Metabolic Syndrome Is Not Associated With Increased Mortality or Cardiovascular Risk in Nondiabetic Patients With a New Diagnosis of Coronary Artery Disease

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Background—Metabolic syndrome (MetSyn) is associated with increased cardiovascular risk in the general population. Its prognostic implications are less well defined in patients with coronary artery disease.

Methods and Results—We analyzed patients in the Duke Database for Cardiovascular Disease with a diagnosis of incident obstructive coronary artery disease. Diabetes mellitus (DM) was classified as a clinical history of DM, use of hypoglycemic drugs, or fasting glucose of ≥126 mg/dL. MetSyn was defined as having 3 of 5 characteristics: fasting glucose ≥100 and <126 mg/dL, low high-density lipoprotein cholesterol (men, <40 mg/dL; women, <50 mg/dL), triglycerides >150 mg/dL, blood pressure ≥130/85 mm Hg, or use of antihypertensive therapy, or body mass index ≥27. Death, myocardial infarction, or stroke was assessed at 6 months, 1 year, then annually. Cox proportional hazards models were generated to compare mortality and cardiovascular events between groups. The primary cohort consisted of 5744 patients; 1831 (31.9%) had DM, 2491 (43.4%) had MetSyn, and 1422 (24.7%) had no DM/MetSyn. Median follow-up was 5 years. Compared with no DM/MetSyn patients, DM patients had a higher adjusted risk for mortality (hazard ratio, 1.47; 95% CI, 1.28 to 1.69) but MetSyn patients did not (hazard ratio, 0.94; 95% CI, 0.81 to 1.08). Similar results were found for the combined end points of death or myocardial infarction, and death, myocardial infarction, or stroke.

Conclusions—In a population of consecutive patients with a new diagnosis of coronary artery disease by angiography, MetSyn without DM was not an independent predictor of mortality or cardiovascular events.

Key Words: metabolic syndrome • diabetes mellitus • coronary artery disease • death • myocardial infarction
WHAT IS KNOWN

- Diabetes and metabolic syndrome have been clearly demonstrated to increase risk of coronary artery disease in primary prevention populations.
- Some analyses have identified metabolic syndrome as risk factor in secondary prevention populations; however, some of these analyses do not control for presence of diabetes, and others do not adjust for the duration of coronary artery disease.

WHAT THE STUDY ADDS

- Our analysis investigated whether metabolic syndrome but not diabetes increased the risk among patients with a de novo diagnosis of coronary disease as established by angiography.
- We found that there was not significant increased risk of metabolic syndrome in the absence of diabetes for subsequent cardiovascular events compared with patients with neither diabetes nor metabolic syndrome.
- This analysis highlights that the relationship between risk factors and outcomes in secondary prevention populations is complex, and consideration should be given to duration of diagnosis of coronary disease when accounting for metabolic risk factors and risk of cardiovascular events.

Methods

Study Population and Data Sources

The protocol for reviewing and analyzing the Duke Database for Cardiovascular Disease and other medical records was approved by the Institutional Review Board of Duke University Medical Center. The Duke Database has been described in detail elsewhere. Briefly, prospective follow-up was obtained at Duke University Medical Center on all patients with angiographically identified significant CAD, defined as having ≥1 lesion of ≥75% stenosis in large vessel or major branch. Follow-up for death, myocardial infarction (MI), and stroke was conducted by telephone and mailed questionnaire at 6 months, 1 year, and annually thereafter. Myocardial infarction was systematically determined from patient self-report and subsequent review of hospital records. Death was cross-referenced with the National Death Index. Patients were censored at last alive contact or at date of death. Data summaries and statistical analyses were prepared using SAS statistical software (SAS Corp, Cary, NC).

We identified patients with a new diagnosis of CAD confirmed by medical history who underwent angiography between June 1998 and December 2001 and whose data were registered in the Duke Database for Cardiovascular Disease and survived for ≥30 days after the index catheterization. Patients who died within 30 days of index angiography were excluded to eliminate events related to initial revascularization of the patient. Patients with congenital or primary valvular heart disease were also excluded. Baseline demographic information, cardiovascular and noncardiovascular medical history, cardiovascular risk factors, and physical examination findings were entered into the database at time of catheterization.

