

# A short course of lithium is safe and significantly increases the cure rate of Graves' hyperthyroidism

Bogazzi F, Giovannetti C, Fessehatsion R, Tanda ML, Campomori A, Compri E, Rossi G, Ceccarelli C, Vitti P, Pinchera A, Bartalena L, Martino E. Impact of lithium on efficacy of radioactive iodine therapy for Graves' disease: a cohort study on cure rate, time to cure, and frequency of increased serum thyroxine after antithyroid drug withdrawal. *J Clin Endocrinol Metab* 2009. 11-11-2009. doi: 10.1210/jc.2009-16559.

## SUMMARY

### BACKGROUND

Although Graves' hyperthyroidism is commonly treated with radioactive iodine (<sup>131</sup>I), its effect might be improved by lithium pretreatment. Still, whether this is safe and can increase the cure rate of hyperthyroidism is uncertain, the examination of which is the aim of this study.

### SUBJECTS AND METHODS

This is a retrospective cohort study of the medical records of patients who were prospectively evaluated during follow-up in the authors' clinic. Because patients were not randomly assigned to treatment with <sup>131</sup>I or with <sup>131</sup>I plus lithium, the propensity score was used to reduce selection bias by adjusting for confounding variables. This provides a more accurate estimate of the effect of treatments that differ in several groups. In addition, multivariate analysis was performed using both the propensity score and significant covariates to control for possible bias from the nonrandomized assignment of patients to treatment.

### How Study Subjects Were Selected

The study subjects were 651 patients with Graves' disease, 508 women (78%) and 143 men (22%) referred to the University of Pisa in Italy from January 2004 through June 2007. Patients 18 years of age or older who had Graves' disease with mild or absent Graves' ophthalmopathy were selected for study unless they had moderate to severe ophthalmopathy, had previously undergone

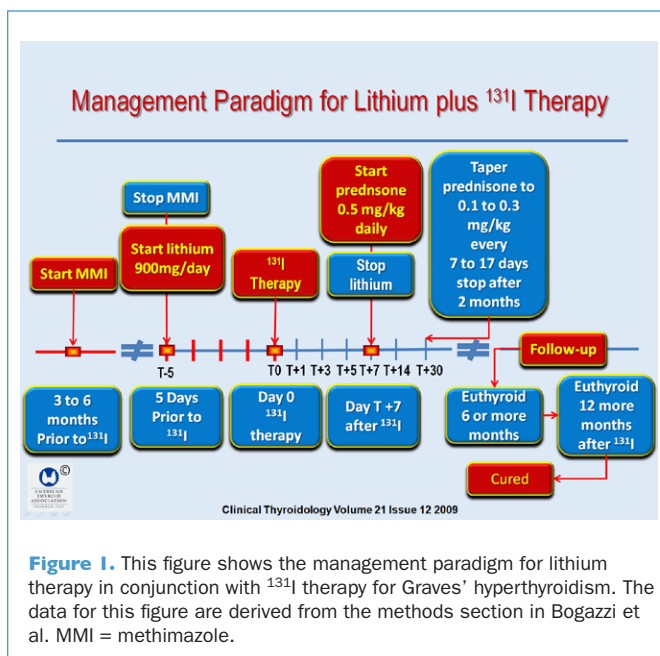
<sup>131</sup>I treatment or partial thyroidectomy, or had contraindications to treatment with glucocorticoids.

