Research article

**Design and intermediate results of the Lower Extremity Arterial Disease Event Reduction (LEADER)* trial of bezafibrate in men with lower extremity arterial disease**

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**Abstract**

**Background** Raised levels of both triglycerides and fibrinogen, each of which are reduced by bezafibrate, may contribute to lower extremity arterial disease (LEAD). This condition is characterized by a particularly high incidence of coronary heart disease (CHD) and stroke, but is little studied thus far in randomised controlled trials.

**Method** Patients were recruited through 85 practices in the British Medical Research Council General Practice Research Framework and through nine hospital vascular clinics. The treatment regimen, which is double-blind and placebo-controlled, is bezafibrate 400 mg/day. The 1568 patients recruited represent 86% of those eligible at screening.

**Results** None of the anticipated side effects (mainly gastrointestinal) differed between the two groups. Nearly 80% of the total person-years accrued at 3 years were spent on trial treatment. Bezafibrate significantly reduced total cholesterol by approximately 8.0% and low-density lipoprotein (LDL)-cholesterol by approximately 9.0%, and increased high-density lipoprotein (HDL)-cholesterol by approximately 11.0% initially, falling to about 6.0% at 3 years. Triglycerides were significantly reduced by about 23.0% and fibrinogen by about 14.0%. Plasma creatinine rose by approximately 11% in those on active treatment. All of these effects were highly significant (P<0.0001). Bezafibrate had no effect on the level of C-reactive protein (CRP).

**Conclusion** The trial recruited an unusually high proportion of eligible patients, ensuring the general applicability of its results. The fibrinogen-lowering and lipid-modifying effects of bezafibrate were confirmed. Although bezafibrate lowers fibrinogen, it has no effect on CRP; this suggests that the reduction in fibrinogen is due to an effect on its metabolism rather than suppression of an inflammatory response.

**Keywords** arterial disease, bezafibrate, fibrinogen, lipid profile

**Introduction**

Accumulating epidemiological and clinical results [1–3] show strong associations of high plasma fibrinogen levels with both the onset and progression of arterial disease at all three main sites (ie heart, brain and lower extremities). High levels are also associated with venous thrombosis.

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CHD = coronary heart disease; CRP = C-reactive protein; HDL = high-density lipoprotein; LDL = low-density lipoprotein; LEAD = lower extremity arterial disease; LEADER = Lower Extremity Arterial Disease Event Reduction (trial).
[4], and there is some evidence [5] that they impair the outcome of interventions such as percutaneous coronary angioplasty. Laboratory studies have indicated how fibrinogen affects several pathways that are known or suspected to be involved in thrombogenesis, principally the degree of blood viscosity, the amount of fibrin produced when the coagulation process is initiated, clot deformability, platelet aggregability and atherogenesis [6]. This evidence suggests that high fibrinogen levels are of causal significance. On the other hand, studies of polymorphisms associated with fibrinogen levels [7,8] have been equivocal regarding the relationship of the former with clinical events of CHD.

Thus, the effects of lowering levels of fibrinogen need to be established through randomised trials so that the role of fibrinogen can be clarified, as well as identifying the clinical implications. This additional evidence would be necessary anyway, as it was for cholesterol, but particularly because of the view that raised fibrinogen levels are an acute-phase or chronic-phase response to the inflammatory nature of atheroma, and are therefore merely markers of underlying vessel wall disease and have no pathogenetic significance.

Apart from ancrord, which is used only in emergency situations and has to be given by infusion, there are at present no selective fibrinogen-lowering agents. However, most fibrates, including bezafibrate, lower fibrinogen levels as well as having the lipid-modifying properties for which they were originally introduced. Depending crucially on the extent to which it may or may not eventually be possible to apportion any clinical benefits between its fibrinogen-lowering and lipid-modifying effects, trials of bezafibrate may therefore offer opportunities for assessing the effects of lowering fibrinogen levels.

The Lower Extremity Arterial Disease Event Reduction (LEADER) trial of bezafibrate is being carried out in men with LEAD. This condition was selected partly because raised levels of triglycerides may be contributory [9] and the greatest effect of bezafibrate is in lowering triglycerides, but also because of the high incidence of CHD events and strokes in patients with LEAD.

