

Rationale for the association of rotational atherectomy and drug-eluting stents

Percutaneous coronary interventions (PCIs) are standard therapy for the treatment of atherosclerotic lesions of the coronary arteries. Since the introduction of rotational atherectomy (RA) in 1989, it has become established as a necessary adjunct to PCI in a small proportion of cases, notably calcified lesions. However, its use is hampered by the recurrent phenomenon of restenosis. The introduction of stent technology (first bare-metal stents and, subsequently, drug-eluting stents) promised a solution to this problem. The most appropriate combination of angioplasty and stent after RA remains controversial. We review results obtained with RA alone, and in combination with angioplasty and/or bare metal or drug-eluting stents, with a view to identifying the most appropriate choice of stent after RA in coronary artery lesions.

KEYWORDS: angioplasty = bare-metal stent = calcified lesion = drug-eluting stent restenosis = rotational atherectomy = stent

Percutaneous techniques for treating coronary lesions have progressed spectacularly in the last two decades. The indications of coronary angioplasty have gradually widened to include even the most complex lesion types, owing to the development of techniques, such as cutting balloon, and directional and rotational atherectomy (RA). Percutaneous coronary interventions (PCIs) are now established as the treatment of choice for coronary stenosis, although their use remains persistently limited by procedural failure and restenosis. The advent of active, or drug-eluting stents (DESs), held the promise of a solution to restenosis, and rapidly became the preferred treatment strategy, replacing other PCI techniques in lesions at high risk of restenosis. Indeed, the indications for DESs have expanded rapidly beyond the approved clinical situations, to cover a variety of situations, such as complex or ostial lesions, left main stem, instent restenosis, chronic occlusion and stenoses on saphenous vein grafts, and rates of DES use have reached record levels - reportedly up to 78.2% [1]. Nonetheless, RA still remains a necessary adjunct to angioplasty and stent implantation in a small proportion of cases, most notably in calcified lesions, with the result that its use has remained constant in recent years, ranging between 4 and 7% [2]. The association of RA and DESs is a logical and promising combination, with the ablation of calcified lesions by RA allowing for optimal implantation of the DES, which, through its active component, should prevent restenosis. In this article, we review published data supporting the use of RA in different

types of lesions, alone or followed by balloon angioplasty and/or implantation of bare-metal stents (BMSs) or DESs.

Rotablator: techniques & early results

The principle mechanism of action of RA is the ablation of heavily calcified plaque within the coronary arteries. The first report of the use of high-speed RA was published in 1989 [2], and this technique became widely used in the mid-1990s. It offered a new approach to the treatment of calcified coronary lesions, using a burr coated with 10-µm diamond chips, rotating at high speed, approximately 100,000– 200,000 rpm. This rotating action resulted in the physical removal of hard surfaces, pulverizing it into small particles released into the coronary circulation.

The first experiences with RA were less than convincing, with only average success rates, and relatively high rates of complications and restenosis. A report from a European registry reported a primary success rate of 86% but, with 7.7% postprocedure myocardial infarction (MI), and an overall angiographic restenosis rate of 37.8% [3]. With increased practice and improved techniques, preferential indications for RA use have been identified over the years, with a corresponding improvement in success rates. However, complication and restenosis rates have remained largely stable [4,5].

Two of the major complications associated with the use of RA were the high rate of post-PCI MI, often caused by no reflow, and high

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Department of Cardiology, Centre Hospitalier Universitaire Jean Minjoz, Université de Franche Comte, EA 3920, Boulevard Fleming, 25000 Besançon, France Author for correspondence: Tel.: +33 381 668 539 Fax: +33 381 668 582 françois.schiele@univ-fcomte.fr restenosis rate. With increasing experience, two strategies with RA were compared, namely the standard so-called 'aggressive' approach, which aimed to remove a maximum of atherosclerotic tissue, owing to a large final burr size (single large burr or stepwise multiple burr strategy) and a high rotation speed. The second, more conservative approach, aimed to reduce the procedural complication and restenosis rates by limiting deep-artery injury by using smaller burrs rotating at lower speeds (burr to artery ratio <0.8, and rotation speed <120,000 rpm). With the conservative approach, RA aimed to modify the plaque composition by removing part of the calcific burden, and to facilitate the subsequent use of balloon angioplasty or stent implantation, rather than enlarge the lumen size. Two randomized studies showed consistent results, with the more aggressive strategy not yielding superior results compared with the conservative approach, with a lower burr: artery ratio [6,7].