### The Treatment Paradigm (Figure 1)

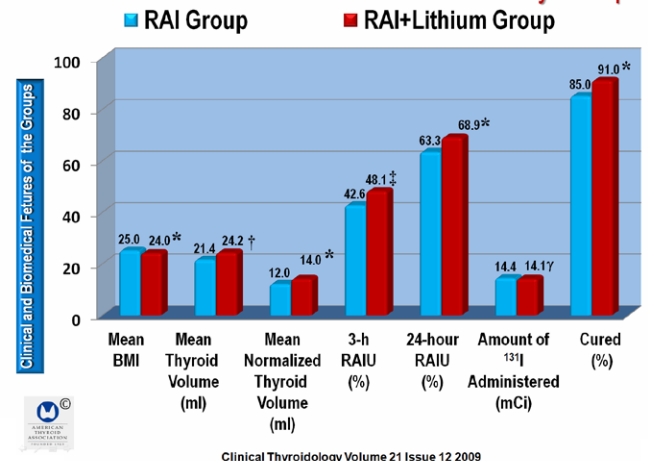
Methimazole (MMI) was started 3 to 6 months before <sup>131</sup>I therapy to restore euthyroidism and was discontinued 5 days (T-5) before <sup>131</sup>I was initiated. On the same day, lithium, 900 mg/day was started. Seven days after <sup>131</sup>I was administered (day T0), lithium was withdrawn, comprising 12 days of lithium, and oral prednisone was started at 0.5 mg/kg daily to avoid <sup>131</sup>I-associated Graves' ophthalmopathy. Prednisone was gradually tapered from 0.1 to 0.3 mg/kg every 7 to 17 days and was withdrawn after 2 months. (Figure 1). Radioactive iodine (<sup>131</sup>I) was given at a dose of 260 μCi/g of estimated thyroid tissue, corrected for the 24-hr radioactive iodine uptake (RAIU).

### The Baseline Evaluation, Follow-up, and Definition of Cure (Figure 2)

The baseline evaluation included thyroid function tests, 3 and 24 hours after RAIU, and a battery of other tests such as blood counts, measurements of blood urea nitrogen and creatinine, urinalysis, and electrocardiography. Serum free thyroxine (FT<sub>4</sub>), free triiodothyronine (FT<sub>3</sub>), and thyrotropin (TSH) measurements were obtained on days T-5, T-3, T-0, and days T+1, T+3 T+5,



## The Clinical and Biochemical Features of Study Groups



**Figure 2.** This figure shows the baseline clinical and biochemical findings that differed slightly between the two treatment groups. Patients who were treated with <sup>131</sup>I plus lithium were slightly thinner, had a slightly larger goiter, and received a slightly smaller dose of <sup>131</sup>I as compared with the group treated with <sup>131</sup>I. \*P = 0.002. †P = 0.005. ‡P = 0.0001. §P = 0.028. The other clinical and biochemical features were approximately the same in the two groups. BMI = body-mass index (the weight in kilograms divided by the square of the height in meters); RAI = radioactive iodine; RAIU = radioactive iodine uptake. This figure and Figure 3 are drawn from the data in Table 1 of Bogazzi et al.

T+7, T+14, and T+30, and then every month during a 1-year follow-up period (Figure 1).

Patients were considered to be cured when permanent hypothyroidism developed or they had stable euthyroidism, defined as serum FT<sub>4</sub>, FT<sub>3</sub>, and TSH within the normal range and confirmed during the entire 12-month follow-up. Thus, a patient who became euthyroid 6 months after <sup>131</sup>I therapy was finally considered cured if euthyroidism continued during the ensuing 12 months. A second <sup>131</sup>I treatment was given to patients with persistent hyperthyroidism after the 1-year follow-up (Figure 1). Side effects of <sup>131</sup>I were evaluated by a patient questionnaire 1 month after the administration of <sup>131</sup>I.

RESULTS

The Baseline Clinical and Biochemical Findings (Figure 2)

Among the 651 patients, 353 (54%) were treated with <sup>131</sup>I and 298 (46%) were treated with <sup>131</sup>I plus lithium. The clinical and biochemical features did not differ between the two treatment groups, except patients treated with <sup>131</sup>I plus lithium were slightly thinner, had a larger goiter, and received a slightly smaller dose of <sup>131</sup>I as compared with the group treated with <sup>131</sup>I. A larger number of patients in the <sup>131</sup>I-plus-lithium group were cured of hyperthyroidism as compared with the <sup>131</sup>I group (91% vs. 85%, P = 0.03) (Figure 2).

The Determinants of Cure by Univariate and Propensity-Adjusted Analysis (Figures 3, 4, and 5)

At 1 year, factors associated with the probability of cure by univariate logistic regression were a higher cure with lower thyroid receptor antibody (TRAb) levels (P = 0.03), lithium treatment, lower thyroid volume (P = 0.0001), lower thyroid hormone levels (P = 0.001) and higher TSH concentrations at T0 (Figures 3 and 4).

However, when the difference in the cure rate in the two groups was adjusted for covariates on meta-analysis, only lithium, TRAb, and thyroid volume maintained a significant effect on outcome (Figure 5). The odds ratio (OR) with lithium use was 2.618 (95% confidence interval [CI], 1.444 to 4.749).

