Fibrinogen Is Associated With an Increased Risk of Alzheimer Disease and Vascular Dementia

Marieke van Oijen, MD; Jacqueline C. Witteman, PhD; Albert Hofman, MD, PhD; Peter J. Koudstaal, MD, PhD; Monique M.B. Breteler, MD, PhD

Background and Purpose—Vascular and inflammatory factors may play an important role in the pathogenesis of dementia. Studies reported an association between plasma levels of inflammation markers and the risk of dementia. Both fibrinogen and C-reactive protein are considered inflammatory markers. Fibrinogen also has important hemostatic properties. We investigated the association of fibrinogen and C-reactive protein with dementia.

Methods—The study was based on the prospective population-based Rotterdam Study. Fibrinogen was measured in a random sample of 2835 persons. High-sensitivity C-reactive protein was measured in the total cohort of 6713 persons. We identified 395 incident dementia cases during follow-up (mean, 5.7 years). We estimated the associations of fibrinogen and C-reactive protein with dementia using Cox proportional hazard models.

Results—Persons with higher levels of fibrinogen had an increased risk of dementia. The hazard ratio for dementia per SD increase of fibrinogen was 1.26 (95% CI, 1.11 to 1.44), adjusted for age and gender, and 1.30 (95% CI, 1.13 to 1.50) after additional adjustment for cardiovascular factors and stroke. For Alzheimer disease, the adjusted hazard ratio was 1.25 (95% CI, 1.04 to 1.49), and for vascular dementia it was 1.76 (95% CI, 1.34 to 2.30). High levels of C-reactive protein were not associated with an increased risk of dementia.

Conclusions—High fibrinogen levels were associated with an increased risk of both Alzheimer disease and vascular dementia, but levels of C-reactive protein were not. This suggests that the increased risk of dementia associated with fibrinogen is because of the hemostatic rather than the inflammatory properties of fibrinogen. (Stroke. 2005;36:2637-2641.)

Key Words: fibrinogen • C-reactive protein • dementia • Alzheimer disease • risk

Vascular factors are believed to play an important role in the pathogenesis of dementia, both Alzheimer disease and vascular dementia.1-2 Both inflammatory and hemostatic factors have been implicated in the development of vascular disease. There is evidence for a role of inflammation in dementia. Signs of inflammation, such as activated microglia and inflammatory mediators including C-reactive protein and complement factors,3 are present in the brain of demented persons. It is thought that this inflammatory response contributes to neuronal death. Also, a beneficial effect of nonsteroidal antiinflammatory drugs has been suggested.4 However, it is less clear how this inflammatory process affects or is affected by peripheral inflammatory disease or markers of disease. Previous studies suggested that peripheral markers of inflammation are elevated in the plasma of patients years before the clinical syndrome of dementia developed.5,6

Both fibrinogen and C-reactive protein are acute-phase proteins. High levels serve as nonspecific markers for inflammatory disease. Fibrinogen also has important hemostatic properties because it affects platelet aggregation and endothelial function. Fibrinogen is a major determinant of plasma viscosity and induces red cell aggregation. High levels of fibrinogen in plasma might reduce blood flow, predispose to thrombosis, and enhance atherogenesis.7

High levels of fibrinogen and C-reactive protein are associated with an increased risk of cardiovascular disease and stroke.7-9 Whether increased levels reflect active involvement in the pathogenesis of atherosclerosis or merely reflect the presence of nonspecific inflammatory disease is not clear. Because dementia is associated with both vascular and inflammatory factors, we hypothesized a relation between both fibrinogen and C-reactive protein and dementia. We investigated this association in the Rotterdam Study, a prospective population-based cohort study among men and women aged 55 years and over.

