Drug Coated Balloon (DCB) angioplasty; DCB Norwich Registry (2009-2015) and a Propensity Score Matched Comparison between DCB and Second Generation Drug Eluting Stents.

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Abstract

Background

Drug coated balloons are semi compliant balloons coated with a chemotherapeutic drug to reduce neo intimal hyperplasia thus reducing the risk of re-stenosis. The lack of any permanent metal/polymer in the coronary artery may reduce future risk of adverse clinical events.

Objectives

The main objective of the DCB NORWICH observational registry was to assess the efficacy and safety of drug coated balloon angioplasty in a real world setting. The propensity matched analysis compared clinical outcomes between DCB-only angioplasty and second generation drug eluting stents (DES).

Methods

All patients who received DCB angioplasty in the Norfolk and Norwich University Hospitals NHS Foundation Trust from 01/01/2009 to 31/12/2015 were included retrospectively in the DCB NORWICH registry study. In the propensity score matched study, DCB-only PCI in de novo vessels were compared to second generation DES. Clinical outcomes were obtained from the National Institute for Cardiovascular Outcomes Research and NHS Digital.

Results

A total of 1394 lesions in 1122 patients were treated with DCBs. There were 1026 lesions in 812 patients in the de novo group. The mean age was 65.8. 60.1% presented with MI or acute coronary syndrome. 12 month all cause death was 3.6%, MI 3.1% and target lesion revascularisation (TLR) 2.1%. MACE (death, MI, TLR) was 8.1%. No definite treated segment thrombosis was noted up to 12 months.

The propensity score matched study had 904 DCB and 1424 DES treated de novo lesions. Results showed no difference in clinical outcomes between PCI with DCB-only strategy vs. 2nd generation DES. The MACE rate for the DCB arm met the pre specified non-inferiority margin of 4.5%.

Conclusions

DCB-only PCI is safe and feasible in a wide range of patients and showed no difference in clinical outcomes compared to second generation DES up to 12 months.

Declaration

I can confirm that this thesis is my own work and has not been submitted elsewhere. The abstracts and other publications generated from this are as listed below. I also confirm that the word count is less than the recommended limit in the university regulations. Where information is obtained from other sources, they are as referenced.

With guidance from supervisors, I drafted the study protocol, applied for approvals from the hospital Research and Development Department, National Research Ethics Committee (North West Haydock), Health Research Authority (HRA), Confidential Advisory Group of HRA, NHS Digital and Healthcare Quality Improvement Programme (HQIP) prior to applying for clinical outcomes data from the National Institute for Cardiovascular Outcomes Research (NICOR). I identified patients under various subgroups and completed the data base with the assistance of Dr Corballis, a co researcher. I reviewed the coronary angiograms of all patients treated with drug coated balloon angioplasty myself. I have also taken part in carrying out drug coated balloon angioplasty in approximately 300 patients during this period, at the Norfolk and Norwich University Hospital and was able to gain vital knowledge and first-hand experience of the technology.

I drafted the abstracts, the review article, the two book chapters and the thesis and they were reviewed and revised by the supervisors.

Dedication

I would like to dedicate this work firstly to my loving wife Dilusha and our son Tharusha. Thank you from the bottom of my heart for all your unwavering support, understanding, encouragement and your sacrifices in order to achieve this goal. This would not have been possible without your love, kindness and the care you took of our family. Little Tharusha may not know that he has contributed to this as yet but every night he slept well was in fact a contribution. I will make up for some of the lost time that otherwise I would have spent with him and you.

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Secondly I would like to thank Professor Marcus Flather, my academic supervisor. You helped me to keep the right balance between the clinical and academic aspects of this project using your vast experience and knowledge in the research field. I have thoroughly enjoyed our conversations and my attempts to make you believe in Interventional Cardiology.

I would also like to thank Dr Natasha Corballis, a co-researcher, for her dedication and support in completing this project without which it would not have been possible. I am very happy to see you rising through the ranks from a senior house officer to a specialist registrar in Cardiology and I am sure you will be an amazing Cardiologist in the not too distant future.

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Abstracts

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Euro18A-OP096 DEB angioplasty for coronary bifurcation lesions, first UK experience WICKRAMARACHCHI U. (1), CORBALLIS N. (1), SAREV T. (1), GILBERT T. (1), FLATHER M. (1), ECCLESHALL S. (1) (1) Norfolk and Norwich University Hospitals NHS Foundation Trust, Norwich UNITED KINGDOM

Euro18A-POS311 DEB angioplasty for coronary in-stent restenosis, a UK single-centre experience WICKRAMARACHCHI U. (1), CORBALLIS N. (1), SULFI S. (1), RYDING A. (1), WISTOW T. (1), SAREV T. (1), GILBERT T. (1), FLATHER M. (1), ECCLESHALL S. (1) (1) Norfolk and Norwich University Hospitals NHS Foundation Trust, Norwich UNITED KINGDOM

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Euro17A-OP0142 DEB-only angioplasty in CTO, a UK single-centre experience. WICKRAMARACHCHI U.(1), CORBALLIS N.(1), MAART C.(1), GILBERT T.(1), ECCLESHALL S.(1) (1) Norfolk and Norwich University Hospital NHS Foundation Trust, Norwich UNITED KINGDOM

Euro17A-POS0135 DEB-only angioplasty in left main stem disease, a stentless approach. WICKRAMARACHCHI U.(1), CORBALLIS N.(1), MAART C.(1), GILBERT T.(1), ECCLESHALL S.(1) (1) Norfolk and Norwich University Hospital NHS Foundation Trust, Norwich UNITED KINGDOM

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Oral Presentations

EuroPCR May 2018.

DCB-only angioplasty in bifurcation lesions.

DCB-only PCI in left main stem disease

2018 Eastern Research Network Meeting, Cambridge

1. Barriers in doing Research

2. DCB-NORWICH registry local results.

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DCB only PCI in Chronic Total Occlusions: A single center experience.

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3. Drug-coated Balloon-only Angioplasty for Native Coronary Disease Instead of Stents. Wickramarachchi U, Eccleshall S. Interv Cardiol. 2016 Oct;11(2):110-115. doi: 10.15420/icr.2016:17:3. PMID: 29588716

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Abbreviations

ACS	Acute Coronary Syndrome
CABG	Coronary Artery Bypass Grafting
CAD	Coronary Artery Disease
CAG	Confidentiality Advisory Group
CVA	Cerebrovascular Accident
CVD	Cerebrovascular Disease
Cx	Circumflex artery
D1	First diagonal artery
DCB	Drug Coated Balloon
DES	Drug Eluting Stent
ECG	Electrocardiogram
EES	Everolimus Eluting Stent
HQIP	Healthcare Quality Improvement Partnership
HRA	Heath Research Authority
ISR	In stent Restenosis
LAD	Left Anterior Descending Artery
LLE	Late Lumen Enlargement
LLS	Late Lumen Loss
MACE	Major Adverse Cardiac Event
MI	Myocardial Infarction
MLA	Minimal Luminal Area
MLD	Minimal Luminal Diameter
NICOR	National Institute for Cardiovascular Outcomes Research
NSTEMI	Non ST Elevation Myocardial Infarction
PCI	Percutaneous Coronary Intervention
PES	Paclitaxel Eluting Stent
POBA	Plain Old Balloon Angioplasty
PPCI	Primary Percutaneous Coronary Intervention
PVD	Peripheral Vascular Disease
RCA	Right Coronary Artery
ST	Stent Thrombosis
STEMI	ST Elevation Myocardial Infarction
TLR	Target Lesion Revascularisation
TLT	Treated Lesion Thrombosis
TVR	Target Vessel Revascularisation

Chapter 1- Introduction

1.1 Background

According to WHO in 2012, 7.4 million people died (13.1% of all deaths) due to coronary artery disease and this is the leading cause of mortality worldwide.[1] This number is continuing to increase despite effective treatment strategies. The two methods of coronary revascularisation available for patients presenting with acute coronary syndromes (ACS) and stable coronary artery disease are percutaneous coronary intervention (PCI) and coronary artery bypass graft surgery (CABG). In the United Kingdom, in 2014, there were 17,513 isolated CABG surgeries and 96,143 PCI procedures. About two thirds of all PCIs were done for ACS and a third for stable coronary artery disease (BCIS audit 2015).[2]

In 1993, stents were used in only about 5% of all PCI procedures in the UK and by 2003 this number has risen to over 90%. Drug eluting stents (DES) are used in about 85% of PCI procedures in the UK both in the setting of stable and unstable coronary artery disease. This number has risen significantly over the years from a mere 17% in 2003. In 2014, 2.5% of all PCI's were done for Stent Thrombosis and 4.8% for In-stent restenosis (BCIS audit 2015). [2]

1.2 Percutaneous Coronary Interventional Treatment Options and Role of Dual Antiplatelets

1.2.1 Balloon only Angioplasty (also known as POBA)

Percutaneous coronary intervention techniques and devices have evolved enormously since Dotter and Judkins performed the first angioplasty in 1964 and Grüntzig the first coronary angioplasty in 1977.[3] Now referred to as Plain Old Balloon Angioplasty (POBA), this technique revolutionised the approach to treating coronary artery disease, but was associated with complications such as acute vessel closure due to vessel dissections, elastic recoil and thrombosis as well as high restenosis rates requiring a second procedure. National Heart, Lung and Blood Institute angioplasty registry from 1977-1981 showed a vessel closure rate of 4% and a dissection rate of 9% out of 1500 enrolled patients.[4] Sixty-nine percent of the patients with angiographic evidence of coronary dissection did not have any associated adverse effects or require emergency bypass surgery.

1.2.2 Bare Metal Stents (BMS)

Bare metal stents were originally developed to overcome the acute and short term complications of balloon only angioplasty/POBA. The Benestent trial investigated the difference of primary clinical end points of death, myocardial infarction, cerebro vascular accident, need for coronary artery bypass graft surgery or a second angioplasty procedure and angiographic end point of minimal luminal diameter at 7 months between balloon angioplasty and bare metal stent insertion in 520 patients with stable angina. This showed evidence for a reduction in the need for a second angioplasty procedure

(relative risk 0.58; 95 percent confidence interval 0.40 to 0.85; P = 0.005) with reduced restenosis rates (22% in stent group vs. 32% in angioplasty group (P = 0.02)).[5] The Stress trial compared angiographic restenosis at 6 months and clinical outcomes between angioplasty and bare metal stents in 410 patients with symptomatic coronary artery disease. Results showed improved restenosis rates (31.6% vs. 42.1%, P = 0.046) with BMS compared to balloon angioplasty but no difference in death, MI, vessel closure or need for a bypass surgery or a second procedure.[6] This improvement of restenosis led to a substantial increase in use of BMS in the 1990's. However, it is important to note that only 5.1% (Benestent) and 6.9% (Stress trial) of patients from the angioplasty-only arm had to cross over to the stent group due to acute complications (ie acute vessel closure, flow-limiting dissection, and a suboptimal angiographic result).

1.2.3 Role of Dual Antiplatelets

Dual antiplatelet therapy (DAPT) with aspirin and clopidogrel (initially ticlopidine) has contributed to the reduction of stent thrombosis and myocardial infarction after percutaneous coronary intervention. The reduction of these events from late 1990's onwards was partly due to the widespread use of DAPT. Publications by Schömig A., Neumann F.J. *et al* and other studies such as STARS, MATTIS and FANTASTIC showed significantly less stent thrombosis with use of aspirin and ticlopidine over aspirin mono-therapy and aspirin with warfarin/heparin.[7-10] Neumann et al in a study of 140 patients who received bare metal stents showed that platelet fibrinogen receptor expression was an independent predictor of sub-acute stent occlusion.[11] Gawaz et al showed reduced activated platelet fibrinogen receptor with asprin and ticlopidine against aspirin and heparin/phenprocoumon after stenting in 46 vs. 151 patients respectively.[12]

Schomig A et al compared 257 patients treated with antiplatelet therapy (ticlopidine) to 260 patients who received anticoagulant therapy (phenprocoumon) after bare metal stent implantation. The group who received antiplatelets had 0 stent thrombosis as opposed to 5% (p <0.001) with anticoagulation, MI rates of 0.8% and 4.2% (p=0.02) and a haemorrhagic event rate of 0% vs. 6.5% (p <0.001) respectively at 30 days.[7] STARS trial which compared aspirin alone, aspirin plus warfarin and aspirin plus ticlopidine after BMS implantation in a total of 1653 patients revealed significantly less stent thrombosis (2.9, 2.7,0.5%, p 0.005) and MI (2.7, 2.0, 0.5%, p 0.01) rates at 30 days in the aspirin and ticlopidine group. Haemorrhagic complications in the aspirin and ticlopidine group were not different to aspirin and warfarin group but was higher than the aspirin alone group.[8] In the MATTIS trial 350 high risk patients who underwent bare metal stenting were randomised to receive either aspirin and ticlopidine or aspirin and an oral anti-coagulant for 30 days after the procedure. There was no statistical difference of the primary end point (composite of cardiac death, MI or repeat revascularisation) between the groups but was numerically lower in the aspirin and ticlopidine group at 30 days. The major vascular bleeding rate was less in the aspirin and ticlopidine group (RR, 4.1; 95% CI, 1.2 to 14.3; P=0.02)[9] 236 patients were randomised to standard anticoagulation (heparin/oral anticoagulant) and 249 to dual antiplatlelets (aspirin plus ticlopidine) in the FANTASTIC study. At 6 months sub-acute stent occlusion and any bleeding complication was less in the dual antiplatelet group.[10] All these studies paved the way for dual antiplatelets to be the conventional treatment after angioplasty as opposed to oral anticoagulation.

1.2.4 Drug Eluting Stents (DES)

Whilst restenosis rates were better with BMS compared to balloon only angioplasty/POBA, they were still in the order of 20-30% over six months as shown in the above two studies. In Benestent, 15% of stented patients required some form of revascularisation at 7 months. Development of a stent covered with a chemotherapeutic drug (drug eluting stent - DES) to reduce neo-intimal proliferation and thus reduce the incidence of clinical in-stent restenosis was the next step.1st generation DES were coated with paclitaxel or sirolimus and the second generation DES utilise everolimus, zotarolimus or biolimus. The TAXUS I, prospective, double blind, randomised, controlled study comparing BMS to paclitaxel coated DES showed a significant reduction of late lumen loss and diameter stenosis in the DES group at 6 months.[13] TAXUS II, III and IV studies showed similar beneficial results of DES over BMS.[14-16] Taxus VI was a prospective, randomised trial comparing paclitaxel eluting DES to BMS comprising 446 patients and the final five year results showed better target lesion revascularisation (TLR) rate of 14.6% in the DES group compared to 21.4% in BMS group (P = 0.0325).[17] SIRIUS (prospective, double blind, randomised, controlled trial comparing sirolimus eluting stent to BMS, 1058 patients) trial showed a TLR of 4.1% versus 16.6% (P<0.001) respectively at 270 days.[18] The prospective, randomised, double blind, controlled RAVEL study comparing sirolimus eluting DES to BMS in 238 patients showed similar improvements with MACE rates (death, MI, CABG, and TVR) of 5.8% vs 28.8% respectively at 12 months.[19]

Second generation stents were introduced with the aim of further reducing restenosis and need for repeat revascularisations. The most commonly used anti proliferative

agents are zotarolimus and everolimus and the drug is mounted to a polymer which is covering a cobalt chromium or platinum chromium metal stent. Significant achievements have been made in reducing the strut thickness and improving deliverability, visibility and pushability. For example the Xience V stent had a strut thickness of 81 μms compared with 130 to 140μms strut thickness of first generation stainless steel stents. The improvements of the polymer to be more haemo-compatible and biocompatible were also notable. The hydrophilicity/hydrophobicity, purity, in-vivo stability and interactions with blood-borne proteins are factors which determine haemo- and bio compatibility of the polymer. The first generation DES used durable polymers such as polyethylene-covinyl (PEVA) and poly n-butyl methacrylate (PBMA) releasing 80% of the drug sirolimus (140 $\mu g/cm^2$) in the first month. The paclitaxel concentration of the Taxus® stent was 1 $\mu g/mm^2$. The second generation DES use polymers such as poly-vinylidene fluoride and hexafluoropropylene (PVDF–HFP) which are considered more bio compatible. The concentration of everolimus in Evrolimus eluting second generation DES was of 1 $\mu g/mm^2$. 80% of everolimus is released within 1 month and 100% released within 4 months after implantation. Resolute Integrity® stent has Cobalt chromium struts with a thickness of 91 μm, biocompatible polymer of 4.1 μm with zotarilimus 160 $\mu g/cm^2$. Drug is released completely in six months. Biodegradable polymer was incorporated in to stents next. Synergy® stent has 71 μm thick Platinum chromium struts with a 4.0 μm bio degradable polylactic-co-glycolic acid (PLGA) polymer. The everolimus concentration is 1$\mu g/mm^2$ and drug release is complete in four months. [20,21, 22] The polymer free BioFreedom™ drug coated stent (DCS) has a 112 μm

thick stent struts with a modified abluminal surface to release biolimus for up to 100 days.[23]

These improvements of drug eluting stents resulted in better clinical outcomes compared to first generation DES. Five year follow up results of the randomised, controlled Endeavor clinical trial programme (zotarolimus eluting stent vs paclitaxel eluting stent vs BMS), showed TLRs of 10.4 vs. 21.5% for ZES and BMS respectively.[24] In the same study the ZES vs PES comparison showed cardiac death/myocardial infarction rate of 5.8% vs. 8.8% (p = 0.003) respectively. These advantages of second generation DES over 1st generation DES were further shown in Spirit II and III studies.[25, 26]

In the United Kingdom alone, there have been 100,294 PCI's undertaken during the year of 2018. In 88.6% of the above procedures, some form of a coronary stent has been used (BCIS audit 2020). This reflects the current standard practice of insertion of stents in both stable and acute coronary artery disease.

Real world studies/Late complications of DES

Even though technology has improved with the stent systems, long-term complications such as late and very late stent thrombosis and in-stent restenosis continue to be a problem. These are associated with both mortality and morbidity and otherwise may lead to difficult repeat revascularisations (Dangas G.D. *et al*).[27] Factors such as delayed endothelialisation, chronic inflammation due to permanent presence of polymer/metal implant, mal- apposition and under expansion of stent and non-homogenous drug delivery all contribute to these long term complications.

In real world studies using DES for off-label indications, similar to current day-to-day practice, event rates are inevitably higher than those quoted in the original controlled studies. The 4 year follow up of the randomised Resolute all comer (included patients presenting with stable coronary artery disease and myocardial infarctions, no limitations on number of lesions/vessels or stent length) study comparing ZES vs EES showed a composite end point (all cause death, MI, any revascularisation) of 30.4% and 28.6% respectively.[28] Target vessel failure (cardiac death, target vessel MI or clinically-indicated target vessel revascularization) was 17.6% and 17.1% for the two groups respectively. A real world randomised study comparing Xience vs Promus DES (Hernandez *et al*), reported event rates (composite of all cause death, MI, revascularisation) of 8.8% and 9.3% after 12 months follow up. [29]

Similarly, a surveillance angiography follow up study carried out in patients receiving DES by Cassese S. *et al* showed a restenosis rate of 12% in patients who received a 2nd generation DES after 6-8 months (4669 patients with a 2nd generation DES).[30]

The COMPARE study examined real life patients receiving second generation everolimus eluting stent (Xience V) and paclitaxel eluting Taxus Liberte stent, and found a composite of all cause death, MI and TVR of 6% in the Xience group after 12 months (897 Xience patients).[31]

Table 1 Real world studies investigating second generation drug eluting stents

Study	Randomised or not	Devices and numbers	Follow up period	Results	p value
Cassese et al[30]	No, retrospective analysis of angiograms to assess restenosis	BMS vs. 1st gen DES vs. 2nd gen DES	6-8months	angiographic restenosis 30.1, 14.6 and 12.2% 1st generation DES vs. BMS (OR 0.35, 95% CI 0.31 to 0.39) and 2nd generation DES vs.1st generation DES (OR 0.67, 95% CI 0.58 to 0.77) were independent predictors of lower rates of restenosis	
COMPARE[31]	Randomised	897 EES (Xience) vs. 903 PES (Taxus liberte)	1 year	composite of all cause death, MI, TVR) 6% vs 9%	0.02
Hernandez et al[29]	Randomised	150 Xience vs. 150 Promus	12 months	Composite of all cause death, MI, revascularisation 8.8% and 9.3%	0.41
Resolute all comer study[28]	Randomised	1152 Resolute vs. 1140 Xience	1 year 4 years	death, MI, revascularisation 8.7% vs.9.7% cardac death, target vessel MI, TLR 8.2%vs. 8.3% death, MI, revascularisation 30.4% and 28.6% cardiac death, target vessel MI, TLR 17.6% and 17.1%	0.42 0.94

DES – drug eluting stent, EES – everolimus eluting stent, PES - paclitaxel eluting stent, BMS – bare metal stent, MI- myocardial infarction, TLR – target lesion revascularisation, TVR – target vessel revascularisation

The event rate with modern DES is therefore deemed lower compared to previously used bare metal stents and 1st generation stents. As expected the adverse outcomes seem to be higher in the real world all comer studies as described in table 1. Whilst the 12 month outcomes are relatively low compared to early days of angioplasty the major adverse cardiac events seem to accumulate over the years to generate higher percentages, in some studies up to 30% at 4 years as described in the table 1.

1.2.5 Bio-resorbable Vascular Scaffolds (BVS)

The argument that perhaps the long term outcomes should be more favourable when there is no permanent coronary implant has driven the development and implantation of bioresorbable vascular scaffolds, with the scaffold being completely reabsorbed in approximately 4 years.[32]

The term bio-resorption refers to total elimination of polymer by dissolution, assimilation and excretion.[32] The most commonly researched polymer at present is poly-L-lactic acid (PLLA) whilst there is evidence emerging for the use of magnesium alloy as a bio-resorbable material. In the Absorb III study, scaffold (PLLA scaffold) thrombosis (1.5%), target vessel MI, target vessel revascularizations were all higher than the 2nd generation DES (but not statistically significant).[33] A meta-analysis by Lipinski et al showed a definite/probable scaffold thrombosis of 1.2%, MI 2.1% and TLR of 2.0% at 6.4 +/- 5.1 months follow up.[34] The ISAR-ABSORB registry showed definite scaffold thrombosis of 2.6% at 12 months follow up.[35] The early problems of scaffold implantation are still widely discussed and debated, but again, we find these event rates higher than the other available treatment modalities. Operators not fully appreciating the importance of mandatory pre dilatation, correct vessel sizing and post dilatation combined with the high strut thickness may have played a role in the reported high incidence of scaffold thrombosis.

A bio resorbable magnesium scaffold (Magmaris®) has shown definite/probable scaffold thrombosis of 0.5% at 12 months in the first 400 patients included in BIOSOLVE IV registry. Although there is no direct comparison available, this figure appears to be low

compared with previously discussed scaffolds. In the initial Biosolve II and III studies, a late loss of 0.25 ± 0.31 mm in-segment and 0.39 ± 0.34 mm in-scaffold was reported after 12 months in 184 patients. No definite or probable scaffold thrombosis reported.[36, 37]

1.2.6 Drug Coated Balloons (DCB)

History

Professor Bruno Scheller and Professor Ulrich Speck are the founding fathers of this technology.[38] Both were interested in contrast media and under Professor Speck's guidance contrast media such as iopromide and gadolinium had been developed. [39-41] Professor Scheller's interests with contrast media were in its effects on micro circulation and thrombotic events after PCI.[42, 43]

Contrast Media and Local Drug Delivery

The duo's first research collaboration was to find out whether contrast media alone had any impact on neo intimal proliferation and restenosis after implantation of a stent in a porcine coronary artery.[44] This showed that there was no difference between saline, iopromide, ioxaglate, and iosimenol. The paper was published in 2003 and their work was based in Homburg/Saar in Germany.

Both were interested in finding a non-stent based treatment method to address in-stent restenosis. The next step was to add an anti-proliferative drug to a contrast agent and test its cardiac tolerability. 16 pigs were subjected to coronary angiography with 4 of them receiving 70-micromol taxane protaxel dissolved in iopromide, and others iosmin,

ioxalgate and iopromide alone. No adverse effects such as thrombotic events, ECG, blood pressure or contractility changes were reported. [45] In a subsequent study an intra coronary bolus of taxane protaxel-iopromide solution showed a reduction of neo intimal formation in a porcine coronary stent. This was achieved despite a short exposure of the solution to the stent. [46] Paclitaxel was used with iopromide in another study testing its effects on bovine vascular smooth muscle cell proliferation in vitro and on neo intimal proliferation in vivo in 34 stents implanted in 17 pigs. The results showed a significant reduction of both vascular smooth muscle cell proliferation in cell cultures and also a dose dependent reduction of neo intimal hyperplasia in the in-vivo arm.[47] In addition their in-vitro studies showed that short time exposure (3s) of paclitaxel induced more apoptosis of coronary artery smooth muscle cells than the beneficial endothelial progenitor cells (EPC). Also migratory potency of EPC is not affected when exposed to paclitaxel for a short time (3s) compared to a longer exposure (24hrs) as seen with a drug eluting stent. Paclitaxel as compared to other anti-proliferative drugs such as sirolimus, upon short-time exposure to a low dose of the drug showed greater effect on cell density through immediate inhibition of the cell cycle at mitosis phase and pro-apoptotic p53 up-regulation. [38] Animal studies and their findings are summarised in table 2.

Table 2 Animal studies investigating effectiveness of paclitaxel with contrast media on neo intimal hyperplasia

Study	Objective	Comparators	Finding	P value
Clauss et al	To investigate the impact of intra coronary contrast media on in-stent restenosis/neo intimal proliferation after coronary stenting	saline, iopromide, ioxaglate, and iosimenol (in vitro- cell density plus in-vivo angiographic study on 12 pigs)	In vitro - no difference of change of cell density. In vivo – late lumen loss after 4 weeks 1.9 +/-0.8 mm, 1.3 +/- 1.0 mm, 1.2 +/- 0.8 mm	0.256
Scheller et al	To test cardiac tolerability of a chemotherapeutic agent added to a contrast medium that is injected to a porcine coronary artery	Coronary angiography performed on 16 pigs. 4 of them received 70-micromol taxane protaxel dissolved in iopromide, and others iosmin, ioxalgate and iopromide alone	No thrombotic occlusions, no adverse effects causing electrocardiographic, blood pressure or contractility changes. No ventricular arrhythmias.	
Scheller et al	Impact of an intra coronary bolus of taxane protaxel-iopromide solution on neo intimal formation in a porcine coronary stent and in vitro cell culture experiment.	Cell culture experiment with bovine aortic smooth muscle cells; Incubation at 3, 10 and 60 minutes in saline vs. iopromide-protaxel medium In vivo: 16 stents in 8 pigs. Iopromide injection of coronaries after stents vs. iopromide-protaxel injection	Cell density significantly reduced in all three incubation times, dose dependent at 12 days. Angiography after 28 days (iopromide vs. iopromide-protaxel solution) Minimal luminal diameter 1.5±0.8 mm vs. 2.6±0.6 mm Late lumen loss 1.9±0.8 mm 0.9±0.6 mm 0.01 Histology: no mono nuclear cells or fibrin but complete endothelialisation of the segments treated with iopromide-protaxel coronary injection.	0.006 0.01
Scheller et al	To test the efficacy of paclitaxel added to contrast agent iopromide in preventing in-stent restenosis.	17 pigs, after bare metal stent insertion randomised to receive control iopromide, iopromide and paclitaxel	Late loss (mm) 1.94 +/- 0.34 (iopromide), 2.25 +/-0.35 (iopromide paclitaxel IV), 1.19 +/- 0.55 (IC iopromide	0.001

		solution intra coronary (IC) and intravenous (IV) paclitaxel and iopromide. Follow up angiography at 28 days.	paclitaxel 100 micrograms/ml) 0.82 +/- 0.54 (IC iopromide paclitaxel 200micrograms/ml)	

Local drug delivery using a balloon catheter

Mounting the antiproliferative drug together with an excipient on a conventional angioplasty balloon catheter was undertaken next. Ethyl acetate and acetone were used as solvents in the first studies. 6% loss of the active ingredient was noted from only inserting and retracting the balloon to a porcine coronary artery (floated for 5 minutes) without inflating it. Approximately 80% of the drug was released to the vessel wall upon balloon inflation. The coronary segments were analysed 40-60 minutes from the balloon inflation under high-performance liquid chromatography (HPLC) which revealed retention of an effective dose by the vessel wall. 8.7% +/- 4.9% of the drug dose was retained when delivered with balloon-only PCI and 17.3% +/- 8.5% was delivered when the balloon was pre-mounted on a stent. Using a matrix with acetone as the solvent and a hydrophilic x-ray contrast medium (as used in PACCOCATH catheters) was proven to be more efficacious compared to a coating without a hydrophilic x-ray contrast.

The next generation, Sequent please catheters used an automated coating technique with volumetric dosing resulting in a re-producible, homogenously distributed drug coating compared to a previous manual dip coating technique. The matrix was kept the same with acetone as the solvent and hydrophilic x-ray contrast being iopromide.

Another in vivo pre-clinical study compared the effects of lower inflation time versus higher inflation time and two sequential balloon inflations (overlap) on late lumen loss in porcine coronary arteries. The control was 10 bare metal stent (BMS) treated porcine coronaries. Test groups were 10, 5mcg/mm^2 paclitaxel coated balloons (PCB) mounted on to bare metal stents inflated for 10 seconds, 10 PCB mounted bare metal stents inflated for 60 seconds, 10 PCB mounted bare metal stents inflated for 60 seconds and post dilated with the same balloon again for 60 seconds and 10 PCB mounted bare metal stents inflated for 60 seconds and post dilated with a second PCB catheter for another 60 seconds. After 4 weeks, histological evaluation of the coronary segments showed that late lumen loss was significantly less in all test groups compared to the control group. It also showed that exposure of paclitaxel to vessel wall for a short period such as 10 seconds was enough to achieve significant reduction of late lumen loss. Whilst 10 mcg/mm3 (two overlapping balloons) of paclitaxel which is equivalent to 3 times the usual dose of paclitaxel on a paclitaxel coated balloon was tolerated well (which was important to understand in terms of overlapping segments in treating human coronaries), there was no difference of late lumen loss compared to other paclitaxel coated catheter test groups.

In summary drug coated balloons are standard (semi-compliant) angioplasty balloons coated with a cytotoxic chemotherapeutic agent. Currently, the majority of commercially available DCBs use paclitaxel. In our center we predominantly use the balloon we feel has the best evidence (SeQuent Please NEO, B. Braun Melsungen AG, Germany). It is the DCB that has been used in most studies and also has the largest pool of treated patients as described in table 4 below.This balloon utilises iopramide (a contrast

medium) to act as the excipient to retain the drug on the balloon and, on balloon inflation, to facilitate rapid delivery to the vessel wall due to its lipophilicity. The dose of paclitaxel is approximately 3 micrograms/mm2. The drug is delivered homogenously to the vessel wall during balloon expansion (unlike the very uneven distribution seen with drug eluting stents). The terminal half-life is almost two months.[48] There are different types of paclitaxel coated balloons available in the market using different coating techniques and excipients (summarized in table 3). Figure 1 shows an example of a drug coated balloon mounted on a wire.

Figure 1 Example of an over the wire drug coated balloon

DCB = semi compliant balloon + excipient + drug

Table 3 Types of paclitaxel eluting balloons and coating techniques used.

DCB type	Excipient/coating technique	Drug dose
SeQuent Please	Iopromide matrix coating	3 μg/mm^2
Pantera Lux	Butyryl-tri-hexyl Citrate (BTHC) matrix coating	3 μg/mm^2
IN PACT Falcon	Freepac^{TM} matrix coating	3 μg/mm^2
Dior second generation	Shellac matrix coating	3 μg/mm^2
Elutax SV	No excipient	2 μg/mm^2
Lutonix	Polysorbate and Sorbitol carriers	3 μg/mm^2
Danubio	BTHC excipient	2.5 μg/mm^2

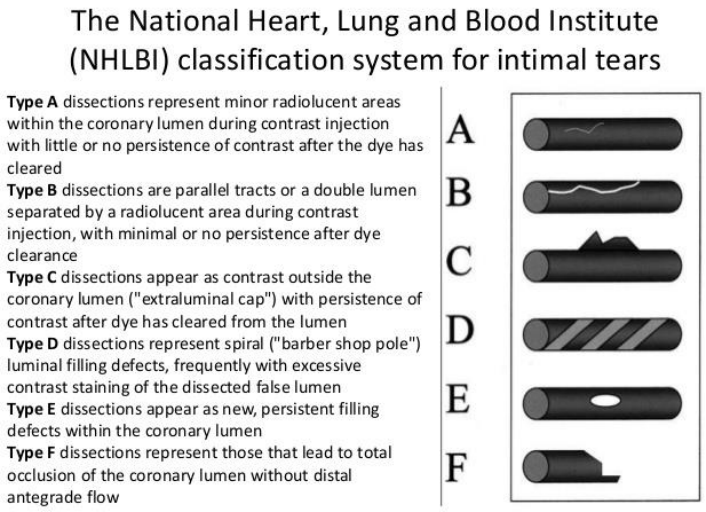
A sirolimus coated (1.27μg/mm^2) balloon (SCB) has been introduced more recently with satisfactory bench testing and clinical outcomes. Data of a registry of 424 patients with 247 de novo lesions treated with Magic touch sirolimus coated balloon were presented at Trans Catheter Therapeutics (TCT) conference, 2018. Composite of cardiac death, target vessel MI and target lesion revascularisation at one year was 4.36%.[49]

To perform DCB-only PCI, care is taken to prepare the lesion adequately before delivering the drug. Standard semi- and or non-compliant balloons, and, if necessary, more specialised cutting or scoring balloons are used in order to achieve an adequate angiographic result. If <30% stenosis is achieved with no dissections of more than type

B, the final treatment is then carried out using the Drug Coated Balloon, which is kept expanded for 30-60 seconds (as per German consensus guidelines).[50]

A good understanding of types of coronary dissections is a must to perform DCB only PCI in de novo lesions. Figure 2 shows the National Heart, Lung and Blood Institute (NHLBI) classification of coronary dissections.

Figure 2 Coronary Dissections; classification by the National Heart Lung Blood Institute (NHLBI)



It is not always easy to classify the dissections you see in real life to these categories hence the importance of one to one proctoring and dedicated learning. Type A coronary dissection is seen mostly as a haziness without any persistence of contrast or flow limitation. It is comprised of only a minor radio lucent area. Type B coronary dissection appears mostly as a parallel line to the contrast in the lumen with no or very little contrast hang up. Sometimes this can give rise to double lumen appearance. Type C dissection could look like a type b initially but there is obvious persistence of contrast. It can also appear as a bulb of contrast that does not clear which may represent an intramural haematoma. Type D is a spiral dissection which can sometimes be difficult to

judge but images taken on at least two different planes will help alleviate any doubt. Type E is a filling defect in the middle of the lumen. Type F represents vessel closure. The angiographic images below illustrate some of the types further.

Once the optimal lesion preparation has been performed with satisfactory lumen gain (less 30% recoil) and no dissections above type B, the DCB is advanced to deliver the drug. It is recommended that the balloon is delivered and fully expanded at the lesion in less than 2 minutes from the time of insertion to the circulation to minimise the drug loss. The DCB should not be of a bigger diameter than the largest pre dilatation balloon and should be about 5mms longer than the pre dilated segment to avoid geographic miss. Once the it's deployed (kept expanded for 30-60s depending on the brand) and removed, a check angiogram should be performed with a longer acquisition period to allow the full contrast clearance to make sure there is no higher than type B dissection left.

Dual antiplatelet therapy is required for only 1 month after DCB-only elective procedures or one year for treatment of acute coronary syndrome.

Figure 3 Example of a type B coronary dissection in the mid Circumflex artery

Arrow indicates the contrast staining that clears with the rest of the coronary.

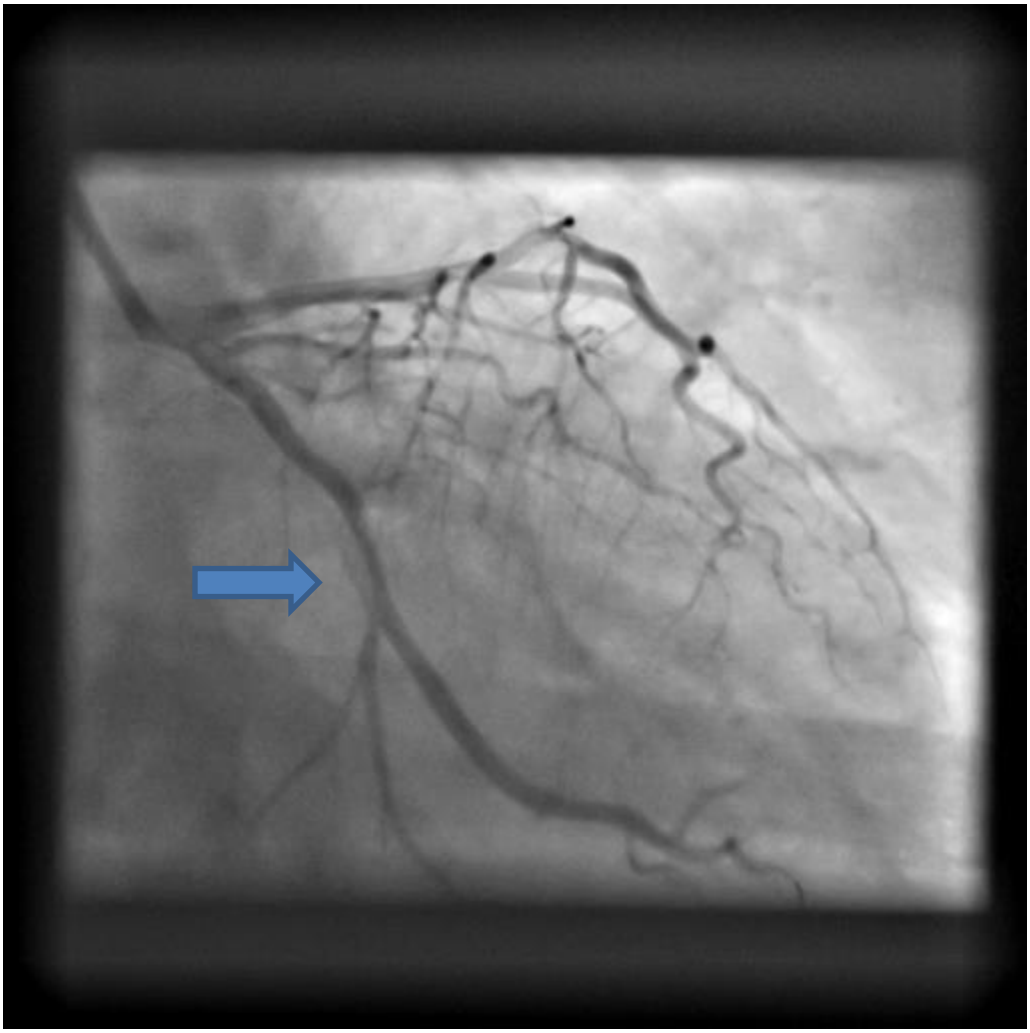
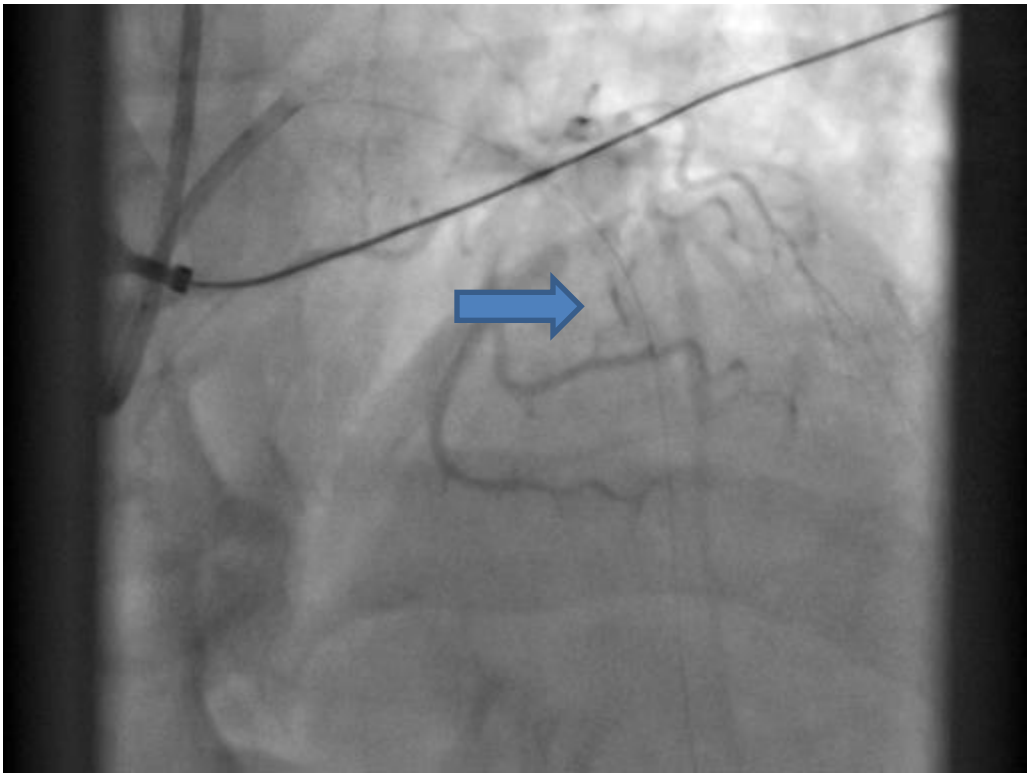


Figure 4 Type C coronary dissection

(a) Arrow points to the contrast staining of the mid left anterior descending (LAD) artery which has persisted after the clearance of contrast from the rest of the coronary.