Recruitment to the trial started in 1992 and was almost completed in 1997, with a few further entrants in 1998. The present report describes the procedures and early stages of the trial, and the treatment effects of bezafibrate on fibrinogen, lipids and other variables during the first 3 years.

Method

Recruitment

LEADER is being carried out in men on the lists of 85 practices throughout the UK in the British Medical Research Council General Practice Research Framework practices, patients with suspected or definite LEAD were identified either through diagnostic indices or through a listing of those taking any medications that may be used in treating LEAD and its complications. The research nurses then reviewed the notes of all of these men in order to exclude those who did not in fact have LEAD. Men with LEAD were ineligible for the following reasons: unstable angina, unless or until it was controlled; serum total cholesterol less than 3.5 mmol/l or more than 8.0 mmol/l (discussed in further detail below); significant renal or hepatic disease; a known hepatitis B or C or HIV positive status; malignant disease (other than non-melanoma skin cancer) within the past 5 years; they were taking or likely to need lipid-lowering agents or monoamine oxidase inhibitors; they were unlikely to comply with trial treatment or procedures; they were in another trial; or at the discretion of the general practitioner for other reasons. There were no upper or lower age limits. Those who had had a myocardial infarct or stroke were eligible for the trial provided that their general management was stable, again at the discretion of the general practitioner.

Men were then sent an invitation to attend a screening visit for an explanation of the trial. At the following baseline medical examination at least 1 week later for those willing to proceed, eligibility for the trial was confirmed by a positive response to the Edinburgh Claudication Questionnaire administered by the research nurse. Occasional atypical responses, such as pain on walking in the thigh or buttock, but not in the calf, were assessed by the doctor, although LEAD was confirmed at a second visit or at the discretion of the general practitioner for other reasons. There were no upper or lower age limits. Those who had had a myocardial infarct or stroke were eligible for the trial provided that their general management was stable, again at the discretion of the general practitioner.

Apart from fibrinogen (Clauss method), total cholesterol, LDL-cholesterol (calculated) and HDL-cholesterol (precipitation method) levels, triglycerides (non-fasting), creatinine of 150 µmol/l or more, because both of these situations increase the risk of muscle necrosis in those taking bezafibrate. All blood tests were performed twice before starting treatment: once at the baseline medical examination and again a day or so before the men started taking tablets.

Apart from fibrinogen (Clauss method), total cholesterol, LDL-cholesterol (calculated) and HDL-cholesterol (precipitation method) levels, triglycerides (non-fasting), creatinine and alkaline phosphate were also measured, alkaline phosphatase providing a measure of compliance with treatment. LDL-cholesterol could not be measured directly, so there may be some imprecision in the results from men with high triglyceride levels (which were from non-fasting samples in order to ensure that as high a proportion as possible of those eligible would enter and remain in the trial).
Men completed questionnaires on symptoms, mostly the known possible side effects of bezafibrate, but also other symptoms such as impotence that are often attributed to treatment by older men, and on quality of life and use of health and related services. In some practices tests of cognitive function and of visual acuity were carried out because high fibrinogen levels may impair cerebral blood flow through its influence on viscosity [10] and contribute to age-related macular degeneration [11], either or both of which might therefore benefit from fibrinogen lowering.

Procedures in the hospital clinics were similar, apart from the initial identification of patients, which was through clinic attendance or diagnostic indices.

**Trial treatment**
Approximately 1 month after the medical examination, and provided that the creatinine result was within the specified limit, random assignment of trial treatment was initiated, balanced between active and placebo treatment within each practice or hospital clinic. Labels identifying containers with either active or placebo tablets were removed at the trial coordinating centre, labelled with the man’s name and trial number, and sent to the practices and hospital clinics.

Active treatment was bezafibrate 400 mg/day (Bezalip-Mono; Boehringer Mannheim UK/Roche Products Ltd, Welwyn Garden City, UK) for men with creatinine levels below 135 μmol/l and was placebo controlled, with all tablets identical in appearance. Men with entry creatinine levels between 135 and 149 μmol/l took 400 mg on alternate days. In men taking daily treatment (i.e. those with creatinine less than 135 μmol/l at entry), this was changed to alternate day treatment if levels rose to 155 μmol/l or more, in which case men were withdrawn from trial treatment. These changes were made for all men, whether they were on active or placebo treatment. (Raised creatinine levels generally fell to previous levels after withdrawal from trial treatment.)

