Drug-eluting balloon catheters for lower limb peripheral arterial disease: the evidence to date

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Abstract: A significant proportion of patients with severe lower limb peripheral arterial disease require revascularization. Over the past decade, an endovascular-first approach even for complex disease has gained widespread use among vascular specialists. An important limitation of percutaneous transluminal balloon angioplasty or stenting remains the occurrence of restenosis. Drug-coated balloons have emerged as an exciting technology developed to overcome the limitations of standard balloon angioplasty and stenting. Drug-eluting devices inhibit neointimal growth of vascular smooth muscle cells with the potential of preventing restenosis. This review provides a synopsis of the up-to-date evidence on the role of drug-coated balloons in the treatment of lower limb peripheral arterial disease. Bibliographic searches were conducted using MEDLINE, EMBASE, and the Cochrane Library electronic database. Eleven randomized clinical trials, two systematic reviews, and a published registry providing the best available evidence were identified. Current evidence suggests that angioplasty with drug-coated balloon is reliable, safe, and efficient in increasing patency rates and reducing target lesion revascularization and restenosis. However, it remains unknown whether these improved results can translate into beneficial clinical outcomes, as current randomized clinical trials have failed to demonstrate a significant benefit in limb salvage and mortality. Further randomized trials focusing on clinical and functional outcomes of drug-eluting balloons and on cost versus clinical benefit are required.

Keywords: drug-eluting balloon, drug-coated balloon, angioplasty, peripheral arterial disease

Introduction

Atherosclerosis is a systemic disease of the large- and medium-sized arteries causing luminal narrowing (focal or diffuse) as a result of the accumulation of lipid and fibrous material between the intimal and medial layers of the vessel.\textsuperscript{1} Atherosclerosis of the noncardiac vessels is defined as peripheral artery disease (PAD). PAD can present clinically as intermittent claudication (IC), which can severely impair lifestyle. More severe disease may present as critical limb ischemia (CLI) with rest pain, ulceration, or gangrene in the lower extremities. The worldwide prevalence of PAD is between 3\% and 12\%.\textsuperscript{2} In Europe and North America, an estimated 27 million individuals are affected, with \textasciitilde{413,000} inpatient admissions annually attributed to PAD.\textsuperscript{2}

The European Society of Cardiology Guidelines, published in 2011, recommended an endovascular-first strategy in all femoral–popliteal TASC A-C and infrapopliteal lesions, when revascularization is indicated.\textsuperscript{1} The low morbidity and mortality of endovascular techniques, such as percutaneous transluminal angioplasty (PTA) and stenting, make it the preferred choice of treatment in diseases such as stenosis and...
to the English language and adult population of any age group. Inclusion criteria were all RCTs, systematic reviews, registries, and large cohort studies evaluating the role of DEB angioplasty in the treatment of de novo femoral–popliteal and infrapopliteal lesions. We focused on the following primary end points: binary restenosis, late lumen loss (LLL), target lesion revascularization (TLR), mortality, and major amputation rate.

Search outcome
The primary search for DEB angioplasty in PAD returned 190 citations. Twenty-four relevant publications met the inclusion criteria for this review. Fourteen of these articles provided the best up-to-date evidence on DEBs in PAD. Seven RCTs and two meta-analyses reported on DEBs in femoral–popliteal disease. Three RCTs and one registry reported on infrapopliteal disease, and another RCT reported on DEB intervention in both femoral–popliteal and infrapopliteal lesions.

Study quality assessment
The Cochrane collaboration’s tool was applied to assess the risk of bias of RCTs.⁹ The Grades of Recommendation Assessment, Development, and Evaluation methodology was used to rate our confidence in each reported outcome as high, moderate, low, or very low on the basis of different domains.¹⁰

Results
Femoral–popliteal disease
Since 2008, eight RCTs¹¹–¹⁸ and two meta-analyses¹⁹,²⁰ have demonstrated favorable technical outcomes with DEBs compared with plain balloon angioplasty in the treatment of femoral–popliteal atherosclerotic disease, as indicated by LLL, restenosis rate, and freedom from TLR. Herein, we present the most important trials, based on the methodological and risk of bias assessment, the sample size, and the length of follow-up. A detailed description of all selected studies is outlined in Table 1. The LEVANT 2¹¹ and IN.PACT SFA¹² are the most recent international multicenter RCTs with the largest number of enrolled patients (331 and 476, respectively).

