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# CARDIOVASCULAR OUTCOMES FOLLOWING ROTATIONAL ATHERECTOMY: A UK MULTI-CENTRE EXPERIENCE

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**Brief Title:** Cardiovascular outcomes of rotational atherectomy

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**Abstract**

**Objectives:**

To identify factors associated with outcomes following rotational atherectomy (RA).

**Background:**

RA is an effective way to mechanically modify heavily calcified lesions before stenting, however its outcomes are not well defined.

**Methods and results:**

Retrospective evaluation of all patients who underwent RA in three large UK centers (Leeds General Infirmary (LGI), Royal Infirmary of Edinburgh (RIE) and University Hospital of North Staffordshire (UHNS)) from March 2005 to January 2013. 518 patients had RA with median follow-up period of 22 months. 68.3% were male, 28.7% had DM and 34.6% were treated because of ACS. Stents were deployed in 97.3% of the patients while 30.7% of the procedures were performed trans-radially. Maximum burr was ≤1.75mm in 85.5% and the mean SYNTAX score was 19.5+/-11.6. Peri-procedural complications occurred in 6.4% and vascular access complications in 1.9%. Outcomes in the follow up period were: MACE 17.8%, cardiac death 7.1%, MI 11.7%, TVR 7.5%, all-cause death 13.7%, definite stent thrombosis (ST) 1.4% and stroke 2.9%. Patients with intermediate and high SYNTAX scores were more likely to suffer MACE, cardiac death, MI, all-cause death and ST. Patients with a SYNTAX score >32 were also more likely to have a peri-procedural complication. Multiple logistic regression analysis showed that the presence of PVD (p=0.026, OR=2.0), DM (p=0.008, OR=2.1), ACS presentation (p=0.011, OR=2.1) and SYNTAX score ≥23 (p=0.02, OR=1.9) had a significant association with MACE.

**Conclusions:**

RA is safe and effective, with high rate of procedural success and relatively low incidence of MACE. PVD, DM, ACS presentation and SYNTAX score were significant predictors for MACE.

## Introduction

Coronary artery calcification represents a challenge in everyday clinical practice for percutaneous coronary interventions (PCI). Heavily calcified lesions predispose to stent delivery failure or a suboptimal final result, with stent under-expansion being associated with restenosis or stent thrombosis, especially in the drug eluting stent (DES) era. For DES implantation, an additional concern of coronary artery calcification is the risk of damage to the polymer of the stent during advancement through the lesion and the potential for inadequate drug diffusion through calcium and into the subintimal layer (1, 2).

Rotational atherectomy (RA) is an effective way of mechanically modifying and debulking calcified coronary artery lesions; according to ESC guidelines for revascularization it has a Class 1 recommendation for preparation of heavily calcified or severely fibrotic lesions that cannot be crossed by a balloon or adequately dilated before planned stenting (3). Given the positive relationship between residual plaque burden behind the stent and the amount of neointimal proliferation post-stenting, it had been hoped that the use of RA may reduce long term restenosis (4, 5). However, the randomised ROTAXUS study showed no benefit in angiographic restenosis using RA and paclitaxel eluting stents (PES) compared to a conservative strategy without RA during a 9 month follow up period (1).

There is a paucity of real world, large scale, multi-centre data on cardiovascular complications and outcomes following RA. Clinical event rates in this typically elderly, high risk population would be predicted to be high, yet the factors associated with poor outcome are ill-defined. The aim of this retrospective study was to identify the factors associated with peri-procedural complications and adverse cardiovascular outcomes from consecutive cases from three large tertiary cardiac centres in the UK.

## Materials and Methods

A retrospective evaluation was performed of all patients who underwent RA and PCI in three high-volume UK tertiary cardiac centres (Leeds General Infirmary (LGI), Royal Infirmary of Edinburgh (RIE) and University Hospital of North Staffordshire (UHNS)) from 14/3/2005 to 18/1/2013. Data were extracted from individual hospital case notes and electronic patient records including local catheter lab and surgical databases and national audit databases.