Laboratory values associated with the index catheterization were obtained from the Duke University Medical Center Information System. Fasting lipid panels and serum glucose values drawn on the morning of catheterization until 12 PM were presumed to be fasting as all elective patients were fasting before the catheterization procedure. For patients without fasting values using these criteria, any fasting measurement obtained between 3 AM and 7 AM during the 30 days immediately surrounding the catheterization was used. If ventriculography was not performed during cardiac catheterization, noninvasive assessments made up to 1 year before the study or during hospitalization were used to estimate ejection fraction. Imputation techniques were used when small amounts of missing data were present. Medication use was obtained from the pharmacy charge codes and the discharge medication lists. Specifically use of hypoglycemic medications, antihypertensive medications, and lipid-lowering medications were recorded.

Definition of Diabetes and Components of MetSyn

Patients were classified as having diabetes if a clinical history of diabetes was recorded, scheduled doses of hypoglycemic medication were prescribed at discharge, or the fasting glucose was ≥126 mg/dL. The components of MetSyn for these analyses were adapted from the revised NCEP Third Adult Treatment Panel (NCEP ATP-III) definition. Nondiabetic patients meeting ≥3 of the following 5 characteristics were classified as having MetSyn: impaired fasting glucose ≥100 and <126 mg/dL, HDL cholesterol <40 mg/dL for men and <50 mg/dL for women, fasting triglycerides >150 mg/dL, BMI ≥27 kg/m², and history of hypertension, use of antihypertensive therapy, or blood pressure ≥130/85 mm Hg. Because abdominal waist circumference, a component of the NCEP MetSyn definition, was not routinely collected, BMI was used as the adiposity measure. Patients determined not to have DM or MetSyn were classified as No DM/MetSyn. If a patient could not be classified as either having or not having MetSyn, the patient was excluded from the analysis population.

Statistical Analysis of Individual Components of MetSyn

The individual components of MetSyn that were analyzed included fasting glucose, BMI, HDL cholesterol, and fasting triglycerides. For the analyses of fasting glucose, patients with a clinical history of diabetes at time of catheterization were excluded from the analysis population. Patients not receiving hypoglycemic therapies were classified as either having or not having MetSyn, the patient was excluded. To model convex or concave shapes from each continuous variable, 2 linear factors were derived and constructed in tandem to form a linear spline. A grid search was used to determine the optimal split point for the linear spline, fitting Cox proportional hazards models over a series of split points and finding the best fitting model. Spline results were evaluated with the NCEP ATP-III thresholds to ensure that the definitions of MetSyn were appropriate for our population. Using spline-fitting methodology, 5-year survival estimates were examined across each of these continuous variables and by sex for HDL cholesterol for a graphical display of these relationships (Figure 1).

Statistical Analysis of Patients With Diabetes, MetSyn, or No DM/MetSyn

Baseline characteristics of the diabetic patients, the MetSyn population, and the No DM/MetSyn populations were tabulated and summarized as percentages or medians and 25th and 75th percentiles. Demographic characteristics included age, sex, ethnicity, height, and weight. Cardiovascular characteristics included history of hypertension, history of heart failure, severity of CAD, ejection fraction, valvular heart disease including mitral regurgitation, smoking history, and peripheral or cerebrovascular disease. Distributions of noncardiac medical history data included history of kidney disease, liver disease, chronic lung disease, connective tissue disease, prior tumor or metastatic cancer. A modified Charlson index that excluded diabetes, heart failure, and MI as a comorbidity was examined to characterize the severity of noncardiovascular disease.