(b) Arrow points to the contrast hanging up in the proximal right coronary artery when the rest of the coronary is clear of contrast.

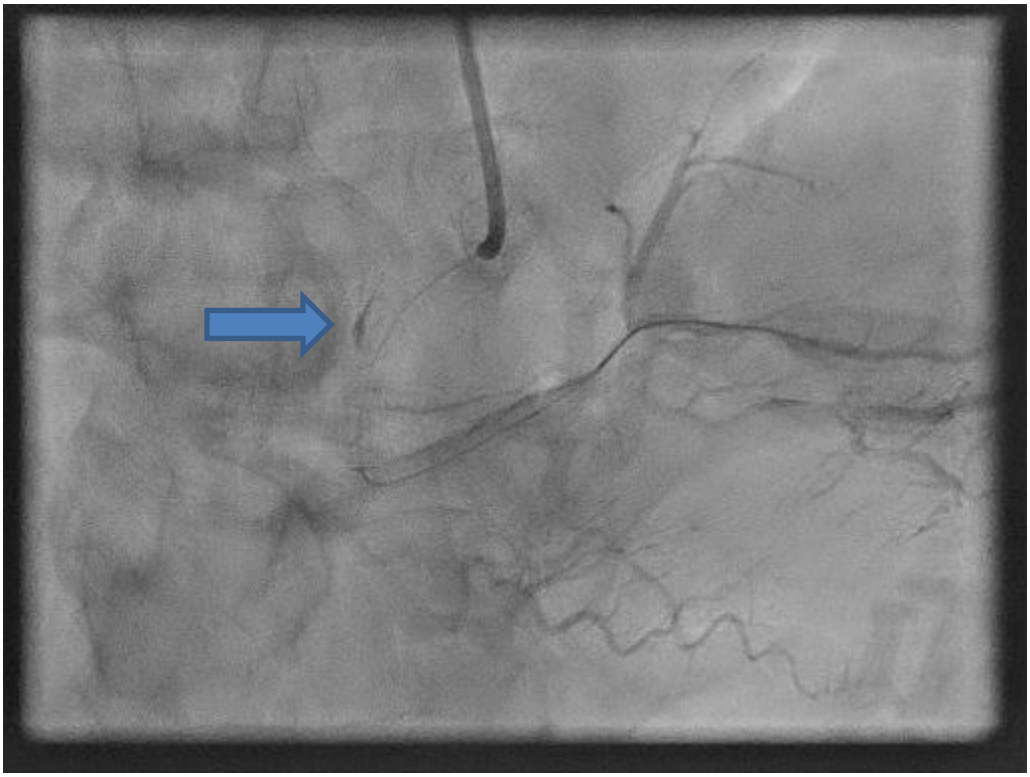


Figure 5 Type D/Spiral dissection

Arrows point at the visible sections of the spiral dissection

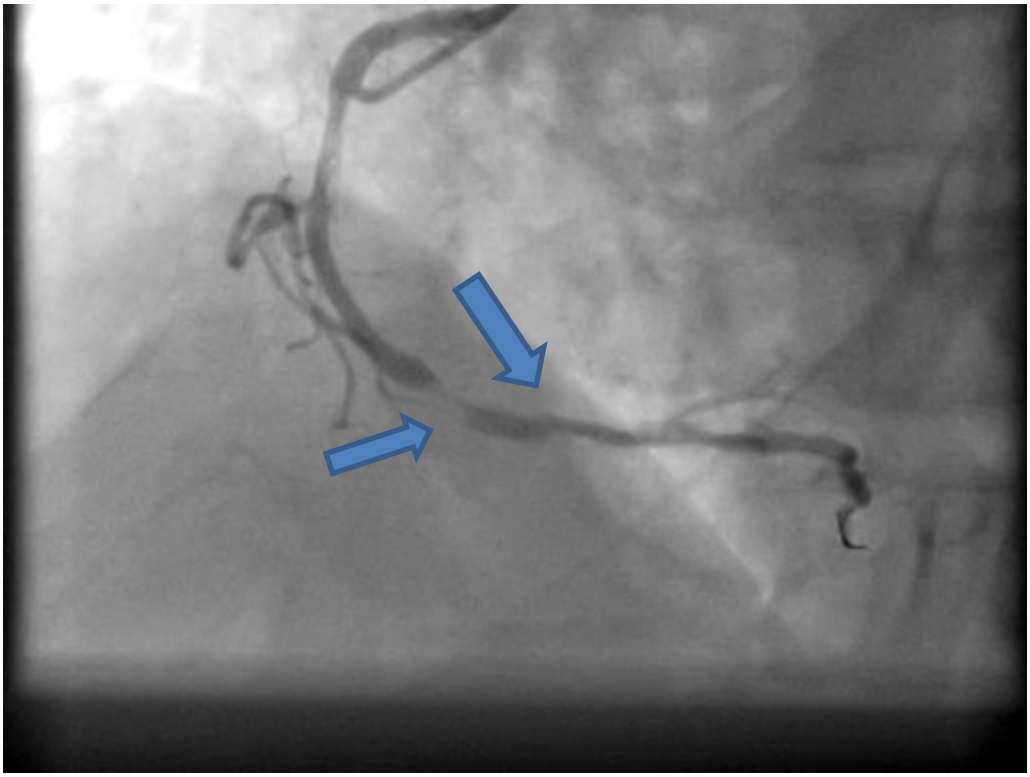
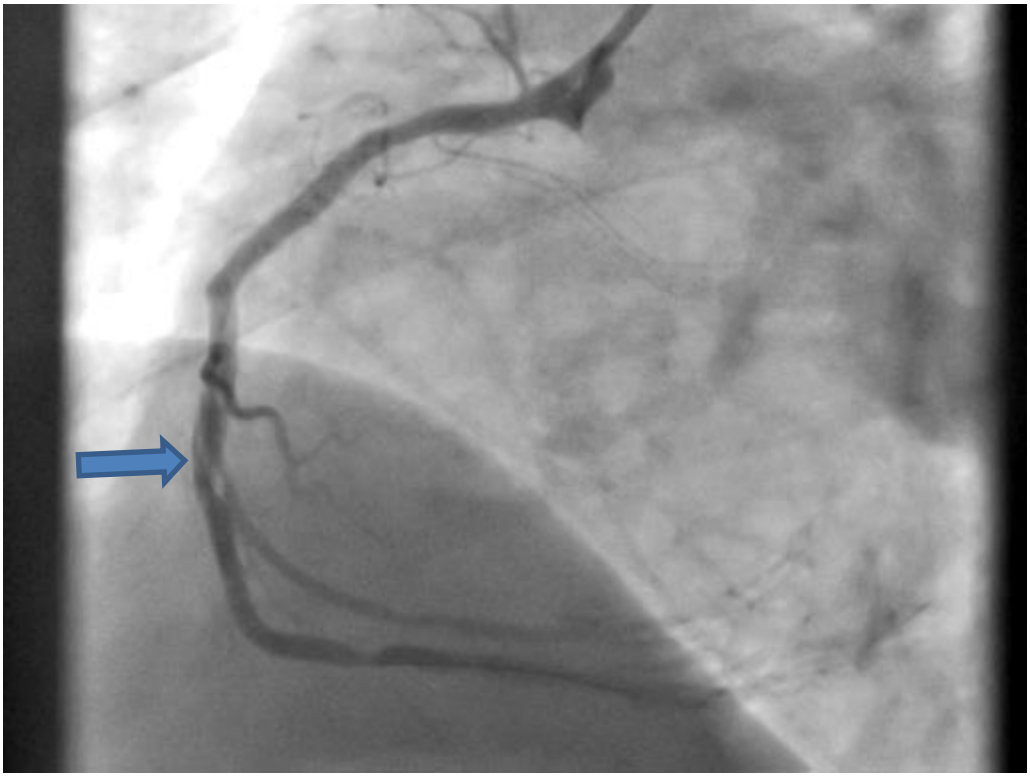


Figure 6 Type D/Spiral coronary dissection

Arrow pointing at the spiral shaped radio lucent area.



1.3 Evidence for angioplasty with DCB

DCBs were first used to treat in-stent restenosis i.e. a luminal narrowing within a previously placed stent. This was driven by the appeal of not having to implant another layer of metal on top of the existing one when DCB is used. The pathophysiology, treatment and use of DCBs in in-stent restenosis is discussed below. Also most early DCB studies (PEPCAD IV, PEPCAD V, DEBAMI, and PEPCAD CTO) were carried out in conjunction with implantation of a BMS which, in our view, takes away the long term advantages of no permanent implant.[51-54] We will therefore not discuss these further.

1.3.1 In-Stent Restenosis (ISR)

Sigwart reported the first human coronary stent implantation in 1986 in 24 lesions (17 restenoses, 4 abrupt closures after angioplasty and 3 deteriorated bypass grafts).[55] Since then the use of stents has increased exponentially and is now considered to be the standard treatment for significant flow limiting coronary artery disease. This paved the way for a new disease entity called in-stent restenosis which is the development of a stenosis within or in association to the previously stented segment. In a retrospective study involving 10,004 patients Cassese et al reported ISR incidence of 30.1%, 14.6% and 12.2% for bare metal stents (BMS), first generation DES and second generation DES respectively at 6-8 months angiography. [30] Even though the percentage of ISR has reduced with drug eluting stents (DES), their absolute number is ever increasing due to wide spread use of stents.

1.3.1.1 Angiography patterns of ISR

Mehran et al identified four patterns of ISR which is described as Type 1 (Focal) - <10mm in length, Type 2 (Diffuse) - >10mm in length, Type 3 (Proliferative) - >10mm in length and extending beyond the stent and Type 4 (Occlusive) – complete occlusion within the stent. [56] Better clinical outcomes have been reported after treatment of focal ISR compared to diffuse ISR. [57, 58] All types of ISR have been reported with both BMS and DES but BMS-ISR tends to be more of diffuse whilst DES-ISR is more focal nature.[57]

1.3.1.2 Pathophysiology

Pathophysiology of ISR consists of two important mechanisms namely neointimal hyperplasia due to smooth muscle cell proliferation and neoatherosclerosis.

1.3.1.3 Neointimal hyperplasia (NIH)

Angioplasty results in a vessel wall injury and the vessel wall responds triggering a healing process. Re stenosis after balloon-only angioplasty is considered to be due to a combination of elastic recoil, vessel remodelling and neo intimal hyperplasia (NIH). Histopathological and IVUS studies showed that vessel remodelling (reduction of area under internal elastic lamina/external elastic lamina) played a greater role compared with NIH in restenosis after balloon-only PCI.[59,60, 61]

In-stent restenosis is mainly due to NIH and neoatheresclerosis. Platelet rich thrombi (up to 30 days) as well as fibrin rich thrombi (commonly up to 12 days) are formed around stent struts.[62] In addition medial injury and penetration of the lipid core by stent struts seem to instigate an inflammatory process.[62] The presence of acute inflammatory cells (neutrophils) around stent struts has been demonstrated up to 30 days after angioplasty and chronic inflammatory cells (macrophages and lymphocytes) from less than 3 days to more than 30 days.[62] A linear correlation between presence of monocytes and degree of smooth muscle cell proliferation has been shown after stent implantation in a rabbit iliac artery. [63] NIH is comprised of smooth muscle cells and proteoglycan rich matrix and the formation of NIH is believed to be detectable at approximately two weeks from stent insertion. [62] Clinical events due to restenosis in BMS (which is mainly due to NIH) has been reported increasingly up to 12 months but

then plateaus thereafter suggesting NIH is an active process in the first year.[64] Pathophysiology of ISR appears to differ from BMS to DES and NIH due to smooth muscle cell proliferation has been shown to be more prevalent in BMS ISR compared to DES ISR. Presence of proteoglycan rich extra cellular matrix was more common in DES ISR than BMS ISR.[65]

1.3.1.4 Neoatherosclerosis (NA)

The formation of atherosclerotic disease inside a stented segment is termed as neoatherosclerosis. It is reported in different forms such as foamy macrophage clusters with or without calcification, fibro atheroma, thin cap fibro atheroma and ruptured plaque .[66] An absent/incomplete endothelial coverage, dysfunctional endothelium and poorly formed inter cellular junctions which may lead to increased permeability to lipid and inflammatory cells could play a key role in neo atherosclerosis. [66-68] Whilst neo atherosclerosis is commonly seen as a late process compared to neointimal hyperplasia, the former has been reported as early as 70 and 120 days in DES ISR .[66] ISR due to neo atherosclerosis seems to be more prevalent in DES compared to BMS .[66, 69] When it occurs in BMS-ISR, it is of late onset compared to DES-ISR (median of 2160 days as oppose to 420 days).[66] Otsuka et al has demonstrated that there is no difference of neo atherosclerosis formation between first and second generation DES. [70] Necrotic core and thin cap fibro atheroma appear more commonly in DES ISR than BMS ISR. [71]

1.3.1.5 Risk factors and clinical presentation

Patient factors such as diabetes mellitus, multi vessel disease, small vessel diameter, drug resistance and hypersensitivity are associated with increased risk of developing ISR. [64, 72-75] Similarly as mentioned above BMS implantation has higher risk of ISR than DES. Length of stented segment, stent fracture, stent under expansion, multiple stents, bifurcation stenting, stent overlap and non-uniform stent struts are also associated with higher incidence of ISR. [65, 73, 76-79]

Patients with ISR can present with stable angina or acute coronary syndromes (unstable angina, non ST elevation MI or STEMI) and studies have reported acute coronary syndrome rates of 18% and 35.9%. [57, 80]

1.3.1.6 Treatment options

Balloon only angioplasty (POBA), vascular brachytherapy (VBT), excimer laser coronary angioplasty (ELCA), DES and drug coated balloons (DCB) are recognized treatment modalities for ISR. Out of these DCB and DES are the most widely used methods at present.

Balloon only Angioplasty (POBA)

Aggressive dilatation with semi and or non-compliant balloons was the first method of treatment for ISR lesions. But its high restenosis rates such as 22% after 6 months in focal ISR and up to 75% after 3 months in diffuse ISR has made its use obsolete in current practice.[81, 82]

Vascular Brachytherapy (VBT)

VBT involves delivery of a radio-active isotope directly inside the diseased stent with the help of a radio-active ribbon. Use of VBT has been described by Teirstein et al (reduced angiographic re stenosis at angiography after 6 months compared to placebo), Alli OO et al (no significant difference of MACE compared to sirolimus eluting stents after five years) and Leon MB et al (reduced re stenosis rates compared to placebo but increased thrombosis rate at 9 months). [83-85] Benjo et al showed an increased risk of TLR (OR 2.37; CI 1.55-3.63; $P < 0.001$) and TVR (OR 2.23; CI 1.01-4.94; $P = 0.05$) at 2-5 year follow up in a meta-analysis of 1375 patients comparing VBT to DES. [86] These high rates of late stent thrombosis and revascularisations prompted a search for an alternative safer treatment modality.

Excimer Laser Coronary Angioplasty (ELCA)

ELCA is carried out using a laser fibre catheter to deliver energy for tissue ablation inside a stenosed stent and has shown mixed results. Mehran et al showed better luminal gain with adjunct ELCA in comparison to POBA alone, but no significant difference in target vessel revascularization (TVR) after 6 months in a study of 107 ISR lesions.[87] Köster R et al showed high restenosis rate (54%) and re intervention rate (31%) after adjunct ELCA in a study of 141 stents at 6 months clinical and angiography follow up.[88] Bejarano et al showed high repeat restenosis rates of 24.2% at 6 months and 27.3% at 12 months in a study of 33 lesions treated with ECLA.[89] Similar to VBT, due to high restenosis and clinical event rates ECLA is not used routinely for ISR treatment in the present day practice.

BMS/DES/BRS/DCB

Bare Metal Stents (BMS)

Early studies comparing BMS to POBA in treatment of ISR showed no difference in mortality or event rates but better luminal gain after BMS. A study involving 63 patients undergoing repeat BMS stenting for ISR revealed a restenosis rate of 30% at 6 months angiographic follow up.[90] RIBS I showed similar restenosis rates for BMS (38%) and POBA (39%) at six months but no significant difference of event rates. For vessels larger than 3mm event free survival and restenosis were better with BMS. [91]

Drug Eluting Stents (DES)

Introduction of DES as a treatment option for ISR led to reduction of restenosis and event rates. RIBS II study compared outcomes of ISR treatment with angioplasty to sirolimus eluting stents (SES) and showed lower TVR rate in the SES arm at one year follow up (29.7% vs. 10.5% respectively, p 0.003) as well as lower recurrent restenosis rate at 9 months angiography(39% vs. 11%; $p < 0.001$).[92] ISAR DESIRE showed restenosis rates of 44.6% (41/92) in the balloon angioplasty group, 14.3% (13/91) in the sirolimus stent group (P<.001 vs balloon angioplasty), and 21.7% (20/92) in the paclitaxel stent group (P = .001 vs balloon angioplasty) at 6 months follow up angiography. [93] Better outcomes are expected for second generation DES over first generation in treating ISR due to the thinner struts of former. However two studies have shown comparable results of the two methods. In 66 cases of diffuse DES ISR, in-segment restenosis rate (5.0% vs. 14.3%, p = 0.32), and the composite incidence of death, myocardial infarction, or target lesion revascularization (9.6% vs. 8.8%, p > 0.99)

did not differ between SES group (n = 32) and everolimus eluting stent (EES) group (n = 34) in a randomized trial by Song et al.[94] In another prospective registry of 198 patients, no significant difference of MACE, TVR and restenosis was noted between the EES and PES arms. [95]

Whether a drug eluting stent with the same drug (homo-DES) or a different drug (hetero-DES) is better in treating ISR is still debated and has mixed evidence. Garg et al showed no significant difference in TVR-MACE at one year follow up of 116 patients with DES-ISR treated with same or different DES.[96] A meta-analysis by Vyas et al which included 1680 patients revealed treatment with hetero-DES reduces TLR and TVR but not MI or death.[97] ISAR-DESIRE 2 trial showed no difference in restenosis, TLR, MI or death in hetero-DES vs. homo-DES groups.[98] The subgroup analysis of homo-DES and hetero DES groups in RIBS III trial showed better minimal luminal diameter at angiographic follow up (median of 278 days, IQR: 226 to 409 days) of the hetero-DES group but similar TLR, TVR, MI and death rates for both groups.[99]

Biovascular Resorbable Scaffolds (BRS)

Biovascular resorbable scaffolds (BRS) have been tried in the treatment of ISR aiming for better long term outcomes as the scaffold is re-absorbed fully in 3 to 4 years. But their high strut thickness, low radial strength and low burst pressures make them unattractive for this cohort of patients. An Italian multicenter prospective registry of 116 patients has shown a composite cardiac death, target vessel myocardial infarction, and ischemia-driven target lesion revascularization rate of 9.1% at 15 months follow up .[100] Moscarella et al in a study of 315 patients showed a MACCE rate of 12%, TLR 7.7%

and 1.1% definite BRS-in-stent thrombosis at median of 7 (IQR 3-18) months follow-up.[101] Jamshidi et al in a cohort of 84 ISR lesions treated with BRS showed TLR rate of 3.1% at six months and 12.2% at 12 months.[102] Whilst BRS is not routinely used for ISR at present further improvements such as reduced strut thickness may increase its role in ISR treatment.

1.3.2 Drug Coated Balloons for ISR

1.3.2.1 Advantages of DCB in ISR

The most advantageous factor over other stenting options is that no permanent or semi-permanent metal/polymer is left in the already diseased stented segment. Thereby it arguably avoids stent induced accumulation of inflammatory cells and other disadvantageous factors of stents such as stent fractures, mal-apposition, under-expansion, stent overlap, stent gap and non-uniform struts.

Stent strut thickness has been shown to influence percentage of endothelial coverage after stent insertion.[67, 103] Therefore two or more layers of stent struts could lead to delayed and less endothelial coverage.

In addition a higher percentage of covered stent has been reported after DCB in comparison to everolimus eluting stent (EES) after 9 months of BMS-ISR treatment.[104]

The Ability to undergo repeat angioplasty if needed without additional stent layers would also be an advantage.

Requirement for a shorter duration of dual antiplatelet therapy (4 weeks after DCB vs. 12 months with DES) will be another advantage.

1.3.2.2 Evidence for DCB in ISR

DCB vs. POBA

Randomised PEPCAD-DES study showed less late luminal loss (0.43 ± 0.61 mm versus 1.03 ± 0.77 mm ($p < 0.001$)) and reduced restenosis rates (17.2% vs. 58.1% ($p < 0.001$)) with DCB compared to POBA in 110 DES-ISR patients at 6 months follow up. Composite of cardiac death, target vessel related MI and TLR was 16.7% vs 50.0% ($p < 0.001$) respectively.[105] DCB continued to show better outcomes both in terms of TLR (19.4% vs. 36.8%; $p = 0.046$) and MACE (20.8% vs. 52.6%, log-rank $p = 0.001$) over POBA in the 3 year follow up study of this cohort.[106]

Five year follow up results of Paccocath ISR I and II (randomised study of 108 patients with mainly BMS-ISR (96%)) showed better outcomes of DCB over POBA (MACE of 27.8% vs. 59.3%, $p = 0.009$). This was largely driven by low rates of TLR (9.3% vs. 38.9 ($p = 0.004$)).[107]

DCB vs. PES

In the randomised PEPCAD II study (131 patients with BMS-ISR) which compared PES (65 patients) vs. DCB (66 patients), at 12 months, the rate of major adverse cardiac events were 22% and 9% (P=0.08), respectively.[108] This difference was primarily due to the need for target lesion revascularization of 6% in the coated-balloon group, compared with 15% in the stent group (P=0.15). At 6 months angiographic follow-up, in-segment late lumen loss was 0.38±0.61 mm in the drug-eluting stent group versus 0.17±0.42 mm (P=0.03) in the drug-coated balloon group. Three year follow up data showed persistently better results for DCB over PES.[109]

Randomised controlled PEPCAD CHINA study (DCB vs. PES in DES-ISR) showed non inferior in segment late lumen loss (LLL) in the DCB group compared to DES group (0.46 ± 0.51 mm vs. 0.55 ± 0.61 mm; difference: -0.06 mm with 95% confidence interval: -0.23 to 0.10; p for non-inferiority = 0.0005) and no significant difference of binary restenosis rates at 9 months angiographic follow up. No significant difference of target lesion failure rate both at 12 months and 24 months was noted.[110, 111]

DCB vs. DES

In a propensity matched retrospective study involving 685 real life patients (777 ISR lesions) who received DCB vs DES (471 lesions in the repeat DES group; 177 (37.6%) were treated by SES, 164 (34.8%) by PES, and 130 (27.6%) by EES), there was no difference in binary restenosis, TLR, and major adverse cardiac events. A sub group analysis showed a significant trend favouring DCB with respect to binary restenosis and TLR in non-focal type lesions and bifurcation lesions. [112]

DCB vs. POBA vs. PES

ISAR DESIRE III (POBA vs DCB vs PES for DES-ISR, 402 patients) showed no significant difference between DCB and PES in treatment of ISR (clinical follow up at 1 year showed a death rate 2.2% in DCB vs. 4.6% in DES and restenosis on 6-8 months angiography was 26.5% vs. 24% respectively). Both PES and DCB were superior to POBA. [113]

3 year follow up results of this cohort showed no significant difference of TLR (29 (24.2%) vs. 44 (33.3%), p 0.11) between the PES and DCB groups but both cardiac (10

(8.1%) vs. 3 (2.4%), p 0.03) and all cause death (19 (15.3%) vs 8 (6.0%), p 0.02) rates were better in the DCB arm.[114]

DCB vs. EES

Almalla M et al in an observational study involving 86 patients compared DCB to EES in treatment of DES-ISR. This showed TLR rates of 4.3% and 22.5% respectively (P = 0.029) at 1 year follow up. There was no difference in MI rates (2% vs. 5%, P = 0.595).[115]

In the SEDUCE study (OCT and clinical follow up of 50 patients with BMS-ISR randomized to angioplasty with DCB and EES), better strut coverage (1.4% vs. 3.1%, p=0.025) and well healed dissections were noted in the DCB arm at 9 months follow up. Minimal lumen diameter was better in the EES arm (2.13 vs. 2.54 mm, p=0.006) and no significant difference was noted in neo-intimal hyperplasia area (2.4±1.08 mm in DCB vs. 1.92±0.67 mm in EES (p=0.1806)). No significant difference in clinical outcomes was noted at 12 months.[104]

RIBS IV trial (EES vs. DCB in 309 DES-ISR patients) has shown better outcomes of EES over DCB. At 1-year clinical follow-up (100% of patients), the main clinical outcome measure (composite of cardiac death, myocardial infarction and target vessel revascularization) was significantly reduced in the EES arm (10% vs. 18%; p = 0.04).[116] However, immediate post procedure stenosis of <50% was considered as an acceptable result in the DCB arm whereas in most centers <30% stenosis is considered as acceptable. Also in the EES group, only 47% of the repeated ISR lesions underwent TLR but 74% in the DCB group.

RIBS V showed no significant difference of outcomes between EES and DCB in treatment of BMS-ISR in 189 patients after 12 months. Notably, as in RIBS IV final angiographic minimal luminal diameter of <50% in the DCB arm was accepted in this study too. Occurrences of the combined clinical outcome measure (cardiac death, myocardial infarction, and target vessel revascularization) were 6% vs. 8%; hazard ratio [HR]: 0.76; 95% CI: 0.26 to 2.18, p = 0.6).[117] Three year follow up results have shown no significant difference in cardiac death, MI and target vessel revascularization rates. However TLR rate with EES was better compared DCB (2% vs. 8%; p = 0.04). [118]

Pleva et al showed significantly lower LLL with DCB compared to EES (0.02 versus 0.19 mm; P=0.0004) in BMS-ISR at 12 months follow up in another prospective randomized study involving 136 patients. The difference in the incidence of repeated binary restenosis (8.7% versus 19.12%; P=0.078) and 12-month MACE (10.29% versus 19.12%; P=0.213) was not significant. [119]

Normal PTCA+DCB vs. Scoring balloon + DCB

Byrne et al presenting results of ISAR DESIRE IV study (252 DES-ISR patients randomized to scoring balloon plus DCB and normal PTCA balloon plus DCB) at TCT October, 2015 reported better outcomes in the scoring balloon plus DCB arm (Angiographic stenosis at 6-8 months 35% vs. 40.4%, p = 0.047 and restenosis rate of 18.5% vs. 32%, p = 0.03). Though numerically better there was no statistically significant difference in TLR rates (16.8% vs. 22.6%, p = 0.25). [120]

Drug coated scoring balloon vs. standard scoring balloon

Scheller et al recently published the first in man study of a drug coated scoring balloon (DCSB) for ISR treatment (61 patients with BMS-ISR randomized to DCSB vs. standard scoring balloon angioplasty) and showed better in-segment late luminal loss (0.17 ± 0.40 mm vs. 0.48 ± 0.51 mm, P = 0.01; ITT analysis) and binary restenosis rate (7% vs 41%, P = 0.004) in the DCSB arm at 6 months follow up angiography. Clinical follow up at 1 year showed MACE rate of 6% vs 32% (P = 0.016), mainly driven by low TLR rate of 3% vs. 32% (P = 0.004) in favour of the DCSB group. [121]

In conclusion both second generation drug eluting stent and drug coated balloon angioplasty seem to be safe and effective treatment options for this cohort of patients. DCB is an attractive option especially as it does not add an additional stent layer. Large randomized trials comparing DCB over second generations DES are necessary to assess superiority of one over the other. DCB has shown better outcomes over first generation drug eluting stents and plain old balloon angioplasty. Initial results of novel drug coated scoring balloon is encouraging and may indeed offer even better results. We have used drug coated balloons for treatment of ISR in all settings in our department. The registry of ISR lesions treated with DCBs will give valuable information regarding their outcomes in a real world setting.

We have used Drug Coated Balloon therapy in both de-novo and in stent restenosis/stent thrombosis groups in all settings of coronary artery disease in our centre.

1.3.3 De novo disease/Small vessel disease:

There are a number of registries showing low event rates with DCB-only angioplasty in de novo small vessel disease. Studies are summarised in table 4. PEPCAD I study (82 patients with 2.25 to 2.80mm vessel diameter) showed MACE rate (composite of death, MI, TLR, treated lesion/stent thrombosis) of 6.1% and a TLR rate of only 4.9% at 3 year follow up.[122] Zeymer U *et al*. in a real world prospective registry of 479 patients with small vessel coronary artery disease ((≥2.0 mm, ≤2.75 mm) treated with DCB angioplasty showed TLR rate of only 3.6% at 9 months follow up.[123] There were no cardiac deaths. In the Sequent please worldwide all-comer registry, the DCB-only group (390 patients) showed event rates for MI 0.7%, cardiac death 1%, TVR 1% and TLR 1% at 9 months follow up.[124] Elutax small vessel registry with 251 real world patients, 59% of whom had native vessels treated with DCB angioplasty showed TLR rate of 2.0%, cardiac death of 0.8% and no target vessel MI or thrombosis at an average 225 days follow up.[125]Ho et al reported TLR of 4% at 9 months in a real world registry of 320 South East Asian patients (76% of whom were for de novo disease, 54% small vessels and 76% presented with ACS).[126] The single arm, prospective, multicentre Valentines-II trial (103 patients, treated with the DIOR DCB) showed a TLR rate of 2.9%, a TVR of 6.9% (including TLR), 1% MI and 0% cardiac death at 7.5months.[127] The Leipzig Prospective Drug-Eluting Balloon-Registry reported 76 patients treated with DCB-only for native coronary artery disease with no TLR at over 2 years.[128] The incidence of MI was 3.9% with 9 deaths (all causes) during follow up. It is important to note that most of these registries were real life studies which included patients from high risk categories such as post STEMI, NSTEMI and bifurcation lesions.

The randomised controlled multicentre BELLO study (total of 180 patients) showed better outcomes of DCB-only treatment as compared to paclitaxel eluting stent for vessels with a diameter of less than 2.8mm.[129] The primary endpoint of in-stent (or "in-balloon") late loss was significantly less with DEB compared with PES (0.08 ± 0.38 mm vs. 0.29 ± 0.44 mm; difference -0.21; 95% CI: -0.34 to -0.09; p (non-inferiority) < 0.001; p (superiority) = 0.001). Of note, bailout stenting was required in 20% of lesions in the DEB group. The three year results of the BELLO study showed a significant reduction of MACE in the DCB arm compared to PES (DCB group: 13 [14.4%], and PES group: 28 [30.4%], p 0.015) but the study was underpowered to assess this outcome.[130]

Table 4 Drug coated balloon angioplasty in de novo disease; summary of studies

Name of Study	Study Design	DCB type	Number of patients	Follow up period	Outcomes	Target lesion revascularisation (TLR)
PEPCAD 1[122]	Single arm DCB De novo small vessels 82 patients	SeQuent® Please	82	3 years	MACE 6.1%	TLR 4.9%
Zeymer, U et al[123]	Real world prospective registry Small vessels 479 patients	SeQuent® Please	479	9 months	Deaths 0%	TLR 3.6%
Sequent Please[124]	Worldwide all comer registry DCB only group 390 patients	SeQuent® Please	390	9 months	MI 0.7% Cardiac death 1% TVR 1%,	TLR 1%
Elutax Small Vessel Registry[125]	Real world patients- Native vessels 251 patients	Elutax SV	251	225 days	Cardiac death 0.8%	TLR 2%
Ho et al[131]	Real world registry South east Asians 320 patients	SeQuent® Please	320	9 months		TLR 4%
Valentines	Single-arm,	Dior (2nd	103	7.5	TVR 6.9%	TLR 2.9%

II[127]	prospective,multi center	generation)	patients	months	MI 1% Cardiac death 0%	
Leipzig Prospective Drug Eluting Balloon Registry[128]	Native coronaries 76 patients	SeQuent® Please	76	2 years	MI 3.9%	TLR 0%
BELLO[130]	Randomised Control DCB Vs Paclitaxel Eluting Stent 180 patients Vessel diameter<2.8mm	IN.PACT Falcon	180	3 years	In-balloon/stent late loss 0.08 ± 0.38 mm vs. 0.29 ± 0.44 mm; difference -0.21; 95% CI: -0.34 to -0.09; p < 0.001 MACE:13 [14.4%] vs 28 [30.4%], p 0.015)	TLR 6.7 vs. 13% (p 0.14)
PEPCAD-BIF[132]	Randomised Bifurcation lesions DCB vs POBA 64 patients	SeQuent® Please	64	9 months	Binary restenosis: 6% vs 26% (p=0.045) Late luminal loss: 0.13mm vs 0.51mm (p=0.013)	TLR: 3.125 vs 9.38%
Rosenberg M et al[133]	Multicentre prospective registry 731 De novo lesions Vessel size 2-4 mm	SeQuent® Please	731	9 months	MACE 5.6%	TLR 2.3%
DEBUT [134]	Randomised trial De novo lesions in patients with high bleeding risk 102 DCB vs 106 BMS	SeQuent® Please	208	9 months	MACE: 1% vs 14%	TLR 0% vs. 6%

Li M et al[135]	Systematic review and metanalysis small vessel lesions DCB vs DES 1800 patients	581- SeQuent® Please 186- IN.PACT Falcon 28-Dior	1800	Follow up period 6-12 months	Non- fatal MI 0.53% OR CI 0.31-0.90, p=0.02 Other outcomes; no difference	TLR OR 1.24 (95% CI 0.73-2.1, p=0.43)
FALCON[136]	Registry with de novo lesions and ISR 757 patients	IN.PACT Falcon	757	12 months	MACE 9.7%	TLR 4.9%
Venatsanos D et al[137]	Small vessel DCB vs DES 1197 lesions in each arm, propensity score matched	816- SeQuent® Please 150- IN.PACT Falcon 231- Pantera® Lux ™	2394	965 days	Target lesion thrombosis: 0.2% vs 1.1%	TLR 7% vs 6.2%
BASKET SMALL 2[138]	Randomised controlled trial, DCB vs DES in small vessel coronaries 756 lesions	SeQuent® Please	756	12 months	MACE: 7.5% vs 7.3% HR 0.97 (95% CI 0.58-1.64), 4% non-inferiority margin met.	TLR 3.4 vs. 4.5%

The PEPCAD-BIF trial randomised 64 patients with bifurcation lesions to DCB-only or balloon only angioplasty/POBA treatment and showed binary restenosis rate of 6% vs 26% (p = 0.045) respectively at 9 month follow up.[132] Late luminal loss was significantly less with DCB-only treatment (0.13 mm in the DCB and 0.51 mm in the control POBA group, p = 0.013; 95 % CI (-0.66 to -0.08)), whilst the TLR rates were 3.12% for DCB and 9.38% for POBA (not statistically significant).

Rosenberg M et al. showed a TLR rate of only 2.3% in 731 de novo lesions (vessel size of 2-4mm and lesion length of less than 25mm) after 9 months clinical follow up.[133] This was a prospective, international, multi center registry with a total of 1025 patients with both de novo and ISR lesions.

Cortese *et al.* have reported angiographic follow up data at a mean 201 days post procedure of 48 DCB treated patients, who had a type A-C dissection (18, 25 and 5 patients respectively) left uncovered with a stent.[139] Of these, 45 (93.8%) had healed completely, 3 had persisting dissections and 1 received a DES at the time of follow up. No cardiac death or other TLRs occurred in this group of patients with un-stented dissections. This latter study highlights the issue of safe outcomes after balloon angioplasty only despite the angiographic appearances of vessel dissection.

Rissanen T. et al in randomised, non- inferiority DEBUT trial (Drug-coated balloon for treatment of de-novo coronary artery lesions in patients with high bleeding risk) showed that coronary angioplasty with DCB is superior to bare metal stents in patients with high bleeding risks. There were 102 DCB treated patients and 106 BMS treated patients. MACE at 9 months were 1% in the DCB group and 14% in the BMS group (absolute risk difference −13·2 percentage points [95% CI −6·2 to −21·1], risk ratio 0·07 [95% CI 0·01 to 0·52]; p<0·00001 for non-inferiority and p=0·00034 for superiority). There were two definitive stent thrombosis in the BMS group and no acute vessel closures in the DCB group.[134]

Li M. et al in their systematic review and meta analysis encompassing 6 studies with 1800 patients showed non inferiority of DCB angioplasty to drug eluting stents in small vessel (<3mm) coronary lesions. [135] The DCB group showed a significant reduction of non-fatal MI (OR 0.53, 95% CI 0.31-0.90, P=.02).

Widder JD in the FALCON registry showed a 12 months MACE rate of 9.7% for 757 patients (43.1% - de novo, 56.9% - ISR) treated with IN.PACT Falcon paclitaxel coated balloon. In the de novo group 12 months TLR rate was 4.9%.[136]

Venetsanos D. et al compared DCB vs. DES in 1197 lesions in each arm after propensity score matching. At a median follow up of 965 days TLR and target lesion thrombosis were 7.0 vs. 6.2% and 0.2 vs. 1.1%.(adjusted HR 1.05; 95% CI 0.72–1.53). DCB was associated with significantly lower rate of target lesion thrombosis compared to new generation DES (adjusted HR 0.18; 95% CI 0.04–0.82).[137] There was no difference in TLR between Sequent Please, Pantera Lux and In.Pact Falcon DCBs.

Jeger RV et al in the randomised BASKET SMALL -2 trial compared DCB Vs. DES angioplasty in small vessel (<3mm) coronary lesions. 756 patients were randomised 1:1 to DCB and second generation drug eluting stents. 12 months MACE rates were 7.5 and 7.3% ([HR] 0·97 [95% CI 0·58-1·64], p=0·9180). Non inferiority of MACE for DCB arm to DES was confirmed as the absolute difference of the MACE was below the pre-defined 4% non-inferiority margin ([HR] 0·97 [95% CI 0·58-1·64], p=0·9180).[138]

1.3.4 DCB angioplasty as Primary Percutaneous Coronary Intervention (PPCI)

The management of ST-elevation myocardial infarction (STEMI) has evolved significantly with the introduction of new pharmacological therapies as well as interventional procedures and devices. The GISSI and ISIS-2 studies showed a mortality benefit of streptokinase over standard therapy (heparin +/- oral anticoagulation)/placebo which lead to the widespread use of streptokinase in the late 1980's. [140, 141] The use of recombinant tissue plasminogen activator (rt-PA) was shown

to be more beneficial than streptokinase in the TIMI and GUSTO trials.[142, 143] Results of other studies such as CLARITY and COMMIT paved the way for addition of clopidogrel to the drug regime which further reduced mortality. [144, 145]

Primary percutaneous coronary intervention (PPCI) became the preferred choice of treatment for acute STEMI, with balloon angioplasty (BA) showing an improvement in mortality and the combined endpoint of mortality and MI over thrombolysis in a meta-analysis comparing the two.[146, 147] Subsequently, bare metal stent (BMS) implantation in STEMI showed a reduction in target vessel revascularisations (TVR) in comparison to BA but without a reduction in death or MI in the Stent PAMI and CADILLAC trials. [148, 149] The percentage of vessels with TIMI III flow was numerically higher in the BA group as compared to the BMS group, whilst mortality and MI rates were numerically but not statistically lower.[148] When stenting (BMS) was compared with thrombolysis as in the STAT study, the results were similar with stenting showing a reduction in TVR but no reduction in death or MI. [150] When both first and second generation drug eluting stents (DES) were compared to BMS in the setting of an acute STEMI, target vessel/lesion revascularization rates were shown to be lower with DES but yet again no reduction in death or MI was shown.[151-154] Brodie et al in a single center study of 2195 patients over a follow up period of 16 years showed long term target vessel MI and stent or lesion thrombosis were significantly higher with both BMS and DES as compared to BA (after landmark analysis at 1 year).[155]

Theoretically stenting may work as a method of mechanical plaque sealing however this has not been proved in studies. It could be argued that this potential advantage will be lost when carrying out DCB-only PCI in acute myocardial infarction. The CADILLAC trial

which compared BA vs. BMS with or without Abciximab did not show any difference in post procedure TIMI flow grades between the two groups[149]. Also the below mentioned DCB studies which show high post procedure TIMI III flow rates would provide some evidence against this argument. The theory that less instrumentation in a thrombotic lesion might improve TIMI III flow should also be considered.

Despite the advances in the care of this high risk group, the case mix standardised 30 day mortality after AMI remains at 8.4% and 9.7% for Sweden and the United Kingdom respectively.[156] The annual UK wide audit conducted by the British Cardiovascular Intervention Society (BCIS) in 2014 revealed a 30 day mortality of 6.9% for all patients who received PPCI.[2] This was 7.9% for the 2017/18 financial year.[157]

Evidence for DCB angioplasty in PPCI.

Several studies have reported their experience of using DCB without stenting in the PPCI setting. Vos et al carried out a pilot study involving 100 patients presenting with acute STEMI using the paclitaxel coated Pantera LuxTM. Cardiogenic shock and intubated out of hospital arrests were excluded. 59% had DCB-only PCI, with the rest requiring BMS implantation due to dissections of type C or greater (National Heart, Lung and Blood Institute - NHLBI classification). 12 month follow up revealed cardiac death in 2%, MI 0% and target lesion revascularization rate of 3% in this selected group. TIMI III flow was achieved in 96% of patients. [158]

Ho et al reported their preliminary experience with paclitaxel coated balloon (SeQuent Please) in the PPCI setting for 89 patients. 70% had TIMI 0 flow pre procedure and TIMI III flow was achieved in 98% patients. Glycoprotein IIb/IIIa inhibitors were used in 80%

and thrombus aspiration was carried out in 56%. DCB-only PCI was carried out in 96% whilst the other 4% had bail out stenting for significant acute recoil or dissections. They reported a death rate of 4.5%, MI 0% and TLR/TVR of 0% at 30 days. [159] Whilst results are impressive it should be noted that these are observational studies therefore will have their inherent limitations such as selection and treatment bias.

