Clinical experience with CorMatrix extracellular matrix in the surgical treatment of mitral valve disease

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Objectives: To determine the clinical utility of an acellular bioscaffold as a structural material for mitral valve repair (MVR).

Methods: This was a retrospective study of patients undergoing partial or subtotal leaflet replacement and/or leaflet extension to treat mitral regurgitation or acute endocarditis and/or reconstruction of atrial–ventricular continuity after annular decalcification. The material used for repair was a bioresorbable extracellular matrix (ECM) material indicated for cardiac tissue repair (CorMatrix Cardiovascular, Inc, Roswell, Ga). After the necessary debridement, the ECM bioscaffold was tailored and sewn to the native mitral valve tissue. Intraoperative photographs and serial, follow-up echocardiograms were used for evaluation.

Results: From September 2008 to February 2013, MVR requiring the addition of patch material was performed in 19 patients. The median echocardiographic follow-up was 10.9 months (range, 4 days to 48 months). One early and 2 late deaths were unrelated to MVR. No perioperative or late strokes occurred. Two patients with a history of cancer, chemotherapy, and radiotherapy experienced failure of the initial MVR, necessitating reintervention. The other MVRs continued to show good valvular function and no calcification on echocardiographic follow-up of 4 days to 48 months.

Conclusions: The ECM bioscaffold is a satisfactory material for MVR in a variety of surgical situations, including endocarditis. It appears to resist calcification and infection. Additional studies are warranted to determine the long-term durability of repairs made with ECM, and its appropriate use in patients who have previously undergone radiotherapy or chemotherapy. (*J Thorac Cardiovasc Surg* 2014;148:1370-8)

Mitral valve (MV) repair (MVR) offers clinical advantages compared with MV replacement (MVR); therefore, evidence-based guidelines have recommended MVR instead of MVR when possible.¹⁻⁴ For many repairs, leaflet augmentation or annular reconstruction with foreign material patching could be required.

A patch material sturdy enough to withstand the mechanical forces within the heart but that does not provoke a foreign body response would be desirable. The biosynthetic materials commonly used for cardiac tissue repair, such as xenografts (eg, glutaraldehyde bovine pericardium), and synthetic materials, such as polytetrafluoroethylene or polyethylene terephthalate, might not be

suitable for MVR, because their use results in the permanent implantation of an immunologically reactive foreign body, raising concerns about inflammation, calcification, and degeneration.¹⁻⁷ Arguably the best-accepted material for valve repair has been autologous pericardium.⁸⁻¹¹ However, concerns about fresh pericardium's lack of material strength and long-term durability have made glutaraldehyde fixation common, potentially undermining its advantages as a natural biologic material. Finally, because synthetic and fixed biologic materials are inert, they are incapable of adapting to somatic growth in young patients.

During the past 4 years, we have used a material composed of the decellularized extracellular matrix (ECM) of porcine small-intestinal submucosa for MVR.¹² Unlike previously used materials, the ECM bioscaffold is a noncrosslinked, cell-free bioscaffold that serves as a biologically active substrate for constructive remodeling. It has been shown to recruit host stem cells in preclinical models of cardiac and other tissue types and has exhibited growth potential in a preclinical vascular graft model.¹²⁻¹⁷ These experimental studies have demonstrated that the ECM provides the unique environment necessary to promote progenitor cell attachment, migration, expansion, and maturation. With time, the ECM bioscaffold will be remodeled by the host progenitor cells to resemble native tissue.

Preliminary findings in both experimental animals and humans have shown that the ECM bioscaffold does not evoke a strong inflammatory response and is resistant to

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Abbreviations and Acronyms

ECM = extracellular matrix
 MV = mitral valve
 MVr = mitral valve repair
 MVR = mitral valve replacement

calcification.^{12,18,19} It is available for clinical use in the United States and Europe, with indications for pericardial closure, cardiac tissue repair, and carotid artery repair.

METHODS

Study Design and Patients

The Western institutional review board approved the present retrospective chart review. Patient consent requirements were waived. Preoperative, intraoperative, and follow-up data were collected from the charts of all patients who had undergone MVr after August 2007, when the ECM biomaterial was adopted into our practice.

