PREPARE-CALC: A Randomized Trial of High-speed Rotational Atherectomy Prior to Drug-Eluting Stent Implantation in Severely Calcified Coronary Lesions

Gert Richardt, MD

Heart Center Segeberger Kliniken, Bad Segeberg Germany

for the PREPARE-CALC investigators

Clinicaltrials.gov: NCT02502851

Disclosure Statement of Financial Interest

I, Gert Richardt have received speaker's honoraria from Boston Scientific and Biotronik.

Patients with Severely Calcified Lesions

- Elderly with numerous comorbidities
- Growing demand for revascularisation
- Increased periprocedural complications
- More long-term adverse events
- Mostly excluded from randomized PCI trials
- Poor evidence for best PCI practice

Madhavan et al. J Am Coll Cardiol 2014;63:1703 - Généreux et al. J Am Coll Cardiol 2014;63:1845

Lesion Preparation in Severe Calcification

- Essential to facilitate stent delivery and adequate stent expansion (1)
- Compared to standard balloons, rotational atherectomy (2)
  - Increases acute success of the procedure
  - Achieves more acute luminal gain
  - Stimulates neointima formation and causes more late lumen loss
- Availability of modified balloons (scoring/cutting) and new generation DES may impact PCI practice

(1) Barbato et al. EuroIntervention 2017;13:696 - (2) Abdel-Wahab et al. JACC Cardiovasc Interv 2013;6:10

