Articles

Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE)

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Summary

Background To determine whether specific angiotensin II receptor blockade with losartan offers safety and efficacy advantages in the treatment of heart failure over angiotensin-converting-enzyme (ACE) inhibition with captopril, the ELITE study compared losartan with captopril in older heart-failure patients.

Methods We randomly assigned 722 ACE inhibitor naive patients (aged 65 years or more) with New York Heart Association (NYHA) class II–IV heart failure and ejection fractions of 40% or less to double-blind losartan (n=352) titrated to 50 mg once daily or captopril (n=370) titrated to 50 mg three times daily, for 48 weeks. The primary endpoint was the tolerability measure of a persisting increase in serum creatinine of 26·5 µmol/L or more (\geq 0·3 mg/dL) on therapy; the secondary endpoint was the composite of death and/or hospital admission for heart failure; and other efficacy measures were total mortality, admission for heart failure, NYHA class, and admission for myocardial infarction or unstable angina.

Findings The frequency of persisting increases in serum creatinine was the same in both groups (10.5%). Fewer losartan patients discontinued therapy for adverse experiences (12.2% vs 20.8% for captopril, p=0.002). No losartan-treated patients discontinued due to cough compared with 14 in the captopril group. Death and/or hospital admission for heart failure was recorded in 9.4% of the losartan and 13.2% of the captopril patients (risk reduction 32% [95% Cl -4% to +55%], p=0.075). This risk reduction was primarily due to a decrease in all-cause mortality (4.8% vs 8.7%; risk reduction 46% [95% Cl 5-69%], p=0.035). Admissions with heart failure were the same in both groups (5.7%), as was improvement in NYHA

Correspondence to: Dr Bertram Pitt, Division of Cardiology, University Hospital, 1500 East Medical Center Drive, Ann Arbor, MI 48109-0366, USA functional class from baseline. Admission to hospital for any reason was less frequent with losartan than with captopril treatment ($22 \cdot 2\% vs 29 \cdot 7\%$).

Interpretation In this study of elderly heart-failure patients, treatment with losartan was associated with an unexpected lower mortality than that found with captopril. Although there was no difference in renal dysfunction, losartan was generally better tolerated than captopril and fewer patients discontinued losartan therapy. A further trial, evaluating the effects of losartan and captopril on mortality and morbidity in a larger number of patients with heart failure, is in progress.

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Introduction

Angiotensin-converting-enzyme (ACE) inhibitors reduce morbidity and mortality in patients with chronic heart failure and systolic left-ventricular dysfunction as well as in patients who have had a myocardial infarction.¹⁻⁹ The benefits of ACE inhibitors have been mostly attributed to blockade of angiotensin II production and/or to a decrease in the breakdown of bradykinin.^{10,11} Bradykinin has been shown to have beneficial effects associated with the release of nitric oxide and prostacyclin, which may contribute to the haemodynamic effects of ACE inhibition. Bradykinin may, however, also be responsible for some of the adverse reactions to ACE inhibitors such as cough, angio-oedema, renal dysfunction, and hypotension,¹⁰⁻¹⁴ and these sideeffects may explain in part why ACE inhibitors are used in less than 30% of patients with heart failure despite the proven clinical benefit of these agents.¹⁵

Orally active, non-peptide angiotensin II type 1 receptor antagonists such as losartan can block this receptor specifically without increasing bradykinin levels,¹⁶ and since angiotensin II may be produced by alternate pathways¹⁷⁻²⁰ such drugs may have additional advantages over ACE inhibitors where blockade of the effects of angiotensin II is incomplete. Losartan is licenced for the treatment of hypertension in many countries, and in earlier studies in patients with symptomatic heart failure, oral losartan produced beneficial haemodynamic effects both acutely and with chronic dosing.^{21,22}

The Evaluation of Losartan in the Elderly (ELITE) study has compared effects on renal function, morbidity/mortality, and tolerability of long-term treatment with losartan or captopril in patients aged 65 years and older with symptomatic heart failure. The primary endpoint was the tolerability measure of a persisting increase in serum creatinine of 0.3 mg/dL (26.5

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Panel 1: Enrolment criteria

Inclusion criteria

Age ≥65

NYHA class II, III, or IV and ejection fraction ≤40% Never received an ACE inhibitor and stable cardiovascular therapy