The LEVANT 2 pivotal Investigational Device Exemption trial is a prospective, multicenter (42 in US and 12 in European Union), single-blind, randomized (2:1) clinical trial comparing Lutonix DEB to standard PTA for the treatment of occlusive disease in native femoral–popliteal arteries. The primary patency at 1 year was 65.2% for the DEB group, which was superior to that of conventional PTA (52.6%;
Table 1 Randomized control trials of drug-eluting balloon for femoral–popliteal disease

<table>
<thead>
<tr>
<th>Study name/GRADE</th>
<th>No of pt</th>
<th>Age (years)</th>
<th>Anatomical location</th>
<th>Lesion length (mm)</th>
<th>Clinical severity</th>
<th>Aim</th>
<th>Primary end points</th>
<th>FU</th>
<th>Key results</th>
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<tr>
<td>LeVANT 2 trial (2015)$^{16++}$</td>
<td>476</td>
<td>69.2±9.4</td>
<td>Femoral–popliteal</td>
<td>84.4±48.5</td>
<td>IC</td>
<td>DEB vs standard PTA</td>
<td>12 months</td>
<td>The primary efficacy end point was primary patency of the target lesion at 12 months. The primary safety end point was a composite of freedom from perioperative death from any cause and freedom from limb-related death at 12 months</td>
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<tr>
<td>iN.PACT SFA I and II trial (2015)$^{17++}$</td>
<td>331</td>
<td>67.5±9.5</td>
<td>Femoral–popliteal</td>
<td>89.4±4.85</td>
<td>IC</td>
<td>IN.PACT Admiral DEB vs standard PTA</td>
<td>12 months</td>
<td>Efficacy end point: primary patency of the target lesion at 12 months. Safety end points: 30-day mortality, limb salvage, target vessel thrombosis</td>
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<td>DeBellum trial (2014)$^{13++}$</td>
<td>50</td>
<td>66±4</td>
<td>Femoral–popliteal or BTK arteries</td>
<td>75±35</td>
<td>IC + CLI</td>
<td>DEB vs standard PTA</td>
<td>6–12 months</td>
<td>In the femoral–popliteal region, the overall LLL was 0.61±0.8 mm for DEB vs 1.84±0.3 mm for standard PTA (P&lt;0.02). BTK, the overall LLL was 0.66±0.9 mm (DEB) vs 1.69±0.5 mm (standard PTA) (P&lt;0.03). The overall TLR was 12.2% for DEB and 35.3% for standard PTA (P&lt;0.05). Amputation rate was 4% (DEB) vs 12% (standard PTA) (P&lt;0.05). Thrombosis was 4% (DEB) vs 8% (standard PTA) (P&lt;0.05). Major AEs 24% (DEB) vs 60% (standard PTA) (P&lt;0.05). ABI improved more in the DEB group: 0.81±0.3 vs 0.68±0.13 (P&lt;0.02). Fontaine stage increased (from Iib to I) 80% DeB vs 56% standard PTA (P&lt;0.05)</td>
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<td>LeVANT I trial (2013)$^{15++}$</td>
<td>101</td>
<td>68.5</td>
<td>Femoral–popliteal</td>
<td>81±38</td>
<td>IC</td>
<td>Lutonix DEB vs standard PTA</td>
<td>92 patients at 6 months, 87 patients at 12 months, 83 patients at 24 months</td>
<td>LLL at 6 months 0.46 mm (DEB) vs 1.09 mm (standard PTA; P=0.016); composite 24-month major AEs 39% (DEB; including 15 TLRs, one amputation, four deaths) vs 46% (standard PTA; including 20 TLRs, one thrombosis, five deaths) (P=0.45)</td>
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<td>DEBATe-SFA trial (2013)**++</td>
<td>104</td>
<td>75±9</td>
<td>Femoral–popliteal</td>
<td>94±60</td>
<td>IC + CLI</td>
<td>DEB and BMS vs standard PTA and BMS</td>
<td>12 months</td>
<td>Binary restenosis 17% (DEB and BMS) vs 47.3% (standard PTA and BMS; P=0.008); freedom from TLR 83% (DEB and BMS) vs 66.7% (standard PTA and BMS; P=0.07); restenosis 17% (DEB and BMS) vs 47.3% (standard PTA and BMS; P=0.008); LLL 0.86 mm (DEB and BMS; MQR 0.8–0.94) vs 1.68 mm (standard PTA and BMS; MQR 1.6-4.2; P=0.001); no major amputation in either group</td>
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<td>PACiFieR trial (2012)**+++</td>
<td>85</td>
<td>71±7</td>
<td>Femoral–popliteal</td>
<td>70±53</td>
<td>IC</td>
<td>DEB vs standard PTA</td>
<td>6 months</td>
<td>LLL at 6 months</td>
<td></td>
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<tr>
<td>THUNDeR trial (2008)**+++</td>
<td>154</td>
<td>68±8</td>
<td>Femoral–popliteal</td>
<td>74±65</td>
<td>IC</td>
<td>DEB vs standard PTA vs PTA with paclitaxel dissolved in contrast medium</td>
<td>6 months</td>
<td>LLL at 6 m 0.4 mm (DEB) vs 1.7 mm (standard PTA) vs 2.2 mm (paclitaxel/contrast PTA) (P=0.001) DEB vs standard PTA; P=0.11 DEB vs paclitaxel/contrast PTA; TLR at 6 m 4% (DEB) vs 37% (standard PTA; P=0.001); TLR at 24 m 15% (DEB) vs 52% (standard PTA; P=0.001)</td>
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<tr>
<td>FemPac trial (2008)**+++</td>
<td>87</td>
<td>68.7</td>
<td>Femoral–popliteal</td>
<td>40±21</td>
<td>IC</td>
<td>DEB vs standard PTA</td>
<td>128 angio FU at 6 months; 146 clinical FU at 6 months</td>
<td>Less LLL in the DeB group (0.5±1.1 vs 1.0±1.1 mm; P=0.031). TLR was lower in the DEB group than in control subjects (three of 45 vs 14 of 42 patients; P=0.002). Improvement in Rutherford class was greater in DEB (P=0.045), whereas the improvement in ABI was not different. The difference in TLR between treatment groups was maintained up to &gt;18 months. No AEs were assessed as related to balloon coating</td>
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Note: Quality of study as per GRADe system: ****, high; ***, moderate; **, low; *, very low.

