MHIF FEATURED STUDY: PIONEER III

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

CONDITION: Stable CAD, acute coronary syndromes without ST-segment elevation-UA, NSTEMI
PI: M. Nicholas Burke, MD
RESEARCH CONTACT: Carmen Chan-Tram
carmen.chan-tram@allina.com | 612-863-5507
SPONSOR: Sino Medical Sciences Technology

OPEN AND ENROLLING: Please Refer Patients!
Critical Limb Ischemia

5/20/2019

Critical limb ischemia (CLI)

- Any patient with chronic ischemic rest pain, ulcers, or gangrene attributable to objectively proven arterial occlusive disease.

- “End-stage” of peripheral arterial disease
<table>
<thead>
<tr>
<th>Classification</th>
<th>Stage</th>
<th>Clinical description</th>
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<tbody>
<tr>
<td>Fontaine</td>
<td>I</td>
<td>Asymptomatic</td>
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<td></td>
<td>IIa</td>
<td>Mild claudication</td>
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<tr>
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<td>IIb</td>
<td>Moderate-to-severe claudication</td>
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<tr>
<td></td>
<td>III</td>
<td>Rest pain</td>
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<td></td>
<td>IV</td>
<td>Ulceration or gangrene</td>
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<tr>
<td></td>
<td>5</td>
<td>Minor tissue loss</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>Severe tissue loss or gangrene</td>
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**CLI**
Natural history of PAD

- Patients with CLI represent 1% of the total number of patients with PAD
  - Prevalence 0.23% (Medicare)
- Significant morbidity:
  - Cardiovascular event rates surpass those in patients with symptomatic CAD.
- Overall mortality approaches 50% at 5 years and 70% at 10 years.
- More than 5 billion dollars annually spent on CLI care in the US.
Outcomes of Patients With Critical Limb Ischemia

Primary Treatment → One Year Later
- Primary Amputation 20%
- Medical Treatment 25%
- Revascularization 50%
- Amputation 25%
- CLIResolved 25%
- Died 25%

TASC II (2007). JOURNAL OF VASCULAR SURGERY
Volume 45, Number 1, Supplement S

CLI algorithm

Confirmatory testing
- CTA/MRA
- Angiogram

Medical therapy alone:
- Stable, uncomplicated tissue loss
- AND
- Poor surgical candidate

Amputation:
- Unreconstructable disease
- Terminal illness
- Limited life expectancy
- Dementia
- Spreading infection
- Non-ambulatory pre-operatively
- Poor surgical candidate

Revascularization
- Not in any of the other arms
- AND
- Ambulatory pre-op
Outcomes of Patients With Below-the-Knee Amputations

TASC II. (2007). JOURNAL OF VASCULAR SURGERY Volume 45, Number 1, Supplement S

BKA vs. AKA

<table>
<thead>
<tr>
<th>Post-op Morbidity</th>
<th>BKA</th>
<th>AKA</th>
<th>p</th>
<th>OR</th>
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<tr>
<td>Wound Infection</td>
<td>3.6%</td>
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<td>P&lt;0.05</td>
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<td>Wound Dehiscence</td>
<td>1.9%</td>
<td>1.1%</td>
<td>P&lt;0.05</td>
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<td>PE</td>
<td>0.4%</td>
<td>0.8%</td>
<td>P&lt;0.05</td>
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<td>Failure to wean</td>
<td>3.7%</td>
<td>6.5%</td>
<td>P&lt;0.05</td>
<td>-</td>
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<tr>
<td>UTI</td>
<td>4.2%</td>
<td>6%</td>
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<tr>
<td>CVA</td>
<td>0.4%</td>
<td>1.3%</td>
<td>P&lt;0.05</td>
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</table>

Mortality 6.5% vs. 12.7% (OR 2.1)
ANW Amputations

- Jan 2014-March 2019: 141 amputations
- Avg LOS: 11.9 days
- Avg ICU days: 5.5
- Avg total cost: $44,539
CLI algorithm

Confirmatory testing
CTA/MRA
Angiogram

Medical therapy alone:
Stable, uncomplicated tissue loss
AND
Poor surgical candidate

Amputation:
Unreconstructable disease
Terminal illness
Limited life expectancy
Dementia
Spreading infection
Non-ambulatory pre-operatively
Poor surgical candidate

Revascularization
Not in any of the other arms
AND
Ambulatory pre-op

Seen through the eyes of a patient

VS
BASIL trial (1999-2004)

- 450 patients randomized to bypass or balloon angioplasty for the initial treatment of infrainguinal disease.
- No difference in overall survival (OS) and amputation free survival (AFS) at 2 years.
- For patients surviving more than 2 years, open bypass has significantly increased OS and a trend towards increased AFS.
- Prosthetic grafts performed poorly compared to vein.
- Bypass after angioplasty had worse outcomes than bypass as initial therapy.

