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Investigating Cell Therapy to Address the Challenges of the Poor-Option Critical Limb Ischemia Patient

Experts discuss the potential for further investigation of cell therapy for the treatment of PAD/CLI

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Peripheral artery disease (PAD) is a chronic disorder that affects more than 8 million Americans and is defined by atherosclerotic stenosis and arterial occlusions in the extremities (typically the legs).[1] Despite current therapies, PAD often leads to disability and, in some cases, amputation and death. This disease worsens over time due to the cumulative effects of cardiovascular risk factors that intensify with age (eg, hypertension, diabetes, and dyslipidemia), and thus the burden of PAD is projected to grow along with the aging population.[2,3]

Lifestyle modification (exercise, diet, and smoking cessation) and medications used in the initial treatment of PAD that target underlying cardiovascular risk factors and prevent development and progression of atherosclerotic lesions (eg, antihypertensive agents, statins, and antiplatelet therapies) may improve function and slow disease progression.[4,5] However, many patients go on to require multiple endovascular and/or surgical revascularization procedures (eg, percutaneous transluminal angioplasty, stents, atherectomy, and bypass surgery), which may fail to confer lasting benefit.[6]

In some cases, PAD presents as and/or progresses from chronic leg pain with ambulation to rest pain, ischemic ulcers, and gangrene; the presence of one or more of these manifestations constitutes critical limb ischemia (CLI).[7] Given the challenges in achieving satisfactory long-term perfusion and the poor prognosis associated with CLI, symptom relief and limb preservation are the primary treatment goals. In pursuit of these goals, CLI patients typically undergo repeated revascularization procedures.[8,9] Moreover, many patients present late in the disease spectrum and are unsuitable candidates for current endovascular and surgical revascularization procedures. Without a viable revascularization option, these patients frequently progress to limb amputation and subsequently face a poor quality of life, along with loss of independence and mobility, requiring long-term care.[10] In view of the lack of suitable therapeutic options for a growing population of CLI patients, new approaches to revascularization are currently being investigated, including cellular therapies.[7,11,12]

In this article for *Endovascular Today*, colleagues John R. Laird, MD, and Mahmood Razavi, MD, join me to discuss current gaps in CLI patient management and treatments and technologies in development that merit further investigation as a means of optimizing care. We hope that you find our discussion interesting and thought provoking as clinical investigators continue to research new approaches to improve the lives of our patients with CLI.

Sincerely,

Krishna J. Rocha-Singh, MD, FACC, FAHA

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UNDERSTANDING REVASCULARIZATION FAILURE IN CLI

Factors Associated With Treatment Failure

Revascularization failure may be associated with multiple patient/disease characteristics, including smoking, diabetes, advanced age, heart failure, renal failure, gangrene, calcification of vessels, diffuse disease, and prior treatment failure.

Dr. Laird: Failure is most likely to occur in patients with end-stage renal disease (ESRD) on dialysis. In addition, many patients have diffuse infrapopliteal disease with long occlusions that enhance their risk for recurrent restenosis and disease progression. Even if major amputation is avoided, CLI patients may continue to experience chronic nonhealing wounds that have a significant negative impact on their quality of life.

Dr. Razavi: In addition to the factors listed previously, long, calcified, chronically occluded lesions have a high rate of anatomic failure, and in my experience, distal lesions also recur more often. Clinical failure is more common in patients with the conditions mentioned. In addition, the absence of a suitable conduit and presence of severe comorbidities such as congestive heart failure (CHF) and chronic obstructive pulmonary disease (COPD), along with advanced age, make patients high risk for bypass surgery.

Revascularization Failure in the Clinic and in the Literature

Cases of revascularization failure are most likely to occur within 6 months after an intervention, due to either insufficient revascularization to support wound healing, or restenosis before healing is complete. Failure within 12 months is associated with poor prognosis for the limb.

Dr. Laird: The common dogma is that restenosis is not a problem once tissue healing has occurred, but that's not always the case. There are patients in whom I've observed recurrent development of CLI every time they experience restenosis or disease progression. And, I think it's important to note that although rates of limb salvage are high following successful bypass, when grafts do fail, it leaves the patient worse off because the likelihood of major amputation is then quite high.