Clinical exclusion criteria

Systolic BP <90 mm Hg or uncontrolled hypertension (diastolic >95 mm Hg)

Significant obstructive valvular disease or symptomatic ventricular or supraventricular arrhythmia

Constrictive pericarditis or active myocarditis

Cardiac surgery likely during study period or angioplasty within previous 72 h, bypass surgery within 2 wk, or ICD within 2 wk Acute myocardial infarction in previous 72 h, unstable angina (requiring admission) within 3 mo, or angina (requiring 5 glyceryl trinitrate tablets/wk) within 6 wk

Stroke or transient ischaemic attack in previous 3 mo Digitalis toxicity, uncontrolled diabetes, chronic cough of any aetiology, untreated thyrotoxicosis or hypothyroidism, renal-artery stenosis, angio-oedema of any aetiology, haematuria of unknown aetiology

Condition that would contraindicate a vasodilator Unlikely survival for length of study or risk to patient

Laboratory exclusion criteria

Serum creatinine \geq 221 µmol/L (2·5 mg/dL) potassium <3·5 or >5·5 mmol/L, magnesium <0·7 mmol/L Transaminases >twice upper limit of normal Haemoglobin <10 g/dL or haematocrit <30%, white blood cell count 3000×10°/L, or platelets 100×10°/L

Other exclusion criteria

Another investigational drug in previous 4 wk Inability to give informed consent Potentially noncompliant (eg, alcohol or drug abuse) Previous treatment with losartan or other angiotensin II antagonist

µmol/L) or more on therapy; the secondary endpoint was the composite efficacy measure of death and/or hospital admissions for heart failure. Other prespecified efficacy measures included total mortality and hospital admission for heart failure separately, New York Heart Association (NYHA) functional class, and admission to hospital for myocardial infarction or unstable angina.

Patients and methods

The ELITE study¹⁰ was a prospective double-blind, randomised, parallel, captopril-controlled clinical trial conducted at 125 centres in the United States, Europe and South America. The study was approved by institutional review boards at each site; all patients gave written informed consent. An independent Data and Safety Monitoring Committee monitored the progress of the study.

Patient population

Patients were aged 65 years or more (two-thirds were 70 or older) with symptomatic heart failure (NYHA II–IV), decreased left-ventricular ejection fraction of 40% or less, and no history of prior ACE inhibitor therapy. Enrolment and exclusion criteria are summarised in panel 1.

Randomisation and study therapy

After a 2-week placebo run-in, patients were randomised to 48 weeks of active therapy, either to captopril 6.25 mg titrated to 12.5, 25, and then 50 mg three times daily (plus placebo for losartan) or to losartan 12.5 mg, titrated to 25 and then 50 mg once daily (plus placebo for captopril). Titration generally occurred at 7-day intervals as tolerated. Treatment with all other concomitant cardiovascular therapies was permitted with the exception of open-label ACE inhibitors. Randomised patients were stratified by age (<70, \geq 70).

Evaluation of patients

Clinical assessments were done weekly during titration and 3-monthly thereafter. Laboratory evaluations were done at weeks 3, 6, and 12, and every 3 months after that.

Study endpoints

The primary endpoint was a safety measure of renal dysfunction, defined as an increase in serum creatinine by 26.5 µmol/L or more (0.3 mg/dL or more) from baseline (last measurement before randomisation) that was confirmed by a repeat measurement 5-14 days later, during continued treatment. Allcause mortality and hospital admission for heart failure were also prespecified endpoints. The composite of death and/or admission for heart failure was added as the secondary endpoint by protocol amendment on completion of patient participation in the study before unblinding. This change was prompted by data from two placebo-controlled 12-week exercise studies (of about 350 patients each), demonstrating a beneficial effect on this endpoint.23 The Data and Safety Monitoring Committee was notified in advance. Hypotension-related symptoms, clinically important serum potassium increases (0.5 mmol/L or more), and cough (all originally secondary endpoints) became tertiary endpoints. All deaths (including cause of death) and hospital admissions were adjudicated on by an independent Clinical Endpoint Adjudication Committee, blinded to study treatment (see panel 2 for mortality classification). Other prospectively defined endpoints were admission to hospital for myocardial infarction or unstable angina, worsening of heart failure (NYHA functional classification), withdrawal from the study due to study drug intolerance, and changes in neurohormonal profile.

