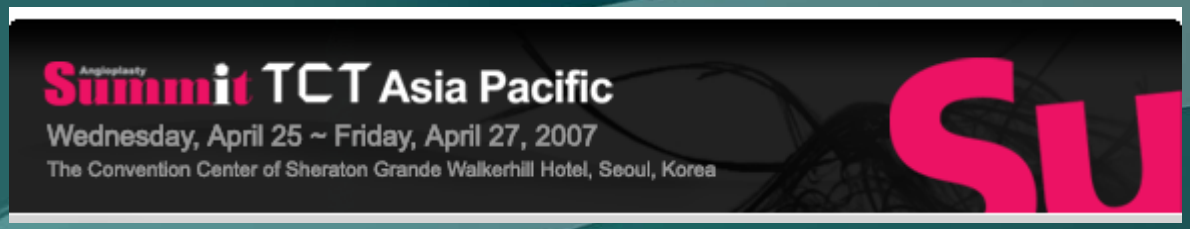
Presenter Disclosure Information

Name: Giora Weisz, MD

Within the past 12 months, the presenter or their spouse/partner have had a financial interest/arrangement or affiliation with the organization listed below.

Company Name	Relationship
FlowMedica	nothing to disclose



Targeted Intra-Renal Infusion of Fenoldopam to Prevent Contrast Induced Nephropathy

FEN-1, BeRITe, TIFFANY, and other Clinical Trials

Giora Weisz, MD

The Cardiovascular Research Foundation
Columbia University Medical Center

Presenter Disclosure Information

We use large volumes of contrast

And we suggest a novel way

to reduce patient's risk

Contrast Induced Nephropathy: Most common complication in Cath lab

- 3rd most common cause of hospital acquired renal failure
- Occurs in less than 1% of general population
- Occurs in "only" 5.5% of patients with renal insufficiency
- But, occurs in 50% of patients with both renal insufficiency and diabetes mellitus

Parfrey PS, et al, *NEJM* 1989; 320:143-149

CIN: Not a Benign Event!

Parameter	CIN n=381	No CIN n=1599	Significance
Length of hospital stay (days)	6.8 ± 7.1	2.3 ± 2.5	<0.0001
Mortality (in-hospital)	6.3%	0.8%	<0.0001
MACE (in-hospital)	9.3%	1.1%	<0.0001
Mortality (1 year)	22.6%	6.9%	<0.0001

*Def. Of CIN: >0.5 mg/dl or >25% increase Cr at 48 hours

G. Dangas, et al. Contrast-Induced Nephropathy After Percutaneous Coronary Interventions and Relation to Renal Vascular Disease and Hemodynamic Variables. Am J Cardiol 2005;95:13-19.

Mehran's CIN risk score

Risk Factors	Integer Score
Hypotension	5
IABP	5
CHF	5
Age >75 years	4
Anemia	3
Diabetes	3
Contrast media volume	1 for each 100 cc^3
Serum creatine > 1.5mg/dl	4
OR	
eGFR <60ml/min/1.73 m^2	2 for 40 – 60 4 for 20 – 40 6 for < 20