Operative Techniques

All procedures were performed at the same institution by the same surgeon (M.W.G.). Transesophageal echocardiography was used to confirm the valve pathologic features immediately before surgery and to evaluate the repair afterward. The surgical approaches and procedures varied according to the specific pathologic features; however, generally, a midline sternotomy was performed. Cardiopulmonary bypass was initiated and the heart arrested with cold antegrade and retrograde cardioplegia. Cardioplegia was subsequently administered intermittently. The left atrium was entered through the interatrial groove and the diseased MV tissue debrided or resected as necessary. The resulting leaflet defects, or other pre-existing deficiencies, were patched with the ECM bioscaffold (CorMatrix Cardiovascular, Inc, Roswell, Ga) tailored to the appropriate size and shape. The material was sutured into place with running 5-0 polypropylene suture (Prolene; Ethicon Inc, Somerville, NJ). Horizontal sutures of 2-0 polyester (Ethibond, Ethicon Inc) were placed around the circumference of the annulus using an appropriately sized annuloplasty ring (Physio, Edwards Lifesciences, Irvine, Calif; ATS, LeviBio Medica, Rome, Italy; CG Future, Medtronic, Minneapolis, Minn; or 3D, Medtronic). The potential for the development of systolic anterior motion and resulting obstruction of the left ventricular outflow tract was minimized using best-practice techniques, such as “sliding leaflet” valvuloplasty.²⁰⁻²²

For decalcification and reconstruction of the mitral annulus, the valve leaflets were dissected away from the annulus when possible to allow removal of calcified tissue and then reattached using 4-0 polypropylene suture. The resulting defects in annular tissue were repaired by sewing into place an appropriately tailored piece of the ECM bioscaffold using 4-0 polypropylene sutures. The patch was made redundant and then imbricated into the defect to fill it with ECM. An annuloplasty ring was sewn into place, as described.

The chordae tendineae were either preserved or replaced with polytetrafluoroethylene neochordae (Gore-Tex, W L Gore & Assoc, Inc, Flagstaff, Ariz). Concurrent procedures (eg, valve replacement, Cox-maze IV) were performed as needed (Table 1). Two cases required MVR, one with a Mosaic tissue valve (Medtronic, Inc) and one with an On-X mechanical valve (On-X Life Technologies, Austin, Tex). The reconstructed valves were tested for leaflet coaptation and competence, the left atrium was closed and the heart de-aired, and the patients were rewarmed and weaned from cardiopulmonary bypass. Valve function was confirmed using transesophageal echocardiography before chest closure.

Echocardiographic Assessments

All patients underwent preoperative and intraoperative transesophageal echocardiography. The patients were evaluated by transthoracic echocardiography approximately 1 week postoperatively, within 1 to 3 months postoperatively, and at least annually thereafter.

RESULTS

From September 2008 to February 2013, 19 patients underwent MVr or reconstruction requiring the addition of patch material. Detailed case information is listed in Table 1, and representative intraoperative photographs are shown in Figures 1 to 3. The etiology of MV dysfunction included calcific-degenerative disease in 6, endocarditis in 5, congenital disease in 3, myxomatous disease in 2, degeneration of previous repairs in 2, and intraoperative correction of valve distortion secondary to aortic root replacement in 1. The specific procedures included 12 leaflet reconstructions, 5 annular reconstructions after decalcification, and 2 combined leaflet reconstructions and annular reconstructions after decalcification. All were performed using the CorMatrix ECM product as the repair material.

The median duration of follow-up (calculated from the date of the procedure to the date of the latest echocardiographic evaluation) was 10.9 months (range, 4 days to 48 months). This included 8 patients for whom follow-up echocardiographic data >12 months were available.

Four of the MV procedures were second (redo) repairs and one was a third-time repair. Annuloplasty rings were used in 16 patients. Neochordae were implanted as a part of 7 repairs. Two annular decalcification cases required MVR. Concurrent procedures included tricuspid valve repair in 2, aortic valve replacement in 7, repair of the ascending aorta and proximal arch in 1, Cox-maze IV in 6, left atrial appendage occlusion in 1, coronary artery bypass grafting in 3, and removal of an infected implantable cardioverter-defibrillator in 1.