Statistical methods

The study was designed¹⁰ with 90% power to detect a 40% reduction in persistent renal dysfunction events, assuming a rate of 30% for such an event in the captopril group. The event rate proved to be only 10.5% for captopril so the power to detect a 40% reduction was substantially decreased. Analysis of increases in serum creatinine was based upon a modified intent-to-treat population—ie, all patients were analysed according to their randomisation group, and an endpoint was declared only if the initial and confirmatory increases in creatinine occurred while the patient was on double-blind therapy. Patients who withdrew from the study without meeting this endpoint were censored in the time-to-event analysis at the time of study discontinuation.

Analyses of deaths and heart-failure admissions (adjudicated endpoints) were based on an intent-to-treat population; all patients who discontinued prematurely were followed up to the specified 48 weeks. Patients not meeting the endpoint were censored in the time-to-event analysis either at the time of study completion for patients who completed or at the end of the 48-week follow-up period for patients who discontinued.

For all time-to-event data, survival analyses were based upon the log-rank test. The effect of treatment group in the model was tested with a control for stratification (age <70 or \geq 70). The time to first event was used for each endpoint. Risk reductions were based upon Mantel-Haenszel adjusted (for age category) relative risk estimates.

Panel 2: Mortality classification

Sudden cardiac death—Without warning or within 1 h of symptoms Death due to progressive heart failure—Preceded by worsening signs and/or symptoms of heart failure, including cardiogenic shock Fatal myocardial infarction—Necropsy-verified myocardial infarction or death within 28 days of a hospital-verified acute myocardial infarction, provided no other cardiac or non-cardiac cause of death is found

Death due to other cardiac causes—Such as arrhythmia Death due to other vascular causes—Such as stroke, pulmonary embolus, and ruptured aneurysm

Death due to non-cardiovascular causes—Not due to any cardiac or vascular events



*While on study therapy;[†] withdrawn from assigned therapy but still followed-up for the intention-to-treat analysis of secondary of secondary endpoint.

Figure 1: Study profile

Adverse effects, such as discontinuations for study drug intolerance, cough, and hypotension-related symptoms, were analysed by the Cochran-Mantel Haenszel general association test adjusted for age category. Changes in NYHA functional class were analysed by Wilcoxon rank-sum test.

No adjustments were made for the multiplicity of the secondary or other endpoints; unadjusted p values are presented.

Results

Recruitment began in May, 1994; the last patient was enrolled in July, 1995; and follow-up was completed in June, 1996. Enrolment of patients at the 125 participating centres ranged from 1 to 93 (median of 4); recruitment proved difficult and a substantial number of sites were required to achieve the study sample. Of the 722 patients enrolled, 352 were randomised to losartan and 370 to captopril (figure 1). The two treatment groups were similar with respect to all baseline characteristics (table 1). Concomitant therapies during the study were similar between the two treatment groups; diuretics were used in over 75% of patients, digitalis in over 55% of patients, and non-ACE-inhibitor vasodilatory drugs (including hydralazine and nitrates) in over 40% of patients in both treatment groups. 300 patients (85%) were titrated to the target dose of losartan 50 mg once daily and 310 patients (84%) in the captopril group were titrated to the target dose of 50 mg three times a day. 75% of losartan-treated patients were receiving the targeted dose of 50 mg daily (mean daily dose 42.6 mg for all patients) and 71% of captopril patients were receiving the targeted dose of 50 mg three times a day (mean 122.7 mg).

Renal dysfunction

There was no significant difference between losartan and captopril in the frequency of the primary endpointnamely, persisting (confirmed) increases in serum creatinine (10.5% in each group, table 2; risk reduction 2% [95% CI -51% to +36%], p=0.63). Single rises in serum creatinine of 26.5 µmol/L or more were documented in 92 losartan-treated patients (26.1%) and 110 captopril-treated patients (29.7%). Of these 202 patients, 68% (137) had confirmation measurements done while on active therapy per protocol, and 55% (76) of those with confirmation measurements met the endpoint.