After adjusting for the propensity score for lithium treatment and for TRAb values, the variables significantly affecting the propensity score were age (P = 0.005) and normalized thyroid volume (P = 0.007). Even when adjusting for the propensity score and TRAb values, the effect of lithium on cured patients was highly significant (OR, 2.459; 95% CI, 1.383 to 4.374; P = 0.002), even after adjusting for the propensity score and TRAb values (Figure 5).

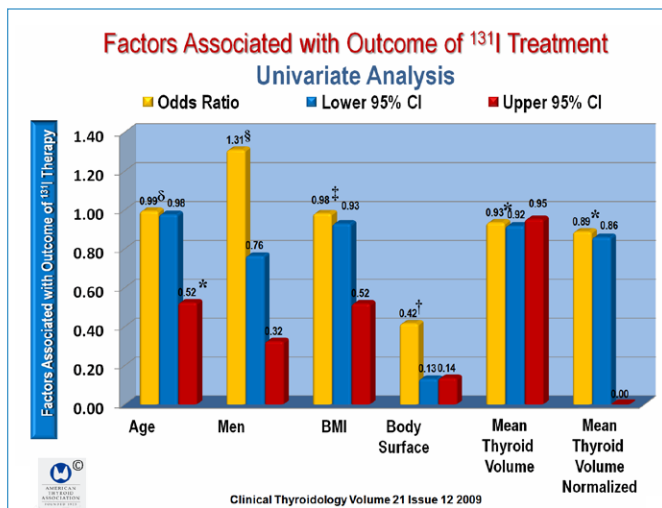


Figure 3. This figure shows the factors associated with the outcome of <sup>131</sup>I therapy by univariate analysis. BMI = body-mass index (the weight in kilograms divided by the square of the height in meters); OR = odds ratio. \*P = 0.0001. †P = 0.135. ‡P = 0.158. §P = 0.327. δP = 0.528. γP = 0.028. P = 0.846. ¶P > 0.5.

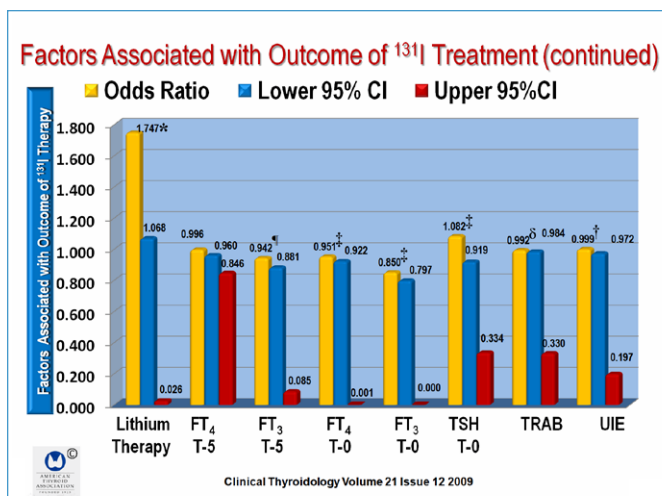


Figure 4. This figure shows the variables associated with outcomes of <sup>131</sup>I therapy that were significantly associated with a cure rates on univariate analysis. FT<sub>3</sub> = free triiodothyronine; FT<sub>4</sub> = free thyroxine; TRAb = thyroid receptor antibody; TSH = thyrotropin; UIE = urinary iodine excretion. \*P = 0.026. †P = 0.001. ‡P = 0.001. §P = 0.000. δP = 0.033.

