Intravenous Streptokinase for Acute Myocardial Infarction
Effects on Global and Regional Systolic Function

Gary V. Martin, MD, Florence H. Sheehan, MD, Michael Stadius, MD,
Charles Maynard, PhD, Kathryn B. Davis, PhD,
James L. Ritchie, MD, and J. Ward Kennedy, MD

The Western Washington Intravenous Streptokinase Trial randomized 368 patients with acute myocardial infarction to receive either intravenous streptokinase or standard therapy. The ventriculograms and coronary angiograms obtained in 170 patients 10.4±7.4 days after infarction were analyzed to evaluate the effects of thrombolytic therapy on global and regional systolic function. Streptokinase treatment resulted in a higher patency rate of the infarct-related artery (68.5%) than did standard therapy (44.8%) (p=0.003). Ejection fraction was higher in streptokinase-treated patients (54% vs. 51%, p=0.056), and the difference was most marked in patients with anterior myocardial infarction (53% vs. 44%, p=0.03). Regional wall motion was measured by the centerline method and expressed in mean±SD motion in 52 normal subjects. There was a trend toward better function of the infarct zone in streptokinase-treated patients (SD, –2.48 vs. –2.70, p=0.24). Additionally, streptokinase-treated patients had significantly better wall motion of noninfarct areas (SD, 0.36 vs. –0.08, p=0.02). Treatment effects on function of noninfarct regions were most apparent in the subset of patients with multivessel disease. Thus, intravenous streptokinase preserves left ventricular function in patients with acute myocardial infarction. This benefit includes favorable effects on the function of regions remote from the site of infarction. (Circulation 1988;78:258–266)

Recent data indicate that the early and long-term prognosis of patients with acute myocardial infarction is improved by the early administration of intravenous thrombolytic therapy.1–3 Because most early deaths are related to pump failure, the hypothesized mechanism for this effect is preservation of mechanical function. Supporting evidence has been obtained from studies in which ventricular function was measured before and after thrombolytic therapy. Successful reperfusion has usually resulted in an improvement in global or regional function, whereas nonreperfusion has been associated with no improvement or further functional impairment.4–6

For several reasons, major differences in global ventricular function have been infrequently observed in randomized trials comparing intracoronary streptokinase (SK) treatment with conventional therapy.7–11 One probable explanation is the time delay involved in instituting intracoronary therapy. The study demonstrating the most favorable effect of intracoronary SK on left ventricular function was the one that treated patients the earliest.7 In another study showing a benefit of intracoronary SK on left ventricular function, early intravenous SK preceded intracoronary therapy in some patients.12 Intravenous thrombolysis is recognized as a more expedient method for achieving thrombolysis for most patients. However, fewer data are available regarding the overall impact of intravenous SK compared with conventional therapy on ventricular function.3,13,14

Our purpose was to compare prehospital discharge ventricular function of patients receiving intravenous SK with that of patients receiving standard care for acute myocardial infarction. The study group comprised patients enrolled in the Western Washington Intravenous Streptokinase Trial. Left ventricular function has been analyzed with reference to the status of

From the Department of Medicine, University of Washington School of Medicine, Seattle, and the Seattle Veterans Administration Hospital.

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Address for correspondence: Gary V. Martin, MD, Department of Cardiology (111c), V.A. Medical Center, 1660 South Columbian Way, Seattle, WA 98108.

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reperfusion and the anatomy of the noninfarct vessels with particular emphasis given to the effects of thrombolysis on regional wall motion.

Patients and Methods

Data for this analysis were obtained from the angiograms of patients enrolled in the Western Washington Intravenous Streptokinase Trial. Between 1983 and 1986, 368 patients with acute myocardial infarction were randomized to receive intravenous SK (1.5 million units) or continual therapy. Mortality data have been previously reported.\textsuperscript{15} Entry criteria included age less than 75 years, duration of symptoms less than 6 hours, and ST-segment elevation on the electrocardiogram greater than 1.5 mV in V\textsubscript{1}–V\textsubscript{3} or greater than 1 mV in other leads. Patients with contraindications to thrombolytic therapy, including life-limiting noncardiac disease, previous SK therapy, bleeding diathesis, severe hypertension, or recent surgery, were excluded. The mean time from onset of symptoms to initiation of SK was 209 minutes, with 42.9% starting treatment within 3 hours.

