Insertion/Deletion Polymorphism in the Angiotensin-Converting Enzyme Gene and Risk of and Prognosis After Myocardial Infarction

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Objectives. We sought to prospectively investigate whether genetic variation at the angiotensin-converting enzyme gene locus defined by an insertion (I)/deletion (D) polymorphism influences the risk of myocardial infarction or prognosis after infarction, or both.

Background. It has been suggested that the deletion allele of the angiotensin-converting enzyme gene, and specifically the DD genotype, may increase the risk of myocardial infarction, although previous studies have produced conflicting reports. No studies have yet examined the effect of I/D polymorphism on survival after infarction.

Methods. Angiotensin-converting enzyme genotypes in 684 patients with myocardial infarction recruited at the time of the acute event through coronary care units in two centers were compared with those of 537 control subjects recruited from the base populations. All patients were followed up to assess the impact of the angiotensin-converting enzyme genotype on prognosis.

Results. We found no difference (p = 0.89) in the genotype distribution between patients and control subjects (patients DD 31%, ID 47%, II 22%; control subjects DD 30%, ID 48%, II 22%). The odds ratio for myocardial infarction for DD compared with II/ID genotype adjusted for age, gender and center was 1.16 (95% confidence interval [CI] 0.82 to 1.65, p = 0.44). The study had 90% power to detect a 1.5-fold increase in risk of myocardial infarction associated with the DD genotype. For one center, data were available for other risk factors (hypertension, diabetes, angina, previous myocardial infarction, smoking, body mass index, total and high density lipoprotein cholesterol) in both patients and control subjects. In a stepwise logistic regression analysis the odds ratio for DD versus ID/II genotypes remained nonsignificant (1.44, 95% CI 0.84 to 2.46, p = 0.20) for these subjects. Over a median follow-up period of 15 months (range 3 to 22), 155 patients (22.7%) died. There was no difference in mortality between subjects with the DD genotype and those with ID/II genotypes. (21.8% vs. 23.1%, p = 0.25). Likewise, there was no difference in the distribution of survival times in the two groups (p = 0.62). The study had 70% power to detect a 1.5-fold increase in mortality during follow-up associated with the DD genotype.

Conclusions. We conclude that in the groups studied, genetic variation at the angiotensin-converting enzyme gene locus defined by I/D polymorphism does not significantly influence either the risk of or the short- to medium-term prognosis after myocardial infarction.

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chromosome 17, and is characterized by an insertion/deletion polymorphism based on the presence (insertion [I]) or absence (deletion [D]) within intron 16 of a 287-base pair alu repeat sequence, resulting in three genotypes (DD and II homozygotes and ID heterozygotes) (7). The DD genotype is associated with an ~two-fold increase in plasma angiotensin-converting enzyme activity over that of the II genotype, with intermediate levels in the heterozygotes (7). In 1992, in a retrospective multicenter, case-control study, Cambien et al. (5) reported that the frequency of the DD genotype was also increased in patients recruited 3 to 9 months after myocardial infarction. The frequency was particularly increased in patients considered to be at low risk of infarction on the basis of body weight and apolipoprotein B levels. Since then, studies both supporting the finding (8–16) as well as those questioning the veracity of the association (17–19) have been published, leading to uncertainty about the importance of the polymorphism.

A major limitation of several studies (5,14,17,19) has been the recruitment of patients with myocardial infarction several months if not years after the event, raising the possibility that selective survival may have influenced the results. In addition, no study has specifically examined the effect of the angiotensin-converting enzyme genotype on survival after myocardial infarction. This is potentially a very important issue, not only because it may identify a novel factor influencing prognosis after myocardial infarction but also because angiotensin-converting enzyme inhibitors have been shown to improve survival after infarction (20–22) and possibly decrease the incidence of recurrent infarction (20). In this study, we therefore examined the association of the angiotensin-converting enzyme DD genotype with myocardial infarction in patients recruited at the time of admission with acute infarction and also investigated the influence of the angiotensin-converting enzyme genotype on prognosis up to 22 months after infarction in this group.

