## MHIF FEATURED STUDY: PIONEER III

<table>
<thead>
<tr>
<th>CONDITION:</th>
<th>PI:</th>
<th>RESEARCH CONTACT:</th>
<th>SPONSOR:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable CAD, acute coronary syndromes without ST-segment elevation-UA, NSTEMI</td>
<td>M. Nicholas Burke, MD</td>
<td>Carmen Chan-Tram&lt;br&gt;<a href="mailto:carmen.chan-tram@allina.com">carmen.chan-tram@allina.com</a></td>
<td>Sino Medical Sciences Technology</td>
</tr>
</tbody>
</table>

### DESCRIPTION:
A prospective, multicenter, global randomized (2:1) controlled trial assessing safety and efficacy of the BuMA Supreme™ Biodegradable Drug Coated Coronary Stent System (made of cobalt chromium with sirolimus) for coronary PCI or coronary stenting in patients with stable coronary artery disease or non-ST segment elevation acute coronary syndromes.

### CRITERIA LIST/ QUALIFICATIONS:

**Inclusion**
1) Male or non-pregnant female ≥20 and not greater than 99 years of age
2) Symptomatic ischemic heart disease-chronic stable angina, UA, NSTEMI requires elective or urgent PCI
3) Comply with specified follow-up evaluation
4) De novo lesion, 2 target lesions per epicardial vessel and max of 3 target lesions

**Exclusion**
1) History of bleeding, on chronic anticoagulation therapy
2) STEMI at index or within 7 days
3) LVEF < 30%, eGFR < 30 mL/min/1.73 m²
4) Previous 3 months PCI in target vessel with stent placement
5) Discontinuation of DAPT within 6 months of index procedure
6) Transplant or on waitlist, receiving immunosuppressant therapy
7) No CTO, LM or graft
MHIF FEATURED STUDY: XIENCE 90

DESCRIPTION:
A prospective, single-arm, multi-center, open label trial to evaluate the safety of 3-month (as short as 90 days) dual antiplatelet therapy (DAPT) in subjects at high risk of bleeding (HRB) undergoing percutaneous coronary intervention (PCI) with the approved XIENCE family of coronary drug-eluting stents.

CRITERIA LIST/QUALIFICATIONS:

Inclusion
1) Subject is considered at high risk of bleeding, defined as meeting one or more of the following:
   a. ≥ 75 years of age
   b. Clinical indication for chronic (at least 6 months) or lifelong anticoagulant therapy
   c. History of major bleeding which required medical attention within 12 months of the index procedure
   d. History of stroke (ischemic or hemorrhagic)
   e. Renal insufficiency (creatinine ≥ 2.0 mg/dl) of failure (dialysis dependent)
   f. Systematic conditions associated with increased bleeding risk
   g. Anemia with hemoglobin < 11 g/dl
2) Subject must be at least 18 years of age
3) Subject must provide written informed consent
4) Subject is willing to comply with protocol
5) Subject must not agree to participate in any other clinical trial for a period of one year following index procedure

Exclusion
1) STEMI at index procedure
2) Known hypersensitivity or contraindication to aspirin, heparin/bivalirudin, P2Y12 inhibitors, everolimus, cobalt, chromium, nickel, tungsten, acrylic and fluoro polymers or contrast sensitivity that cannot be adequately pre-medicated
3) Previous PCI with another stent other than XIENCE within 9 months prior to Index procedure
4) Known LVEF < 30%
5) Judged as inappropriate by physician for discontinuation from P2Y12 inhibitors at 3 months
6) Planned surgery or procedure within 3 months of PCI necessitating discontinuation of P2Y12 inhibitor
7) Life expectancy of less than 12 months
8) Subject intends to participate in another investigational study within 12 months
9) Pregnant or nursing subjects and those who plan to become pregnant within 1 year
10) Subject is part of a vulnerable population
11) Subject is currently participating in another clinical trial
MHIF FEATURED STUDY:
XIENCE 28

DESCRIPTION:
A prospective, single-arm, multi-center, open label trial to evaluate the safety of 1-month (as short as 28 days) dual antiplatelet therapy (DAPT) in subjects at high risk of bleeding (HRB) undergoing percutaneous coronary intervention (PCI) with the approved XIENCE family of coronary drug-eluting stents.