Established Techniques for Lesion Preparation

- **High-speed rotational atherectomy**

  Plaque modification by differential cutting

- **Scoring/cutting balloon**

  Focal concentration of dilatation force with controlled incisions of the lesion

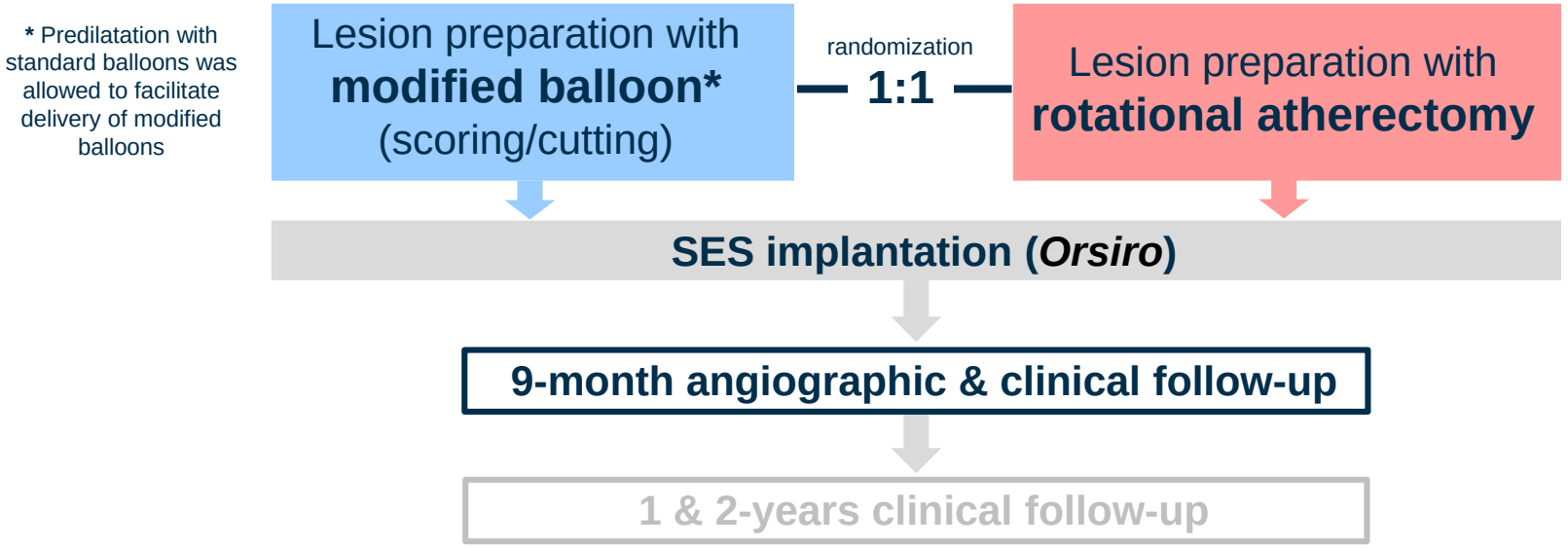
Objective

... to compare rotational atherectomy with modified balloons (scoring/cutting) in severely calcified lesions regarding acute success and intermediate-term efficacy.

Study Design

Prospective, randomized, active-controlled clinical trial in two German centers

PCI in 200 patients with severely calcified lesions



Key In- & Exclusion Criteria

INCLUSION

- Anginal symptoms and/or evidence of ischemia
- De-novo lesion in native coronary artery
- Ref. vessel diameter 2.25-4.0 mm
- Luminal diam. reduction of 50-100%
- Severe calcification of the target lesion *

EXCLUSION

- Myocardial infarction within one week
- Decompensated heart failure
- Target lesion in a coronary bypass
- Target lesion is an in-stent restenosis
- Thrombus in the target vessel

* Mintz et al. Circulation 1995;91:1959-65

Primary Endpoints

- **Strategy success**

  (successful stent delivery and expansion with < 20% in-stent residual stenosis and TIMI 3 flow without crossover or stent failure; ***powered for superiority***)

- **In-stent late-lumen-loss at 9 months**

  (***powered for non-inferiority***)

Secondary Endpoints

- Procedural duration
- Contrast dye amount
- Peri-procedural myocardial infarction
- In-segment LLL
- Binary restenosis (in-stent and in-segment)
- Stent thrombosis
- Target vessel failure (TVF) at 9 months

Determination of Study Size

Assumptions:

Strategy success: RA 90% vs MB 75%*
100 patients in each arm to detect **superiority**

LLL: 0.2 mm in both groups
74 patients in each arm with 1.3 lesions/patient
to detect **non-inferiority** (non-inferiority margin 0.2mm)

For both 80% power at an alpha level of 0.05

* Abdel-Wahab et al. JACC Cardiovasc Interv 2013;6:10

Study Organization

Steering Committee: Mohamed Abdel-Wahab, Ralph Toelg, Gert Richardt

Participating Centers

Heart Center, Segeberger Kliniken, Bad Segeberg, Germany
German Heart Center, Technical University of Munich, Munich, Germany

Study devices

Flextome cutting balloon (Boston Scientific)
AngioSculpt scoring balloon (Biotronik)
Scoreflex scoring balloon (OrbusNeich Medical)
Rotablator (Boston Scientific)
Sirolimus-eluting Orsiro stent (Biotronik)

Independent Clinical Event Committee *(Chair: M. Ferenc, Bad Krozingen, Germany)*

Independent QCA Core Lab (ISAR Research Center, Munich, Germany)

Independent Statistical Core Lab (Derek Robinson, Sussex, UK)

Baseline Characteristics

	Modified balloon (n = 100 pts.)	Rotational atherectomy (n = 100 pts.)	p-value
Age (years)	75.0 ± 6.9	74.8 ± 7.1	0.79
Males	75 (75%)	77 (77%)	0.74
Diabetes mellitus	34 (34%)	33 (33%)	0.88
Hypertension	93 (93%)	93 (93%)	1.00
Dyslipidemia	69 (69%)	68 (68%)	0.88
Current smokers	9 (9%)	15 (15%)	0.19
Chronic renal failure*	21 (21%)	26 (26%)	0.40
Previous MI	22 (22%)	21 (21%)	0.86
Previous CABG	13 (13%)	6 (6%)	0.09
Unstable angina	9 (9%)	8 (8%)	0.80
Left main disease	**37 (37%)**	**23 (23%)**	**0.03**
Multivessel disease	70 (70%)	74 (74%)	0.52
LV ejection fraction (%)	56.9 ± 10.6	55.7 ± 11.7	0.45