Methods

Study group. The study patients were recruited from patients admitted to the coronary care units at the Leicester Royal Infirmary, Leicester and the Royal Hallamshire Hospital, Sheffield who satisfied the World Health Organization criteria for myocardial infarction in terms of symptoms, serum cardiac enzyme elevations or electrocardiographic (ECG) changes (23). The two coronary care units, each serving ~300,000 persons, account for the majority (>65%) of patients admitted with myocardial infarction in the two cities. The period of recruitment was between July 1993 and April 1994 in Leicester and between May 1993 and December 1994 in Sheffield. In both centers, >95% of eligible patients were recruited.

In Leicester, control subjects were recruited from adult visitors of patients with noncardiovascular illnesses on general medical, surgical, orthopedic and obstetric wards to provide subjects likely to be representative of the source population from which the study patients came. Subjects who reported a

history of coronary heart disease were identified but not excluded. Patients and control subjects completed a standard questionnaire about their personal history, had their height and weight measured and provided blood samples for genotype analysis and measurement of serum total and high density lipoprotein cholesterol. In Sheffield, a local hospital staff and student population was used as the control group. Age and gender were recorded and blood was taken for genotype analysis only. The studies in both centers were approved by the respective local clinical research ethics committees.

Determination of angiotensin-converting enzyme genotypes. Deoxyribonucleic acid (DNA) was prepared from a small aliquot of whole blood collected in ethylenediamine tetraacetic acid by using a DNA extraction matrix (Instagene, Biorad, Hemel Hempstead, Hertfordshire, England). Genotypes were determined by polymerase chain reaction amplification of the I/D region of the angiotensin-converting enzyme gene using oligonucleotide primers and resolving the amplified products (I allele = 490 base pairs, D allele = 190 base pairs) on 1.5% agarose gels containing ethidium bromide as previously described (24) with modifications to prevent mistyping of I/D individuals as DD homozygotes (25). Blank controls were routinely included with each set of amplifications to exclude contamination. Genotypes were determined without knowledge of the case-control status and, as a further check, 20% of subjects were randomly chosen to undergo repeat genotyping with the use of freshly prepared DNA. In all cases the previously assigned genotype was confirmed.

Biochemical measurements. Serum total and HDL cholesterol were measured by using a Kodak Ektachem E700 CXR Automatic Analyzer in a quality-controlled hospital biochemistry laboratory. In patients, the first blood sample taken after admission was used for the analysis.

Patient follow-up. Information on patients who died during their stay in the coronary care unit or in the hospital was obtained from the clinical notes. All patients who were discharged were flagged in the United Kingdom National Health Service Central Register for notification to us of their death. Through this mechanism a 100% mortality follow-up was obtained. Follow-up was carried out to April 1995.

