Outcome after Endografting in Small and Large Abdominal Aortic Aneurysms: A Metanalysis.

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Aim. To compare the results of endovascular repair (EVAR) in large and small (diameter < 5.5 cm) abdominal aortic aneurysms (AAA).

Methods. A systematic review was performed to identify studies comparing the outcomes after EVAR of large and small aneurysms. Outcomes considered were: risk of death (perioperative, all cause, aneurysm-related), ruptures, and complications (conversion, reintervention). Weighted pooled estimates of outcomes in patients with small versus large aneurysms were calculated. The inverse variance method was used (random-effect model). Subgroup analyses by a follow-up longer or shorter than 24 months were performed.

Results. Five studies, with published and unpublished data, totaling 7,735 patients, were included. Overall, the weighted pooled estimates were: OR 0.68; 95% CI 0.51–0.90 for operative mortality, OR 0.77; 95% CI 0.69 to 0.86 for all cause mortality, OR 0.58; 95% CI 0.40 to 0.87 for aneurysm-related mortality and OR 0.61; 95% CI 0.47 to 0.79 for rupture in favour of small AAA group. Pooled estimates were not influenced by follow-up length. Conversion and reintervention rates were not significantly lower for small AAA.

Conclusions. EVAR in small versus large AAA might be associated with lower operative mortality, aneurysm-related mortality and aneurysm rupture. Better evidence is needed to support these suggestions.

Keywords: Aortic aneurysm; Small aneurysm; Metanalysis; Systematic review.

Randomized controlled trials (RCT) have shown that the “waiting and watching” policy is preferred to surgical treatment for abdominal aortic aneurysms (AAA) of 5.5 cm or less since early surgical risks will not be overcome by late risks of rupture. However, the optimal strategy to treat patients with small AAA has been challenged since the introduction of endografting with the appealing prospective of offering fewer perioperative risks but undefined durability in the long term.

RCTs comparing open vs. endovascular aneurysm repair (EVAR) have failed to show evident mid-term benefit for EVAR in terms of improving all cause mortality with respect to open repair. Nevertheless, RCTs on EVAR analyzed populations exclusively with large AAA, whereas RCTs on small AAA established their results based on populations treated by open surgery or medical treatment. Consequently, it has been questioned whether the findings from both types of RCTs can be applied to small AAA treated by EVAR. The majority of studies reporting on EVAR include patients with both small and large aneurysms, whereas only a few studies have specifically addressed the outcome in subgroups of small vs. large AAA using a threshold diameter. Some Authors reported better early and mid-term results in patients with small AAA, but the precise relationship between aneurysm size and outcome is yet to be defined. Furthermore, since small AAs also represent an earlier stage of disease, the consequent expected benefit may be low and more extensive efforts are needed to clarify the issue.

A systematic review of recent studies comparing the outcome of small vs large AAA treated by EVAR was performed to investigate early and long-term
outcomes using a threshold diameter of 5.5 cm (small < 5.5 cm vs large: > 5.5 cm).

Materials and Methods

An extensive search of the literature was performed using a strategy designed to identify all relevant studies on EVAR with stratified results according to aneurysm diameter (small vs. large AAA). To avoid the confounding effect of old generation devices no longer in use today, case series before 1996 were excluded, and the search was restricted to English-language articles published between January 2000 and February 2007. Studies were initially identified from the Cochrane Library and Medline Database using the search terms “aneurysm endografting”, “aneurysm diameter”, “small aneurysm”, “large aneurysm”, “aortic endovascular”. Additional papers were identified from reference lists of retrieved articles or by hand search of the 2 most frequently identified journals by the electronic search (Journal of Vascular Surgery and European Journal of Vascular and Endovascular Surgery).

The search attempted to identify all comparative studies, case series studies, and population-based registries assessing efficacy of EVAR in large or small AAA using a threshold diameter of 5.5 cm.