Baseline characteristics (demographic, clinical, and procedural) and medium-term outcome data (minimum 6 months) were collected. Pre-procedural data included all demographics, co-morbidities and haematological data. Chronic kidney disease was defined by the occurrence of impaired renal function (estimated GFR<60 mL/min/1.73 $m^2$) for three or more months, irrespective of the cause. Peripheral arterial disease (non-coronary artery disease causing reduced blood flow in either the brain, kidneys or limbs) and Diabetes Mellitus (defined according to WHO criteria) were recorded directly from the hospital case notes or electronic patient records, from prior established clinical diagnoses. Procedural data included indication for procedure and urgency, adjuvant pharmacotherapy (oral antiplatelet agents, anticoagulants and glycoprotein IIb/IIIa receptor inhibitor (GPI)), burr size, SYNTAX scores (overall and target vessel scores were calculated according to the SYNTAX score algorithm), access site, sheath and guiding catheter size, number and type of stents (DES or BMS), use of temporary pacemaker during procedure, number of attempted vessels and procedural complications. For the purpose of this study, coronary dissection was not considered as a significant complication and was treated in each case by planned stent implantation or additional stent implantation in cases of edge dissection from a prior implanted stent. Post-procedural data were collected on vascular access complications, peri-procedural myocardial infarction (MI) and discharge vital status (dead or alive).

Follow-up data focused on study-defined major adverse cardiovascular events (MACE; defined as cardiac death, MI, target vessel revascularisation (TVR). Other reported clinical outcomes included all-cause mortality, stroke and definite stent thrombosis (ST). MI was defined as the typical elevation and fall of cardiac enzymes (troponin or CK-MB) with at least one of the following: ischemic chest pain symptoms, ST depression or ST elevation or new LBBB, development of pathological Q waves and imaging findings of new myocardial necrosis (6, 7, 8). TVR was defined as a repeated procedure, either PCI or CABG, on the original target vessel. Stroke was defined as any persistent focal neurological deficit lasting >24h. (9).

RA was performed using the standard Boston Scientific Rotablator system. This included the 0.009in Rotawire, the Rotalink or Rotalinkplus advancer, and console. Typical burr speeds were between 150,000 and 180,000rpm with a 'run duration' of 15–20s, or less in cases where there was a drop of more than 5000rpm, which can be an indication of increased resistance and overheating. All procedures used a slow (~1 drop/s) continuous intracoronary infusion via the burr sheath of verapamil, isosorbide dinitrate (ISDN) and heparin to reduce the risk of thrombus formation and vessel spasm. IV heparin, bivalirudin and GPI were used at the operator's discretion. All patients were pre-treated with aspirin and clopidogrel. Prasugrel and ticagrelor were not used in any of our cases. Heparin was given to maintain an activated clotting time >250s, or 200-250s if a GPI had been administered. Procedures were performed via the radial or femoral route according to individual operator preference.

**Statistical analysis**

Data were analysed using IBM SPSS® Statistics 21.0 (IBM Corp., Armonk, NY). Chi-square tests and Fisher's exact test were conducted to identify possible associations between the existence of the outcomes and categorical variables, while t-test analysis was used to test for

differences in means of continuous variables between the occurrence or not of an outcome. Multiple logistic regression analysis (forward stepwise) was used to predict the outcomes of MACE based on the presence of important co-morbidities (chronic kidney disease (CKD), hypertension (HTN), peripheral vascular disease (PVD), diabetes mellitus (DM), smoking status, prior MI, prior CABG, prior stroke and LV systolic function), procedural urgency (acute coronary syndrome (ACS), age and SYNTAX score≥23. Odds ratio was used to evaluate the effect of significant factors associated with the presence of the outcomes examined. Kaplan Meier survival curves were constructed for freedom from MACE and all-cause death and compared using Log-rank, Breslow and Tarone-Ware tests. Statistical significance was defined as $p \leq 0.05$.

## Results

A total of 518 patients underwent PCI with RA during the study period. The total number of cases performed in all three sites over the study period was 37172 showing that a 1.4% of the cases was done with RA (LGI: 182/16718, RIE: 182/11275, UHNS: 154/9179). Baseline patient characteristics are shown in Table 1. Median follow up period was 22 months (range 6 to 85 months).

The mean SYNTAX score of the target vessel was 12.8±8.0 and the mean overall SYNTAX score was 19.5±11.6 (Table 2). Procedures were performed via the trans-radial route in 30.7%, including a 3.3% where a sheathless guiding catheter was used. Only 17.2% of the procedures were performed using large 8 or 9F sheaths and only 15.6% needed a guiding catheter of 8 or 9F. The starting burr size was 1.25mm in 30%, 1.5mm in 52.5% and 1.75mm in 13.1%. In 85.5% of the cases the maximum burr size was ≤1.75mm (1.25mm in 11.9%, 1.5mm in 41.4% and 1.75mm in 32.2%). Coronary stents were implanted in 97.3% of patients, with 75.9% having at least one DES implanted.