Statistical analysis. Distribution of angiotensin-converting enzyme I/D genotypes and qualitative risk factors between patients and control subjects or different genotype groups were compared by using the chi-square test. Quantitative sample means were compared by analysis of variance. Odds ratios and 95% confidence intervals (CI) estimating the relative risk of myocardial infarction associated with the DD genotype were calculated by using the Mantel-Haenszel method with stratification, where described, for age, gender and center. Logistic regression was used to analyze the influence of other factors on the odds ratio. Mortality rates at specified time points between patients with different genotypes were compared by the Mantel-Haenszel method and survival time distributions were compared by using the generalized Wilcoxon (Breslow) test.
In all, 684 patients and 537 control subjects from the two centers were analyzed (Table 1). More than 90% of the patients and control subjects in both centers were white. The distribution of the angiotensin-converting enzyme I/D genotypes in the two groups is shown in Table 2. The D allele frequency in the Leicester and Sheffield control groups was 52.7% and 54.2%, respectively, and in both centers the genotype frequencies were in agreement with the frequencies predicted by the Hardy-Weinberg equilibrium. Despite the significant difference in age between the control subjects in the two centers (Table 1), the angiotensin-converting enzyme genotype frequencies were very similar between the two groups (Table 2) and in neither center nor in the overall study group did the genotype frequencies differ between patients and control subjects (Table 2). The crude odds ratio for myocardial infarction for DD compared with II/ID genotypes was 1.06 (95% CI, 0.82 to 1.36, p = 0.67) and when adjusted for age, gender and center the ratio was 1.16 (95% CI 0.82 to 1.65, p = 0.44). A total of 135 patients (19.7%) had had a previous myocardial infarction. The odds ratio remained nonsignificant (1.26 [95% CI 0.86 to 1.84], p = 0.25) when the analysis was restricted to index (first myocardial infarction) patients and control subjects (26). The relative risk of the DD genotype was higher in patients with previous angina and myocardial infarction were all higher in the patients (Table 3). Body mass index was similar in the two
groups. Data on total and HDL cholesterol levels were available for 75% of patients and 97% of control subjects and did not differ between groups. Although somewhat surprising, the finding is similar to that seen in other studies such as the Framingham study (26). Cholesterol levels can decrease by up to 25% within 48 h after myocardial infarction, and this decrease may have masked differences, although efforts were made to minimize this effect by measuring lipids on the first sample obtained soon after admission. A more likely explanation is that although the risk of myocardial infarction is clearly increased in persons with elevated cholesterol levels, in populations with a high average cholesterol level it is not a good discriminator between patients and control subjects (26). In stepwise logistic regression analyses on the Leicester patients and control subjects, the odds ratio for myocardial infarction for DD versus II/ID adjusted for the above factors in addition to age and gender remained nonsignificant (1.44 [95% CI 0.84 to 2.46], p = 0.20). In the study by Cambien et al. (5), the relative risk of the DD genotype was higher in patients with values for body mass index and apolipoprotein B below the median values of these variables in the control subjects. However, in a comparable analysis, we found no differences in the distribution of genotypes between our patients and control subjects (p = 0.49) when the analysis was restricted to those with body mass index and total cholesterol less than the median values for the control subjects (25.3 kg/m² and 5.6 mmol/liter, respectively). The odds ratio for DD versus II/ID genotypes for this subanalysis was 1.03 (95% CI 0.41 to 2.59, p = 0.93).

Characteristics of patients with myocardial infarction combined from both centers grouped on the basis of angiotensin-
ACE gene and myocardial infarction

Table 4. Characteristics of Patients With Myocardial Infarction According to Angiotensin-Converting Enzyme Genotype

<table>
<thead>
<tr>
<th></th>
<th>DD (n = 209)</th>
<th>ID (n = 321)</th>
<th>II (n = 154)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>65.2 ± 12.0</td>
<td>65.7 ± 11.2</td>
<td>66.5 ± 11.3</td>
<td>0.52</td>
</tr>
<tr>
<td>Men</td>
<td>69%</td>
<td>65%</td>
<td>63%</td>
<td>0.39</td>
</tr>
<tr>
<td>Previous MI</td>
<td>17%</td>
<td>20%</td>
<td>23%</td>
<td>0.29</td>
</tr>
<tr>
<td>Hypertension</td>
<td>34%</td>
<td>35%</td>
<td>31%</td>
<td>0.63</td>
</tr>
<tr>
<td>Diabetes</td>
<td>11%</td>
<td>11%</td>
<td>9%</td>
<td>0.75</td>
</tr>
<tr>
<td>Current smokers</td>
<td>35%</td>
<td>32%</td>
<td>29%</td>
<td>0.39</td>
</tr>
<tr>
<td>Total cholesterol (mmol/liter)*</td>
<td>5.8 ± 1.3</td>
<td>5.6 ± 1.1</td>
<td>5.5 ± 1.4</td>
<td>0.36</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/liter)*</td>
<td>1.2 ± 0.3</td>
<td>1.2 ± 0.3</td>
<td>1.3 ± 0.4</td>
<td>0.45</td>
</tr>
<tr>
<td>Body mass index (kg/m²)*</td>
<td>26.0 ± 4.1</td>
<td>26.2 ± 3.9</td>
<td>25.0 ± 3.5</td>
<td>0.12</td>
</tr>
<tr>
<td>Site of infarction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterolateral</td>
<td>47</td>
<td>43</td>
<td>42</td>
<td>0.55</td>
</tr>
<tr>
<td>Inferoposterior</td>
<td>45</td>
<td>52</td>
<td>51</td>
<td>0.26</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>8</td>
<td>5</td>
<td>7</td>
<td>0.32</td>
</tr>
<tr>
<td>Peak CK value (IU/liter)</td>
<td>1,788 ± 1,425</td>
<td>1,933 ± 1,786</td>
<td>1,981 ± 1,395</td>
<td>0.71</td>
</tr>
</tbody>
</table>