CRITERIA LIST/ QUALIFICATIONS:

Inclusion
1) Subject is considered at high risk of bleeding, defined as meeting one or more of the following:
   a. ≥ 75 years of age
   b. Clinical indication for chronic (at least 6 months) or lifelong anticoagulant therapy
   c. History of major bleeding which required medical attention within 12 months of the index procedure
   d. History of stroke (ischemic or hemorrhagic)
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1) STEMI at index procedure.
2) Known hypersensitivity or contraindication to aspirin, heparin/bivalirudin, P2Y12 inhibitors, everolimus, cobalt, chromium, nickel, tungsten, acrylic and fluoro polymers or contrast sensitivity that cannot be adequately pre-medicated.
3) Previous PCI with another stent other than XIENCE within 12 months prior to index procedure.
4) Known LVEF < 30%.
5) Judged as inappropriate by physician for discontinuation from P2Y12 inhibitors at 1 month.
6) Planned surgery or procedure within 1 month of PCI necessitating discontinuation of P2Y12 inhibitor.
7) Life expectancy of less than 12 months.
8) Subject intends to participate in another investigational study within 12 months.
9) Pregnant or nursing subjects and those who plan to become pregnant within 1 year.
10) Other reasons in the investigator’s opinion could limit compliance with follow-up or impact scientific soundness of results.
11) Subject is currently participating in another clinical trial.

CONDITION:
Stable CAD, acute coronary syndromes without ST-segment elevation-UA, NSTEMI

PI:
M. Nicholas Burke, MD

RESEARCH CONTACT:
Kalina Yang
kalina.yang@allina.com | 612-863-9271

SPONSOR:
Abbott Cardiovascular Systems, Inc.

Study Status: In process
Minneapolis Heart Institute Foundation® Cardiovascular Grand Rounds

Title: Drug-coated balloons: the missing piece in the puzzle

Speaker: Michael S. Megaly, MD, MS, Cardiovascular Disease Fellow
Minneapolis Heart Institute® at Abbott Northwestern Hospital &
Hennepin Healthcare

Date: May 13, 2019
Time: 7:00 - 8:00 AM
Location: ANW Education Building, Watson Room

OBJECTIVES
At the completion of this activity, the participants should be able to:
1. Summarize what drug-coated balloons are.
2. Identify drug-coated balloons use in coronary interventions.
3. Apply future directions for drug-coated balloons.

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Signature: __________________________________________________________________________
My signature verifies that I have attended the above stated number of hours of the CME activity.

Allina Health - Learning & Development - 2925 Chicago Ave - MR 10701 - Minneapolis MN 55407
Drug-coated balloons: the missing piece in the puzzle

Michael Megaly, MD, MS
May 13th, 2019

No disclosures
Objectives

1- What are drug coated balloons? History? How do they work?

2- Uses of drug coated balloons in coronary artery disease.

3- Future directives and concerns

What are DCBs?

Paclitaxel
Hydrophobic

Very high pharmacokinetic transfer rate into the vessel wall

Sirolimus
MagicTouch

Drug-Coated Balloon Technology

Active drug
Excipient

Balloon surface
Matrix coating
Endothelium
Plaque or neointima
Tunica media

Why?

Case

- 64 year old gentleman
  - NSTEMI
- History of DES to mid-LAD and D1
History of drug-coated balloons

Local delivery of paclitaxel to the vessel wall reduces neointimal proliferation

1-porous catheter (rabbits) (Axel 1997)

2-double balloon catheter (porcine) (Herdeg 2000)

3-intra-pericardial (porcine) (Hou 2000)
First use of paclitaxel-coated balloons
Scheller 2004, circulation (cited by 95 patents)

Paclitaxel mounted on regular PTCA balloons

Solvents: ethyl acetate (EEE) or acetone (AC) →
1.3-2.5 μg/mm² → 40 porcine arteries

6% of the drug lost in blood stream
0% lost during inflation
Dose in the vessel wall in 40-60 mins (8%-17%)

First use of paclitaxel-coated balloons
At 35 days: Dose-dependent response

control

EE

ER

AcL

AcR
First use of paclitaxel-coated balloons
Scheller 2004
AC preparation more effective

hydrophilic x-ray contrast-medium substance in the coating preparation in the case of the Ac version

This technology could be helpful in the treatment of in-stent restenosis (as an alternative to brachytherapy or stent-in-stent)

Mechanism of drug-coated balloons

The balloon delivers paclitaxel to the endoluminal surface during inflation

Therapeutic drug levels are sustained in the deeper layers of the arterial wall but not in the endothelium allowing re-endothelialization
What affects the efficiency of DCBs?

