Early Clinical Results After Stentless Mitral Valve Implantation and Comparison With Conventional Valve Repair or Replacement

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Background—A new quadricusp stentless mitral bioprosthetic valve (QMV) is evaluated and compared with current standards.

Methods and Results—Since August 1997, 67 patients were prospectively evaluated: 23 patients received a QMV, 23 had mitral valve repair (MVR), and 21 received conventional mitral valve replacement (MVP). Patient age was 69 ± 8, 64 ± 10, and 62 ± 9 years for QMV, MVR, and MVP treatment, respectively. The underlying pathology was mitral stenosis, incompetence, and mixed disease in a corresponding 8, 9, and 6 patients for QMV, 1, 22, and 0 patients for MVR, and 2, 12, and 7 patients for MVP. The papillary muscles were sufficient in all QMV cases to suspend the valve. Cross-clamp time was 59 ± 19 minutes for QMV implantation. In-hospital mortality for QMV, MVR, and MVP was 1, 0, and 0 patients, respectively, and thoracotomy had to be performed again in 1, 1, and 2 patients, respectively (these outcomes were not valve related). At baseline transthoracic echocardiography, respective maximum flow velocities were 1.6, 1.4, and 1.7 m/s, and valve orifice area was 2.6, 3.5, and 3.4 cm². Mild transvalvular reflux was seen in 8, 7, and 2 patients; moderate reflux, in 1, 1, and 1 patients. Left ventricular ejection fraction was 52%, 54%, and 51% in the respective treatment groups. At follow-up, hemodynamic parameters had further improved in all groups.

Conclusions—One year after clinical implantation, the QMV appears to function well and has no additional risks compared with MVR or MVP. The subvalvular apparatus is preserved by suspending the QMV at the papillary muscles; this arrangement is hemodynamically advantageous. Echocardiography reveals an excellent valve performance that resembles native mitral valve morphology and hemodynamic function. The QMV is a promising alternative for biological mitral valve replacement. (Circulation. 1999;100[suppl II]:II-78–II-83.)

Key Words: mitral valve ■ surgery ■ echocardiography ■ prosthesis

Mitral valve surgery is characterized by improved methods of valve repair in selected patients. Mitral valve replacement (MVP) is indicated mainly for advanced disease with severe destruction or calcification. Although a routine operation, valve selection is still controversial, since no ideal artificial heart valve is available at the moment.1,2 Bioprostheses are usually indicated in patients older than 70 years.3 Nevertheless, complications such as structural valve failure, calcification, thrombosis, and anticoagulation-related hemorrhage are associated with artificial heart valves.4–6 In the mitral position, freedom from these complications is ≈70% at 10 years and 35% at 15 years for porcine bioprostheses and ≈77% at 10 years for pericardial bioprostheses.7–9 Currently, no standard for valve selection exists; the best option would be a durable, flexible biological prosthesis resembling the native mitral valve.

Anatomically, the mitral valve is a complex structure, like the individual fingerprint. Perfect function is guaranteed through the interaction of valve leaflets, chordae, papillary muscles, and the left ventricle together as a functional unit. Conventional MVP is associated with a nonphysiological inflexible annulus due to the stent. Furthermore, the annuloventricular continuity to support left ventricular function is partially or completely lost by resection of the chordae. This loss of continuity results in nonphysiological hemodynamics and impairment of left ventricular function.

To overcome this dilemma, a chordally supported stentless mitral valve (Quadricusp mitral valve [QMV], Glycar Inc) has been developed. The present study was performed to evaluate the initial 1-year clinical outcome after implantation of the QMV and to compare the results with those from a group of patients undergoing conventional mitral valve repair (MVR) or MVP.