Dr. Razavi: We routinely attempt to treat all eligible lesions in all three infrapopliteal vessels. Clinical symptoms of CLI (nonhealing wound, rest pain, etc.) recur in about 10% of our cases, despite about a 40% 1-year lesion failure rate (restenosis or reocclusion) in our non-drug-eluting stents (DES) patients (mean lesion length of 11 cm) (Razavi, unpublished data).

Early (<30 day) anatomic failure of angioplasty alone in tibial arteries is surprisingly common. A meta-analysis investigating such found about a 10% 30-day technical failure in the infrageniculate arteries.[13] Deterioration of the clinical condition of the foot sometimes occurs despite adequate arterial flow to the foot, and, conversely, the condition of the foot sometimes remains stable under circumstances of worsening arterial disease. We see anatomic disease recurrence rates of 40% to 50% of treated lesions within a year, which is consistent with large prospective studies, and do not re-treat without a clinical indication.[14,15]

Dr. Rocha-Singh: The previous comments highlight the widely held belief that it requires more blood flow to heal a wound than to maintain tissue integrity once a wound is healed and a vessel potentially is occluded. However, under this circumstance, patients do experience recurrent wounds because the underlying pathology has not been fundamentally changed. The clock has essentially been reset. This is where surveillance and follow-up are critical.

CONSIDERATIONS FOR REINTERVENTION AFTER INITIAL REVASCULARIZATION FAILURE

When to Initiate Reintervention

Reintervention is typically deferred until recurrent CLI is documented with the return of ischemic rest pain, new ulceration, or gangrene.

Dr. Laird: Though the general rule is to defer reintervention until recurrent CLI has been confirmed, perhaps the one exception is when the patient has a stent/stent graft that has developed severe in-stent restenosis or severe edge stenosis. In such cases, prophylactic intervention might be performed to preserve patency of the stent/stent graft. It is much easier to treat in-stent restenosis or edge stenosis than to address stent/stent graft occlusion.

Considerations for Repeat Reintervention and Associated Challenges

Approaches to repeated post-failure reintervention may include alternative endovascular procedures or surgical bypass. Amputation is ultimately considered after repeated revascularization attempts fail and all reasonable options have been exhausted.

Dr. Razavi: All patients undergo detailed vein mapping so we understand and can discuss all options with the patient. Early failures of endovascular therapy are considered for surgical bypass if a suitable con-

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duit exists and no clear cause for endofailure is found. Those with identifiable causes for endofailure undergo a repeat procedure using alternate therapeutic strategies (eg, DES instead of balloon angioplasty, debulking or DES, or more aggressive endotherapy). Late failures are usually treated with repeat endotherapy, unless the treating physician is of the opinion that bypass is a better option based on factors including the patient's condition and existence of comorbidities. In our practice, multiple endovascular reinterventions are typically done in those with no good bypass options.

We have been able to identify most failing bypass grafts early, before they thrombose, through intensive clinical follow-up and imaging, and employ endovascular therapy as the initial method of treatment. Patients with acute symptoms are considered for catheter-directed thrombectomy/thrombolysis first. If unsuccessful, we may attempt revascularization of the native vessels, which can be quite involved and difficult.

Amputation is considered once all revascularization options have been exhausted or if they have failed, and is unfortunately not altogether uncommon. In a real-world study of a Medicare population in the United States who underwent infrapopliteal interventions, 24% received amputation in the first month, with 30% requiring rehospitalization.[16]

TREATMENT STRATEGIES FOR PATIENTS WITH LIMITED OR NO REVASCULARIZATION OPTIONS

Therapeutic Angiogenesis With Vascular Growth Factors

Though initially viewed as a promising approach based on early data, vascular growth factors failed to demonstrate a benefit in phase 2 and 3 trials.