Abbreviations: ABI, ankle brachial index; AE, adverse event; BMS, bare metal stent; BTK, below the knee; CLI, critical limb ischemia; DeB, drug-eluting balloon; FU, follow-up; GRADe, Grades of Recommendation Assessment, Development, and Evaluation; IC, intermittent claudication; LLL, late lumen loss; m, months; MQR, median quartile range; pt, patients; PTA, percutaneous transluminal angioplasty; TLR, target lesion revascularization.
In the DEBATE-BTK trial,23 investigated the efficacy of a paclitaxel DEB for the reduction of restenosis in diabetic patients with CLI. Binary restenosis, assessed by angiography in >90% of patients, occurred in 20 of 74 (27%) lesions in the DEB group versus 55 of 74 (74%) lesions in the standard PTA group (P<0.001), TLR in 12 (18%) versus 29 (43%) (P=0.002), and target vessel occlusion in 12 (17%) versus 41 (55%) (P<0.001). There was one major amputation, which occurred in the standard PTA group (P=0.9).

In the IDEAS trial,24 50 patients were randomized to infrapopliteal DEB angioplasty (25 arteries in 25 limbs) or primary DES placement (30 arteries in 27 limbs). The binary restenosis rate was significantly lower in DES (28% vs 57.9%; P=0.0457). There were no significant differences in TLR (7.7% in DES vs 13.6% in PTA; P=0.65). At 6 months, five patients died (two in DES vs three in DES; P=1.00) and three suffered a major amputation (one in DES vs two in DES; P=1.00).