Nijhoff et al in a subgroup analysis from the DEBAMI trial showed that there was no difference in major adverse cardiac events in 40 patients treated with DCB-only PPCI in comparison to BMS only, BMS+DCB and paclitaxel eluting stent implantation at 6 months follow up. [160]

The REVELATION trial randomised 120 patients presenting with STEMI to DCB and DES. Randomisation was carried out if more than 50% luminal diameter was achieved after initial pre dilatation. Primary end point was fractional flow reserve after 9 months. The mean fractional flow reserve value was 0.92 ± 0.05 in the DCB group (n = 35) and 0.91 ± 0.06 in the DES group (n = 38) (p = 0.27) indicating non inferiority of DCB to DES in FFR follow up at 9 months.[161]

These publications suggest that DCB-only PPCI may be a safe alternative to standard stent implantation in this high risk group.

Technical Tips and Tricks with DCB-only Angioplasty in Primary PCI

It is recommended to follow the German consensus guidelines but with additional steps to successfully perform DCB-only PPCI.[50]

1. Lesion preparation:

Aspiration thrombectomy is recommended when faced with a high thrombus burden i.e.: TIMI thrombus grade 3 or more, aiming to reduce the thrombus burden to TIMI thrombus grade of 2 or less. A thrombus- laden lesion is more likely to hamper effective drug delivery to the vessel wall.

This should be followed by mandatory pre dilatation of the lesion using semi or non-compliant balloons with a balloon to vessel ratio of 0.8 to 1.0. This should be done carefully and slowly with enough pressure only to fully inflate the balloon (usually 6-8 atm). Liberal use of intra coronary nitrates is recommended as this helps accurate vessel sizing. We have a low threshold for the use of glycoprotein IIb/IIIa inhibitors in treating lesions with high thrombus burden. Whilst bleeding risks could be higher with glycoprotein IIb/IIIa inhibitor use, risk of intracerebral bleeding or stroke was not higher compared with placebo and most early studies were carried out when arterial access was transfemoral.[162] A more recently published study analysing 110,327 patients in the BCIS registry has shown that routine (>75%) use of Glycoprotein IIb/IIIa inhibitors reduced mortality over a 5 year period.[163]

The fluoroscopic acquisitions after pre dilatation should be of a slightly longer duration to carefully look for evidence of vessel threatening dissections, in particular any contrast hang up or accumulation within a dissection plane indicating a NHLBI type C dissection and possible early vessel closure due to intramural haematoma formation.

Coronary dissections are an inevitable result of BA, but most are micro dissections that cannot be seen on angiography and are of no clinical significance. However, abrupt

vessel closure remains one of the most fearful complications of BA usually associated with NHLBI dissection grades of type C and above. With a good knowledge of the different NHLBI grades of coronary dissection, careful selection of those patients suitable for DCB-only angioplasty is possible.[164] Ho et al in their study reported no abrupt closure of the culprit artery. Only 4% of patients required bailout stenting for significant recoil/dissections of type C and above.

2. Drug delivery:

If there are no dissections of more than NHLBI type C, TIMI III flow and not more than 30% residual stenosis, drug delivery should be considered with the deployment of the DCB. DCB diameter should be the diameter of the largest balloon used to pre dilate the lesion. The DCB should be used only for drug delivery and not for further angioplasty. It is good practice to check the guide catheter and wire position and ensure the O-ring is fully open before start delivering the DCB. Care should be taken not to touch the DCB prior to introduction. We recommend following manufacturer's instructions for use to ensure adequate drug delivery. This will include maximum transit time to the lesion and balloon inflation times.

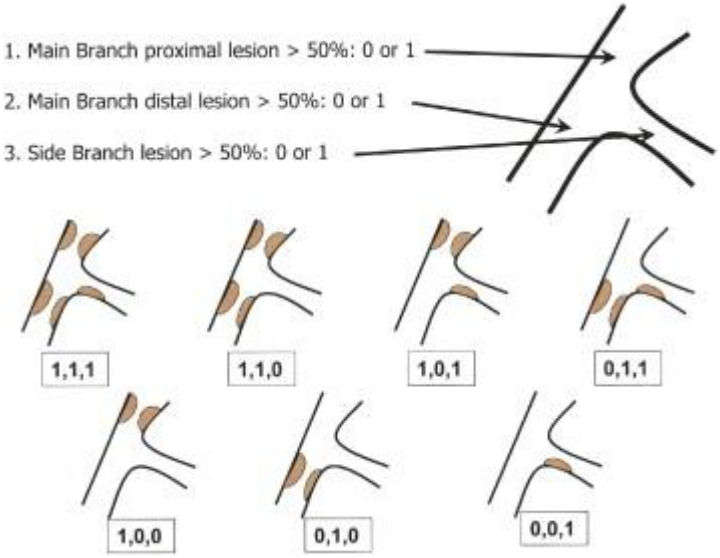
The use of DCB as primary therapy in primary PCI represents a novel approach in treating STEMI patients. This approach is possible with appropriate patient selection and by performing 2 key preconditioning steps namely aspiration thrombectomy for lesions with high thrombus burden and careful lesion preparation. However, it is recommended to perform DCB-only angioplasty in stable patients first, preferably with proctoring before treating such high risk patient groups.

1.3.5 Bifurcation PCI

It is estimated that PCI for bifurcation lesions account for about 20% of the total coronary interventions undertaken[165]. It is perceived to be a challenging area due to reasons discussed below.

There are numerous criteria for classification of bifurcation lesions but the most commonly used one is the Medina Classification which is shown below in figure 7.

Figure 7 Medina classification for bifurcation lesions



True Bifurcation lesions are considered to be the ones affecting both main and side branches. (1,1,1, 1,0,1 and 0,1,1).

Intervention to such lesions is challenging due to location, angle of the side branch/distal main branch, technical difficulties such as lesion visualisation and accurate stent placement as well as higher adverse outcome rates as compared to intervention in non-bifurcation lesions. Side branch occlusion due to plaque/carina shift, flow limiting dissections of the side branch and compromise of flow in main branch

stents due to strut deformation as well as increased re-stenosis and thrombosis rates are a few specific adverse outcomes in addition to the known complications of PCI.

Major adverse cardiac events in this group were reported to be very high prior to use of DES. Al Suwaidi et al reported MACE rates of 32% at 1 year follow up.[166] Even after the introduction of DES, adverse events such as side branch restenosis rates remain high compared to non-bifurcation lesions. The British Bifurcation Coronary (BBC) study which compared simple vs. complex two stent strategy for bifurcation lesions in 500 patients showed a composite of death, MI and TVR of 8.0% vs. 15.2% (hazard ratio 2.02, 95% confidence interval 1.17 to 3.47, P=0.009) at 9 months follow up.[167] Side branch restenosis rates of 14.6% and 12.5% at six months were reported in the two arms of the CACTUS study which tested crush vs provisional techniques using sirolimus eluting Cypher stents.[168] In the Nordic Baltic III bifurcation study, at 8 months angiography follow-up, the percentage of binary restenosis (diameter stenosis ≥50%) in the entire bifurcation lesion (MV and SB) was 11.0% in the final kissing balloon dilatation (FKBD) and 17.3% in the no-FKBD group.[169] Recently published DKCRUSH VI study (comparison between angiography guided vs FFR guided provisional stenting) reported MACE (Cardiac death, MI, ischaemia driven TVR) rates of 18.1% for both arms at one year follow up.[170] Dedicated bifurcation stents have been developed and tested in studies involving small number of patients but they are not yet in use as part of day to day practice.

There are various approaches/techniques of angioplasty/stent insertion described in literature and being used in practice. Provisional approach (Stenting the main branch with a jailed wire in the side branch, and stenting of side branch only if required) is the

current preferred approach. When a two stent strategy is required, stent insertion techniques such as culotte, crush, T stenting and TAP, with or without final double kissing balloon inflation are used, with the choice of technique dictated by angiographic characteristics as well as operator preference.

DCB-only treatment in Bifurcation Lesions.

As there is no permanent metal implant/polymer left behind, DCBs are an attractive option in treating bifurcation lesions. In most dual stent techniques there is overlap of stent struts which potentially increases the risk of stent thrombosis, side branch occlusion and dissections. Furthermore the amount of plaque/carina shift will be less intense with a balloon-only approach because no permanent implant is deployed (the latter always requires optimisation of the lumen as assessed by angiography +/- intravascular imaging). There is evidence of late luminal gain after DCB alone treatment due to restoration of normal vasomotion and positive remodelling.[171] This will be hugely beneficial in this cohort of patients as it will help restore flow dynamics.

There have been studies conducted using DCB's in bifurcation lesions but most adopted a strategy of implanting a BMS in the main branch/vessel (DEBUIT and PEPCAD V).[52, 172] This is at odds with the biggest potential benefit of DCB use, which is in the setting of no permanent implant (stent). The literature available suggests that DCB plus BMS is a flawed concept with no advantage over BMS alone.

Schulz A et al has published an observational study of 39 patients who were treated with DCB only strategy and follow up angiography at 4 months. MACE was reported as

7.7% and restenosis rates were low at 3.3 % of the side branch and 6.7 % of the main branch. No deaths, MI or strokes were reported.[173]

DCB-only group of the PEPCAD-BIF (comparison of DCB-only vs POBA) study had restenosis rates of only 6% at 9 months and LLL of only 0.15mm.[132]

1.3.6 Chronic Total Occlusions

A chronic total occlusion is defined as 100% occlusion in the coronary artery with TIMI 0 flow of at least 3 months duration. [174]

CTOs are complex lesions encountered in 15-30% of patients referred for coronary angiography and are considered a significant challenge in percutaneous coronary intervention (PCI).[175] Due to the lower rates of success compared to sub-total stenosis, CTOs remain the strongest independent predictive factor for referral for coronary artery bypass grafting.[175] Successful recanalization is known to reduce angina, reduce the ischaemic burden and improve left ventricular function. It is also thought to have a reduction in mortality rates (on the basis of observational studies).[176] Certainly, patients who have an acute coronary syndrome (ACS) with a CTO are known to have significantly worse outcomes compared to those without a CTO, even accounting for patients with multi-vessel coronary disease. [177-180]

CTO PCI procedural success has always been associated with poorer outcomes than sub-total stenosis PCI, with rates currently at about 77% angiographic success (Pooled Estimate Rate).[181]

Instent restenosis (ISR) rates in CTO PCI are relatively high, although the introduction of drug eluting stents (DES) has seen a reduction in ISR from 41% to 11% compared to bare metal stents (BMS). [182]Therefore, the majority of CTO PCI practice involves the use of DES (82.2%).[176] The fact still remains however that ISR rates in CTO are still significantly high at 10-15% at one year. [182-187] TLR rate of 6.3% and MACE rate of 10% at 12 months have been reported after everolimus eluting stent implantation.[188] TVR of 7.5% and 13.8% at 12 months were reported with sirolimus and zotarolimus eluting stents respectively in another study by Park HJ et al.[186]

The pathophysiological changes in CTOs after intervention are complex. *Galassi et al.* looked at the transient vasomotor impairment following successful recanalization of the CTO. He reported that after recovery of antegrade flow and a period of hibernation of the vessel wall, distal vessel diameter increased as a result of recovery of vasomotor tone.[189] One IVUS study has shown 69% of the re-canalized vessel had a mean increase in diameter of 0.4mm at 6 month follow-up.[190] This may well account for the higher rate of instent restenosis seen in CTOs due to distal stent segment malapposition, as stent sizing may be underestimated.[191]

A multicenter registry of 34 patients who received DCB treatment for CTOs showed restenosis rate of 11.8% (n=4) and re-occlusion rate of 5.9%.[192] Benefits of DCB only angioplasty in CTOs may be attributable to anti restenotic drug delivery reducing restenosis whilst avoiding other stent related issues such as chronic inflammation, neo atheroma, stent fracture, stent gap, stent overlap, non- uniform stent struts, non-homogenous drug delivery, uncovered stent struts and under expansion. It is further advantageous as late lumen gain caused by recovery of vasomotor tone which would

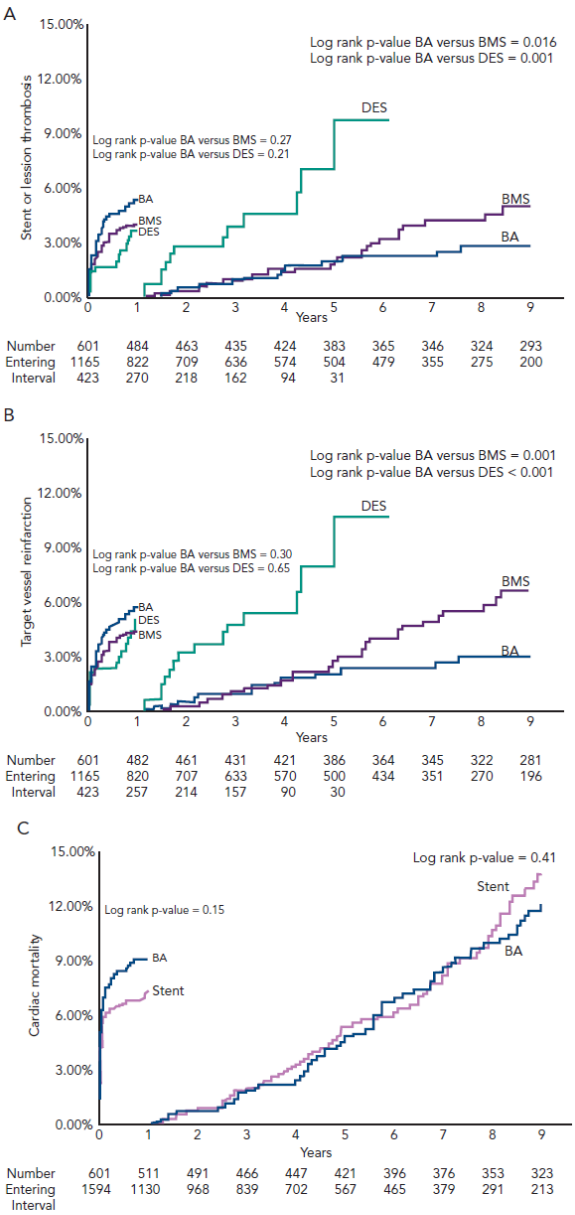
have led to malaposition of a stent is no longer an issue as there is no permanent or temporary implant in DCB angioplasty. It may be further beneficial over stents as longer coronary segments are treated during angioplasty of CTOs.

1.4 Potential Advantages and Disadvantages of DCB angioplasty

1.4.1 Potential advantages of not having a permanent metal implant in de novo disease.

Brodie *et al* have published a long term longitudinal follow up registry of 2,195 consecutive patients treated for STEMI, comparing POBA to BMS and DES and showed better long term outcomes in the balloon angioplasty arm (POBA (n = 601), stenting (n = 1,594) from 1994 to 2010).[155] Target vessel re-infarction and stent/lesion thrombosis were better with POBA compared to stents between 1 and 9 years (3.1 vs 7.9%, $p<0.001$ and 2.9 vs 6.1 %, p 0.002 respectively). Landmark analysis at 12 months showed a trend in favour of stenting with a non-significantly lower re-infarction rate only (figure 8). However it should be noted that there was no bail out stent option in case of a vessel threatening complication (stents were only used from 1999 onwards outside of research procedures) and only single anti-platelet therapy was often used. In this cohort of BA cases only 23% were discharged on thienopyridines. However, all patients received standard treatment of the time. The authors concluded that there is a long-term risk associated with a permanent coronary metallic implant.

Figure 1: Kaplan–Meier Estimates of Event Rates and Cardiac Mortality in Patients Treated with Drug-eluting Stents, Bare Metal Stents and Balloon Angioplasty for ST Segment Elevation Myocardial Infarction at a Single Centre Over 16 Years



A: Stent or lesion thrombosis (ST/LT); B: target vessel re-infarction. Patients treated with both drug-eluting stent (DES) and bare metal stent (BMS) had greater frequency of ST/LT and target vessel re-infarction after 1 year compared with balloon angioplasty (BA). C: Kaplan–Meier estimates of cardiac mortality event rates at 0–1 year and >1 year in patients treated with stenting versus BA. Source: Brodie et al., 2014. Reproduced with permission from Wiley Periodicals, Inc © 2013.*

Figure 8 Kaplan-Meier estimates of event rates and cardiac mortality in patients treated with drug eluting stents, bare metal stents and balloon angioplasty for ST segment elevation myocardial infarctions at a single center over 16 years. Figures (a) Stent or lesion thrombosis, (b) Target vessel infarction, (c) cardiac mortality. Brodie et al.

A DCB-only strategy has the potential to overcome the long-term complications of stent systems by avoiding a permanent implant, thus allowing the blood vessel to regain its original vasomotion and undergo positive remodelling. Togni *et al* illustrated how stented segments do not undergo any vasodilatation during exercise, whilst those segments adjacent to Sirolimus stents showed paradoxical vasoconstriction on exercise.[193] Adverse effects of Sirolimus stents on local endothelium dependent vasomotion have also been shown by Hofma *et al.*[194] In contrast, whilst there is no published data on restoration of normal endothelial vasomotor function after DCB-only PCI, there is evidence of positive remodelling resulting in late luminal gain as shown by Kleber *et al.*[171] This remodelling process is beneficial post DCB-PCI, but in the presence of a permanent metallic cage could result in late mal-apposition with subsequent late complications. The role of DCB angioplasty in late lumen enlargement is discussed in the following section in detail. The disadvantages of delayed endothelialisation, chronic inflammation, mal-apposition and under-expansion are all irrelevant when there is no permanent implant.

The major difference between DCB and other treatment options is that the DCB option does not require even a temporary implant. Hence we suggest that a strategy which tackles the problem of restenosis whilst not involving a permanent metal stent or semi-permanent polymeric scaffold could be attractive in the vast majority of patients who undergo angioplasty when acute complications such as a flow limiting dissection, vessel closure or recoil do not occur (that is, more than 90% of patients undergoing angioplasty as shown in Benestent and Stress trials, but we do accept current PCI practice incorporates much more complex anatomy and techniques). We propose this is where

Drug Coated Balloon angioplasty has a role to play. It does not leave a permanent implant but targets restenosis with the delivery of a cytotoxic/cytostatic drug to vessel wall. Obviously, DES and BVS will be very necessary tools to have in the armoury in case of acute complications mentioned above.

1.4.2 The Role of Drug-Coated Balloons on Late Lumen Enlargement

Late lumen enlargement (LLE) is defined as an increase of the minimal luminal diameter or area of a coronary artery at follow up angiography as compared to the minimal luminal diameter or area immediately after a percutaneous coronary intervention. This has been described in the treated segment of the coronary artery as well as segments distal to the treated lesion. The latter downstream late lumen enlargement is considered to be due to re-establishment of vasomotor tone in the hibernating vessel wall and may be observed, for example, after recanalization of a chronically occluded or severely stenosed artery. [189, 190] In this section focus is on in-segment late lumen gain in the setting of drug coated balloon (DCB)-only angioplasty.

Importance of LLE

Any late lumen enlargement should be considered beneficial by way of mitigation against the development of flow limiting coronary restenosis. However, in the presence of a permanent or semi- permanent implant it may theoretically result in late mal-apposition and subsequent implant-related complications (particularly stent or scaffold thrombosis).

Possible contributory factors for LLE

In a very early study of 47 patients who received balloon only angioplasty, Johnson et al described the three possible luminal outcomes at angiographic follow up (in this case 7.2+/-3 months). A decreased lumen diameter was seen in 34.8%, the dimensions were unchanged in 30.4% whilst an increased lumen diameter was seen in 34.8%. [195] Two theories were postulated for the late lumen gain; coronary spasm during the procedure which subsequently resolved or intimal plaque fracture resulting in late plaque retraction with healing and re-endothelialisation.

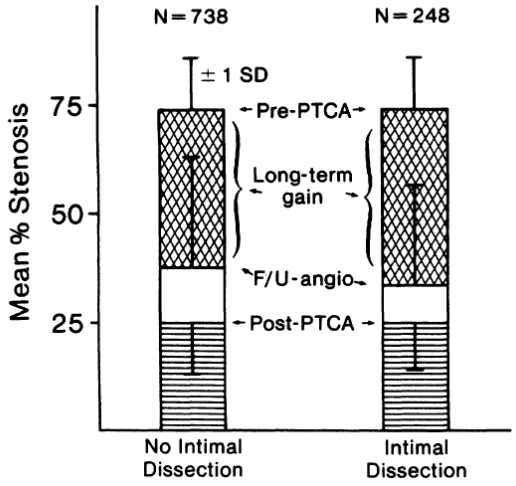
Coronary Dissections

Adding to the Johnson et al data, there are other studies suggesting late lumen enlargement may be enhanced by the presence of a coronary dissection. Cappelletti et al studied 129 consecutive patients treated with POBA only, of whom 49 had a non-occlusive dissection (NHLBI type A-E, figure 2, page 48) left uncovered.[196] Restenosis rates at 6 months angiographic follow up were lower in the dissection group as compared to the group without a dissection (12 vs. 44% ($p<0.001$)) A matched cohort of 60 patients who had bail out stenting after a coronary dissection had a restenosis rate of 25%.

In a study of 986 patients treated with POBA, of whom 248 had intimal dissections, restenosis rates were numerically lower in the group left with a dissection (24 vs 30%, p 0.08). [197] In the group with a post procedure trans-stenotic pressure gradient of less than 15 mmHg, the restenosis rate was significantly better in the group left with a

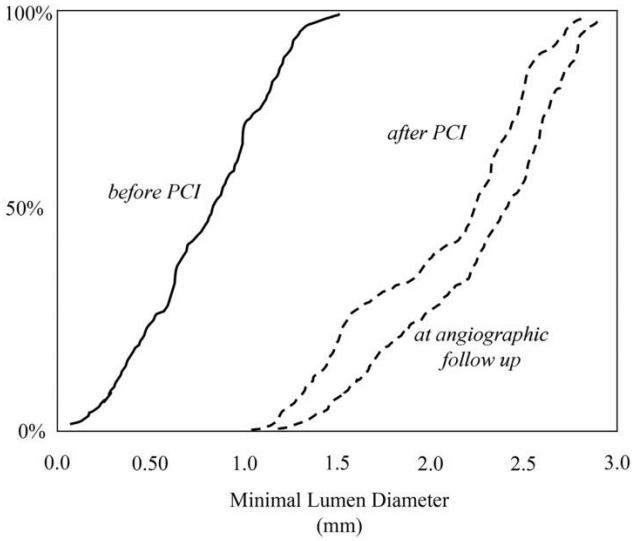
coronary dissection (19 vs. 28%, p <0.05). As Figure 9 shows the long term gain was significantly better in the group left with a coronary dissection (35 vs 40%, p 0.01).

Figure 9 Mean percent stenosis (+/- SD) in patients without intimal dissection and in patients with intimal dissection before angioplasty (pre-PTCA), immediately after angioplasty (post-PTCA), and at the time of follow-up angiography (F/U-angio). (Leimgruber et al)



Cortese et al published a prospective registry of 48 patients with uncovered type A to C dissections after treatment with a paclitaxel eluting balloon. [139] The late lumen loss at 6 months angiographic follow up was only 0.14 (−0.14 to 0.42) mm. Figure 10 shows how the curve representing minimal lumen diameter (MLD) has shifted to the right at follow up angiography. Whilst this may have been influenced by the presence of paclitaxel which we will discuss later, the association with uncovered dissections should not be ignored.

Figure 10 Minimal luminal diameter before DCB PCI, after DCB PCI, and at angiographic follow-up in patients left with a dissection (Cortese et al)



Whilst the exact mechanism of LLE is unknown after POBA dissections, it has been suggested that healing and fibrosis occur with retraction and endothelialisation of the separated intimal flaps, resulting in a larger lumen area and smoothening the inner contour. [198]

Resolved acute recoil and coronary spasm

Resolved acute recoil and coronary spasm are two other possible contributory factors to late lumen gain when there is no permanent or semi–permanent stent, but we are not aware of any specific data on this subject.

Absence of an implant

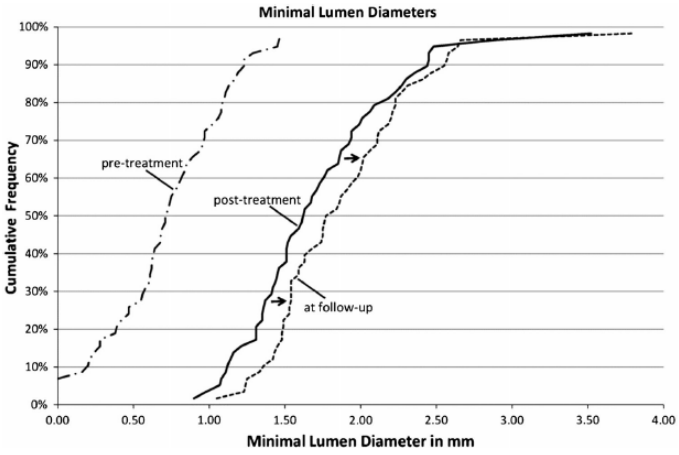
A coronary artery that has been caged with an implant does not have the ability to change its dimensions or respond to vasomotor reflexes as compared to a non-caged

artery. There are no studies to our knowledge that show late lumen enlargement after stenting (unlike POBA as described above). However late stent mal-apposition is reported in about 10-25% of drug eluting stent implantations and may represent the same pathophysiology. [199, 200] Togni et al demonstrated sirolimus DES treated segments do not change their lumen size due to a loss of vasomotion. Interestingly however, adjacent segments paradoxically constrict on exercise. [193]

DCB (Paclitaxel coated balloon) and late lumen enlargement.

Kleber et al described late lumen enlargement after paclitaxel coated balloon-only percutaneous coronary intervention in a study of 58 coronary artery lesions with a mean reference vessel diameter of 2.58 ± 0.47 mm. [171] Quantitative coronary angiography analysis at 4.1 ± 2.1 months revealed 69% of lesions demonstrating late lumen gain. Interestingly, the mean luminal diameter increased not only of the drug coated balloon (DCB) treated segment but also occurred in the 2 adjacent 5mms segments.

Figure 11 Minimal lumen diameter of the lesion site during pre, post and follow up angiography (Kleber et al)



The authors suggest late lumen enlargement with paclitaxel coated balloon may be explained by paclitaxel driven inhibition of smooth muscle cell proliferation by modulation of microtubule formation and upregulation of pro-apoptotic factors and also possibly due to thinning and enlargement of tunica media. [201-203] We therefore presume the effect is due to a combination of inhibition of cell proliferation and cell death.

Ann et al found a significant increase of mean vessel and lumen area of 28 de novo lesions treated with paclitaxel coated balloon-only angioplasty at 9 months follow up angiography (12.0 ± 3.5mm^2 to 13.2 ± 3.9mm^2, p <0.001; and 5.4 ± 1.2mm^2 to 6.5 ± 1.8mm^2, p <0.001).[204] IVUS virtual histology during the follow up assessment showed no change in the mean plaque area (6.6 ± 2.6mm^2 to 6.6 ± 2.4mm^2, p = 0.269) but reduction of percentage atheroma volume (53.4 ± 7.9% to 49.5 ± 6.4%, p = 0.002). Plaque composition did not change significantly. Serial changes of percentage atheroma volume and minimal lumen area are shown in figure 8 whilst figure 9 shows the changes of pre, post and follow up mean vessel, lumen and plaque areas.

Figure 12 Serial changes in percent atheroma volume and minimal lumen area. (Ann SH et al)

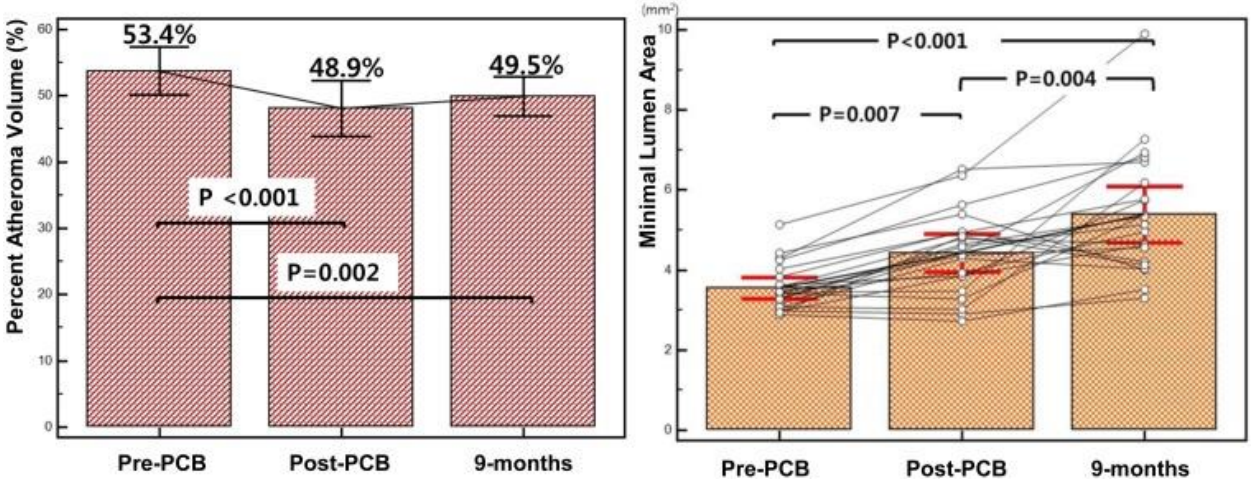
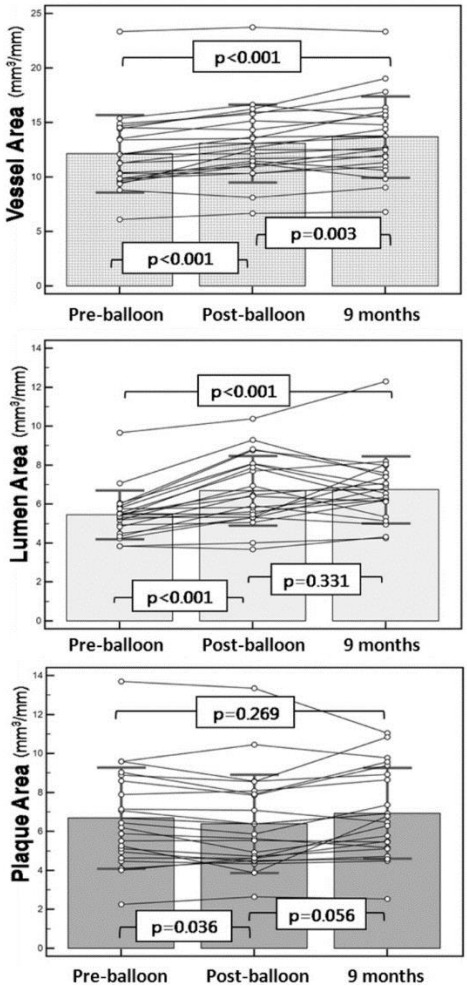


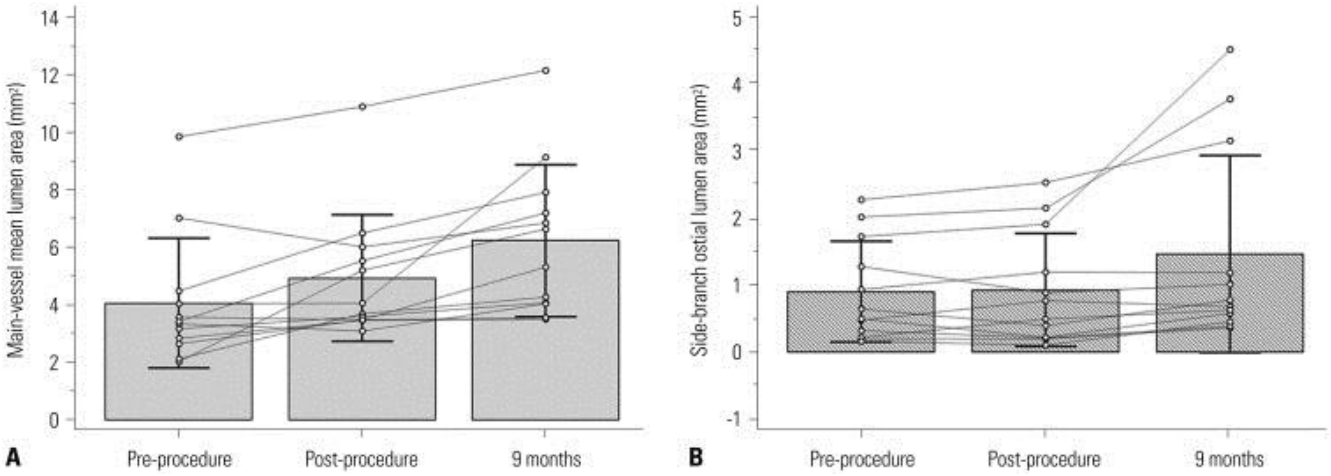
Figure 13. Serial changes of mean vessel, lumen and plaque area (Ann SH et al)



Similar to Kleber, the authors attributed these findings to arrest of micro-tubule function resulting in prolonged anti-proliferative and anti-migration effects and prolonged retention of paclitaxel. [201, 202, 205]

Her et al assessed the size of 28 side branches where the main vessel has been treated with a paclitaxel coted balloon-only angioplasty and found increased ostial size of the side branch at 9 months follow up using optical coherence tomography (OCT).[206] Inclusion criteria were lesion stenosis of >70%, vessel diameter of 2.5-3.5mm, lesion length of ≤24mm and a side branch (SB) of ≥1.5 mm. Angiographic and OCT assessments were carried out pre, immediate post angioplasty and at 9 months from the index procedure. The minimum lumen area of SB ostia were pre PCI 0.92±0.68 mm^2, immediate post PCI 1.03±0.77 (p 0.726) and at follow up 1.42±1.18 (p0.013). In addition, the main vessel minimal luminal diameter and mean luminal area were both significantly increased by both angiographic and OCT follow up at 9 months. This late enlargement of side branch ostia could be attributed to overall lumen enlargement and/or effects of paclitaxel alone. Figure 10 shows serial changes of main vessel and side branch ostial mean lumen area.

Figure 14. Serial changes of mean lumen area of main vessel and side branch ostia (Her AY et al)



Levin et al studied intra mural drug distribution and transport properties for paclitaxel and rapamycin in bovine internal carotid segments.[207] It was shown that paclitaxel which binds microtubules remained primarily in the sub intimal tissue, mainly the tunica adventitia. Figure 11 shows the tissue binding capacity of dextran, paclitaxel and rapamycin in 0.040-mm-thick bovine internal carotid tissue segments.

This could explain the positive vessel re-modelling (increased vessel diameter/area) shown above resulting in late lumen enlargement in an effect similar to described by Glagov et al. [208] They reported an enlargement of the vessel area of coronary arteries thus maintaining the lumen area during plaque progression, up to the point of 40% stenosis of internal elastic lamina area. Figure 12 (a and b) illustrates this phenomenon.

Figure 15 Transmural equilibrium distribution of labeled dextran (♦), paclitaxel (□), and rapamycin (◊) in 0.040-mm-thick bovine internal carotid tissue segments. (Levin AD et al) TBC – tissue binding capacity

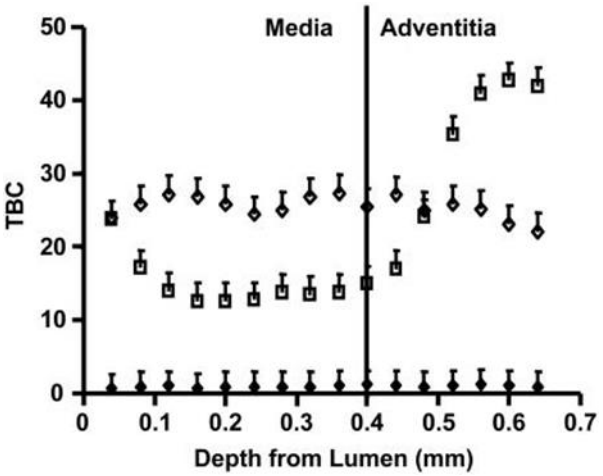
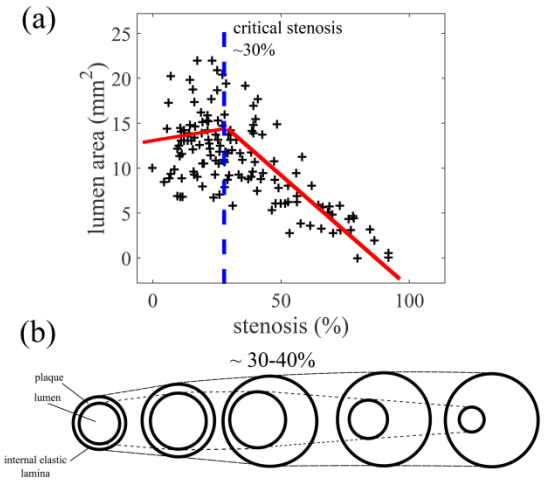


Figure 16 (a and b). Adaptive remodeling of coronary artery (Glagov et al)



As described above, paclitaxel is a potent cytotoxic drug which arrests microtubule function resulting in prolonged anti proliferative and migration effects and upregulation of pro-apoptotic factors.[201, 202, 205] Additionally paclitaxel has been shown to cause a reduction in smooth muscle cell and collagen content in the intima as well as the media after local delivery. [203] Late lumen enlargement may also be partly explained by positive vessel remodeling (increased vessel diameter/area) as described by Glagov et al. [208]

In summary the effects of paclitaxel, the presence of coronary dissections and the lack of either a metallic or polymeric cage implant may all contribute to late lumen enlargement seen after paclitaxel coated balloon-only angioplasty.

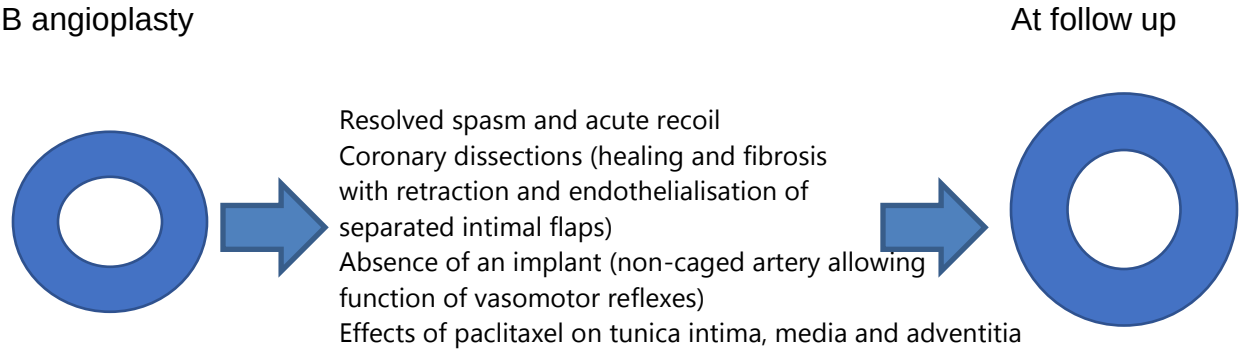


Figure 17 Possible causes for late lumen gain after DCB-only angioplasty

The implications for PCI are enormous. The initial results of balloon-only angioplasty no longer need to be "stent-like" in order to achieve an adequate long term result. The application of the German consensus guidelines accepting a residual post balloon stenosis of <30% will allow many patients to have successful procedures without the long term hazard of a permanent metallic implant, with the added benefit of a return to normal endothelial and vasomotor function.

1.4.3 Potential disadvantages

Acute recoil and NHLBI dissections of type c and above would be two not so uncommon drawbacks of DCB only PCI in de novo vessels. Unlike in the POBA only days, the availability of DES as a bail-out option helps mitigate this issue effectively. Also use of cutting/scoring balloons will be helpful in overcoming acute recoil. The percentage of

bail out stenting tends to vary from study to study. The cross over rate from POBA arm to stent arm was 5-6% in the Stress and Benestent trials. The SCAAR registry showed 8% bail-out stenting whilst REVELATION study showed bail out stenting/additional stents in 18% of the 60 patients in the DCB arm.

It is also perceived that deliverability of DCB is less compared to conventional stents and also the time limit of 2 minutes to deliver the DCB to a lesion and fully expand can make it challenging in difficult/complex lesions.

Acute vessel closure/instability requiring patients to be brought back to the catheter lab will be the most feared draw back out of all. This study will give valuable information on the incidence of acute vessel closure of an all comer population in the real world setting. DCB arm of the BASKET-SMALL randomized study had no acute vessel closures. Similarly Sequent Please world-wide registry which included 453 de novo lesions had no acute vessel closures in the DCB only arm. SCAAR registry data does not provide this information.[124, 137, 138]

Enhanced quality of imaging over the years will undoubtedly help identifying vessel threatening dissections that can lead to acute vessel closures. Additionally one to one proctoring in the initial stages of DCB-only PCI will be beneficial to understand how these dissections behave and progress in the acute setting and what could be safely left without a bail-out stent.

Impact of Paclitaxel on mortality

Konstantinos K. et al published a systematic review and a meta-analysis of 28 randomised controlled trials including 4663 patients who received a paclitaxel coated

device (stent or balloon) or a non-paclitaxel treatment for femoro-popliteal arterial disease. At two years all-cause death (12 RCTs with 2316 cases) was significantly increased in the case of paclitaxel versus control (7.2% versus 3.8% crude risk of death; risk ratio, 1.68; 95% CI, 1.15–2.47; number-needed-to-harm, 29 patients [95% CI, 19–59]). This trend in increased all-cause death persisted up to 5 years (3 RCTs with 863 cases) in the paclitaxel arm (14.7% versus 8.1% crude risk of death; risk ratio, 1.93; 95% CI, 1.27–2.93; number-needed-to harm, 14 patients [95% CI, 9–32]).[209] Not having patient level data for the analysis is a major limitation of this study.