With 2 exceptions (detailed below), all patients demonstrated sustained repair integrity and valve competence throughout the follow-up period, with evidence of only mild leaflet thickening, zero to mild regurgitation, and no development of stenosis. No echocardiographic evidence of calcification of the ECM patch was identified in any patient. All patients experienced an improvement in New York Heart Association functional classification (Table 1).

Adverse Events

No early or late strokes occurred. The intraoperative and early postoperative complications were typical of complex valve operations in patients with severe comorbidities. They included new permanent pacemaker implantation in 4, blood transfusions in 7, methicillin-resistant *Staphylococcus aureus* bacteremia in 1, and right ventricular failure requiring extracorporeal membrane

TABLE 1. Relevant preoperative history and postoperative outcomes in a series of 19 patients undergoing mitral valve repair using CorMatrix ECM

Pt. No.	Age	Gender	Preoperative scores			MV disease etiology, presentation, history, and comorbidities	Procedures*	Postoperative echocardiographic findings at longest follow-up visit		
			MR	NYHA	EuroSCORE			Outcomes	MR	NYHA
1	69	F	4+	IV	17	Posterior leaflet retraction and fibrosis; cardiogenic shock; previous MVr (1997); previous tracheostomy, chemotherapy, and radiotherapy for stage 4 laryngeal cancer; severe pulmonary HTN, AF, CRI, COPD, HTN	Redo MVr (posterior leaflet ECM patch, P1-P3); MV annuloplasty ring; Cox-maze IV	Normal valve function at 3 mo; endocarditis from infected pacemaker with severe MR at 7 mo; reoperation with bioprosthetic MVR; incomplete healing of patched area (see text for details); late death (pneumonia; 2 y)	0	NA
2	63	M	4+	IV	28	Endocarditis with dehiscence of previous annuloplasty ring; previous MVr (2007); previous esophagectomy, chemotherapy, and radiotherapy for esophageal cancer; CVA, DM, HTN	Redo MVr (anterior leaflet ECM patches to A1 and A2-A3), MV annuloplasty ring	Normal valve function at 6 mo; declining valvular function ending in reoperation at 18 mo (MVR, AVR, TVr); incomplete healing of patched area (see text for detail)	1+	II
3	72	F	4+	II	2.5	Barlow valve bileaflet involvement; bilateral pleural effusion; longstanding persistent AF, HTN	MV annular decalcification and ECM reconstruction; 6 Gore-Tex neochordae; MV annuloplasty ring; TV annuloplasty ring; Cox-Maze IV	Early return to OR to repair AV tear caused during MVr; normal valve function after 4 y	1+	I
4	68	F	4+	IV	29	Anterior leaflet calcification and annular dilatation; TR (4+); bilateral pleural effusion, severe pulmonary HTN; longstanding persistent AF, ARI, CRI, DM, HTN	MVr (resection of calcified anterior leaflet and subtotal ECM patch replacement; commissural decalcification); MV annuloplasty ring, TV annuloplasty ring; Cox-maze IV	Normal valve function at 3 y; late death (ESRD; 3.5 y)	1+	II
5	49	F	4+	IV	2.8	MV endocarditis, septic shock, septic brain emboli, multiple CVAs, respiratory failure, DM, HTN	MVr (subtotal P1 leaflet ECM patch replacement); no annuloplasty ring	Normal valve function at 3.5 y	0	I
6	64	F	2+	III	20.5	Intraoperative distortion of mitral annulus; severe AS, moderate AI; previous AVR (2002), persistent AF, HTN	Redo aortic root replacement, which exacerbated MR; MVr (anterior leaflet ECM patch augmentation); MV annuloplasty ring; Cox-maze IV	Normal valve function at 3 y	1-2+	II
7	78	F	4	IV	15	Healed endocarditis; CHF, HTN	MVr (ECM patch repair of large P2 defect; lateral commissural chordal	Normal valve function at 2.5 y	0	I

(Continued)