* defined as glomerular filtration rate < 60 ml/min

Angiographic & Procedural Characteristics

	Modified balloon (n = 137 lesions)	Rotational atherectomy (n = 141 lesions)	p-value
Location			0.30
Left main	20 (14.6%)	15 (10.6%)	
Left anterior descending	61 (44.5%)	78 (55.3%)	
Left circumflex	16 (11.7%)	16 (11.3%)	
Right coronary artery	40 (29.2%)	32 (22.7%)	
Reference vessel diameter (mm)	3.31±0.44	3.25±0.47	0.25
Diameter stenosis (%)	83.54±8.76	83.02±10.35	0.80
Ostial location	35 (25.5%)	40 (28.4%)	0.52
Bifurcation	61 (44.5%)	55 (39.0%)	0.37
Chronic total occlusion	4 (2.9%)	4 (2.8%)	1.00
B2/C lesion	129 (94.2%)	137 (97.2%)	0.62
7 Fr guiding catheter	**111 (81.0%)**	**130 (92.2%)**	**0.002**
Cutting/scoring balloon diameter (mm)	2.94±0.34	--	--
Max. burr size (mm)	--	1.53±0.18	--
Balloon predilatation	**103 (75.2%)**	**119 (84.4%)**	**0.04**
Total stent length / lesion (mm)	35.41±18.00	35.63±15.69	0.94
Max. stent implantation pressure (atm)	**17.47±3.54**	**16.47±2.87**	**0.02**
Balloon postdilatation	117 (83.0%)	111 (81.0%)	0.70
Max. postdil. balloon diameter (mm)	3.70±0.54	3.68±0.49	0.76
Max. postdil. balloon pressure (atm)	21.86±4.65	20.95±4.88	0.12

Procedural and In-Hospital Outcome

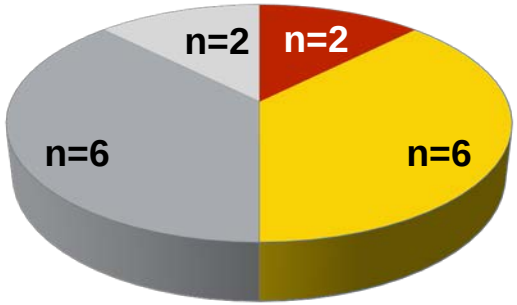
	Modified balloon (n = 100 pts.)	Rotational atherectomy (n = 100 pts.)	p-value
Procedural duration (min)	78.5±40.6	88.2±34.9	0.07
Fluoroscopy time (min)	**19.6±13.4**	**23.9±12.2**	**0.03**
Contrast amount (ml)	230.0±93.8	233.0±109.1	0.83
Large dissection (> 5mm)	7 (7%)	3 (3%)	0.33
Side branch compromise	13(13%)	6 (6%)	0.09
Perforation	2 (2%)	4 (4%)	0.68
Pericardial effusion	0 (0%)	3 (3%)	0.24
Death	0 (0%)	0 (0%)	1.00
Myocardial infarction	1 (1%)	2 (2%)	1.00
TVR	0 (0%)	0 (0%)	1.00
Stent thrombosis	0 (0%)	0 (0%)	1.00
Access site complications	5 (5%)	3 (3%)	0.72

Primary Endpoint – Strategy Success

	Modified balloon (n = 100 pts.)	Rotational atherectomy (n = 100 pts.)	p-value
Strategy success	**81 (81%)**	**98 (98%)**	**0.0001**
Final TIMI flow < III	0 (0%)	1 (1%)	0.99
Residual stenosis >20%	2 (2%)	0 (0%)	0.49
Stent failure	4 (4%)	1 (1%)	0.36
Crossover	**16 (16%)**	**0 (0%)**	**<0.0001**