Characteristic	Losartan (n=352)	Captopril (n=370)
Demographic M/F Age (<70/≥70) Mean age (yr) Race (white/black/other) Current cigarette smokers	234/118 95/257 74 (5·8) 320/16/16 39	248/122 119/251 73 (6·1) 326/18/26 45
Clinical Heart failure* due to ischaemic/ non-ischaemic heart disease NYHA class II/III/IV	242/110 231/116/5	250/120 237/126/7
Drug therapy Diuretics Digitalis Hydralazine Nitrates Calcium channel blockers Potassium Anticoagulants Aspirin B-blockers Antiarrhythmics	260 199 12 180 123 91 60 178 55 37	275 209 12 191 121 89 69 166 63 39
Secondary diagnoses* Myocardial infarction Hypertension Atrial fibrillation Diabetes mellitus Renal insufficiency Stroke Moceuromete	184 201 86 94 21 32	177 212 82 89 26 37
Measurements Ejection fraction (%) Serum creatinine (µmol/L) Serum potassium (mmol/L) Heart rate (b/min) Systolic BP (mm Hg) Diastolic BP (mm Hg) Weight (kg)	31 (7-2) 106 (35) 4 · 3 (0·4) 73 (11-7) 137 (17·6) 79 (9·4) 76 (33·1)	30 (7·6) 106 (35) 4·3 (0·5) 74 (10·4) 137 (19·1) 79 (10·6) 74 (33·8)

*Based on patient history. Table shows numbers or, for age and for measurements, mean (SD).

Table 1: Baseline clinical characteristics and drug therapy

Death and/or heart failure admission

Follow-up data on death and hospital admission were complete except for one losartan-treated patient who discontinued after one dose. During the course of the study, death and/or heart failure admissions occurred in 33 of 352 losartan-treated patients (9.4%) and 49 of 370 captopril-treated patients (13.2%). The risk reduction was 32% (95% CI -4% to +55%, p=0.075; table 3). This risk reduction was primarily due to a decrease in all-cause mortality (4.8% vs 8.7%; risk reduction 46% [95% CI 5-69%, p=0.035 (table 3). The cumulative survival curves (intent-to-treat) separated early and remained separated throughout the 48 weeks (figure 2). Analyses by cause (table 3) suggests that, though the numbers of events are small, the lower total mortality in the losartan group is primarily due to a reduction in sudden cardiac deaths. The mortality difference was generally consistent across different subgroups-namely, age, ejection fraction, aetiology of heart failure, NYHA functional class, and concomitant digoxin use, the exception being deaths in women (9/118 losartan vs 8/122 captopril).

Age	Treatment	No	Event rate*
All patients	Losartan	352	37 (10.5%)
	Captopril	370	39 (10.5%)
<70	Losartan	95	8 (8.4%)
	Captopril	119	10 (8.4%)
≥70	Losartan	257	29 (11.3%)
	Captopril	251	29 (11.6%)

*Defined as a rise of 26.5 µmol/L (0.3 mg/dL) or more, confirmed within 5-14 days. Table 2: Frequency of increases in serum creatinine

Endpoint	Losartan (n=352)	Captopril (n=370)	Risk reduction (CI)*	pt
Combined death and/or hospital admission for heart failure	33 (9.4%)	49 (13.2%)	0.32 (-0.04 to +0.55)	0.075
All deaths	17 (4.8%)	32 (8.7%)	0.46 (0.05–0.69)	0.035
Cardiovascular				
Sudden death	5 (1.4%)	14 (3.8%)	0.64 (0.03–0.86)	
Progressive heart failure	1	1	-0.11 (-20.23 to +0.94)	
Myocardial infarction	1	4 (1.1%)	·1%) 0.76 (-0.83 to +0.97)	
Other vascular	5 (1.4%)	5 (1.4%)	-0.03(-2.63 to +0.71)	
Non-cardiovascular	5 (1.4%)	8 (2.2%)	0.35 (-0.94 to +0.78)	
Hospital admissions				
For heart failure	20 (5.7%)	21 (5.7%)	0.04 (-0.74 to +0.47)	0.89
For any reason	78 (22.2%)	110 (29.7%)	0.26 (0.05-0.43)	0.014

*Reduced risk of endpoint on losartan compared with captopril (negative number denotes increase in risk); estimates control for age category; CI=95% confidence interval. †Log-rank test (survival analysis) with age category included as stratification factor.