The primary outcome was all-cause mortality for all patients surviving ≥30 days after index catheterization, and subsequent analyses were conducted for the combined end points of death and...
MI, and death, MI, and stroke. Candidate variables included the baseline demographic, cardiovascular and noncardiac medical history, and modified Charlson index. Univariable predictors of survival were characterized in terms of strength of association by $\chi^2$ value from Cox proportional hazard regression models. Linearity assumptions for continuous variables were assessed and variables were transformed to satisfy these assumptions. Unadjusted Kaplan-Meier survival analysis was performed. Multivariable Cox proportional hazards models including terms for the DM, MetSyn, and No DM/MetSyn patients were created using forward stepwise selection of variables and adjusted survival curves were produced for each of the end points. A stepwise procedure was used to reduce covariates in the model for parsimony. Statistical significance was determined using 2-tailed tests with a significance value of $P<0.05$. Plots of adjusted survival estimates were produced and stratified by observational groups. To evaluate the robustness of the BMI and fasting glucose criteria, additional sensitivity models were created using similar statistical methods but different thresholds of $\geq 110$ mg/dL for fasting glucose and $\geq 30$ kg/m² for BMI to define MetSyn among nondiabetic patients. These values were selected in accordance with the historic ADA and NCEP definitions of impaired fasting glucose and the National Health and Nutritional Examination Survey (NHANES) definition of obesity.

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

**Results**

**Study Population**

We identified 6646 patients in the Duke Database with significant disease on a first catheterization (index catheterization) at Duke University Medical Center after January 1, 1998, and before January 1, 2002. Of these, 443 did not survive $\geq 30$ days after their index catheterization, and an additional 459 patients were excluded due to missing laboratory data needed to determine DM or MetSyn status, leaving 5744 patients in the primary analysis cohort. Of note, 778 patients identified with an index catheterization could not be classified due to missing data. The median follow-up time was 5 years.
Baseline Characteristics

Compared with the No DM/MetSyn patients, the median age of MetSyn patients was 3 years younger, and MetSyn patients were less likely to be black than white (Table 1). Baseline lipid, glucose, and hypertension characteristics in the MetSyn population reflected the criteria used to define MetSyn. The extent of CAD and other atherosclerotic disease was similar between MetSyn and the No DM/MetSyn populations. Utilization of percutaneous coronary intervention and bypass surgery after index catheterization was similar between these groups.

More than 94% of the diabetic patients were classified as type 2 DM and nearly 80% of the diabetic patients met the definition for MetSyn. DM patients were younger than the No DM/MetSyn patients, were slightly older than the MetSyn patients, and were more likely to be women and to be black.

<table>
<thead>
<tr>
<th>Table 1. Baseline Clinical Characteristics</th>
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<tbody>
<tr>
<td>Variable</td>
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<tr>
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<tr>
<td>Age, y, median (25th, 75th percentile)</td>
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<tr>
<td>Women, %</td>
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<tr>
<td>Black, %</td>
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<tr>
<td>LDL cholesterol, mg/dL, median (25th, 75th percentile)</td>
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<td>BMI, kg/m², median (25th, 75th percentile)</td>
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<tr>
<td>Hypertension, %</td>
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<td>Fasting glucose, median (25th, 75th percentile)</td>
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<td>HDL cholesterol, median (25th, 75th percentile)</td>
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<td>Fasting triglycerides, median (25th, 75th percentile)</td>
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Proportion with individual metabolic syndrome criteria

| BMI ≥27, %                                 | 15.5         | 75.0               | 69.7       | 58.6          |
| Fasting glucose ≥100 mg/dL, %              | 13.9         | 50.7               | 59.2       | 44.3          |
| Women <50; men <40 mg/dL, %                | 27.0         | 80.6               | 70.8       | 64.2          |
| Fasting triglycerides, % ≥150 mg/dL        | 11.2         | 46.6               | 39.5       | 35.6          |
| BP ≥130/≥85 mm Hg, %                       | 92.9         | 98.1               | 98.6       | 97.0          |

Components of metabolic syndrome, %

| 0                                         | 1.3          | 0                  | 0.1        | 0.3           |
| 1                                         | 37.2         | 0                  | 3.3        | 10.3          |
| 2                                         | 61.5         | 0                  | 17.3       | 20.7          |
| 3                                         | 0            | 58.3               | 32.9       | 35.7          |
| 4                                         | 0            | 32.5               | 31.3       | 24.1          |
| 5                                         | 0            | 9.2                | 15.2       | 8.9           |