Significant peri-procedural complications occurred in 6.4% of the patients and vascular access complications in 1.9% (Table 3). Three patients (0.6%) died of cardiac causes before hospital discharge, one of whom died on the day of the PCI-RA procedure (cardiogenic shock following ACS presentation requiring PCI to LMS-LAD and IABP insertion). Patients with a SYNTAX score ≥33 were more likely to have a significant peri-procedural complication (13.9% vs. 5.0%, p=0.008) (table 4). Trans-femoral compared to trans-radial procedures were not associated with increased vascular access complications (2.5% vs. 0.6%, p=0.297) or peri-procedural complications (5.8% vs. 7.5%, p=0.443) (table 5).

Clinical outcomes in the follow up period were: total MACE 17.8% (n=92), cardiac death 7.1% (n=37), MI 11.7% (n=60), TVR 7.5% (n=39), all-cause death 13.7% (n=71), ST 1.4% (n=7) and stroke 2.9% (n=15) (Table 3). Patients with an overall SYNTAX score ≥23 compared to patients with a SYNTAX score ≤22, were more likely to have MACE (26.0% vs. 13.2%, p<0.001), cardiac death (11.6% vs. 4.5%, p=0.004), MI (18.8% vs. 7.8%, p<0.001), all cause death (20.4% vs. 9.9%, p=0.001) and ST (3.3% vs. 0.3%, p=0.009) (Table 4). Patients with a SYNTAX score ≥33 compared to patients with a SYNTAX score ≤32 were also more likely to have MACE (31.9% vs. 15.3%, p=0.001), cardiac death (16.7% vs. 5.4%, p=0.002), MI (23.6% vs. 9.7%, p=0.002) or all cause death (31.9% vs. 10.6%, p<0.001) (Table 4).

The use of GPI did not have an impact on total MACE (19.5% vs. 17.0%, p=0.465), but was associated with more TVR (11.2% vs. 5.7%, p=0.033) and ST (3.6% vs 0.3%, p=0.006). The use of DES vs. BMS was not associated with superior outcomes in terms of total MACE (16.1% vs. 19.3%, p=0.465), cardiac death (5.8% vs. 9.2%, p=0.269), MI (11.1% vs. 10.1%, p=0.862) or TVR (7.8% vs 5.5%, p=0.530) (Table 5). There was also no difference between

the use of radial vs. femoral access in terms of total MACE (20.1% vs 16.7%, p=0.383), stroke (4.5% vs 2.4%, p=0.256), peri-procedural complications (7.5% vs 5.8%, p=0.443) and vascular access complications (0.6% vs 2.5%, p=0.297) (Table 5).

Multiple logistic regression analysis (forward stepwise) using the variables of age, SYNTAX score, indication for the procedure (elective or ACS) and past medical history (Table 1) was used to test the association with occurrence of total MACE. The presence of PVD (p=0.026), DM (p=0.008), ACS indication (p=0.011) and the SYNTAX score ≥23 (p=0.02) had a significant impact on the tested outcome (MACE) (Table 6). Specifically, the presence of PVD had an odds ratio of 2.0 (95%CI: 1.1-3.7), DM odds ratio 2.1 (95%CI: 1.2-3.7), ACS indication odds ratio 2.1 (95%CI: 1.2-3.6), and SYNTAX score ≥23 odds ratio 1.9 (95%CI: 1.1-3.3) (table 6). Kaplan Meier survival curves were constructed to assess differences between specific pre-defined sub-groups (clinical: ACS presentation, DM, PVD; angiographic: SYNTAX scores; procedural factors: use of DES, use of GPI, incidence of peri-procedural and vascular complications) for freedom from total MACE and all-cause death. Only the occurrence of peri-procedural complications showed a significant impact on outcomes (Figures 1a-1b).

## Discussion

We have shown that 1) angiographic disease severity, as expressed by a SYNTAX score≥23, had a significant impact on the incidence of MACE, cardiac death, MI, all cause death and ST after RA; 2) patients with a SYNTAX score≥33 were more likely to have a peri-procedural complication; and 3) clinical factors such as a history of PVD, DM and ACS presentation had a significant association with total MACE.

Patients selected for RA prior to stent implantation tend to be elderly, have multiple risk factors for coronary artery disease and in general are a population with high pre-procedural risk (10). As a result, the total combined MACE rate over a long follow up period is anticipated to be high. Most of the published studies have shown a MACE rate ranging between 11.3% and 20.7%, with the exception of the ROTAXUS study which showed a 24.2% MACE rate in patients with RA and DES implantation (1, 11-16). Our multi-centre data represent one of the largest observational studies with one of the longest follow up periods, and show a 17.8% MACE rate which is comparable to other studies with smaller sample size and shorter follow up.