The trial was approved by the 69 Local Research Ethics Committees that were responsible for the participating practices and hospitals. The question most frequently raised before final approval was given was whether men should routinely be taking statins, largely regardless of cholesterol levels, but particularly in those with high levels and those who had previously had myocardial infarcts. When the trial began, it was clear that expense would often preclude this, although participation in the trial would at least provide a 50% chance of receiving lipid-modifying treatment. Thus, after verbal and/or written exchanges with several committees, the entry criteria were accepted. As a matter of principle, no advice was given to the doctors responsible for the day-to-day management of recruited patients regarding treatments outside the requirements of the trial. However, the attention of general practitioners, whether in Framework practices or those responsible for patients recruited through the hospitals, was drawn to the results of the Scandinavian Simvastatin Survival Study [12], and decisions regarding treatment with a statin were left to their discretion. General practitioners and hospital doctors were also given pre-treatment cholesterol levels so that they could initiate statin treatment before trial treatment started if they wished to do so, and they were also notified regarding raised levels at follow-up visits. In 1999, the data monitoring and ethics committee of the trial recommended that reminder letters should be sent to doctors caring for all trial patients with total cholesterol levels above 7.0 mmol/l, which resulted in several men being started on statin treatment and their withdrawal from trial treatment.

**Follow up and ascertainment of endpoints**
Men were seen 1 month after treatment started and then at 3-month intervals to receive new supplies of tablets. Blood for repeat tests was taken at 1 and 3 months, and then at 6-month intervals. At the 1-month and 3-month visits men completed further questionnaires regarding symptoms and health service usage. At the annual visits, nurses asked about possible endpoint events (i.e. myocardial infarction and stroke). Details regarding such events were mostly provided by the Framework practices as they occurred, but were also sought at an annual check through the practice notes for each patient. Such details included events in those who had withdrawn from trial treatment, because these patients were nearly all known to the practices throughout the course of their routine clinical care. Few men moved from their addresses at the time of recruitment, and they will be followed up as described elsewhere [13]. In the hospitals, checks for endpoints were also made annually (as for men in the general practices). Hospital patients who withdrew from trial treatment were given change of address cards to be returned if they moved and were sent annual questionnaires about their progress. All deaths, whether in general practice or in hospital participants, were automatically notified by the National Health Service Central Registry.

All possible endpoint episodes notified were documented and assessed independently and without knowledge of trial treatment allocation [13]. Follow up for recording of events was continued in those who had withdrawn or been withdrawn from trial treatment. Initially, the occurrence of probable endpoints led to discontinuation of trial treatment. However, because patients who had had previous heart attacks or strokes were eligible for the trial and because of requests to continue treatment from some patients in whom treatment had been discontinued following an event, treatment was restarted after the acute episode was resolved and recurrent episodes were recorded. Thus, it will be possible to give results according to the numbers of men who experienced events and according to the number of events.
Participation in the trial was for a minimum of 3 years and sample size (indicated below) was based on participation for 4 years. Earlier trials in the Framework showed considerable advantages in a common finishing date, so those who entered the trial early on were asked to consider continuing until this date, and will therefore have been in the trial for up to 8 years. At 3 years, only 11 out of 340 (3.2%) men asked to continue declined to do so.

Cognitive function was re-assessed once, after 15 months, and visual acuity was assessed annually.

In just under 200 men, CRP was measured at screening and trial entry (i.e. twice before treatment start), and then at 1, 3 and 6 months. Values are log-transformed and geometric means given.