Further improvements were made to the environment for RA use, by means of drug combinations aiming to limit no reflow, spasm and periprocedural MI. The Rota-ReoPro study, which compared the glycoprotein (Gp) IIb/IIIa inhibitor abciximab (ReoPro®, Eli Lilly, IN, USA) with placebo, significantly reduced the rate of CK-MB release after PCI, as well as the incidence of slow flow [8]. Another study, from the same researchers, reported that intracoronary verapamil infusion during the procedure could reduce the rate of postangioplasty enzyme release [9]. A more recent study observed that a 'flush cocktail' of nicardipine and adenosine prevented no reflow and, consequently, post-PCI MI during RA [10]. Similarly, Matsuo et al. reported a reduction in post-RA MI with nicorandil, compared with verapamil, after RA [11]. The α -1-adrenergic blocker, urapidil, was also reported to have a beneficial effect on microcirculation after RA, by reducing vasoconstriction, but has not been integrated into routine practice in this indication [12]. With this improved technique, and despite profound changes in angioplasty techniques over time [9], and even the disappearance of all other atherectomy devices, RA still remains an option in heavily calcified or complex coronary lesions, and is used in 1-3% of cases [13].

RA versus balloon angioplasty

The first studies comparing RA with balloon angioplasty in selected cases showed that RA yielded a better success rate. A notable exception was the Development of Antiretroviral Therapy in Africa (DART) study, but the lesion characteristics differed between groups in this study. Compared with balloon angioplasty, RA was not reported to result in a higher rate of complications (TABLE 1). However, in randomized comparisons, RA did not reduce the rate of restenosis compared with balloon angioplasty, with similar or higher rates reported (TABLE 1). Overall, RA helps to optimize procedural success rates in calcified and complex lesions compared with balloon angioplasty, without an increased risk of complications. However, the rates of restenosis and long-term target-lesion revascularization (TLR) procedures remain similar to those observed with balloon angioplasty alone.

In-stent restenosis

Similarly to restenosis after balloon angioplasty, in-stent restenosis (ISR) is caused by endothelial hyperplasia, but grows within the stent. However, repeat angioplasty of an ISR lesion is associated with a higher risk of recurrence than after balloon restenotic lesions, where stent implantation provides favorable results. The rationale for RA in case of ISR is to ablate as much tissue as possible to improve the lumen size with limited artery wall injury; reports using intravascular ultrasound confirmed that RA was able to remove a large amount of the neo-intimal tissue within the restenotic stent safely [14]. Several studies have compared RA with balloon angioplasty in the setting of ISR. First, the Angiographic Analysis of the Angioplasty Versus Rotational Atherectomy for the Treatment of Diffuse In-Stent Restenosis Trial (ARTIST) [15] demonstrated that, while RA followed by low-pressure balloon angioplasty was feasible in diffuse ISR, it did not yield better longterm results than conventional balloon angioplasty. Conversely, in the Balloon Angioplasty Versus Rotational Atherectomy for Intra-Stent Restenosis (BARASTER) registry, a reduction in 1-year events (e.g., death, MI or revascularization) was observed with a strategy combining RA and adjunctive balloon angioplasty [16]. These findings were confirmed by the more recent Rotational Atherectomy Versus Balloon Angioplasty for Diffuse In-Stent Restenosis (ROSTER) study, which showed that RA followed by high-pressure balloon angioplasty resulted in less residual neointimal hyperplasia, less recourse to repeat stent implantation, and fewer repeat revascularization procedures compared with balloon angioplasty [17]. These conflicting results could be explained by the differences in adjunctive therapy after RA (i.e., lowpressure balloon inflation in the ARTIST study,

Study	Success rate	Complications	TLR	Ref
rotational atherec	tomy with balloon angiop	plasty.		
Table 1. Success ra	tes, complications and tai	rget-lesion revascularization in ran	domized studies compari	ng

Study	Success fale			complications			ILK			Rei.
	RA (%)	BA (%)	p-value	RA (%)	BA (%)	p-value	RA (%)	BA (%)	p-value	
ERBAC	89	80	0.0019	3.2	3.1	0.71	42.4	31.9	0.013	[35]
DART	91.6	94.1	0.036	5.3	2.3	0.14	25	23		[36]
COBRA	85	78	0.038	No differer	nce reported	k	25.2	29.5		[37]
BA: Balloon angioplasty; COBRA: Comparison of Balloon Angioplasty Versus Rotational Atherectomy in Complex Coronary Lesions; DART: Development of										