TABLE 1. Continued

Pt. No.	Age	Gender	Preoperative scores			MV disease etiology, presentation, history, and comorbidities	Procedures*	Postoperative echocardiographic findings at longest follow-up visit		
			MR	NYHA	EuroSCORE			Outcomes	MR	NYHA
8	58	M	4+	IV	2.3	Bileaflet myxomatous disease and extensive annular calcification; HTN	and papillary fenestration); MV annuloplasty ring MV annular decalcification and ECM reconstruction; MVr (posterior leaflet sliding plasty); 8 Gore-Tex neochordae; MV annuloplasty ring; LAA clip	Normal valve function at 2.5 y	0	I
9	29	F	4+	III	5.5	Cleft anterior leaflet and inadequate posterior leaflet surface area; 2 previous MVr (aged 2 and 8 y); persistent AF	Redo-redo MVr (ECM patch augmentation of P2 and P3); 4 Gore-Tex neochordae; MV annuloplasty ring; Cox maze IV	Normal valve function at 1.75 y	0	I
10	60	F	4+	III	7	Calcific restriction of P3; 3+ AI, aneurysm of ascending aorta; persistent AF, HTN, Turner syndrome	AVR; ascending aorta and proximal arch repair; MV annular decalcification and ECM reconstruction; MVr (P3 ECM patch augmentation); 4 Gore-Tex neochordae; MV annuloplasty ring	Normal valve function at 1.25 y	1+	I-II
11	65	M	1+	IV	26.5	Severe calcific MS and AS; multivessel CAD with left main stenosis, near-circumferential MV annular calcification with ventricular extension; bilateral pleural effusion, severe pulmonary HTN; previous renal transplant (1998); severe COPD, DM, HTN	MV annular decalcification and ECM reconstruction; MVR and AVR; CABG; ECMO	Repair and prosthetic valves intact with good biventricular function at 4 d; early death (MSOF; 7 d)	NA	NA
12	71	M	4+	III	50.3	Calcific MS; recent MI; severe AS; previous CABG (1996); CAD, COPD, DM, HTN	MV annular decalcification and ECM reconstruction; MVR and AVR; CABG	Normal prosthetic valve function at 11 mo	0	I
13	69	F	4+	III	5.1	Severe MR, moderate MS after previous MVr (2007); COPD, HTN, RA	Redo MVr (ECM patch augmentation of P2 and P3); MV annuloplasty ring	Normal valve function at 11.5 mo	1+	I-II
14	37	F	4+	II	0.8	Congenitally aberrant P3; isolated severe MR	MVr (ECM patch augmentation of P2 and P3 leaflets); 6 Gore-Tex neochordae; MV annuloplasty ring	Normal valve function at 7.5 mo	0	I

(Continued)

TABLE 1. Continued

Pt. No.	Age	Gender	Preoperative scores			MV disease etiology, presentation, history, and comorbidities	Procedures*	Postoperative echocardiographic findings at longest follow-up visit		
			MR	NYHA	EuroSCORE			Outcomes	MR	NYHA
15	61	M	4+	III	1.6	Calcific restriction of P1 and P2; moderate AS; bicuspid AV; HTN	MV annular decalcification and ECM reconstruction; MVr (ECM patch augmentation of P1 and P2); MV annuloplasty ring; AVR	Normal valve function at 1.5 mo	0	I
16	73	M	4+	III	5.6	MV endocarditis; ARF	MVr (debridement and ECM patch reconstruction of P2); 4 Gore-Tex neochordae; MV annuloplasty ring; CABG	Normal valve function at 1.5 mo	0	I
17	67	M	4+	III	4.2	P1 and P2 restriction status after previous MVr (2007); persistent AF	Redo MVr (ECM patch augmentation of P1 and P2); MV annuloplasty ring; Cox-maze IV	Normal valve function at 1.5 mo	0	I
18	44	M	4+	IV	3	Bileaflet myxomatous MR; extensive annular calcification; 1+ TR with annular dilation; pulmonary edema; severe pulmonary HTN	MV annular decalcification and ECM reconstruction; MVr (posterior leaflet sliding plasty); chordal transfer and 6 Gore-Tex neochordae; MV annuloplasty ring; TV annuloplasty ring; LAA clip	Normal valve function at 1.5 mo	0	I
19	35	M	3+	III	1.9	AV-MV endocarditis with 3-4+ AI and MV perforation; splenic venous thrombosis, positive lupus anticoagulant, HTN	MVr (anterior leaflet debridement and ECM patch repair); MV annuloplasty ring; AVR	Normal valve function at 1.3 mo	0	I