*Leicester patients only. Data presented are mean value ± SD or percent of group. CK = creatine kinase; HDL = high density lipoprotein; MI = myocardial infarction.

converting enzyme genotype are shown in Table 4. There was no difference between the genotype groups with respect to either preexisting risk factors or the site or size of myocardial infarction as judged by highest creatine kinase levels. For all patients, survival status was analyzed at the end of April 1995, allowing a median follow-up period of 15 months (range 3 to 22). By using the National Health Service Central Register, to which all deaths in the United Kingdom must be statutorily notified, 100% mortality follow-up was obtained. At the censoring point, 155 of the total cohort of 684 patients had died, giving an overall mortality rate of 22.7%. There was no difference in mortality between patients with the DD genotype and those with the ID/II genotypes (46 [21.8%] or 212 versus 109 [23.1%] or 472, p = 0.25). Figure 1 shows the cumulative mortality curves (calculated by the Kaplan-Meier method) for DD and II/ID genotypes. There was no difference in the distribution of survival times in the two groups (p = 0.62). The difference remained insignificant (p = 0.98) when analysis was restricted to index cases.

Discussion

In this study we provide further insights on the involvement of genetic variation at the angiotensin-converting enzyme gene locus in cardiovascular disease. The topic has aroused great interest since the report of Cambien et al. (5) associating the DD genotype at the locus with increased risk of myocardial infarction and subsequent reports indicating an association of this genotype with other cardiovascular disorders such as left ventricular hypertrophy (27) and restenosis after coronary angioplasty (28). The fact that the DD genotype is also associated with higher plasma (6) and tissue (29) angiotensin-converting enzyme levels compared with ID and II genotypes and that angiotensin-converting enzyme plays a crucial role in the generation of angiotensin II and the degradation of bradykinin, two powerful vasoactive molecules (6), has provided a plausible potential intermediary phenotype through which its effects on cardiovascular phenotypes could be manifested. In this context, it is perhaps important to bear in mind that the I/D polymorphism, located in intron 16, is probably not directly responsible for the effect of the locus on angiotensin-converting enzyme levels (and therefore presumably cardiovascular risk) but is simply acting as a marker for an as yet undefined susceptibility polymorphism (Ss) at the locus (30).

Angiotensin-converting enzyme gene I/D polymorphism and risk of myocardial infarction. Since the report of Cambien et al. (5), several studies have examined the role of angiotensin-converting enzyme I/D polymorphism in coronary artery disease by using a variety of approaches (8–19). In addition to its association with myocardial infarction in Amer-
ican (14) and Japanese (12) subjects, the DD genotype has been reported to be more frequent in European (8) and Scandinavian (9) children and Australian (15) grandchildren of persons with a history of coronary events; in Irish subjects with a fatal myocardial infarction (10); in French patients with non-insulin-dependent diabetes and clinical coronary heart disease (11); and in low risk Welsh subjects with coronary heart disease identified by use of a Rose questionnaire and ECGs (13). Despite these reports, other equally if not more robust studies failed to observe any association of the genotype with myocardial infarction or angina, or both, in Scandinavian (17), American (18) or New Zealand (19) subjects. Disparate results have also been reported in relation to other phenotypes (28,31,32). In addition, although Ludwig et al. (14) found an association with myocardial infarction, their subjects with the DD genotype did not have more extensive coronary stenosis, thereby suggesting that the genotype may influence not the process of atherogenesis but events causing the conversion to myocardial infarction and raising doubts about reported associations with manifestations of coronary artery disease not related to infarction. A recent study in Japanese subjects (33) found subjects with the DD genotype to be more prone to ergonovine-induced coronary artery spasm at cardiac catheterization. As coronary artery spasm may contribute to the pathogenesis of myocardial infarction (34), this relation could provide an alternative mechanism by which the DD genotype may selectively increase the risk of myocardial infarction.