Dr. Laird: Over the past 15 to 20 years, there has been a great deal of interest in the possibility of therapeutic angiogenesis via the delivery of vascular growth factors or cell therapy. The most common route of such experimental therapies was intramuscular injection into the affected limb for the purpose of new vessel growth and to increase perfusion. Some of the important early research was conducted by Dr. Jeffrey Isner, who treated no-option patients with vascular endothelial growth factor (VEGF165) delivered via an adenoviral vector. Alternatively, plasmid-bound vascular growth factors were explored in other studies.[17]

Promising results were reported in phase 1 studies with a variety of growth factors, including vascular endothelial growth factor, fibroblast growth factor, and hypoxia-inducible factor-1α (HIF-1α). Baumgartner and Isner showed promising results with VEGF165.[18] Kusumanto also showed promising results with VEGF165 in a CLI patient population, as did Comerota and colleagues with fibroblast growth factor 1 (FGF1).[19,20]

However, subsequent larger, more rigorous phase 2 and 3 trials failed to show a benefit of angiogenic therapy. Some of these trials included patients with intermittent claudication (IC), while others were for patients with no-option critical limb ischemia. The RAVE trial was a randomized, blinded trial that evaluated adenoviral VEGF121 for claudicants and demonstrated no benefit of angiogenic therapy.[21] The WALK trial evaluated intramuscular injection of HIF-1α for patients with severe intermittent claudication. The results of this trial were also disappointing, with no improvement in treadmill walking time.[22] The TALISMAN trial was a randomized trial of naked plasmid FGF1 for patients with CLI. This trial also failed to show convincing improvement in CLI outcomes.[23]

DIFFICULT-TO-MANAGE PATIENT POPULATIONS IN CLI

- A subset of patients will exhaust all currently available treatment options
- This population typically comprises diabetics, smokers, and/or patients with ESRD
- Diabetics with ESRD requiring dialysis are considered the toughest patient population to treat
- These patients often have very calcified arteries, small vessel disease, and poor collateralization

Cell Therapy for Vascular Regeneration

Cell therapy is currently being evaluated as an innovative approach to therapeutic angiogenesis. There was consensus among the faculty that the hypothesized mechanism of action of cell therapy is clinically sound and warrants further investigation. Early data involving the injection of cell concentrates into the affected limb have demonstrated the potential utility of the technology. Profiles of cell therapies in development and related ongoing clinical trials are shown in Table 1.

Dr. Laird: Interest in cell-based therapies for vascular regeneration began with the discovery of a vasculogenic endothelial progenitor cell subpopulation by Asahara and colleagues in 1997.[24] These cells have the ability to

"home" to the site of ischemic tissue injury and secrete a variety of vascular growth factors that could lead to clinically meaningful neovascularization.[24] Therapeutic cells for vascular regeneration can be harvested from the autologous bone marrow, blood, or tissue, and are potentially appealing candidates for vascular regeneration due to the fact that they do not have to overcome an immunologic barrier and can incorporate into the vascular network. These cells can contribute to angiogenesis by secreting angiogenic cytokines and matrix metalloproteinases and can help stabilize endothelial networks.[25]

The first clinical trial of cell therapy for PAD involved the use of bone marrow-derived mononuclear cells (BMMNCs) via intramuscular injection (Tateishi-Yuyama and colleagues) in 45 symptomatic patients.[26] There was improvement in all of the study-defined primary outcomes following this novel approach (ankle-brachial index [ABI], transcutaneous oxygen tension [TcPO2], and rest pain). Numerous other small, non-randomized studies, many including rather heterogeneous patient populations, utilizing BMMNCs and/or peripheral blood mononuclear cells followed and reported few adverse events. The results of this early research supports further research in the form of randomized, controlled clinical trials evaluating the safety and effectiveness of cell therapies in CLI.

The current industry-sponsored, larger randomized trials of concentrated BMMNCs for limited-option CLI patients are critically important to our understanding of the true effectiveness of this approach. Given that most cell therapy trials involved cells administered via an intramuscular injection, general anesthesia may not be necessary.[27]

Cell Therapy: Future Applications in PAD

Cell therapy offers hope to poor-option/no-option CLI patients. Further investigations via randomized, controlled clinical trials are warranted to determine the utility of cell therapy (either alone or adjunctively) in earlier stages of the disease with the goal to preclude or delay the need for repeat revascularization procedures and enhance patient outcomes.