An information anglopiasty, Conna. Comparison of Balloon Anglopiasty versus Rotational Atherectority in Complex Coronary Lesions, DART. Development of Antiretroviral Therapy in Africa; ERBAC: Excimer Laser, Rotational Atherectority and Balloon Angloplasty Comparison; RA: Rotational atherectority; TLR: Target-lesion revascularization.

compared with high-pressure balloon inflation in BARASTER and ROSTER trials). While it is clear that RA is certainly a feasible technique for treating diffuse ISR, evaluated through randomized trials, RA was not widely adopted in daily practice, and is no longer indicated in ISR lesions. This is partly owing to the equivocal results, but mainly because other, competing strategies emerged around the same time, such as cutting balloon, brachytherapy and, later, DESs.

Atherectomy in the era of bare-metal stents

Stent implantation has never been compared with RA, since both devices have totally different mechanisms of action and indications. Nevertheless, the advent of first-generation BMSs significantly reduced the use of RA. However, angioplasty of long and/or calcified lesions remains challenging, and several technical difficulties conspire to reduce the chances of procedural success. First, in long and calcified lesions, it can be difficult, or even impossible, to cross the lesion with the balloon catheter, owing to the presence of calcified deposits. Second, the rigidity of the artery from calcification can hinder the expansion of the stent, and incomplete expansion, or malapposition of the stent, are frequent problems. Unsuccessful or suboptimal implantation of the stent can lead to an increased risk of thrombosis and ISR.

The use of RA provides a solution to some of these challenges. The rotation of the burr ablates the calcified tissue, improving artery compliance, which makes it easier for the operator to cross the lesion, thereby facilitating stent implantation.

Data from the American College of Cardiology (ACC)-National Cardiovascular Data Registry (NCDR) confirmed the efficacy of combining RA with stent implantation compared with other therapeutic strategies (TABLE 2) [13]. Indeed, the association of RA with stenting yields better results in terms of angiographic success, as well as a lower risk of restenosis, than with stenting alone [18]. However, despite these encouraging results, restenosis rates remain high, with a rate of 22.5% reported in one study [19]. Kobayashi et al. tried to resolve the challenge of restenosis after RA and stenting by proposing a more aggressive strategy, increasing initial angiographic gain. As postulated, they observed a lower rate of restenosis and TLR, but at the price of a higher complication

Table 2. Rate of use, angiographic success rate and complications, according to the device used during percutaneous coronary interventions.

	Balloon angioplasty	RA	Stent	RA plus stent	Others	p-value
By lesion						
Lesions (n)	25,900	2554	99,294	2038	7865	
Angiographic success (%)	82	96	97.1	97.4	91.2	<0.0001
By procedure						
Procedures (n)	11,570	1463	71,341	2557	9008	
Angiographic success (%)	81.9	96.2	97.2	97.6	85.7	<0.0001
Post-PCI MI (%)	0.6	0.2	0.4	0.9	0.6	<0.0001
CABG (%)	6.5	0.8	1	1.1	3.3	<0.0001
Death (%)	2.7	0.6	1.3	1.2	1.5	<0.0001
Secondary events (%)	91	98.5	97.6	97.3	94.9	<0.0001
Length of stay (days)	3.2	1.9	2.5	2.1	2.7	<0.0001

Data from the American College of Cardiology National Cardiovascular Data Registry.

CABG: Coronary artery bypass graft; MI: Myocardial infarction; PCI: Percutaneous coronary intervention; RA: Rotational atherectomy. Data taken from [13]. rate and more short-term acute coronary syndrome (ACS) post-PCI [20]. The combination of RA and BMS, thus, appears to be a useful strategy for treating long and/or calcified lesions, with a greater success rate than after balloon angioplasty alone. However, this combination strategy remains persistently limited by a high rate of restenosis.

Use of DESs in calcified lesions

A major advancement in stent technology has been the advent of DESs, allowing local drug delivery directly at the site of the lesion. Since active stents have become available, their use has become widespread, and the indications for angioplasty have been widened considerably to cover longer and more complex lesion types. Early results obtained with paclitaxeland sirolimus-eluting stents for the treatment of calcified lesions have been encouraging, with a significant reduction in ISR and revascularization rates [21-23]. Similar positive findings have been observed in patients with diabetes [24] and elderly patients [25].

