 25 seconds, hepatojugular reflux, weight loss > 4.5 kg in 5 days in response to treatment of congestive HF], or the presence of 1 major criterion and ≥ 2 minor criteria (i.e., bilateral ankle edema, nocturnal cough, dyspnea on ordinary exertion, hepatomegaly, pleural effusion, decrease in vital capacity by 33% from maximal value recorded, and tachycardia rate ≥ 120 beats/min). Minor criteria were counted only if they could not be attributed to another medical condition. Ejection fraction (EF) was determined by echocardiography and classified as preserved EF ($\geq 50\%$) or reduced EF ($< 50\%$).

CV risk factors. The following CV risk factors were abstracted from the medical records at baseline and longitudinally throughout the followup as described⁵, and were defined according to standardized diagnostic criteria as follows. Hypertension was defined according to the criteria of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure as ≥ 2 ambulatory blood pressure readings ≥ 140 mm Hg systolic and/or ≥ 90 mm Hg diastolic obtained during a 1-year period, physician diagnosis, or documented use of antihypertensive medications¹⁹. Dyslipidemia was defined in accord with Adult Treatment Panel III guidelines²⁰ as elevated lipid values of total cholesterol ≥ 240 mg/dl (≥ 6.2 mmol/l), low-density cholesterol ≥ 160 mg/dl (≥ 4.1 mmol/l), triglycerides ≥ 200 mg/dl (≥ 2.3 mmol/l) or high-density cholesterol < 40 mg/dl (< 1.0 mmol/l), physician diagnosis or documented use of lipid-lowering medications. Obesity was present if body mass index (BMI) was ≥ 30 kg/m² based on the guidelines on the Identification, Evaluation and Treatment of Overweight and Obesity in Adults²¹. Diabetes mellitus was defined as fasting plasma glucose ≥ 126 mg/dl (≥ 7.0 mmol/l), physician diagnosis or documented use of insulin and/or oral hypoglycemic agents in accord with the diagnostic criteria adopted by the American Diabetes Association^{22,23}. Personal history of coronary heart disease (CHD) was defined at baseline and throughout the followup as the presence of one of the following: angina pectoris, coronary artery disease, myocardial infarction (MI; including silent events), and coronary revascularization procedures (i.e., coronary artery bypass graft, percutaneous angioplasty, insertion of stents, and atherectomy). MI was defined using standardized epidemiologic criteria²⁴, and Minnesota coding²⁵ of the electrocardiogram (ECG). Silent MI was considered as present at the date of the first documentation of a characteristic ECG or a recorded physician's diagnosis in a patient with no documented history of MI. The definition of alcohol abuse was based on physician diagnosis of chronic alcoholism documented in the medical records. Smoking status (categorized as never, current, or former) and family history of premature CHD (defined as presence of CHD in first-degree relatives at age < 65 yrs females and < 55 yrs males) were collected only at baseline.

RA characteristics and medications. The information on RA characteristics included RF status, erythrocyte sedimentation rate (ESR) at RA incidence and repeatedly high ESR (i.e., ≥ 3 ESR measures ≥ 60 mm/h with a minimum interval of 30 days between 2 measurements), large-joint swelling, joint erosions/destructive changes on radiographs, joint surgeries (i.e., arthroplasty and synovectomy) and extraarticular manifestations of RA (ExRA). ExRA were classified according to criteria used in our previous studies²⁶. Severe ExRA were defined according to Malmö criteria²⁷ and included pericarditis, pleuritis, Felty's syndrome, glomerulonephritis, vasculitis, peripheral neuropathy, scleritis, and episcleritis. Data regarding start and stop dates for use of systemic corticosteroids (e.g., oral/parental/intraarticular forms of prednisone, prednisolone, methylprednisolone, hydrocortisone, dexamethasone), disease-modifying antirheumatic drugs (DMARD: MTX, hydroxychloroquine, other DMARD), and biologic response modifiers [anti-tumor necrosis factor- α (anti-TNF- α) agents, anakinra, abatacept, rituximab] were collected for all patients. Data on the use of nonsteroidal antiinflammatory drugs (NSAID) and coxibs were also recorded. Data on the use of acetylsalicylic

acid (ASA) for arthritis were collected, i.e., the use of > 6 tablets of ASA per day (> 1950 mg/day) for at least 3 months. The history of rheumatic fever was documented.