All patients were encouraged to undergo coronary angiography and left ventriculography before hospital discharge. One hundred thirty-eight (72.3%) treated and 112 (63.3%) control patients agreed to have follow-up cardiac catheterization 10.4±4.4 days after infarction; 241 (96.4%) of the patients’ films were reviewed by the angiographic committee, and 170 (70.5%) of the 241 films showed left ventriculograms of adequate quality for analysis. Of these 170, 49 showed anterior and 121 showed inferior infarctions. Each analyzed ventriculogram met rigid quality control criteria, and only well-opacified, nonpotentiated sinus beats were analyzed. These 170 ventriculograms compose the data for this study.

Quantitative analysis of global and regional left ventricular systolic function was performed in each patient. Briefly, the end-diastolic and end-systolic left ventricular endocardial contours from a normal, nonpostectopic beat are traced from the 30° right anterior oblique view and entered into a VAX computer (model 11/750, Digital Equipment, Maynard, Massachusetts) with an X-Y digitizer (model 1201, Summagraphics, Fairfield, Connecticut). Ejection fraction was determined based on relative chamber volume calculations with the area-length method.\textsuperscript{16} Regional wall motion was measured along 100 chords constructed perpendicular to a centerline drawn midway between the end-diastolic and end-systolic contours (Figure 1), corrected for heart size, and expressed in mean±SD motion in 52 normal subjects. “Normal subjects” were patients suspected of having heart disease who underwent diagnostic cardiac catheterization but were found to have normal cardiac anatomy, normal coronary arteries, and normal ventricular function. The severity of hypokinesis in the infarct site was calculated as the mean motion of chords lying in the most hypokinetic half of the infarct artery territory and expressed in SD per chord. Hyperkinesis was similarly calculated in the most hyperkinetic half of the artery territory opposite the infarct site. The derivation of the centerline method has been previously reported.\textsuperscript{17}

Coronary anatomy was reviewed by an angiographic reading committee blinded to the treatment assignment. The infarct-related vessel was identified as patent or nonpatent, and the residual diameter stenosis of the patent vessels was measured with a digital caliper. Reperfusion was measured as in the Thrombolysis in Myocardial Infarction trial (TIMI): grade 0, no perfusion; grade 1, penetration of the thrombus by contrast with minimal distal perfusion; grade 2, partial perfusion; and grade 3, complete perfusion. The extent of disease in the noninfarct arteries was also assessed. Any diameter stenosis greater than 50% in noninfarct vessels was defined as “significant” for the purposes of determining the presence or absence of multivessel disease.

The t test was used to test for treatment-control differences in continuous variables. The χ\textsuperscript{2} statistic was used for categorical variables.

Results

Two hundred fifty (67.9%) of the 368 patients entering the trial underwent follow-up cardiac catheterization for 10.4±4.4 days (range, 1–48 days) after infarction. A comparison of those patients who underwent catheterization with those in whom catheterization was not performed is shown in Table 1. The group undergoing catheterization was younger and had a higher percentage of men than did the group of survivors who did not undergo catheterization. Figure 2 summarizes the coronary angiographic data. A patent infarct-related artery (TIMI grade 2 or 3 perfusion) was present in 68.5% of treated patients versus 44.8% of controls (p=0.003). The patency rate was significantly higher for treated than for control patients in the subgroups with anterior and inferior myocardial infarction. Among SK-treated patients, patency rates were higher for anterior (85.4%) than for inferior myocardial infarction (60.7%). The residual diameter stenosis of patent infarct-related arteries was similar for SK-treated patients (65.0±19.0%) and controls (70.1±17.6%).

Ejection fraction data for all patients and for selected subsets are shown in Figure 3. Patients treated with SK had a slightly higher ejection fraction (54±12.1% vs. 51±12.6% for control patients) (p=0.056). Subset analysis shows that ejection fraction differences were most prominent for those with anterior myocardial infarction and were confined to those patients with a patent infarct-related artery at the time of catheterization.