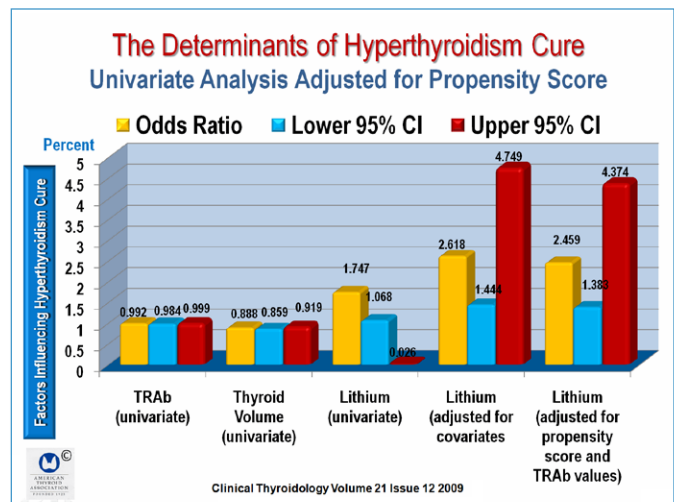


Figure 5. This figure shows the determinants of hyperthyroidism in univariate analysis, and after adjusting for the propensity score for lithium treatment and for thyroid receptor antibody (TRAb) values, the variables significantly affecting the propensity score were age (P = 0.005) and normalized thyroid volume (P = 0.007). Even when adjusting for the propensity score and TRAb values, the effect of lithium on cured patients was highly significant, even after adjusting for the propensity score and TRAb values. CI = confidence interval. The data for this figure are from Table 2 of Bogazzi et al.

**The Time Required to Cure Hyperthyroidism with Lithium**

The median time for cure of hyperthyroidism was 60 days in the <sup>131</sup>I-plus-lithium group and 90 days in the <sup>131</sup>I group (P = 0.0001). Control of hyperthyroidism was more rapid in the <sup>131</sup>I-plus-lithium group during the first months after <sup>131</sup>I. The hazard ratio of a favorable effect of lithium on median cure time was 1.512 (95% CI, 1.220 to 1.875), even when adjusted for the covariates that were significantly associated to the median cure time as shown by Cox univariate analysis (TRAb = 0.007; normalized thyroid volume P = 0.0001; and FT<sub>3</sub> P = 0.046

**The Effect of Serum Lithium Levels on Cure Rate**

The mean serum lithium level was 0.56±0.23 mEq/L; only four were >1, and one was >1.5 mEq/L. A receiver operating curve found that the optimal lithium cutoff was 0.45 mEq/L, with a sensitivity of 70% and specificity of 56%. The cure rate was higher with lithium levels ≥0.45 mEq/L (OR, 2.97; 95% CI, 1.04 to 8.81; P = 0.042). The cure rate was 93% when the lithium level was 0.45 mEq/L and 83% when it was <0.45 mEq/L.

**The Time Trend of Serum Thyroid Hormone Levels**

Mean serum FT<sub>4</sub> levels, which initially did not differ in the two <sup>131</sup>I groups, increased significantly in both groups after MMI withdrawal, reaching a peak between days T+3 to T+5 in the <sup>131</sup>I group, (P<0.001 for both times). However, in the group treated with <sup>131</sup>I and lithium, the serum FT<sub>4</sub> levels increased after both MMI withdrawal and <sup>131</sup>I therapy but remained within the normal range, with peaks at day T+3 (P = 0.0138) and T+5 (P = 0.050). The mean serum FT<sub>4</sub> levels at days T+3 and T+5 were

significantly higher in the <sup>131</sup>I group (P = 0.0139) as compared with the <sup>131</sup>I-plus-lithium group (P = 0.0373). Serum FT<sub>4</sub> levels declined, reaching the normal range between days T+14 and T+30. The mean serum FT<sub>3</sub> levels had a similar trend.