Cross-Over Patients

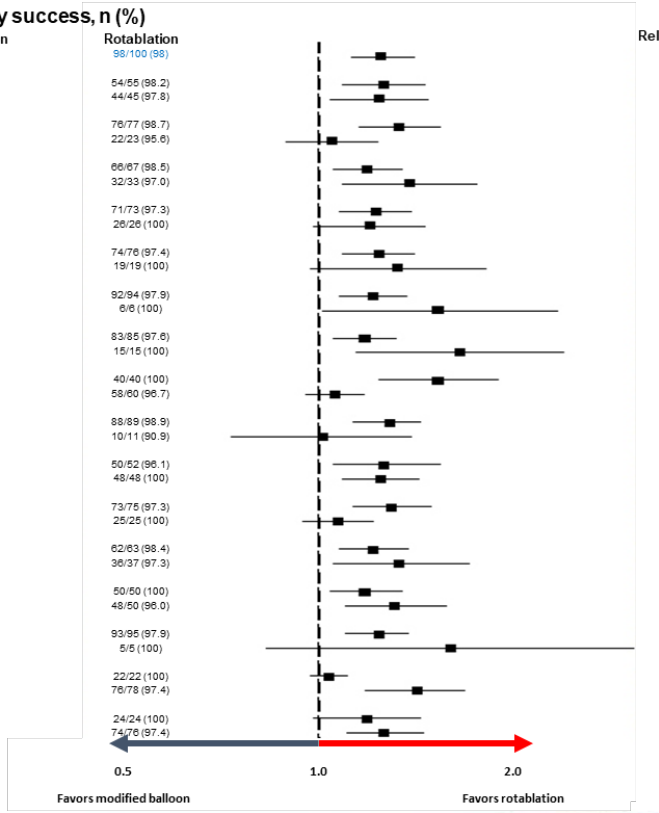
	Modified balloon (n = 100 pts.)	Rotational atherectomy (n = 100 pts.)	p-value
Strategy success	**81 (81%)**	**98 (98%)**	**0.0001**
Final TIMI flow < III	0 (0%)	1 (1%)	0.99
Residual stenosis >20%	2 (2%)	0 (0%)	0.49
Stent failure	4 (4%)	1 (1%)	0.36
Crossover	**16 (16%)**	**0 (0%)**	**<0.0001**



- not crossable by any balloon
- not crossable by modified balloon
- not adequately dilatable
- stent not deliverable

