Rotational Atherectomy for the Treatment of In-Stent Restenosis

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With the dramatic rise in stent use over the past several years has come recognition that in-stent restenosis can at times be refractory to treatment with balloon angioplasty. This appears to be particularly true when the in-stent restenosis is diffuse, tight, recurrent or occurs early (1-3), features suggestive of a more aggressive restenotic process. To address the problem of refractory in-stent restenosis, modalities other than plain balloon angioplasty have been evaluated for more durable benefits. Early observational data supported the safety of debulking for in-stent restenosis (4), which led to further studies evaluating long-term outcomes. However, data from randomized trials comparing rotational atherectomy with balloon angioplasty for in-stent restenosis has been conflicting. Additionally, brachytherapy has emerged as being highly effective at limiting recurrent tissue growth in the management of in-stent restenosis.

Although brachytherapy has been shown to be more effective than other strategies in managing in-stent restenosis, the optimal role for intravascular radiation is still being investigated and there are current limitations to its use. Because intravascular radiation therapy has only been evaluated over the past several years, long-term efficacy is still unknown. External-beam radiation, used to treat Hodgkin's disease, causes accelerated coronary artery disease only after several decades, so there is still potential for untoward late-term events after intravascular radiation. Current strategies of brachytherapy are still being worked out to address geographic miss, edge restenosis, and other manifestations of low-level radiation induction of a hyperproliferative response. Furthermore, it is not yet known if brachytherapy is applicable to all situations. Bifurcation lesions and previously irradiated arteries, for example, are two scenarios where brachytherapy has not been evaluated. Therefore, there still remains a role for other strategies with potential to reduce the incidence of recurrent restenosis (Figure 1).

Debulking for in-stent restenosis with rotational atherectomy or other devices has been demonstrated to be associated with a high rate of initial success and low complications (4) (Figure 2). One of the first
studies to evaluate the efficacy of debulking in managing in-stent restenosis was the BARASTER registry, which examined the initial experience in the use of rotational atherectomy in managing in-stent restenosis (4). This registry compared the outcomes of balloon angioplasty with two different strategies of rotational atherectomy, thus there were three arms. One of the debulking strategies focused upon the use of rotational atherectomy primarily, with only low-pressure adjunctive balloon inflations used, to minimize barotrauma injury. This minimal barotrauma approach was done because of animal data suggesting that barotrauma could stimulate intimal proliferation. This arm embraced the hope that debulking without barotrauma might minimize restenosis (5). (The STRATAS trial was designed to tested this hypothesis, however it did not demonstrate any benefit of minimizing barotrauma after rotational atherectomy (5)). The first debulking arm in BARASTER employed a strategy of minimizing barotrauma by relying on aggressive rotational atherectomy, and little (≤ 2 atmospheres) or no adjunctive balloon angioplasty. The other strategy used more aggressive balloon angioplasty after rotational atherectomy, to maximize the final luminal area, under the theory that the larger lumen obtained would be associated with a lower restenosis rate, embracing the concept that Bigger is Better. This was an observational series, and as such lesions were not randomly assigned to one strategy or the other, but rather depended upon the philosophies and preferences of the performing interventionalists. An important potential bias against the aggressive adjunctive balloon angioplasty arm was present in this registry because lesions with suboptimal results after rotational atherectomy were invariably treated with adjunctive balloon angioplasty. Because there was no assigned treatment, intention-to-treat analysis was not possible. Despite this bias, the rate of subsequent event (death, myocardial infarction, or target lesion revascularization) was significantly lower in the combination group 38% versus 60%, P < 0.01 (Figure 3).