The study protocol was approved by Review Boards from the Mayo Clinic and Olmsted Medical Center.

Statistical methods. Descriptive statistics were used to characterize the demographics, traditional CV risk factors, and RA disease characteristics. Cox proportional hazard models were used to examine the association of HF with RA characteristics. Adjustment for age and sex was performed using age as the time scale and stratifying by sex. The models were additionally adjusted for calendar year of RA incidence. Time-dependent covariates were used to represent factors that developed during followup. Each RA disease characteristic was examined individually in models adjusted for age, sex, and calendar year. In addition, models adjusted for age, sex, calendar year, CV risk factors, and CHD were examined. Medications were modeled 2 ways: (1) as use at any time where the time-dependent covariates reflected medication start dates only; and (2) as current use where the time-dependent covariates represented the time each patient was taking each medication, beginning at start date and ending at stop date for each medication. For each analysis of medications, all medications were assessed simultaneously in a multivariable model.

RESULTS

Patients' characteristics. Among 815 incident RA cases identified during the 1980-2007 period, 20 fulfilled the Framingham criteria for HF before RA incidence, and were excluded from the study. The remaining 795 patients comprised the study cohort. Baseline characteristics are reported in Table 1. Mean age at RA incidence was 55.3 years; 69% were women. Patients were followed for a mean 9.7 years (total of 7692 patient-years). Hypertension, dyslipidemia, and obesity were the most common CV risk factors at baseline (65%, 57%, and 41% of patients, respectively), and their prevalence increased during followup. At the time of RA incidence, 22% of patients were current smokers and 33% were former smokers. Family history of premature CHD was noted in 22% of patients. At baseline, 10% of patients had a personal history of CHD, and 23% had CHD at any time during fol-

Table 1. Characteristics of 795 incident RA patients (1980–2007, Olmsted County, Minnesota) at RA incidence and during the followup. The values are given as number (%) if not indicated otherwise.

| Variable | At RA Incidence | At Any Time During Followup |
|--|-----------------|-----------------------------|
| Age, yrs, mean \pm SD | 55.3 \pm 15.5 | — |
| Female | 546 (69) | — |
| Length of followup, yrs, mean \pm SD | 9.7 \pm 6.9 | — |
| Smoking status | | |
| Current | 171 (22) | — |
| Former | 254 (33) | — |
| Alcohol abuse | 54 (7) | 63 (8) |
| Hypertension | 490 (65) | 676 (88) |
| Dyslipidemia | 431 (57) | 569 (74) |
| Obesity (BMI ≥ 30 kg/m ²) | 302 (41) | 368 (49) |
| Family history of premature coronary heart disease | 172 (22) | — |
| Personal history of coronary heart disease | 72 (10) | 170 (23) |
| Diabetes mellitus | 77 (11) | 147 (20) |

BMI: body mass index.

lowup. The proportion of patients with diabetes mellitus increased from 11% at baseline to 20% at any time during followup. Alcohol abuse was documented in 7% of patients at baseline and in 8% of patients at any time during followup.

During the followup, 92 patients developed HF. Of these, 31 patients had HF with reduced EF and 36 patients had HF with preserved EF. For the remaining 25 patients data on EF were not available. Of the above CV risk factors and CV comorbidities, family history of CHD (HR 1.6, 95% CI 1.03, 2.6), personal history of CHD (HR 3.1, 95% CI 1.96, 4.9), particularly angina (HR 2.3, 95% CI 1.4, 3.6) and revascularization procedures (HR 2.3, 95% CI 1.3, 3.97), and alcohol abuse (2.4, 95% CI 1.2, 4.8) were significantly associated with the risk of HF. No time trends in the risk of HF were found ($p = 0.5$).