Nonetheless, as before, the use of DESs in complex lesions also poses several challenges. The fragility of the polymer that carries the active molecule is such that repeated maneuvering within small and tortuous vessels can be damaging, and may alter its efficacy, leading to a risk of restenosis. One study comparing DESs and BMSs for the treatment of long and complex lesions showed that, at 9 months, DESs had significantly reduced late loss compared with BMSs $(0.26 \pm 0.56 \text{ vs } 0.51 \pm 0.48 \text{ mm}; \text{ p})$ = 0.015) within the calcified lesion segment [23]. However, a more recent study observed that stent underexpansion and residual reference segment stenosis, which are frequent problems with DES implantation, are associated with a higher rate of stent thrombosis [26]. The ongoing Rotational Atherectomy Prior to Taxus Stent (ROTAXUS) study may provide additional evidence for the benefit of RA prior to DES [101].

Combination therapy with RA & DESs

As with BMSs, the use of DESs in complex and calcified lesions is, thus, limited by the recurring problems of crossing the lesion and deploying the stent adequately, as well as in the right position. The ablation of calcific deposits increases vessel compliance, thus optimizing stent placement. This, in turn, contributes to procedural success and reducing restenosis and stent thrombosis. Furuichi *et al.* examined the outcome of

96 patients treated with a combination of RA followed by DES implantation, and observed a high rate of procedural success at 95.8%, and a low rate of TLR, at 9.5% at 14 months [27]. Similarly, Clavijo et al. compared outcomes between 150 consecutive patients with heavily calcified lesions undergoing DES implantation with (n = 81) versus without (n = 69) adjunctive RA [28]. They noted that outcomes were similar in both groups, with a high procedural success rate, although there was a significantly higher proportion of patients with complex type C lesions in the RA plus DES goup (30.4 vs 48.1%; p = 0.01). Mezilis *et al.* observed no safety concerns for up to 6 years in a cohort of 150 patients undergoing RA followed by DES implantation [29]. Nakamura et al. even demonstrated a reduction in ISR and TLR after DES implantation and adjunctive RA [30]. In summary, DES in combination with RA has shown persistent efficacy for the treatment of long and complex calcified lesions.

Rationale for associating DESs & RA, & available results

Rotational atherectomy facilitates angioplasty in calcified or narrow coronary arteries, and improves stent placement and deployment. The optimized stent placement makes it possible to achieve better initial angiographic results, although there is no persistent benefit on TLR and ISR in the longer term. DESs, on the other hand, do have a favorable impact on risk of ISR, through the antiproliferative effects of the locally delivered drug, and have been shown to reduce the risk of ISR, even in complex lesions. However, the use of DESs in long and calcified lesions has been limited by difficulties in crossing the lesion and adequately placing the stent at the lesion site. Therefore, it would appear perfectly logical to associate these two complementary therapeutic strategies, and limited series have shown that the association is feasible.

To date, the only studies available comparing a strategy of RA plus a DES with RA plus a BMS are observational monocentric studies, with small sample sizes. Registry data from Rao *et al.* demonstrated that patients treated by atherectomy and DESs had similar outcomes to those observed in patients treated with DES alone. In comparison with a group treated with BMSs, patients who received a DES after RA had a lower risk of death, whereas the difference in major adverse cardiac events (MACEs) or revascularization was not significant [31]. Conversely, Tamekiyo *et al.* observed reduced MACE and Table 3. Published registry studies comparing bare-metal stents and drug-eluting stents after rotational atherectomy.

Author	Follow-up (months)	Number		TLR			MACE			Ref.
		DES	BMS	DES (%)	BMS (%)	p-value	DES (%)	BMS (%)	p-value	
Khattab (2007)	9	27	34	7.4	35.3	0.006	7.4	38.2	0.004	[33]
Rao (2006)	6	36	42	2.8	9.6		2.8	19		[31]
Tamekiyo (2009)	24	79	144	25	39.1	0.022	30.1	43.1	0.024	[32]
Rathore (2010)	9	391	125	10.6	25	0.001				[38]
RMS: Bara-matal stant: DES: Drug-aluting stant: MACE: Major advarse cardiac event: TLR: Target-lesion revascularization										

BMS: Bare-metal stent; DES: Drug-eluting stent; MACE: Major adverse cardiac event; TLR: Target-lesion revascularization.

TLR rates in patients treated by RA and a DES [32], which was consistent with the favorable angiographic and clinical results observed by Khattab et al. with the combination of RA and DESs, compared with RA and BMSs [33]. In this study, there was significantly less neointimal proliferation in active stents compared with BMS at 9 months (0.11 ± 0.7 vs 1.11 ± 0.9 mm; p = 0.001), and this difference was reflected by higher mortality, TLR and ISR rates in the group treated by RA plus a BMS (TABLE 3) [33]. Recently, a study comparing RA plus a DES to RA plus a BMS with adjustment on a propensity score confirmed the benefit of DESs over BMSs after RA in terms of MACE, TLR and even 1-year mortality [34]. However, in the absence of a large randomized controlled trial, these data should be interpreted cautiously.