**Statistical analysis**
Cardiovascular mortality and incidence in LEAD have been reported in several studies and estimates vary. It appears probable that approximately 13% of patients with LEAD die of major coronary events or strokes over a 4-year period [15]. It has been assumed that there are 1.5 nonfatal events for each fatal event, and therefore some 33% of trial patients were likely to experience an event. Increasing the duration of participation beyond 4 years for some men and including recurrences (see above) will increase the numbers of events. About two-thirds of the men were taking platelet-active agents (mostly aspirin), and this was expected to reduce the proportion of men having an event from 33% to approximately 28% in the placebo group. Allowing for a further attenuation of any treatment effect due to 15% of men withdrawing from treatment, a 30% reduction in endpoints suggests an event-rate of approximately 20% in those on active treatment compared with 28% in those in the placebo group. This effect could be detected in 1500 men at the 5% level of significance with 80% power. CHD events, fatal and nonfatal events separately, and stroke separately are secondary endpoints.

In assessing the effect of active treatment on biochemical variables, the change from baseline within each individual was calculated and differences in these changes between groups were tested by unpaired t tests.

**Results**
**Recruitment**
Recruitment is illustrated in Fig. 1. Of approximately 3200 men invited to attend the first or screening visit (precise numbers not recorded), either in the Framework or in the hospitals, 2505 (78%) did so. Of the 2505 men who attended 937 (37%) were excluded at screening, at the baseline medical examination or at trial entry for the reasons shown in Table 1. Most of the 277 men who were considered not to have LEAD came from general practice, where identification of patients was largely through prescribing information that was often not specific for LEAD (see above). The 1568 patients entered represent 86% of the 1816 who were eligible. Inadvertently, 10 men with entry cholesterol levels of more than 8.0 mmol/l were entered.

**Characteristics of participants**
Table 2 summarizes the characteristics of the men recruited. Their mean age was 69 years, ranging from 35 to 92 years. Just over 4% claimed never to have smoked. The current smokers had smoked for 49 years on average and the ex-smokers for 39 years. Approximately two-thirds were taking platelet-active agents, nearly all of which were in the form of aspirin. Over 30% had previously had myocardial infarcts or strokes or had stable angina, this figure being more than those for individual conditions because some men had a history of more than one of them. Table 2 also shows entry values of fibrinogen and lipids.

**Symptomatic and biochemical effects of treatment**
Table 3 gives the responses from all the 15,279 on-treatment symptom questionnaires that were completed at follow-up visits up to March 2001 by men in the trial for at least 3 years. No symptoms were reported more frequently by those taking active treatment. Table 4 shows reasons for withdrawing from trial treatment for all men (i.e. regardless of treatment group), because blindness on this
The aspect will be maintained until the main results are reported. The withdrawal rate of 37.7% at 3 years was higher than anticipated, but 80% of person-years at 3 years were spent on allocated treatment. The cumulative proportions of persons who withdrew over 3 years are shown in Fig. 2. One man had to withdraw because of severe muscle pain associated with a raised creatine kinase level. Nearly all those who withdrew because of incompatible medication had begun treatment with a statin. Withdrawals classified as 'patient decision' were for a variety of mostly vague and unspecified reasons.

Fig. 3 shows the effects of treatment on lipids graphically, and the percentage changes attributable to trial treatment on these and other variables are summarized in Table 5. Active treatment led to a sustained reduction in total cholesterol of approximately 8%. There was an unexplained downward 'drift' in LDL-cholesterol levels in the laboratory.
that analysed the samples, which is reflected in the placebo group (and in all of the hospital’s routine clinical samples analysed in the laboratory concerned). Nevertheless, the effect of active treatment in raising HDL-cholesterol can be seen, although the difference declined from 10.6 to 6.2% over the 3 years. There may have been a small increase in absolute LDL-cholesterol levels as a result of the drift in HDL-cholesterol (because the calculated difference method has been used for LDL-cholesterol), but the sustained difference between the two groups represents a reduction of approximately 9% in LDL-cholesterol at 3 years attributable to active treatment. There was also a substantial reduction in triglyceride levels, as expected. Fig. 4 shows that there was a sustained reduction of approximately 14% in plasma fibrinogen attributable to active treatment.

Fig. 5a shows the expected rise in creatinine due to bezafibrate administration, initially approximately 13% and...
falling to 10% at 3 years. Fig. 5b shows a fall of about 33% in alkaline phosphate. Table 6 shows the data for alkaline phosphatase according to the proportions of men with changes of the specified magnitudes, suggesting a high level of compliance in those who remained on trial treatment.