RA characteristics and medications and their effects on HF. Data on RA characteristics are summarized in Table 2. RF positivity was present in 66% of patients. Mean ESR at RA incidence was 24.2 mm/h and 12% of RA patients had ≥ 3 ESR measures of ≥ 60 mm/h. Most patients (78%) experienced large-joint swelling at some time during followup. The great majority of patients (95%) had at least one radiograph. Joint erosions/destructive changes were found in 53% of patients. Joint surgery, i.e., arthroplasty or synovectomy, was performed in 17% and 11% of patients, respectively. Severe ExRA developed in 11% of patients. The most common other ExRA were rheumatoid nodules (in 33% of patients). History of rheumatic fever was noted in 3% of patients.

RF positivity (HR 1.6, 95% CI 1.0, 2.5; $p = 0.049$), increased ESR at RA incidence (HR 1.6 per 30 mm/h increase, 95% CI 1.2, 2.0), repeatedly high ESR (HR 2.1, 95% CI 1.2, 3.5), and severe ExRA (HR 3.1, 95% CI 1.9, 5.1) were significantly associated with HF (Table 2). Patients with RA disease duration < 1 year were twice as likely to develop HF com-

pared to patients with RA duration ≥ 1 year (HR 2.0, 95% CI 1.1, 3.8). The results remained essentially unchanged after adjustment for CV risk factors and CHD (data not shown).

Table 3 shows the data on antirheumatic medications. During followup, 58% of patients were treated with MTX, 60% were treated with hydroxychloroquine, 32% were treated with other DMARD, and 17% were treated with biologic response modifiers, of which the majority (95%) received anti-TNF- α therapy. Most patients received corticosteroids at some time during followup (77%). The majority of patients (91%) used NSAID at some time during followup. About half the patients were treated with coxibs (49%). Analysis of medications used at any time revealed no significant associations with HF. Additional analyses of current use of medications were also performed (Table 3). Patients currently using MTX were half as likely to develop HF as nonusers (HR 0.5, 95% CI 0.3, 0.9). The association changed only minimally (HR 0.4, 95% CI 0.2, 0.8) following additional adjustment for RA characteristics including RF positivity, RA duration, ESR at RA incidence, and severe ExRA. Patients currently using biologic response modifiers or other DMARD were also somewhat less likely to develop HF than those who did not currently use these agents; however, these associations were not statistically significant. The association of anti-TNF- α treatment with HF was identical to the effect of biologic response modifiers overall. Use of hydroxychloroquine did not appear to be associated with HF. Current use of corticosteroids was associated with 2-fold increased risk of HF (HR 2.0, 95% CI 1.3, 3.2). These associations remained unchanged after adjustment for CV risk factors and CHD (data not shown).

Additional analyses were performed to elucidate the influence of concurrent MTX and corticosteroid use. Among MTX users, 76% were using corticosteroids concurrently, and no increased risk of HF was found among these concurrent users

Table 2. RA characteristics and their associations with the risk of heart failure (HF) in 795 incident RA patients. Values are given as number (%) if not indicated otherwise.

| Characteristics | Value | Hazard Ratio ** (95% CI), Adjusted for Age, Sex, and Calendar Year of RA Incidence |
|--|-----------------|--|
| RF-positive | 527 (66) | 1.6 (1.0, 2.5) |
| ESR at RA incidence, mm/h, mean \pm SD | 24.2 \pm 19.9 | 1.6 (1.2, 2.0)[†] |
| ≥ 3 ESR ≥ 60 mm/h | 99 (12) | 2.1 (1.2, 3.5) |
| Large-joint swelling | 624 (78) | 1.1 (0.7, 1.8) |
| Joint erosions/destructive changes | 424 (53) | 1.1 (0.8, 1.7) |
| Joint surgery | | |
| Arthroplasty | 134 (17) | 1.5 (0.9, 2.5) |
| Synovectomy | 86 (11) | 1.1 (0.6, 2.2) |
| Rheumatoid nodules | 266 (33) | 1.1 (0.7, 1.7) |
| Severe ExRA* | 87 (11) | 3.1 (1.9, 5.1) |
| History of rheumatic fever | 22 (3) | 1.0 (0.4, 2.7) |

* Malmö criteria³². ** Significant ($p < 0.05$) hazard ratios are shown in bold type. [†] Per 30 mm/h increase. RA: rheumatoid arthritis; RF: rheumatoid factor; ESR: erythrocyte sedimentation rate; ExRA: extraarticular manifestations of RA.