Schneider PA published a patient level meta-analysis including 1837 patients treated with paclitaxel coated balloon and 137 balloon-only angioplasty treated patients and this did not show a significant difference in mortality after 5 years.[210] Secemsky EA et al showed no increase in mortality after drug coated devices treatment compared to balloon only or bare metal stent treatment of femoro-popliteal disease in a study including 16560 patients. 5989 patients had received a drug coated device therapy. Median follow up was 389 days. Drug-coated devices arm showed a lower incidence of all-cause death compared with treatment with non–drug-coated devices through 600 days post procedure (32.5%vs 34.3%, log-rank P = .007).[211]

Albrecht et al published a pooled analysis of four randomized controlled multicentre trials (433 patients) to compare two year mortality of paclitaxel coated balloons (PCB) with uncoated balloons for femoro-popliteal disease. Importantly this included individual patient level data. At two years, mortality was numerically low in the PCB group but not statistically significant (7% vs. 8.7% (p 0.55).[212]

Whilst the debate is ongoing there certainly is no study/evidence to suggest increased mortality in use of paclitaxel in coronary PCI.

A recent publication by Scheller et al which included 4590 patients in 26 randomised controlled trials (RCT) comparing paclitaxel coated balloons (PCB) vs. non-DCB devices in coronary artery disease showed no difference of death at two years (RR: 0.84; 95% CI: 0.51 to 1.37; p = 0.478). At 3 year follow up (9 RCTs, 1775 patients) mortality was significantly lower (RR: 0.73; 95% CI: 0.53 to 1.00; p = 0.047) in the paclitaxel coated balloon group.[213] Cardiac death showed a similar reduction in the paclitaxel coated balloon treated group (RR: 0.53; 95% CI: 0.33 to 0.85; p = 0.009).

This certainly is an encouraging finding for the use of PCB in coronary artery disease but more studies with longer term follow up are required to ascertain these findings further.

1.5 Hypothesis

DCBNORWICH Registry: Main hypothesis is DCB angioplasty is a safe and effective method of percutaneous coronary intervention. A target vessel revascularisation (TVR) rate of 4.9 to 11.1% or less at 12 months for de novo lesions and approximately 20% or less for the ISR group were considered to be within expected ranges based on real world data of DES studies. Assuming 830 patients in the de novo lesions group and a TVR rate of 4.9% and a censoring rate of 0.5% for all groups, the study would be able to estimate the survival rate with a standard error of 0.8 percentage points (estimated using Greenwood's formula). The registry data is most importantly also seen as hypothesis generating.

DCBNORWICH propensity score matched comparison of DCB vs. 2nd generation DES:

Major adverse cardiac outcomes (MACE) of DCB angioplasty is non-inferior to DES by a non-inferiority margin of 4.5%. The DCB outcomes will be considered non-inferior to DES, if the 95% CI of the estimated OR from the logistic regression model excludes 1.56.

2 Chapter 2: Methods

2.1 DCBNORWICH Registry

2.1.1 Study Design

This was a single centre, retrospective, all-comer, observational registry to assess the outcomes of patients who received Drug Coated Balloon Angioplasty treatment from 01/01/2009 to 31/12/2015 at Norfolk and Norwich University Hospital (NNUH). We have included patients with both acute and stable coronary artery disease using DCB, in all sizes of coronary arteries and all vessels including left main stem.

2.1.2 Patient Identification

Up until June 2011, all PCI data has been entered to a data base named PATS and thereafter INTELLECT, which is in use to date in the Norfolk and Norwich University Hospital NHS Foundation Trust. PCI operators enter data that are mandatory for submission to British Cardiac Interventional Society (BCIS) data base as well as other data required by the trust data base for each PCI procedure.

Patients who have undergone DCB angioplasty were identified from these two data bases by the manager in charge of the data base, thereby allowing extraction of their demographic details, coronary risk factors and procedural details.

2.1.3 Patient Eligibility Criteria

Inclusion Criteria

All patients who have undergone DCB angioplasty at the Norfolk and Norwich University Hospital from 01/01/2009 to 31/12/2015 were eligible for the study.

Exclusion Criteria

No patients were excluded.

2.1.4 Approvals

NNUH Research and Development

Firstly the project proposal was forwarded to the NNUH Research and Development department and it was registered as a research study. It was agreed that NNUH would be the project sponsor.

Caldicott Guardian

Following this an application was forwarded to trust's Caldicott Guardian together with the project proposal to obtain a letter of support.

National Research Ethics Committee Approval

Thirdly an application for ethics approval was forwarded to a national ethics committee via the centralized application system (Integrated Research Application System – IRAS) of the Health Research Authority (HRA) of the United Kingdom.

Health Research Authority Approval

Following the favourable response from the ethics committee, HRA approval was sought. HRA recommended seeking Confidentiality Advisory Group recommendations prior to giving its approval, as HRA considered National Institute for Cardiac Outcomes Research (NICOR) a third party for the study's purpose. The role of NICOR in this study is described in subsequent paragraphs.

Confidentiality Advisory Group (CAG)

Confidentiality Advisory Group is an independent body that provides expert advice to the HRA on use of confidential personal information of patients for the use of research activities. It also provides advice to the Department of Health on use of patient confidential information for non-research work. The HRA web site quotes 'The key purpose of CAG is to protect and promote the interests of patients and the public, while at the same time facilitating appropriate use of confidential patient information for purposes beyond direct patient care'.

As per recommendations made by the HRA, an application form (IRAS based application) together with required supporting documents was forwarded to CAG to seek legal support in order to share patient identifiable details (NHS number, date of birth and gender) with NICOR. Supporting documentation including a confidentiality advisory team advice form and a public notice that was to be uploaded in the hospital web site was forwarded.

NICOR

The National Institute for Cardiovascular Outcomes Research is the national body that collects data of cardiovascular procedures carried out in the United Kingdom. It also

analyses outcomes of these procedures and publishes them annually. This is a vital source of data that helps hospitals and healthcare bodies to monitor and draw plans to improve outcomes of the cardiovascular patients. NICOR consists of clinicians, IT experts, analysts, academics and managers who run the national audit programmes as well as registries. There are six national clinical audits run by the NICOR. They are

1. Adult cardiac surgery
2. Adult percutaneous interventions
3. Cardiac rhythm management
4. Congenital heart disease
5. Heart failure
6. MINAP (Myocardial Ischaemia National Audit Project)

An application together with the supporting documents was forwarded requesting outcome data. Approvals of the three audit leads (Adult percutaneous interventions, Adult cardiac surgery and MINAP) were obtained.

HQIP (Healthcare Quality Improvement Partnership)

An application was forwarded to HQIP data access request group (DARG) meeting requesting permission for NICOR to release outcome data.

The HQIP is an independent organisation established in 2008 to improve quality of healthcare and specifically to enhance the use of national clinical audits in achieving this. Academy of Medical Royal Colleges, the Royal College of Nursing and National Voices lead the HQIP.

Researchers requesting data from NICOR are required to forward an application to Data Access Request Group (DARG) of the HQIP. An application together with the supporting documents from the trust, HRA and CAG was forwarded to HQIP as an amendment to the previously forwarded application.

Time frames for each of the approval stages and the length of the completed application forms are listed below in table 5.

NICOR had the legal authority to provide researchers with mortality data at the time of planning this study. However this mandate had been taken away from the NICOR by the time we obtained ethics committee and HRA approvals. Upon inquiry from the cardiac department at NNUH, we found out that the department is in possession of up to date mortality data obtained through the spine portal of the NHS Digital. We therefore submitted an amendment to the ethics committee and HRA seeking permission to use this data, permission for which was granted.

The time taken for the approval process and to receive data from the NICOR was about 31 months. This was a major hurdle in completing this study. The data extraction was costly at £ 15,558.

Table 5 Stages of approval process and time taken for completion

Approving body	Time duration	Length of application
Research and Development (NNUH)- initial registration	1 week	Email
Caldicatt guardian	3 months	5 pages
NREC	2 weeks	24 pages
HRA	4.5 months (including time taken for CAG)	Email
NNUH Information governance (IG) and NHS Digital for IG tool kit assessment	4 weeks	
CAG	3.5 months	34 pages
NREC amendment	2 weeks	2 pages
HQIP	4 weeks	29 pages
NICOR	From application to receipt of data: 22 months Cost £ 15,558.00 (data on MI and revascularisation only)	

2.1.5 Consent

This was a retrospective study obtaining data from the existing hospital data base, medical records and NICOR. We did not plan to carry out any activity which would have led to any patient or relative contact.

We did not plan to obtain consent from the patients included in the study for the following reasons:

Firstly, we believed attempting to gain consent would add bias to the study. For example, for deceased patients there was no method of obtaining consent and mortality is the most important outcome. Lack of mortality figures would have added bias to MACE rates and had a significant impact on the study. Equally if patients elected not to give consent, the value of this study as an all-comer study would have lessened. The reasons for patient refusal are complex, but might have followeda pattern adding confounding factors that would be impossible to accommodate within our analysis. If a decision was made to include patients who were deceased, but patients who were alive were given a chance to opt out, this would certainly have had an impact on event rates.

Secondly due to the large number of patients involved (more than 1000 expected), retrospectively consenting them would have increased the cost and labour requirement significantly.

Thirdly, as this is was retrospective study, consenting would have had no impact on the clinical procedures already performed or the appropriate care provided.

Most importantly, utmost care was given to protect patient confidentiality. All identifiable data were only handled by members of the research team who also are members of the Cardiology department (Cardiology doctors). All data were anonymised after initial identification from the data base (very early in the study) and had no identifiable data on the excel sheet where data is entered, which were the source data. Hence no identifiable data were used for statistical analysis or publication.

A patient group discussion was carried out to test the methodology of the study, to obtain suggestions and to find out any concerns from a patient perspective. No concerns were raised and the response was a very positive one.

In addition a public notice was displayed in the Norfolk and Norwich University Hospital web site regarding the study and the proposed methodology explaining the data sharing with the NICOR. This included contact details of the principal investigator if a patient wished to opt out from the study and none such request was received.

As the HRA recognised National Institute of Cardiac Outcomes Research (NICOR) as a third party, we were recommended to seek legal permission from the Confidentiality Advisory Group (CAG) of the HRA to share patient identifiable data with the NICOR. Subsequently an application was forwarded to the CAG seeking legal permission to share the NHS number, date of birth and gender with NICOR in-order to track outcomes through the three national cardiac audits namely Myocardial Infarction National Audit Programme (MINAP), British Cardiovascular Interventional Society (BCIS) PCI audit and Society of Cardio-thoracic Surgery (SCTS) audit. The application was approved by the CAG.

2.1.6 Study Observations

The study observations were categorised under demographic details, indication for the procedure, procedural details and clinical outcomes (table 6)

Table 6 Study observations of the DCB Norwich registry study

Demographic details	Indication and antiplatelet therapy	Procedural details	Clinical Outcomes
N	N	N	N
Age	Stable coronary artery disease	Cardiogenic shock	MACE (death, MI, TLR)
Gender	STEMI – Primary PCI	Out of hospital cardiac arrest	Death
Previous MI	Other acute coronary syndrome	pH and Lactate if so	MI
Previous PCI	Dual antiplatelet combination	Access	Target vessel revascularisation (TVR)
Previous CABG	Duration of dual antiplatelets	Vessel treated	Target lesion revascularisation (TLR)
Hypertension		Number of vessels treated	Acute vessel closure

Dyslipidaemia		Denovo/ISR/ST	Treated lesion thrombosis/ Stent thrombosis
Diabetes Mellitus		Coronary dissection and type	
Chronic Kidney disease (stage)		Any peri/immediate post PCI complication	
Family history		Additional stent/s if used	
Smoking history		If stents used was it as bail-out	
		Bifurcation lesion	
		Bifurcation type	
		Calcific lesion	
		Tortuous vessel	
		Small vessel/diffuse disease	
		Thrombus present	
		Pre dilatation balloon	
		Additional devices used	
		Intra coronary imaging	
		DCB diameter	
		TIMI flow pre procedure	
		TIMI flow post	
		Length of treated segment	

		Procedure duration	
		Contrast volume	
		Radiation dose	

Follow up data/Outcomes.

At the protocol stage, our primary outcome was considered to be MACE, defined as the composite of death, myocardial infarction and target vessel revascularisation. This was because we were confident the revascularisation data from the NICOR would be correct to a vessel level but to determine whether a revascularisation was a target lesion revascularisation (TLR), angiographic images would have been required. After receipt of data from the NICOR it was clear that apart for one event, data was available for us to determine whether a revascularisation was a TLR or not.

Therefore, primary outcome (MACE) was defined as a composite of all cause death, MI and TLR. Secondary outcomes were acute vessel closure events and TLR. All components of the primary outcome were described individually too. Clinical outcomes were obtained from NICOR which is the national data base holding data of any revascularisation and MI. Death data were obtained from the spine portal of the NHS Digital.

At the time of writing the protocol and forwarding for ethics approval, the NICOR could share mortality data with research group. But a subsequent change in the data sharing agreement led to NICOR not being able to do so. However department of Cardiology at NNUH had up-to-date mortality data available through the Spine portal of the NHS

Digital. We applied for hospital's Caldecott guardian's approval to use these data and also made a major amendment to our protocol enabling us to do so. This amendment was forwarded for ethics committee and HRA approval which was obtained subsequently.

Acute vessel closures were reported from information derived from local data base. We reported TLR by reviewing angiograms of the revascularisations performed.

Outcomes were reported for pre specified groups, mainly DCB for de novo disease and DCB for ISR. Of the first group three sub groups namely, DCB-only for de- novo CAD, DCB-only for PPCI, and DCB-only angioplasty with balloon diameter of 3mm or more were reported. A small group of patients who had bypass grafts treated and chronic total occlusions were reported separately.

2.1.7 Definitions

2.1.7.1 Primary Outcome

The primary outcome, MACE, was a composite (time to first event) of all-cause mortality, myocardial infarction and target lesion revascularisation up to 12 months after the procedure. Individual outcomes of the primary outcome were also presented.

All-cause Mortality.

Defined as death due to any cause.

MI

An MI was defined as per MINAP definition (a hospital diagnosis reported as a troponin positive MI as recorded in the MINAP data base). Whilst it is likely, it was difficult to ascertain whether the reported events met the universal definition i.e. a rise/fall of troponin and one value above 99th percentile or upper reference limit, with one other feature from the list below.[214]

1. Symptoms of acute myocardial ischaemia
2. New ischaemic ECG changes
3. Development of pathological Q waves
4. Imaging evidence
5. Identification of coronary thrombus by angiography or by autopsy

When the reported event was local it was cross checked with hospital data. This reporting method applied to both DCB and DES arms in the propensity score matched study.

Target lesion revascularisation (TLR)

A TLR was defined as any repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel performed for restenosis or other complication of the target lesion. The target lesion was defined as the treated segment from 5 mm proximal and 5 mm distal to the treated lesion (by visual assessment).

2.1.7.2 Secondary outcomes.

Target Vessel Revascularisation (TVR)

A TVR was defined as any repeat percutaneous intervention or surgical bypass of any segment of the target vessel. The latter was defined as the entire major coronary vessel proximal and distal to the target lesion, including upstream and downstream branches and the target lesion itself.

Acute Vessel Closure

Acute vessel closure was defined as an event where a patient had to be taken back to cardiac catheterisation lab and require repeat angioplasty (during the same hospital stay) for a complete or partial occlusion of the artery due to a dissection.

Stent/Treated Lesion Thrombosis

Stent or treated lesion thrombosis was categorized as acute (<1 day), subacute (1 to 30 days), and late (>30 days) and defined in parallel to the ARC guidelines on Stent Thrombosis. It is as follows: definite: acute coronary syndrome and angiographic or pathological confirmation of thrombus in the previously treated lesion and 5mm proximal or distal to it, probable: unexplained death ≤30 days or target vessel MI without angiographic information; and possible: unexplained death >30 days after treatment.

Longer term up to date follow up data wereobtained from NICOR and were incorporated into the database prior to final analysis.

All interventional centres in the UK enter patient and procedural details into a local database which in turn downloads to the national British Cardiovascular Interventional Society (BCIS) database. NICOR obtain these data from BCIS as well as data from the Myocardial Ischaemia National Audit Project (MINAP) and Society of Cardiothoracic

Surgery (SCTS) database and publish annual national audit reports. NICOR complete data acquiring by June each year for the preceding year and process data before it publishes the report in the autumn.

We obtained data from NICOR in 2019 (data valid until March 2017) allowing us to record a minimum of 12 months follow up for all patients. NICOR was the trusted third party linking the outcomes. The percutaneous revascularisation data obtained from the NICOR were vessel specific allowing us to determine target vessel revascularisations. We obtained graft details from the Royal Papworth Hospital to determine TVR for the patients who have had CABG. Reviewing angiographic data allowed us to determine whether a revascularisation was a target lesion revascularisation.

MI data were obtained from MINAP dataset version 9.1. For revascularisation events, data from Adult percutaneous intervention dataset version 5.6.1 and Adult cardiac surgery data set version 4.1.2 will be obtained. Appendix 3 describes the specific variables we requested from each of these data sets. Mortality data were obtained from the spine portal of the NHS Digital.

We plan to obtain follow up data out to ten years for this cohort of patients from NICOR, which will give us the opportunity to assess long term impact of DCB treatment.

2.1.8 Sample size

We considered a TVR rate of 4.9 to 11.1% or less at 12 months for de novo lesions and approximately 20% or less for the ISR group to be within expected ranges based on real world data of DES studies.[112, 215, 216]

Assuming 830 patients in the de novo lesions group and a TVR rate of 4.9% and a censoring rate of 0.5% for all groups, the study would be able to estimate the survival rate with a standard error of 0.8 percentage points (estimated using Greenwood's formula). If the TVR rate was as high as 11.1%, the corresponding standard error would be 1.2 percentage points. Assuming 235 ISR patients and a TVR rate of 20% in this group, the standard error for the survival estimate for this group would be 2.9 percentage points.

2.1.9 Statistical analysis plan

A CONSORT style diagram was produced to show patients flow through the registry (figure 19). Anonymised data were analysed by an independent statistician. Continuous variables were presented as mean and SD whilst discrete variables werepresented as counts and percentages. Time-to-event data were shown as Kaplan-Meier curves and were compared using log rank tests. Cox proportional hazards were used for the multivariate regression analysis in order to assess the risk factors pre-disposing to MACE after treatment.

Table 7 Variables used in the multivariate regression analysis to find out association between the composite of all cause death, MI and target lesion revascularisation.

Age (10y increase)
Female
Device diameter>=3mm
Bifurcation lesion
Current smoker
Diabetes
Previous MI
NSTEMI/UA
STEMI(PPCI)
Previous PCI
Hypertension
Vessel treated
Thrombus present

MI – myocardial infarction, NSTEMI- Non ST elevation MI, UA- unstable angina, STEMI – St elevation MI, PPCI- primary percutaneous coronary intervention, PCI- percutaneous coronary intervention

Descriptive statistics were presented on baseline characteristics, procedural and lesion details and clinical outcomes. The main groups considered were

- De novo lesions (native coronary artery receiving first time PCI)
- In stent restenosis (lesion has been previously treated with a stent which has a stenosis)
- Primary PCI cohort (patients with ST elevation MI treated with DCB)
- Bifurcation lesions (stenosis involves two or more major arteries)
- Device diameter of 3mm or more (large vessel) group

Other smaller groups like chronic total occlusions (CTO) and left main stem were considered for descriptive purposes. For each of the three main groups descriptive tables were presented for baseline characteristics, procedural details and outcomes:

- Age <70 and ≥ 70 years
- Female and male
- Diabetes/ no diabetes
- ST elevation MI/ Non ST elevation MI (including unstable angina)/ stable angina (not for the PPCI group)

A comparison between the bifurcation lesions and non- bifurcation lesions and also between the device diameter of less than 3mm (small vessels) vs. device diameter equal or more than 3mm (large vessels) were carried out.

2.1.10 Data quality assurance

It is mandatory that all PCI operators in the UK enter a BCIS specified data set following each procedure. These data bases of individual centres are accessed by BCIS before formulating the country wide audit annually. NICOR is the main body which holds data sets generated by BCIS, Society of Cardiothoracic surgeons (SCTS) and MINAP. Data from these sources are eventually used to understand UK wide PCI practice hence recognized to be of good quality. Each year missing data percentages are published in the annual audit report. The most recent BCIS audit presented in 2019 reports a UK wide completion rate of 92.9% with regards to PCI procedures. [157] Revascularisation data were available for all patients and mortality data were available for 99.71% (3 patients did not have NHS numbers).

In this study we not only obtained data from the NICOR but also from the patients' medical records which enabled us to provide a complete and an accurate data set.

2.2 DCBNORWICH propensity score matched study

2.2.1 Study Design

The study was a retrospective observational comparative study. In addition to the drug coated balloon treated cohort, patients who received second generation Drug eluting stents for de novo disease from June 2011 (inception of the Intellect database) to 31/12/2015 were identified by the data base manager at Norfolk and Norwich University Hospital. The methodology used to record their demographic details, risk factors, procedure details and clinical outcomes was as same as for the DCB Norwich registry study. This is described in section 2.1.

Null hypothesis: Outcomes of DCB-only angioplasty in de novo coronary artery disease are inferior to the outcomes of treatment with drug eluting stents (DES) by a margin (M) or more.

Alternative hypothesis: Outcomes of DCB-only angioplasty in de novo coronary artery disease are not inferior to the outcomes of treatment with drug eluting stents (DES) by more than the pre-specified margin (M).

The choice of the margin M has been discussed in the sample size calculation section.

2.2.2 Patient Identification

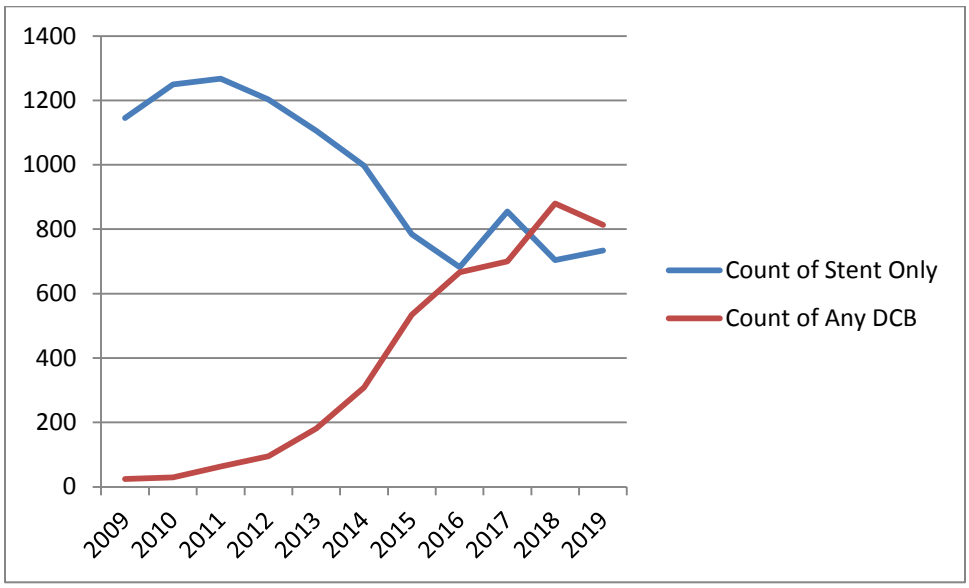
Up until June 2011, all PCI data have been entered to a data base named PATS. Thereafter to a database called INTELLECT, which is in use to date in the Norfolk and Norwich University Hospital NHS Foundation Trust. PCI operators enter data that are mandatory for submission to British Cardiac Interventional Society (BCIS) data base as well as other data required by the trust data base for each PCI procedure.

Patients who have undergone DCB angioplasty were identified from these two data bases by the manager in charge of the data base, thereby allowing extraction of their demographic details, coronary risk factors and procedural details.

Patients who underwent DES angioplasty were identified from the INTELLECT data base i.e. from June 2011 onwards by the data manager. The difference in start date in the two arms was partly due to adopting the new data base in June 2011 and also wide spread use of second generation drug eluting stents during the time. Even though our start time goes back to 2009 for the DCB arm (enabling to include every patient treated

with a DCB) the vast majority of DCB use in de novo vessels is recorded from 2011 onwards. For example only 6 patients had DCB PCI in de novo vessels during 2009 and 2010. Figure below depicts the use of DCB vs. stents in our department from 2009 to 2019.

Figure 18 Use of DCB vs. stents in the department from 2009 to 2019



X axis; year. Y axis; number of procedures

2.2.3 Patient Eligibility Criteria

Inclusion Criteria

1. All patients who have undergone DCB angioplasty at the Norfolk and Norwich University Hospital from 01/01/2009 to 31/12/2015 were eligible for the study.

2. All patients who received a second generation drug eluting (Promus, Xience, Endeavour, Synergy and Onyx) stent from 01/06/2011 to 31/12/2015 at the Norfolk and Norwich University Hospital.

Exclusion Criteria

1. The patients who received a first generation drug eluting stent treatment were excluded as second generation stents have shown better outcomes than the first and also as it is the current standard practice.

2. Patients who received a DES in one procedure and a DCB in a second procedure appeared in both arms of the study. As follow up was until the first clinical event or 12 months, the patients who had a DES in the first procedure and had a clinical event prior to the DCB procedure were excluded from the DCB arm and remained in the DES arm. Others remained in the DCB arm (for example a patient who had a DES and a DCB in two successive procedures and if a MI occurred due to stent thrombosis after the DCB procedure and prior to 12 months, this would have been still counted under DCB arm)

2.2.4 Approvals

As described in section 2.1.4 under DCB Norwich registry study, approvals were sought from the NNUH Research and Development, caldicott guardian, confidentiality advisory group (CAG), NICOR and HQIP (Healthcare Quality Improvement Partnership), as an amendment to include the patients treated with drug eluting stents during the mentioned period.

2.2.5 Consent

This is a retrospective study obtaining data from the existing hospital data base, medical records and NICOR. We did not plan to carry out any activity which will lead to any patient or relative contact.

We did not plan to obtain consent from the patients included in the study for the same reasons described in the DCBNORWICH Registry methodology under the section 2.1.5.

In addition, the public notice which was displayed in the Norfolk and Norwich University Hospital web site regarding the DCBNORWICH study was amended to include the drug eluting stent treated patients. This included contact details of the principal investigator if a patient wished to opt out from the study and none such request was received.

2.2.6 Study Observations

The study observations are the same as in DCBNORWICH registry as described in 2.1.6.

2.2.7 Definitions

The primary outcome was MACE, a binary indicator of either death, MI or TLR. The secondary outcomes were death, MI, TVR, TLR individually and also acute vessel closure and treated lesion/stent thrombosis. The definitions were as same as for the registry study as described in 2.1.7.

2.2.8 Sample Size

The sample size is described below under the statistical analysis plan.

2.2.9 Statistical Analysis Plan

Additional statistical analysis involved forming matched groups of DCB and DES patients using propensity scores (Rosenbaum and Rubin 1983) and then using logistic

regression analysis to compare patients' outcomes between the DCB and DES groups.[217]

Outcome variables

We considered MACE as the primary outcome. We also analysed death, MI and TVR individually as secondary outcomes. The researcher conducting the propensity matching analysis was blinded to the outcome data to minimise any selection bias.

Dealing with correlated observations within the matched sample

The statistical balance in terms of covariate distributions in a propensity score matched sample does not come without a price. It has been argued that propensity score matched sample does not contain independent observations.[218] Subjects within the same matched set have similar values of the propensity scores, therefore, are more likely to have similar outcomes than are randomly selected subjects. The lack of independence in the propensity score matched sample should be accounted for when estimating the standard error of the estimated treatment effect (group difference) which affects statistical inference (p-value and confidence intervals). We took account of possible correlation structure of the outcomes within the matched sets by including a random effect for the marching ID within the logistic regression analysis. The logistic regression analysis including random effects is termed mixed effects logistic regression analysis.

Effect measure for assessing group difference

We used mixed effects logistic regression analysis on the matched sample considering MACE (a binary indicator of any major adverse cardiac event) as the primary outcome and the binary group indicator (DCB=1, DES=0) as the exposure variable. The coefficient of the group indicator from the mixed effects logistic regression model represented the difference of the outcome (in terms of log-odds of MACE events) between the two groups. Conveniently, the regression coefficients from the logistic regression could be expressed as Odds Ratios (OR) which were easily interpretable. We considered the estimated OR from the logistic regression model as an effect measure for comparing the outcome measure (MACE) between DCB and DES groups. No difference in outcome (proportion of MACE events) between the two group would be indicated by OR=1. Estimated OR <1 would indicate that patients undergoing DCB only angioplasty are less likely to experience MACE than those undergoing DES procedure. On the other hand, estimated OR >1 would indicate that patients in the DCB group are more likely to experience MACE than the patients in the DES group. The mixed effects logistic regression analysis would also provide 95% confidence interval for the estimated OR taking account of the intra-class correlation of the outcome measures within matched sets which were used for testing statistical significance of the null hypothesis. As stated earlier, with 9.3% MACE rate in the DES group, 4.5% non-inferiority margin for DCB vs. DES comparison is equivalent to an OR=1.56. If the 95% CI of the estimated OR from the logistic regression model exclude 1.56, the null hypothesis would be rejected in favour of the DCB group implying that DCB outcomes are not inferior to DES by more than 4.5% (the margin of non-inferiority).

The analysis and interpretations for the secondary outcomes (death, MI, TLR and TVR) were carried out in the same manner.

Propensity score matching

Propensity score matching involves creating comparable (matched) groups of subjects who share a similar value of the propensity score. Propensity score matching allows observational studies to mimic some of the desirable characteristics of randomised controlled trials (RCTs) which are considered as gold standard approach for estimating the effects of treatments or interventions. Propensity score is a balancing score: observed distributions of the baseline covariates will be similar between the matched groups, so that subsequent comparisons made between the matched groups are not confounded by the differences in covariate distributions.

Selection of covariates for the propensity score model: A logistic regression model with the binary group indicator (DCB=1, DES=0) as the dependent variable was used to calculate propensity scores. The predictor variables for the propensity score model were considered from the following list of baseline covariates (which are available for patients in both the hospital database and NICOR database):

- Demographics: age and sex.
- Behavioural factor: smoking status.
- Co-morbidity/medical history: Previous history of MI/PCI/CABG, diabetes mellitus, hypertension, history of renal disease, cerebrovascular disease, peripheral vascular disease, cardiogenic shock, out of hospital cardiac arrest, indication:

STEMI/NSTEMI/UA/stable angina, length of the longest treated segment, diameter of the balloon/stent used, vessel treated, number of vessels treated, and CTO or not.

We examined the proportion of missing data and only covariates with acceptable amount (less than 5%) of missing data were considered in the propensity score calculation. If the majority of the covariates were found to have unacceptable level (more than 5%) of missing data, the plan was to use multiple imputation techniques to deal with missing data, in which case maximum likelihood method under missing at random (MAR) assumption with standard covariate adjustments in a logistic regression model (rather than propensity score method) was to be used for the main analysis. But this was not necessary.

Matching algorithm

We used nearest neighbour matching within caliper (NNC) algorithm to match each patient in the DCB group with one or more (up to 3) patients from the DES group (NICOR database). The nearest neighbour matching without caliper runs the risk of picking up bad matches in the sense that patients in the DCB group may get matched to DES patients with very different propensity scores. For this reason, a tolerance level, defined as caliper, was imposed on the maximum propensity score distance. Bad matches could be avoided, since anything that exceeds the caliper was not considered hence the matching quality is expected to be better. Although one-to-one (1:1) matching is the most common practice, we used one-to-many (1:M) with M=3 to take advantage of higher statistical power. The choice between 1:1 and 1:M matching depends on the trade-off between bias and variability (precision): higher M improves precision, but also

increases bias. It has been recommended in the literature that researcher should consider either M=1 (1:1 matching) or M=2 (1:2 matching in most settings when using propensity score matching.[219] Although we proposed to consider 1-to-many matching with M=3, actual number of matched patients in the DES group for each DCB patient varied due to imposing a caliper within the nearest neighbour matching. We restricted the maximum number not to exceed 3. Therefore, on average, the effective matching ratio was similar to what has been recommended in the literature (e.g., 1:2). Allowing a variable number of matched subjects within 1-to-M settings was found to be more effective in reducing bias compared to matching with a fixed number. [219]

Statistical software

We used Stata (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.) for the propensity score matching and the mixed logistic regression analysis. We used the psmatch2 module in Stata for propensity score matching. The mixed effects logistic regression analysis on the matched sample was performed using the xtmelogit command. Any lacks in the capabilities of the Stata module psmatch2 (such matching without replacement for 1-to-many matching) was supplemented by the R software (R Core Team, 2016. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, https://www.R-project.org/). In R, the Matching, MatchIt and Optmatch packages provide implementations of various propensity score matching methods.

Sample size calculation

We estimated the required sample size for the proposed propensity score matched analysis based on the average MACE rate (9.3%) found in three DES studies, and assuming a non-inferiority margin, M=4.5% (absolute risk difference between DCB and DES).

Effect size:

- MACE rates in DES=0.093 (9.3%) – average from three studies [215, 216, 220]
- Non-inferiority margin (M) = 0.045 (4.5%) – the absolute difference in MACE rates between DCB and DES.
- MACE rate difference of 4.5% is equivalent to Odds Ratio (OR) for the upper boundary of the 95% confidence interval = 1.56 (DCB vs. DES)

Chosen statistical power and level of significance:

- Power = 80%
- Level of significance (one-sided) = 0.025

Intra-class correlation (ICC) and variance inflation factor (VIF):

- Assumed ICC of MACE events within matched set: 0.05 (5%)
- VIF= 1+(m-1)*ICC=1.1 (assuming m=3, 1 DCB patient matched to 2 DES patients on average)

Estimated sample size (N):

- Minimum total sample size (N) required (assuming 1:2 allocation ratio) = 1619. The sample size was calculated to achieve 80% power at one-sided 2.5% level of significance. All else remaining the same, the required sample size was 2169 to detect the effect size at 90% power. The sample size calculation has taken into account the possibility that patients' outcomes within matched sets are likely to be correlated (assumed ICC=5%) due to propensity score matching.

Expected available sample size: There were approximately 750 eligible patients in the DCB treated group (hospital database). Using propensity score matching and assuming each DCB treated patient matched to two DES patients on average, we expected to recruit 1500 DES treated patents from the DES cohort. This would have led to a total simple size of 2250 patients from both databases, which is higher than that is required (N=1619) and therefore sufficient to conduct the proposed statistical analyses with adequate statistical power. If the size of matched sample reached 2250, the 4.5% non-inferiority margin could have been detected with 90% power.

2.2.10 Data Quality Assurance

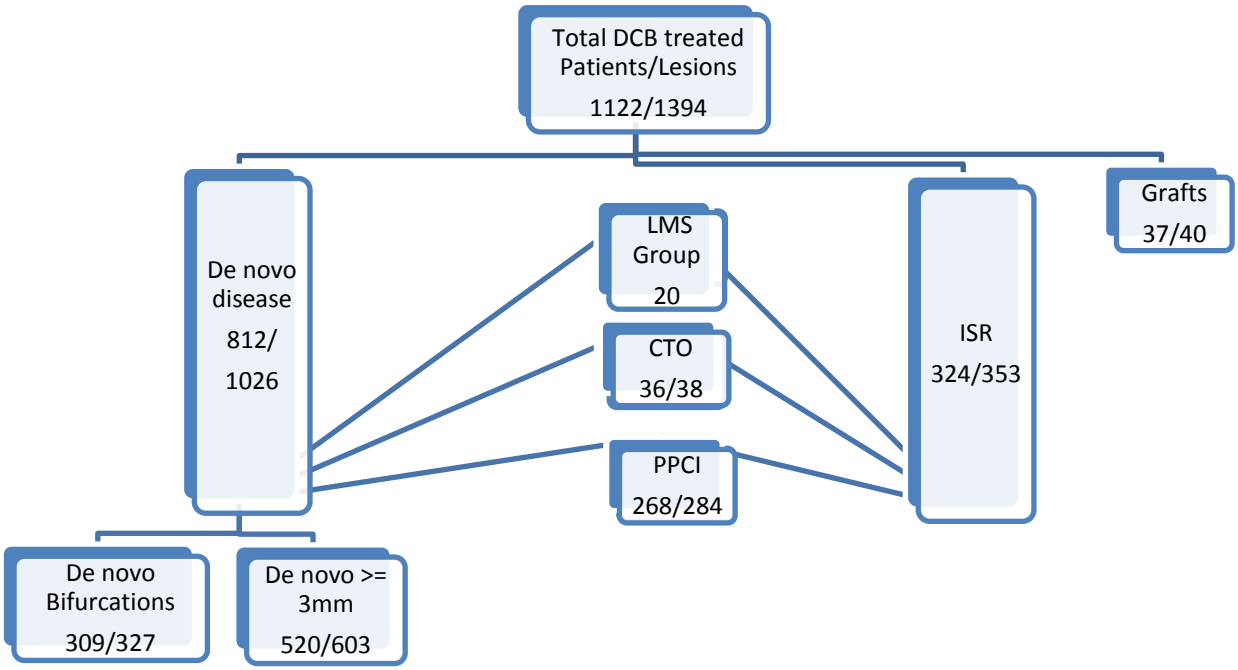
The mechanisms put in place both locally and countrywide to ascertain the data is collected and maintained at highest standards is described in section 2.1.10 in the DCB Norwich registry study.

3 Chapter 3 Results

3.1 DCBNORWICH Registry

A total of 1394 lesions in 1122 patients have been treated with drug coated balloons from 01/01/2009 till 31/12/2015 at Norfolk and Norwich University Hospital. The results will be described separately in three sub chapters for de novo group, in-stent restenosis (ISR) group and for the other sub groups.

Figure 19 Schematic representation of various subgroups of the DCB Norwich registry study



3.1.1 De Novo group

Results of patients who had a native coronary artery treated with PCI for the first time are included in this group.

3.1.1.1 Patient Characteristics

From 01/01/2009 to 31/12/2015, a total of 1026 de novo lesions in 812 patients have been treated with DCB angioplasty. Approximately 40% was for stable angina, 25% for ST elevation MI and 35% for non ST elevation MI/unstable angina. Mean age was 65.8 and vast majority were male patients (75.6%). Table 8 outlines the patient characteristics further.

Table 8 Patient characteristics of de novo group

Attribute	Freq. n 812	Percent
Age mean (SD)	65.8 (12.2) Min 24.0, Max 93.0	
Female/Male	198	24.4%
Previous MI	199	24.5%
Previous PCI	221	27.2%
Previous CABG	33	4.1%
Hypertension	412	50.7%
Dyslipidaemia	297	36.6%
Diabetes	137	16.9%
Family history	189	23.3%
Never smoked	308	37.9%

Ex-smoker	292	36.0%
Current smoker	181	22.3%
Smoking not known	31	3.8%
Stable	324	39.9%
NSTEMI/UA	271	33.4%
STEMI(PPCI)	217	26.7%
Cardiogenic shock	10	1.2
Out of hospital cardiac arrest	18	2.2

MI- myocardial infarction, NSTEMI- non ST elevation MI, STEMI- ST elevation MI, PCI- percutaneous coronary intervention, PPCI- primary percutaneous coronary intervention

3.1.1.2 Lesion/Procedural Characteristics

Table 9 Lesion/Procedural characteristics of the de novo group

Attribute	Freq. (n 1026)	Percent
Access (per patient data) Radial Femoral Right Ulnar	 731 58 1	 90.0 7.1 0.1
Number of vessels treated – 1	576	70.8%
Number of vessels treated - 2 or more	237	29.2%
Lesion Level		
LAD	529	51.6%
RCA	245	23.9%

CX	238	23.2%
LMS	14	1.4%
CTO	30	2.9%
Heavy calcification	222	21.6%
Diffuse disease / small vessel	407	39.7%
Severe tortuosity	174	17.0%
Thrombus present	207	20.2%
Stable	467	45.5%
NSTEMI/UA	329	32.1%
STEMI(PPCI)	230	22.4%
DCB type Sequent please Falcon Sequent please + Falcon Dior	 875 136 14 1	 85.3 13.3 1.4 0.1
Mean (SD) treated lesion length	24.5 (12.5)	
Mean (SD) device diameter	2.9 (0.6)	
Coronary dissections Type A Type B Type C or above	148 41 85 22	14.6 4.0 8.2 2.3
Bail – out stents after DCB During the index procedure During the same hospital stay for acute vessel	42 4	4.1 0.4

closure/instability		
Stents used elective	19	1.8
Drug coated balloon therapy and stent(s)	61	5.9%
DCB-only PCI	965	94.1

As shown in table 8, 217 (26.7%) patients presented with ST elevation MI, whilst 271 patients (33.4%) presented with NSTEMI or unstable angina. This constitutes 60.1% of the de novo patient population. 323 patients (39.9%) had stable angina.

In most patients (90%) access was through the radial artery. One patient had ulnar arterial access and the rest femoral or femoral and radial combination. 576 (70.9%) of the patients had a single vessel treated and 29.1% had two or more vessels treated. 14 (1.4%) were left main stem (LMS) lesions whilst 529 (51.6%) were left anterior descending (LAD) artery lesions. The circumflex artery (Cx) was treated in 238 (23.2%) instances whilst the right coronary artery was treated in 245 (23.9%) patients. Out of the 1026 de no lesions treated 350 (34.1%) were in a bifurcation. 30 (2.9%) were chronic total occlusions.

The most commonly used DCB type was Sequent please (in 881; 85.9% of lesions) and the Inpact falcon was used in 143 (13.9%) lesions. Dior balloon was used in one lesion. The mean (SD) DCB diameter was 2.9 (0.6) mm and in 603 (58.8%) lesions, a DCB with a diameter of 3mm or more was used. The mean (SD) treated length was 24.5. (12.5) mm.