In the IN.PACT DEEP trial,22 358 patients with CLI were randomized 2:1 to IN.PACT Amphilior DEB angioplasty or standard PTA at 13 European sites. After 12 months, the decision was made to recall the IN.PACT Amphilior DEB based on a trend toward a higher rate of major amputation in the DEB arm (8.8% vs 3.6%; P=0.08) and no significant benefit for the efficacy end points of clinically driven TLR (11.9% vs 13.5%; P=0.682), LLL (0.605±0.775 mm vs 0.9 mm DEB vs 1.69±1.5 mm PTA; P<0.05), TLR (15.3% DEB vs 47.0% PTA; P<0.05), and primary patency (84.6% DEB vs 41.1% PTA; P<0.05). However, major adverse events (defined as major or minor amputation, thrombosis, or death) did not differ significantly between DEBs and standard PTA presumably because of the limited number of lesions and patients treated.

The DEBATE-BTK trial34 investigated the efficacy of paclitaxel DEB for the reduction of restenosis in diabetic patients with CLI. Binary restenosis, assessed by angiography in >90% of patients, occurred in 20 of 74 (27%) lesions in the DEB group versus 55 of 74 (74%) lesions in the standard PTA group (P<0.001), TLR in 12 (18%) versus 29 (43%) (P=0.002), and target vessel occlusion in 12 (17%) versus 41 (55%) (P<0.001). There was one major amputation, which occurred in the standard PTA group (P=0.9).

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<th>Study name/GRAGE</th>
<th>No of pt</th>
<th>Age, mean ± SD</th>
<th>Anatomical location</th>
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<tr>
<td>IDEAS trial (2014)</td>
<td>50</td>
<td>69±8</td>
<td>Infrapopliteal</td>
<td>IC + CLI</td>
<td>DEB: 148±56.7; DES: 127±46.5</td>
<td>DEB vs DES</td>
<td>Target lesion restenosis &gt;50% assessed by digital angiography at 6 months</td>
<td>6 months</td>
<td>At 6 months, five patients died (two in DEB vs three in DES; P=1.00) and three suffered a major amputation (one in DEB vs two in DES; P=1.00). Binary (&gt;50%) angiographic restenosis rate was significantly lower in DES (seven of 25 [28%] vs eleven of 19 [57.9%] in DEB; P=0.0457). There were no significant differences with regard to TLR (two of 26 [7.7%] in DES vs three of 22 [13.6%] in DEB; P=0.65). Positive vessel wall remodeling was observed in three cases in the DEB arm (three of 19 [15.8%] vs zero of 19 [0%] in DES; P=0.07).</td>
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<tr>
<td>DEBBELLUM trial (2014)</td>
<td>50</td>
<td>66±4</td>
<td>Femoral–popliteal or infrapopliteal</td>
<td>IC + CLI</td>
<td>75±35</td>
<td>DEB vs standard PTA</td>
<td>LLL at 6 months</td>
<td>6–12 months</td>
<td>In the femoral–popliteal region, the overall LLL was 0.61±0.8 mm for DEB vs 1.84±0.3 mm for standard PTA (P=0.02). BTK, the overall LLL was 0.66±0.9 mm (DEB) vs 1.69±0.5 mm (standard PTA) (P=0.03). The overall TLR was 12.2% for DEB and 35.3% for standard PTA (P&lt;0.05). Amputation rate was 4% (DEB) vs 12% (standard PTA) (P=0.36). Thrombosis was 4% (DEB) vs 8% (standard PTA) (P=0.05). Major AEs 24% (DEB) vs 60% (standard PTA) (P=0.05). ABI improved more in the DEB group: 0.81±0.3 vs 0.68±0.13 (P=0.02). Fontaine stage increased (from IIb to I) 80% DEB vs 56% standard PTA (P&lt;0.05).</td>
</tr>
<tr>
<td>DEBATE-BTK trial (2013)</td>
<td>132 (158 lesions)</td>
<td>74±9</td>
<td>Infrapopliteal</td>
<td>CLI (pt with diabetes)</td>
<td>129±83</td>
<td>DEB vs standard PTA</td>
<td>Binary in-segment restenosis at 1-year angiographic or ultrasonographic FU</td>
<td>12 months</td>
<td>Binary restenosis, assessed by angiography in &gt;90% of patients, occurred in 20 of 74 lesions (27%) in the DEB group compared with 55 of 74 lesions (74%) in the standard PTA group (P&lt;0.001). TLR, DEB 12 (18%) vs standard PTA 29 (43%; P=0.002); and target vessel occlusion, DEB 12 (17%) vs standard PTA 41 (55%; P&lt;0.001). Only one major amputation occurred in the standard PTA group (P=0.09).</td>
</tr>
<tr>
<td>iN.PACT DEEP trial</td>
<td>358</td>
<td>102±129</td>
<td>Infrapopliteal</td>
<td>CLI</td>
<td>DEB vs standard PTA</td>
<td>Clinically driven TLR and LLL at 12 months. All-cause mortality, major amputation, and clinically driven TLR at 6 months served as the primary safety end points</td>
<td>12 months</td>
<td>Primary efficacy results of DEB vs standard PTA were clinically driven TLR of 9.2% vs 13.1% (P=0.291) and LLL of 0.61±0.78 mm vs 0.62±0.78 mm (P=0.950). Primary safety end points were 17.7% vs 15.8% (P=0.021) and met the noninferiority hypothesis. A safety signal driven by major amputations through 12 months was observed in the DEB arm vs the standard PTA arm (8.8% vs 3.6%; P=0.080).</td>
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DeB catheters for lower limb peripheral arterial disease