Table 3. Antirheumatic medications and their associations with risk of heart failure (HF) in 795 incident RA patients.

| Antirheumatic Medications | N (%) | Hazard Ratio * (95% CI), Adjusted for Age, Sex, and Calendar Year of RA Incidence |
|-----------------------------|----------|---|
| Used at any time | | |
| Methotrexate | 465 (58) | 0.9 (0.6, 1.5) |
| Hydroxychloroquine | 475 (60) | 0.9 (0.6, 1.4) |
| Other DMARD | 255 (32) | 0.9 (0.5, 1.6) |
| Biologic response modifiers | 135 (17) | 0.8 (0.2, 2.6) |
| Corticosteroids | 614 (77) | 1.2 (0.7, 1.9) |
| NSAID | 732 (91) | 1.0 (0.5, 1.9) |
| Coxibs | 386 (49) | 1.5 (0.9, 2.3) |
| ASA | 330 (43) | 1.0 (0.6, 1.7) |
| Current use | | |
| Methotrexate | | 0.5 (0.3, 0.9) |
| Hydroxychloroquine | | 1.0 (0.5, 1.8) |
| Other DMARD | | 0.5 (0.2, 1.5) |
| Biologic response modifiers | | 0.5 (0.1, 3.5) |
| Corticosteroids | | 2.0 (1.3, 3.2) |

* Significant ($p < 0.05$) hazard ratios are shown in bold type. DMARD: disease-modifying antirheumatic drugs; NSAID: nonsteroidal antiinflammatory drugs; ASA: acetylsalicylic acid for arthritis [> 6 tablets per day (> 1950 mg/day) for at least 3 months]

compared to patients using neither MTX nor corticosteroids (HR 0.8, 95% CI 0.3, 2.0; $p = 0.67$). An increased risk of HF persisted among patients taking corticosteroids without MTX (HR 2.2, 95% CI 1.3, 3.6; $p = 0.002$). However, no significant difference in risk of HF was noted among patients taking MTX without corticosteroids (HR 0.6, 95% CI 0.3, 1.4; $p = 0.27$).

We also investigated whether risk factors differ for HF with preserved EF and HF with reduced EF. We found that males were more likely to have HF with reduced EF than females (HR 3.7, 95% CI 1.8, 7.7). This association remained significant after adjustment for CV risk factors and CHD. No gender difference was found for HF with preserved EF (HR 0.9, 95% CI 0.5, 1.9 in males vs females). No other statistically significant differences were found between risk factors for HF with reduced EF and HF with preserved EF (data not shown).

DISCUSSION

We report risk factors for HF in a population-based incident RA cohort. We have shown that several RA characteristics including RF positivity, increased ESR at RA incidence, and repeatedly high ESR, as well as the presence of severe ExRA were significantly associated with HF after adjustment for CV risk factors and CHD. Patients with RA duration < 1 year were twice as likely to develop HF as patients with RA duration ≥ 1 year.

Some measures of RA activity including RF positivity and increased ESR were previously linked to HF in RA in our studies and others^{5,7,8,10}. The association of increased ESR at RA incidence with the risk of HF in RA corroborates our earlier observations regarding ESR as a potential signal for the subse-

quent development of HF⁸. The associations of RF positivity and repeatedly high ESR with HF support the hypothesis that chronic immune inflammation may promote the development and progression of HF in RA²⁸. The association of severe ExRA with HF is concordant with the literature describing poor CV prognosis and increased likelihood of myocardial function impairment in patients with ExRA^{29,30,31}.

Several studies showed an association of myocardial dysfunction^{32,33} and/or HF⁹ with RA duration, while others did not find this relationship²⁹. Our study extends these observations, showing that the risk of HF is significantly increased during the first year of RA. Active inflammation in early RA could be one of the reasons for this finding. However, the role of confounding factors (including use of antirheumatic medications and preexisting comorbidities) cannot be excluded. Thus, the clinical implications of this finding are unclear and require further investigation.