Dr. Laird: The goal of cell therapy is to promote collateral vessel formation and to ultimately improve blood flow to ischemic tissues, thereby alleviating symptoms of claudication and ischemic rest pain, facilitating wound healing, and promoting limb preservation. It is hoped that ongoing

TABLE 1. ONGOING CELL THERAPY TRIALS IN PAD/CLI

Company	Autologous	Point-of-Care	Minimally Manipulated	Device	Study Phase and Status
Zimmer Biomet	✓	✓	✓	✓	Phase 3 ongoing
Harvest (Terumo)	✓	✓	✓	✓	Phase 3 terminated enrollment
Thermogenesis (Cesca)	✓	✓	✓	✓	Phase 3 study pending
Arteriocyte	✓	✓	✓	✓	Phase 1 ongoing
Aastrom (Vericel)	✓	✗	✗	✗	Phase 3 terminated enrollment
Aldagen (Cytomedix)	✓	✗	✗	✗	Phase 1 complete (CLI) Phase 2 ongoing (IC)
Baxter	✓	✗	✗ (CD34+)	✗	Phase 1 complete
Medistem (Intrexon)	✗ (menstrual/endometrial)	—	✗	✗	Phase 1 not yet enrolling
Pluristem	✗	—	✗	✗	Phase 1 complete (CLI) Phase 2 ongoing (IC)
Hemostemix	✓	✗	✗	✗	Pilot and Phase 1 complete Phase 2 ongoing

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clinical trials will demonstrate use of cell therapies as standalone, or adjunctive approaches will provide improved rates of limb salvage and more durable outcomes. If proven effective, cell therapies will also offer a needed clinical approach to no-option patients with inadequate distal vessel targets for bypass or endovascular treatment. In addition, further research is warranted to determine if cell therapy could ultimately be a useful adjunct for patients with advanced PAD, particularly for the diabetic patient population and possibly for patients with renal disease or other high-risk features.

INVESTIGATION OF CELL THERAPIES FOR CLI: CONSIDERING CLINICAL TRIAL DESIGN

Dr. Rocha-Singh: Preliminary clinical research suggests the ability of cell therapy to improve tissue perfusion by promoting angiogenesis and should be a subject of future research. This potential mechanism of action is fundamentally different than endovascular therapies (ie, increasing arterial in-flow through improving arterial luminal patency) or surgical bypass (ie, re-routing arterial in-flow past occlusive disease). Both endovascular and surgical approaches promote wound healing and salvage limbs ostensibly through their durable patency, resulting in enhanced tissue perfusion.

While simplistic in their underlying mechanism of action, these traditional endovascular and surgical approaches to revascularization are unsuitable for many CLI patients, whether due to technical inability to recanalize long arterial occlusions, inadequate run-off distal to the recannulized segment or surgical bypass, poor surgical bypass conduit, or the multiple comorbidities that may render a CLI patient too high risk to undergo these procedures. The distinct mechanism by which cell therapies are hypothesized to improve tissue perfusion therefore requires unique approaches to clinical trial design and primary endpoints to assess its safety and efficacy.

"Device-Centric" and "Patient-Centric" Clinical Trial Endpoints in CLI

When evaluating new treatment options in CLI, it is important to differentiate between treatment success in the clinic, as defined by patients and physicians, and treatment success in clinical trials. The roundtable faculty agreed that clinical trial design in CLI must incorporate more patient-centric outcomes.

Dr. Rocha-Singh: Traditional regulatory and effectiveness/safety endpoints in clinical trials of CLI are typically driven by device claims and include a combination of vessel patency assessment at a specific time point (ie, after drug-coated balloons) and freedom from major amputation. As such, there is a discrepancy between what physicians use to define clinical success or patient-centric outcomes (ie, time to wound healing, preserved mobility, pain relief, and freedom from major amputation) versus regulatory device-centric claims (ie, vessel patency). Ongoing clinical device trials using combination devices (ie, drug-coated balloons) must, by virtue of their claims, make some assessment of vessel patency. This device-centric endpoint approach has evolved to be combined with freedom from major adverse limb events, which reflects the durability of the technology's effect, typically through a 12-month endpoint. Specifically, this would include freedom from extremity reintervention and major amputation. These device-centric endpoints do not completely reflect the more relevant patient-centric endpoints of time to wound healing, maintenance or improvement in mobility, pain relief, and avoidance of debridement procedures, all of which are of primary importance to patients, physicians, and payors. These endpoints are frequently and inappropriately referred to as "soft endpoints" and are, unfortunately, designated as unpowered secondary endpoints that are assessed but are not part of any regulatory device claim.