**The Outcome of Thyroid Volume and Graves' Ophthalmopathy (Figure 6)**

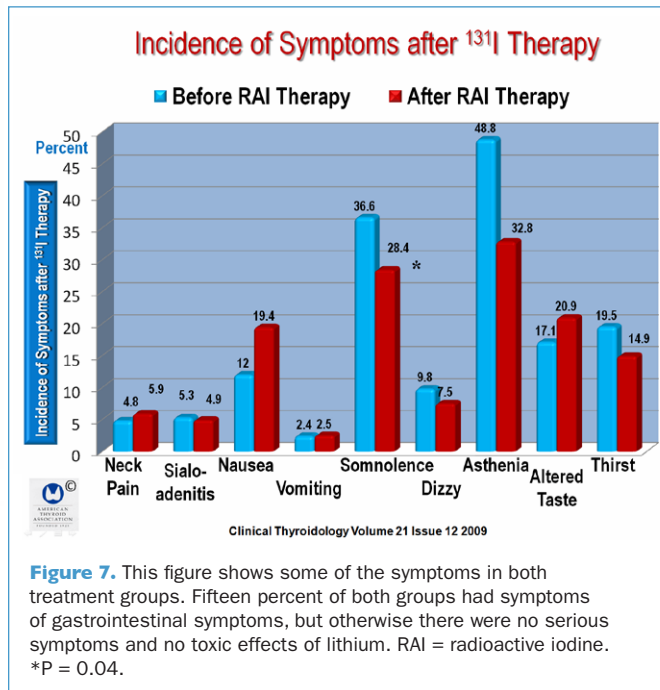
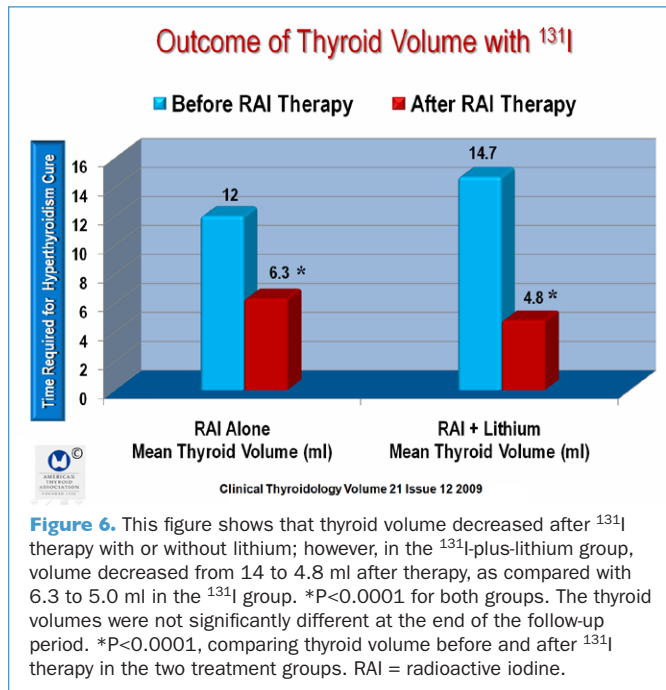
Thyroid volume decreased significantly after <sup>131</sup>I in both groups but was greater in the <sup>131</sup>I-plus-lithium group, which decreased from a mean of 14.0±7.0 to 4.8±4.5 ml (P<0.0001), as compared with the <sup>131</sup>I group, which changed from 12.0 ± 6.3 to 5.0 ± 3.9(P<0.0001); still, by the end of follow-up, thyroid volume did not differ in the two groups (P = 0.762). No patient in the study had worsening of eye disease after <sup>131</sup>I therapy.

**Symptoms Attributed to <sup>131</sup>I plus Lithium versus <sup>131</sup>I (Figure 7)**

Although 25% of patients in both groups had mild symptoms, which lasted 2 to 3 days, 15% in both groups had gastrointestinal symptoms, which did not differ in the two groups. Patients reported no toxic effects of lithium, including the four patients with lithium concentrations of >1mEq/L.

**CONCLUSION**

The short course of lithium is safe and of considerable benefit for patients who are treated with <sup>131</sup>I. It increases the cure rate for hyperthyroidism, shortens the time for cure, and prevents an abrupt increase in thyroid-hormone levels immediately after <sup>131</sup>I therapy.



**COMMENTARY**

Although Graves' hyperthyroidism may be treated with surgery, antithyroid drugs, or <sup>131</sup>I, none of the three has yet emerged as the best form of therapy. A prospective, randomized study

by Torring et al. (1) that analyzed the risks and benefits of the three forms of treatment found after a follow-up of at least 48 months that all three treatments normalized the mean serum thyroid hormone levels within 6 weeks. The risk of relapse was highest in the young and old adults (42% vs. 34%) treated with