Studies were included when compliant with the following criteria:

1. The numbers of operative deaths and/or late deaths after EVAR were indicated.
2. The risk of perioperative or late death, aneurysm-related death, conversion, and reintervention after EVAR was defined and calculable, per operation.
3. A 5.5 cm threshold diameter to separate large and small AAA was used.

Studies were excluded when:

1. The risks of EVAR were considered but data on small vs. large aneurysms were not reported separately.
2. The risks of EVAR were reported by aneurysm diameter but without the threshold diameter of 5.5 cm.
3. Thoracic and thoracoabdominal aortic aneurysms or patients with symptomatic or ruptured aneurysms were included.
4. Case series comprised fewer than 50 patients or case reports.

Two researchers (P.D.R. and D.B.) screened the list of references individually to identify any report that stratified EVAR outcome according to aneurysm diameter. The methodological quality of all papers was assessed by one reviewer and then checked independently by another. A data extraction form was developed specifically to record details of the design of included studies, characteristics of participants, and outcome measures of interest. Data on the outcomes during the operative and postoperative period were recorded. Where duplication was considered likely, only one paper was included. Duplicated publications from the same Authors were included once, based on the largest series and the most detailed information presented. Attempts also were made to detect any possible overlapping of cases in the multicenter published series. After exclusion of duplicates, a final database of articles was created for analysis. Authors were contacted for additional unpublished data where necessary. Unpublished data from the authors own single centre experience also were included in the analysis according to the above criteria.

Meta analysis was performed to calculate the overall risk of peri-operative (within 30 days of procedure) and late death, aneurysm-related death, rupture, conversion to open repair, and re-intervention after EVAR in small and large AAA. We followed the QUORUM guidelines in the preparation of our review (http://www.consort-statement.org).

Statistical analysis

Statistical analysis was carried out using the Revman software Version 4.2 for Windows (The Cochrane Collaboration, Oxford, UK).

Results were reported as odds ratios (OR). The odds of any outcome in patients with small aneurysms treated by EVAR were compared to the corresponding odds in patients with large AAA treated by EVAR. Forest plots were used to illustrate the information from the individual studies in terms of OR and 95% confidence interval (CI). The plots demonstrated the variation between studies and a pooled point estimate of the overall results, with 95% CI, which represented the diameter-outcome relationship in EVAR populations.

Pooled weighted estimates were calculated with random-effect model of inverse variance method. This method, widely applicable for meta-analyses, is suggested particularly for analysis of non-randomized studies.12

Heterogeneity, sensitivity analysis and subgroup analyses

Heterogeneity between estimates from individual studies was tested for using a standard $\chi^2$ test. A $p$ value
of 0.10 was considered statistically significant. Sensitivity analyses were performed by comparing the results obtained through both fixed and random effects analyses. Subgroup analyses were applied according to different lengths of mean follow-up (longer and shorter than 24 months) to determine whether studies with shorter mean follow-up might have influenced the results.

Results

Search Results

From a total of 60 papers identified in the literature search, 17 were potentially relevant for EVAR in small vs. large AAA. Full papers were obtained and assessed in detail. One RCT using a threshold of 5 cm and one single centre study that had an undetermined threshold for large AAA were excluded. Papers analyzing predictors of outcome in large versus small AAA without detailed information on major outcome data and studies published exclusively using life table methods without calculable crude numbers and numbers at risk also were excluded when a complete data sheet was not available after direct contact with the authors. Two other excluded studies were duplicated publications from the same authors. Finally, 4 papers were excluded because they analyzed exclusively large or small AAA without comparison between the two groups.

Four full-text papers met the criteria for inclusion. Two were observational studies comparing small versus large AAA.

1. Brewster et al., reviewed a prospective series of 873 EVAR and compared early and late outcomes in 424 < 5.5 cm and 439 > 5.5 cm AAA.

2. Ouriel et al. reported 700 EVAR patients, 416 with small AAA and 284 patients with large AAA, over a 6-year period.

Two studies were large multicentre EVAR registries: one European and one Australian.