Methods

Study Population and Design

The Rotterdam Study is a population-based prospective cohort study that was designed to investigate the incidence and causes of...
cardiovascular, neurodegenerative, locomotor, and ophthalmologic
diseases in the elderly. From 1990 to 1993, all 10 275 residents aged
≥55 years of Ommoord, a district of the city of Rotterdam, were
invited to participate, and 7983 (78%) men and women agreed. The
Medical Ethics Committee of the Erasmus Medical Center approved
the study, and written informed consent was obtained from all of the
participants. At the baseline clinical examination, 7047 persons were
screened for dementia and had blood samples drawn. Prevalent
dementia was diagnosed in 334 persons, resulting in a cohort of 6713
persons at risk for dementia. Follow-up examinations were con-
ducted in 1993 to 1994 and in 1997 to 1999. In addition, through
linkage with records of general practitioners, the total cohort was
continuously monitored for morbidity and mortality. This resulted in
a virtually complete follow-up until January 1, 2000.

Measurement of Fibrinogen and
C-Reactive Protein
Platelet poor plasma was frozen in liquid nitrogen and stored at
−80°C until determination. Fibrinogen measurements were done at
baseline in a random sample and were available for 2835 of the
persons at risk. Fibrinogen levels were derived from the clotting
curve of the prothrombin time assay using Thromborel S as a reagent
on an automated coagulation laboratory (ACL 300, Instrumentation
Laboratory). The coefficient of variation was 5%. High-sensitivity
C-reactive protein (HsCRP) was measured for the total cohort in
baseline serum samples kept frozen at −20°C, using a rate near-
infrared particle immunoassay method (Immage, Beckman Coulter).
The range of measurement was 0.2 to 1440 mg/L with a variation
coefficient of 3.1%. In a random sample of the study (n=29), we
compared HsCRP measurements from baseline blood stored at
−20°C and −80°C. The correlation between the measurements was
high (Spearman correlation 0.99; P<0.001). HsCRP levels were
somewhat lower in blood stored at −20°C (mean difference,−0.5097; 95% CI,−1.637 to 0.618). Because the lowering of
HsCRP levels was proportional, we do not expect it to affect the
estimate.

Diagnosis of Dementia
The diagnosis of dementia was made following a 3-step protocol.
Two brief tests of cognition (Mini-Mental State Examination10 and
Geriatric Mental State schedule11 organic level) were used to screen
all of the subjects. Screen-positives (Mini-Mental State Examination
score ≤26 or Geriatric Mental State organic level >0) underwent the
Cambridge examination for mental disorders of the elderly (Cam-
dex).12 Subjects who were suspected of having dementia were, if
necessary, examined by a neuropsychologist. In addition, the total
cohort was continuously monitored for incident dementia through
computerized linkage between the study database and digitalized
medical records from general practitioners and the Regional Institute
for Outpatient Mental Health Care. The diagnoses of dementia and
Alzheimer disease were made in accordance with internationally
accepted criteria for dementia (Diagnostic and Statistical Manual
of Mental Disorders, Third Edition-Revised),13 Alzheimer disease (Na-
tional Institute of Neurological and Communicative Disorders and
Stroke and the Alzheimer Disease and Related Disorders Associa-
tion),14 and vascular dementia (National Institute of Neurological
Disorders and Stroke and the Association Internationale pour la
Recherche et l’Enseignement en Neurosciences)15 by a panel of a
neurologist, neuropsychologist, and research physician.

Covariates
At baseline, trained investigators interviewed all of the participants
at home, collecting information on current health status and medical
history. Additionally, at the research center, clinical measures were
obtained. The body mass index was calculated [weight (kg)/length
(m)^2]. Blood pressure was measured at the right brachial artery using
a random-zero sphygmomanometer with the participant in sitting
position. Nonfasting blood samples were drawn and immediately
frozen. Total cholesterol, high-density lipoprotein cholesterol, and
glucose were measured within 2 weeks. Immediately after blood
sampling, white blood cell count was assessed in citrate plasma using
a Coulter Counter T540 (Coulter Electronics). The quality of assess-
ments was continuously monitored by Instruchemi. Genotyping for
apoE was performed on coded DNA specimens without knowledge
of the diagnosis. Persons were categorized on the basis of the
presence or absence of an apoE 4 allele. Furthermore, ultrasonog-
raphy of both carotid arteries was performed. As an indicator of
atherosclerosis of the carotid arteries, we used intimamedia thickness
(IMT) and presence of carotid plaques. Common carotid IMT was
determined as the average of the maximum IMT of near- and far-wall
measurements, and the average of left and right common carotid
IMT was computed.16 Carotid plaques were determined at 6 different
locations: common carotid artery, carotid bifurcation, and internal
carotid artery at both the left and right side.16 To assess the presence
of atherosclerosis of the lower extremities, we obtained the ankle-
to-brachial index by computing the ratio of the systolic blood
pressure at the ankle to the systolic blood pressure at the arm. We
defined diabetes mellitus as a random or postload glucose level
≥11.1 mmol/L or the use of blood glucose-lowering medication.