Help is on the way (?)

- BEST CLI
  - US & Canada
  - 140 sites
  - 1700 patients (2100)
  - MHI Vascular Surgery
Help is on the way (?)

- **BASIL 2**
  - Multicenter RCT
  - ‘vein bypass first’ vs ‘best endovascular first’
  - Clinical efficacy and cost-effectiveness
  - CLI
  - Tibial disease
  - 300 patients to date (2020)

- **BASIL 3**
  - Multicenter RCT
  - Clinical efficacy and cost-effectiveness of DCB, DES and PBA for severe limb ischemia (SFA/POP)
  - PAUSED

**SVS WIFI System**

- Wound, Ischemia, and Foot Infection.
- More accurately represents the complete status of the threatened ischemic limb.
- Based on existing literature and Delphi consensus.

Wound

- **Grade 0**: no ulcer/gangrene
- **Grade 1**: small, shallow ulcer, no gangrene (coverage or digit amp)
- **Grade 2**: ulcer with tendon/bone, digital gangrene (multiple digit amps or TMA)
- **Grade 3**: deep heel ulcer, extensive forefoot/midfoot gangrene (complex foot reconstruction vs need for major amp)

Ischemia

- **Grade 0**: ankle > 100 mm Hg; toe > 60 mm Hg
- **Grade 1**: ankle 70-100 mm Hg; toe 40-59 mm Hg
- **Grade 2**: ankle 50-70 mm Hg; toe 30-39 mm Hg
- **Grade 3**: ankle < 50 mm Hg; toe < 30 mm Hg
Foot Infection

- **Grade 0**: no signs/symptoms of infection
- **Grade 1**: swelling, erythema, purulence, tenderness—but superficial
- **Grade 2**: erythema margin of > 2 cm, extending deep to skin and subcutaneous tissues
- **Grade 3**: local infection + SIRS (temp, HR, WBC)

The Angiosome concept

Lida et al, J Vasc Surg 2012
Angiosomal Revascularization

- **Direct vs indirect** revascularization of the affected angiosome in isolated BTK disease results in substantial outcome improvements
  - AFS (49% vs 29%)
  - Freedom from MALE (51% vs 28%)
  - Freedom from major amp (82% vs 68%)

- Iida et al., J Vasc Surg 2012

**CLI**

**OPEN REVASCULARIZATION**
Open revascularization: Aortoiliac disease

Hybrid procedures
Open revascularization: Infrainguinal disease

- Femoral endarterectomy/Profundaplasty:
  - Sometimes performed to augment collateral flow in severe distal disease.
  - Open Profunda artery is needed to heal a below knee amputation.

- Above knee/Below Knee/Pedal bypass:
  - Donor vessel
  - Target
  - Conduit
  - Need in-line flow to heal wounds.

The Vein
The Vein

- A greater saphenous vein of adequate caliber is the conduit of choice for open bypass.
- Superior durability compared with all other conduit choices.
- In the absence of a good-caliber greater saphenous vein for bypass, endovascular revascularization becomes a more attractive option.
ANW LE Bypasses

- Jan 2014-March 2019: 301 Bypasses
- Avg LOS: 7.6 days
- 30 day readmissions: 23.8%
- ICU admission %: 29.6%
- ICU days: 3.9
- Average total Variable costs: $25,425
CLI
ENDOVASCULAR REVASCULARIZATION

Endovascular Revascularization
Endovascular devices

- Wires
- Catheters
- Crossing devices
- Atherectomy devices
- Re-entry devices
- Balloons
  - Drug eluting balloons (Paclitaxel)
- Stents
  - Balloon expandable.
  - Self expanding.
  - Stent grafts
  - Drug eluting stents (Paclitaxel)

CLI: Endovascular Revascularization

CROSSING THE LESION
Crossing the lesion

Intraluminal Angioplasty

Subintimal Angioplasty

Intraluminal angioplasty
subintimal angioplasty
CLI: Endovascular revascularization

RE-ENTRY TECHNIQUES
Outback® LTD Re-Entry Catheter

Pioneer Catheter

- Requires Volcano IVUS
Contralateral Access

- Retrograde approach
  - Most common (80-90%)
  - Easier technique
  - Can address iliac disease also
  - Must be used if anatomy unknown
  - Crossover sheath
  - Problems with:
    - Steep bifurcation
    - Iliac tortuosity
Antegrade Access