Coronary dissections are classified in to Type A to F as per NHLBI classifications (figure 3, Chapter 1.4.2). There were 148 (14.6%) coronary dissections noted. Out of which 41(4%) were type A coronary dissections, 85 (8.2) type B and 22 (2.3%) type C or above.

In 42 (4.1%) instances, bail out stents were used during the index procedure after DCB angioplasty. 4 (0.4%) further patients had to be taken back for angioplasty with bail out stenting during the first 24 hours after the index procedure due to ongoing chest pain or acute vessel closure. In 19 (1.8%) lesions stents were used electively in addition to the DCB. DCB-only PCI were carried out in 965 (94.1%) lesions.

3.1.1.3 Clinical outcomes

Table 10 Clinical outcomes of the de novo group, DCB Norwich registry study

Outcome	Freq.	Percent
Per patient (n 809)		
All cause death – 30 days	10	1.2%
Death 12 months	29	3.6%
TVR 12 months	40	4.9%
MI 12 months	25	3.1%
MACE (TVR) 12 months	85	10.5%
MACE (TLR) 12 months	66	8.2%
Death at 3 years	61	7.5%
Per lesion (n 1026)		

TLR 12 months	22	2.1%
Acute vessel closure/instability (per lesion)	4	0.4
Definite treated segment thrombosis	0	0.0

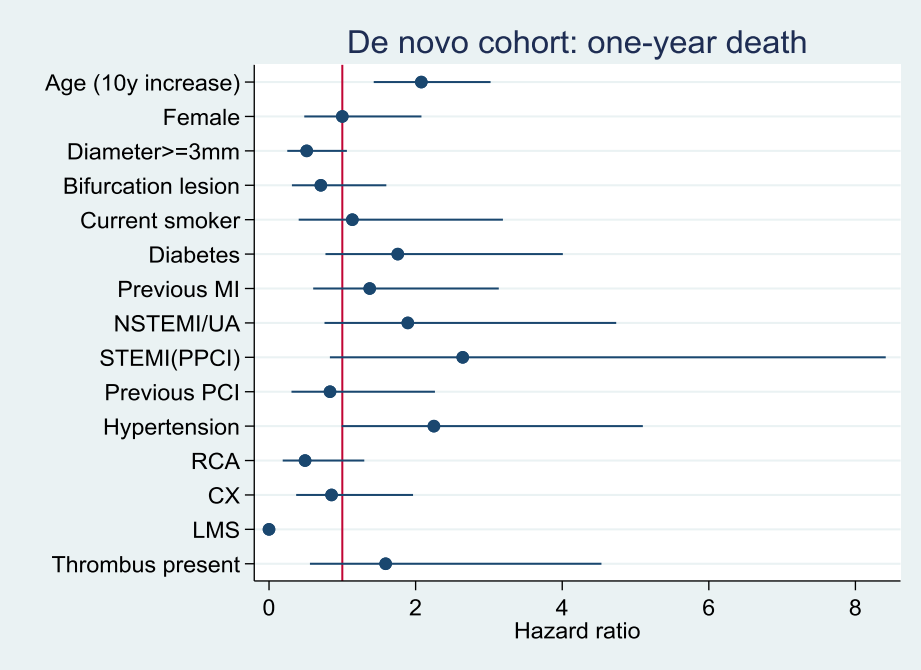
Table 11 Cox regression analysis of the de novo cohort for one year death,

Cox regression de novo cohort: one-year death

	Hazard Ratio	z	P>|z|	[95% Conf	Interval]	Sig
Age (10y increase)	2.078	3.82	0.000	1.428	3.022	***
Female	1.000	-0.00	0.999	0.481	2.079	
Diameter>=3mm	0.514	-1.80	0.072	0.249	1.062	*
Bifurcation lesion	0.707	-0.83	0.406	0.313	1.600	
Current smoker	1.137	0.24	0.808	0.405	3.191	
Diabetes	1.757	1.34	0.181	0.770	4.009	
Previous MI	1.374	0.76	0.450	0.602	3.134	
NSTEMI/UA	1.893	1.36	0.172	0.757	4.736	
STEMI(PPCI)	2.643	1.65	0.100	0.830	8.414	
Previous PCI	0.832	-0.36	0.719	0.306	2.263	
Hypertension	2.249	1.94	0.052	0.992	5.100	*
RCA	0.492	-1.43	0.152	0.186	1.300	
CX	0.853	-0.37	0.709	0.370	1.965	
LMS	0.000	0.00	1.000	0.000	.	
Thrombus present	1.591	0.87	0.385	0.558	4.535	

***** p<0.01, ** p<0.05, * p<0.1**

Figure 20 Forest plot of cox proportional hazard multivariate modelling on one year death, de novo cohort



x axis- hazard ration, y axis- co variate

Figure 21 Kaplan-Meier curve for three year death, de novo cohort

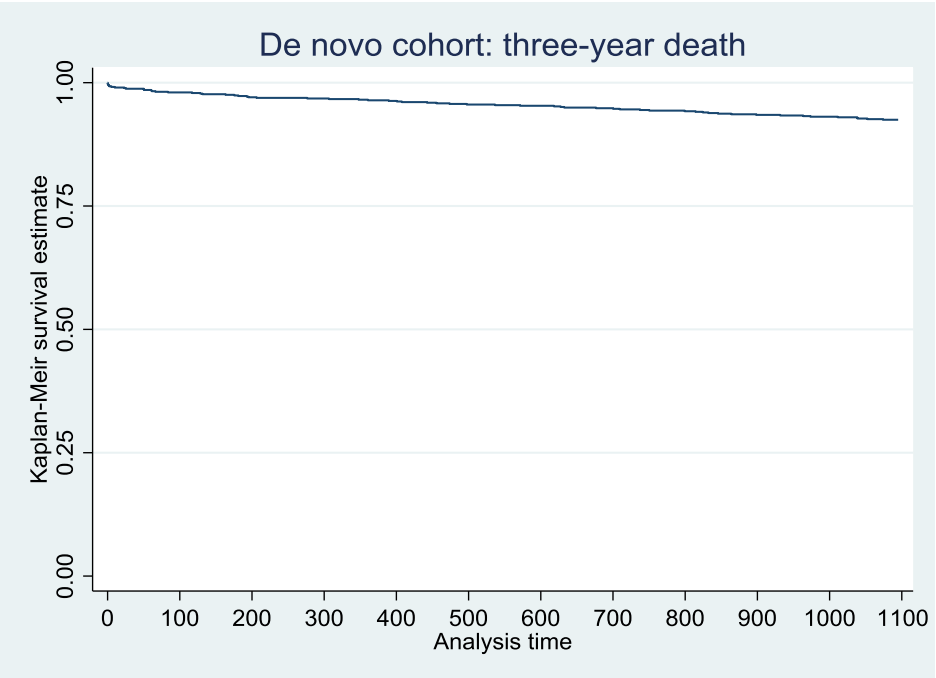


Figure 22 Kaplan-Meier curve for one year target vessel revascularisation (TVR), de novo cohort

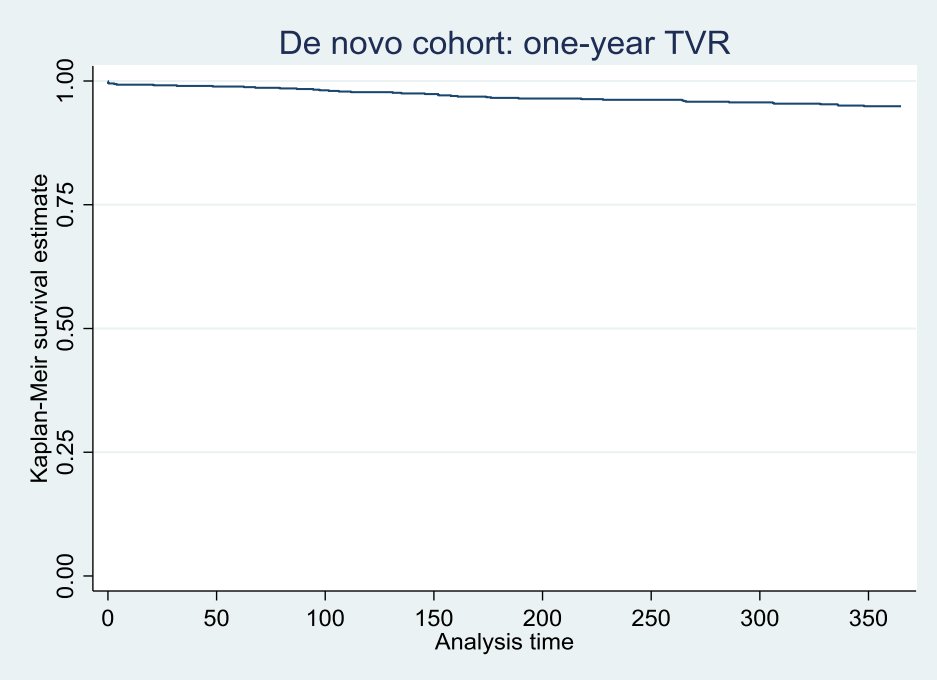
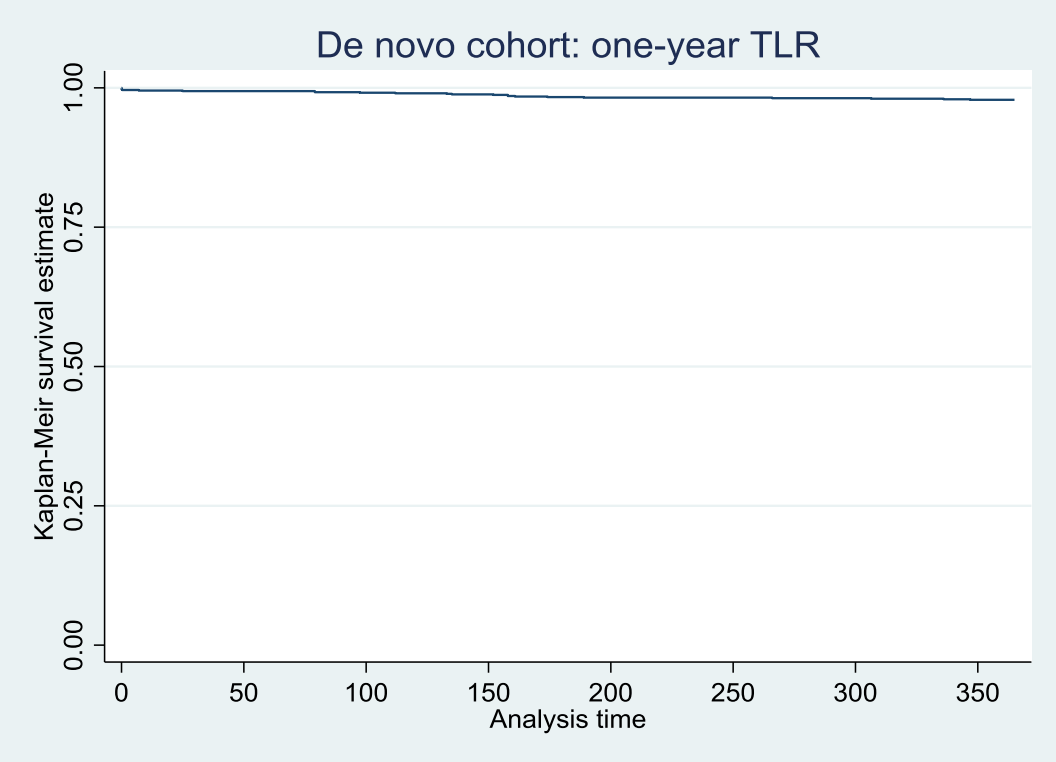


Figure 23 Kaplan-Meier curve for one year target lesion revascularisation, de novo cohort



As the table 10 shows, the 30 day mortality was 1.2% (10 patients). There were 29 (3.6%) deaths within the first year. 11 were cardiac deaths and exact cause of death was not known for 8. 10 others were non-cardiac. We obtained death data from the spine portal of the NHS Digital but it was not possible to obtain cause of death. The information we have on death is from our local records. The details of the 10 cardiac deaths are as follows. One died same day after PCI due to heart failure (known severe left ventricular impairment), same admission day 3 (hypoxic brain injury, presenting with out of hospital cardiac arrest), out of hospital cardiac arrest on day 5 (combination of DES and DCB), MI on day 6 (self-discharged and presented to another hospital on day 6, likely to be non-compliant), cardiac arrest due to a complication following an elective staged PCI day 19, MI on day 24 (angiography not performed as unfit for procedure with poor known left ventricular failure), MI on day 52, STEMI related to another vessel day 61, death due to heart failure and pneumonia at day 62, cardiac arrest during a staged procedure day 129 and MI day 193 (no intervention due to oesophageal Ca). 14 out of the 29 were STEMI presentations as primary PCIs (PPCI). Another 8 were after PCI for acute coronary syndrome. 4 patients have been in cardiogenic shock. 4 patients died due to metastatic cancers (two due to metastatic lung cancer and another due to metastatic renal cancer and a fourth patient had an oesophageal cancer). One patient died due to an intracerebral haemorrhage (day 131 on triple therapy) and another one due to a gastro intestinal haemorrhage day 1. 1 patient died of severe pulmonary hypertension due to obesity and another due to interstitial lung disease (was on home oxygen). 3 patients died due to prolonged hospital stays complicated with pneumonia and heart failure. The numbers of days to death for the 8 patients whose cause of death

is not known are 2, 2, 10, 84, 164, 182, 196 and 348). Table 11 and figure 20 depict the multivariate cox regression analysis on one year death which shows that age (10 year increment) and hypertension were the most predictive variables. Figure 21 shows Kaplan-Meier survival curve for 3 year death, figure 16 for one year TVR and figure 17 for one year TLR.

25 (3.1%) patients had a myocardial infarction (MI) within the first 12 months from the index PCI. Spontaneous myocardial infarction presenting after the index event as well as a peri-procedural infarction that resulted in a troponin rise after an elective procedure (1 patient) was also included. There were 3 deaths following MIs (Day 6, 24 and 61). The patient who died on day 6 is a self-discharged patient following the index PCI therefore carries high chance of non-compliance. The patient who died on day 24 after a MI was an 81 year old known to have severe triple vessel disease and on his recurrent presentation was deemed to be unfit for any intervention due to severe left ventricular impairment and heart failure. The patient who had a MI and died on day 61 presented with an anterior STEMI on the second time and had PCI to LAD whereas the index PCI was to his RCA. Out of the 25 MIs, 6 lead to target vessel revascularisations and 4 of those were target lesion revascularisations. Therefore target vessel MI (MI leading to a repeat revascularisation of the same vessel) is 0.7%. Two of the 25 were ST elevation MIs (day 61 and 359 post index PCI) and both were due to occlusion of another vessel.

There were 40 (4.9%) patients who underwent subsequent target vessel revascularisations within the first 12 months. 8 patients had bypass graft surgeries and the rest were repeat PCIs. No emergency bypass graft surgeries were required. 1

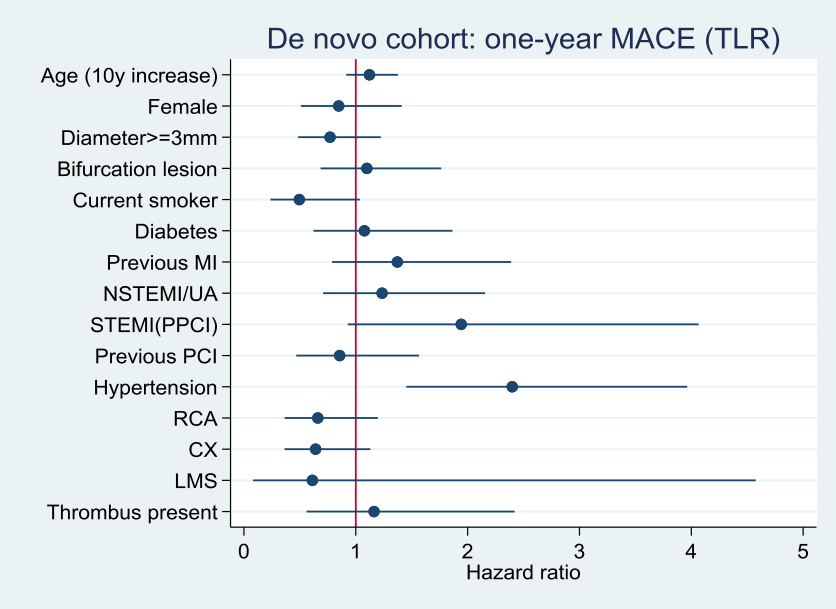
patient underwent CABG at Basildon therefore graft details are not known, assumed TVR as there was distal stenosis. Out of the 40 patients who had target vessel revascularisation, 22 lesions (2.2% per lesion) were target lesion revascularisations. Included are 4 (0.4%) patients who had to be taken back to the catheter laboratory on the same day for suspected acute vessel closure and had repeat PCI to the same lesion. No events definite target lesion thrombosis reported. Table 13 and figure 25 show the multivariate cox regression for one year TLR. STEMI was the most predictive factor for TLR up to one year.

MACE (all cause death, MI, TLR) was 8.2% (66 patients) during the first 12 months. The multivariate cox regression analysis showed that hypertension and STEMI were associated with worst MACE outcomes (table 12 and figure 24). The composite of death, MI and TVR was 10.5% (85 patients).

Table 12 Cox regression de novo cohort: one-year MACE (death, MI, TLR)

	Hazard Ratio	Robust St.Err.	z	P>|z|	[95% Conf	Interval]	Sig
Age (10y increase)	1.122	0.117	1.11	0.268	0.915	1.377	
Female	0.848	0.220	-0.64	0.525	0.509	1.411	
Diameter>=3mm	0.770	0.182	-1.10	0.269	0.484	1.224	
Bifurcation lesion	1.099	0.265	0.39	0.695	0.685	1.764	
Current smoker	0.496	0.187	-1.86	0.062	0.237	1.037	*
Diabetes	1.077	0.301	0.27	0.791	0.622	1.864	
Previous MI	1.372	0.388	1.12	0.264	0.787	2.389	
NSTEMI/UA	1.235	0.351	0.74	0.457	0.708	2.156	
STEMI(PPCI)	1.943	0.732	1.76	0.078	0.929	4.065	*
Previous PCI	0.856	0.264	-0.51	0.614	0.468	1.565	
Hypertension	2.399	0.614	3.42	0.001	1.452	3.963	***
RCA	0.661	0.201	-1.36	0.172	0.364	1.198	
CX	0.641	0.185	-1.54	0.124	0.363	1.130	
LMS	0.612	0.628	-0.48	0.632	0.082	4.576	
Thrombus present	1.163	0.435	0.41	0.685	0.559	2.420	
*** p<0.01, ** p<0.05, * p<0.1							

Figure 24 Forest plot of cox proportional hazard multivariate modelling on one year MACE (TLR), de novo cohort



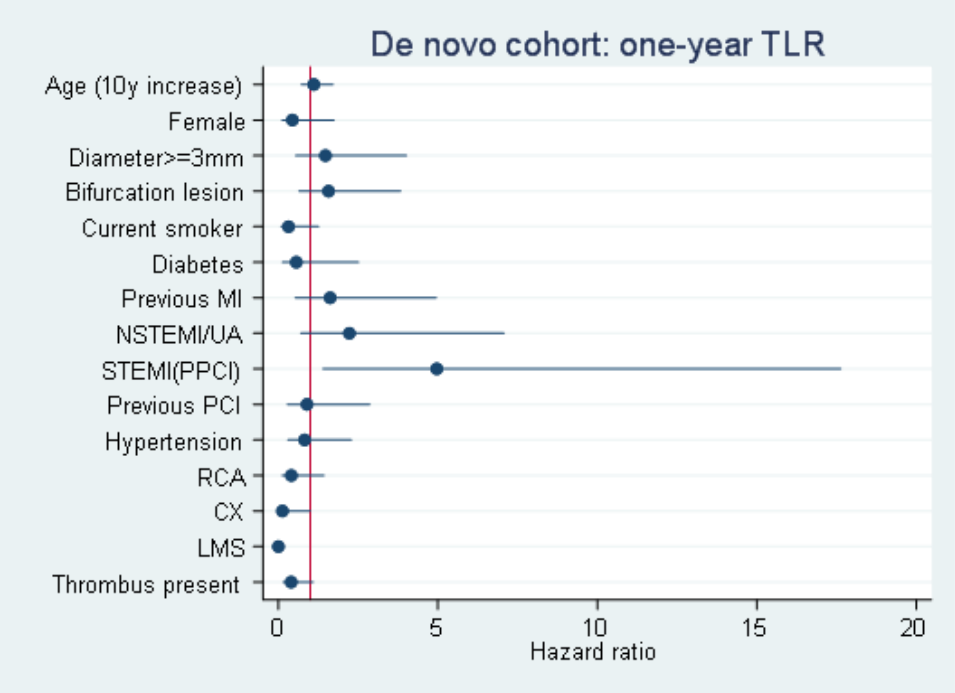
MACE: Major adverse cardiac events, TLR: Target lesion revascularization

Table 13 Cox regression de novo cohort: one-year TLR

	Hazard Ratio	z	P>|z|	[95% Conf	Interval]	Sig
Age (10y increase)	1.111	0.47	0.636	0.719	1.717	
Female	0.440	-1.17	0.243	0.111	1.748	
Diameter>=3mm	1.476	0.76	0.447	0.542	4.019	
Bifurcation lesion	1.573	1.00	0.319	0.645	3.835	
Current smoker	0.318	-1.63	0.104	0.080	1.265	
Diabetes	0.562	-0.76	0.450	0.126	2.511	
Previous MI	1.622	0.85	0.396	0.531	4.953	
NSTEMI/UA	2.225	1.36	0.175	0.700	7.073	
STEMI(PPCI)	4.966	2.48	0.013	1.399	17.631	**
Previous PCI	0.897	-0.18	0.855	0.281	2.868	
Hypertension	0.822	-0.38	0.707	0.295	2.287	
RCA	0.406	-1.40	0.160	0.116	1.428	
CX	0.127	-1.96	0.050	0.016	0.999	*
LMS	0.000	-64.96	0.000	0.000	0.000	***
Thrombus present	0.401	-1.79	0.073	0.147	1.091	*

***** p<0.01, ** p<0.05, * p<0.1**

Figure 25 Forest plot of cox proportional hazard multivariate modelling on one year target lesion revascularization (TLR), de novo cohort



3.1.2 De novo Bifurcations

Percutaneous coronary intervention (PCI) in a lesion involving a side branch of 2mm or more (visual assessment) was considered a bifurcation lesion and is included in this analysis. This cohort is comprised of only de novo bifurcation lesions and not the in-stent restenosis lesions.

There were 327 lesions in 309 patients. For this analysis if both coronary branches/arms were treated in a bifurcation lesion, it was considered as a single lesion rather than two separate lesions. Mean age was 66, predominantly male and almost half were due to some form of an acute coronary syndrome (48.3%) (Table 14).

Table 14 Demographics for de novo bifurcation cohort

Attribute	Frequency (n 309)	%
Number of patients	309	
Number of lesions	327	
Male/Female	237	76.7%
Mean Age (SD)	66 (12.2)	
STEMI/NSTEMI/UA	158	48.3%
Stable	169	51.7%
Out of hospital cardiac arrest	6	1.9%

Lesion Characteristics

Predominantly LAD/D1 bifurcations have been treated. 37.1% of lesions were true bifurcation lesion i.e. Medina 1,1,1 or 0,1,1 lesions. 21 lesions have both branches/arms treated. Of note there were 10 lesions involving the left main stem.

Table 15 Lesion characteristics of de novo bifurcation lesions

Attribute	Frequency (n 327)	%
Left main stem (LMS)	10	3.1%
LAD/D	208	63.6%
Circumflex (Cx)	87	26.6%
RCA	22	6.7%
Bifurcation type Medina 1.1.1 Medina 0.1.1 Other Medina types	 95 26 206	 29.1% 8.0% 62.9%
Side branch occlusions (Peri procedural, flow regained in all)	4	1.2%

Medina classification is explained in section 1.3.3

Procedural characteristics

Most procedures were done using radial access. Mean DCB diameter was 3mm and 59% had a DCB diameter of 3mm or more. 15% had some form of a coronary dissection and 2 (0.6%) had bail out stenting during the procedure and another 5.2% had additional stent/s placed. Accordingly 94.2% had DCB only PCI. Vast majority were paclitaxel eluting Sequent please DCBs.

Table 16 Procedural characteristics for de novo bifurcation lesions

Attribute	Frequency (n 327)	%
Radial access	292	89.3%
Mean (SD) DCB diameter	2.9 (0.5) mm	
DCB diameter of 3mm or more	193	59.0%
Mean (SD) length	24.2 (11.3) mm	
IVUS/OCT	23	7.0%
Guideliner	29	8.9%
Cutting/scoring balloon	22	6.7%
Rotational atherectomy	3	1.0%
Coronary dissections Type A and B Type C and above	 46 3	 14.1% 0.9%

Additional stents during the index procedure	17	5.2%
DCB-only PCI	310	94.8%
Bail-out stents during the index admission	2	0.6%
DCB Type Sequent please Falcon Dior	 283 43 1	 86.5% 13.1% 0.3%

Clinical Outcomes

Table 17 Clinical outcomes for de novo bifurcation cohort

Clinical outcomes for all patients – 12 months	Number (%)
Per Patient (n 309)	
All cause death	8 (2.6%)
MI	12 (3.8%)
TVR	14 (4.5%)
death, MI, TVR	31 (10.0%)
MACE (death, MI, TLR)	27 (8.7%)
Per Lesion (n 327)	
TLR	10 (3.1%)

12 months all cause death was 2.6% (8 patients). 4 were primary PCIs and 1 patient was ventilated pre PCI. Another was in cardiogenic shock requiring IABP. 12 (3.8%) patients returned with a myocardial infarction after the index procedure but only two of them required target vessel revascularisations. Out of the 12 one was a STEMI but this was due to occlusion of a different vessel.

There were 14 (4.5%) target vessel revascularisations (TVR). 2 were after acute myocardial infarctions. Out of the 14 TVRs 10 (3.1%) were target lesion revascularisations (TLR). There were neither acute vessel closures nor definite treated lesion thrombosis during the first 12 months.

Out of the 47 lesions with coronary dissections, none had target lesion revascularisation within the first 12 months. Two returned with MI's, one due to severe disease in a non-target vessel requiring further PCI and a second at 253 days post PCI (presented to another local DGH) but has not had further angiography or revascularisation. 1 patient died due on day 173 due to metastatic renal cell carcinoma.

Comparison of bifurcation and non-bifurcation lesions.

We carried out a comparison between the bifurcation lesions and the non-bifurcation lesions as bifurcations are generally considered to be a high risk group. As above, all lesions which involved a side branch of 2mm or more on visual assessment were included in the bifurcation arm and other lesions in the non-bifurcation arm. If a patient has had both a bifurcation and a non-bifurcation treated he/she was attributed to the bifurcation arm for the comparison's sake.

Patient characteristics are as described in the table below. Apart for the indication (higher percentage of ACS/MI patients in the non-bifurcation group) other variables were well matched.

Table 18 Comparison of de novo bifurcation and non-bifurcation cohorts: demographics

Attribute	Non-bifurcation (n=503)		Bifurcation (n=309)		P-value†
	Freq.	Percent	Freq.	Percent	
Female	126	25.0%	72	23.3%	0.573
Previous MI	115	22.9%	76	24.6%	0.572
Previous PCI	121	24.1%	88	28.5%	0.162
Previous CABG	19	3.8%	14	4.5%	0.598
Hypertension	256	50.9%	155	50.2%	0.839
Dyslipidaemia	180	35.8%	115	37.2%	0.680
Diabetes	86	17.1%	51	16.5%	0.827
Fhx of CAD	111	22.1%	76	24.6%	0.406
Current smoker	119	23.7%	63	20.4%	0.278
Indication					<0.001
Stable	177	35.2%	156	50.5%	
NSTEMI/UA	163	32.4%	105	34.0%	
STEMI(PPCI)	163	32.4%	48	15.5%	
Cardiogenic shock	9	1.8%	1	0.3%	0.066
Attribute	Mean	SD	Mean	SD	
Age (y)	65.9	12.2	65.5	12.2	0.633

* Patient taken as "bifurcation" if any bifurcation lesion, only bifurcation lesions taken if patient has both types
† Based on χ^2 tests for categorical variables and t-tests for continuous

Lesion characteristics

Table below describes the lesion characteristics. Apart from vessel treated and presence of thrombus, the two groups appeared well matched.

Table 19 De novo bifurcation and non-bifurcation comparison: lesion characteristics

Attribute	Non-bifurcation (n=584)		Bifurcation (n=327)		P-value†
	Freq.	Percent	Freq.	Percent	
Vessel treated					<0.001
LAD	267	45.7%	208	63.6%	
RCA	189	32.4%	22	6.7%	
CX	127	21.7%	87	26.6%	
LMS	1	0.2%	10	3.1%	
Device diameter ≥3mm	355	60.8%	193	59.0%	0.601
Diffuse disease / small vessel	223	38.2%	135	41.3%	0.358
Heavy calcification	109	18.7%	83	25.4%	0.017
Thrombus present	149	25.5%	49	15.0%	<0.001
Severe tortuosity	87	14.9%	67	20.5%	0.031
Drug coated balloon therapy and stent(s)	39	6.7%	17	5.2%	0.373
Bail out stent	27	4.6%	11	3.4%	0.362
CTO	16	2.7%	10	3.1%	0.782
Attribute	Mean	SD	Mean	SD	
Longest stented / treated section	24.6	12.6	24.2	11.3	0.5937
Device diameter (n=632/371)	2.96	0.61	2.87	0.54	0.0159

† Based on χ^2 tests for categorical variables and t-tests for continuous

Clinical Outcomes

Clinical outcomes are described in table 20 and 21. There was no significant difference in individual outcomes as well as MACE. Apart for death, other outcomes were numerically better for non-bifurcation lesions. Figures 20, 21, 22, 23 and 24 show the KM survival curves for three year death, one year MI, MACE, TVR and TLR for the bifurcation and non-bifurcation group. The survival curves are almost overlapping each other indicating a non- significant difference.

Table 20 De novo bifurcation vs. non bifurcations: patient level clinical outcomes

Outcome	Non-bifurcation (n=503)		Bifurcation (n=309)		Log rank p
	Freq.	Percent	Freq.	Percent	
TVR by one year	22	4.4%	14	4.5%	0.909
MI by one year	12	2.4%	12	3.9%	0.22
MACE (death, MI, TLR) by one year	38	7.6%	27	8.7%	0.535
Dead by one year	21	4.2%	8	2.6%	0.242
Dead by three years	38	7.6%	23	7.4%	0.939

Table 21 Lesion-level outcomes: bifurcation vs non-bifurcation

Outcome	Non-bifurcation (n=584)		Bifurcation (n=327)		
	Freq.	Percent	Freq.	Percent	
TLR by one year	10	1.7%	9	2.8%	0.289

Figure 26 Kaplan-Meier curve for three year death, bifurcation vs. non bifurcation lesion comparison

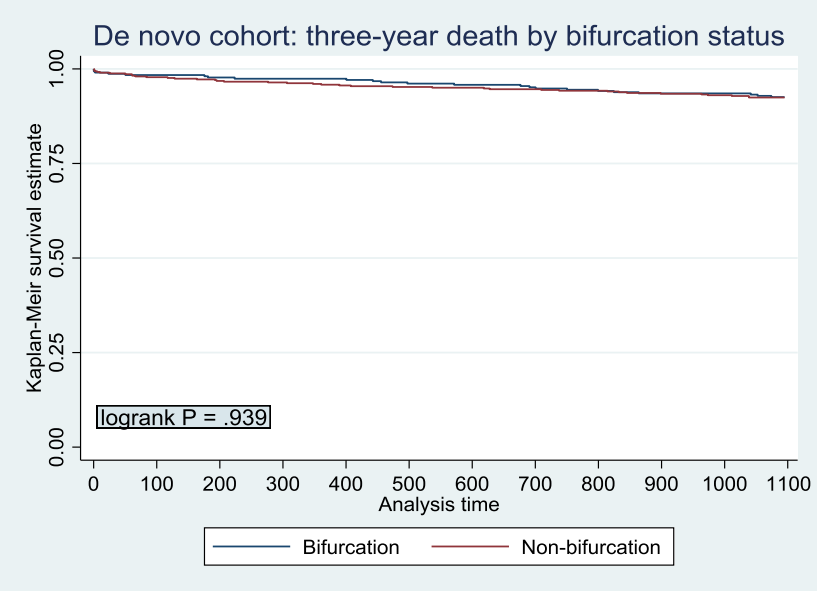


Figure 27 Kaplan-Meier curve for one year myocardial infarction (MI), bifurcation vs. non bifurcations

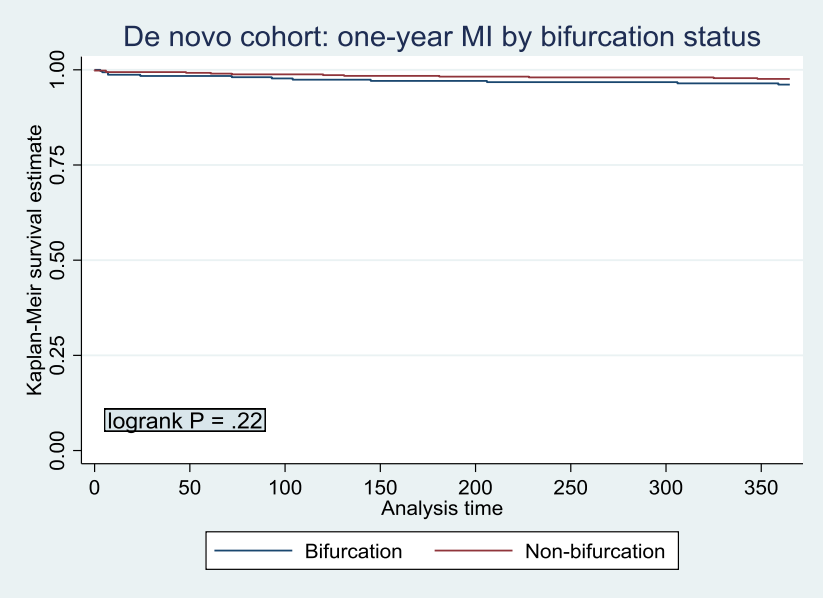


Figure 28 Kaplan-Meier curve for one year target vessel revascularisation (TVR), bifurcation vs. non bifurcations

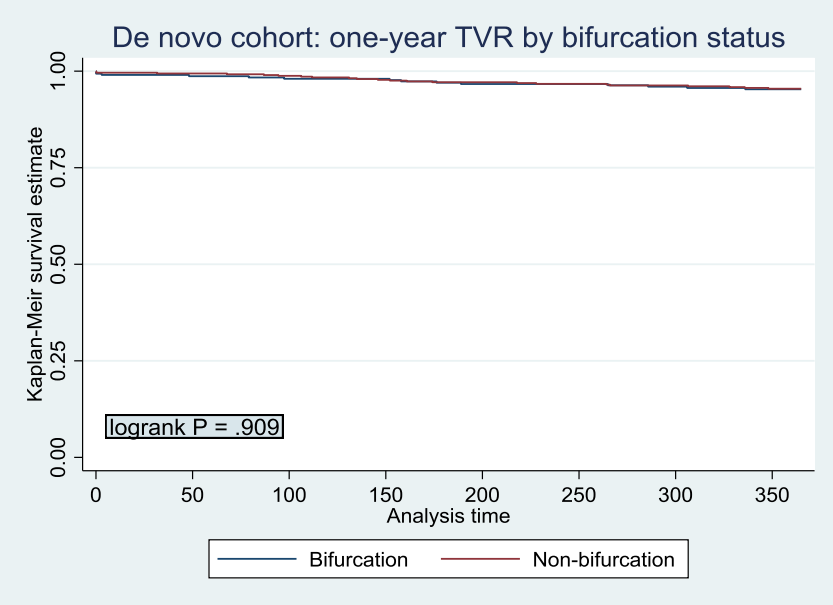


Figure 29 Kaplan-Meier curve for one year major adverse cardiac events (MACE with target lesion revascularisation/TLR), bifurcation vs. non bifurcations

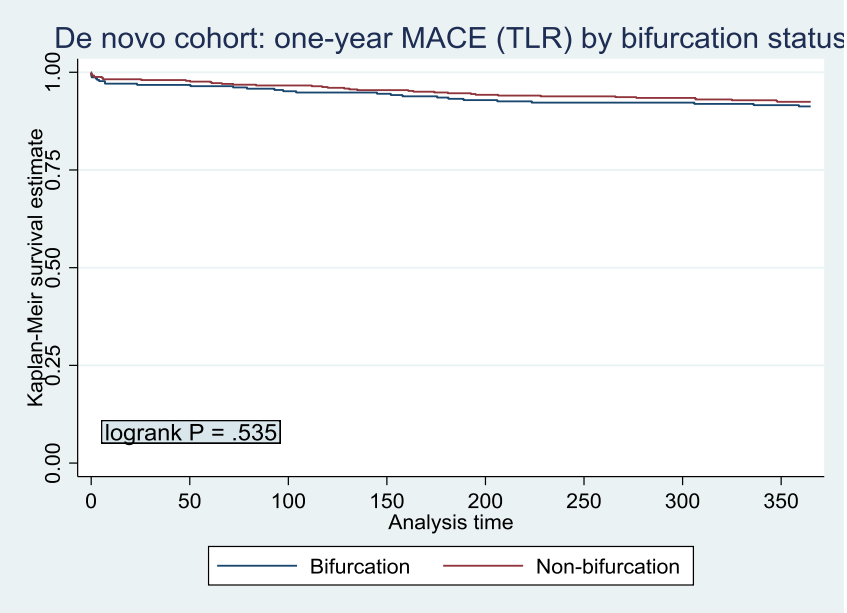
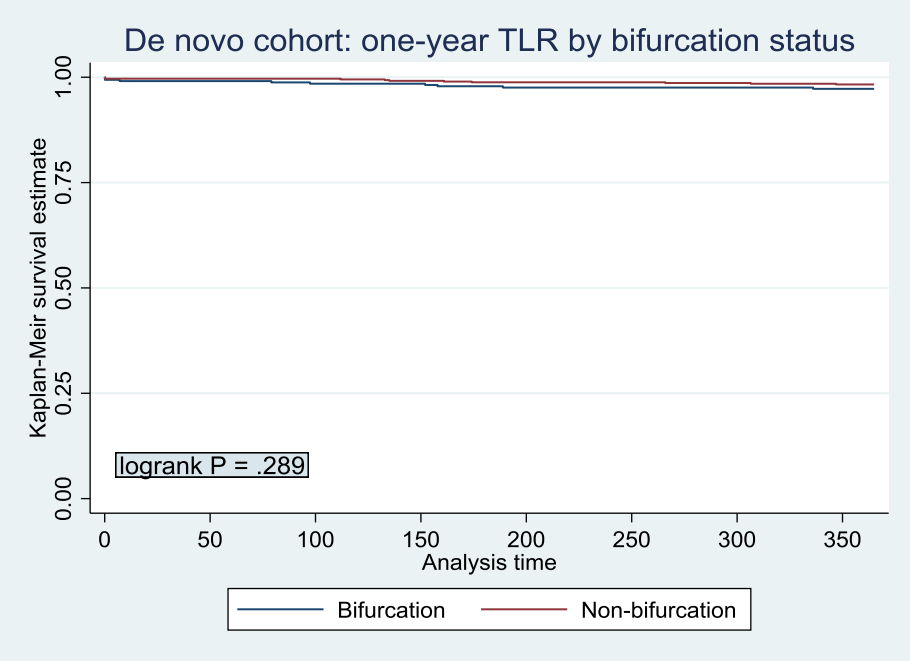


Figure 30 Kaplan-Meier curve for one year target lesion revascularisation (TLR), bifurcation vs. non bifurcations



3.1.3 De novo large vessel cohort

All lesions treated with a DCB diameter of 3mm or more were considered as large vessel lesions for this analysis. This cohort includes 603 lesions in 520 patients. We carried out a comparison between vessels treated with a device diameter of <3mm and =>3mm to find out whether there is any difference in outcomes. Table 22 describes the patient characteristics of the two groups whilst lesion characteristics are described in the table 23.