History of smoking, %

| 60.8                                      | 60.5         | 49.7               | 57.1       |

Charlson Index, median (25th, 75th percentile)

| 0 (0, 0)                                  | 1 (1, 2)     | 0 (0, 1)           |

History of heart failure, %

| 15.9                                      | 13.3         | 27.6               | 18.5       |

Ejection fraction, median (25th, 75th percentile)

| 55 (45, 64)                               | 56 (45, 65)  | 54 (42, 64)        | 55 (44, 65) |

CHF class, %

| None                                      | 85.3         | 87.7               | 74.0       | 82.8          |
| I                                         | 2.2          | 1.9                | 3.8        | 2.6           |
| II                                        | 4.3          | 3.5                | 7.1        | 4.8           |
| III                                       | 5.0          | 4.6                | 8.8        | 6.0           |
| IV                                        | 3.2          | 2.4                | 6.3        | 3.8           |

Systolic blood pressure, median (25th, 75th percentile)

| 145 (126, 163)                           | 141 (125, 159) | 149 (131, 171) | 144 (127, 164) |

History of angina, %

| 79.6                                      | 81.1         | 80.4               | 80.5       |

History of myocardial infarction, %

| 45.6                                      | 49.1         | 38.6               | 44.9       |

History of cerebrovascular disease, %

| 8.7                                      | 7.6          | 11.1               | 9.0        |

History of peripheral vascular disease, %

| 6.5                                      | 5.3          | 10.9               | 7.4        |

PCI 30 d after index catheterization, %

| 55.1                                      | 60.3         | 47.4               | 54.9       |

CABG 30 days after index catheterization, %

| 23.7                                      | 24.0         | 26.0               | 24.6       |

PCI indicates percutaneous coronary intervention; CABG, coronary artery bypass graft.
DM patients were also more likely to have more extensive CAD, other atherosclerotic disease, and a history of heart failure compared with the other 2 groups.

DM, MetSyn, and Outcomes

Kaplan-Meier analysis of unadjusted survival revealed that 538 (41.9%) DM, 426 (32.5%) MetSyn, and 342 (36.8%) No DM/MetSyn patients died during follow-up, and the 5-year mortality rates were 26.7%, 15.3%, and 20.2%, respectively (Figure 2A). These relationships in mortality were consistent throughout follow-up. After adjustment for covariates, patients with DM were found to have a significantly increased risk of death (hazard ratio [HR], 1.47; 95% CI, 1.28 to 1.69) compared with patients with No DM/MetSyn (Table 2 and Figure 3A). In contrast, no significant difference in survival was observed between patients with MetSyn and those with No DM/MetSyn (HR, 0.94; 95% CI, 0.81 to 1.08). Similarly, no significant difference in the risk of the combined end points of death or MI, and death, MI or stroke was found between the MetSyn and no DM/MetSyn patients (Figure 3A). Patients with DM were found to be at increased risk of these events. In sensitivity analyses altering the fasting glucose and BMI thresholds to 110 mg/dL and 30 kg/m² slightly changed the number of patients classified with MetSyn, with no significant changes in the qualitative relationships or level of significance for any of the clinical end points (Figure 3B, 3C, and 3D).

Analysis of Individual Components of MetSyn

Results of the survival trend plots demonstrated associations with survival for each of the components of MetSyn (Figure 1). Lower BMI was associated with worse outcome, and the optimal cut-point for risk from the grid search was 29 kg/m². Lower values of fasting glucose were also associated with increased risk, but an inflection point suggesting increasing risk was noted between 100 and 110 mg/dL. The optimal cutpoint for risk was 131 mg/dL. Among nondiabetic men, an inverse relationship was noted between HDL cholesterol and mortality, and the optimal cut-point was 33 mg/dL. Among nondiabetic women, low levels of HDL were not associated with increased risk, but extremely high values were associated with reduced risk with an optimal cut-point of 59 mg/dL. Finally, the analysis of triglycerides demonstrated no clear relationship between triglycerides and survival, although an optimal cut-point of 92 mg/dL was identified.