Data Analysis
Fibrinogen was normally distributed, and we examined the associa-
tion of fibrinogen and the risk of dementia and subtypes of dementia
using Cox proportional hazard models. First, we entered fibrinogen
as a linear term (per SD) in the model. Next, quintiles of fibrinogen
were made, and the lowest quintile was used as the reference
category. Because both dementia and fibrinogen are associated with
age and cardiovascular and inflammatory factors, we adjusted for
age (and gender) and, additionally, for cardiovascular risk factors
including smoking, body mass index, presence of diabetes mellitus,
systolic and diastolic blood pressure, total cholesterol, high-density
lipoprotein cholesterol, and measures of atherosclerosis. Other po-
tential confounders that we considered were presence of an apoE 4 allele, stroke, and the inflammatory markers white blood cell count
and HsCRP.

To examine the influence of atherosclerosis, we constructed a
composite measure of atherosclerosis.17 A point was added to the
atherosclerosis score if the following characteristics were present: (1)
plaques in ≥3 locations of carotid arteries; (2) average wall thickness
of common carotid arteries in the highest quintile of the distribution;
and (3) evidence of peripheral arterial disease, defined as the
ankle-brachial index <0.90. The atherosclerosis sum score was
analyzed in 4 categories corresponding to score values of 0 to 3.
To assess whether the effect of inflammatory markers was
different in people with and without previous stroke, we performed
stratified analysis. We repeated the analyses excluding previous
stroke and censoring incident stroke cases.

Because the distribution of HsCRP levels was skewed, we used
log-transformed HsCRP in the analyses. Extreme high values may
indicate the presence of an active inflammatory disease. Therefore,
we excluded persons with HsCRP levels >3 times the SD of the
log-transformed HsCRP, resulting in a total of 6247 measurements.
We examined the association between log-transformed HsCRP and
dementia entering C-reactive protein as a linear term (per SD) in the
model. Then, quintiles were made, and the lowest quintile was used
as the reference category. Adjustments were made for cardiovascular
risk factors, presence of apoE 4 allele, previous stroke, white blood
cell count, and fibrinogen.

Results
In the total cohort (random sample), we identified 349 (192)
patients with incident dementia, of whom 230 (124) patients
were diagnosed with Alzheimer disease, 26 (16) patients with
Alzheimer disease and cerebrovascular disease, and 52 (31)
patients with vascular dementia. Seventeen (7) patients de-
veloped dementia in Parkinson disease, and 24 (14) patients
had dementia because of other causes, such as multisystem
atrophy, frontotemporal dementia, and Lewy body dementia.
TABLE 1. Characteristics of Random Cohort and Total Cohort at Risk

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total Cohort At Risk, n=6713</th>
<th>Random Cohort, n=2835</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (SD)</td>
<td>69.5 (9.1)</td>
<td>70.3 (8.6)</td>
</tr>
<tr>
<td>Women, %</td>
<td>60</td>
<td>63</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg (SD)</td>
<td>139.3 (22.3)</td>
<td>138.2 (21.3)</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L (SD)</td>
<td>6.6 (1.2)</td>
<td>6.7 (1.2)</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>C-reactive protein, mg/L*</td>
<td>1.9 (0.9 to 3.6)</td>
<td>1.8 (0.9 to 3.6)</td>
</tr>
<tr>
<td>Intima-media thickness, mm (SD)</td>
<td>0.8 (0.2)</td>
<td>0.8 (0.2)</td>
</tr>
<tr>
<td>Carotis plaques, 1–6 locations (SD)</td>
<td>1.5 (1.7)</td>
<td>1.5 (1.7)</td>
</tr>
<tr>
<td>Ankle brachial index (SD)</td>
<td>1.1 (0.2)</td>
<td>1.1 (0.2)</td>
</tr>
<tr>
<td>Current smokers, %</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>Presence of apoE ε4 allele, %</td>
<td>25</td>
<td>26</td>
</tr>
<tr>
<td>White blood cell count, 10^9/L (SD)</td>
<td>6.7 (2.1)</td>
<td>7.0 (2.3)</td>
</tr>
<tr>
<td>Fibrinogen, g/L (SD)</td>
<td>...</td>
<td>2.8 (0.7)</td>
</tr>
</tbody>
</table>