Table 22 De novo large vessels vs. small vessels, patient characteristics

Attribute	Device diameter <3mm (n=292)		Device diameter ≥3mm (n=520)		P-value†
	Freq.	Percent	Freq.	Percent	
Female	101	34.6%	97	18.7%	<0.001
Previous MI	77	26.4%	110	21.2%	0.090
Previous PCI	93	31.8%	112	21.5%	0.001
Previous CABG	14	4.8%	18	3.5%	0.349
Hypertension	164	56.2%	248	47.7%	0.020
Dyslipidaemia	119	40.8%	176	33.8%	0.050
Diabetes	57	19.5%	79	15.2%	0.113
Family history	72	24.7%	116	22.3%	0.446
Current smoker	53	18.2%	130	25.0%	0.025
Indication					<0.001
Stable	144	49.3%	183	35.2%	
NSTEMI/UA	84	28.8%	184	35.4%	
STEMI(PPCI)	64	21.9%	153	29.4%	
Cardiogenic shock	2	0.7%	8	1.5%	0.290
Attribute	Mean	SD	Mean	SD	
Age (y)	66.6	11.5	65.3	12.5	0.155

* Patient taken as "device diameter≥3mm" if any lesion had device diameter ≥3mm
† Based on χ^2 tests for categorical variables and t-tests for continuous

Table 23 De novo large vessels vs. small vessels, lesion characteristics

Attribute	Device diameter <3mm (n=333)		Device diameter ≥3mm (n=603)		P-value†
	Freq.	Percent	Freq.	Percent	
Vessel treated					<0.001
LAD	184	55.3%	287	47.6%	
RCA	43	12.9%	191	31.7%	

CX	105	31.5%	112	18.6%	
Graft	1	0.3%	13	2.2%	
LMS	0	0.0%	0	0.0%	
Bifurcation lesion	112	33.6%	193	32.0%	0.611
Diffuse disease / small vessel	205	61.6%	151	25.0%	<0.001
Heavy calcification	61	18.3%	142	23.5%	0.063
Thrombus present	41	12.3%	164	27.2%	<0.001
Severe tortuosity	67	20.1%	92	15.3%	0.058
Drug coated balloon therapy and stent(s)	21	6.3%	38	6.3%	0.998
Bail out stent	8	2.4%	32	5.3%	0.035
Chronic total occlusion	12	3.6%	15	2.5%	0.329
Out of hospital cardiac arrest	7	2.1%	11	1.8%	0.767
Attribute	Mean	SD	Mean	SD	
Longest stented / treated section	24.6	13.2	24.6	12.2	0.983
Device diameter (n=364/665)	2.35	0.25	3.30	0.41	<0.001

† Based on χ^2 tests for categorical variables and t-tests for continuous

In the comparison between the two groups, the large vessel group had a higher percentage of patients who presented with acute myocardial infarction or acute coronary syndrome. Also a higher percentage of lesions in the large vessel group had thrombus in them

Clinical outcomes

There was no significant difference in one year death, three years death, one year TVR and one year TLR, although numerically death rates were higher in the smaller vessel group (table 25 and 26). Figures 31, 32, 33, 34 and 35 show the KM survival curves for three year death, one year MI, TVR, TLR and MACE.

Table 24 De novo large vessels vs. small vessels, patient-level clinical outcomes

Outcome	Device diameter <3mm (n=292)		Device diameter ≥3mm (n=520)		Log rank p
	Freq.	Percent	Freq.	Percent	
TVR by one year	13	4.5%	26	5.0%	0.77
MI by one year	9	3.1%	16	3.1%	0.981
MACE (death, MI, TLR) by one year	23	7.9%	42	8.1%	0.885
Death by one year	15	5.1%	14	2.7%	0.069
Death by three years	27	9.2%	34	6.5%	0.147

Table 25 De novo large vessels vs. small vessels, lesion-level outcomes

Outcome	Device diameter <3mm (n=333)		Device diameter ≥3mm (n=603)		Log rand p
	Freq.	Percent	Freq.	Percent	
TLR by one year	4	1.2%	15	2.5%	0.183

Figure 31 Kaplan-Meier curve for three year death, de novo small vs. large vessel disease

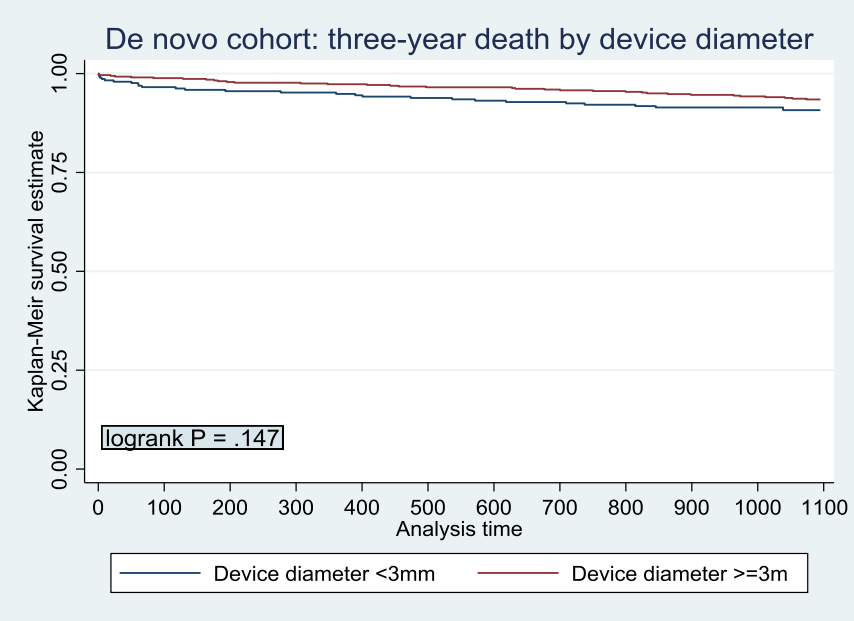


Figure 32 Kaplan-Meier curve for one year myocardial infarction, de novo small vessel vs. large vessel disease

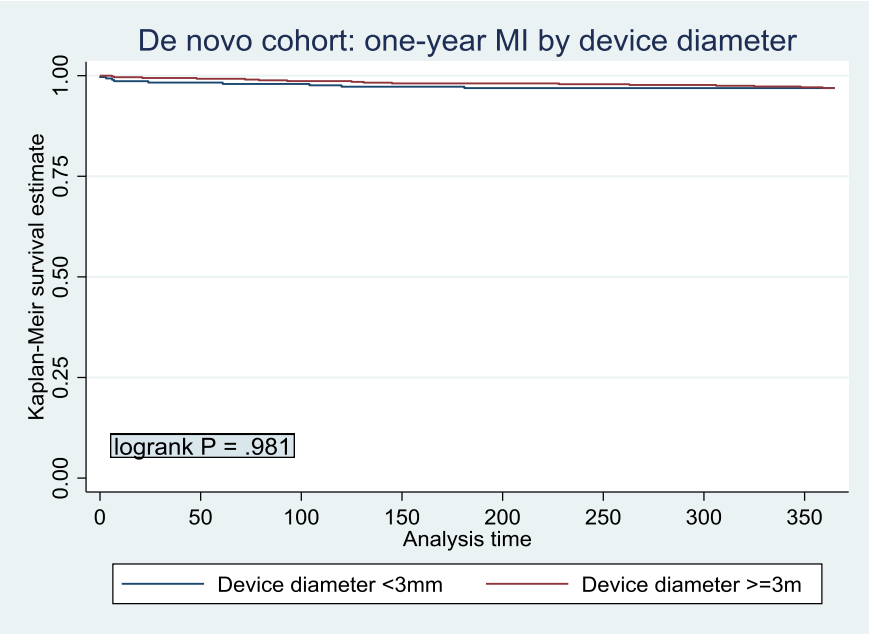


Figure 33 Kaplan-Meier curve for one year target vessel revascularisation (TVR), de novo small vessel vs. large vessel disease

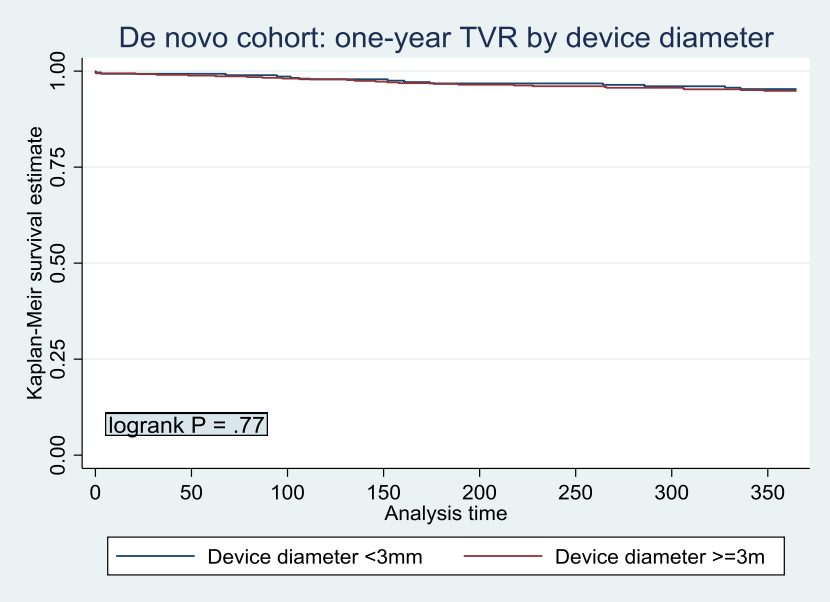


Figure 34 Kaplan-Meier curve for one year target lesion revascularisation (TLR), de novo small vessel vs. large vessel disease

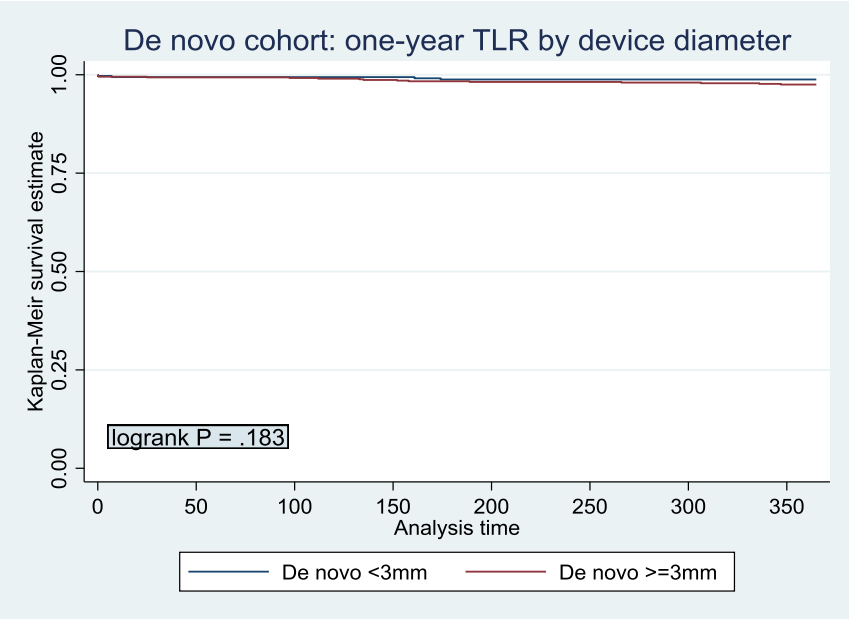
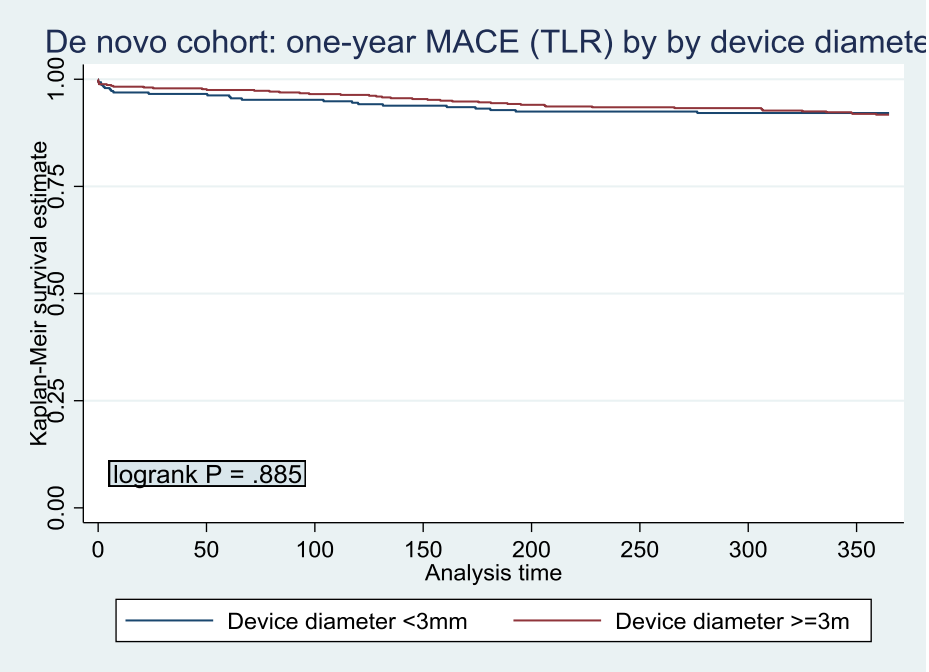


Figure 35 Kaplan-Meier curve for one year MACE with TLR, de novo small vessel vs. large vessel disease



3.1.4 Primary PCI cohort

DCB-only treated primary PCI cohort is another important group in this registry. There were 284 lesions in 268 patients treated. Vast majority (81%) were de novo lesions and large vessels with a device diameter of 3mm or more (73.2%). 3.7% were in cardiogenic shock 6.3% were out of hospital cardiac arrests. Patient characteristics are described in table 26.

Table 26 Patient demographics; primary percutaneous coronary intervention (PPCI) cohort

Attribute (n 268)			Freq.	Percent
Female			71	26.5%
Previous MI			60	22.4%
Previous PCI			64	23.9%
Previous CABG			5	1.9%
Hypertension			123	45.9%
Dyslipidaemia			78	29.1%
Diabetes			29	10.8%
Family history of CAD			45	16.8%
Current smoker			90	33.6%
Cardiogenic shock			10	3.7%
Out of hospital cardiac arrest			17	6.3%
Ventilated prior to PCI			8	3%
Attribute	Min	Max	Mean	SD
Age (y)	36	95	65.3	13.6

Lesion and Procedural characteristics

There were 205 (72.2%) lesions with thrombus and in 87.5% of them thrombus aspiration was carried out. This constitutes 63.4% of total lesions. In 135 (50.4%) lesions glycoprotein IIb/IIIa inhibitors was used. All patients are treated with a loading dose of aspirin 300mg and Clopidogrel 600mg by the paramedical team unless there was an absolute contraindication and 67 (23.6%) lesions were treated with aspirin and clopidogrel whilst 192 (67.6%) lesions were treated with a combination of aspirin and

Ticagrelor post PCI. 90.1% patients had DCB-only PCI.

Table 27 Lesion-level attributes (n=284); PPCI cohort

Attribute (n 284)	Freq.	Percent
Vessel treated		
LAD	127	44.7%
RCA	102	35.9%
CX	51	18.0%
LMS	2	0.7%
De novo disease	230	81.0%
ISR/stent thrombosis	54	
Device diameter >=3mm	208	73.2%
Diffuse disease / small vessel	80	28.2%
Bifurcation	64	22.5%
Heavy calcification	45	15.8%
Thrombus present	205	72.2%
Thrombus aspiration	180	63.4%
TIMI 0 flow pre PCI	175	61.6%
TIMI III flow post PCI	267	94.0%
Glycoprotein IIb/IIIa inhibitors	135	50.4%
Severe tortuosity	33	11.6%
Coronary dissections A,B	11	
Coronary dissection type C and above	8	
Drug coated balloon therapy and stent(s)	28	9.9%
Bail out stent	14	4.9%
DCB-only PCI	256	90.1%

Attribute	Min	Max	Mean	SD
Longest stented / treated section	10	100	25.9	13.9
Device diameter (n=289)	2	4	3.18	0.59

Clinical Outcomes

30 day all cause death was 6 (2.2%). One year death was 16 (6.0%). MI by one year was 8 (3.0%). TVR by one year was 20 (7.5%). Target lesion revascularization (TLR) was 10 (3.5%). MACE (TVR) was 40 (14.9%) whilst MACE with TLR was 31 (11.6%) All-cause mortality at 3 years was 32 (11.9%). There were two acute vessel closures 0.7% which were bailed-out with stents with no further complications at 12 months. No events of definite lesion thrombosis. Table 28 describes the clinical outcomes and

figures 36-38 show the CM curves for three year death, one year MACE and one year TLR.

Table 28 Clinical outcomes; PPCI cohort

Outcomes (n 268)	Freq.	Percent
Per patient (n 268)		
Death 30 days	6	2.2%
Death 12 months	16	6.0%
MI 12 months	8	3.0%
TVR 12 months	20	7.5%
MACE (death, MI, TLR) 12 months	31	11.6%
Dead by three years	32	11.9%
Per lesion (n 284)		
TLR by one year (per lesion)	10	3.5%

Figure 36 Kaplan-Meier curve for three year death; PPCI cohort

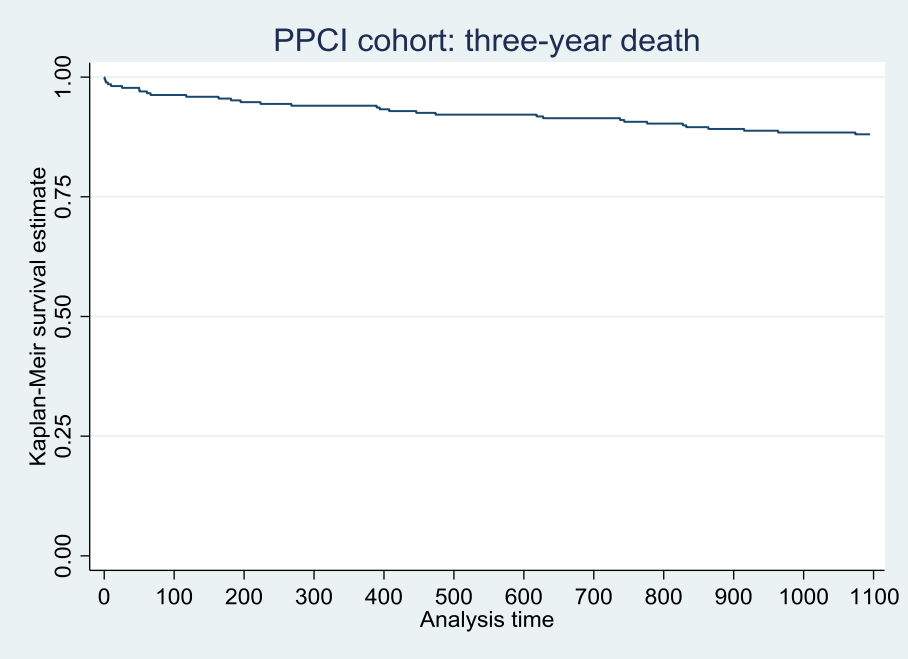


Figure 37 Kaplan-Meier curve for one year MACE (death, MI, TLR); PPCI cohort

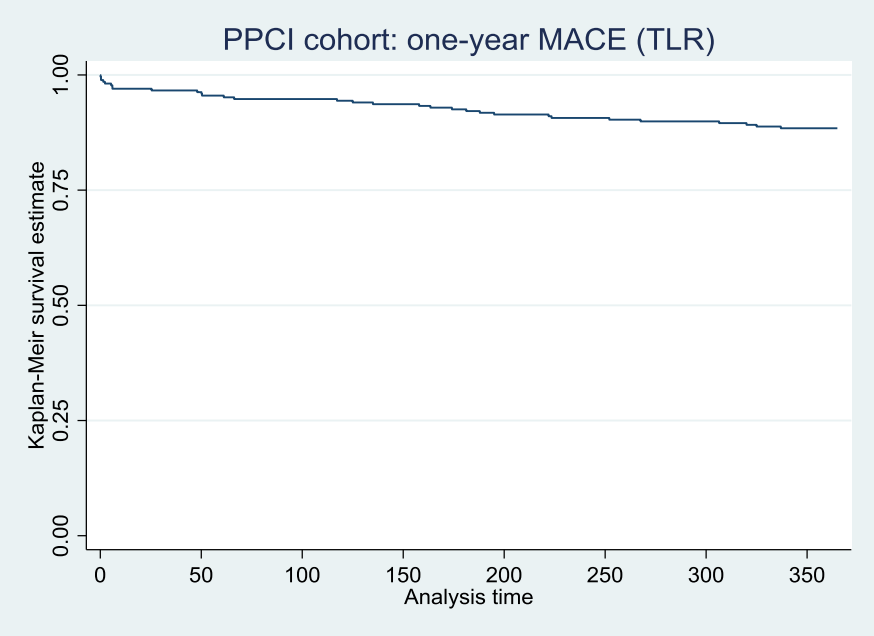
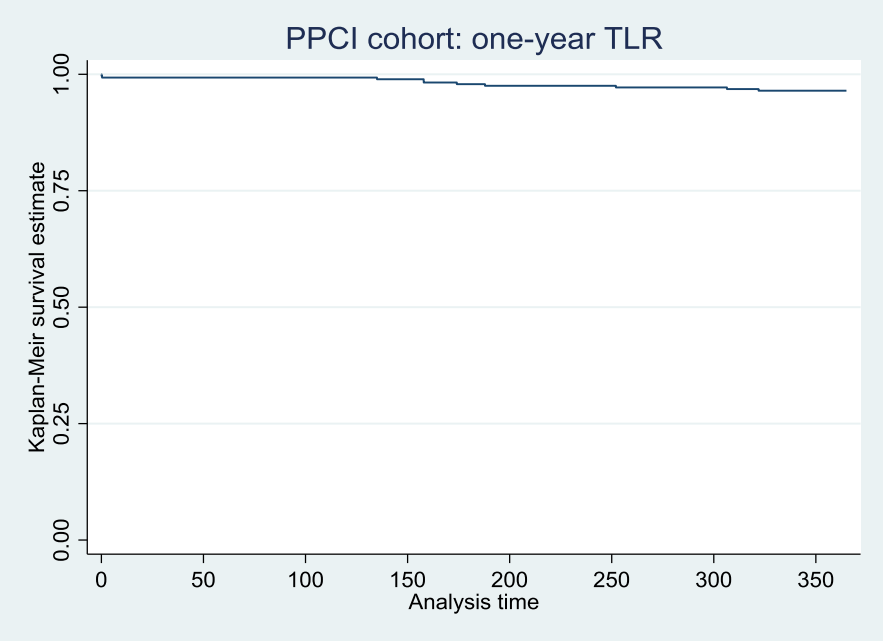


Figure 38 Kaplan-Meier curve for one year target lesion revascularisation (TLR); PPCI cohort



3.1.5 Left Main Stem Cohort

20 patients who received DCB-only PCI (consecutive patients) during the study period are described in this section. Mean (SD) age was 68.8(10.6) and 13 were unprotected LMS patients. 14 were de novo lesions. Patient level characteristics are described in table 29.

Table 29 Left main stem cohort; patient-level attributes (n=20)

Attribute (n20)			Freq.	Percent
Female			4	20.0%
Previous MI			9	45.0%
Previous PCI			10	50.0%
Previous CABG			7	35.0%
Hypertension			14	70.0%
Dyslipidaemia			16	80.0%
Diabetes			5	25.0%
Family history of CAD			4	20.0%
Current smoker			2	10.0%
Attribute	Min	Max	Mean	SD
Age (y)	46	87	68.8	10.6

Lesion and procedural characteristics are described in table 30.

Table 30 Left main stem cohort; Lesion-level attributes (n=20)

Attribute (n 20)	Freq.	Percent
Unprotected LMS	13	65%
De novo lesions	14	70%
STEMI	2	10%
NSTEMI	7	35%
Stable	11	55%
Bifurcation	15	75.0%
Heavy calcification	7	35.0%
Thrombus present	1	5.0%

Drug coated balloon therapy and stent(s)			1	5.0%
DCB only PCI			191	95.0%
Attribute	Min	Max	Mean	SD
Longest stented / treated section	10	60	22.8	10.8
Device diameter (n=20)	2.5	4	3.63	0.51

Outcomes

Apart from a MI due to a distal LAD occlusion at 21 days post index PCI, there were no other adverse outcomes. There was one death up to three years follow up. An 87 year old patient died due to pneumonia 497 days after PCI. No cerebro vascular accidents up to one year. Figure 39 shows the KM curve for three year death.

Table 31 Left main stem cohort; patient - level outcomes

Outcomes 12 months	Freq.	Percent
Death	0	0.0%
MI	1	5.0%
TVR	0	0.0%
TLR	0	0.0%
MACE (TLR) by one year	1	5.0%
MACCE*	1	5.0%
Dead by three years	1	5.0%

** MACCE: Major adverse cardiac and cerebral events (death, MI, TLR, Stroke)

Figure 39 Kaplan- Meier curve for three years death; left main stem cohort

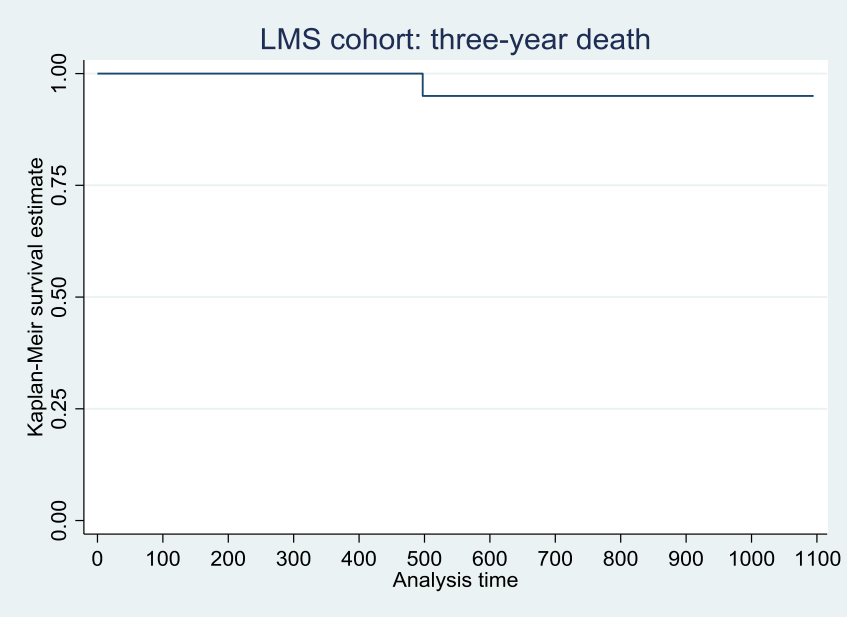


Figure 40 (a) shows critical distal LMS disease with Thrombolysis In Myocardial Infarction (TIMI) II flow. Figure 34(b) shows follow up angiographic appearance after 4 months from DCB-only angioplasty to LMS.

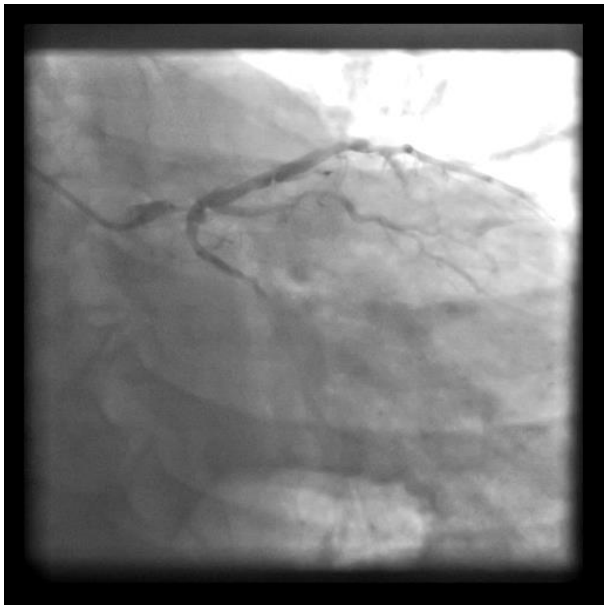


Figure 40 (a)

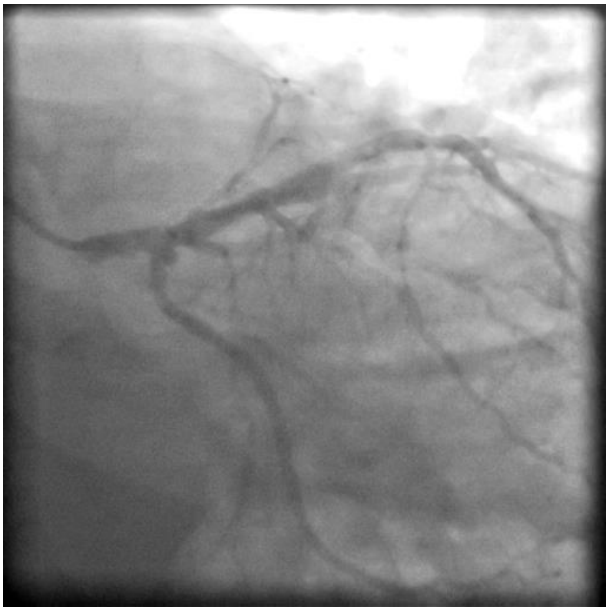


Figure 40 (b)

3.1.6 Chronic total occlusions (CTO)

Results of 38 consecutive chronic total occlusions in 36 patients treated with DCB angioplasty during the study period (01/01/2009 to 31/12/2015) is described in this section.

Method of treatment and all aspects of the procedure were at the discretion of the operator. There is a dedicated CTO list and two experienced operators perform the procedure. Dual access was gained as felt appropriate by the operator/s and guide catheters, wires, crossing technique and other adjunctive devices used were at their discretion. DCB was applied only as a mode of drug delivery after successful recanalization and lesion preparation. A DCB with a 1:1 balloon-to-artery ratio was inflated for 30 to 60 seconds. Patients were monitored overnight prior to discharge. The German consensus guidelines on DCB angioplasty was followed generally i.e. greater

than 30% residual stenosis or dissections of more than type B of National Heart, Lung, and Blood Institute (NHLBI) classification were considered for bail-out stenting however this was not adhered to strictly, given higher occurrence of dissections in this cohort. Bail-out stenting was an individual patient based decision considering factors such as grade of dissection, TIMI flow grade and haemodynamic status. Patient level characteristics are described in table 32.

Table 32 Chronic total occlusions; patient -level attributes (n=36)

Attribute (n 36)				Freq.	Percent
Female				6	16.7%
Previous MI				12	33.3%
Previous PCI				21	58.3%
Previous CABG				5	13.9%
Hypertension				19	52.8%
Dyslipidaemia				25	69.4%
Diabetes				10	27.8%
Fhx of CAD				14	38.9%
Current smoker				3	8.3%
Attribute	Min	Max	Mean		SD
Age (y)	42	82	63.8		9.7

Lesion and procedural characteristics are described in table 33. Of note 79% were de novo lesions and in 37% of lesions, the JCTO score was 2 or more. Antegrade wire escalation technique was used in all lesions. In 90% of cases DCB only PCI was feasible.

Table 33 Chronic total occlusions; lesion and procedural characteristics (n=38)

Attribute (n38)	Freq.	Percent
Vessel treated		
LAD	18	47.4%
RCA	16	42.1%
CX	4	10.5%
JCTO =>2	14	36.8%
Antegrade wire escalation	38	
Coronary dissections Type a type b type c	17 3 10 4	44.7%
DCB only PCI	34	89.5%
Device diameter >=3mm	20	52.6%
De novo	30	78.9%
ISR	8	
Access Dual Single	 20 18	 52.3% 47.7%
Technique Anterograde wire escalation	 38	 100%
Guidewires Fielder XTA BMW Sion blue Pilot 50 Pilot 200 Gaia Corsair Guideliner	 29 11 9 3 6 3 22 4	 76.3% 28.9% 23.7% 7.9% 15.8% 7.9% 57.9% 10.5%
Additional devices used Scoring balloon	 5	 13.2%

Cutting balloon Rotational atherectomy	1 1	2.6% 2.6%
Number of DCBs per lesion	1.6	
SeQuent please Falcon	33 5	86.8% 13.2%
Bifurcation	10	26.3%
Heavy calcification	7	18.4%
Severe tortuosity	2	5.3%
Drug coated balloon therapy and stent(s)	4	10.5%
Bail out stent	2	5.3%

Attribute	Min	Max	Mean	SD
Longest stented / treated section (mm)	15	120	41.6	27.1
Device diameter (mm)	2	4	2.81	0.59

Clinical Outcomes

There were no cardiac deaths in the first 12 months and one death up to three years (one patient suffered a non- cardiac death at 456 days from the index procedure due to traumatic chest and head injuries). One patient (2.8%) suffered a non ST elevation MI (non- target vessel related). There were 2 TLRs (5.3%) at 112 and 161 days after the index procedure respectively. One of them was a repeat intervention to an in-stent restenosis adjacent to the previously treated CTO and the second TLR was for restenosis of the index lesion. There was one (2.3%) non target lesion related TVR and this was a staged procedure for a CTO of posterior descending artery (PDA) after an initial successful opening of a proximal RCA CTO. There were no acute vessel closure or treated lesion thrombosis. 15 (39.5%) lesions have been assessed by further follow up angiography and no re occlusions seen. Out of the16 patients who had coronary dissections, apart for one patient who presented with a non- target vessel related MI, no

other adverse outcomes were noted. Figures 41-43 show the KM survival curves for three year death, MACE and TLR.

Table 34 Chronic total occlusions; clinical outcomes

Outcome	Freq.	Percent
Per Patient (n 36)		
Death by one year	0	0.0%
MI	1	2.8%
TVR	3	8.3%
MACE (TVR) by one year	3	8.3%
MACE (TLR) by one year	3	8.3%
Death by three years	1	2.8%
Per lesion (n 38)		
TLR by one year	2	5.3%

Figure 41 Chronic total occlusions; Kaplan-Meier curve for three year death

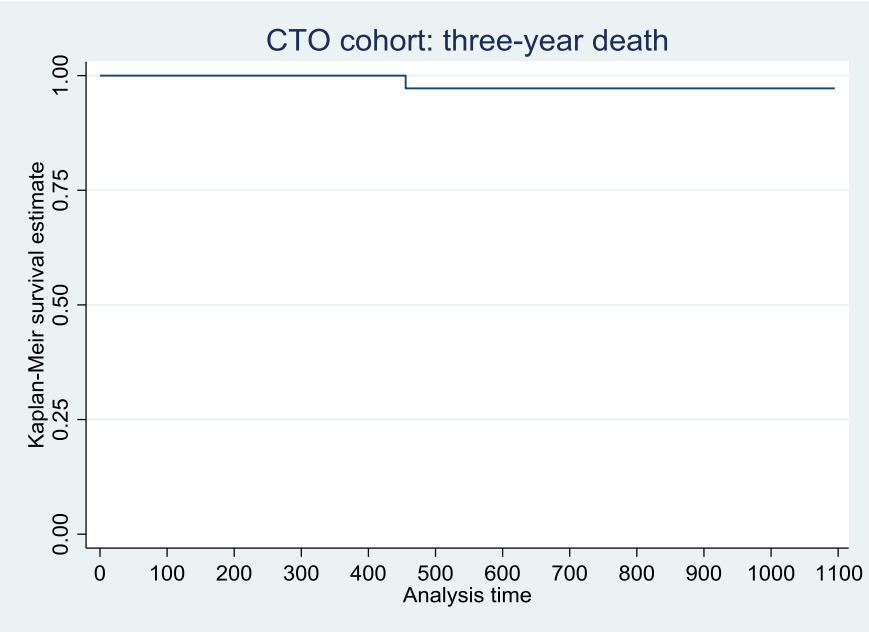


Figure 42 Chronic total occlusions; Kaplan-Meier curve for one year MACE (all cause death, MI, TLR)

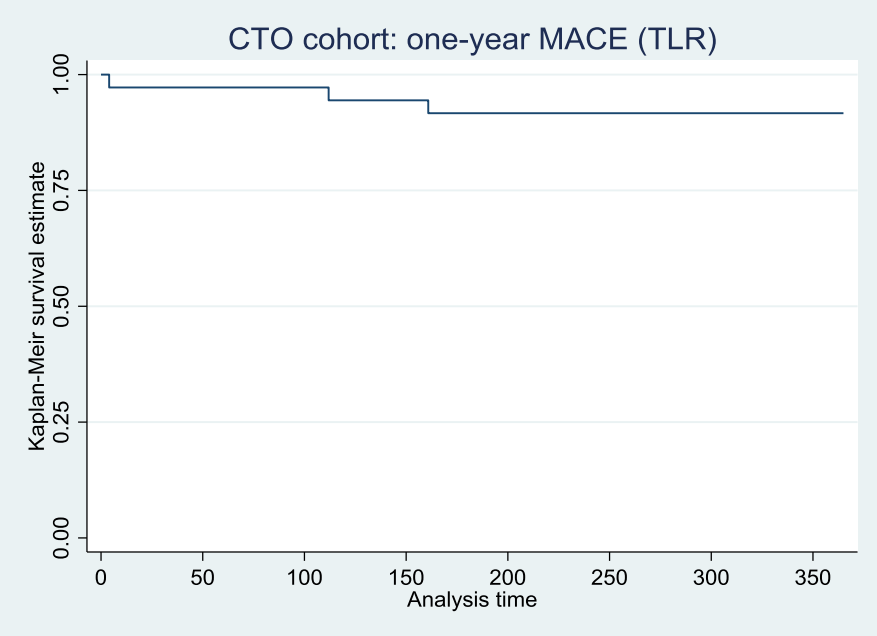


Figure 43 Chronic total occlusions; Kaplan-Meier curve for one year target lesion revascularisation

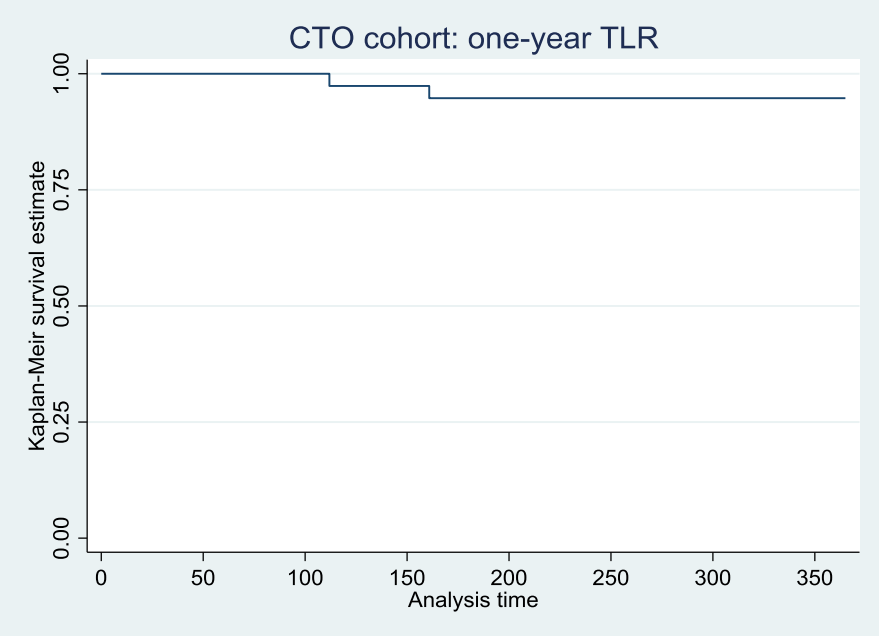


Figure 44 Pre (a), immediate post treatment (b) and follow up (c) images of a proximal left anterior descending artery chronic total occlusion.

Figure 44 (a) - pre treatment

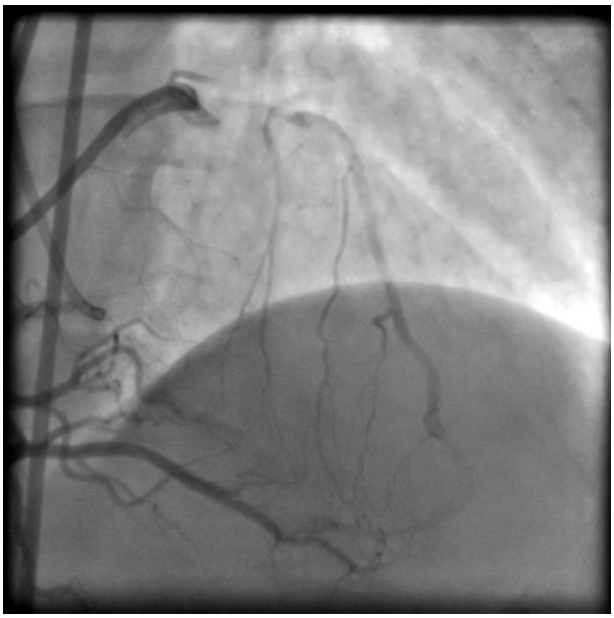


Figure 44 (b) – immediate post treatment

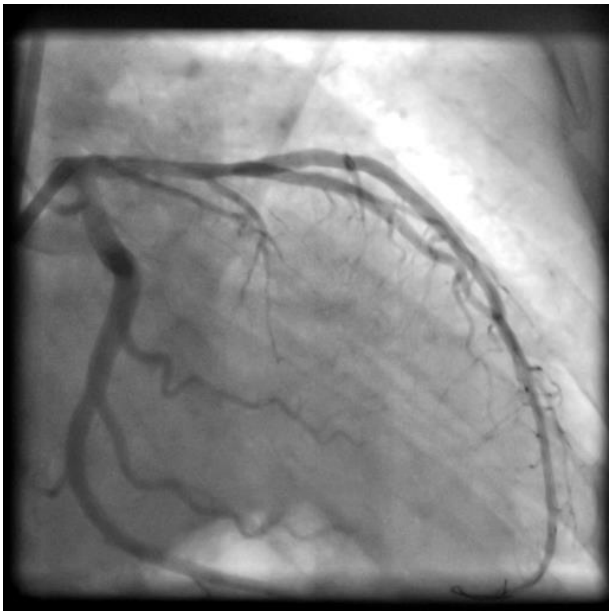


Figure 44 (c) – appearance at 24 months

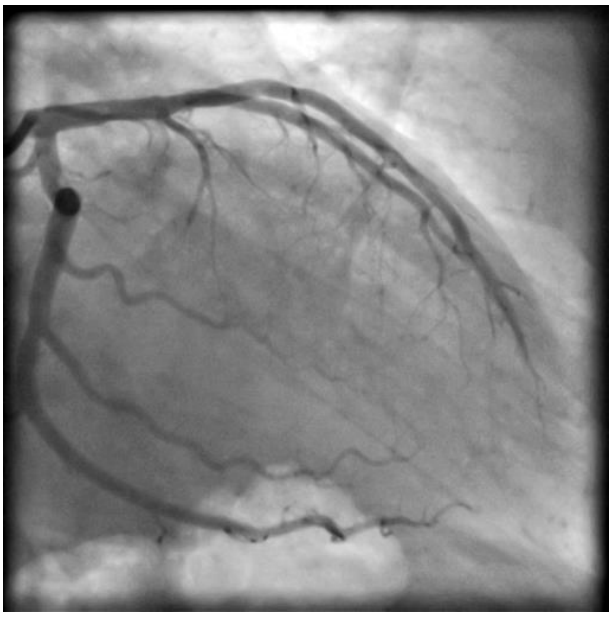


Figure 45 Pre-treatment (a) and follow up (b) images of a right coronary artery chronic total occlusion.