- Less frequently used
- Difficult in the obese pt
- Higher risk for complication
- Natural wire course is into PFA

CLI: Endovascular revascularization

RETROGRADE/PEDAL ACCESS
Retrograde access

- Ultrasound guided micropuncture of pedal/distal calf artery
- Wire will often traverse “uncrossable” chronic total occlusion (CTO).
- Can perform some interventions via pedal access
- Risks include compartment syndrome, occlusion of access vessel
CLI: Endovascular revascularization

**STENTS**

- **Viabahn**
  - Heparin bonded, PTFE stent graft
  - **RCT:**
    - Viabahn vs Bypass
    - 30% CLI patients
    - Equivalent results at 1 year
      - PP 65%
      - 100% limb salvage
Mimic Stent

- Designed to promote natural swirling blood flow
- Protect the endothelium
- Enable coil-spring shortening of the stented segment during knee bending to reduce the risk of stent fracture
- Freedom from (CD-TLR) @ 24 months was 84.2%,
  - Comparable with the performance at 2y of DES and DCB
  - Claudication/SFA
• At 12 and 24 months, the overall primary patency rates were 81.5% and 67.2%.
• Primary assisted patency was 94.9% and 84.8%.
CLI: Endovascular interventions

SPECIALTY BALLOONS
Chocolate

- Semi-compliant balloon encased in a nitinol-constraining cage.
- Allows for 1:1 vessel sizing.
- No flow limiting dissection in chocolate BAR study
- 1.6% bail-out stenting
- 78.5% freedom from TLR @1year
- 97.2% freedom from major amputation @ 1year

POPLITEAL CTO
Chocolate Balloon

TIBIAL DISEASE
TP TRUNK RUPTURE
CLI: Endovascular revascularization

ATHERECTOMY

DIRECTIONAL ATERECTOMY
Final Result: palpable pulse
84 yo with gangrene right foot

4 passes with ES

2 passes with ES

SFA, POP CTO: DIRECTIONAL ATERECTOMY AND DCB
AT and PT

- Chocolate
ANW Endo CLI interventions

ANW Endo CLI Interventions

- Average variable costs
- Number of cases performed

- 2014: $10,000
- 2015: $15,000
- 2016: $20,000
- 2017: $25,000
- 2018: $15,000
- 2019: $5,000
ANW Endo

- Jan 2014-March 2019: 980 procedures
- 40% outpatient status
- Avg LOS: 5.3 days
- ICU admission % 18.8
- ICU days: 4.2
- Avg total variable costs 17,285 (25425 for LEB)

CLI: Endovascular revascularization

DRUG ELUTION
Re-stenosis prevention

- Our Achilles’ heel is the *maintenance* of that arterial flow
- Biologic modification of restenosis takes PAD treatment to the “next level”
Drug coated devices (FDA approved)

- Coronary DES do not possess indication for noncoronary use
  - Off label use of coronary DES platforms for focal lesions and PTA salvage in distal popliteal/tibials

- DES: SFA Zilver PTX (Cook Medical), Eluvia (Boston Scientific)

- Bard/Lutonix and Medtronic Admiral paclitaxel-coated balloons approved for use in SFA/Pop

Zilver PTX Paclitaxel-Eluting Stent

- Approved in US, EU, Japan
- Scaffold plus drug
  - Mechanical scaffold:
    - Zilver Flex® Stent Platform
  - Drug therapy: Paclitaxel only
    - No polymer or binder
    - 3 µg/mm² dose density

- Image courtesy of Cook Medical
Eluvia

Clinically Driven TLR Rate 12 Months

Eluvia: 4.9%
Zilver PTX: 9.0%

12-Month Kaplan-Meier Estimate Primary Patency Rate

Eluvia: 88.5%
Zilver PTX: 79.5%

IN.PACT Admiral

Platform: Admiral™ PTA balloon
4-7 mm diameters
40, 60, 80, 120, 150, 200, 250 mm lengths

Drug: Paclitaxel
Proven anti-proliferative drug
3.5 µg/mm² dose density

Excipient: Urea
Facilitates drug transfer
Naturally occurring, non-toxic

Process: Medtronic
Reliable, scalable, uniform
drug coating process
IN.PACT Global Complex Lesion Analysis
Freedom from CD-TLR\(^1\) through 360 Days

Number at risk
DCB 227 213 192
93.0%

IN.PACT Global Study
24-month Freedom from CD-TLR\(^1\)

Number at risk
DCB 808 1406 1272 193
83.3%

1. Clinically-driven TLR adjudicated by an independent Clinical Events Committee, blinded to the assigned treatment based on any re-intervention at the target lesion due to symptoms or drop of ABI of ≥20% or >0.15 when compared to post-procedure baseline ABI.
2. Number at risk represents the number of evaluable subjects at the beginning of each 30-day window.
Is There a Role for Infrapopliteal DCBs?