Methods

From August 1997 onward, 67 elective patients with nonischemic mitral valve disease were prospectively evaluated. Implantation of the QMV was approved by the International Freiburger Ethical committee, by the federal “Regierungspräsidium,” and by the local ethical committee for a clinical trial. All patients gave informed consent after the study protocol had been outlined in detail. Patients...
suitable for bioprosthetic mitral valve replacement were informed that valve reconstruction would be attempted if possible; otherwise, the QMV would be implanted. Thus, one control group consisted of patients in whom MVR was performed, and the other group consisted of patients subjected to conventional MVP (because of their younger age) during the same time period. All operations were performed by one surgeon (F.W.M.) using median sternotomy or lateral minithoracotomy with the port-access technique. Extracorporeal circulation was initiated, and cold crystalloid cardioplegia (Bretschneider HTK solution, Köhler Chemie) and moderate hypothermia were applied. In all patients, follow-up was performed at our outpatient clinic after 6 and 12 months and annually thereafter. No patient was lost to follow-up. Data are available for 100% of patients at a mean interval of 9.1 ± 4.4 months. At all visits, the patients were assessed for functional state, the specific activity questionnaire (SAQ) was applied, and clinical examination and routine transthoracic echocardiography were performed.

**Quadricusp Mitral Valve**

The QMV is a stentless mitral valve made of bovine pericardium only. This material is selected for strength, thickness, and fiber direction to fulfill in excess the function of the natural valve. The pericardium is tanned by glutaraldehyde for collagen cross-linking and for removal of immunogenicity. Residual aldehydes known to be responsible for tissue calcification are being capped by additional polyol treatment. This anticalcification treatment has proven effective in weanling rat subcutaneous implants and in weanling sheep whole-valve implants. The QMV is designed to have one large anterior and one posterior leaflet consisting of 3 scallops. All pieces are aligned by non–load-bearing sutures. The sewing ring consists of 3 layers of pericardium and thus can function as an annuloplasty ring. There are 2 joint papillary flaps at the anterolateral and postero medial sides; each papillary flap supports the anterior as well as the posterior leaflet. The annulus is D-shaped, and during valve closure, the anterior leaflet meets the other 3 scallops. A QMV is shown in panel A of the Figure. Accelerated wear testing proved valve durability up to 800,000,000 cycles, exceeding the FDA requirements.

**Surgery**

QMV implantation is performed according to standard techniques after 3 minutes of rinsing. The diseased mitral valve is completely excised by using a straight-line cut from immediately in front of the lateral to the medial commissure. The posterior leaflet is completely excised, leaving a small rim of native valve. A stump of anterior leaflet chordae should be temporarily left on each papillary muscle for traction during implantation. Appropriateness is performed by matching the sizer (small, medium, or large) to the cut subaortic curtain between the commissures. A special sizer is used to measure the exact distance to the papillary muscles. The papillary flaps are implanted by use of 2 polytetrafluoroethylene-armed Tevdek II 3/0 sutures (Deknatel) each; for knot tying, a specially designed knot pusher is used (Figure, panel A). At the annulus, 2 or 3 continuous 3–0 prolene sutures with 4 to 6 interruptions are used (Figure, panel B). The valve is competent if inserted in a neutral position; furthermore, it is forgiving over a range of 1.5 cm below or above this point because of its relatively large coaptation area.

**Echocardiography**

Transthoracic echocardiography (TTE) was performed before surgery to confirm mitral valve pathology, after surgery before discharge, and at every follow-up visit. During surgery, multiplane transesophageal echocardiography (TEE) was used. System Five (Sonotron Vingmed) was used by 2 experienced echocardiographers. Standard views were chosen. At TTE, cardiac morphology (chamber and wall sizes, wall motion, and valve structure) and function (fractional shortening and ejection fraction) as well as transvalvular hemodynamics determined by Doppler ultrasound and color Doppler were assessed. Intraoperative TEE was applied to confirm the underlying pathology and to control postoperative valvular and ventricular function. In addition, TEE was used for valve sizing, measuring the exact distance from the annulus to the papillary flaps under hemodynamically stable conditions before surgery. Mitral valve incompetence was graded according to the regurgitant jet area in relation to left atrial area as mild (<20%), moderate (20% to 40%), or severe (>40%). Effective orifice area was derived from transvalvular continuous-wave Doppler recordings using the pressure half-time method. Mean transvalvular gradients were assessed from continuous-wave Doppler examinations using the modified Bernoulli equation.