3. Eurostar analyzed three aneurysm sized groups: group A, diameter < 5.5 cm, n = 1962 patients; group B, 5.5 to 6.4 cm, n = 1528; group C, diameter 6.5 cm or more, n = 902. Groups B and C (combined in the present meta-analysis) were compared to group A.

4. Golledge et al. reported a multicentre prospective registry on small AAA (Australian Registry, ASERNIP). Unpublished data from the large AAA control group were obtained by direct contact with the author for some of the outcomes.

Literature data were combined with the authors own single centre experience on 835 EVAR (details are reported in the Appendix) leaving a total of 5 studies available for meta-analysis.

All the included studies were non-randomized with no level 1 evidence. The check list used to assess the quality of these studies was adapted from Current Methods of the U.S. Preventive Services Task Force: A Review of the Process by Harris et al., and from Downs and Black and included the quality in reporting, confounding bias and external validity. The overall methodological quality of the included studies was rated as ‘fair’ according to this formal assessment. A summary of the main characteristics of the included studies are shown in Table 1.

Depending on the reported outcome being available, the total number of included patients ranged from 2398 to 7735. Mean follow-up for each study ranged from 12.1 to 39 months; in two studies it was < 24 months and in the other three > 24 months. All studies had at least 5 years of maximum follow-up to assess late outcomes, ranging from 6 to 10 years in 4/5 studies.

Meta Analysis results

Table 2 shows the main characteristics of the patient population in each study.

Pooled estimates of outcomes using random-effect model of inverse variance method are displayed in Figs. 1 to 6.

Peri-operative mortality in a total of 6090 cases ranged from 0% to 1.6% after EVAR in the small aneurysm group and from 2% to 3.2% in the large group. In the pooled estimate of the 3 studies reporting on this outcome, lower peri-operative mortality was observed in the small AAA group (OR 0.68; 95% CI 0.51 to 0.90; test for heterogeneity p = 0.30) (Fig. 1).

Data on all cause mortality were available from 3 studies (2398 cases), data on aneurysm-related death rate from 3 studies (6090 cases) and data on AAA ruptures, after AAA repair, from 5 studies (7735 cases). All cause mortality (OR 0.77; 95% CI 0.69 to 0.86; test for heterogeneity p = 0.21), aneurysm-related mortality (OR 0.58; 95% CI 0.40 to 0.87; test for heterogeneity p = 0.07) and aneurysm rupture rates, (OR 0.61; 95% CI 0.47 to 0.79; test for heterogeneity p = 0.70) were all in favour of the small AAA group (Figs. 2–4). Statistical heterogeneity was found for AAA-related mortality.
Conversion and re-intervention rates after EVAR were reported in three studies including 2643 patients; all were studies with follow-up of longer than 24 months. Although the conversion rate appeared lower in the small AAA group, this was not significant (OR 0.93; 95% CI 0.73 to 1.18; test for heterogeneity \( p = 0.23 \); Fig. 5). The secondary intervention rates were similar in the small AAA (range 10–12%) and large AAA groups (range 10.5–14.5%), OR 0.96; 95% CI 0.86 to 1.06; test for heterogeneity \( p = 0.71 \); Fig. 6.

Subgroup analysis results

Subgroup analyses according to follow-up length were performed for all-cause mortality, AAA-related mortality, and rupture (Figs. 2–4). All results are reported with random effect model, although fixed effect models also were used and generated similar results.

In the 3 studies reporting on all cause mortality there was a significant association with lower all cause mortality in the small AAA group that persisted after excluding the study with shortest follow-up (OR 0.80; 95% CI 0.71 to 0.90; test for heterogeneity \( p = 0.22 \); Fig. 2), although these results were not adjusted for age (higher in the large AAA group).