Table 3: Deaths (and causes of death) and admissions for heart failure or for any reason

Fewer losartan-treated patients were admitted to hospital for any reason during the 48 weeks but frequency of admission because of heart failure was identical (5.7%) (table 3).

NYHA class

NYHA functional class improved similarly with losartan and captopril treatment ($p \le 0.001$ versus baseline for both groups); 80% of losartan-treated patients and 81% of captopril-treated patients were class I or II at the end of the study compared with 66% and 64%, respectively, at baseline.

Plasma norepinephrine

A 3% decrease from a geometric mean at baseline of 2.78μ mol/L (469 pg/mL) was observed at 48 weeks with losartan treatment, as compared with a 5% increase from 2.51 μ mol/L (424 pg/mL) with captopril (p=0.49).

Safety, tolerability and discontinuations

65 (18.5%) of the losartan-treated patients discontinued study therapy or died compared with 111 (30%) captopriltreated patients (p \leq 0.001) and the reasons are listed in table 4. Excluding deaths, 43 (12.2%) losartan-treated patients discontinued for adverse effects versus 77 (20.8%) captopril-treated patients. Discontinuations due to worsening heart failure occurred in nine captopril-treated patients and three losartan-treated patients. 14 captopril-treated patients but none of the patients on losartan discontinued study therapy due to cough.

The differential discontinuation rate did not account for





the 46% difference in total mortality in the intent-to-treat analysis because this difference was observed predominantly in patients who remained on study therapy. Per protocol analysis gave death rates of 3.7% (11/298) for for losartan and 8.5% (24/282) for captopril (risk reduction 57% [95% CI 13–78%], p=0.013).

There were no differences between the two treatment groups with respect to hypotension-related symptoms (occurring overall in 24% of patients). First-dose hypotension was reported in seven captopril and four losartan treated patients. Persisting increases in serum potassium of 0.5 mmol/L or more above baseline while on therapy was observed in 66/352 (18.8%) losartan-treated and 84/370 (22.7%) captopril treated patients (p=0.069).

Discussion

ELITE is the first long-term (48 weeks) study comparing an angiotensin II type 1 receptor antagonist with an ACE inhibitor in patients with symptomatic heart failure and systolic left-ventricular dysfunction. Captopril was chosen as the comparison ACE inhibitor drug because it may have fewer renal effects than longer-acting ACE inhibitors.²⁴ The incidence of persistent renal dysfunction was not different between the losartan and captopril groups (both 10.5%), and fewer than 2% of patients discontinued for this reason in either group.

Reason	Losartan (n=352)	Captopril (n=370)
All	65 (18·5%)*	111 (30.0%)
Adverse event (excluding death)†	43 (12.2%)*	77 (20.8%)
Cought	0*	14 (3.8%)
Worsening heart failure	3	9
Hyperkalaemia†	2	6
Taste perversion/appetite decreased	0	6
Rash	0	4
Hypotension†	8	5
Angio-oedema	0	3
Arrhythmia	1	4
Myocardial infarction	3	4
Renal dysfunction†	5	3
Stroke	4	3
Angina/unstable angina	3	2
Other non-cardiac cause	14	14
Death	1	5
Therapy ineffective	0	1
Protocol deviation	5	7
Patient withdrew	16	19
Other	0	2

*p≤0-002. These individual adverse experiences causing discontinuation were tested for significance (according to protocol) and are based on reasons cited by investigator.

Table 4: Primary reason for discontinuation of study medication before completion of study



Figure 3: 3-monthly mortality in SOLVD-treatment, exercise studies, and ELITE

Discontinuation due to other adverse effects was significantly more common in patients randomised to captopril. 27 patients withdrew from the captopril group because of altered taste sensation, rashes, or angio-oedema, all side-effects recognised with ACE inhibitors.¹²⁻¹⁴ None of the losartan-treated patients stopped the drug for any of these reasons and the overall tolerability of losartan was superior to that to captopril.