Regional wall motion analysis revealed that function in the infarct territory was significantly impaired. Mean wall motion in the infarct territory was 2.48 SD below normal for SK-treated patients and 2.70 SD below normal for control patients (p=0.24). Fig-
Figure 1. Diagram of centerline method of regional wall motion analysis. A: End-diastolic and end-systolic left ventricular endocardial contours and centerline constructed by computer midway between the two contours. B: Motion measured along 100 chords constructed perpendicular to centerline. C: Motion at each chord is normalized by end-diastolic perimeter to yield a shortening fraction. Motion along each chord is plotted for the patient (solid line). Mean motion in the normal ventriculogram group (dashed line) ± SD (dotted lines) are shown for comparison. D: Standardized motion. Wall motion of patient is now plotted in SD from normal mean (dotted line). Normal ventriculogram group mean is represented by horizontal zero line. Vertical lines delimit most hyperkinetic and hypokinetic parts of anterior and inferior regions. Dotted lower curve defines regional akinesis.

Figure 4 shows that trends toward better function for SK-treated patients were present in several subgroups, though not in those patients treated after 3 hours or with occluded infarct-related vessels.

Regional function in the wall opposite the infarct territory was significantly better in treated patients (SD, 0.36) than in controls (SD, −0.08) (p = 0.02). These areas were slightly hyperkinetic in SK-treated patients with a patent infarct artery, whereas wall motion was normal or even hypokinetic in SK-treated patients with a nonpatent infarct vessel and in control patients (Figure 4). Significant differences were present in subgroups with anterior infarction and in those treated within 3 hours of symptom onset.

Although wall motion in noninfarct regions is greater in treated than control patients with single-vessel disease, significant differences between treated and control patients are confined to those with multivessel disease (Table 2). This difference is significant regardless of whether patients with a history of a previous myocardial infarction are excluded from the analysis.

Discussion

Intravenous thrombolytic therapy has been adopted as the most expedient method for achieving reperfusion in the majority of patients with acute myocardial infarction. Several randomized trials, including the Western Washington Intravenous Streptokinase Trial, have provided evidence that treatment with intravenous SK results in improved early survival after myocardial infarction. Presumably, cardiogenic shock and death are averted
by early reperfusion resulting in myocardial salvage. An additional issue is whether and to what extent thrombolytic therapy improves ventricular function in the group of patients surviving the hospital phase of acute myocardial infarction and the impact of this improvement on the long-term prognosis of these patients.

The pre–hospital discharge ejection fraction data reported in the present study are similar to those measured by Intravenous Streptokinase in Acute Myocardial Infarction and TIMI investigators\textsuperscript{13,18} at a similar point in time after intravenous thrombolysis. The results suggest a modest overall benefit for SK-treated patients. Because no angiographic data were obtained in patients who died, we were not able to relate this difference in ejection fraction to any differences in early survival. It is possible, however, that the observed differences in ventricular function are minimized by the inability to include nonsurvivors who were likely to have had the worst function. Whether the small treatment-control difference in ejection fraction among survivors will convey additional long-term survival benefits remains uncertain.

Because ventriculograms were not performed before treatment in the present study, it is possible that the difference in ejection fraction at 10 days between SK-treated and control patients was because of baseline differences in ejection fraction. However, this seems unlikely. The incidence of

\begin{table}[h]
\centering
\caption{Hyperkinesis}  
\begin{tabular}{lccc}
 & Streptokinase-treated patients & Control patients & $p$ \\
\hline
Single-vessel disease & 0.44 ± 0.18 & 0.23 ± 0.18 & 0.40 \\
 & (45) & (37) & \\
Single-vessel disease\textsuperscript{*} & 0.44 ± 0.18 & 0.21 ± 0.19 & 0.38 \\
 & (41) & (35) & \\
Multivessel disease & 0.28 ± 0.15 & -0.35 ± 0.21 & 0.02 \\
 & (47) & (40) & \\
Multivessel disease\textsuperscript{*} & 0.24 ± 0.15 & -0.27 ± 0.23 & 0.07 \\
 & (35) & (32) & \\
\end{tabular}
\end{table}

\texttt{Values are mean ± SEM. Number of patients in parentheses. *No previous myocardial infarction.}
previous myocardial infarction and other baseline clinical parameters were similar in the two groups. In fact, the incidence of pulmonary edema at presentation was higher in SK-treated patients (6%) than in control patients (3%).