### Rotational atherectomy for In-stent Restenosis

**Procedural Safety**

<table>
<thead>
<tr>
<th></th>
<th>BARASTER</th>
<th>ROSTER</th>
<th>ARTIST</th>
</tr>
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<tbody>
<tr>
<td>30 day Death</td>
<td>1.5%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>No/slow-reflow</td>
<td>0%</td>
<td>3%</td>
<td>5%</td>
</tr>
<tr>
<td>Spasm</td>
<td>NA</td>
<td>NA</td>
<td>8%</td>
</tr>
<tr>
<td>Procedural MI</td>
<td>NA</td>
<td>2%</td>
<td>3.3%</td>
</tr>
<tr>
<td>CABG</td>
<td>0.5%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
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NA = Not available; MI = myocardial infarction  
CABG = coronary artery bypass graft surgery

Figure 2
Although the event rates were lower with a combination of rotational atherectomy and adjunctive balloon angioplasty, these numbers do not indicate if the combination strategy is better than balloon angioplasty alone. To address this question, a cohort of lesions of in-stent restenosis treated with balloon angioplasty alone were obtained for comparison (4). This cohort came from the databases of The Mayo Clinic in Rochester, Minnesota and Beth Israel Medical Center in Boston. Although some baseline differences existed between the groups treated with balloon angioplasty and those treated with rotational atherectomy, most of the differences were biased against rotational atherectomy. These differences included longer lesion and stent lengths, smaller reference artery diameters, and more recurrent in-stent restenosis in the rotational atherectomy cohorts. Despite these differences, the recurrent event rate was lower in lesions treated with the combination of rotational atherectomy and balloon angioplasty than those treated with balloon angioplasty alone. Foretelling the results of the ARTIST trial (6), those lesions treated with minimal or no adjunctive balloon angioplasty did no better than those treated with balloon angioplasty alone. The important findings of the BARASTER Registry were 1) rotational atherectomy could be done safely in lesions with in-stent restenosis, and 2) the long-term results appeared to be improved when rotational atherectomy was combined with aggressive balloon angioplasty, compared with either device used alone.

The findings of the BARASTER Registry could only be considered preliminary because of its non-randomized character and inability to control for confounding elements and bias. This registry was designed to be a pilot study, to be followed up with a randomized trial comparing balloon angioplasty with the more favorable of the two strategies, (which turned out to be the combination approach). However, the United States FDA was not supportive of the concept of placing an ablative device inside another device, a stent. In-vitro evaluations performed by SCIMED, the maker of the rotational atherectomy device, demonstrated mild ablation of the stent structure itself. Due to concerns regarding loss of structural integrity of the stent, and the theoretical possibility of device related complications, the FDA stated they would not be supportive of an indication for rotational atherectomy to treat in-stent restenosis, even if a randomized trial were favorable. This limited the possibility for industry sponsorship of such a trial. However, there have been two randomized trials of rotational atherectomy versus balloon angioplasty for in-stent restenosis. One study came from Europe, the ARTIST trial, and the other was a non-sponsored single-center study in the United States, the ROSTER trial. The lack of funding precluded routine angiographic follow-up for this US single-center study, so a clinical primary endpoint was used in this trial, whereas the primary endpoint for the ARTIST trial was angiographic minimum lumen diameter at 6 months.

The ARTIST trial from Europe (6), and the ROSTER trial from Mount Sinai Hospital in New York (7,8), each randomized lesions with in-stent restenosis to either rotational atherectomy with low pressure (< 6
atmospheres) adjunctive balloon angioplasty, or balloon angioplasty alone. There were similar inclusion and exclusion criteria with one important exception (Figure 4). In the ROSTER trial intravascular ultrasound imaging was performed prior to randomization. If the stent being treated was under-expanded, it was not included in the randomization process, but was treated only with balloon angioplasty. (A stent was defined as under-expanded if the minimal stent-area inside the stent was less than 60% of the average vessel area of the proximal and distal reference segments, as defined by Colombo et al. (9)) By excluding under-expanded stents (pseudo-in-stent restenosis), it was insured that the restenotic process was due to tissue growth, to which debulking is particularly suited. In this trial, a clinical benefit was seen in the use of rotational atherectomy as an adjunct to balloon angioplasty, compared to balloon angioplasty alone (7,8) (Figure 5). Specifically, 6-month freedom from death, myocardial infarction or need for target lesion revascularization was 32% in patients treated with rotational atherectomy and 45% in those treated with balloon angioplasty (8).