*Because of the skewed distribution of C-reactive protein, instead of the mean (SD), the median (interquartile range) is given.

Table 1 shows that the cohort with fibrinogen measurements (n=2835) was a random cohort compared with the total cohort at risk (n=6713). Table 2 shows that increasing levels of fibrinogen were associated with an increased risk of dementia. The association could not be explained by cardiovascular or inflammatory factors. Table 3 shows that higher levels of fibrinogen were associated with an increased risk of both Alzheimer disease and vascular dementia, although the association was stronger with vascular dementia. The hazard ratio adjusted for age and gender for dementia per SD increase of fibrinogen was 3.26 (95% CI, 1.68 to 6.35) for people with previous stroke (n=91) and 1.21 (95% CI, 1.05 to 1.38) in those without previous stroke (n=2808). The P value of the interaction term of fibrinogen and previous stroke was <0.001. Excluding previous stroke cases (n=91) and censoring incident stroke cases (n=13) at time of stroke did not change the estimates.

Higher levels of log-transformed HsCRP were not associated with an increased risk of dementia in our study (Table 4). We investigated whether the association was present in the random subset with fibrinogen measurements. The hazard ratio per SD increase of log-transformed HsCRP was similar (0.95; 95% CI, 0.81 to 1.11). For Alzheimer disease and vascular dementia, the hazard ratios per SD increase of log-transformed HsCRP were 0.97 (95% CI, 0.84 to 1.11) and 1.15 (95% CI, 0.86 to 1.54), respectively. The association of fibrinogen and C-reactive protein with dementia was not different in carriers and noncarriers of the apoE ε4 allele.

**Discussion**

We found that higher levels of fibrinogen but not of HsCRP were associated with an increased risk of both vascular dementia and Alzheimer disease. This association was independent of cardiovascular risk factors and other inflammatory markers, such as white blood cell count. The occurrence of clinical stroke could not explain this association.

The strengths of the Rotterdam study are its prospective design, the population-based setting, and its large number of subjects. Because follow-up with respect to the diagnosis of dementia was virtually complete, selection bias is unlikely. Unfortunately, no data were available on other indicators of the coagulation and fibrinolytic system. It is difficult to differentiate between vascular dementia and Alzheimer disease, and some misclassification could have occurred classifying these subtypes.

An association between HsCRP level and the risk of dementia >20 years later has been reported in a nested case-control study in the Honolulu-Asia Aging Study, a study of Japanese-American men followed for several decades. A 3-fold significantly increased risk of dementia, both Alzheimer disease and vascular dementia, was found in men in the upper 3 quartiles of HsCRP compared with men in the lowest quartile. Although the differences in study population might explain the different results, in our study, we did not find differences in the association between men and women. Also, it is possible that midlife HsCRP is associated with risk of late-life dementia, as seems to be the case for more cardio-