In this study, in almost 700 predominantly white patients with myocardial infarction collected through coronary care units in two British cities, we found no excess of the DD genotype compared with the level in control subjects. Our findings, based on the largest collection of myocardial infarction cases so far, concur more with the negative findings of the more recent reports (18,19) investigating the role of the angiotensin-converting enzyme locus in coronary artery disease. An important feature of our study, in contrast to several others (5,14,17,19), is that the patients with myocardial infarction were recruited consecutively at the time of their acute event, thereby reducing the possibility that genotype-related selective survival influenced the findings. In addition, our follow-up findings suggest that this is probably not so in any case (see later).

A critical feature of any association study is the control subjects, who need to provide a reliable estimate of the genotype frequencies in the base population from which the study patients are recruited. In this study, control subjects were recruited in different manners in the two centers. In Leicester, they were recruited concurrently with the patients with myocardial infarction from persons visiting patients admitted to the hospital for a wide range of conditions. From information in our coronary care unit data base on the age and gender distribution of the patients with myocardial infarction admitted to the coronary care unit in the previous year, we attempted to recruit control subjects of a mix similar to that of the patients with probable myocardial infarction, although no individual willing to participate was excluded. In Sheffield, a much younger cohort of control subjects, again unselected, was obtained from hospital workers and students. Despite this difference, the genotype distributions were remarkably similar in the two control groups and to those of control groups reported in several other studies (5,13,14,17–19). Thus, we believe that our control cohorts provide a reliable estimate of the prevalent distribution of genotypes in their respective populations.

In some studies, the coronary risk associated with the DD genotype has been found to be either increased (5) or only present (13) in subjects described as at low risk on the basis of selected classic risk factors. Because most coronary risk factors act additively or synergistically (1,4), the explanation for this finding is unclear. In our study we examined several factors but were unable to identify any that significantly influenced the effect of the angiotensin-converting enzyme genotype, although our analysis was at reduced power because of a combination of smaller group sizes and incomplete information. In this respect, as well as overall, our findings agree with those reported by Lindpaintner et al. (18) in subjects of the American Physicians study.

The reasons for the discrepant findings in different studies remain unclear. In addition to the choice of control subjects and the timing of collection of cases (see earlier), possibly important genetic and environmental influences may vary between populations. For example, Tiret and coworkers (35) recently reported synergistic effects of angiotensin-converting enzyme and angiotensin-II type 1 receptor gene polymorphisms on risk of myocardial infarction in the patients of the original study by Cambien et al. (5). The frequencies of the two angiotensin-converting enzyme alleles have been shown to vary among ethnic populations (36); thus, ethnic heterogeneity between patients and control subjects may also confound an association. In our study >90% of both patients and control subjects were white. Exclusion of nonwhite subjects did not affect the result (data not shown), although we cannot exclude subtle heterogeneity within the white patients and control subjects. As indicated earlier, the I/D polymorphism is probably only a marker for the putative susceptibility polymorphism and the relation between the two may also vary between populations.

Apart from biologic explanations, statistical factors need to be considered. Despite reaching different conclusions, the 95% CI of the odds ratio for DD versus ID/II genotypes for most of the positive and negative studies (5,12,14,18,19) are wide and overlap, thus suggesting that the findings may be less heterogeneous than at first sight and partly reflect the statistical power of the studies to detect or exclude an effect. Further studies are therefore required to investigate the various possibilities and to determine the precise impact of genetic variation at the angiotensin-converting enzyme gene locus on risk of myocardial infarction. Nonetheless, what is perhaps equally important is whether the marker will be clinically useful in evaluating risk of myocardial infarction. From this perspective, our study had 90% power (alpha 0.05) to detect a 1.5-fold increase in risk of myocardial infarction associated with the
DD genotype. Thus, as it stands, our findings suggest that, at least in our populations, the angiotensin-converting enzyme I/D polymorphism is not a useful marker for assessing the risk of myocardial infarction.