Although no significant difference was observed for the primary endpoint (persistent renal dysfunction) or the secondary endpoint (composite of death/heart failure admissions), treatment with losartan was associated with less all-cause mortality than captopril, a drug known to have survival benefits.^{57,9} The survival benefit of losartan was observed early in the study, persisted throughout the 48 weeks, and was consistent among all subgroups except female patients. Only one-third of the patients enrolled in ELITE were women, and mortality in women with heart failure taking losartan or captopril requires further study. The greater drop-out rate in patients on captopril did not account for the beneficial effects of losartan on total mortality; the difference in total mortality was primarily observed in those who remained on active therapy.

An improvement in survival with losartan of similar magnitude has been observed in two placebo-controlled 12-week exercise studies in about 350 patients with symptomatic heart failure.²³ Losartan did not improve treadmill exercise duration (the primary endpoint) but was associated with an unexpected reduction in mortality. Mortality rates in the placebo controls in the exercise studies and the captopril controls in ELITE are comparable with the rates for the placebo and enalapril groups, respectively, in the SOLVD trial² (figure 3). Apart from age (ELITE patients were older), the patient populations in these studies are similar. The limitations of cross-study comparisons and the greater age of the patients in this study notwithstanding, treatment with losartan in the exercise studies and in ELITE was associated with comparably low mortality rates which were less than the observed mortality rates for both placebo and enalapril in SOLVD.

Before the availability of ACE inhibitors, progressive heart failure accounted for about 50% of deaths in patients with heart failure.²⁵ In patients with mild-tomoderate heart failure who are treated with an ACE inhibitor, death due to progressive heart failure is much less common and sudden cardiac death is now the predominant category. For example, in the discontinued SWORD trial—in which patients with mild-to-moderate heart failure or left-ventricular dysfunction were randomised to *d*-sotalol or placebo on a background of usual therapy, including an ACE inhibitor—arrhythmia accounted for about two-thirds of total mortality in the placebo group while progressive heart failure accounted for only one-sixth.²⁶ In ELITE sudden cardiac death was the most common cause of death in the captopril patients, and the apparent mortality advantage for losartan seems primarily to be due to a reduction in sudden cardiac death. Few patients died due to progressive heart failure or to fatal myocardial infarction in either group in ELITE.

If it is confirmed that losartan does reduce the risk of sudden cardiac death it will be necessary to find out if this property is specific to this agent or is a class effect of angiotensin II type 1 receptor antagonists and due to the more complete blockade of angiotensin II that these antagonist drugs achieve. ACE activity may not be completely suppressed by captopril. However, the captopril regimen in ELITE (target dose 50 mg three times daily) is one that has been found effective in several studies in heart failure,5,7,9 and considered to have mortality benefits^{27,28} Angiotensin II may also be formed by non-ACE-dependent pathways,17-20 and the more complete blockade of angiotensin II effects by losartan may result in more complete suppression of catecholamines at the tissue level.²⁹ Furthermore, bradykinin, which releases norepinephrine,³⁰ is not increased with direct angiotensin II blockade¹¹ while it is with ACE inhibitors.

In this study NYHA functional class improved significantly and to a comparable extent from baseline after long-term treatment with both losartan and captopril, and rates of hospital admission for heart failure were similar too. Another similarity was the low incidence of death due to progressive heart failure (less than 1% for both losartan and captopril).

This study was in patients aged 65 years and older with systolic left-ventricular dysfunction, and the results cannot be extrapolated to younger heart-failure patients or patients with diastolic dysfunction. Elderly patients were chosen because most patients with heart failure are over 65. Elderly patients tend to be under-represented in randomised trials in heart failure (eg, in SOLVD the mean age was about 61 years compared with 73.5 in ELITE).

We chose an active drug as the control arm in ELITE so that no patient would be denied any benefit of reninangiotensin system blockade and we selected captopril because there may be less renal dysfunction (the primary endpoint in ELITE) with this shorter-acting agent than with a longer-acting ACE inhibitor.²⁴ Captopril had been shown to be effective in heart failure and left-ventricular systolic dysfunction,^{57,9} and a meta-analysis suggests that the reduction in mortality is consistent among the various ACE inhibitors in a broad range of patients with heart failure.²⁷ This study demonstrated that losartan reduced mortality compared with captopril; whether the apparent mortality advantage for losartan over captopril holds true for other ACE inhibitors requires further study.

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