antithyroid drugs, intermediate in those treated with  $^{131}\text{I}$  (21%), and lowest in the surgically treated young and old adults (3% vs. 8%). Moreover, there is little consensus regarding the most appropriate regimen for  $^{131}\text{I}$  in the treatment of hyperthyroidism; with some suggesting that 100 mCi may be the most appropriate amount of  $^{131}\text{I}$  for patients with Graves' hyperthyroidism (2). Still, this is an amount of  $^{131}\text{I}$  in the range usually selected for patients with thyroid cancer. Some physicians use a fixed dose of  $^{131}\text{I}$  without measuring uptake in order to prevent recurrence of Graves' hyperthyroidism. However, there is conflicting evidence about whether giving a fixed dose of  $^{131}\text{I}$  for this purpose is better than a more elaborate calculation of the dose based on goiter size, and iodine uptake and turnover (3). Also of concern is the substantial rise in thyroid hormone levels that occur when antithyroid drugs are withdrawn just before  $^{131}\text{I}$  therapy is initiated (4). Another concern is that simultaneous antithyroid drug therapy interferes with the outcome of  $^{131}\text{I}$  therapy. However, a relatively recent randomized trial found that withdrawal of an antithyroid drug 3 days before  $^{131}\text{I}$  treatment does not diminish the therapeutic effect of  $^{131}\text{I}$  (5).

Some have failed to find a favorable effect of lithium as an adjuvant in  $^{131}\text{I}$  therapy for patients with hyperthyroidism. A randomized study by Bal and associates (6) examined the role of lithium in 350 patients treated with  $^{131}\text{I}$  for hyperthyroidism. The study patients were treated with 300 mg of lithium three times a day for 3 weeks starting on the day that  $^{131}\text{I}$  was administered at an initial  $^{131}\text{I}$  dose of approximately 6 mCi, which was the same in the control group that was treated with  $^{131}\text{I}$  alone. The overall cure rate at the end of the study was the same in both groups (96.7% and 96.3%) and the authors concluded that lithium as an adjuvant in  $^{131}\text{I}$  treatment of hyperthyroidism is insignificant after a mean follow-up of  $33.3 \pm 9.8$  months. The fact that lithium was started on the same day that  $^{131}\text{I}$  was administered is a major difference from the studies by Bogazzi et al that likely account for the negative results in the study by Bal and associates.

The Bogazzi protocol, which is shown in Figure 1, was meticulously designed to avoid interference with antithyroid drugs, and to deliver lithium at the most favorable time. In the current study, lithium was given for only 9 days, beginning 5 days before  $^{131}\text{I}$  therapy was initiated, and maintained for 7 days thereafter. This

is a shorter protocol (12 vs. 19 days) than that of a previous pilot study by Bogazzi and associates (7) that found that the effect of lithium on serum thyroid hormone concentrations occurred 3 to 5 days after  $^{131}\text{I}$  was administered.

Although this is a retrospective study, the scrupulous statistical analysis takes into account the possibility of selection bias by adjusting for confounding variables. Multivariate analysis was performed using both the propensity score and significant covariates to control for possible bias from the nonrandomized assignment of patients to treatment. The main findings of the study were that patients treated with  $^{131}\text{I}$  plus lithium had a higher cure rate (91%) than those treated with  $^{131}\text{I}$  alone. Treatment with lithium also prevented an increase in serum free  $\text{T}_4$  and  $\text{T}_3$  levels after withdrawal of MMI, which had been given for 3 to 6 months prior to  $^{131}\text{I}$  therapy. Side effects of lithium were mild and transient and were not different in the two study groups with and without lithium pretreatment for  $^{131}\text{I}$  therapy. None of the patients had ophthalmopathy, and the thyroid volume decreased much more rapidly in the patients pretreated with lithium as compared with the group treated with  $^{131}\text{I}$  alone. Lastly, and of considerable importance, the study found that serum lithium concentrations of 0.7 mEq/L or greater were not associated with a higher cure rate, indicating that lithium increases  $^{131}\text{I}$  efficacy at blood levels far lower than those considered risky for the occurrence of side effects.

This large well-analyzed robust study shows that lithium is of substantial benefit in the treatment of patients with Graves' hyperthyroidism. The authors suggest that a short course of lithium is safe and beneficial for patients treated with  $^{131}\text{I}$ , increasing the cure rate for hyperthyroidism and shortening the time for cure, and preventing an abrupt increase in thyroid hormone levels.

It is highly likely that this important study will provide a strong impetus for a change in practice paradigms for patients with Graves' hyperthyroidism. It must be kept in mind, however, that all the positive effects of lithium found in this study rely upon careful adherence to a meticulous treatment protocol described in this article. The utilization of the protocol described in this study may well emerge as the dominant treatment of Graves' hyperthyroidism.

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## References

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