Figure 45 (a) – pre treatment

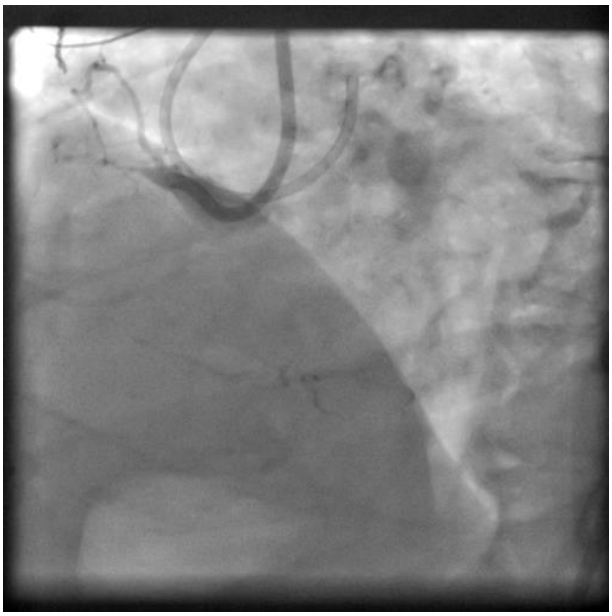
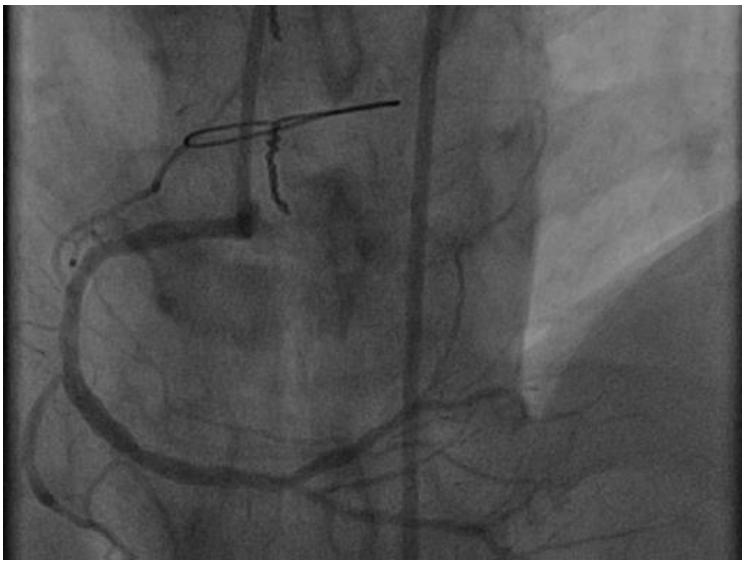


Figure 45 (b) – appearance at 17 months



3.1.7 In-stent Restenosis group

There were 353 in stent restenosis (ISR) lesions in 324 patients treated with DCB angioplasty during the study period. 31 lesions had bare metal stent (BMS) restenosis and 77 were drug eluting stent (DES) re stenosis. 1 lesion was a restenosis of a bio resorbable scaffold. Stent type of other lesions was not known. Patient demographics are described in table 36 whilst lesion and procedural characteristics are described in table 37. In 20.7% of lesions a cutting or scoring balloon was used as part of lesion preparation which is a higher percentage compared to de novo lesions.

Table 35 In-stent restenosis cohort; patient-level attributes (n=324)

Attribute (n324)	Freq.	Percent
Female	77	23.8%
Previous MI	203	62.7%
Previous CABG	52	16.0%
Hypertension	202	62.3%
Dyslipidaemia	157	48.5%
Diabetes	98	30.2%
Family history of CAD	64	19.8%

Current smoker			51	15.7%
Cardiogenic shock			2	0.6%
Out of hospital cardiac arrest			3	0.8%
Attribute	Min	Max	Mean	SD
Age (y)	33	95	66.8	11.1

Table 36 In-stent restenosis; lesion and procedural characteristics (n=353)

Attribute (n 353)	Freq.	Percent
Vessel treated		
LAD	150	42.5%
RCA	101	28.6%
CX	70	19.8%
LMS	6	1.7%
Graft	26	7.4%
BMS restenosis	31	8.8%
DES restenosis	77	21.8%
BVS restenosis	1	0.3%
Stent unknown	244	69.1%
Device diameter >=3mm	296	83.9%
Diffuse disease / small vessel	113	32.0%
Bifurcation	80	22.7%
Heavy calcification	44	12.5%
Thrombus present	55	15.6%
Severe tortuosity	34	9.6%
Drug coated balloon therapy and stent(s)	65	18.4%
Bail out stent	20	5.7%
Chronic total occlusion	8	2.3%
Cutting/scoring balloons	73	20.7%

Attribute	Min	Max	Mean	SD
Longest stented / treated section	10	110	28.6	17.3
Device diameter (n=403)	2	4	3.24	0.52

Clinical outcomes

As described in table 38, at 12 months all cause death is 3.4%, MI 8%, TVR 9.6%, MACE (TVR) 15.7%, MACE (TLR) 13.0%. TLR rate was 4.8%. Out of the MIs reported 5 patients had ST elevation MI and two of them led to target vessel revascularizations.

Out of the other 21 patients who represented with a MI, 14 had a target vessel revascularization and 9 had a target lesion revascularisation. Out of the 17 target lesion revascularization one was a definite lesion thrombosis which occurred after 2 hours from the index PCI which was bailed out with a bare metal stent. Figures 46-48 show the KM survival curves for three year death, one year MACE and one year TLR.

Table 37 In-stent restenosis; clinical outcomes

Outcome at 12 months	Freq.	Percent
Patient level outcomes (n 324)		
All cause death	11	3.4%
TVR	31	9.6%
MI	26	8.0%
MACE (death, MI, TLR)	42	13.0%
All cause death at 3 years	34	10.5%
Lesion level outcomes (n 353)		
TLR	17	4.8%

Figure 46 In-stent restenosis; Kaplan-Meier curve for three year death

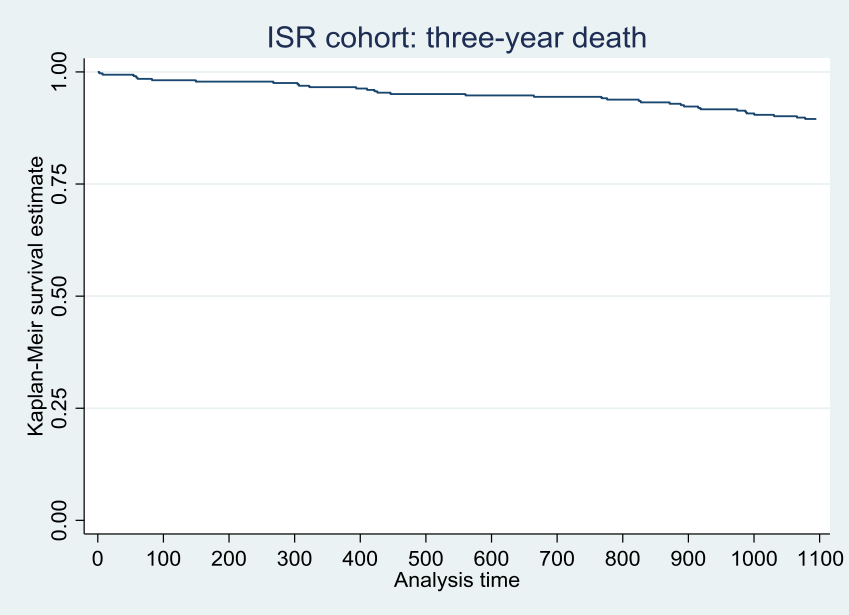


Figure 47 In-stent restenosis; Kaplan-Meier curve for three year MACE (all cause death, MI, TLR)

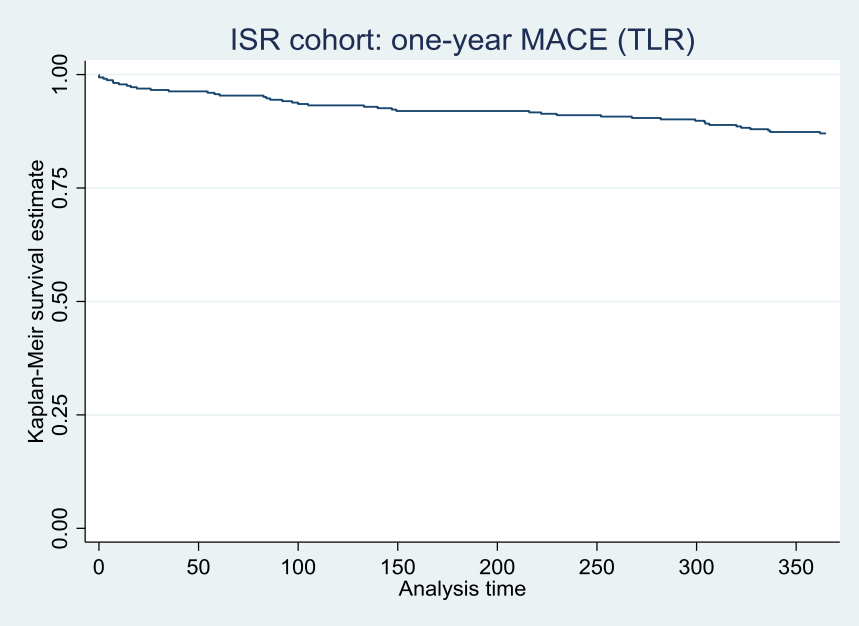
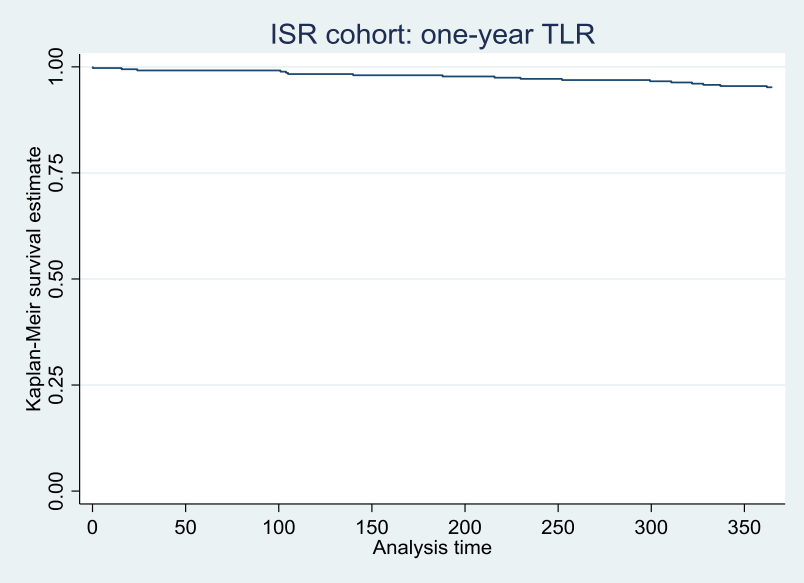


Figure 48 In-stent restenosis; Kaplan-Meier curve one year target lesion revascularisation



3.1.8 DCB in bypass graft stenosis

40 lesions in 37 patients who received DCB angioplasty to coronary artery bypass grafts are included in this cohort. Patient and lesion characteristics are as described in the tables 38 and 39. Of note 65% of lesions were in stent restenosis within bypass grafts.

Table 38 Bypass grafts; patient-level attributes (n=37)

Attribute (n37)				Freq.	Percent
Female				9	24.3%
Previous MI				24	64.9%
Previous PCI				29	78.4%
Previous CABG				37	100.0%
Hypertension				27	73.0%
Dyslipidaemia				31	83.8%
Diabetes				14	37.8%
Family history of CAD				5	13.5%
Current smoker				1	2.7%
Cardiogenic shock				0	0.0%
Attribute		Min	Max	Mean	SD
Age (y)		47	87	72.8	7.9

Table 39 Bypass grafts; lesion and procedural characteristics (n=40)

Attribute (n 40)				Freq.	Percent
Graft de novo				14	35.0%
Graft in stent restenosis				26	65.0%
Device diameter >=3mm				34	85.0%
Diffuse disease / small vessel				14	35.0%
Bifurcation				5	12.5%
Heavy calcification				3	7.5%
Thrombus present				6	15.0%
Distal emboli protection device (Spider)				11	27.5%
Severe tortuosity				5	12.5%
Drug coated balloon therapy and stent(s)				6	15.0%
Bail out stent				0	0.0%
Attribute		Min	Max	Mean	SD
Longest stented / treated section		14	66	26.1	13.9
Device diameter (n=40)		2	4	3.31	0.53

Clinical Outcomes

Clinical outcomes are much worse than the previously described sub sets. Both MACE and TVR are high at 21.6% at 12 months. Clinical outcomes are summarized in table 40. Figures 49-51 show KM survival curves for three year death, MACE and TLR.

Table 40 Bypass grafts; clinical outcomes

Outcome	Freq.	Percent
Patient level (n37)		
Death by one year	1	2.7%
TVR by one year	8	21.6%
MI by one year	4	10.8%
MACE (TLR) by one year	8	21.6%
Death by three years	4	10.8%
Lesion level (n40)		
TLR by one year	8	20.0%

Figure 49 Bypass grafts; Kaplan-Meier curve for three year death

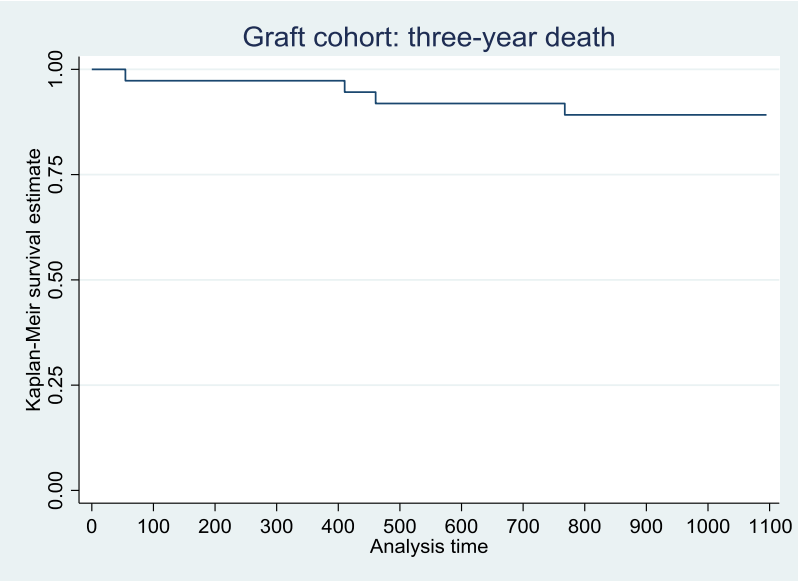


Figure 50 Bypass grafts; Kaplan-Meier curve for one year MACE (all cause death, MI, TLR)

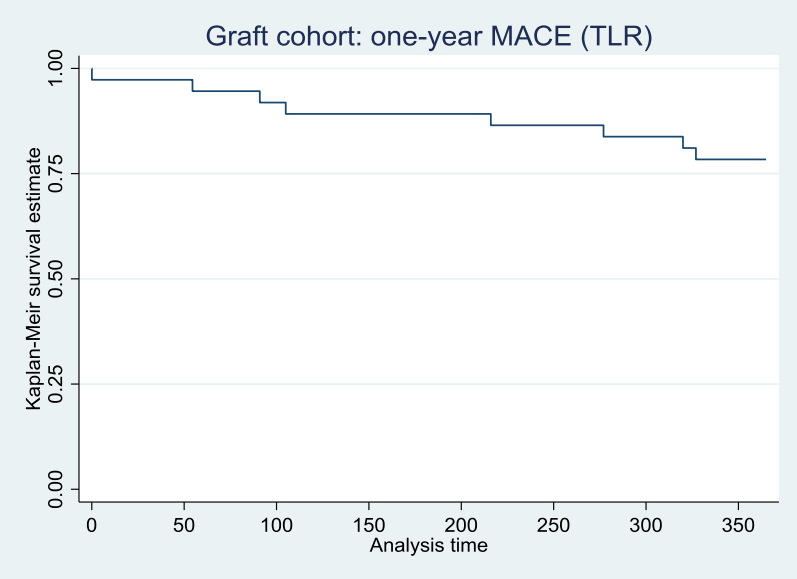
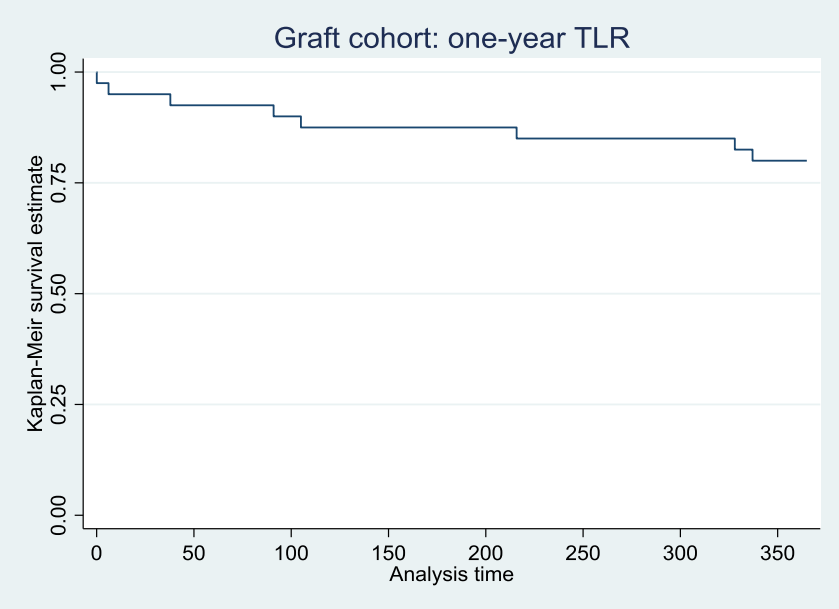


Figure 51 Bypass grafts; Kaplan-Meier curve for one year target lesion revascularisation



3.2 Propensity score matched study; comparison of clinical outcomes between DCB angioplasty vs. 2nd generation DES

A total of 3938 patients (4939 de novo lesions) treated with stents and 812 patients (1026 de novo lesions) treated with drug coated balloon (DCB) angioplasty were identified from the hospital data base. 38 patients who had a DCB as well as a stent in the same lesion (+/- 5mm proximal or distal to index lesion) were excluded from the DCB arm. Also another 43 patients who had received a prior drug eluting stent (DES) and had a clinical event prior to DCB angioplasty were excluded from the DCB arm. 1044 patients who received bare metal stents (BMS) or 1st generation DES were excluded from the DES arm as per protocol. Finally 2894 patients (3473) lesions treated with 2nd generation DES and 731 patients (922 lesions) treated with DCB were selected for propensity score matching. Pre propensity matching patient and lesion characteristics are described in tables 41 and 42. Consort style diagram in figure 52 describes the patient flow.

Propensity score matching.

The method of propensity score matching is described in the analysis plan in detail. A nearest neighbour matching within caliper algorithm was used. 1:3 lesion level matching was used to alleviate the differences noticed in the pre propensity matching cohort.

Figure 52 Consort style diagram describing patient enrolment, propensity score matching and follow up.

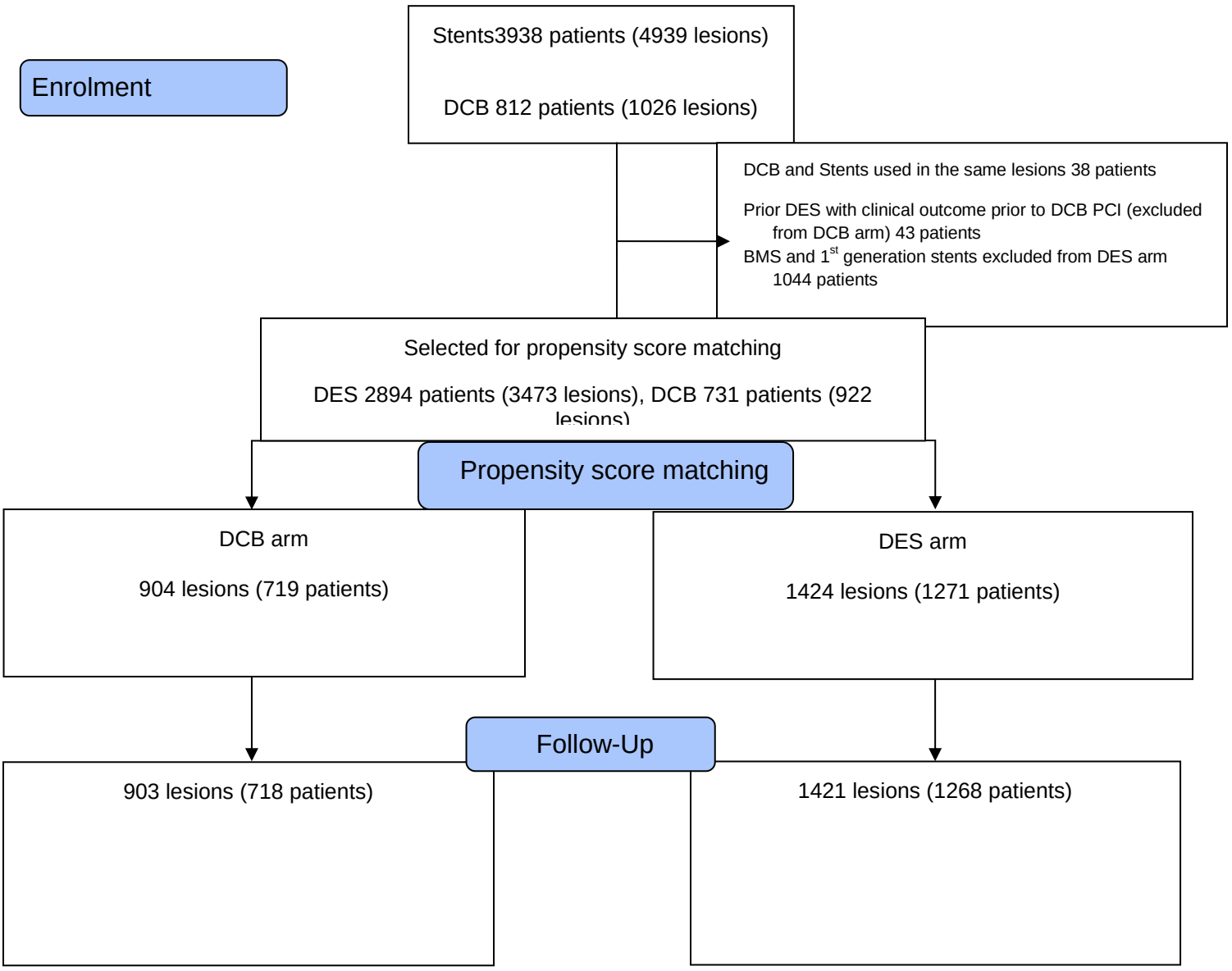


Table 41 Patient characteristics; pre-propensity score matching.

	DCB 731	%	DES 2894	%	P value
Male gender	558	76.3	2,213	76.5	Pr = 0.939
Diabetes	121	16.6	349	12.1	Pr = 0.001
Hypertension	371	50.8	1,256	43.4	Pr = 0.000
Previous MI	159	21.8	479	16.6	Pr = 0.001
Previous PCI	154	21.1	454	15.7	Pr = 0.001
Previous CABG	33	4.5	104	3.6	Pr = 0.243
Primary PCI	186	25.5	999	34.5	Pr = 0.000
ACS/AMI Stable	424 307	58.0 42.0	1,906 988	65.9 34.1	Pr = 0.000
Cardiogenic shock	9	1.2	44	1.5	Pr = 0.561
OOHCA	16	2.2	45	1.6	Pr = 0.234

MI-myocardial infarction, PCI-percutaneous coronary intervention, CABG- coronary artery bypass graft, ACS- acute coronary syndrome, AMI- acute myocardial infarction

There was no difference in the number of patients who had out of hospital cardiac arrest, cardiogenic shock, previous bypass grafts and gender between the two groups. Primary PCI, acute coronary syndrome, length of the treated segment and presence of thrombus were higher in the drug eluting stent arm. All of the other risk factors such as diabetes, hypertension, previous MI, previous PCI, small device diameter, bifurcation lesions, diffuse disease, calcific lesions and severe tortuosity were higher in the DCB arm indicating that the DCB cohort is a more complex lesion group.

Table 42 Lesion characteristics; Pre- propensity score matching

	DCB 922 lesions	%	DES 3473 lesions	%	P value
LMS LAD Cx RCA	14 467 227 214	1.5 50.7 24.7 23.2	92 1,600 694 1,087	2.6 46.1 20.0 31.3	Pr = 0.000
Device diameter mean(SD)	2.9 (.59)		3.4 (.61)		Pr(T > t) = 0.0000
Length of treated segment	23.56 (10.9)		29.65(16.4)		Pr(T > t) = 0.0000
Bifurcation lesion	314	34.1	743	21.4	Pr = 0.000
Heavy calcification	195	21.1	607	17.5	Pr = 0.010
Diffuse disease/SVD	358	38.8	876	25.2	Pr = 0.000
Severe tortuosity	158	17.1	495	14.3	Pr = 0.029
Thrombus	191	20.7	1,020	29.4	Pr = 0.000

Gender, previous CABG, cardiogenic shock and out of hospital cardiac arrest were not used in the propensity score model as these covariates did not differ between the groups before matching. Demographics and lesion characteristics post propensity matching are listed in table 43.

Table 43 Post propensity score matching demographics and lesion characteristics

Covariate	DCB n904 lesions (719 patients)	DES n1424 lesions (1271 patients)	p
Age	65.8	64.9	Pr(T > t) = 0.9586
Previous MI	209 (23.1)	301 (21.1)	Pr = 0.260
Previous PCI	210 (23.2)	289 (20.3)	Pr = 0.093
Hypertension	463 (51.2)	682 (47.9)	Pr = 0.118
Diabetes	152 (16.8)	219 (15.4)	Pr = 0.357
Indication			Pr = 0.155
Stable	399 (44.1)	586 (41.2)	
ACS/MI	505 (55.9)	838 (58.8)	
Primary PCI	209 (23.1)	363 (25.5)	Pr = 0.195
Vessel treated			Pr = 0.198
LMS	14 (1.5)	31 (2.20	
LAD	452 (50)	716 (50.3)	
Circumflex	226 (25)	311 (21.8)	
RCA	212 (23.5)	366 (25.7)	
Length of the treated segment	**23.7 (11.0)**	**25.6 (11.8)**	**Pr(T > t) = 0.0001**
Device diameter	**3.0 (0.6)**	**3.2 (0.5)**	**Pr(T > t) = 0.0000**
Bifurcation lesion	**297 (32.9)**	**376 (26.4)**	**Pr = 0.001**
Heavy calcification	187 (20.7)	278 (19.5)	Pr = 0.494
Diffuse disease/small vessel disease	**340 (37.6)**	**445 (31.3)**	**Pr = 0.002**
Severe tortuosity	149 (16.5)	225 (15.8)	Pr = 0.662
Thrombus present	191(21.1)	339 (23.8)	Pr = 0.133

Length of the treated segment, device diameter, diffuse disease and bifurcation lesion covariates were different in the two arms even after propensity score matching.

Clinical outcomes

Pre propensity score matching.

Pre propensity matching clinical outcomes at 12 months are described in table 44. There was no significant difference between the individual outcomes as well as MACE.

Table 44 Clinical outcomes; pre-propensity matching, unadjusted.

	DCB (922 lesions, 731 patients)	DES (3473 lesions, 2894 pts)	P value	OR	95% CI
12 months death	26 (3.6%)	71 (2.5%)	0.10	1.47	0.93 – 2.32
12 months MI	20 (2.7%)	85 (2.9%)	0.77	0.93	0.57-1.52
12 months TVR	34 (4.7%)	104 (3.6%)	0.18	1.31	0.88-1.95
12 months TLR (per lesion)	21 (2.3%)	88 (2.5%)	0.66	0.90	0.55-1.45
12 months MACE (death, MI, TLR)	60 (8.2%)	200 (6.9%)	0.23	1.20	0.89-1.63

Clinical outcomes after propensity score matching are described in table 45. The covariates: length of treated segment, device diameter, bifurcation lesion and diffuse disease were adjusted for in the logistic regression analysis as they were not well balanced by propensity matching. There was no difference between MACE or individual outcomes between the two groups. MACE for the DCB arm met the pre-specified non-inferiority criteria (non-inferiority margin of 4.5%, upper bound of the 95% confidence interval of the odds ratio was 1.47, which is below the pre specified 1.56 margin). Death was numerically higher in the DCB are at one year and at 3 years but not statistically

significant. Occurrence of myocardial infarction and target lesion revascularisation was numerically better in the DCB arm. TVR was higher in the DCB arm. No definite lesion thrombosis was noted in the DCB cohort whilst this was 0.6% with DES. Acute vessel closure/need for repeat intervention on the same day was 0.4% for the DCB group and 0.3% for the DES group.

Table 45 Clinical outcomes; post propensity score matching, risk adjusted

	DCB 718 patients /903 lesions[1]	DES 1268 patients /1421 lesions[2]	OR	P value	95% confidence interval
Per patient outcomes					
Death 12 months	26 (3.6%)	37 (2.9%)	1.10	0.723	0.65-1.86
Death 3 yrs	57 (7.9%)	80 (6.3%)	1.20	0.336	0.83-1.72
Death/MI	43 (6.0%)	71 (5.6%)	0.99	0.955	0.66-1.48
MI	19 (2.6%)	41(3.2%)	0.74	0.744	0.42-1.31
TVR	34 (4.7%)	48 (3.8%)	1.12	0.627	0.71-1.78
Death, MI, TVR	72 (10.0%)	102 (8.0%)	1.16	0.384	0.83-1.60
MACE (death, mi, TLR)	**59 (8.2%)**	**93 (7.3%)**	**1.04**	**0.834**	**0.73-1.47**
Per lesion					
TLR	21 (2.3%)	35(2.5%)	0.86	0.726	0.37-2.02
Definite lesion/stent thrombosis	0 (0%)	8 (0.6%)	0.09	0.10	0.01-1.60
Acute vessel closure/re intervention on the same day	4 (0.4%)	4 (0.3%)	1.58	0.52	0.39-6.32

[1] One loss to follow up. [2] 3 loss to follow up.

3.3 Summary of Results

The DCBNORWICH registry included 1394 lesions in 1122 patients that have been treated with drug coated balloons from 1st of January 2009 till 31/12/2015 at Norfolk and Norwich University Hospital. The results were described under de novo group, de novo bifurcations, large vessel group, primary PCI group, left main stem, chronic total occlusions, instent restenosis and bypass graft groups.

1. **De novo cohort**: 12 months all cause death rate for the de novo group was 3.6%. The rate of myocardial infarction was 3.1%. Target vessel revascularisation (TVR) was 4.9%. Target lesion revascularisation was 2.1%. MACE was 8.1%.There were 4 (0.4%) acute vessel closures/instability requiring a repeat procedure within 24 hours after DCB. No definite treated segment thrombosis was noted.
2. **De novo bifurcation cohort**: There were 327 lesions in 309 patients. 12 months all cause death rate was 2.6%. The rate of myocardial infarction was 3.8%. Target vessel revascularisation (TVR) was 4.5% and the target lesion revascularisation was 3.1%. MACE was 8.7%. The comparison between bifurcation lesion and non-bifurcation lesions showed no statistically significant difference between the outcomes.
3. **Large vessels/device diameter 3mm or more cohort**: The group had 603 lesions in 520 patients. 12 months all cause death was 2.7%. The rate of myocardial infarction was 3.1% and target vessel revascularisation (TVR) was 5%. Target lesion revascularisation was 2.5%. MACE was 8.1%. The comparison between less than 3mm and 3mm or more group showed no

significant difference in individual outcomes or MACE. Death by one and three years was numerically worse with small vessels whilst TLR was numerically better in the small vessel group.

4. **PPCI cohort**: 284 lesions in 268 patients were included in this cohort. 30 day mortality was 2.2% whilst 12 months mortality was 6%. The rate of myocardial infarction was 3%. Target vessel revascularisation (TVR) was7.5% and target lesion revascularisation was 3.5%. MACE was 11.6%.
5. **The left main stem (LMS) cohort:** There were 20 patients who received DCB PCI to their LMS during the study period. There was no cardiac death up to three years. One non-target vessel related MI was reported and no repeat revascularisations within the first year. MACCE (death, MI, TLR, Cerebro vascular event) 0.5%. No cerebro-vascular accidents occurred.
6. **Chronic total occlusions (CTO):** There were 38 lesions in 36 patients. No deaths reported in the first 12 months and one patient (2.8%) had a non-target vessel MI. There were 3 (5.3%) target lesion revascularisations (TLR) and overall MACE rate was 8.3%.
7. **ISR cohort**: 353 lesions in 324 patients were included in this cohort. All cause death was 3.4% at 12 months and TVR was 9.6%. MI rate was 8% whilst TLR rate was 4.8%. MACE was 13.0% at 12 months.
8. **Bypass graft cohort**: 37 patients (40 lesions) received DCB angioplasty during the study period. All cause death at one year was 2.7% and TVR was 21.6%. MI at one year was 10.8% and MACE was 21.6%. At 12 months TLR rate was 20%.

9. **Propensity score matched comparison between DCB and 2nd generation stents**: There were 904 lesions (719 patients) in the DCB arm and 1424 lesions (1271 patients) in the DES arm after propensity score matching. 12 months outcomes were all cause death 26 (3.6%) vs. 37 (2.9%), MI 19 (2.6%) vs. 41(3.2%), TLR 21 (2.3%) vs. 35 (2.5%), TVR 34 (4.7%) vs.48 (3.8%) and MACE 59 (8.2%) vs. 93 (7.3%) for the DCB and DES groups respectively. Differences were not statistically significant. The MACE outcome for DCB met the non-inferiority criteria. The definite treated lesion thrombosis/stent thrombosis was 0% vs. 0.6% for 12 months.

4 Discussion

The discussion will cover aspects of both the DCBNORWICH Registry including its sub groups and the propensity score matched comparison of the DCB vs. Drug eluting stent study.

4.1 Discussion on DCB NORWICH Registry

4.1.1 Key Findings

1. DCB angioplasty is feasible and safe, and provides clinical outcomes in the expected range in a broad spectrum of coronary lesions and indications including de novo lesions, STEMI, bifurcations, CTO, post CABG and most importantly larger (>3.0mm) coronary arteries

2. Main factors associated with target lesion revascularisation in multivariate analysis in the de novo population are STEMI and NSTEMI/ACS.

3. Findings show that DCB in STEMI provides comparable outcomes to established stent registries

4. Extends the experience of DCB angioplasty to more complex patients e.g. CTO and post CABG

5. There was no definite treated lesion thrombosis in the de novo cohort up to one year.

4.1.2 De Novo Group

During the study period a total of 1026 lesions in 812 patients have been treated with DCB angioplasty. This constitutes the largest cohorts of DCB treated bifurcations, large vessels (3mm or more device size) and primary PCI reported thus far. It should be noted that as in most centers, DCB angioplasty was first carried out in patients with in-stent restenosis. The next stage of natural progression was to treat small calibre vessels and diffusely diseased segments which otherwise would have required very long segments of stents. Encouraging results from other studies such as the Sequent please world-wide registry and observing satisfactory results of the previously treated lesions especially in the context of staged procedures would have played a role in adopting this technology for wider indications[123, 124, 132].

De Novo Group Patient demographics.

This was an all comer study which included all patients treated with drug coated balloons during the given period. Therefore this cohort reflects contemporary UK practice. Table 46 outlines the demographic details of the patients in the de novo registry against the UK BCIS audit data published in 2019[157]. Apart from comprising lesser number of diabetics in the DCBNORWICH registry, other characteristics were comparable in the two groups. This would further support that the DCB treated cohort is not a selected sample of simple cases but a cohort reflective of contemporary practice.

Table 46 Patient demographics of DCB Norwich registry vs. UK BCIS audit report

Patient Characteristics	DCBNORWICH registry – de novo group	UK BCIS report 2019
Number of patients	812	102258
Age – Mean (SD)	65.8	65.4
Gender Male %	75.6	74.3
Previous MI %	24.5	27
Previous PCI %	27.2	26.9
Previous CABG %	4.1	7.5
Diabetes Mellitus%	16.9	23.5
Current smoker%	22.7	22.7

DCB de novo group indications, lesion complexity and procedural details

Vast majority (60.1%) of DCB angioplasty were done for acute coronary syndromes. ST elevation MI comprised of 26.7% and NSTEMI/Unstable angina percentage was 33. In the UK wide BCIS data 27.2% were for STEMI, 38.6% were for NSTEMI/UA and 30.4% were for stable disease. Table 47 outlines these percentages.

Table 47 Indication for PCI; DCB Norwich registry vs. UK BCIS audit report

Indication	DCB de novo group	UK BCIS data
STEMI %	26.7	27.2
NSTEMI/UA %	32.5	38.6
Stable %	40.8	30.4 (34.1 including staged procedures)

Most procedures were carried out through the radial artery which comprised of 89.9% of procedures conforming to the current UK practice. 70.9% of patients had a single vessel treated and the balance had two or more vessels treated at the same sitting. This in comparison to 77.7% in the UK BCIS data indicate more multi-vessel treatment in the DCB group.

As in most studies left anterior descending artery (LAD) is the most commonly treated artery at 51.6%.The left main stem was treated in 1.4% of DCB de novo patients whilst the UK BCIS data showed LMS PCI of 4%.

Chronic total occlusions (CTO) constituted 2.9% of the total de novo group and were 8.8% of the total stable disease cohort. UK BCIS data showed 11.6% CTOs out of the stable disease cohort.

Other variables such as heavily calcifications (21.6%), lesions in a bifurcation (34.1%) severe tortuosity (17%), diffuse disease/small vessel disease (39.7%), presence of thrombus (20.2%) and lesion length of more than 2cm (41.3%) would indicate that this

a mix of type A, B and C lesions not a selected cohort of simple lesions. Mean (SD) treated lesion length was 24.5 (12.5) and mean (SD) device diameter was 2.9 (0.6) mm. DCB of a 3mm or more diameter was used in 603 (58.8%) lesions indicating large vessels.

Procedural aspects were left to operator's discretion entirely. German consensus guidelines on DCB angioplasty were largely followed but not all type C coronary dissections have been bailed-out with stents especially in the case of CTO lesions[50].

Results

Out of the 1026 de novo lesions 965 (94.5%) lesions were successfully treated with DCB-only angioplasty. In total 148 (14.6%) coronary dissections were noted and 22 (2.3%) of these were type C and above. 42 (4.1%) lesions required bail-out stents during the index procedure, for type C or above dissections or due to severe recoil. In another 19 (1.8%) lesions stents have been used electively. Sequent Please world-wide registry reported a smaller rate of coronary dissections of 3.1% in the de novo arm but this consisted of only small vessel coronaries.[124] In our registry 100% of lesions were pre dilated and good lesion preparation was considered a must. DCB was used only to deliver the drug. It is common practice to start pre dilatation with non-compliant balloons rather than semi compliant ones expecting a better angioplasty result. Cutting or scoring balloons have been used in 77 (7.5%) lesions as part of pre dilatation. In the case of a coronary dissection of type C or above after DCB use, bail-out stenting with a second generation DES is recommended rather than a BMS. The results of a small study comparing BMS vs. DES bail out after DCB angioplasty was published in collaboration

with a team of researchers from Tan Tock Seng Hospital, Singapore and it is included in the appendix. Dual antiplatelets were recommended for 1 month for a stable lesion and 1 year for a lesion with ACS/MI.

Clinical Outcomes

The target lesion revascularisation rate for 12 months was 2.1%. This is in keeping with other DCB studies such as 1% at 9 months in Sequent please world-wide registry, 3.6% at 9 months in a prospective registry by Zeymer et al and 2.6% at 9 months in the registry by Rosenberg et al.[123, 124, 133] There were 4 (0.4) acute vessel closure/instability that required bail-out stenting during the same admission and all those 4 patients are alive at 3.5 (for two), 4 and 5 year follow up respectively from the procedures and have not had further MIs or revascularisations. Even though we did not perform quantitative coronary analysis, naked eye assessment suggests under sizing during pre-dilatation is a potential reason for TLR. It should be noted that this registry includes every lesion treated with a DCB which includes early learning curves of the DCB operators.

Target vessel revascularisation was 4.9% (40) at 12 months. TVR was 3.4% in the BASKET-SMALL trial at 12 months.[138] One patient had repeat PCI in another hospital but we did not have access to angiograms to determine whether this was a TLR or not.

25 patients (3.1%) had a MI within the first 12 months from the index PCI. Out of the 25 MIs, only 6 led to target vessel revascularisations and 4 of those were target lesion revascularisations. Therefore MI leading to a repeat revascularisation of the same vessel is 0.7%. Two of the 25 were ST elevation MIs (day 61 and 359 post index PCI) and both were due to occlusion of another vessel. 0% treated lesion thrombosis in the

first 12 months was a positive result for DCB-only PCI and could be due to full re endothelialisation of the lesion in the absence of a permanent metallic stent.

We did not have access to death certificates to determine the cause of death of all deaths. All cause death was 3.6% (29). There were 10 definite cardiac deaths, 8 cause unknown (no information) and 11 non-cardiac. Assessing relationship of DCB-only PCI to death becomes difficult in this cohort due the heterogeneity of the group. For example 27.2% of patients have had previous PCIs and some with POBA, bare metal stents, first and second generation stents.