Discussion

In our analysis, we found that a majority of patients with incident CAD met criteria for MetSyn. However, in the absence of DM, MetSyn did not portend to higher long-term risk of death or cardiovascular events. This finding was consistent regardless of variation in the thresholds used for fasting glucose and BMI to define MetSyn.
Characteristics of MetSyn Patients

Among the 3 patient categories, the group having MetSyn without DM was the largest. More than 70% of patients were categorized as having MetSyn or had DM, and among the DM patients nearly 80% had 3 or more characteristics of MetSyn. Moreover, the majority of patients classified our study as having neither MetSyn nor DM met 2 of the MetSyn diagnostic criteria. These findings demonstrate that the prevalence of clinical features of insulin resistance is high among patients at the time of an initial diagnostic angiogram, and these findings are consistent with those of other studies of patients with CAD.14,23,24 In addition, this is considerably higher than the estimated prevalence of 25% of US adults in the NHANES study.10

Importantly, the majority of MetSyn patients had only 3 diagnostic criteria. Thus they were more similar than dissimilar to the No DM/MetSyn patients, which may partially explain why no difference in outcomes was observed between the groups. Age was also an important difference between the demographics of the MetSyn and the No DM/MetSyn patients, as the MetSyn patients were younger. In the unadjusted survival analysis, the MetSyn population had a better survival than the No DM/MetSyn patients, giving the paradoxical impression that MetSyn is protective (Figure 2). However, this difference was not appreciated after adjustment for covariates such as age, which is strongly correlated with outcome.

Definitions of MetSyn

The current thresholds used for categorical determination of each of the component criteria for MetSyn were derived from a variety of observational databases of primary prevention populations.15,16,20 Although these thresholds and other markers have been correlated with direct measures of insulin resistance, considerable variability exists in their individual association with cardiovascular risk. Despite data supporting the components of MetSyn as markers of risk, only recently have these markers been validated as a group of traits that predict death and cardiovascular events in primary prevention populations.2–5,9–11 However, no studies have assessed the combined validity of these thresholds on predicting clinical events over long-term follow-up in populations with prevalent CAD.

On the basis of analysis of the individual components of the metabolic syndrome and prediction of survival, we found that the thresholds used to predict risk in primary prevention patients are comparable in a secondary prevention population when limiting the analysis only to those patients with incident CAD. The inflection points of fasting glucose in our population were similar to those observed in larger datasets and support the decision by the NCEP to revise the fasting glucose component for the definition of MetSyn in accordance with the 100 mg/dL threshold used to define impaired fasting glucose by the ADA.20 The HDL cholesterol spline results suggest an inverse relationship with survival. Among nondiabetic women, the relationship between low HDL and cardiovascular clinical events was not appreciated, suggesting that in women with CAD the relationship between low HDL and cardiovascular clinical events is strongly associated with DM. The triglyceride spline plots did not identify a clear threshold of increased risk, a finding consistent with other observational studies.25,26 The analysis of BMI suggested that the best discriminator of risk was a threshold of 29 kg/m². This result is consistent with the NHANES findings that suggest an increasing mortality risk in primary prevention patients with BMI values of >30 kg/m².27 In general, the analysis of the individual components of MetSyn supports their use as markers of risk in a secondary prevention population, with the
understanding that the relationship between BMI and triglycerides is not as strong as other criteria.

**Clinical Implications**

Our results support the existing literature that the presence of DM in patients with a new diagnosis of CAD is associated with a considerable increase in risk even with adjustments for other known predictors of mortality among patients with CAD. These findings support the aggressive approach to risk reduction for patients with DM recommended by the current NCEP and ADA guidelines, particularly among patients with CAD. In addition, this finding demonstrates the importance of screening patients with a new diagnosis of CAD for DM due to its impact on long-term prognosis.

In contrast, MetSyn in the absence of DM was not associated with increased risk among patients with an index diagnosis of CAD by catheterization. Although this does not reduce the importance of recognizing patients with increased risk of developing DM, it does highlight an important distinction in risk between patients with DM and those with MetSyn but not DM.