While patients and physicians are interested in limb preservation, in many cases, this can be achieved in the face of persistent and debilitating pain and loss of mobility and, as such, is a poor surrogate. Additionally, freedom from amputation does not necessarily mean that a patient has healed a wound in a timely manner. Therefore, the patient-centric outcomes reflecting quality of life, maintenance of mobility, time to complete wound healing, and freedom from amputation are all essential and important endpoints that are frequently poorly or inadequately assessed in regulatory trials.

Unfortunately, physician and patient access to new technologies is impossible without first going through the more traditional regulatory endpoints, which are dictated by the device claims. Physicians, industry, and policymakers must continue to work together to devise trial designs with more patient-centric outcomes that still emphasize safety and effectiveness.

However, the issue of patient-centric safety and effectiveness endpoints remains essential. A patient is less concerned about the "angiographic patency" of a vessel than the presumed outcome of a patent vessel—a healed wound, improved or maintained mobility, or reduced pain. Indeed, hundreds of millions of dollars are spent in the United States in the treatment of ischemic wounds, especially in the diabetic population. As the incidence of diabetes continues to skyrocket and patients live longer, more attention must be paid to the device impact on these patient-centric outcomes, particularly in high-risk patient populations.

Given the requirement for inclusion of device-centric outcomes in regulatory trials, new trial designs that elevate patient-centric endpoints must be considered. In this

regard, endovascular therapies or adjuncts to endovascular therapies, specifically biologics, could potentially use a primary efficacy endpoint that combines time to wound healing with freedom from major adverse limb events. The issue of vessel patency may then be less of an issue, particularly if the vessel was treated with a commercially available device.

Recommended Clinical Trial Endpoints in CLI

Industry and physicians caring for patients with CLI must work together to identify and validate noninvasive surrogate markers for vessel patency that protect patients from unnecessary exposure to contrast and/or radiation.

Dr. Rocha-Singh: The use of an invasive contrast angiogram to assess infrapopliteal vessel patency is increasingly perceived as a safety issue, particularly in a high-risk, frail, aging population who frequently have concurrent renal insufficiency. Other noninvasive modalities to assess a change from baseline in percent diameter stenosis, an essential element that defines vessel patency, have not been validated in regulatory trials—specifically, Duplex ultrasound, MRA, and CTA. These latter modalities, while noninvasive, still expose patients to contrast and, in the case of CTA, to radiation. Nonetheless, these may be preferable to an invasive angiogram with the exposure to iodinated contrast, but the fidelity of these therapies to adequately assess change in percent diameter stenosis from a baseline intervention has been problematic. In this regard, industry and physicians must challenge traditional regulatory paradigms to consider evolving surrogates such as change in "tissue perfusion." While it may be difficult to directly associate a patent vessel with improved tissue perfusion, it is the latter that most likely correlates with improved time to wound healing, pain control, and maintaining a limb. In this regard, a noninvasive assessment of "binary patency" (ie, "flow or no flow") could theoretically be assessed and correlated with an assessment of tissue perfusion. This, and other potential methods that avoid an invasive angiogram, must be considered.

Concern has been voiced that the assessment of ischemic wounds, time to complete wound healing, or binary wound healing are extremely variable and subjective, reflecting the diverse CLI demographic and local medical expertise. Nonetheless, new wound healing scoring systems and attention to a multidisciplinary approach to CLI—which integrates excellent podiatric care, endocrinologists, and infectious disease specialists and extends care into the home setting—must be emphasized. Additionally, there are a variety of validated quality of life scales (specifically, the Peripheral Vascular Disease Questionnaire [PVDQ]), pain scales, and activity scales, including the 6-minute walk test, that can all be used to adequately assess these patient-centric outcomes. Fundamentally, it must be recognized that the elements of CLI care are rapidly evolving and so too must the elements of trial design.

The Problem With the Poor-Option/No-Option Patient Definition in CLI

The definition of the poor-option/no-option patient population in CLI is problematic and its application has been non-uniform.