1-Drug carrier

The relative uptake by the vessel wall (retention during transit, transfer efficiency)

Total drug load required on the balloon (to decrease downstream effect of the drug)

Most common carriers used

Paclitaxel loading 2-3 μg/mm2
What affects the efficiency of DCBs?

2-Manufacturing process

Ensure that the coating can withstand intra-arterial conditions (vessel tortuosity, heavy plaque burden, or calcification) to ensure there is no drug loss during transit.

Drug-coated balloons and drug-eluting stents

<table>
<thead>
<tr>
<th>DES</th>
<th>DEB</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Platform of drug delivery</strong></td>
<td>Stent scaffolding</td>
</tr>
<tr>
<td><strong>Retention</strong></td>
<td>Polymer based</td>
</tr>
<tr>
<td><strong>Drug dose</strong></td>
<td>Low: &lt;100 to 200 μg</td>
</tr>
<tr>
<td><strong>Release kinetics</strong></td>
<td>Slow and controlled</td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
<td>Strut-based vascular penetration</td>
</tr>
<tr>
<td><strong>Advantages</strong></td>
<td>Mechanical support</td>
</tr>
<tr>
<td></td>
<td>Abluminal trapping</td>
</tr>
<tr>
<td></td>
<td>Less drug spillage into the circulation</td>
</tr>
<tr>
<td></td>
<td>Proven efficacy in many indications</td>
</tr>
<tr>
<td></td>
<td>No acute recoil tackled dissection</td>
</tr>
</tbody>
</table>

Drug-coated balloons and drug-eluting stents

Drug-coated balloons vs. drug-eluting stents

- Small profile
- Promotes plaque reduction and stabilization
- Promotes vascular healing
- Low risk of restenosis
- Short duration of dual antiplatelet therapy (4 weeks)
Deployment

**Preparation of the lesion** (balloon angioplasty)

1. Intracoronary nitrates: accurate vessel sizing
   2. TIMI III flow
   3. No dissections greater the NHLBI types A or B
   4. Not more than 30% residual stenosis

The DCB should be used only for drug delivery and not for further angioplasty

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Deployment

**Using the drug-coated balloon**

Balloon to vessel ratio (at least 1:1)
Prevent downstream loss of the drug

Do not touch the DCB prior to introduction

Prolonged inflation (30-60 seconds)
Deployment

Coronary dissection of type C or above after DCB use

Bailout stenting with second-generation DES

Drawbacks

Restenosis due to neointimal hyperplasia is a slow process
(the need for prolonged or repeated drug administration)

DES provide better angiographic outcomes
Persistent residual stenosis, acute vessel recoil, and dissections
(requiring bailout stenting)
Drug-coated balloons use in coronary artery disease

1- In-stent restenosis

2- De-novo lesions (Small-vessels, large vessels)

3- Bifurcation lesions

4- Diabetic patients

5- Acute coronary syndrome (STEMI)

Drug-coated balloons use in in-stent restenosis
**Guidelines**

Balloon angioplasty, BMS, DES

DES, DCB

Non-stent strategy
Not adding additional metal layers to an ISR lesion

**DCB superior to balloon angioplasty**

*Scheller 2006 (NEJM)*
52 patients (DCB vs. BA)
DCB vs. balloon angioplasty and PES

**ISAR-DESIRE 3 (Byrne 2013, Lancet)**

402 patients (1:1:1 PEB, PES, or angioplasty)

**DCB vs. DES**

**RIBS V trial (Alfonso 2014)**

189 patients (BMS ISR) (Sequent please DCB, Xience DES)
**SEDUCE trial (Adriaenssens 2014)**

50 patients (BMS ISR) (Sequent please DCB, Xience DES)

OCT at 9 months → EES

Lower percentage of diameter stenosis at nine-month angiography 

did not translate into differences in clinical outcome

<table>
<thead>
<tr>
<th></th>
<th>DEB (n=24)</th>
<th>EES (n=25)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>1 (4.2%)</td>
<td>1 (4%)</td>
<td>0.976</td>
</tr>
<tr>
<td>Stent thrombosis (*)</td>
<td>0 (0%)</td>
<td>1 (4%)</td>
<td>0.322</td>
</tr>
<tr>
<td>Clinical restenosis</td>
<td>2 (8.3%)</td>
<td>1 (4%)</td>
<td>0.148</td>
</tr>
<tr>
<td>Target lesion revascularisation</td>
<td>1 (4.2%)</td>
<td>2 (8%)</td>
<td>0.576</td>
</tr>
<tr>
<td>Target vessel revascularisation</td>
<td>2 (8.3%)</td>
<td>4 (15%)</td>
<td>0.413</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0 (0%)</td>
<td>1 (4%)</td>
<td>0.322</td>
</tr>
</tbody>
</table>