Subgroup Analysis

Variable	Modified balloon	Rotablation	Relative Risk (95% CI)	P-value for Interaction
All patients	81/100 (81)	98/100 (98)	1.21 (1.10-1.34)	
Age				
≥75 years	46/57 (80.7)	54/55 (98.2)	1.22 1.07 – 1.39	0.9
< 75 years	35/43 (81.4)	44/45 (97.8)	1.20 1.03 – 1.40	
Gender				
Male	58/75 (77.3)	76/77 (98.7)	1.28 1.13 – 1.45	0.03
Female	23/25 (92.0)	22/23 (95.6)	1.04 0.90 – 1.20	
Diabetes				
No	56/66 (84.8)	66/67 (98.5)	1.16 1.04 – 1.29	0.29
Yes	25/34 (73.5)	32/33 (97.0)	1.32 1.07 – 1.63	
GFR				
>60 ml/min/1.73m^2	63/77 (81.8)	71/73 (97.3)	1.19 1.06 – 1.33	0.86
≤60 ml/min/1.73m^2	18/21 (85.7)	26/26 (100)	1.17 0.98 – 1.39	
LV function				
≥50%	65/80 (81.2)	74/76 (97.4)	1.20 1.07 – 1.34	0.69
<50%l	11/14 (78.6)	19/19 (100)	1.27 0.97 – 1.67	
Previous CABG				
No	72/87 (82.8)	92/94 (97.9)	1.18 1.06 – 1.31	0.30
Yes	9/13 (69.2)	6/6 (100)	1.44 1.01 – 2.08	
Left main				
No	68/80 (85.0)	83/85 (97.6)	1.15 1.04 – 1.27	0.08
Yes	13/20 (65.0)	15/15 (100)	1.54 1.12 – 2.12	
Left anterior descending				
No	34/49 (69.4)	40/40 (100)	1.44 1.20 – 1.74	0.002
Yes	47/51 (92.2)	58/60 (96.7)	1.05 0.96 – 1.15	
Vessel diameter				
≥3mm	72/90 (80.0)	88/89 (98.9)	1.24 1.11 – 1.37	0.18
<3mm	9/10 (90.0)	10/11 (90.9)	1.01 0.76 – 1.33	
Lesion length				
≥27 mm	33/42 (78.6)	50/52 (96.1)	1.22 1.04 – 1.45	0.9
<27 mm	48/58 (82.8)	48/48 (100)	1.21 1.07 – 1.36	
Stenosis severity				
≥80%	64/82 (78.0)	73/75 (97.3)	1.25 1.11 – 1.41	0.05
<80%	17/18 (94.4)	25/25 (100)	1.06 0.95 – 1.18	
Ostial location				
No	59/71 (83.1)	62/63 (98.4)	1.18 1.06 – 1.32	0.51
Yes	22/29 (75.9)	36/37 (97.3)	1.28 1.04 – 1.59	
Bifurcation				
No	40/46 (87.0)	50/50 (100)	1.15 1.03 – 1.29	0.34
Yes	41/54 (75.9)	48/50 (96.0)	1.26 1.08 – 1.48	
Severe tortuosity				
No	77/94 (81.9)	93/95 (97.9)	1.20 1.08 – 1.32	0.44
Yes	4/6 (66.7)	5/5 (100)	1.50 0.85 – 2.64	
Type C lesion				
No	34/35 (97.1)	22/22 (100)	1.03 0.97 – 1.09	0.001
Yes	47/65 (72.3)	76/78 (97.4)	1.35 1.15 – 1.57	
Grade 3 calcification				
No	19/22 (86.4)	24/24 (100)	1.16 0.98 – 1.37	0.59
Yes	62/78 (79.5)	74/76 (97.4)	1.22 1.09 – 1.38	