TABLE 2. The Association Between Fibrinogen and Risk of Dementia

<table>
<thead>
<tr>
<th>Fibrinogen, g/L</th>
<th>Model 1*</th>
<th>Model 2†</th>
<th>Model 3‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per SD increase fibrinogen</td>
<td>1.26 (1.11 to 1.44)</td>
<td>1.30 (1.13 to 1.50)</td>
<td>1.23 (1.03 to 1.46)</td>
</tr>
<tr>
<td>1st quintile</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>2nd quintile</td>
<td>1.42 (0.81 to 2.48)</td>
<td>1.50 (0.83 to 2.73)</td>
<td>1.44 (0.80 to 2.60)</td>
</tr>
<tr>
<td>3rd quintile</td>
<td>1.29 (0.74 to 2.22)</td>
<td>1.31 (0.72 to 2.37)</td>
<td>1.21 (0.67 to 2.16)</td>
</tr>
<tr>
<td>4th quintile</td>
<td>1.10 (0.63 to 1.92)</td>
<td>0.95 (0.51 to 1.76)</td>
<td>1.04 (0.58 to 1.87)</td>
</tr>
<tr>
<td>5th quintile</td>
<td>1.92 (1.15 to 3.21)</td>
<td>2.09 (1.19 to 3.68)</td>
<td>1.67 (0.95 to 2.91)</td>
</tr>
<tr>
<td>P trend</td>
<td>0.03</td>
<td>0.05</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Hazard ratio (95% CI) for dementia (192 cases). *Adjusted for age and sex; †Adjusted for age, sex, current smoking, presence of apoE ε4 allele, body mass index, presence of diabetes mellitus, systolic blood pressure, diastolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, atherosclerosis sum score, and previous stroke; ‡Adjusted for age, sex, C-reactive protein, and white blood cell count.
vascular risk factors, such as cholesterol and high-blood pressure. A case-cohort study within the Rotterdam study showed that high levels of inflammatory proteins \(\alpha\)-antichymotrypsin and interleukin 6 were associated with an increased risk of dementia. Elevated levels were present years before the onset of clinical disease.\(^6\) In this study, the association between HsCRP and dementia was weak and not significant (hazard ratio, 1.12; 95% CI, 0.99 to 1.25). Our findings regarding HsCRP in the present study do not contradict this observation. \(\alpha\)-Antichymotrypsin is known to reinforce the formation of \(\beta\)-amyloid deposits and could thereby directly affect the development of dementia. We could not confirm a positive association between HsCRP and the risk of dementia.

Both fibrinogen and HsCRP are acute-phase proteins, and high levels serve as nonspecific markers for inflammatory disease. The correlation between these 2 markers is high (0.40 with a \(P<0.001\)). Because we found that fibrinogen was independently associated with the risk of dementia, whereas HsCRP was not, other properties of fibrinogen play a role. Fibrinogen is an inflammatory marker, as well as an important factor in the coagulation cascade. It is also a major determinant of plasma viscosity and affects endothelial function.\(^3\) Hyperfibrinogenemia may lead to reduced blood flow and enhanced thrombosis. These hemostatic properties can explain the association with dementia. We cannot exclude that increased fibrinogen levels occur as an epiphenomenon of dementia-related processes and are not causally related. However, there is mounting evidence that vascular factors play a role in cognitive decline and dementia, both the vascular dementia and the Alzheimer disease subtype.

The role of plasma fibrinogen in the pathogenesis of dementia is not known. In a cross-sectional study, Stott et al\(^18\) showed raised levels of plasma fibrinogen in patients with ischemic stroke and vascular dementia. Other case-control studies did not find significant differences in the levels of fibrinogen between patients with vascular dementia or Alzheimer disease and controls.\(^19,20\) To our knowledge, the association of fibrinogen and vascular dementia and Alzheimer disease has not been studied in a large, prospective population-based setting.

High levels of fibrinogen are associated with cerebrovascular disease, which may explain the association with dementia. Because adjustment and censoring for previous or incident stroke did not change the association, other mechanisms might be suggested. Possibly, small vessel disease (white matter lesions) or silent cerebral infarction mediates the association. Silent brain infarcts are common in an elderly population and are associated with the risk of dementia.\(^21\)

In patients with symptomatic small vessel disease, fibrinogen has been correlated with the amount of leukoaraiosis.\(^22\) Also, significantly higher levels of fibrinogen in plasma have been