DEB: drug-eluting balloon; EES: everolimus-eluting stent; (*): definite stent thrombosis according to ARC (Academic Research Consortium) criteria

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**RIBS IV trial (Alfonso 2015)**

309 patients (DES ISR) (Sequent please DCB, Xience DES)

24% > 1 stent layer
RIBS IV trial (Alfonso 2018)

Landmark analysis at 3 years

![Graph C](image)

DARE trial (Baan 2017)

237 patients (DES or BMS ISR) (Sequent please DCB, Xience DES)

![Graph D](image)
**Meta-analysis of RCTs**

**Cai 2018, BMJ open**

**Elgendy 2019, AJC**

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**Multiple stent layers**

**Yabushita 2018**

304 patients with ISR (groups of 1, 2, and 3 or more metallic layers)

**DCBs are less effective** for ≥3L in-stent restenosis lesions

Number of stent layers is an independent predictor of MACE

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**Outcome** vs **Outcome worse with DCB**

- Target lesion revascularization: 1.89 (0.77, 3.77)
- Target vessel revascularization: 1.24 (0.87, 1.81)
- Myocardial infarction: 0.85 (0.48, 1.57)
- Baren thrombosis: 0.70 (0.33, 1.49)
- All-cause mortality: 1.07 (0.68, 1.59)
- WEX: 1.10 (0.68, 1.82)

**Outcome better with DCB**

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**MACE**

- Freedom from MACE [%]
- Log rank P > 0.01

**TLR**

- Freedom from TLR [%]
- Log rank P > 0.01

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**Number of events (number at risk)**

<table>
<thead>
<tr>
<th>Event</th>
<th>1 stent layer</th>
<th>2 stent layers</th>
<th>3 or more stent layers</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st event</td>
<td>1 (14)</td>
<td>3 (14)</td>
<td>15 (14)</td>
</tr>
<tr>
<td>2nd event</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>3rd event</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
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23 of 41
DCB in de-novo coronary artery lesions

Valentines II trial (**Waksman 2013**, EuroIntervention)
103 patients (POBA+DCB)

<table>
<thead>
<tr>
<th>Baseline</th>
<th></th>
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<tbody>
<tr>
<td>Reference vessel diameter (mm)</td>
<td>2.40±0.51</td>
</tr>
<tr>
<td>Diameter stenosis (%)</td>
<td>65.06±14.16</td>
</tr>
<tr>
<td>Minimum luminal diameter (mm)</td>
<td>0.84±0.38</td>
</tr>
<tr>
<td>Lesion length (mm)</td>
<td>10.45±5.25</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>In-hospital</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0</td>
</tr>
<tr>
<td>Acute myocardial infarction due to abrupt closure</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>TLR/TVR</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Major adverse cardiac events</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Length of stay (days)</td>
<td>3.8±3.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>From discharge to 7.5-month follow-up</th>
<th></th>
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<tbody>
<tr>
<td>All-cause death</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>0</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Target lesion revascularisation</td>
<td>3 (2.9%)</td>
</tr>
<tr>
<td>Target vessel revascularisation</td>
<td>7 (6.9%)</td>
</tr>
<tr>
<td>Vessel thrombosis</td>
<td>0</td>
</tr>
<tr>
<td>Cumulative major adverse cardiac events*</td>
<td>9 (8.7%)</td>
</tr>
</tbody>
</table>
DCB in de-novo coronary artery lesions

Rosenberg 2019, CCI
(The DCB-only All-Comers Registry- 66.9% de-novo lesions)

The TLR rate was lower in the de-novo group (2.3%) when compared to BMS-(2.9%) and DES-ISR(5.8%) (P = 0.049).