Even though the ROTAXUS study was a randomised trial with a short follow up period of 9 months and a highly selected patient population (patients with LMS disease and/or recent MI were excluded), the MACE rate of 24.2% seems extremely high and questions the generalizability of the results to real-world clinical practice. Therefore, the results of ROTAXUS should not discourage the use of RA prior to stent implantation in patients with severe calcific coronary artery disease. Furthermore, the need for TVR in our observational study was much lower, even with the use of BMS (5.5%), which supports the selective use of BMS after RA in patients that cannot receive longer term dual antiplatelet therapy or have a contraindication for DES implantation.

Interestingly, the use of GPI was not shown to have any impact on either total MACE or procedural complications, suggesting that it should remain an option for bail-out use, at the discretion of the operator, in cases where there is slow flow/no reflow or thrombotic complications. RA has been shown to induce platelet activation and the main activator of platelets is ADP, released by lysed dense granules and the cytoplasmic pool (17, 18). Platelet inhibition with GPI has been demonstrated to significantly inhibit platelet aggregation during

RA and reduce peri-procedural MI (18, 19). However, in real-world clinical practice, use of GPI during RA is not uniform; published series showing usage rates of 2.9%, and 3.4% in the ROTAXUS study, which may reflect operator confidence in contemporary dual antiplatelet therapy and a desire to avoid bleeding complications (1, 2, 12).

Rates of peri-procedural complications in the literature range from 1.6% to 14.4% whilst vascular access complications range from 1.6% to 5.8% (14, 16, 20-26). In our multi-centre, observational study we have confirmed the low rates of peri-procedural (6.4%) and vascular access complications (1.9%), in a high-risk, all-comers population. This may reflect the use of relatively small burr sizes (≤1.75mm in 85.5% of our cases), allowing the use of smaller calibre arterial sheaths and guiding catheters. Using smaller burr sizes reflects the contemporary use of RA where in modern intervention, RA is not just a debulking device, but also a modifier of calcific lesions, to allow balloon dilatation and optimum stent deployment (27). The planned use of a smaller sheath size is associated with less major femoral artery access bleeding and also increases the potential for trans-radial access, an established arterial access route with low access site bleeding rates (20, 28, 29). Trans-radial arterial access for patients undergoing RA has already been shown in other studies to have comparable rates of procedural success, procedure time, and patient radiation exposure, compared to femoral arterial access (20, 30). In our study, the trans-radial access route was used in 30.7% of cases with clinical outcomes similar to procedures performed with the femoral arterial access. RA has also been associated with a higher rate of stroke compared to conventional PCI, a potential mechanism being the use of larger guiding-catheters (31, 32). In our observational study there were no peri-procedural strokes, and the stroke rate was relatively low (2.9%) throughout the follow up period. One final observation was the relatively low usage of temporary pacing in our study (18.7%), again perhaps reflecting an increasingly common

strategy of avoiding routine temporary wire insertion, so as to minimize the risk of peri-procedural complications.

Multivariate analysis has showed that most of the significant predictors for MACE are clinical factors (DM, PVD and ACS) and also the angiographic lesion complexity (SYNTAX score). History of smoking, HTN, MI, stroke, CABG, poor LV systolic function and CKD have not been shown to be significant factors for the occurrence of MACE (table 6). Angiographic lesion complexity (SYNTAX score) was also associated with the occurrence of peri-procedural complications, which had an impact on MACE-free survival and all cause death as shown in Figure 1a. Therefore, we have shown that patient outcomes are influenced by a combination of clinical and angiographic characteristics, which can be used to potentially identify a higher risk sub-group. Patients with DM, PVD, ACS presentation and high SYNTAX scores were more likely to have MACE in the follow up period.

**Conclusion:**

Our multi-centre, observational, all-comers study represents one of the largest consecutive series of patients treated with RA prior to stent implantation in heavily calcified coronary lesions. In this elderly, high-risk population, RA appears to be a safe, feasible and effective method, with a high rate of procedural success and relatively low incidence of total MACE in this complex patient and lesion group. PVD, DM, ACS presentation and the SYNTAX score were significant predictors for MACE.

There is no relation of this work with the industry and there is no conflict of interest to declare.

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Figure 1a. Free of MACE curve for the occurrence of peri-procedural complications.

Figure 1b. Survival curve for the occurrence of peri-procedural complications.