Although caution is warranted in interpreting post hoc analysis, the subset analysis of ejection fraction is of interest. More striking differences in ejection fraction between SK-treated and control patients were present in patients with anterior myocardial infarction than in those with inferior myocardial infarction. These findings agree with previously published data regarding the effect of intravenous SK on ventricular function. Like in our present study, Bassand et al14 found no treatment-control differences in ejection fraction for inferior myocardial infarction. However, a significant ejection fraction difference favoring SK-treated patients (40% vs. 33%) was reported for the subset with anterior myocardial infarction. White et al3 found a small but statistically significant difference in ejection fraction (60% for SK-treated vs. 55% for control patients) in patients with inferior myocardial infarction and no previous infarction. A larger difference was present for anterior myocardial infarction (57% for SK-treated vs. 49% for control).

Thus, ejection fraction is relatively well preserved, even in control patients with inferior infarction, and is not substantially improved by treatment with SK. This is consistent with the low 1-year mortality previously reported for both treated and untreated patients with inferior myocardial infarction.15,19 The more substantial effects of SK on ventricular function in patients with anterior myocardial infarction may explain the striking reduction in 1-year mortality among patients with anterior myocardial infarction who are successfully reperfused.19

There may be several reasons for the lesser benefit in patients with inferior myocardial infarction. Because the right coronary artery supplies a smaller mass of left ventricle than the left anterior descending artery,20 the impact of infarction on global function and maximum amount of salvage possible are less for inferior than for anterior myocardial infarction. A second possible explanation is the lower rate of infarct vessel patency for inferior infarctions at the time of catheterization. Among patients treated with SK in this trial, the left anterior descending artery was patent (TIMI grade 2 or 3) in 85.4% of patients with anterior infarctions, whereas the right coronary artery was patent in only 60.7% of inferior infarctions. A third possible mechanism may relate to the higher incidence of collateral vessels in inferior myocardial infarction as opposed to anterior myocardial infarction observed in this and other studies.21 In the present study, collaterals were present in 43.2% of inferior myocardial infarctions and 26.7% of anterior myocardial infarctions. Collateral vessels could provide a protective effect in patients failing to reperfuse,22,23 thereby tending to minimize treatment-control differences in ventricular function. However, because we have no data on the prevalence of collaterals in the first few hours of infarction and because collaterals often develop rapidly over the first 2 weeks after myocardial infarction,24 we cannot be certain of the effect of collaterals in the present study.

The ejection fraction difference between treated and control patients was greatest among those with a patent infarct-related vessel (57% vs. 50%). Presumably, the key difference between these groups was that the vessels in patients receiving SK opened earlier, whereas spontaneous reperfusion in control patients occurs gradually over the initial 24 hours after acute myocardial infarction.25 The importance of early reperfusion in achieving functional recovery has been amply demonstrated. In the TIMI trial, the ejection fraction increased significantly in patients who had a patent infarct artery by 90 minutes after initiation of thrombolytic therapy but not in those whose arteries opened after the 90-minute angiogram and before the predischarge angiogram.18

Analysis of regional wall motion demonstrates that most patients, regardless of thrombolytic therapy, have severe hypokinesis in the infarct-related territory. The magnitude of the dysfunction measured in the present study is almost identical to that measured by the centerline method in the TIMI trial18 after treatment with either intravenous SK or tissue plasminogen activator. It is interesting to note that the defect in wall motion was similar in severity despite the shorter time to treatment in this trial (3.5 vs. 4.75 hours). In the present study, there was a slight trend toward better regional function for SK-treated patients who were randomized under 3 hours, and in the TIMI trial, recovery was greater in patients reperfused within 4 hours after onset of symptoms. However, both trials had only a few patients who were treated within 2 hours, which is when the potential for salvage appears to be greatest.26