MACE, there was a trend toward fewer events in the de-novo group (5.6%) than in the BMS- (7.8%) and DES-ISR cohort (9.6%) (P = 0.131)

DCB in small-vessel coronary artery lesions

Smaller profile compared with DES
(easier access to complex lesions, particularly in small vessels)

Avoidance of foreign body implantation
(Smaller vessels cannot accommodate neointimal growth)
DCB in small-vessel coronary artery lesions
Single-arm registries

Unverdorben 2010

108 patients, RVD (2.35 +/- 0.19 mm), 30% bailout stenting

TLR at 12 months was 12%
MACE at 12 months was 15%

Zeymer 2014

479 patients, RVD (≥2.0 mm, ≤2.75 mm)
23.5% acute coronary syndrome of which 9.2% had STEMI

6% bailout stenting

TLR at 9 months – 3.6%
**DCB in small-vessel coronary artery lesions**  
**RCTs (DCB vs. balloon angioplasty)**

**Funatsu 2017**  
133 patients, RVD <2.75 mm  
DCB (Sequent Please) or balloon angioplasty

6-months follow up  
Lower binary restenosis with DCB (13.3% versus 42.5%, p<0.01)  
Similar TLR (3.4% versus 10.3%, p=0.2)

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**DCB in small-vessel coronary artery lesions**  
**RCTs (DCBs vs. DES)**

**PICCOLETO 2010**  
57 patients, RVD <2.75 mm  
DCB (DIOR I) or first generation DES

**Stopped early**  
Angiographic stenosis worse in DCB (32.1 vs 10.3%, p=0.043)  
MACE (35.7% vs. 13.8% p=0.054)

DIOR I- lack of eluting matrix  
Bailout stenting was high (34%)  
Lesion preparation (<90%)
DCB in small-vessel coronary artery lesions
RCTs (DCBs vs. DES)

**BELLO 2012**
182 patients, RVD <2.8 mm
DCB (IN.PACT FALCON) or first generation DES
20% bailout stenting

6-months follow-up
Similar binary restenosis (8.9% versus 14.1%, p=0.25)
Similar TLR (4.4% versus 7.6%, p=0.37)
Similar MACE (7.8% versus 13.2%, p=0.77)

DCB in small-vessel coronary artery lesions
RCTs (DCBs vs. DES)

**BASKET-SMALL 2, 2018 (Lancet)**
758 patients, RVD <3 mm
DCB (Sequent Please) or DES (first (24%) or second generation)
5% bailout stenting

12-months follow-up
Similar TVR (3.5% versus 4.5%, p=0.44)
Similar MACE (7.5% versus 7.3%, p=0.92)
DCB in small-vessel coronary artery lesions

RCTs (DCBs vs. DES)

**RESTORE-SVD China 2018 (non-inferiority)**

230 patients, RVD (RVD < 2.25 mm)
DCB (Restore) or DES (RESOLUTE Integrity DES)

9-months follow-up
Percent diameter stenosis (29.6±2.0% vs. 24.1±2.0%), p < 0.001 for non-inferiority

One-year TLF was similar (4.4% versus 2.6%, p=0.72)
DCB in small-vessel coronary artery lesions

Outcomes with DCB versus BA in small vessel coronary artery disease

- TLR: 1.00% (DCB) vs. 8.00% (BA) p=0.03
- BINARY RESTENOSIS: 10.20% (DCB) vs. 38.00% (BA) p <0.0001

DCB in small-vessel coronary artery lesions

Outcomes with DCB versus DES in small vessel coronary artery disease

- TLR: 5.50% (DCB) vs. 5.90% (DES) p=0.97
- MACE: 11.00% (DCB) vs. 13.50% (DES) p=0.57
- BINARY RESTENOSIS: 15.00% (DCB) vs. 13.00% (DES) p=0.62
### DCB in bifurcation lesions (side branch)