Leipzig Registry (2011) 104  73.6±6.7  Infrapopliteal IC + CLI 173±87

DEB for long infrapopliteal lesion

3 months angiographic follow-up. Clinical improvement was defined as marked (50%) reduction in ulcer size or depth or increase of at least one Rutherford-Becker category.

Notes: Stopped prematurely. Quality of study as per GRADE system: ++++, high; ++, moderate; +, low; +, very low.

Abbreviations: ABi, ankle brachial index; AE, adverse event; BTK, below the knee; DEB, drug-eluting balloon; CLI, critical limb ischemia; DES, drug-eluting stent; FU, follow-up; GRADE, Grades of Recommendation Assessment, Development, and Evaluation; IC, intermittent claudication; LLL, late lumen loss; m, months; pt, patients; PTA, percutaneous transluminal angioplasty; TLR, target lesion revascularization.

Discussion

All available RCTs demonstrate equivalent or favorable technical outcome for DEBs in comparison to standard PTA. Several factors can result in improved clinical outcomes. In the treatment of infragingual PAD, the RCTs focused on one of the following primary efficacy end points: LLL, binary restenosis, and freedom from TLR. The follow-up period varied from 6 to 12 months. Baerlocher et al 20 recently published a meta-analysis of eight RCTs demonstrating superior results with DEBs over standard PTA for femoral-popliteal disease, as indicated by LLL, restenosis, and TLR. However, no benefit was found in clinical end points, such as major amputation and mortality.

In terms of new trials currently recruiting patients, the BASIL 3 trial 25 is a multicenter RCT currently recruiting in 60 UK centers, which aims to determine whether DEB angioplasty with or without bare metal stent, plain balloon angioplasty with or without bare metal stent alone is the most effective revascularization. In terms of new trials currently recruiting patients, the BASIL 3 trial 25 is a multicenter RCT currently recruiting in 60 UK centers, which aims to determine whether DEB angioplasty with or without bare metal stent, plain balloon angioplasty with or without bare metal stent alone is the most effective revascularization.