Similarly, aneurysm-related death rate reported from 3 studies showed a lower risk in small versus large group of AAA, a finding that remained when the study with shortest follow-up was excluded. However, the heterogeneity in this outcome was

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Studyperiod Years</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Mean Follow-up</th>
<th>Notes</th>
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<td>Brewer, 2006</td>
<td>1994–2005</td>
<td>Monocentric observational study</td>
<td>Small AAA vs large AAA</td>
<td>EVAR</td>
<td>Perioperative mortality, overall mortality, AAA related mortality rupture, conversion, reinterventions</td>
<td>27 months (maximum: 10 years)</td>
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<td>EUROSTAR, 2004</td>
<td>1996–2002</td>
<td>Multicentric registry</td>
<td>Small AAA vs large AAA</td>
<td>EVAR</td>
<td>Perioperative mortality, overall mortality, AAA related mortality, rupture</td>
<td>20.4 months (maximum: 6 years)</td>
<td>European registry; 3 groups of AAA by size: Group A (4 to 5.4 cm), Group B (5.5 to 6.4 cm) and Group C (6.5 cm or larger)</td>
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<tr>
<td>Golledge, 2007</td>
<td>1999–2001</td>
<td>Multicentric registry</td>
<td>Small AAA vs large AAA</td>
<td>EVAR</td>
<td>Perioperative mortality, overall mortality, AAA related mortality rupture, conversion, reinterventions</td>
<td>38 months** (maximum: 6 years)</td>
<td>ASERNIP-S Australian registry (Safety and Efficacy Register of New Interventional Procedures-Surgical). Unpublished data from large aneurysm group (contact with Authors)</td>
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<td>1996–2002</td>
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<td>EVAR</td>
<td>Overall mortality, rupture</td>
<td>12.1 months (maximum: 5 years)</td>
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<td>Perugia, 2007</td>
<td>1997–2007</td>
<td>Monocentric observational study</td>
<td>Small AAA vs large AAA</td>
<td>EVAR</td>
<td>Perioperative mortality, overall mortality, AAA related mortality rupture, conversion, reinterventions</td>
<td>39 months (maximum: 10 years)</td>
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* reliable data.
unpublished data.
\(^{\text{†}}\) published and unpublished data.
\(^{*}\) median.
Five studies reported on aneurysm rupture. Similar differences were shown in longer (OR 0.58; 95% CI 0.39 to 0.87; test for heterogeneity p = 0.35) and shorter follow-up subgroups (OR 0.63; 95% CI 0.44 to 0.88; test for heterogeneity p = 1) in favour of the small AAA group (Fig. 4).

Discussion

Currently there is no available evidence from RCT on early and long-term efficacy of EVAR based on aneurysm diameter. Therefore, the data for this systematic review originated from non-randomized controlled studies, of only fair quality. According to the analysis of over 6,000 pooled cases, endovascular treatment for small aneurysms in comparison to large aneurysms was associated with a lower peri-operative mortality rate. AAA-related mortality and AAA rupture at a mean follow-up of 3.2 years and a maximum of 10 years also were lower in the small AAA group. Although all-cause mortality also was lower in the small AAA group, the results were not adjusted for age and the small AAA patients were younger than the large AAA patients.

The surgical decision to treat any aneurysm is based on AAA diameter, expansion rate, patient's risk factors, centre experience with EVAR and expected long-term clinical benefit of treatment. There are two major issues in this respect: the size of aneurysm, which determines the risk of rupture, and the case mix of patients in terms of age and comorbidities.

<table>
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<th>Study or sub-category</th>
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<th>Weight %</th>
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<td>95% CI</td>
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<tr>
<td>Eurostar 2004</td>
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<tr>
<td>Total (95% CI)</td>
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<td>Test for heterogeneity: Chi² = 2.40, df = 2 (P = 0.30)</td>
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Fig. 1. The odds of periprocedural death for small versus large AAA: weighted pooled results by random-effect model of inverse variance method. u/d: unpublished data.

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A number of questions arise from the results of this review on the challenging issue of small AAA treatment. 1) Why did large AAA diameter have higher peri-operative mortality rates? 2) What are the durability and the clinical benefit of this treatment effect?