Fig. 6 shows effects on CRP and fibrinogen levels. There were 96 men on active treatment and 92 on placebo at each timepoint for both variables. There was no effect of active treatment on CRP levels, but the effect on fibrinogen is confirmed. (Omission of those with CRP values of over 20 mg/l at any stage – probably reflecting the further short-term effect of an inflammatory response [e.g. respiratory tract infection] – also resulted in no difference between the two groups.)

**Discussion**

Thus far, clinical endpoint results have been reported from two randomised trials of bezafibrate.

The Bezafibrate Infarction Prevention trial [16,17] recruited 3090 male and female patients aged 45–74 years with an established history of CHD (78% with myocardial infarction), who had fasting total cholesterol levels between 180 and 250 mg/dl and triglyceride levels of less than 300 mg/dl. Follow-up was for 6.2 years on average (range 4.7–7.6 years). Overall, the 9.4% reduction in the combined primary endpoint of fatal or nonfatal myocardial infarction or sudden death was not statistically significant. In those whose triglyceride levels were 200 mg/dl or greater, the 39.5% reduction was significant ($P=0.02$), whereas there was no difference among those with lower levels. The net rise in HDL-cholesterol due to treatment was 14.4% (i.e. greater than in LEADER). The reduction of 25.2% in triglyceride levels in that study was similar to the reduction achieved in the LEADER trial, but the changes in cholesterol of 4.7%, LDL-cholesterol of 5.2% and fibrinogen of 10% were rather less than in LEADER.

The Bezafibrate Coronary Atherosclerosis Intervention Trial [18] was carried out in 92 survivors of myocardial infarction who were younger than 45 years with a mean serum cholesterol of at least 5.3 mmol/l and/or mean serum triglycerides of at least 1.6 mmol/l. The main purpose of that trial (which administered bezafibrate 200 mg three times a day) was to determine whether treatment could retard or prevent the progression of atherosclerotic lesions, as assessed using coronary angiography at baseline and then at 2, 3 and 5 years. This objective was achieved, and in addition three of the 47 patients receiving active treatment had coronary events as compared with 11 out of the 45 patients in the placebo group, a reduction of nearly 75% ($P=0.019$). Total cholesterol fell by 14%, LDL-cholesterol by 3.5% and triglycerides by 26.3%. HDL-cholesterol rose by 8.6%. Fibrinogen fell by 13.3%. Thus, the Bezafibrate
Infarction Prevention trial and the Bezafibrate Coronary Atherosclerosis Intervention Trial suggest that bezafibrate may result in some reduction, of uncertain magnitude, in major events of CHD.

The Diabetes Atherosclerosis Intervention Study, which used micronized fenofibrate [19], recently reported lipid-modifying effects very similar to those found in the present study. In that study angiographic progression of coronary artery disease was reduced by active treatment, and there were 38 and 50 clinical endpoints among those on active and placebo treatment, respectively, although the difference was not significant. Two trials using gemfibrozil

Table 6

<table>
<thead>
<tr>
<th>Changes in alkaline phosphatase at different time points</th>
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<td>Number of patients and change in alkaline phosphatase</td>
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<td>3–6 months</td>
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<td>n</td>
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<tr>
<td>694</td>
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<tr>
<td>Decrease ≥20%</td>
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<tr>
<td>Decrease 0–20%</td>
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<td>Increase</td>
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Percentage changes in alkaline phosphatase by treatment group between baseline and 3–6 months, and 1, 2 and 3 years, as a measure of compliance.
[20,21], which has different properties from those of bezafibrate and fenofibrate, showed that it significantly reduces clinical endpoints.