Compared with other studies, our findings are consistent with others demonstrating that DM increases the risk of death and cardiovascular events in secondary prevention populations, but our findings are different regarding the clinical risks associated with MetSyn in cohorts with CAD. Specifically, several prior works had reported that MetSyn in the absence of DM was a risk factor for increased cardiovascular events among patients with CAD. Post hoc analysis from the Women's Ischemic Syndrome Evaluation found an increased risk of cardiovascular events associated with MetSyn among a population undergoing coronary angiography, although most but not all of the patients had CAD in this cohort. In an unadjusted analysis from the and the Women's Angiographic Vitamin and Estrogen trial, presence of MetSyn significantly predicted increased risk of cardiovascular events but not angiographic progression of disease.

The Intermountain Heart Collaborative Study Group found that the prevalence of CAD was predicted by MetSyn in a cohort of patients undergoing coronary angiography, and further analysis demonstrated that fasting glucose and low HDL cholesterol were the chief predictors of disease. A key difference between many of these analyses and our analysis is that patients with DM were not distinguished from the MetSyn populations. Because MetSyn is highly prevalent in most populations of DM and vice versa, it is difficult to distinguish whether DM or MetSyn lead to increased risk in comparison with a CAD population without DM or MetSyn.

More recently, the Secondary Manifestations of Arterial Disease (SMART) study group found that MetSyn predicted an increased risk of cardiovascular events in a broad cohort of patients with atherosclerotic disease. Interestingly, an increased risk of cardiovascular events was noted among MetSyn patients with and without DM and the risk was similar. Post hoc analysis from the Treating to New Targets study also identified MetSyn as an independent predictor of outcome. However, these analyses included a mixed population of new and previously diagnosed CAD that can vary with regard to history of revascularization, duration and use of medical therapy, and severity of atherosclerosis. Our study population deliberately separated DM patients from non-DM patients and was limited to patients with an index diagnosis of CAD at angiography. As a result, our findings demonstrate that duration of CAD is important to consider in evaluating the impact of MetSyn on subsequent outcome in non-DM patients.

**Limitations**

There are several key limitations to our study. The Duke Database for Cardiovascular Disease has specific methodologic limitations as it is a single-center, clinical database. The study population was derived from patients referred for cardiac catheterization that excluded both low risk and extremely ill patients. However, as the majority patients with suspected CAD are referred for catheterization in the United States, we believe our population is representative of most patients diagnosed with CAD and is similar to other high-volume, academic, tertiary care cardiovascular facilities.

Although the laboratory values were not collected prospectively for this study but as part of routine patient care, we believe we have made reasonable assumptions in an effort to identify fasting laboratory values surrounding the index catheterization; as a result, <10% of potentially eligible patients were excluded because of missing data. Importantly, the fasting laboratory values do reflect a precatheterization state that may differ from those obtained in a stable outpatient setting, but no significant difference in the observed associations was appreciated when doing sensitivity analyses using different thresholds for the fasting glucose criterion to define MetSyn. Also, we did not have data on diet, which has been associated with outcome.

Finally, we used BMI as a surrogate marker for central obesity as other anthropomorphic measures such as abdominal waist circumference were not available for analysis. Clearly, these measures are better predictors of cardiovascular risk; however, BMI has been used effectively as surrogate marker for obesity in several studies and is a component of other criteria to identify insulin resistance. We made an effort to examine the relationship of BMI with survival and evaluated the impact of BMI on the analysis by varying the thresholds and found no significant difference in the results. As a result, we believe that it would be unlikely that use of abdominal waist circumference rather than BMI would significantly alter the results of the study.

**Conclusions**

Among patients with a new angiographic diagnosis of CAD in the Duke Database for Cardiovascular Disease, non-diabetic patients meeting criteria adapted from the NCEP definition of MetSyn did not have an increased risk of death or cardiovascular events compared with patients without MetSyn or DM. In contrast, DM was associated with significantly worse outcome. Patients meeting the definition of MetSyn tended to be younger, suggesting that MetSyn may predispose to an earlier diagnosis of CAD.

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References
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