- Schmidt performed paclitaxel DCB (InPact) treatment of 109 pts with long (17 cm) lesions

- Historic POBA comparison group had patency of 31% at 3 month angio

- New DCB cohort had patency of 73% over same time frame and amp rate of less than 5%
  
  - Schmidt, J Amer Coll Cardiol 2011;58:1105-09
  - Schmidt, Cathet Cardiovasc Intervention 2010: 76:1047-1054

In.Pact DEEP

- 12 month data presented at LINC 2014

- No signal of expected biologic activity
  - Failed to meet primary efficacy endpoints
  - No difference in LLL, TLR, occlusion rates

- Trend towards higher amputation rates in DCB arm

- Amphirion DEEP product removed from EU market
  
  *Data presented by Zeller at LINC 2014
## LUTONIX BTK TRIAL

### PRIMARY ENDPOINTS
- Safety at 30 days
- Limb salvage & primary patency at 12 months

### NUMBER OF PATIENTS/SITES
- 480 patients at 55 global sites (US, EU, Japan)

### FOLLOW-UP
- **Clinical:** 1, 6, 12, 24, and 36 Months
- **Duplex Ultrasound (DUS):** 0–30 days, 6, 12, 24, & 36 months
- **Angiography in subset of patients:** 12 months
- **Telephone:** 48 and 60 Months

### NATIONAL PRINCIPAL INVESTIGATORS
- **Patrick Geraghty:** Washington University, St. Louis, MO
- **Jihad Mustapha:** Metro Health Hospital, Wyoming, MI
- **Marianne Brodmann:** Medical University Graz, Austria

### SPONSOR
- Lutonix Inc., Minneapolis, MN

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## Coronary DES: BTK Trials

**Use of coronary stents in the tibial arteries is NOT APPROVED by the FDA**

- **DES shows improved one year primary patency in 2-3 cm length lesions**

- **Applicability to broader CLI patient population likely limited**
  - Multiple long lesions
  - Device costs

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\*1 Scheinert et al. J Am Coll Cardiol (2012), 60:2290-2295
BTK DES

- Saval Boston Scientific
- Study completion: 2024

SYSTEMATIC REVIEW AND META-ANALYSIS

Risk of Death Following Application of Paclitaxel-Coated Balloons and Stents in the Femoropopliteal Artery of the Leg: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Konstantinos Koltsakis, MD, PhD, MSc, EBIR; Stavros Spiliopoulos, MD, PhD; Panagiotis Kitisli, MD, PhD; Mittdios Koskopoulos, MD, PhD; Dimitrios Kanaliakakis, MD, PhD

Conclusions—There is increased risk of death following application of paclitaxel-coated balloons and stents in the femoropopliteal artery of the lower limbs. Further investigations are urgently warranted.
Paclitaxel doses

- 3.5×32 mm coronary TAXUS stent contains around 200 μg paclitaxel compared with:
  - 1.2 mg for the ZILVER-PTX 6.0×120 stent
  - 4.5 mg for the LUTONIX 6.0×120
  - 8.5 mg for the IN.PACT 6.0×120 balloon

FDA March 2019

- “Discuss the risks and benefits of all available PAD treatment options with your patients. For most patients, alternative treatment options to paclitaxel-coated balloons and paclitaxel-eluting stents should generally be used until additional analysis of the safety signal has been performed.”
INVESTIGATIONAL THERAPIES

Venous arterialization

A B C
Cell-Based Therapies

- Several trials of circulating pluripotent cells, harvested/expanded stem cells, etc.

- No FDA-approved therapies yet

Implications on CLI practice

- Endovascular first has become the approach of the majority of interventionalists and surgeons.

Implications on CLI practice

- BEST CLI /BASIL 2 and 3 trial results are important in establishing standards of care
- With the increasing cost of medical devices, total cost of care should be given significant consideration.

Device Trials: MHI vascular surgery

- Mimic
- IN.Pact
- Best CLI
- Transcend
Introducing new Advanced Peripheral Arterial Disease (APAD) Center

Thank you