ECM, CorMatrix extracellular matrix bioscaffold; *Pt. No.*, patient number; *MR*, mitral regurgitation; *NYHA*, New York Heart Association (functional classification); *EuroSCORE*, EuroSCORE operative mortality risk; *MV*, mitral valve; *F*, female; *MVr*, mitral valve repair; *HTN*, hypertension; *AF*, atrial fibrillation; *CRI*, chronic renal insufficiency; *COPD*, chronic pulmonary obstructive disease; *MR*, mitral regurgitation; *MVR*, mitral valve replacement; *NA*, not available; *M*, male; *CVA*, cerebrovascular event; *DM*, diabetes mellitus; *AVR*, aortic valve replacement; *TVr*, tricuspid valve repair; *TV*, tricuspid valve; *OR*, operating room; *AV*, aortic valve; *TR*, tricuspid regurgitation; *ARI*, acute renal insufficiency; *ESRD*, end-stage renal disease; *CVA*, cerebrovascular accident; *AS*, aortic stenosis; *AI*, aortic insufficiency; *CHF*, congestive heart failure; *LAA*, left atrial appendage; *CAD*, coronary artery disease; *CABG*, coronary artery bypass grafting; *ECMO*, extracorporeal membrane oxygenation; *MSOF*, multisystem organ failure; *MS*, mitral stenosis; *MI*, myocardial infarction; *RA*, rheumatoid arthritis; *ARF*, acute renal failure. *See "Methods" section for prosthetic valve and annuloplasty ring types.

oxygenation in 1. One patient was returned to the operating room because of new-onset aortic insufficiency attributable to inadvertent damage during MVr. The tear in the aortic valve leaflet was repaired with a small patch of CorMatrix ECM bioscaffold. Systolic anterior motion was not detected in any patient.

One early death occurred on the seventh postoperative day from multisystem organ failure after combined MVR, aortic valve replacement, and coronary artery bypass grafting. This patient had presented in cardiogenic shock with a history of severe pulmonary hypertension and previous renal transplantation (EuroSCORE, 26.5).

Two late deaths occurred in the present series. Patient 4 died 3 years, 7 months postoperatively of end-stage renal disease. Patient 1, who had a history significant for laryngeal cancer, chemotherapy, radiotherapy, tracheostomy, and recurrent pneumonia, had undergone redo MVr with an ECM bioscaffold patch of the posterior leaflet. She presented 7 months postoperatively with endocarditis originating from her pacemaker and severe recurrent mitral regurgitation. On reoperation, 1 of the leaflet sutures was found to be broken. The ECM patch did not appear to have healed or undergone reconstructive remodeling, and a segment at the edge of the patch appeared to have torn

FIGURE 1. Patient 15, posterior leaflet repair. A and B, Decalcification of the mitral valve annulus and P1-P2 segments. C, Extracellular matrix bioscaffold patch augmentation. D, Completed mitral valve repair tested under pressure for valve competence.

away from the suture line. The patient recovered after receiving a bioprosthetic MV and repair of the tricuspid valve and subsequently returned to work. However, she died of pneumonia 15 months after the second operation.

A second occurrence of incomplete graft integration developed in 1 patient who remained alive. This patient's

history was also significant for cancer (esophageal), chemotherapy, radiotherapy, and esophagectomy. He had originally presented with endocarditis and ring dehiscence of a previous MVr. He recovered well after redo patch repairs to the A1 and A2-A3 portions of the anterior leaflet. However, 1 year after surgery, evidence was found of

FIGURE 2. Patient 10, decalcification and repair of annulus and P3. A, Debridement of calcified tissue. B, Extracellular matrix bioscaffold patch augmentation. C, Adjustment of neochordae. D, Completed mitral valve repair.

FIGURE 3. Patient 18, annular decalcification and leaflet repair. A, Decalcification. B, Annular reconstruction with extracellular matrix bioscaffold. C, Leaflet reattached and neochordae implanted. D, Completed mitral valve repair.

progressive asymptomatic MV regurgitation. He became symptomatic 18 months postoperatively and underwent reoperation. Visual inspection suggested that although the ECM patch repair to A1 had healed completely, healing of the A2-A3 patch was incomplete along the edge adjoining the A3 segment. Histopathologic examination showed that portions of the patch distal to the suture line contained CD31-positive staining consistent with vascularization, and the sections close to the proximal edge appeared avascular (Figure 4). Because the patient had also developed grade 3+ aortic and tricuspid insufficiency, his mitral and aortic valves were replaced, and his tricuspid valve was repaired. He recovered well and was still alive at the latest follow-up visit.