#### DCB vs. Balloon angioplasty

<table>
<thead>
<tr>
<th></th>
<th>Mingues et al. (BABILON)</th>
<th>Herrador et al.</th>
<th>Stella et al. (DEBUT)</th>
<th>Kleber et al. (PEPCAD BIF)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Year</strong></td>
<td>2014</td>
<td>2013</td>
<td>2012</td>
<td>2016</td>
</tr>
<tr>
<td><strong>Country</strong></td>
<td>Spain</td>
<td>Spain</td>
<td>Four countries in Europe</td>
<td>Germany</td>
</tr>
<tr>
<td><strong>Study design</strong></td>
<td>RCT</td>
<td>Observational</td>
<td>RCT</td>
<td>RCT</td>
</tr>
<tr>
<td><strong>Side branch definition</strong></td>
<td>≥2 mm in diameter</td>
<td>&gt;2.5 mm in diameter and &lt;10 mm in length</td>
<td>&gt;2 mm in diameter</td>
<td>Within 5 mm of bifurcation point, 2-3.5 mm in diameter, and &lt;10 mm in length</td>
</tr>
<tr>
<td><strong>Total study population</strong></td>
<td>108 patients</td>
<td>100 patients</td>
<td>77 patients</td>
<td>64 patients</td>
</tr>
<tr>
<td><strong>Intervention to main branch</strong></td>
<td>BMS in DCB group and DES in the BA group</td>
<td>DES in both groups</td>
<td>BMS in both groups</td>
<td>No proximal main branch lesions</td>
</tr>
<tr>
<td><strong>Study groups</strong></td>
<td>52 DCB patients</td>
<td>50 DCB patients</td>
<td>40 DCB patients</td>
<td>32 DCB patients</td>
</tr>
<tr>
<td></td>
<td>56 BA patients</td>
<td>50 BA patients</td>
<td>37 BA patients</td>
<td>32 BA patients</td>
</tr>
<tr>
<td><strong>Stenting performed</strong></td>
<td>7.8% in DCB group</td>
<td>10% in DCB group</td>
<td>10% in DCB group</td>
<td>0% in DCB group</td>
</tr>
<tr>
<td></td>
<td>8.9% in BA group</td>
<td>4% in BA group</td>
<td>5.4% in BA group</td>
<td>18.8% in BA group</td>
</tr>
<tr>
<td><strong>Type of side-branch stent [if used]</strong></td>
<td>BMS in DCB group and DES in BA group</td>
<td>BMS in DCB group and DES in BA group</td>
<td>BMS in both groups</td>
<td>At the discretion of the interventionalist</td>
</tr>
<tr>
<td><strong>Follow-up period</strong></td>
<td>24 months</td>
<td>12 months</td>
<td>12 months</td>
<td>9 months</td>
</tr>
<tr>
<td><strong>Type of DCB</strong></td>
<td>SeQuent Please [B. Braun, Germany]</td>
<td>SeQuent Please [B. Braun, Germany]</td>
<td>Olim [EuroCer, Germany]</td>
<td>SeQuent Please [B. Braun, Germany]</td>
</tr>
<tr>
<td><strong>Angiographic follow-up</strong></td>
<td>82.6% DCB 76.7% BA</td>
<td>80% DCB 86% BA</td>
<td>82.5% DCB 95% BA</td>
<td>78.3% DCB 71.9% BA</td>
</tr>
</tbody>
</table>
DCB in bifurcation lesions

<table>
<thead>
<tr>
<th></th>
<th>DCB (n=174)</th>
<th>BA (n=175)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64.1 ± 10.9</td>
<td>64.4 ± 10.6</td>
<td>.79</td>
</tr>
<tr>
<td>Male</td>
<td>71.6%</td>
<td>73.7%</td>
<td>.66</td>
</tr>
<tr>
<td>Diabetes</td>
<td>25.6%</td>
<td>30.3%</td>
<td>.32</td>
</tr>
<tr>
<td>Hypertension</td>
<td>58.4% [142]</td>
<td>60.9% [143]</td>
<td>.66</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>61.3% [142]</td>
<td>56.6% [143]</td>
<td>.42</td>
</tr>
<tr>
<td>Smoking</td>
<td>53.1%</td>
<td>56.5%</td>
<td>.52</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>21.1% [142]</td>
<td>16.0% [143]</td>
<td>.26</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>33.3%</td>
<td>34.8%</td>
<td>.76</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>55.6% [90]</td>
<td>51.7% [87]</td>
<td>.60</td>
</tr>
</tbody>
</table>

Medina type 0,0,1 lesions were 70%

1. Main Branch proximal lesion > 50%: 0 or 1
2. Main Branch distal lesion > 50%: 0 or 1
3. Side Branch lesion > 50%: 0 or 1

Mean follow-up of 9.1 ± 2.1 months.
DCB was associated with **less late lumen loss**

(mean difference, -0.19 mm; 95% CI, -0.37 to -0.01; P=.04)
DCB in bifurcation lesions

DCB versus BA in the treatment of SB in coronary bifurcation lesions.