**Statistics**

Absolute and relative frequencies were calculated. Results are given as mean±SD. The Kolmogorov-Smirnov test was used to assess normal distribution; Student’s t test for matched pairs was then applied. A value of P<0.05 was considered significant. Postoperative valve-related morbidity and mortality were evaluated according to standard guidelines.
TABLE 1. Preoperative Demographics for QMV, MVR, and Conventional MVP

<table>
<thead>
<tr>
<th></th>
<th>QMV (n=23)</th>
<th>MVR (n=23)</th>
<th>MVP (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>69±8</td>
<td>64±10</td>
<td>62±9*</td>
</tr>
<tr>
<td>BSA, m²</td>
<td>1.74±0.2</td>
<td>1.84±0.2</td>
<td>1.87±0.2</td>
</tr>
<tr>
<td>NYHA, class</td>
<td>3.2±0.4</td>
<td>2.9±0.4*</td>
<td>2.9±0.6</td>
</tr>
<tr>
<td>Sinus rhythm</td>
<td>8</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Presence of cardiac risk factors</td>
<td>15</td>
<td>17</td>
<td>13</td>
</tr>
<tr>
<td>Preoperative cardiac decompensation</td>
<td>6</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>15</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>63±13</td>
<td>62±17</td>
<td>65±13</td>
</tr>
<tr>
<td>EDD, mL</td>
<td>122±41</td>
<td>151±48</td>
<td>146±46</td>
</tr>
<tr>
<td>O₂ saturation, %</td>
<td>61±7</td>
<td>64±6</td>
<td>63±9</td>
</tr>
<tr>
<td>LA pressure, mm Hg</td>
<td>23±5</td>
<td>18±7</td>
<td>19±6</td>
</tr>
<tr>
<td>Cardiac index</td>
<td>1.8±0.6</td>
<td>2±0.5</td>
<td>1.9±0.5</td>
</tr>
<tr>
<td>Valve annulus, mm</td>
<td>28.6±0.9</td>
<td>28.6±0.9</td>
<td>29±1</td>
</tr>
</tbody>
</table>

Values are mean±SD or number of patients. BSA indicates body surface area; EDD, end-diastolic left ventricular volume; and LA, left atrial.

*p<0.05 vs QMV group.

Results

Patient Population QMV
Twenty-three (17 female and 6 male) patients received the QMV (mean age, 69±7.8 years). Eight patients had predominant mitral stenosis, 9 had predominant incompetence, and 6 had combined disease. The preoperative NYHA functional class was 3.2±0.4, SAQ was 3.8±1, and body surface area was 1.74±0.2 m². One patient had undergone previous MVR, and 3 patients had undergone previous balloon commissurotomy for mitral stenosis. Nine patients were in sinus rhythm, 9 had atrial fibrillation, and 5 had a permanent pacemaker. Left ventricular ejection fraction as assessed by cardiac angiography was 63±14% (patients having mitral incompetence were included); end-diastolic left ventricular volume, 122±41 mL; central venous oxygen saturation, 61±7%; left atrial pressure, 23±5 mm Hg; and cardiac index, 1.8±0.6 L·min⁻¹·m⁻². In mitral stenosis, the mean valve orifice area was 0.9±0.4 cm² at a mean pressure of 13±10.5 mm Hg. For mitral incompetence or combined lesions, reflux was graded as 2.5±1 according to standard criteria. Preoperative demographics for all groups are shown in Table 1.

Intraoperative Results
A 28-mm (medium) QMV was implanted in 15 patients, and a 30-mm (large) QMV was implanted in 8 patients. All patients had uneventful valve implantation at good exposure by use of a conventional (n=21) or a minimally invasive (n=2) approach. The papillary muscles were sufficient in all cases to suspend the papillary flaps. The anterolateral and posteromedial annuloplasty distances were 32±4 and 33±5 mm, respectively, by intraoperative sizing and 36±5 and 34±3 mm, respectively, by echocardiographic measurements. Four patients had additional single coronary artery bypass grafting, and 2 patients had tricuspid reconstruction according to DeVega’s technique. Most recently, in 2 patients with concomitant atrial fibrillation, intraoperative radiofrequency ablation in the left atrium was performed; both had persisting sinus rhythm after surgery. Cross-clamp time was 59±19 minutes. Perioperative results and valve disease etiology are summarized in Table 2.