**Angiotensin-converting enzyme gene I/D polymorphism and prognosis after myocardial infarction.** Patients who have had a myocardial infarction have a much increased standardized mortality ratio over the next few years, with further cardiovascular events being the main causes of death (37). Several factors are known to influence postmyocardial infarction prognosis including size of infarction and residual left ventricular function (38). In the last few years, several major clinical trials (20–22) have demonstrated a significant improvement in prognosis in patients treated with inhibitors of angiotensin-converting enzyme. The precise mechanisms underlying the beneficial effects of angiotensin-converting enzyme inhibitors remain to be fully elucidated, although a major contribution may be through a limitation of infarct expansion and cardiac remodeling (39). In experimental studies (40), angiotensin-converting enzyme has been shown to be induced in the left ventricle in heart failure after myocardial infarction. Given the impact of the angiotensin-converting enzyme genotype on angiotensin-converting enzyme levels (6,28), the observation that the DD genotype may adversely influence prognosis in hypertensive subjects (41), and the finding in an exploratory study (42) that the DD genotype may be associated with increased ventricular dilation after an anterior myocardial infarction, two obvious and clinically important questions arise: 1) does the angiotensin-converting enzyme genotype influence prognosis after myocardial infarction, and 2) are the beneficial effects of angiotensin-converting enzyme inhibitors related to the angiotensin-converting enzyme genotype? To examine the first question we followed up all our patients with myocardial infarction for 3 to 22 months (median 15). Although the overall mortality rate was similar to that reported in other series (20,21), we found no difference in the survival of patients with the DD genotype versus those with the II or ID genotype. The study had 70% power to detect a 1.5-fold increase in mortality during the follow-up period associated with the DD genotype. Thus, it would seem that genetic variation at the angiotensin-converting enzyme gene locus defined by angiotensin-converting enzyme I/D polymorphism by itself is not a major determinant of prognosis after myocardial infarction. However, our study cannot provide an answer to the second question. To examine this question correctly, one would ideally need to prospectively treat all patients with myocardial infarction (or predefined subjects with specific features, such as left ventricular dysfunction) with an angiotensin-converting enzyme inhibitor, maintain them on this treatment for the duration of the study and assess whether the prognosis then varies according to angiotensin-converting enzyme genotype. Such a study remains to be done, although it may be possible to obtain some information on this question from examining the treated groups in some of the postmyocardial infarction angiotensin-converting enzyme inhibitor trials (20–22).

**Limitations of study.** Although we found no differences in the genotype frequencies in our two control cohorts, which also agree with genotype frequencies observed in other white populations, the imbalance in age of patients and control subjects, particularly in the Sheffield arm of the study, remains problematic, at least theoretically. However, the limited data on age-related changes in angiotensin-converting enzyme genotype frequencies are conflicting. In one study, there was a decline in DD genotype frequency with age in hypertensive patients (41), whereas in another study (43) the DD genotype was paradoxically, overrepresented in older compared with younger subjects. The age issue could be particularly relevant in women because of the additional impact of the postmenopausal status on cardiac risk. No studies to date have reported a significant effect of the angiotensin-converting enzyme genotype on risk of myocardial infarction in women, and this requires specific evaluation in appropriately powered studies.

To try to avoid a possible confounding effect of angiotensin-converting enzyme genotype on early survival we recruited subjects as soon as possible (within 12 h) after admission to the coronary care unit. However, it is well recognized that a significant proportion of patients with acute myocardial infarction die before they enter the hospital. If the DD genotype increases the risk not only of myocardial infarction but also of very early death, it is possible that an impact of the genotype could have been missed despite early recruitment on the coronary care unit, as the two effects would tend to cancel out each other. There is some retrospective evidence that the angiotensin-converting enzyme genotype may increase the risk of fatal myocardial infarction (10), but the question of genotype effect on very early mortality can really be answered only by population-based prospective studies with postmortem confirmation of cause of death.

Finally, because we did not systematically collect information on medications that the patients were taking at the time of admission or during the follow-up period, we cannot exclude the possibility of an interaction between specific drugs, especially angiotensin-converting enzyme inhibitors, and angiotensin-converting enzyme genotype on either risk of myocardial infarction or subsequent survival.

**Conclusions.** In summary, in a two-center study of patients with myocardial infarction recruited at the time of infarction, we were unable to demonstrate a significant effect of variation at the angiotensin-converting enzyme gene locus defined by the I/D polymorphism on either risk of or prognosis after myocardial infarction. We conclude that, at least in the groups studied, angiotensin-converting enzyme gene typing will not provide clinically valuable information toward assessing the risk of myocardial infarction or the prognosis after it.

**References**

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