Out of the 42 lesions which had a bail-out stent after DCB PCI there were no TLRs in the first 12 months. There was one death and one MI reported in this group which supports the safety of bail-out stenting with a new generation drug eluting stent. Out of the 147 lesions with coronary dissections (other than the ones already included in the acute vessel closures) there was only one TLR. There were 3 deaths, 2 due to metastatic carcinomas and the other had no information available on cause of death. Two patients have had subsequent MIs and one had target vessel revascularisation at day 79. Treated lesion remained patent and had no further PCI. These results would further strengthen the old data from POBA days that all coronary dissections do not need bail-out stenting[196, 197]

MACE was 66 (8.1%) and these rates are in keeping with other real world studies and also it should be noted that patients who were in cardiogenic shock and out of hospital cardiac arrests, intubated and ventilated are also included in our registry. Zanchin et al in their Bern registry of patients comparing biodegradable polymer vs. durable polymer

stents reported a device oriented end point (cardiac death, target vessel MI and TLR) of 7.8 and 7.1% in each arm which is somewhat similar to MACE outcome in the DCBNORWICH registry. [221]

The multivariate regression analysis as described in tables 11,12, 13 and figures 24 and 25 showed that 10 year increment in age is associated one year death, hypertension with MACE and primary PCI with target lesion revascularisation. Whilst effectiveness of the drug delivery to the vessel wall in a primary PCI setting could be questioned, the fact that presence of thrombus was negatively affecting the TLR makes the said argument not so valid. It is understood that PPCI is a high risk setting and clinical outcomes are worse compared to stable CAD.It is likely this effect that we are observing rather than a specific failure of DCB in PPCI setting. As described in the PPCI section separately the one year mortality of the PPCI cohort of the DCBNORWICH registry is lower than the 30 day mortality described for PPCIs in the UK wide BCIS registry. In the Sequent Please world-wide registry, the most predictive factor for TLR was diabetes mellitus but in our registry there was no significant association[124].

In summary these results show that DCB-only angioplasty in de novo lesions is not only technically feasible but safe and effective at 12 months.

The encouraging results observed in this study after DCB angioplasty may be attributable to anti proliferative drug delivery reducing restenosis whilst avoiding other stent related issues such as chronic inflammation, neo atheroma, stent fracture, stent gap, stent overlap, non- uniform stent struts, non-homogenous drug delivery, uncovered stent struts, under expansion and late malapposition.

4.1.3 De Novo Bifurcations

Apart from the studies by Shultz et al (39 patients) and Her et al (16 large vessels), there are no studies identified with DCB-only PCI in bifurcation lesions[173, 206]. Most studies published are with either a DES or a BMS in the main vessel and DCB used in side branch. DCB Norwich appears to be the largest number of bifurcation lesions reported under DCB-only PCI category.[52, 132, 172, 173, 222, 223]

There were 350 separate lesions involving a bifurcation in this cohort. For the purpose of describing them under the heading bifurcation, a lesion where both arms were treated was considered as a single lesion. Hence the total number of bifurcation lesions was considered as 327 (309 patients). A lesion was defined as a bifurcation if the side branch was 2mm or more by visual assessment.

Bifurcation lesions are the Achilles heel in Interventional Cardiology and higher event rates have been reported.[170] Technical complexities such as plaque/carina shift compromising the ostium of the side branch, difficulties in re-crossing through a stent, complexities with two stent strategies and amount of metal/polymer layers overlapped are some of the issues that PCI operators have to face when carrying out a bifurcation PCI using stent/s. DCB-only PCI would be very attractive as it simplifies the procedure with no re-crossing, no metal overlap or gap and not requiring numerous kissing balloon dilatations.

It should be noted that 94.8% of the bifurcation lesions were treated with DCB-only PCI. 37.1% were true bifurcations (medina 1.1.1, or 0.1.1). 21 lesions had both the main branch and the side branch treated with sequential DCBs. There were 4 side branch

occlusions during the procedure but operator was able to re-establish the flow of all 4 before the end of the procedure.

Outcomes.

At 12 months all cause death was 8 (2.6%), MI 12 (3.8%), TVR 14 (4.5%), MACE was 27 (8.7%). TLR was 10 (3.1%). 2 (0.6) lesions had bail out stenting during the index admission. No definite treated lesion thrombosis. These outcomes are largely comparable with other reported bifurcation studies treated with stents. Schulz in her study with 39 bifurcation lesions treated with DCBs reported a MACE rate of 7.7% at 4 months. Follow up angiography at 4 months showed restenosis of 3/39 lesions requiring treatment. TLR rate in our registry is better than some of the bifurcation studies using stents. For example, the BBC study reported TLR rate of 5.6% in the single stent arm and 6.8% in the two stent (complex) arm at 9 months[167]. DKCRUSH V study showed TLR of 7.9% vs. 3.8% at 12 months in the provisional arm and two stent arm respectively[224] . Absence of definite treated lesion thrombosis is another important factor favouring DCB-only PCI. Her et al showed that when the main branch is treated with a paclitaxel coated balloon the minimal luminal diameter of the ostium of the side branch(SB) increases at 9 months in their OCT pre, post treatment and 9 months follow up study involving 16 main vessels and 26 side branches. Minimal luminal diameter of the side branch was 0.97±0.44 mm at pre-procedure, 1.02±0.33 mm at post-procedure and 1.04±0.38 mm at 9-months, the late luminal loss of SB ostium was -0.02±0.22 mm.[206]

In the comparison we carried out between bifurcation and non-bifurcation lesions there was no statistically significant difference in individual outcomes. Apart from death other outcomes were numerically in favour of the non-bifurcation group though not statistically significant. These results may indicate that DCB-only PCI could influence outcomes of bifurcation lesions to reach levels similar to non-bifurcation lesions in the first 12 months of follow up.

In summary DCB-only PCI in bifurcation lesions is not only feasible but also has other advantages such as simplification of the procedure, less or no permanent overlapping metal layers, less or no plaque/carina shift and also presence of late lumen gain in the side branch ostium. Our current practice is sequential DCB delivery unless there is a significant size mismatch between the proximal and distal vessel. The simultaneous delivery of two DCBs take time resulting in loss of drug and also has the potential to cause a dissection in the proximal vessel. If there is significant plaque/carina shift post DCB, there is always the option of carrying out a final kissing balloon dilatation.

As shown above the initial 12 months results are very positive and encouraging. This is the largest DCB-only de novo bifurcation study reported thus far hence these results will be important as a benchmark for future studies.

4.1.4 De Novo large vessel cohort

Evidence for DCB-only PCI in de novo large vessels is small but growing. Lu et al published a registry of 94 lesions in 92 patients who received DCBs with diameter of 3mm or more[225]. Bail-out DES was used in only 6.4% cases. There were two acute vessel closures due to haematoma formation (detected by IVUS and OCT). At 9 months

angiographic follow up late lumen loss was -0.02 +/- 0.49 mm. The TLR rate and overall MACE rates were 4.3% and 4.3%. Quantitative coronary angiography data (QCA) showed that 61.5% (n = 48) of patients showed luminal enlargement indicating late lumen enlargement does occur in large vessel coronaries too after DCB treatment.

Yu et al reported a comparison of large vessel disease (LVD) vs. small vessel disease (SVD) treated with DCB strategy in 222 and 373 lesions respectively[226]. Large vessel group had no MACE events at 10 months clinical follow up. A significant late lumen gain was shown in QCA analysis in follow up angiography LVD group (2.26 ± 0.66 vs. 2.09 ± 0.40 mm, P = 0.067) as well as the small vessel group.

Rosenberg et al published a propensity score matched comparison of LVD vs. SVD treated with DCB-only PCI comprising of 117 patients in each arm showed a MACE rate of 6.1% and 5.7% respectively at 9 months[227].

DCBNORWICH registry is comprised of 603 large vessel coronary lesions in 520 patients treated with DCBs. Patient demographics were similar to our previously described overall de novo cohort. Clinical outcomes at 12 months for the LVD group were similar to other studies with MACE rate of 8.3%, TVR 27 (5.2%), MI 16 (3.1%), all cause death of 14 (2.7%). We carried out a comparison between the LVD and SVD treated with DCB-only PCI. The large vessel group had more patients presenting with MI and more lesions with thrombus. The results showed no significant difference between the clinical outcomes at 12 months. Numerically lower TLR rate was reported in the SVD cohort. Higher number of acute MIs and lesions with thrombus in the large vessel cohort could be attributed for this finding. The mortality was numerically higher in

the SVD group which may be due to the inherently poor outcomes associated with this group.

This will be an important set of findings in benchmarking outcomes for DCB angioplasty in large vessel coronary disease as the existing evidence is very limited.

4.1.5 Primary PCI Cohort

Primary PCIs (PPCI) are high risk procedures associated with higher rates of major adverse cardiac outcomes. The PPCI cohort described in the DCBNORWICH registry includes patients with cardiogenic shock (3.7%), out of hospital cardiac arrests(6.3%) and also patients who were intubated and ventilated prior to PCI(3%). This is the largest DCB-only PPCI patient cohort reported thus far. Previously described (section 1.3.4) DCB PPCI studies by Vos et al, Ho et al, Nijhoff et al, and Revelation studies have a smaller number of patients comparatively.[158] [159] [160] These showed that DCB-only PCI is feasible in PPCI setting and the randomised Revelation study showed the FFR at 9 months was non inferior in DCB treated lesions compared to DES in the PPCI setting in a total of 120 patients.

As described in the introduction section we recommend thrombus aspiration prior to the deployment of the DCB to enhance drug delivery especially in a lesion with heavy thrombus burden. This will explain the large proportion (63.4%) of thrombus aspiration reported in this cohort. This number amounts to 87.5% of lesions with thrombus. In the PPCI sub study of the BIOSCIENCE trial which compared biodegradable polymer DES (BP-DES) to durable polymer DES (DP-DES), 34 and 39% had thrombus aspiration in each arm[228]. BIOSCIENCE had 58 and 52% TIMI 0/1 flow lesions in each arm whilst our

registry has 70% of lesions with TIMI 0/1 flow. Final TIMI III flow was gained in 97% in BIOSCIENCE study whilst it was 94% in the DCBNORWICH registry. The use of glycoprotein 11b/111a inhibitors was also noted to be high at 50.4% in our study. More than 1 vessel was treated in 14.8% of the cases.

The BCIS registry published in 2019 showed a 30 day mortality of 7.8% across the United Kingdom in 25, 612 patients.[157] All STEMI patients with no cardiogenic shock had a 30 day mortality of 4.4%. Patients who were in cardiogenic shock had a mortality of 43.1% at 30 days. As described in the results section in the DCBNORWICH registry, 30 day all cause death was low at 6 (2.2%) and one year death was 16 (6.0%). Of note, our registry includes all intubated patients whereas the BCIS registry does not. Possible causes of low mortality could be absence of metal implant enabling the vessel healing and complete re endothelialisation. Our use of glycoprotein IIb/IIIa inhibitors (GPI) was higher than the UK-wide use recorded in the BCIS data (50.4% vs. 37.4%) and may have had in impact on the low mortality rate. Orzalkiewicz M. et al recently showed that routine use of GPI was associated with lower all-cause mortality in comparison to selective use, in a study of 110,327 patients undergoing PPCI in the UK.[163]

TIMI III flow was achieved in 94% of the cases in our study cohort. Whilst UK BCIS data did not provide this information, the National Cardiovascular Data Registry (NCDR) of the United States which included 291,280 acute MI (62% STEMI) patients reported TIMI III flow in 94% patients post angioplasty.[229] In the US registry, 44% of patients had TIMI 0 flow pre intervention whereas in our registry it was higher at 62% indicating that our post procedure TIMI III flow rate was comparatively better.

Target lesion failure (cardiac death, target vessel MI and clinically indicated TLR) of the BIOSCIENCE study was 8.8% and 3.4% in the DP-DES and BP-DES arms respectively. Whilst the MACE (all cause death, MI, TLR) defined in DCBNORWICH registry is not as specific as target lesion failure, it was recorded at 11.6%. TLR rate was 3.5% and MI was 3%. It should be noted that 19% of our cohort had PCI to either instent restenosis or stent thrombosis which are considered risk factors for further repeat revascularisations. No definite lesion thrombosis was recorded. There were two acute vessel closures and both were successfully bailed out with stents.

Target lesion revascularisation rate of 3.5% and MI rate of 3% at 12 months are encouraging results in this high risk group of patients. 90.1% patients had DCB-only PCI indicating that ubiquitous use of stents is not a necessity even in this high risk group.

In summary, this largest reported DCB PPCI cohort shows that DCB-only PCI is feasible and safe in this high risk category. The chance of under sizing and causing late mal-apposition as in the case with a stent is not an issue with DCB-only PCI. This factor is more pertinent to this group as coronary vessels constrict during an acute MI.

4.1.6 Left Main Stem PCI with DCB

Significant LMS disease (greater than 50% stenosis), is present in approximately 6% of all patients undergoing coronary angiography with 80% having complex bifurcation lesions or multi-vessel disease.[230-234] PCI to the LMS is a high-risk procedure due to the large area of myocardium at risk plus the complex nature of the anatomy, with higher major adverse cardiac event (MACE) rates largely driven by repeat revascularisations.[235, 236]

The Synergy Between PCI With Taxus and Cardiac Surgery (SYNTAX) trial comparing PCI and CABG for LMS lesions showed, major adverse cardiac or cerebrovascular events at 12 months were significantly higher in the PCI group (17.8%, vs. 12.4% for CABG; P=0.002) largely due to repeat revascularisations. The rates of MI and death were similar in the two groups.[237] The 5 year outcome analysis of the SYNTAX trial have shown no difference in MACCE between the two groups whilst PCI group had similar individual outcomes (death, MI, stroke and repeat revascularisations) in low to intermediate SYNTAX score (SS) group (SS of less than 32).[238] The Nordic-Baltic-British Left Main Revascularisation Study (NOBLE) and Evaluation of Xience versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularisation (EXCEL) study showed no difference in mortality and stroke (individually) between CABG and PCI for LMS disease.[239, 240] Both showed higher non procedural MI rates in the PCI group whilst EXCEL showed a higher rate of peri- procedural MIs in the CABG group. The percentage of any revascularisation was higher in the PCI arm in both studies. There was no significant difference in ischaemia driven TLR between PCI and CABG but it was numerically less in the CABG arm. The NOBLE trial reported a MACCE rate of 7% in the PCI arm at one year.

Our cohort, whilst a small number of patients, had a 1 year MACE rate of 4.2% suggesting that DCB-only angioplasty to LMS lesions is effective and safe in the short to medium-term. We found no evidence of acute complications, such as acute vessel closure, flow limiting dissections, acute recoil or vessel thrombosis as has previously been associated with plain old balloon angioplasty (POBA). Access to better quality angiography imaging, use of dual antiplatelet therapy, intravascular imaging techniques

and improved angioplasty devices could provide a plausible explanation for this difference.

A significant number of lesions in this patient group involved distal LMS (82.6%). Analysis of the DELTA registry by Naganuma et al has demonstrated a higher incidence of target lesion revascularisation in distal LMS lesions following PCI with stents.[236] Distal LMS lesions are known to pose a significant anatomical challenge in relation to optimal stent treatment. The efficacy of DCBs particularly in these lesions, as we have demonstrated, may provide an attractive alternative treatment strategy. We suggest that part of the appeal of DCB-only PCI for the distal LMS is that of a simplified procedure avoiding plaque and carina shift and the resultant multiple layers of stents.

4.1.7 DCB-only PCI in CTO (chronic total occlusions)

The implications of use of DES and potential benefits of DCB in this cohort have been discussed in section 1.3.6 in detail. Koln et al reported a re-occlusion rate of 5.9% and restenosis rate of 11.8% at 8 months follow up in 39 de novo lesions treated with DCB PCI.[192] Ours is the second registry of DCB PCI in CTO lesions. EUROCTO trial reported ischaemia driven target revascularisation of 2% and MACCE rate of 5.2% at 12 months in the PCI arm (274 patients with 91% of DES use).[241] The TLR rate of 5.3% and an overall MACE rate of 8.3% reported in our registry are encouraging. Also the absence of any re occlusions in the 15 lesions which have had follow up angiography should be highlighted.

Not having long stented segments or so called full metal jackets and being able to avoid mal apposition due to late lumen gain are two advantages of DCB-only PCI in this

setting. This report also highlights the safety of type B as well as some type C dissections left without any bail-out stenting. As reported all these lesions were treated with the antegrade wire escalation technique suggesting no sub intimal delivery of DCBs. In the case of dissection re-entry approach, perhaps spot stenting the dissection and treating the rest of the lesion/disease with DCBs will be an option.

4.1.8 In stent restenosis (ISR) group.

Drug coated balloon angioplasty was first utilized in treating in stent restenosis as deploying a second or third metal layer inside a previous stent was deemed unfavourable. There have been many registries and randomised controlled trials to assess efficacy of DCBs in treating ISR. Evidence of DCB in ISR has been widely discussed in section 1.3.2.

We were unable to identify the type of original stent in 69% of patients. From the recorded ones DES-ISR proportion was higher than the BMS-ISR. We carry out 1:1 balloon pre dilatation and aggressive lesion preparation when treating ISR lesions. Although less than 30% stenosis is considered an acceptable result before deploying a DCB, in ISR cases we aim to achieve near 100%. Non- compliant balloons are used most commonly at high pressures and in 21% of lesions cutting or scoring balloons have been used for lesion preparation.

In our registry TLR at one year was 17 (4.8%) and MACE was 42 (13.0%). In RIBS IV (EES vs. DCB in 309 DES-ISR patients) study, 1 year TLR rate was 4.5% and 13% for EES and DCB arms respectively. MACE was 16% and 7%. Number of MIs reported in our registry is 26 (8%), higher than what is reported in other studies. DAEDALUS study

reported MI rate of 4.7% at 3 years and RIBS IV reported 3% at one year.[242] One reason could be the inclusion of bypass graft ISR lesions, 5 of which had recurrent MIs within the first year. Apart for one definite target lesion thrombosis which occurred 2 hours after the procedure, no other late thromboses were reported.

However the overall MACE rate in our study is within the observed range in other studies despite having a higher rate of MIs.

4.1.9 Coronary bypass grafts

This sub set of lesions are a high risk group in terms of success of the procedure as well as long term outcomes. 65% were ISR lesions which would elevate the risk in terms of long term clinical outcomes, even further. Redfors et al reported a target vessel failure of 20.4%, death 4.5%, myocardial infarction 7.9% and ischemia-driven target vessel revascularization of 13.0% at one year in vein graft PCI arm comprised of 405 patients to 8177 non bypass graft PCIs.[243] In our cohort TLR rate was 20% and MACE was 21.3%. These higher rates perhaps could be explained by the high number of ISRs present. In summary, these findings further supports the fact that clinical outcomes of percutaneous coronary intervention to bypass grafts is linked with high rates of adverse outcomes despite the device used in PCI.

4.2 Discussion on propensity score matched study; comparison of DCB vs. DES

Key Findings

1. There were no significant differences in clinical outcomes between DCB angioplasty in de novo lesions and a matched cohort receiving second generation DES at one year.
2. Rates of target lesion revascularisation and myocardial infarction were numerically lower with DCB compared to a matched cohort receiving second generation DES over 12 months.
3. Definite lesion/stent thrombosis was higher in the DES arm (0.6%) compared to DCB (0%).
4. The risk adjusted composite of death, MI and TLR of DCB is non-inferior to second generation DES (the upper bound of the 95% confidence interval of the odds ratio was 1.47, below the pre specified 1.56).
5. Propensity matching was feasible for clinical parameters but not for some lesion based parameters (length of the treated segment, device diameter, bifurcation lesion and diffuse disease)

There are no data available in the literature to our knowledge for a comparison between 2nd generation DES and DCB in all size coronaries. The previously available such comparisons namely the BASKET-SMALL trial and the SCAAR registry data are confined to largely small vessel coronaries.[137, 138] Our comparison includes all vessel sizes representing day to day practice. The BASKET-SMALL randomised trial showed non inferiority for MACE (cardiac death, MI, TVR) in DCB-only angioplasty compared to

DES in coronaries of 2-3mm diameter in 382 and 376 patients respectively. The SCAAR registry showed no difference in target lesion restenosis (7.0% vs. 6.2%) but significantly less target lesion thrombosis (0.2% vs. 1.1%, adjusted HR 0.18; 95% CI 0.04–0.82) with DCB angioplasty compared to 2nd generation DES, in a propensity matched cohort of 1197 lesions in each arm at a median follow up of 901 days. This however did not give information on target lesion revascularisation, target vessel revascularisation and myocardial infarctions, which our study does. Also this included only 5.8% lesions treated with a DCB with a diameter of 3mm or more indicating largely a small vessel cohort in contrast to ours which had 61% of the lesions treated with a DCB diameter of 3mm or more.

As mentioned in section 3.2 under the results, the complexity of lesions pre propensity matching was higher in the DCB arm compared to the DES arm. After propensity score matching most variables were comparable for the two cohorts apart for length of the treated segment, device diameter, bifurcation status and presence of diffuse disease. There appeared to be systematic differences between the two groups for these parameters. The length of the treated segment was shorter in the DCB arm which would be favourable for clinical outcomes. However, the presence of a higher number of bifurcation lesions, diffuse disease and smaller device diameter in the DCB arm are risk factors for adverse clinical outcomes. These factors were further adjusted in the analysis post propensity scoring.

The MACE (all cause death, MI, TLR) rates of 8.2% vs. 7.3% for DCB and DES arms respectively in our study are consistent with the MACE (cardiac death, MI,TVR) rates in

the randomised BASKET-SMALL-2 trial (7.5% vs 7.3% respectively). The individual outcomes are discussed below.

Death

1 year (3.6% vs 2.9%) and 3 year death is numerically high in the DCB group but not statistically significant. The cardiac death rate in the BASKET-SMALL 2 trial at one year was slightly better than our DCB arm at 3.1% but all cause death was not stated. We did not have access to cause of death which was a major limitation on asserting actual aetiology. In the post propensity matched cohort, DCB arm had a shorter length of treated segment which will have been favourable but also had more bifurcations, more diffuse and small vessel disease which are unfavourable in terms of outcomes. As described in section 3.1.1 device diameter of 3mm or more was inversely associated with death in the DCB registry. Though not statistically significant, mortality for small vessel coronary disease was constantly higher in comparison to large vessels as depicted in figure 31. The final outcomes were further risk adjusted for these unmatched variables to minimise the impact.

The heterogeneity of these two cohorts in terms of treatment methods may have confounded the patient level outcomes such as death and makes it difficult to interpret. For example the DCB arm consists of patients who have received drug eluting stents/bare metal stents in the past for different lesions in same or different vessels. If for example a death has occurred due to a late or very late stent thrombosis in a similar patient, it still would have fallen under the DCB arm.

Myocardial infarctions

The rate of myocardial infarction is numerically less in the DCB arm (2.6% vs 3.2%) but not statistically significant. The MI rate in the DCB arm of the BASKET-SMALL 2 trial was lower at 1.6%. The comparatively lax definition of MI in our study may have led to this. One of the expected advantages with DCBs is a reduction of MIs due to absence of permanent metal/polymer (and associated stent related factors such as fracture, overlap, bifurcation stents, under expansion and mal apposition), reduced inflammation and complete endothelialisation. Not having enough event specific details to clarify whether these are target vessel specific MIs, makes it difficult to assess what percentage is lesion/vessel specific. However it should be noted that there was 0% definite treated segment thrombosis in the DCB arm whilst it was 0.6% in the DES arm. The pathophysiology of persistent inflammation, neo intimal hyperplasia and neo atherosclerosis associated with stents is discussed in detail in the section 1.3.1. Whilst the difference of MI is not statistically significant at 12 months it could be expected to swing in favour of DCB in the long term due to above reasons and absence of definite lesion thrombosis in the DCB arm is a very positive signal in this regard.

Target lesion Revascularisations (TLR)

Target lesion revascularisation could be considered the outcome that is directly related to the treatment modality in this study given the confounding factors for other outcomes such as death, MI or target vessel revascularisation. TLR rate is numerically better with DCBs at 2.3% vs. 2.5% at 12 months, but not statistically significant, despite having a higher number of bifurcation lesions and diffusely diseased lesions. Interventionists may have a low threshold for intervention in a previously DCB treated lesion than a lesion with a stent as the former is technically similar to a de novo lesion given the absence of

metal. The 2.3% TLR rate in the DCB arm includes the 4 (0.4%) lesions that were intervened on during the same admission due to haemodynamic instability/persisting ST changes. As described in section 4.2.2, primary PCI was the most associative variable to TLR in the DCB registry study. But presence of thrombus was inversely associated with TLR which will dispute the theory of reduced drug delivery to the vessel wall after DCB PCI in the setting of a STEMI. Under sizing during pre-dilatation and selecting DCB, geographical miss and spending more than 2 minutes to deliver and fully expand the DCB at the lesion site could all be leading to repeat revascularisations.

Target vessel revascularisation (TVR)

TVR was numerically better with DES compared to DCB in this study at 3.8% vs. 4.7% but not statistically significant. There seemed to be a tendency to treat the affected area only during DCB PCI compared to normal to normal segment stenting in DES PCI which could be argued as a reason for higher percentage of TVR seen. However In the BASKET SMALL-2 trial, TVR was higher in the DES arm (4.5% vs. 3.4%) which would go against this. Also two of the TVR in the DCB arm in our study were staged procedures. Previously mentioned heterogeneity of the cohorts, i.e. having stents in the same vessel in the past makes TVR analysis complex in our study. For example one TVR was for an ISR of a separate lesion of the same vessel.

4.3 Limitations

This is a single centre observational study. Selection bias and confounding errors are inherent limitations of such studies. Baseline characteristics and data on PCI procedures were collected in a prospectively established bespoke departmental database (Intellect) which is used to collect departmental data for quality assurance and audit purposes as well as transfer to national datasets. The departmental database is subject to routine quality assurance of the data for completeness and consistency. Outcome data (MI and repeat revascularisations) were derived from the NICOR databases which are quality assured for completeness and consistency and forms the main source of National PCI, MI and cardiac surgery data. Mortality was derived from the NHS digital which is recognised to be a reliable data source. Specific validation of outcome events by cross checking with our own hospital based data and also with surgical data from Royal Papworth Hospital (our cardiac surgical referral center) was carried out for this analysis. The cause of death was not available for all the deaths making it difficult to delineate the aetiology. We were not able to scrutinize (no access to ECGs for example) the myocardial infarctions that were reported outside NNUH. MINAP definition of a MI had to be adopted as we obtained clinical outcomes from it and this could be considered lax comparing to stringent criteria usually adopted in research studies. However it could be argued that this was an issue for both arms of the study. As per latest BCIS audit results, 92.9% of the UK wide PCI procedures has been recorded with NICOR. This leaves some room for a small number of repeat revascularisations to be missed in the NICOR data. However the chance of such event will be the same for both DCB and DES arms. NNUH being the only PCI center for most

of the Norfolk County helps to secure follow up for these patients at our center. This reduces the chance of not recording an event.

It is appreciated that the rate of use of DCB was largely driven by a single operator in the initial period and was increasing steadily throughout the period of study as shown in Figure 18. These factors will affect the validity and interpretation of the propensity matched analysis as the DCB group characteristics will potentially be changing over time and therefore the results may not be generalisable for future patients. To address this further comparative studies of DES and DCB are in progress

DCB angioplasty has a learning curve and operators were at different stages of this curve during the study ranging from zero experience to being well experienced whereas they were all very experienced in angioplasty with stents.

It is recognised that the analyses carried out have been retrospective in nature with all the limitations associated with this type of study design including selection bias, missing data, and potential for misclassification of outcome events. Patients selected for DCB procedures will likely have been “healthier” in the earlier phase of the study although several patient comorbidities occurred more frequently in the DCB group compared to DES pre-propensity matching including diabetes, prior MI and hypertension (Table 41). The DES group had a higher percentage of patients presenting with STEMI and acute coronary syndrome (high risk) pre- propensity score matching. The lesion complexity was higher in the DCB arm. Propensity matched analysis helps to reduce variation between groups but cannot eliminate bias and any results need to be interpreted with caution. The need for carefully conducted prospective observational studies and

randomised controlled trials, as well as health economic analysis (costs and cost efficacy specially given that cost of a DCB is higher than that of a DES at present) to evaluate the safety and efficacy of DCB angioplasty are needed to provide greater confidence in this approach.

We used a non-inferiority test as part of the assessment of DCB angioplasty compared to DES in the propensity scored analysis. This approach is limited by identifying the clinically acceptable boundaries to determine non-inferiority. We used thresholds that have been used in previous studies and as advised by the United States Food and Drug Administration (FDA).[244]Numerical differences in outcomes between DCB and DES were generally small at 1-2%, providing further confidence that our findings provide encouraging results for DCB angioplasty compared to standard DES.

One of the major limitations was the time taken to obtain clinical outcomes from the NICOR. NICOR was undergoing major changes within, including change of hands in terms of management by the University College of London to Barts and the London NHS Trust. From the first application to obtaining clinical outcomes data took 22 months (July 2019). This is much longer than European counterparts take. For example the investigators of the Swedish SCAAR registry of DCB, which included patients treated in 2016, were able to finish their study and publish the results by September 2017. When data was finally provided by the NICOR in July 2019, it was able to provide clinical outcomes (MI and revascularisation data) valid up to beginning of 2017 only. This limited our follow up duration for all patients to 12 months whereas mortality data was valid for 3 years. The cost involved in obtaining clinical outcome data amounting to £15,000 is far higher than what is charged in the USA for example. The Healthcare Cost

and Utilization Project (HCUP) web site of the USA quoted data from Nationwide Readmission Database (NRD) for a student, costed $200 for the year 2015, and $150 for each year from 2010 till 2015. The time taken for approvals and the number of bodies involved was another limitation. The bodies/persons included caldicott guardian of the hospital, Research and development of NNUH, Information governance of NNUH and NHS Digital, National Research Ethics Committee, Confidentiality advisory group (CAG), Health Research Authority and finally Healthcare Quality Improvement Partnership, before requesting data from the NICOR. The process is described in section 2.1.4. A simplified process will be immensely helpful to the researchers especially where the primary sponsor is a NHS Trust/body, to publish data in a timely manner.

4.4 Conclusion

This analysis has shown that DCB only angioplasty in de novo coronary angioplasty is technically feasible and produces clinical outcomes that are not statistically different to outcomes with second generation drug eluting stents at 12 months. Its safety and efficacy has been shown in many sub groups such as large vessels, primary PCIs, chronic total occlusions and bifurcation lesions in the registry study. The composite of all cause death, MI and target lesion revascularisation of drug coated balloon arm is non-inferior to that of second generation drug eluting stents.

Randomised clinical trials comparing drug coated balloons to conventional drug eluting stents in the above mentioned different cohorts as well as real world all comer comparisons are warranted to further investigate these findings.

DCB coronary angioplasty has the potential to change the current practice of ubiquitous stenting to using stents when only vessel threatening dissections or severe acute recoil is present. It is certainly a useful tool in the armamentarium of an Interventional Cardiologist. Studies with long term follow up will reveal whether the expected beneficial results of not having permanent metal/polymer are leading to fewer clinical events.

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6 Appendix

6.1 Appendix 1: Letters of approval from National Research Ethics Committee

NHS
Health Research Authority

North West - Haydock Research Ethics Committee
3rd Floor - Barlow House
4 Minshull Street
Manchester
M1 3DZ

Telephone: 0207 104 8004

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

04 May 2017

Dr Upul Wickramarachchi
Clinical Research Fellow in Cardiology
Norfolk and Norwich University Hospital NHS Foundation Trust
Department of Cardiology
Colney Lane
Norwich
NR4 7UY

Dear Dr Wickramarachchi,

Study title:	**Outcomes of Drug Coated Balloon Angioplasty, A UK Real Life Experience from 2009 to 2015.**
REC reference:	**17/NW/0278**
IRAS project ID:	**195002**

The Proportionate Review Sub-committee of the North West - Haydock Research Ethics Committee reviewed the above application on 02 May 2017.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact hra.studyregistration@nhs.net outlining the reasons for your request. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Favourable opinion

On behalf of the Committee, the sub-committee gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA Approval (England)/ NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion").

Approved documents

The documents reviewed and approved were:

Document	*Version*	*Date*
Covering letter on headed paper [REC covering letter]		11 April 2017
IRAS Application Form [IRAS_Form_18042017]		18 April 2017
Other [Approval from Caldicott Guardian]		04 April 2017
Other [Appendix 1. Request for repeat revascularisation (PCI) data (from BCIS data set)]	5.6.1	25 October 2013
Other [Appendix 2. Request for repeat revascularisation (CABG) data (from SCTS data set)]	4.1.2	
Other [Appendix 3. Request for information on MIs (from MINAP data set)]	9	01 December 2010
Other [Dr Simon Eccleshall]		
Research protocol or project proposal [Study protocol]	1.6	30 January 2017
Summary CV for Chief Investigator (CI)		26 February 2016
Summary CV for supervisor (student research) [Professor Marcus Flather]		12 March 2017

Membership of the Proportionate Review Sub-Committee

The members of the Sub-Committee who took part in the review are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

<u>Reporting requirements</u>

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments

- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

With the Committee's best wishes for the success of this project.

17/NW/0278	**Please quote this number on all correspondence**

Yours sincerely

Signed on behalf of:
Dr Ben Johnson
Active Chair

Email: nrescommittee.northwest-haydock@nhs.net

Enclosures: List of names and professions of members who took part in the review

"After ethical review – guidance for researchers"

Copy to: Ms Julie Dawson, Norfolk and Norwich University Hospital NHS Foundation Trust
Mr Michael Sheridan, Norfolk and Norwich University Hospital NHS Foundation Trust

NHS
Health Research Authority

North West - Haydock Research Ethics Committee
3rd Floor - Barlow House
4 Minshull Street
Manchester
M1 3DZ

Tel: 0207 104 8004

18 December 2017

Dr Upul Wickramarachchi
Clinical Research Fellow in Cardiology
Norfolk and Norwich University Hospital NHS Foundation Trust
Department of Cardiology
Colney Lane
Norwich
NR4 7UY

Dear Dr Wickramarachchi,

Study title:	**Outcomes of Drug Coated Balloon Angioplasty, A UK Real Life Experience from 2009 to 2015.**
REC reference:	**17/NW/0278**
Amendment number:	**1**
Amendment date:	**28 November 2017**
IRAS project ID:	**195002**

The above amendment was reviewed by the Sub-Committee in correspondence.

Favourable opinion

This amendment consisted of the use of identifiable data without consent.

No material ethical issues were raised.

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Notice of Substantial Amendment (non-CTIMP)	1	28 November 2017
Other [Patient group discussion 14th June 16]		
Other [Data flow chart]	1	08 August 2017
Participant information sheet (PIS) [For public]	1	08 August 2017

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

Working with NHS Care Organisations

Sponsors should ensure that they notify the R&D office for the relevant NHS care organisation of this amendment in line with the terms detailed in the categorisation email issued by the lead nation for the study.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R&D staff at our Research Ethics Committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

17/NW/0278:	**Please quote this number on all correspondence**

Yours sincerely

PP Dr Tim S Sprosen
Chair

E-mail: nrescommittee.northwest-haydock@nhs.net

Enclosures:	List of names and professions of members who took part in the review
Copy to:	Mr Michael Sheridan, Norfolk and Norwich University Hospital NHS Foundation Trust Dr Upul Wickramarachchi, Norfolk and Norwich University Hospital NHS Foundation Trust

Health Research Authority

North West - Haydock Research Ethics Committee

3rd Floor - Barlow House
4 Minshull Street
Manchester
M1 3DZ

Tel: 0207 104 8004

Please note: This is the favourable opinion of the REC only and does not allow the amendment to be implemented at NHS sites in England until the outcome of the HRA assessment has been confirmed.

12 September 2018

Dr Upul Wickramarachchi
Clinical Research Fellow in Cardiology
Norfolk and Norwich University Hospital NHS Foundation Trust
Department of Cardiology
Colney Lane
Norwich
NR4 7UY

Dear Dr Wickramarachchi

Study title:	**Outcomes of Drug Coated Balloon Angioplasty, A UK Real Life Experience from 2009 to 2015.**
REC reference:	**17/NW/0278**
Amendment number:	**Amendment 2**
Amendment date:	**01 June 2018**
IRAS project ID:	**195002**

The above amendment was reviewed by the Sub-Committee in correspondence.

Favourable opinion

The purpose of the amendment was to notify the Committee of updates made to the Protocol.

No material ethical issues were raised.

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Notice of Substantial Amendment (non-CTIMP)	Amendment 2	01 June 2018
Other [Amended Public Notice]	2	03 August 2018
Other [Caldicott Guardian's Approval]		24 July 2018
Other [Cardiology Chief of Service Approval]		01 June 2018
Research protocol or project proposal	1.7	02 August 2018

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

Working with NHS Care Organisations

Sponsors should ensure that they notify the R&D office for the relevant NHS care organisation of this amendment in line with the terms detailed in the categorisation email issued by the lead nation for the study.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R&D staff at our Research Ethics Committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

17/NW/0278:	**Please quote this number on all correspondence**

Yours sincerely

PP Dr Tim S Sprosen
Chair

E-mail: nrescommittee.northwest-haydock@nhs.net

Enclosures: List of names and professions of members who took part in the review

Copy to: Mr Michael Sheridan, Norfolk and Norwich University Hospital NHS Foundation Trust
Dr Upul Wickramarachchi, Norfolk and Norwich University Hospital NHS Foundation Trust

6.2 Appendix 2 Public notice

03/08/2018

Public Notice – Outcomes of Drug Coated Balloon Angioplasty, A UK Real Life Experience from 2009 to 2015 (DCBNORWICH).

DCBNORWICH study is a proposed registry to assess outcomes of patients who have received angioplasty treatment with a novel device called a drug coated balloon during the aforementioned period. Norfolk and Norwich University Hospital (NNUH) is the leading hospital in the UK performing these procedures and has been recognized as a center of expertise for this type of treatment.

The study involves retrieving clinical outcomes from the National Institute of Cardiac Outcomes Research (NICOR) which collects patient data of all angioplasty procedures, coronary artery bypass graft surgeries and heart attacks from all NHS hospitals. In order to track the outcomes, patient identifiable data such as the NHS number, DOB and gender will be shared with the NICOR. It is proposed to report outcomes for the next 10 years making this a study with a very long term follow up period. Patient identifiable data will be accessed only by hospital doctors/direct care team members and the NICOR. In a very small number of patients, identifiable information will be shared with a member of the direct care team of another hospital if they have received angioplasty outside Norfolk and Norwich Hospital on a later date. No identifiable data will be published nor divulged to any other party.

All relevant approvals such as Caldicott guardian of the hospital, National Research Ethics Committee and Health Research Authority (HRA) approval have been obtained prior to commencement of the study. HRA advised to apply for recommendations from Confidentiality Advisory Group (CAG) which has been adhered to. The CAG provides a recommendation to the Health Research Authority (HRA) as appointed decision-maker for research applications. The HRA takes the final decision to support an application under Regulation 5 of the Health Service (Control of Patient Information) Regulations 2002 to process patient identifiable information without consent.

This will be one of the largest registries published on this domain once completed and will be invaluable in further advancements of the field.

A patient group meeting has been held to obtain patient views and a patient is in the study steering committee to oversee adherence to guidelines as well as to make sure patient interests are met.

If you are a patient who has received drug coated balloon angioplasty treatment at the NNUH during the above mentioned period and if you have any objection to your data being used in the above manner please do get in touch with us using any of the below mentioned contact portals.

Amendment: A proposal is in place to include all the patients who received drug eluting stent angioplasty during the above period to enable a meaningful comparison between the two treatment modalities. This proposal will also be subjected to approval by all of the above mentioned bodies. If you have received drug eluting stent treatment during the above period at NNUH and if you have any

objection to your data being used as described above please do get in touch using the same contact portals.

Dr Upul Wickramarachchi, Clinical Research Fellow, NNUH – Chief Investigator (upul.wickramarachchi@nnuh.nhs.uk)

Dr Simon Eccleshall, Consultant Cardiologist, NNUH – Primary Supervisor of the project (simon.eccleshall@nnuh.nhs.uk)

Research and Development, Norfolk and Norwich University Hospital NHS Foundation Trust, Colney Lane, NR4 7UY. Telephone 01603 289808 or email rdoffice@nnuh.nhs.uk

6.3 Appendix 3: Data Requests from NICOR

6.3.1 Data request format for BCIS

6.3.2 Data request format for Adult Cardiac Surgery data set

6.3.3 Data request format for MINAP

Please see the attached Excel data sheets for above.

6.4 Publications

6.4.1 The Role of Drug-Coated Balloons on Late Lumen Enlargement.

U. Wickramarachchi and S. C. Eccleshall. © Springer Nature Switzerland AG 2019 129 B. Cortese (ed.), Drug-Coated Balloons,

https://doi.org/10.1007/978-3-319-92600-1_13

6.4.2 Drug-Coated Balloons in STEMI.

Wickramarachchi U, Ho HH, Eccleshall S.

Editors; Watson TJ, Ong PJL, Tcheng JE. Source; Primary Angioplasty: A Practical Guide. Singapore: Springer; 2018. Chapter 12. 2018 Jul 14. PMID: 31314432

6.4.3 Drug-coated Balloon-only Angioplasty for Native Coronary Disease Instead of Stents.

Wickramarachchi U, Eccleshall S. Interv Cardiol. 2016 Oct;11(2):110-115. doi: 10.15420/icr.2016:17:3. PMID: 29588716

6.4.4 Safety of bailout stenting after paclitaxel-coated balloon angioplasty.

Mok KH, Wickramarachchi U, Watson T, Ho HH, Eccleshall S, Ong PJL. Herz. 2017 Nov;42(7):684-689. doi: 10.1007/s00059-016-4502-9. Epub 2016 Nov 17. PMID: 27858114