Control Group
The control groups consisted of 23 patients subjected to MVR and 21 patients subjected to conventional MVP, both during the same time interval. For the respective MVR and MVP treatments, 11 and 13 patients were female, 1 and 2 patients had predominant mitral stenosis, 22 and 12 patients exhibited predominant incompetence, and 0 and 7 had combined disease. SAQ measurements were 4.5±2.5 (MVR) and 4±0.8 (MVP). Annuloplasty ring size for MVR was 28.6±0.9 mm, and valve size for MVP was 29±1.1 mm. Perioperative results are shown in Table 2; all MVR and MVP data are compared with the QMV data.

Morbidity and Mortality
Surgery was uneventful in all 67 patients. Thoracotomy had to be performed again in 2 QMV, 1 MVR, and 2 MVP patients because of bleeding. One QMV patient, 0 MVR patients, and 1 MVP patient required transient reintubation for respiratory failure. Severe ventricular arrhythmia occurred in 1 QMV patient, 0 MVR patients, and 1 MVP patient; cardiopulmonary resuscitation was required in the latter. There was one perioperative death after QMV implantation due to a tear in the left internal thoracic artery used as bypass graft; subsequent bleeding had required further surgery, and finally, severe low cardiac output syndrome occurred. Ten months after QMV implantation using a minimally invasive approach, one patient presented with severe mitral incompe-
tence and required further surgery for paravalvular leakage. The suture line had torn off at the middle of the previously calcified posterior annulus. Electron microscopy revealed endothelialization of the annulus as well as the tips of the papillary flaps in this valve. Eight months after MVR, another patient required further surgery and received a mechanical valve for severe mitral incompetence due to new onset of chordal rupture at the anterior leaflet. And another patient required cardiac transplantation 7 months after successful MVR because of progressive dilated cardiomyopathy. After MVP, one patient was diagnosed with anterior paravalvular leakage resulting in grade 2 mitral incompetence; thus far, he has been treated conservatively.

Postoperative Hospital Stay and Follow-Up
All other patients were discharged from the hospital in time according to the German standards. Wound healing was uneventful in all patients. After QMV implantation, patients received continuous anticoagulation therapy (warfarin) only if additional atrial fibrillation was present. At follow-up, 12 patients were in sinus rhythm. All patients had clinically improved and tolerated more physical activities with no or only little dyspnea. NYHA functional class at follow-up was 1.5±0.4 (QMV), 1.4±0.6 (MVR), and 1.3±0.6 (MVP); SAQ had improved in all patients and was 4.8±1.5 (QMV), 5.1±1.7 (MVR), and 4.6±1.6 (MVP).

Echocardiography
All patients had intraoperative transesophageal echocardiography. Perfect valve function was seen in all patients, and the trivial transvalvular refluxes observed with most mechanical heart valve prostheses were accepted. There typically is a laminar systolic transvalvular flow profile after QMV implantation. TTE revealed normal mitral valve function in all patients after surgery. Transmural flow velocities were comparable among the QMV, MVR, and MVP groups; mean transvalvular gradients were slightly higher in the QMV group. At follow-up, there was no relevant difference in mitral orifice area index. First degree mitral valve incompetence was diagnosed in 8 (QMV), 7 (MVR), and 2 (MVP) patients after surgery, whereas second-degree mitral incompetence was seen in 1 patient each. The average jet area was 2.2±1 (QMV), 2.1±1.6 (MVR), and 2.6±1.7 (MVP) cm². At the 6-month follow-up, first-degree mitral valve incompetence was diagnosed in 4 (QMV), 9 (MVR), and 2 (MVP) patients; second-degree mitral incompetence, in 1 (QMV), 0 (MVR), and 1 (MVP) patient; and third-degree mitral incompetence in 1 patient after MVR who later on underwent further surgery. The average jet area was 2.1±1.7 (QMV), 3.3±1.7 (MVR), and 2.7±1.2 (MVP) cm². Comparative echocardiographic results are summarized in Table 3.