In our study, current use of MTX was associated with decreased likelihood of HF even after adjustment for RA characteristics. This finding is concordant with previous observations of a protective effect of MTX against CV disease, including HF^{11,34}. The lower risk of HF in MTX users versus nonusers may be secondary to the decrease in inflammatory activity following MTX treatment. However, alternative mechanisms including MTX-specific effects cannot be excluded³⁵. Current corticosteroid use appeared to have an adverse effect on the risk of HF, which is concordant with the literature^{9,12,13}. Our findings of somewhat lower likelihood of HF in current users of biologic response modifiers versus nonusers were similar to those of others suggesting a beneficial effect of biologic response modifiers (particularly, anti-TNF- α treatment) on the risk of HF¹³. However, our results did not reach statistical significance, likely due to insufficient statistical power. Since the majority of biologic response modifier use in our patients was anti-TNF- α treatment, we were unable to analyze the effects of different biologic response modifiers on the risk of HF. Analyses of medications used at any time revealed no significant associations with HF, while analyses of current use were significantly associated with the risk of HF. Thus past use appears to confer less risk than current use. The reasons for this are unclear, but may be due to a dilution of effect over time. Confounding by indication/contraindication when the initiation of an antirheumatic medication depends on prognostic expectations of a physician, particularly with regard to RA activity and CV risk, may also play a role. More studies (preferably randomized controlled trials) are needed to understand the effects of antirheumatic medications on HF in RA.

The association between HF with reduced EF and male gender in our study is concordant with findings from the general population³⁶. In contrast to the findings from the general population, we did not find higher likelihood of HF with preserved EF in females^{36,37}. This raises a possibility that the mechanisms of HF in RA patients differ from those of the gen-

eral population. Except for the gender differences, there were no statistically significant differences in the risk factors for HF with preserved EF versus HF with reduced EF in our study. However, statistical power to draw definite conclusions regarding these associations was lacking.

Our study has several potential limitations. First, the population of Olmsted County, Minnesota, is predominantly white, thus the generalizability of our findings to more ethnically diverse populations may be limited. Second, the retrospective study design requires that only information available from medical records was used to ascertain risk factors and outcomes. Thus, risk factors and outcomes were not measured at regular intervals, and were dependent on physician observation and documentation. However, the use of the comprehensive population-based resources of the REP and standardized case ascertainment likely minimized this bias. Another limitation inherent to the use of medical records is the lack of echocardiography data (particularly the EF measures) in 27% of patients, suggesting that the results of analyses of patients with reduced versus preserved EF should be interpreted with caution. However, this is not likely to significantly affect other findings of the study. The definition of alcohol abuse in our study was based on physician's diagnosis and thus reliability may be somewhat limited. However, the magnitude and the direction of this association are suggestive of increased risk of HF in RA patients with alcohol abuse and this finding is consistent with observations in the general population³⁸. As in any observational study, there is a possibility of confounding by indication/contraindication for the associations of medication use (particularly MTX and corticosteroid use) with the risk of HF. Although the association of MTX with lower likelihood of HF remained essentially unchanged after adjustment for RA characteristics, other potential confounders including unmeasured and unknown confounders cannot be excluded. Finally, the use of the over-the-counter medications (particularly NSAID and coxibs) was recorded as present or absent without a specification of the drug. Therefore, we were unable to analyze the association of each individual NSAID/coxib with the risk of HF in this study.

Our study has several important strengths. It was a large longitudinal population-based cohort study of incident RA patients that identified the spectrum of RA disease in the community. For instance, the rates of joint erosions/destructive changes in population-based studies and other large inception RA cohorts recruited from primary care settings are somewhat lower than in referral-based cohorts, suggesting that these estimates are more representative^{39,40,41}. The availability of extensive data on the use of antirheumatic medications including the use of oral and intravenous corticosteroids is another strength of the study. Finally, we used well established and validated criteria to identify patients with RA, CV risk factors, and CV events.

Several RA characteristics, including RF positivity, increased ESR at RA incidence, repeatedly high ESR, and the

presence of severe ExRA, were significant determinants of HF beyond traditional CV risk factors and CHD. Current use of MTX was associated with decreased likelihood of HF, while current use of corticosteroids was associated with an increased risk of HF. Our findings suggest an independent effect of RA on HF development, which may be further modified by antirheumatic treatment. More research is needed to better understand the mechanisms of HF in RA.

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