On average, SK-treated patients displayed mild hyperkinesis in the noninfarct region, whereas control patients did not. Hyperkinesis in areas of the ventricle remote from the site of acute ischemia has been previously noted in human and animal studies. Semiquantitative analysis of two-dimensional echocardiograms performed in the first 24 hours after myocardial infarction has detected remote hyperkinesis in 50–87% of patients.27,28 Using quantitative analysis of contrast ventriculograms obtained within the first 12 hours of infarction, Stadius et al21 documented hyperkinesis in 32% of patients. Hyperkinesis is most prominent in the early hours of infarction and tends to decrease, though not disappear, in the ensuing days and weeks. This response has been attributed to catecholamine activity or regional alterations in preload secondary to left ventricular dilatation with enhanced function of the nonischemic regions due to the Starling mechanism.
Another possible mechanism is reduced regional afterload due to asynchronous contraction of ischemic and nonischemic areas of the ventricle or to decreased tension development, premature relaxation, or frank systolic bulging in the infarcted region. Irrespective of the mechanism, the development of compensatory hyperkinesis moderates the impact of acute myocardial infarction on global left ventricular function. Indeed, hyperkinesis may be so great as to normalize the ejection fraction, reducing its sensitivity as a measure of function in the infarct region and of response to therapeutic interventions.

Compensatory regional hyperkinesis late after infarction, however, has been less frequently observed. Theroux et al31 related its appearance to the development of hypertrophy in the dog. In the present study, SK-treated patients had significantly more hyperkinesis 1–3 weeks after myocardial infarction than control patients. This difference likely contributed to the overall difference in ventricular function, as measured by the ejection fraction, between SK-treated and control patients. The treatment-control differences in the function of the noninfarct region were greatest in those patients with multivessel disease. Only a small difference was observed between control and treated patients with single-vessel disease. In contrast, SK-treated patients with multivessel disease developed slight hyperkinesis, whereas control patients with multivessel disease had hypokinesis in the contralateral wall as well as the infarct region.

Similar observations regarding the benefit of thrombolytic therapy on the function of noninfarct territories have been made by other investigators.12,14 Serruys et al12 also reported greater function in the noninfarct region in SK-treated patients. Furthermore, hyperkinesis was greatest in patients who had angioplasty after thrombolysis. Their observations were made much later after myocardial infarction than in the present trial, with over one third of patients being studied at a median of 42 days after treatment, suggesting that the hyperkinesis is chronic. (The prevalence of multivessel disease in their patients was not reported.) Bassand et al14 analyzed radionuclide ventriculograms obtained in the 3rd week after myocardial infarction in 96 patients randomized to intravenous SK with heparin or heparin alone. Ejection fraction was higher for SK-treated patients only in the subgroup with anterior myocardial infarction (40% vs. 33%). In this subset, significant beneficial effects of SK on regional function were observed only in areas remote from the site of infarction.

Failure to develop compensatory hyperkinesis or the development of frank dysfunction in regions remote from the site of acute myocardial infarction has also been previously observed.27,28,32 In these studies, remote asynergy was seen primarily in patients with multivessel disease and was observed in only 0–14% of patients with single-vessel disease. Patients who exhibit this response have been noted to have worse survival rates and higher rates of angina and reinfarction, even though some improvement in remote asynergy may occur over time after myocardial infarction.27,32

Several studies of experimental myocardial infarction have sought to determine the mechanism for remote asynergy. Gascho et al33 showed that left anterior descending occlusion in the presence of a severe circumflex stenosis caused a further decrease in subendocardial blood flow in the circumflex region. Furthermore, the circumflex stenosis prevented compensatory increases in posterior myocardial wall thickening. Homans et al34 reported similar findings. Further, they found that when anterior wall dysfunction was produced by an intracoronary injection of pentobarbital instead of by left anterior descending artery occlusion, hyperkinesis of the posterolateral wall was again prevented by a circumflex stenosis, although no significant change in circumflex blood flow occurred in this circumstance. The authors conclude that either absolute hypoperfusion or inability to increase perfusion to support hypercontractility of the myocardium may be the reason some patients with multivessel disease fail to develop compensatory hyperkinesis.

In view of these clinical and experimental data, the beneficial effect of SK on the function of noninfarct areas of the ventricle is most probably due to the higher rate of infarct vessel patency in the SK-treated patients. For example, reperfusion of the infarct vessel may improve blood flow in remote regions of the ventricle. Theoretically, this could occur because the patent infarct vessel no longer requires collateral flow from a stenotic remote vessel or because the patent infarct vessel is able to supply collateral flow to noninfarcted areas that are supplied by a critically stenosed vessel. Another possible explanation is that SK therapy resulted in hemodynamic conditions more favorable for coronary perfusion in noninfarcted myocardium supplied by a stenotic coronary artery. Reversal of hypotension, lowering of heart rate, or reduction in end-diastolic ventricular pressure could improve the ratio of myocardial perfusion to oxygen demand.