Discussion
The complex function of the mitral valve is achieved by interaction of the valve leaflets, annulus, chordae, papillary muscles, and the left ventricle. Mitral valve pathology can be divided into patients suitable for valve reconstruction and into those requiring valve replacement. In the latter, mechanical or stented biological valves have been implanted for years.

Neither treatment is optimal; thus, new treatment options are required. Homografts or stentless mitral bioprostheses seem to be viable alternatives. Both resemble native mitral valve function, which might be of benefit for the patients. At the moment, there is growing enthusiasm for the use of stentless valves; in combination with effective anticalcification treatments, they might even be the first choice in the future.20,21

Options for Mitral Valve Surgery
Early attempts at mitral valve replacement in the 1960s involved devices made of synthetic materials. Dissatisfaction at that time with the imperfections of these first attempts led to experimental and clinical use of biological tissues such as autologous pericardium and fascia lata for partial and even complete mitral valve replacements.22–24 These approaches were defeated by excessive host response. Since then, aldehyde tanning of xenograft and autograft tissue followed later by aldehyde treatments have substantially improved the potential benefits of devices made from pericardium in particular.25 Later, in the 1980s, homograft mitral valve replacements were performed.26,27 Despite further research, the risk for tissue failure and the technical problems of matching donor and host remain.28–33 The use of mitral valve xenografts has been promising, but long-term follow-up data are missing.34,35 Again, matching donor to host remains a problem; thus, the procedure is technically complex. Failure seen at intermediate follow-up may be related to these factors.36 The use of an autologous pericardial valve was accompanied by interindividual mistakes and failures as well.37

**TABLE 3. Postoperative and Follow-Up Echocardiographic Results for QMV, MVR, and Conventional MVP**

<table>
<thead>
<tr>
<th>Postoperative</th>
<th>QMV</th>
<th>MVR</th>
<th>MVP</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDV, mL</td>
<td>69±22</td>
<td>105±47*</td>
<td>100±38*</td>
<td></td>
</tr>
<tr>
<td>EF, %</td>
<td>52±12</td>
<td>54±11</td>
<td>51±10</td>
<td>NS</td>
</tr>
<tr>
<td>CI, L·min⁻¹·m⁻²</td>
<td>2.6±0.9</td>
<td>3.1±1.3</td>
<td>3.2±0.9</td>
<td>NS</td>
</tr>
<tr>
<td>MV Vmax, m/s</td>
<td>1.6±0.2</td>
<td>1.4±0.3*</td>
<td>1.7±0.3</td>
<td></td>
</tr>
<tr>
<td>MV Pmean, mm Hg</td>
<td>4.2±1.5</td>
<td>2.9±1.9*</td>
<td>4±1.4</td>
<td></td>
</tr>
<tr>
<td>MOA, cm²</td>
<td>2.6±0.4</td>
<td>3.5±0.8*</td>
<td>3.4±0.8*</td>
<td></td>
</tr>
<tr>
<td>MOA index, cm²/m²</td>
<td>1.5±0.3</td>
<td>1.9±0.5*</td>
<td>1.8±0.6*</td>
<td></td>
</tr>
</tbody>
</table>

**Follow-up**

| LVEDV, mL     | 89±30 | 109±49 | 103±50 | NS |
| EF, %         | 53±8  | 57±10 | 53±8 | NS |
| CI, L·min⁻¹·m⁻² | 3.5±1.5 | 3±1.3 | 3±0.5 | NS |
| MV Vmax, m/s  | 1.6±0.2 | 1.5±0.4 | 1.7±0.3 | NS |
| MV Pmean, mm Hg | 4±0.9  | 2.9±0.8 | 4±1 |   |
| MOA, cm²     | 2.7±0.5 | 3.1±0.7 | 3.1±0.9 | NS |
| MOA index, cm²/m² | 1.6±0.3 | 1.7±0.5 | 1.7±0.5 | NS |