The answer to the first question is complex. Differences might be due to different patterns of risk factors between the two groups of patients with large and small aneurysms. Small AAA may represent an earlier stage of the disease in healthier patients who have better outcome from treatment. On the other hand, a large body of data suggests that large AAA is more likely to be associated with hostile anatomy and this is an issue in explaining difference in outcomes. Morphological studies suggest that small AAA have less complex anatomy, with longer aortic necks, less neck angulation, and less tortuosity, while AAA maximum diameter is inversely related to the length of the aortic neck. Aneurysm diameter may be the most useful surrogate determinant of feasibility for EVAR. Welborn et al previously reported that 64% of patients with small AAA are candidates for EVAR, whereas only 39% with large AAA are suitable for EVAR when the manufacturers’ instructions for use are strictly followed. Furthermore, the expansion of small AAAs is associated with anatomic changes in aortic aneurysm morphology with a significant change in suitability for EVAR. A relationship between the growth of aneurysms and shorter and wider proximal aortic necks has been demonstrated. These changes may affect aneurysm suitability for EVAR during the surveillance period.

What are the durability of this treatment effect and the long-term clinical benefit for small AAA? Indeed, if the rupture risk in unrepaired small AAA is not large enough, treatment would not be indicated. Literature data based on 5-year survival curves showed that freedom from AAA-related death ranged from 97.2% to 99% and all cause survival rates from 69% to 84.2%. Data from this review (after excluding studies with short follow-up) showed a difference in rupture rate (OR 0.58; 95% CI 0.39 to 0.87) persisting up to 10 years in favour of aneurysms treated at a smaller size. However, risk of rupture needs to be assessed with stronger evidence comparing EVAR versus surveillance.

Based on these two question-points, since optimal EVAR suitability or no co-morbidities, are more frequently found in patients with small AAAs, the strategy to treat small AAA might be considered an elective early treatment that can offer better outcomes. At the same time, there is the objection that the risk of aneurysm-related death in small aneurysms is per se
low, due to the low rupture rates found in patients under surveillance and early EVAR may produce unnecessary operations.\textsuperscript{1,2,31,32} The level 1 evidence on EVAR from the UK EVAR trials has demonstrated the peri-operative superiority of EVAR in fit patients with large AAA with respect to open surgery (OR 0.24; \(P = 0.030\)).\textsuperscript{33} Even if this evidence is translated to small AAA there is still need for further direct level 1 evidence.

EVAR also is affected by need for re-intervention. According to this review differences in re-intervention and conversion rates were not significantly less in the small AAA group. This may underscore the need for further technological improvement in terms of durability of the available endografts. On the other hand, suitability is the key to success for EVAR.

At present, the treatment of small aneurysms is mainly conservative in most centres while intervention is reserved for those expanding beyond a diameter limit of 5.5 cm. Evidence supporting this policy is provided by two large randomized trials showing that early elective open surgery conferred no long-term survival benefits.\textsuperscript{1,2} From these studies it also became evident that approximately 70\% of these small AAA will require “delayed” treatment within 5 years because of significant enlargement or, less likely, symptoms. Since the 12 year results from the UKSAT concluded for no long-term survival benefit of early elective open repair of small AAA,\textsuperscript{2} it could be assumed that patients with small AAA may be safely left untreated for the first 5–6 years in centers where there is a surveillance program. A controversy may derive from the fact that early EVAR in patients with good suitability could be a primary choice in centres with experienced endovascular teams low peri-operative risks and reliable follow-up schedule.

Based on the present review, today the decision to treat a patient with small AAA by EVAR is not justified outside a randomized controlled trial. At the same time, it is premature to use comparisons with either open surgery or unfit patients to mount an argument against EVAR for small AAA.\textsuperscript{31,32}

Study limitations

The pooled data from these non-randomized series of only fair quality cannot provide level 1 evidence. Therefore, our results should be used with caution. Selection or publication bias between the populations at comparison may have impacted on our findings. Differences in co-morbidities and case mix could influence the outcome of patients with large versus small AAA, particularly in terms of survival where no adjustments were made for age and other differences.
This is a review on results of EVAR on small and large aneurysm and not an observational study on small aneurysms. Information on a surveillance group is lacking. Therefore, the key question as to whether “watchful waiting” and delayed treatment is better or worse than early EVAR in a suitable population could not be addressed.