The greater wall motion in noninfarct regions observed in SK-treated patients may have occurred because of nonflow related mechanisms as well. Salavage of even a small rim of epicardial tissue could conceivably produce more favorable loading conditions by either preventing ventricular dilatation or improving the synchrony of mechanical events in the cardiac cycle. Previous studies have shown that chamber dimensions are smaller in SK-treated patients, despite similar aortic and left ventricular end-diastolic pressures, suggesting that lower wall stress may also be present.12 The contribution of these mechanisms in the present study cannot be determined because the necessary data were not collected.
In summary, treatment of acute myocardial infarction with intravenous SK resulted in a higher ejection fraction at the time of hospital discharge. The greatest benefit was seen in patients with anterior myocardial infarction. The improved global function was associated with better function in areas of the ventricle remote from the site of infarction. The small differences in function of the infarct regions did not achieve statistical significance in this trial. These observations indicate that there are multiple mechanisms by which thrombolysis improves ventricular function. The most obvious and most intensively studied mechanism is preservation of mechanical function in the infarct zone by direct salvage of myocardium. However, even when this is not achieved, reperfusion may benefit flow or function in the noninfarct region and thereby also improve global ventricular function, especially in patients with multivessel disease. Further refinement of these observations may lead to a better understanding of the mechanisms by which thrombolytic therapy reduces mortality in acute myocardial infarction.

Appendix 1: Western Washington Intravenous Streptokinase Trial

Principal Investigators
J. Ward Kennedy, MD, codirector; James L. Ritchie, MD, codirector; and Kathryn B. Davis, PhD, investigator.

Angiographic Reading Committee
J. Ward Kennedy, MD, Gary V. Martin, MD, Florence H. Sheehan, MD, and Michael L. Stadius, MD.

Policy Advisory and Data Monitoring Board
William B. Hood, MD (chairman), Lewis C. Becker, MD, Paul Canner, PhD, Jay H. Cohn, MD, Max Halperin, PhD, Thomas Killip, MD, Victor J. Marder, MD, Eliot Rapaport, MD, and Harmon Smith, PhD.

National Heart, Lung, and Blood Institute Program Office
Charles Hollingsworth, DPH, and Patrice Nickens, MD.

Data Coordinating Center
Kathryn B. Davis, PhD, and Charles Maynard, PhD.

Nurse Coordinators
Deanna Erickson, RN, MN, Teri Kempf, RN, Kathy Martin, RN, and Kathleen McFadden, RN.

Clinical Centers
St. Joseph Hospital, Bellingham, Washington: R.S. Trenouth (physician associate) and S. Harrison (study coordinator).

Harrison Memorial Hospital, Bremerton, Washington: A.B. Lee, M.V. Paciotti, and D. Tinker (physician associates) and B. Dunford (study coordinator).


Central Group Health Hospital, Seattle, Washington: J.K. Fritz, A. Resnick, and R. Wallach (physician associates) and A. Hope, E. Normand, and M. Passmore (study coordinators).

Harborview Medical Center, Seattle, Washington: W.D. Weaver, L. Cobb, and G.B. Trobaugh (physician associates) and A. Dreis, P. Wilson, R. Vincent, and S. Dahlberg (study coordinators).


St. Paul Hospital, Vancouver, British Columbia, Canada: A. Dodek, J. Bone, R. Hooper, D. Kavanagh-Gray, M. Kiess, I. MacDonald, and D. Perez (physician associates) and D. Hunt (study coordinator).


University Hospital, Seattle, Washington: J.W. Kennedy, J. Blackmon, B.G. Brown, H.T. Dodge, and D.K. Stewart (physician associates) and R. Schwartz (study coordinator).

Skagit Valley Hospital, Mt. Vernon, and United Hospital, Sedro Woolley, Washington: D.L. Landreth, R.L. Coffey, J. Eisner, R. E. Gubner, and J.S. Halsey (physician associates) and S. Payne and J. Webster (study coordinators).

Highline and Riverton Hospitals, Seattle, Washington: B. Green, F. Cervenka, and M. Jackson (physician associates) and D. Williams and D. Freemout (study coordinators).

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