Like the other fibrate trials, the LEADER trial was conducted primarily to test whether a fibrate reduces CHD and stroke by whatever mechanism(s). Assuming that bezafibrate does reduce clinical endpoints in the LEADER trial, a further question will be how far the benefit can be attributed to its fibrinogen-lowering or lipid-modifying effects, or both. Using Cox proportional hazards models, the independent contributions to the risk of CHD and stroke of changes in fibrinogen and, say, total cholesterol between recruitment and the various follow-up intervals will be estimated for all men and for those on active or placebo treatment. This approach is very similar to that used in the Veterans Affairs High-Density Lipoprotein Intervention Trial [22]. Analyses from that study showed that the effect of gemfibrozil treatment on HDL-cholesterol predicted a significant reduction in CHD, independent of changes in LDL-cholesterol and triglyceride levels. The possibility in the Bezafibrate Infarction Prevention trial [17] that bezafibrate was beneficial in those with high triglyceride levels provides an \textit{a priori} hypothesis for analysing LEADER to determine whether there is an interaction between triglyceride values at entry and response to treatment, particularly because the main effect of bezafibrate is on triglycerides.

Trial participants in LEADER have come from general practices and hospital vascular clinics throughout the UK and a high proportion (some 86\%) of those eligible have entered. Consequently, the main results are likely to have general applicability and the entry characteristics of the participants provide a useful profile of LEAD in the community. Nearly all men are or had been smokers, only 4\% claiming never to have smoked. As expected, many had already developed clinically manifest arterial disease. Perhaps somewhat unexpectedly, entry values of fibrinogen and lipids were not grossly abnormal, entry fibrinogen and (non-fasting) triglyceride values being only moderately raised. The full reduction in fibrinogen levels in LEADER appeared to occur only after approximately 6 months on treatment (Fig. 4).

Bezafibrate did not lead to any excess of the mainly gastrointestinal symptoms that are often associated with it, and other symptoms such as rashes or impotence did not differ between the groups. The proportion of patients who withdrew from randomised treatment was higher than was assumed in our estimation of the required sample size. However, extending the duration of participation for men recruited early on has to some extent offset the effect of this difference, and many withdrawals occurred after several years of participation in the trial. Thus, even at 3 years, some 80\% of the person-years accrued in the trial were spent on randomly assigned treatment. The results on alkaline phosphatase indicate a high level of compliance in those continuing with treatment.

It has been suggested that fibrates may increase mortality from other conditions, including cancer [23], although this remains controversial. Much the greatest risk to the generally elderly men in the trial is from arterial disease, however, so that any possible increase in cancer incidence would need to be balanced against any reduction in CHD and stroke due to bezafibrate.

The extent to which the raised fibrinogen levels associated with arterial disease are due to the inflammatory characteristics of atheroma or inflammation and/or infection is debated. The contrast between the fibrinogen-lowering effect of bezafibrate and the absence of any effect on CRP is clear. CRP is a particularly sensitive index of inflammatory processes. Thus, it appears that the effect of bezafibrate on fibrinogen is independent at any rate of this index of inflammation, suggesting that any benefit due to bezafibrate on fibrinogen levels may not be mediated simply through a reduction in inflammatory stimuli. CRP levels in patients with LEAD are clearly raised, with the geometric mean being more than 3.5 mg/l in contrast to the median value of 0.8 mg/l in volunteer blood donors [24] and the geometric mean of 2.03 mg/l among 464 unselected men aged 64–75 years in the general population [25]. Further data on the effect of fibrates are needed for comparison with the larger body of evidence on statins and in view of recent reports that indicate that bezafibrate may raise homocysteine levels [26], and thus the risk of vascular events if homocysteine is eventually shown conclusively to contribute to these.

In conclusion, a high proportion (86\%) of eligible patients with LEAD were recruited. Despite withdrawals from randomised treatment, 80\% of person-years were spent on allocated treatment at 3 years. There were no differences between those on active and placebo treatment in anticipated side effects. As expected, active treatment led to lipid modifications that would be expected to be beneficial, particularly the lowering of triglyceride levels, and there is a strong \textit{a priori} case for analysing the main clinical endpoint results to determine whether there may be an interaction between initial triglycerides level and any benefit conferred by bezafibrate. There has been a sustained reduction in plasma fibrinogen that would also be expected to be beneficial. There is, however, no clear effect of treatment on CRP. Thus, any benefit due to bezafibrate on fibrinogen may not be mediated simply through a reduction in inflammatory stimuli.

**Competing interests**

None declared.
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References