Inclusion criteria: Rotational Atherectomy for In-stent Restenosis Trials

<table>
<thead>
<tr>
<th>ROSTER</th>
<th>ARTIST</th>
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<tbody>
<tr>
<td>1st time in-stent restenosis</td>
<td>1st time in-stent restenosis</td>
</tr>
<tr>
<td>Length &gt; 10 mm</td>
<td>Length 10-50 mm</td>
</tr>
<tr>
<td>Stent implanted ≥ 3 mm</td>
<td>Stent implanted 2.5-4.0 mm</td>
</tr>
<tr>
<td>Stent identified as well-deployed by IVUS at time of in-stent restenosis</td>
<td>No evidence stent suboptimally expanded angiographically</td>
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Figure 4

Rotational atherectomy for in-stent restenosis trials

Clinical Restenosis

![Graph showing clinical restenosis outcomes for ROSTER, ARTIST, and ARTIST*.](image)

*ARTIST trial includes events before (below line) and after 6-month angiogram.

Figure 5

The ARTIST trial failed to show a benefit of rotational atherectomy for in-stent restenosis (6) (Figure 6). A comparison of some of the baseline and procedural characteristic of the ROSTER and ARTIST trials is shown in Figure 7. Unlike the ROSTER trial, lesions were not excluded from the study based upon pre-
intervention intravascular ultrasound imaging. However, a subset of 78 patients in ARTIST had observational intravascular ultrasound performed pre-intervention, after treatment for in-stent restenosis, and at 6-month follow-up (10,11) (Figure 8). These investigators found that in the balloon arm, in which a mean of 12.6 atm of pressure were employed, minimum stent diameter increased from 2.9 to 3.2 mm, and this was maintained at 6 months. Because the stents used in this trial are known to maintain their dimensions with time, this identified stent underexpansion which must have been present at the time of implantation. Thus, stent "pseudo-restenosis" played an important role in the clinical development of restenosis. Balloon angioplasty at the time of in-stent restenosis led to larger in-stent dimensions.

However, in the rotational atherectomy arm, where only low-pressure adjunctive balloon angioplasty was employed, the stent did not increase in size, from 2.4 to 2.5 mm. Not only were the stents smaller in the rotational atherectomy arm (presumably a chance occurrence from randomization), but the stents were frequently underexpanded, and remained so. Because slotted tube stents do not diminish in size after implantation, the findings in both the ROSTER and ARTIST trials demonstrate that stent underexpansion at the time of implantation is frequently a component of in-stent restenosis. Debulking strategies are less likely to demonstrate a benefit in treating in-stent restenosis when the mechanism is stent underexpansion. This might explain the relatively poor outcome in the ROTA arm of the BARASTER registry.

![Figure 6](image6.png)

![Figure 7](image7.png)
There is supportive data that rotational atherectomy is effective in debulking neo-intimal tissue inside stents. In a porcine model of in-stent restenosis, over twice as much neo-intima is seen when balloon angioplasty is used than rotational atherectomy (10). Because porcine models of in-stent restenosis are created by the use of over-sized stents, stent underexpansion does not play a role and in-stent restenosis is exclusively due to neo-intima. Several authors have demonstrated an early and persistent ability to remove in-stent neo-intimal tissue with rotational atherectomy (11-14). In ARTIST neo-intimal plaque area was reduced 47% in the rotational atherectomy/balloon angioplasty arm, with a 16% reduction in total plaque area (13) (Figure 8). In the balloon-treated group there was initially a 45% reduction in neo-intimal tissue, however, this was due to plaque extrusion, with only an 8% reduction in total plaque area. A 25% reduction in neo-intimal area was maintained at 6-month follow-up in the rotational atherectomy arm, but the neo-intima had virtually returned to the original in-stent stenosis area in the balloon arm.