DISCUSSION

To our knowledge, the present study reports the longest follow-up data on the clinical use of the ECM bioscaffold for MVr. Consistent with findings from preclinical studies, published clinical cases, and small series,²³⁻³⁰ the results of our clinical experience suggest that human cardiac valve repairs using the ECM bioscaffold remain structurally strong and durable at midterm follow-up. No evidence was found of an acute or a chronic inflammatory reaction, and the ECM bioscaffold was pliable and easily tailored for applications commonly encountered during valve surgery. Our patient cohort experienced no strokes, an issue of primary concern for intracardiac foreign body implantation. Calcification was never identified in the

FIGURE 4. Patient 2, histopathologic results from explantation from a patient with a history of chemotherapy and radiotherapy. A, Hematoxylin-eosin stain (×100) showing regions of vascularized (right arrow) and avascular (left arrow) graft material. The arrowhead denotes the hole left by the suture. B, Immunohistochemical stain for CD31 (×400). Positive areas indicate probable endothelial cells, suggesting partial vascularization of some regions of the explanted graft (arrows).

ECM bioscaffold patches on echocardiography. This included our patient with end-stage renal disease at implantation, who had died 3 years, 7 months after surgery, and both of the patients who experienced patch failure. Using qualitative echocardiographic assessment, the ECM bioscaffold geometry appeared grossly preserved in all patients without visually obvious contraction or elongation of the leaflet patches.

Our experience has provided an opportunity to monitor the performance of the ECM bioscaffold in 3 patients with active endocarditis (patients 2, 5, and 16). Consistent with the experience of Sundermann and colleagues,²⁸ no recurrences of infection have developed ≤ 3.5 years after surgery.

In another case (patient 6), an aortic annular enlargement and replacement of the aortic root resulted in unanticipated distortion of the MV architecture such that the leaflets were no longer capable of coaptation. Situations in which the primary intervention leads to anatomic changes elsewhere in the heart can be challenging to resolve. In patient 6, the ECM bioscaffold was used to perform MV leaflet augmentation to restore coaptation and valve function.

The ECM bioscaffold did not appear to integrate completely in patients 1 and 2 (Figure 4). These patients had in common a history of high-dose chemotherapy and radiotherapy for cancer. Although the cause of graft failure was not definitively determined, it is plausible that the cancer treatment negatively affected the patients' resident population of pluripotent cells. Because the suggested mechanism behind constructive ECM remodeling is native stem cell infiltration, proliferation, and differentiation,¹² it is possible that the previous chemotherapy and/or radiotherapy interfered with the patients' intrinsic ability to repopulate the ECM bioscaffold. These cases are anecdotal, and additional experience is necessary to determine the relationship between previous chemotherapy or radiotherapy and successful ECM bioscaffold implantation and integration. Until more definitive answers are available, caution is advised when using the ECM bioscaffold in patients who have undergone treatments that substantially affect the number and function of stem or progenitor cells.

The present report was subject to the limitations of a small retrospective case series. Although some patients have been followed for several years, the median follow-up period of 10.9 months does not allow any definitive conclusions about the long-term durability of the repairs. No opportunities were available for direct or microscopic observation of the ECM bioscaffold in healthy patients after an extended period of implantation. Also, no opportunity was available to make direct comparisons with autologous pericardium or other surgical materials used for this application. Although 1 of the postulated benefits of the ECM material is that it might be capable of accommodating

somatic growth,³¹ the limited nature of our adult population did not allow an evaluation of this property. Other groups are currently using this material in pediatric populations, and any findings with regard to somatic growth potential would be of great interest.²⁴⁻²⁶

CONCLUSIONS

The present results suggest the ECM bioscaffold could be a convenient and safe option for MVr and for support of prosthetic valve implantation after annular decalcification in adults, with caution urged regarding patients who have previously undergone radiotherapy and/or chemotherapy. Continued follow-up and additional studies are needed to appreciate fully the ECM bioscaffold's resistance to long-term inflammation and calcification in humans, its remodeling dynamics in unusual patient populations, and its utility compared with other repair materials.

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