P = 0.22

16.40%

11.70%

16.90%

19.50%

34%

DCBs in diabetic patients
DCBs in diabetic patients
DCBs vs. DES

Smaller profile
smaller vessels which is a common site of pathology in diabetics

No metal left
Increased risk of ISR in diabetics

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of study</td>
<td>Observational</td>
<td>Observational</td>
<td>RCT</td>
</tr>
<tr>
<td>DCB/DES group</td>
<td>39/35</td>
<td>91/129</td>
<td>45/39</td>
</tr>
<tr>
<td>Clinical follow up</td>
<td>12</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Angiographic follow</td>
<td>6</td>
<td>N/A</td>
<td>9</td>
</tr>
<tr>
<td>Country of the study/center</td>
<td>Italy, 15</td>
<td>Argentina, 3</td>
<td>Malaysia and Thailand, NA</td>
</tr>
<tr>
<td>Type of DCB</td>
<td>IN.PACT Falcon paclitaxel DEB (Medtronic, Inc., Santa Rosa, California)</td>
<td>DIOR, (Eurocor GmbH, Germany)</td>
<td>SeQuent Please (BBraun AG, Melsungen, Germany)</td>
</tr>
<tr>
<td>Type of DES used</td>
<td>Taxus Liberté (Boston Scientific, Natick, MA, USA)</td>
<td>Cypher (Cordis, Johnson &amp; Johnson); Taxus (Boston Scientific), Endeavor (Medtronic Vascular); Biodegradable paclitaxel stent (Eucatech,AG)</td>
<td>Taxus Liberté (Boston Scientific, Natick, MA, USA)</td>
</tr>
<tr>
<td>Stenting strategy in the DCB arm</td>
<td>Bailout</td>
<td>Bailout</td>
<td>Provisional</td>
</tr>
<tr>
<td>Stenting percentage in the DCB arm</td>
<td>19%</td>
<td>96%</td>
<td>100%</td>
</tr>
</tbody>
</table>
DCBs in diabetic patients

![Percutaneous Coronary Intervention in Diabetic Patients](image)

- Meta-analysis of three studies, 379 patients with a mean follow-up of 17 months.

- Drug-coated balloons:
  - 8%
  - Binary restenosis: p=0.26
  - 6.9%
  - Target lesion revascularization: p=0.07
  - 13.1%
  - Major adverse cardiovascular events: p=0.11

- Drug-eluting stents:
  - 17%

Back to the case
Back to the case
In-stent restenosis
Small-vessel lesion
Bifurcation lesion

Future directives
Future directives
Cost effectiveness (CAD)

**Bonaventura (TCT, 2012)**
Treatment of BMS ISR

**Initial procedural cost**
- $4,497.27 for DCB
- $4,128.81 for DES implantation

**Over a 12-month time horizon**
- DCB less costly: $5,154.47 versus $6,619.98
- More effective (life expectancy) (0.983 versus 0.976 years)

Future directives
Coming to US for CAD
FDA’s reluctance to approve coronary use of DCB.

**Regulatory bar is higher** in the US than in Europe, with a requirement for larger-scale clinical trials.

DCB trials have been powered for **surrogate endpoints** and not hard clinical outcomes

Safety concerns

---

FDA’s reluctance to approve coronary use of DCB.

**Response from Medtronic**

“**Regulatory hurdles** is what has prevented companies so far to seek US approval for DCB, as the requirements for clinical evidence to demonstrate safety and effectiveness in a US patient population are substantial for a relatively small **market size**. To my knowledge there are currently no clinical trials in the US underway in the field of coronary DCB products.”
Recent concerns
Katsanos 2018, JAHA