The improved outcomes in the ROSTER trial and the Combination arm of the BARASTER registry argue that this reduction in plaque seen in the rotational atherectomy arm is clinically meaningful. The negative outcomes (with regard to benefits of rotational atherectomy) seen in ARTIST may be explained by 1) the smaller arteries seen in the rotational atherectomy arm due to chance, and 2) inadequate stent expansion being an under-recognized component of stent restenosis process. The prevalence of inadequate stent expansion means that neo-intima causing in-stent restenosis, the component of in-stent restenosis which would benefit from debulking, carries less relative importance. Additionally, the low-pressure inflations used after the rotablation was inadequate to further expand the under-deployed stents. A trial of debulking with rotational atherectomy followed by high-pressure balloon inflations has not yet been evaluated with a randomized trial. The favorable findings from the BARASTER registry support the potential value of this strategy.

Brachytherapy is becoming an increasingly important modality in treating in-stent restenosis. Many of the trials have incorporated debulking, particularly with rotational atherectomy, as part of the treatment for in-stent restenosis. Early data does not support much benefit from debulking prior to radiating restenotic stented lesions (15). The effectiveness of radiation therapy in managing in-stent restenosis appears to be more profound than the benefits using debulking alone. However, there is important bias incorporated into the selection of devices prior to radiation therapy, with the most severely restenotic lesions frequently treated with rotational atherectomy or other ablation device. Debubling prior to radiation therapy has not been studied in a controlled fashion. Therefore it is not yet clear if there is a role for debulking prior to intravascular brachytherapy.

CONCLUSIONS (Figures 9 and 10)
Initial interest in the use of rotational atherectomy for in-stent restenosis has diminished by 1) the rise of intravascular brachytherapy, 2) persistently elevated rates of recurrent restenosis after rotational atherectomy, perhaps related to suboptimal strategies and techniques, and 3) the disappointing results from the ARTIST trial. Intravascular ultrasound findings from the ROSTER and ARTIST trials suggest that suboptimal stent expansion remains an important component to in-stent restenosis, a situation which may diminish the potential value of neo-intimal debulking. In the ROSTER trial, 40% of lesions with restenosis after stenting were associated with suboptimal stent implantation. Perhaps this partly explains the lack of efficacy of rotational atherectomy when combined with low-pressure balloon inflations, seen to be ineffective in the BARASTER Registry and in ARTIST. Similar adjunctive inflation pressures to ARTIST were used in ROSTER. The improved clinical benefit seen in ROSTER in the rotational atherectomy arm appears to be due to the exclusion of sub-optimally expanded stents.

### Conclusions (I) from BARASTER, ROSTER and ARTIST

- **IVUS detected suboptimal stent deployment in 40% of cases of in-stent restenosis in ROSTER**
- **No benefit of rotational atherectomy when used with low-pressure balloon inflations, unless restenosis is due solely to a proliferative response**
- **Rotational atherectomy does provide some degree of debulking**

![Figure 9](image)

### Conclusions (II) from BARASTER, ROSTER and ARTIST

- **The combination of rotational atherectomy and aggressive balloon inflations appeared to be better than either alone in BARASTER**
- **The combination of rotational atherectomy with high-pressure inflations, in lesions with clearly well-deployed stents, has not been tested in a randomized trial, and may be an effective treatment of in-stent restenosis**

![Figure 10](image)

Rotational atherectomy does debulk in-stent neo-intimal tissue, and therefore may be a useful adjunct in selected situations. Although it is not yet clear if there is a difference in efficiency or clinical effectiveness of different debulking devices, it is probably the case that the type of ablation device is less important than its efficiency in removing tissue.

A strategy of tissue debulking followed by high-pressure balloon inflations has not been tested with a
randomized study, but the BARASTER Registry suggests this strategy is more likely to be more effective than balloon angioplasty alone or rotational atherectomy with low-pressure adjunctive balloon angioplasty. Ideally, a randomized trial of debulking with adjunctive high-pressure balloon inflations, compared with balloon angioplasty alone, would be performed. Until such data is forthcoming, a reasonable strategy in addressing in-stent restenosis would be to adopt the approach of the ROSTER investigators: perform pre-intervention intravascular ultrasound imaging to identify inadequately expanded stents. Maximally dilate those stents, and use ablative techniques to debulk those lesions with significant intra-stent plaque, followed by aggressive balloon angioplasty to achieve a maximal luminal result.

REFERENCES


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