Values are mean±SD. LVEDV indicates left ventricular end-diastolic volume; EF, ejection fraction according to the Simpson method; CI, cardiac index; MV Vmax, maximum transmural blood flow velocity; MV Pmean, mean transmural pressure gradient; MOA, mitral valve orifice area; and MOA index, mitral valve orifice area index (MOA/BSA). P<0.05 vs QMV.
Requirements for a Stentless Mitral Valve
An ideal mitral prosthesis should be as close as possible to native valve, easy to implant at a low perioperative risk, durable, nonthrombogenic, nonimmunogenic, and endothelialized with a flexible annulus and chordal support. Valve orifice area must be adequate, and central flow, low gradients, low resistance to rapid opening or complete closure, and a sufficient coaptation area should be achieved. These criteria can be met only by a biological prosthesis. The QMV xenograft from 4 pieces of bovine pericardium12,13 fits the anatomic structures, and sizing can be variable because of a large coaptation area. In addition, an effective polyol anticalcification treatment is applied.13 Standard sizes are available to ease clinical implantation. The 3-layer annulus serves as flexible annuloplasty as well. There has been sufficient experimental testing of the QMV, and it fits all requirements of the FDA guidelines.13,14

Evaluation of the Clinical Results
Technically, the QMV is relatively easy to implant when the described technique is used. Exact sizing is crucial: the annulus should not be oversized (excess tissue would restrict transvalvular blood flow). For the adjustment of the papillary flaps, a neutral position should be chosen. Besides mechanical sizing, preoperative TEE measurements of the annulopapillary distance under hemodynamically stable conditions are required. Too-long chordae of the QMV will lead to bulking of the tissue, whereas too-short chordae will straighten the valve, forcing more pressure on annular sutures. Nevertheless, because of the large coaptation area, risk of mitral incompetence is relatively low, even in postoperative ventricular remodeling. One of the early patients who required further surgery had tight papillary flaps; this might have been the cause of the paravalvular leakage that developed. The fact that host endothelium was growing on the explanted valve proves that the polyol-treated tissue is relatively biocompatible. Since there have been no thromboembolic complications thus far, only patients with additional atrial fibrillation have required warfarin for anticoagulation. Restoration of sinus rhythm by radiofrequency ablation will be of additional benefit for future patients.

The hemodynamic results shown in Table 3 were satisfactory compared with conventional valve replacement. Echocardiography revealed a laminar transvalvular blood flow profile in most patients at acceptable flow velocities and valve orifice areas. According to the manufacturer’s instructions, the orifice area should be at the lower edge of the normal range to achieve a perfectly competent valve. As far as the early results are concerned, this goal has been reached. Nevertheless, when using color Doppler, minimal transvalvular reflux can be seen in some patients. This is most likely from the 4 edges of the valve between the different pieces of pericardium. Clinically, this is not relevant at all; it does not exceed the “physiological transvalvular reflux.” All mechanical valves have an obligatory closing volume followed in some designs by a continuing leak, which will be evident by echo quantification as <10% of the atrial area. From an echocardiographic perspective, the QMV resembles native mitral function and perhaps can be considered to be close to an ideal artificial heart valve.

Preservation of the annuloventricular integrity is important18,39 and can be achieved by QMV implantation. Thus, left ventricular function stabilizes and might even improve in the future. There were no clinically relevant differences when the overall outcome of the patients after QMV implantation was compared with that of the MVR and MVP patients. Before surgery, patients receiving MVR usually are in somewhat better condition and have less additional risk factors. This is well reflected by our patient population. Overall satisfactory clinical and functional results can be achieved by implanting the QMV instead of conventional stented mitral valves.

Limitations of the Present Study
The preliminary results after QMV implantation in a small subset of patients are encouraging, but intermediate and long-term results are warranted. Randomization would not be in accordance with ethical guidelines at the moment. Durability as well as effectiveness of the polyol anticalcification treatment can be evaluated only after several years.

Summary/Perspective
This is the first clinical study of QMV implantation in a western community where biological valve replacement is confined to older patients only. The initial results are promising: the valve is relatively easy to implant, and clinical as well as hemodynamic results are satisfactory. The QMV meets most criteria to become an ideal heart valve. As soon as long-term performance is proven, it may become the bioprosthesis of choice for mitral or even tricuspid valve replacement.

References
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Circulation. 1999;100:II-78-II-83
doi: 10.1161/01.CIR.100.suppl_2.II-78

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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