Meta-analysis of paclitaxel-coated devices in femoropopliteal disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Paclitaxel Events Total</th>
<th>Control Events Total</th>
<th>Risk Ratio</th>
<th>RR</th>
<th>95% CI</th>
<th>Weight (fixed)</th>
<th>Weight (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZILVER-PTX</td>
<td>19 207</td>
<td>7 177</td>
<td>1.62</td>
<td>0.60</td>
<td>3.77</td>
<td>20.8% 20.0%</td>
<td></td>
</tr>
<tr>
<td>FINN-PTX</td>
<td>1 23</td>
<td>0 18</td>
<td>2.36</td>
<td>0.10</td>
<td>54.68</td>
<td>1.3% 1.3%</td>
<td></td>
</tr>
<tr>
<td>IN.PACT SFA</td>
<td>18 108</td>
<td>1 106</td>
<td>0.57</td>
<td>1.15</td>
<td>63.70</td>
<td>3.1% 3.7%</td>
<td></td>
</tr>
<tr>
<td>FEMPAD</td>
<td>7 45</td>
<td>3 42</td>
<td>2.16</td>
<td>0.60</td>
<td>7.68</td>
<td>7.4% 8.3%</td>
<td></td>
</tr>
<tr>
<td>LEVANT II</td>
<td>4 49</td>
<td>5 52</td>
<td>0.85</td>
<td>0.24</td>
<td>2.98</td>
<td>11.5% 9.4%</td>
<td></td>
</tr>
<tr>
<td>LEVANT III</td>
<td>21 278</td>
<td>7 140</td>
<td>1.51</td>
<td>0.66</td>
<td>2.47</td>
<td>22.1% 21.4%</td>
<td></td>
</tr>
<tr>
<td>CONSEQUENT</td>
<td>2 70</td>
<td>1 65</td>
<td>1.86</td>
<td>0.17</td>
<td>20.00</td>
<td>2.5% 2.6%</td>
<td></td>
</tr>
<tr>
<td>ILLUMINATE EU</td>
<td>13 199</td>
<td>3 55</td>
<td>1.28</td>
<td>0.36</td>
<td>4.58</td>
<td>11.0% 9.9%</td>
<td></td>
</tr>
<tr>
<td>ISAR-STATI</td>
<td>3 48</td>
<td>1 47</td>
<td>1.66</td>
<td>0.71</td>
<td>4.66</td>
<td>1.5% 2.9%</td>
<td></td>
</tr>
<tr>
<td>ISAR-PEBI</td>
<td>3 28</td>
<td>0 29</td>
<td>7.25</td>
<td>0.36</td>
<td>134.08</td>
<td>1.2% 1.7%</td>
<td></td>
</tr>
<tr>
<td>ACCENT I</td>
<td>6 86</td>
<td>6 95</td>
<td>1.32</td>
<td>0.48</td>
<td>3.06</td>
<td>10.3% 14.2%</td>
<td></td>
</tr>
<tr>
<td>IN.PACT SFA JAPAN</td>
<td>4 66</td>
<td>1 29</td>
<td>1.76</td>
<td>0.21</td>
<td>15.00</td>
<td>3.3% 3.2%</td>
<td></td>
</tr>
</tbody>
</table>

Fixed effect model: 1397 919 [1.27; 2.64] 100.0% –
Random effects model: 1.68 [1.15; 2.47] 100.0%

<table>
<thead>
<tr>
<th>Study</th>
<th>Paclitaxel Events Total</th>
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<th>Risk Ratio</th>
<th>RR</th>
<th>95% CI</th>
<th>Weight (fixed)</th>
<th>Weight (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>THUNDER</td>
<td>12 48</td>
<td>8 54</td>
<td>1.69</td>
<td>0.75</td>
<td>3.78</td>
<td>23.9% 26.9%</td>
<td></td>
</tr>
<tr>
<td>ZILVER-PTX</td>
<td>42 297</td>
<td>12 177</td>
<td>2.09</td>
<td>1.13</td>
<td>3.85</td>
<td>47.7% 46.3%</td>
<td></td>
</tr>
<tr>
<td>IN.PACT SFA</td>
<td>24 164</td>
<td>7 103</td>
<td>1.92</td>
<td>0.86</td>
<td>4.30</td>
<td>28.5% 26.8%</td>
<td></td>
</tr>
</tbody>
</table>

Fixed effect model: 529 334 [1.28; 2.96] 100.0% –
Random effects model: 1.93 [1.27; 2.93] 100.0%
Recent concerns

Death were not uniformly recorded in the studies

Causes of death are missing in most of the studies

Some studies had Clinical Events Committee reviewed the cause of death and could not find a link to the use of paclitaxel (IN.PACT DCB, ZILVER PTX DES)

No plausible mechanism between paclitaxel and deaths could be established

Recent concerns

LINC 2019 (Germany), patient-level data disproved the meta-analysis (IN.PACT DCB, Lutonix DCB, Stellarex DCB, Zilver PTX DES, Eluvia DES and Ranger DCB)

Patient-level meta-analysis (Schneider et al. JACC 2019), 4 prospective registries.
5-year morality: 9.3% vs 11.2%, p=0.399
Summary

Small profile  Promotes plaque reduction and stabilization  Promotes vascular healing  Low risk of restenosis  Short duration of dual antiplatelet therapy (4 weeks)

Outcomes with DCB versus DES in small vessel coronary artery disease

<table>
<thead>
<tr>
<th></th>
<th>DCB</th>
<th>DES</th>
</tr>
</thead>
<tbody>
<tr>
<td>1yR</td>
<td>5.0%</td>
<td>5.0%</td>
</tr>
<tr>
<td>MACE</td>
<td>11.0%</td>
<td>11.0%</td>
</tr>
<tr>
<td>BINARY RESTENOSIS</td>
<td>5.0%</td>
<td>10.0%</td>
</tr>
</tbody>
</table>

p=0.97

p=0.07

Major Adverse Events (%)

P=0.06

Time (months)

Thank you