### TABLE 3. Hazard Ratio (95% CI) for Alzheimer Disease (124 cases) and Vascular Dementia (31 cases)

<table>
<thead>
<tr>
<th>Fibrinogen, g/L</th>
<th>Alzheimer Disease</th>
<th>Vascular Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per SD increase</td>
<td>Model 1*</td>
<td>Model 2†</td>
</tr>
<tr>
<td>1st quintile</td>
<td>1.23 (1.04 to 1.46)</td>
<td>1.25 (1.04 to 1.49)</td>
</tr>
<tr>
<td>2nd quintile</td>
<td>1.46 (0.73 to 2.91)</td>
<td>1.60 (0.77 to 3.35)</td>
</tr>
<tr>
<td>3rd quintile</td>
<td>1.38 (0.71 to 2.70)</td>
<td>1.55 (0.75 to 3.20)</td>
</tr>
<tr>
<td>4th quintile</td>
<td>1.27 (0.65 to 2.49)</td>
<td>1.16 (0.55 to 2.45)</td>
</tr>
<tr>
<td>5th quintile</td>
<td>1.75 (0.92 to 3.33)</td>
<td>1.95 (0.96 to 4.00)</td>
</tr>
</tbody>
</table>

\(P\) trend 0.17 | 0.20 | 0.32 | 0.001 | 0.002 | 0.04

*Adjusted for age and sex; †Adjusted for age, sex, current smoking, presence of apoE e4 allele, body mass index, presence of diabetes mellitus, systolic blood pressure, diastolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, atherosclerosis sum score, and previous stroke; ‡Adjusted for age, sex, \(C\)-reactive protein, and white blood cell count.

### TABLE 4. The Association Between C-Reactive Protein and Risk of Dementia

<table>
<thead>
<tr>
<th>CRP, mg/L</th>
<th>Per SD increase in (CRP)</th>
<th>Model 1*</th>
<th>Model 2†</th>
<th>Model 3‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st quintile</td>
<td>0.79 (0.56 to 1.11)</td>
<td>0.79 (0.56 to 1.11)</td>
<td>0.79 (0.56 to 1.11)</td>
<td>0.79 (0.56 to 1.11)</td>
</tr>
<tr>
<td>2nd quintile</td>
<td>0.66 (0.46 to 0.93)</td>
<td>0.66 (0.46 to 0.93)</td>
<td>0.66 (0.46 to 0.93)</td>
<td>0.66 (0.46 to 0.93)</td>
</tr>
<tr>
<td>3rd quintile</td>
<td>0.63 (0.44 to 0.89)</td>
<td>0.63 (0.44 to 0.89)</td>
<td>0.63 (0.44 to 0.89)</td>
<td>0.63 (0.44 to 0.89)</td>
</tr>
<tr>
<td>4th quintile</td>
<td>0.69 (0.47 to 1.01)</td>
<td>0.69 (0.47 to 1.01)</td>
<td>0.69 (0.47 to 1.01)</td>
<td>0.69 (0.47 to 1.01)</td>
</tr>
<tr>
<td>5th quintile</td>
<td>0.86 (0.64 to 1.13)</td>
<td>0.86 (0.64 to 1.13)</td>
<td>0.86 (0.64 to 1.13)</td>
<td>0.86 (0.64 to 1.13)</td>
</tr>
</tbody>
</table>

\(P\) trend 0.24 | 0.50 | 0.30 | 0.001 | 0.002 | 0.04

*Adjusted for age and sex; †Adjusted for age, sex, current smoking, presence of apoE e4 allele, body mass index, presence of diabetes mellitus, systolic blood pressure, diastolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, atherosclerosis sum score, and previous stroke; ‡Adjusted for age, sex, fibrinogen, and white blood cell count.
found in patients with silent (lacunar) infarction. In the Austrian stroke prevention study, higher serum fibrinogen levels were independently associated with white matter intensities and lacunar lesions on MRI. Because we do not have imaging in this population, we were unable to assess this. We found a strong association with vascular dementia (notwithstanding the small number of incident cases; n=31), which supports the hypothesis of a vascular mechanism. If fibrinogen plays a causal role in both vascular dementia and Alzheimer disease through vascular disease, then new perspectives regarding treatment emerge. Modifying components of coagulation and blood viscosity, such as fibrinogen, could be beneficial in prevention and control of dementia.

Acknowledgments

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References


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