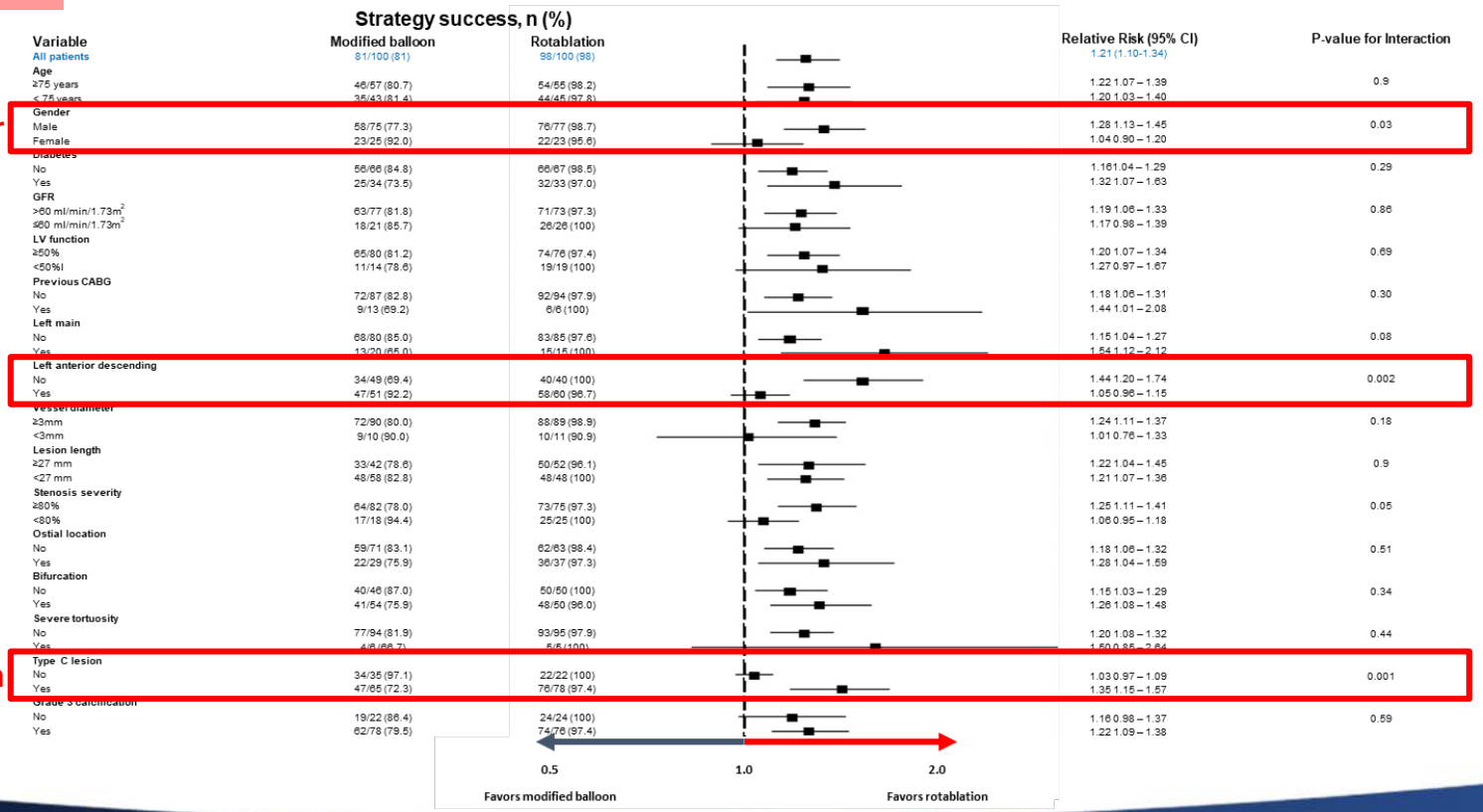
Subgroup Analysis

No
Advantage of RA

Female gender

LAD as target

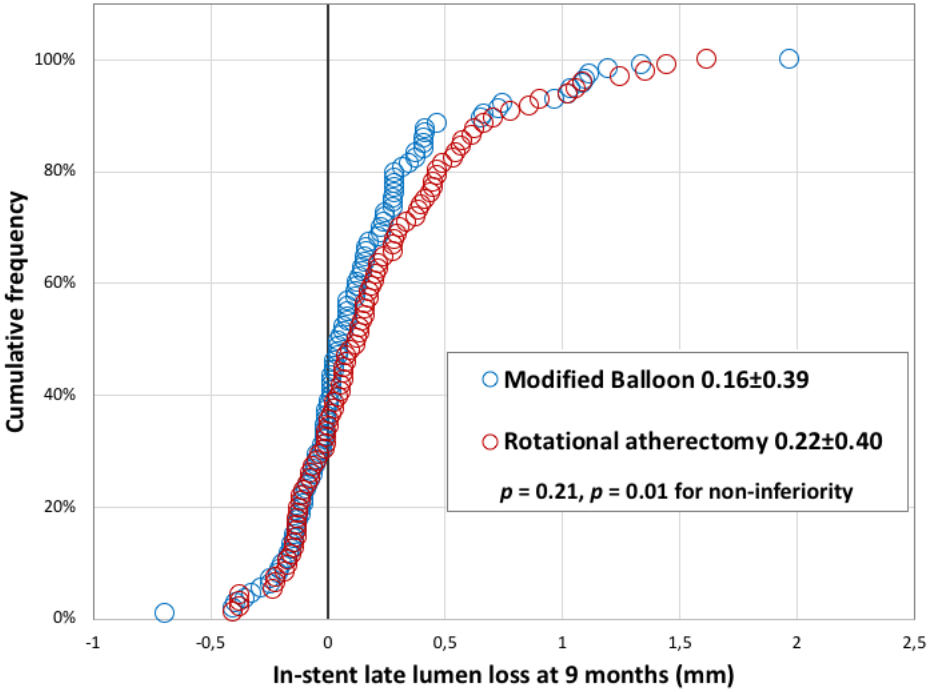
Non Type C lesion



Baseline QCA

	Modified balloon (n = 136 lesions)	Rotational atherectomy (n = 137 lesions)	p-value
Before the procedure			
Lesion length (mm)	20.16±11.88	20.86±12.30	0.63
Reference vessel diameter (mm)	3.08±0.47	3.10±0.49	0.84
Minimal lumen diameter (mm)	1.07±0.34	1.15±0.35	0.07
Diameter stenosis (%)	65.18±9.53	63.43±9.80	0.16
Immediately after the procedure			
Minimal lumen diameter (mm)			
In-stent	2.81±0.47	2.85±0.43	0.56
In-segment	2.58±0.53	2.62±0.67	0.61
Diameter stenosis (%)			
In-stent	12.34±5.14	12.62±5.36	0.63
In-segment	17.12±7.39	17.58±7.31	0.59
Acute gain (mm)			
In-stent	1.74±0.45	1.70±0.42	0.45
In-segment	1.50±0.51	1.47±0.64	0.61

Co-Primary Endpoint – In stent LLL at 9 Month



QCA at 9 Month

	Modified balloon (n = 112 lesions)	Rotational atherectomy (n = 97 lesions)	p-value
Minimal lumen diameter (mm)			
In-stent	2.68±0.59	2.64±0.51	0.59
In-segment	2.50±0.54	2.50±0.55	0.96
Diameter stenosis (%)			
In-stent	18.83±13.42	19.75±11.54	0.49
In-segment	22.40±11.36	23.30±11.43	0.52
Late lumen loss (mm)			
In-stent	0.16±0.40	0.22±0.41	0.21