Conclusion

In contrast with other atherectomy devices, such as directional, transcatheter or laser atherectomy, RA is still used in routine practice. Compared with earlier models (from >20 years ago), RA has undergone only minor technological modifications, suggesting that this device was originally well designed. The improvements in stent technology, which make it possible to directly cross severe, and even calcified, lesions, have reduced the need for adjunctive devices, such as RA, but severely calcified lesions remain difficult to cross, and continue to limit stent expansion. In these particular cases, RA remains indicated, although the complexity of the procedure incurs the risk of more immediate complications, higher procedural costs and more restenosis. The availability of DESs can resolve at least one of the limitations of RA, namely restenosis. Since DESs have been shown to be capable of reducing neointimal proliferation, even in highly calcified lesions, the combination of RA and a DES is logical. Indeed, registry data have shown that the combination leads to favorable clinical outcomes. To identify the best combination of RA and/or DES, evidence-based medicine requires a study with a factorial design. An answer to part of the question of whether we should use RA before DESs or not may come from the ROTAXUS study. However, there is no study ongoing that will answer the other side of the question: after RA, should we implant a DES or a BMS? While awaiting evidence in favor of its safety and efficacy, we only have registry data to support the use of a strategy of DESs rather than BMSs when RA has been used for calcified lesions.

Future perspective

Unusually for medical technology, RA has changed only slightly since its first introduction 20 years ago. Its longevity is probably due to the fact that it bridges a very specialized gap for a specific clinical situation, where no other therapeutic approaches have been possible. Despite the fact that there have never been any randomized trials to prove its efficacy, RA has outlived all other forms of atherectomy devices. It is highly unlikely, at this point, that randomized trials will ever be performed in this indication, because it would be difficult to find a comparator, or 'control' strategy, given that RA is precisely reserved for clinical situations, where angioplasty is impossible or unlikely to yield successful results.

In the DES era, RA prior to stenting has the double advantage of facilitating both stent placement and deployment. Although doubt has been cast on one of the premises that justified the use of RA, namely that optimizing stent deployment would contribute to a reduced risk of stent thrombosis (now thought to be more likely related to the efficacy of antiplatelet medication), nonetheless, it remains true that adequate stent deployment is necessary. Moreover, DESs are effective in preventing restenosis in calcified lesions, even after RA, making the combination highly synergic. Thus, it is probable that RA will continue to exist as a necessary and useful adjunctive therapy in calcified coronary lesions, while DES is necessary and useful to prevent restenosis after RA.

Executive summary

Rotablator: techniques & early results

- The mechanism of action is to ablate heavily calcified plaque within the coronary arteries by means of a burr rotating at high speed (>100,000 rpm).
- Early results have been hampered by high complication rates and high restenosis rate.

Rotational atherectomy versus balloon angioplasty

- Rotational atherectomy (RA) initially yielded better results than balloon angioplasty in early studies.
- However, similar, if not higher, rates of restenosis were reported.
- RA is most suited to long calcified coronary lesions.

In-stent restenosis

- Endothelial hyperplasia causes renewed tissue growth, or calcification within the stent, after stent implantation.
- While RA is feasible for the ablation of in-stent restenosis (ISR), it does not provide significantly better results than balloon angioplasty, while the risk of recurrence remains high.
- Thus, RA is not indicated for the treatment of ISR.

Atherectomy & stents

- The combination of RA and stent implantation is attractive, as initial debulking of the coronary lesion with RA facilitates stent placement and deployment.
- RA followed by bare-metal stent implantation yields better results than balloon angioplasty alone, but with persistently high rates of restenosis.
- RA followed by drug-eluting stent (DES) implantation yields better results than balloon angioplasty, and observational data have shown that this therapeutic combination leads to favorable clinical outcomes.

Conclusion

- RA is indicated in heavily calcified coronary lesions.
- Persistent limitations of this technique include higher risk of complications, higher cost and high rates of restenosis.
- A combination of RA and DES implantation leads to favorable clinical outcomes, particularly in terms of restenosis and reintervention.

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Website

101 Rotational Atherectomy Prior to Taxus Stent http://clinicaltrials.gov/ct2/ results?term=NCT00380809