The results of the risk of bias of the RCTs are outlined in Figure 1 and 2. All RCTs included in this review demonstrated low selection bias as a random sequence generation was used. Terms of performance bias, a higher performance bias was found in the judgment of a high detection bias. In the FemPat 18 and THUNDER 17 trials, there was incomplete outcome data in few patients. The FopPe 19 and TUNEDER 21 trials, there was incomplete outcome data as a few patients did not undergo final angiographic follow-up without a clear explanation. In the judgment of a high detection bias. In the FemPat 18 and THUNDER 17 trials, there was incomplete outcome data in few patients. The FopPe 19 and TUNEDER 21 trials, there was incomplete outcome data as a few patients did not undergo final angiographic follow-up without a clear explanation.
Figure 1 Risk of bias graph for the studies included in this review.

Figure 2 Risk of bias summary: review authors’ judgments about each risk of bias item for each included study.

Note: +, low risk; ?, unclear risk; −, high risk.
strategy for severe limb ischemia due to femoral–popliteal disease. Its primary end point is amputation-free survival. In addition, the BASIL 3 trial considers several clinical aspects (ischemic pain relief, ulcer healing, quality of life, 30-day mortality) as secondary outcome measures. The SWEDGEPAD trial is a Swedish RCT testing the hypothesis that DEB is superior to standard PTA in terms of important clinical outcomes, when applied on femoral–popliteal and/or infrapopliteal PAD. The trial consists of two separate parallel studies, SWEDGEPAD 1 and SWEDGEPAD 2, each defined by the severity of PAD. Patients with CLI are allocated to SWEDGEPAD 1 and patients with IC are allocated to SWEDGEPAD 2. The primary outcome measures are amputation rate (SWEDGEPAD 1) and health-related quality of life (SWEDGEPAD 2). The ACOART-BTK trial, currently recruiting in Italy, is an RCT of DEBs versus standard PTA in the treatment of infrapopliteal disease in patients with CLI. The primary outcome is LLL in the target lesion documented by angiography at 6 months. In Germany, the EffPac trial is looking at the safety and efficacy of DEBs in inhibiting restenosis and in ensuring long-term patency of superficial femoral artery lesion in comparison to standard PTA. The SINGA-PACLITrial is another RCT running in Singapore, which is aiming to study the results of DEBs compared to standard PTA for the treatment of infrapopliteal disease in patients with CLI.

Angioplasty with DEBs can have an adverse effect through downstream drug distribution into tissue distal to the lesion location, which may affect wound healing. There are rare cases of vasculitis published in the literature following the use of DEBs. Furthermore, the endovascular interventionist is potentially exposed to the antiproliferative drug with an unknown long-term risk as all currently used DEBs have the drug coating on top of the balloon.

Even though RCTs have demonstrated technical superiority of DEBs over standard PTA, there are still certain issues to be addressed prior to their widespread use as a primary treatment for patients with PAD. One of the main issues is the lack of a significant difference in major amputation or mortality rates between DEBs and standard PTA. Another issue is the cost implication of DEBs in comparison to standard PTA. Long-term data are still not available from RCTs to support the durability and safety of DEBs.

We noticed a considerable variability in study design, eligibility criteria for patient enrollment, and outcome end points among RCTs. Trials investigating outcomes of DEBs in femoropopliteal disease included mostly patients with IC, whereas patients enrolled in trials investigating treatment of infrapopliteal arterial disease with DEBs had predominantly CLI. One trial examined only diabetic patients with CLI. The arterial lesions treated with DEBs varied among trials, with some of them treating longer lesions than others. Furthermore, TLR was inconsistently reported among the trials, with some of them reporting clinically driven revascularization.

**Conclusion**

DEB provides a novel technique to locally deliver antiproliferative agent into the arterial wall without the need of a chronically implanted delivery system. In PAD, DEB therapy is associated with superior antirestenotic efficacy as compared with standard PTA. DEB angioplasty is a safe procedure. Existing evidence demonstrates no significant differences in major amputation and mortality rate between DEBs and standard balloon angioplasty; however, long-term data are still not available. Further RCTs focusing on the clinical and functional outcomes of DEBs and cost versus clinical benefit are required.

**Acknowledgment**

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**Disclosure**

The authors report no conflicts of interest in this work.

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