In-segment	0.07±0.52	0.18±0.74	0.25
Binary restenosis (%)			
In-stent	6 (5.3%)	2 (2.1%)	0.30
In-segment	5 (4.5%)	2 (2.1%)	0.32

Clinical Outcome at 9 Month

	Modified balloon (n = 100 pts.)	Rotational atherectomy (n = 100 pts.)	p-value
Death	2 (2%)	2 (2%)	1.00
Cardiac death	1 (1%)	1 (1%)	1.00
Non-cardiac death	1 (1%)	1 (1%)	1.00
Myocardial infarction	3 (3%)	2 (2%)	1.00
Target vessel MI	1 (1%)	2 (2%)	1.00
Periprocedural MI	1 (1%)	2 (2%)	1.00
Spontaneous MI	2 (2%)	0 (0%)	0.50
Stent thrombosis (def./prob.)	0 (0%)	0 (0%)	1.00
TVR	8 (8%)	3 (3%)	0.21
Target vessel failure	8 (8%)	6 (6%)	0.78

Limitations

- Cross-over is a potential source of bias
- Not powered for clinical endpoints
- Mainly transfemoral approach
- Exclusion of acute and clinically unstable patients
- Angiography-guided procedures
- Other techniques not tested (Orbital atherectomy, Laser, Lithoplasty etc.)

Summary

In patients with severely calcified coronary lesions

- Elective RA is feasible in nearly all patients and the acute success rate is superior to modified balloons.
- Both approaches (elective RA and balloon plus bailout RA) are equally safe and effective.
- Use of RA is no longer associated with excessive LLL in the era of modern SES.