Dr. Rocha-Singh: Typically, poor-option/no-option CLI patients are defined by regional standards of care, which reflect local expertise, access to specific techniques and technologies by local physicians, and the level of aggressiveness of endovascular surgeons, radiologists, and interventional cardiologists. Given these variables, what constitutes a no-option/poor-option patient may vary considerably across investigative clinical sites. Nonetheless, I believe we should begin to address the important elements of this definition, in the form of an expert consensus document reflecting expert opinion derived from various specialties that care for these complex patients. As with the TASC I, TASC II, and recent Peripheral Academic Research Consortium (PARC) documents, we need a consistent definition.[28-30] Granted, there will never be 100% consensus, and compromise will be required, but this would be a starting point. Whether a poor-option/no-option patient is one who has failed multiple surgical and/or endovascular interventions or has angiographic evidence of no single-patent infrapopliteal artery, and/or has no angiographic evidence of patent pedal pulses, or a specific noninvasive hemodynamic profile, consensus around this definition deserves our closer attention.

CLI Clinical Trial Endpoints and the Poor-Option/No-Option Patient

Management of poor-option/no-option CLI patients is challenging and may require a combination treatment approach. There may be a role for cell therapy in this setting, which merits further investigation and alignment of appropriate clinical trial endpoints.

Dr. Rocha-Singh: Poor-option/no-option patients may, through advanced endovascular techniques, be amenable to the establishment of a single-patent vessel below the knee. However, given the incidence of diabetes, many times a pedal wound may not heal appropriately due to poor pedal runoff. In this regard, the combination of an endovascular intervention in an attempt to improve inflow below the knee, combined with a biologic adjunct (specifically, cell therapy) directed at improving pedal tissue perfusion, is an attractive hypothesis.

The endpoint in such a hypothesis would, therefore, become less an issue of a patent vessel but rather the

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patient-centric outcomes of time to wound healing, reduction of pain, improvement in quality of life, ambulation, and avoiding amputation.

However, from a regulatory point of view, we understand that these patients, by virtue of the fact that they are put into a clinical trial, may benefit from that alone (ie, the Hawthorne effect) and be subjected to more intense wound care, thereby improving their subsequent outcome. As such, "connecting the dots" of improvement of tissue perfusion as an important surrogate that is enhanced with both the endovascular and adjunctive use of cell therapy is essential.

POTENTIAL APPLICATIONS FOR FUTURE INVESTIGATION OF CELL THERAPY IN PAD AND CLI

Since the majority of research has focused on CLI (typically Rutherford classes 4 and 5), it is likely that investigations of safety/effectiveness of cell therapy will first be completed in this population. If outcomes in this population are promising, there will likely be a role for further investigation of cell therapy in earlier stages of disease.

Dr. Rocha-Singh: If such a paradigm of a combined endovascular and adjunctive biologic therapy, whether cell therapy, vectors, or gene therapy, is determined in future clinical investigations to improve the outcomes of patients with more protracted wounds (ie, Rutherford class 5 patients) and is proven to be safe, additional investigations may be undertaken to assess the extension of this concept in subjects with earlier stages of CLI to slow progression to more advanced stages. However, to promote this paradigm, any such combination of an endovascular plus an adjunct biologic intervention would clearly first have to be proven safe, its improvement of tissue perfusion established, and its durability defined, all in robust, controlled clinical trials. The use of biologic agents must be carefully assessed with regard to its economics and the potential requirement for recurrent treatments.

Future investigations of the use of adjunctive biologic therapy should include an assessment of the cost-effectiveness of the therapy when balanced against the expense associated with protracted recurrent visits to wound healing clinics, adjuncts to wound healing, and the potential for protracted pain, loss of function, quality of life, and, potentially, amputation. As such, if future research demonstrates that this treatment paradigm is safe and effective in promoting wound healing, reducing pain, maintaining mobility, and avoiding amputation, the evaluation of the extension of this therapy in a proactive, rather than reactive, response to more advanced disease becomes very attractive avenue for further investigation. In the end, it is the patient-centric outcomes upon which clinical trial designs must focus, and these must be correlated with the established reduction in the cost to society of caring for these patients and, ultimately, the cost associated with the ultimate failure of any therapy. ■

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