Furthermore, variability in length and adherence to follow-up, sample size, and patient inclusion criteria, as patients at different surgical risk, among the studies should also be taken into account.

Although this review used studies from the period 2000 to early 2007, some of the published experiences may have used outdated device technology.
Conclusions

The results of the present meta-analysis, with the above specified limitations, suggest that EVAR in small versus large AAA was associated with a better outcome for peri-operative and aneurysm-related mortality. Screening and surveillance programs play a key role in small aneurysm management. The debate about surveillance or EVAR for small aneurysms has not been answered and better evidence is required. Whether EVAR applied to small AAA produces more benefits than hazards due to over treatment needs to be assessed by randomized trials comparing early endografting versus surveillance.34,35

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Disclaimer: Piergiorgio Cao is Principal Investigator of the Caesar trial (Comparison of Surveillance vs Aortic Endografting for Small Aneurysm Repair), multicenter randomized trial comparing EVAR vs Surveillance in small AAA. The study is partially supported by COOK company.

Appendix

Early and long-term outcome of a consecutive series of 835 EVAR performed at the authors own single centre from April 1997 to January 2007 were reviewed. Only patients treated electively with commercially available devices were included: 336 Zenith (Cook, Bloomington, IN, USA), 238 AneuRx (Medtronic AVE, Santa Rosa, CA, USA), 117 Talent (Medtronic AVE, Santa Rosa, CA, USA), 92 Excluder (WL Gore & Associates, Sunnyvale, CA, USA), 35 Fortran (Cordis, Johnson & Johnson, Warren, NJ, USA), 13 Anaconda (Sulzer Vasutek, Edinburgh, UK), 3 Endologix (Bard, Irvine, CA, USA), 1 Endomed (Endomed, Phoenix, AZ, USA) were implanted.

Patients were followed-up by periodic clinical examination, duplex ultrasound, X-ray and computed tomographic (CT) scan. Mean follow-up was 39.2 months (range 1–114 months; median 32 months).

Fig. 6. The odds of reintervention during follow-up for small versus large AAA (weighted pooled results by random-effect model of inverse variance method). All studies with mean follow-up longer than 24 months. u/d unpublished data; p/d: published and unpublished data.

Results

Of the overall 835 patients, 543 (65%) underwent EVAR for aneurysms smaller than 5.5 cm in diameter and 292 (35%) for aneurysms 5.5 cm or larger in diameter.
With respect to risk factors, patients with large aneurysms were older (74.4 vs. 71.7 years, \( p = 0.001 \)) and more prone to coronary heart disease (50% vs. 42%, \( p = 0.01 \)) and chronic obstructive pulmonary disease (60% vs. 49%, \( p = 0.02 \)) than patients with small aneurysms. With respect to the anatomical features, patients with large AAA were more prone to have neck < 10 mm (9% vs. 4%, \( p = 0.001 \)), angulated neck (23% vs. 13%, \( p = 0.001 \)) and associated iliac aneurysm (32% vs. 21%, \( p = 0.001 \)) than patients with small AAA. There were 9 perioperative deaths, 6 in the large group and 3 in the small group. Furthermore, 6 ruptures (3 in each group), 47 conversions to open repair (30 in the small group and 17 in the large group) and 95 reinterventions (62 in the small group and 33 in the large group) occurred. At 96 months of follow-up life table analysis showed that patient survival decreased (49% vs. 65%, \( p < 0.001 \)), risk of aneurysm-related death (4.1% vs. 1.3%; \( p = 0.05 \)) and risk of reintervention after EVAR (50% vs. 35%; \( p = 0.018 \)) increased in the group with large aneurysms. Risk of rupture (5.7% vs. 1.1%) and risk of conversion (13.9% vs. 22.6%) also increased in the group of large AAA but these data did not reach statistical significance.

References


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