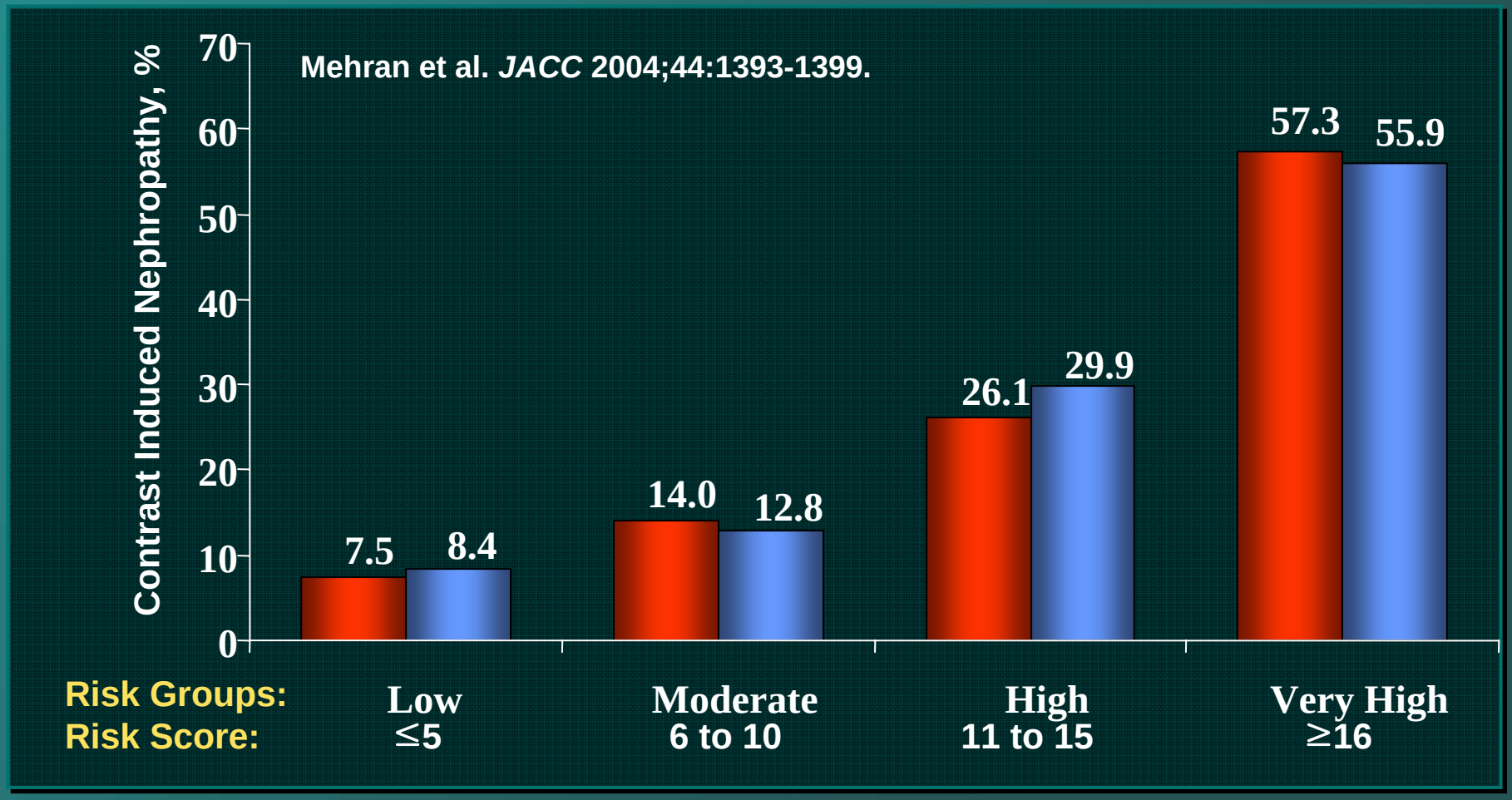
eGFR < 60ml/min/1.73 m^2 = 186 x $(SCr)^{-1.154}$ x $(Age)^{-0.203}$ X (0.742 if female) x (1.210 if African American)

Calculate

Risk Score	Risk of CIN	Risk of Dialysis
≤ 5	7.5%	0.04%
6 to 10	14.0%	0.12%
11 to 16	26.1%	1.09%
≥ 16	57.3%	12.6%

Mehran et al. *JACC* 2004;44:1393-1399.

Mehran's Risk Score - CIN



CIN risk score derived from the development dataset predicted this complication in the validation set. (Red bars = development dataset; blue bars = validation dataset.)

Therapies for CIN Prevention

Either No Benefit or Cause Harm

- Dopamine[1]
- Mannitol[2]
- Furosemide[2]
- Atrial natriuretic peptide[1]
- Mixed endothelin antagonists[3]
- Calcium channel blockers[4]
- Low-ionic contrast media[5]

Some Benefit

- Saline[2]
- Sodium bicarbonate- ?
- NAC - ???

???

[1] Weisberg LS, Kurnik PB, Kurnik BR. Kidney Int 1994;45(1):259-65; [2]Solomon R, Werner C, Mann D, D'Elia J, Silva P. N Engl J Med 1994;331(21):1416-20; [3]Wang A, Bashore T, Holcslaw T, et al. American Society of Nephrology. Philadelphia, PA, 1998:137A; [4]Carraro M, Mancini W, Artero M, Stacul F, Grotto M, Cova M, et al. Nephrol Dial Transplant 1996;11(3):444-8; [5]Mehran, TCT 2006.

Effects of Vasodilators in the Kidney

Dopamine
Cortex ↑
Medulla ↔

Contrast Media
Cortex ↑
Medulla ↓

Mannitol
Cortex ↔
Medulla ↓

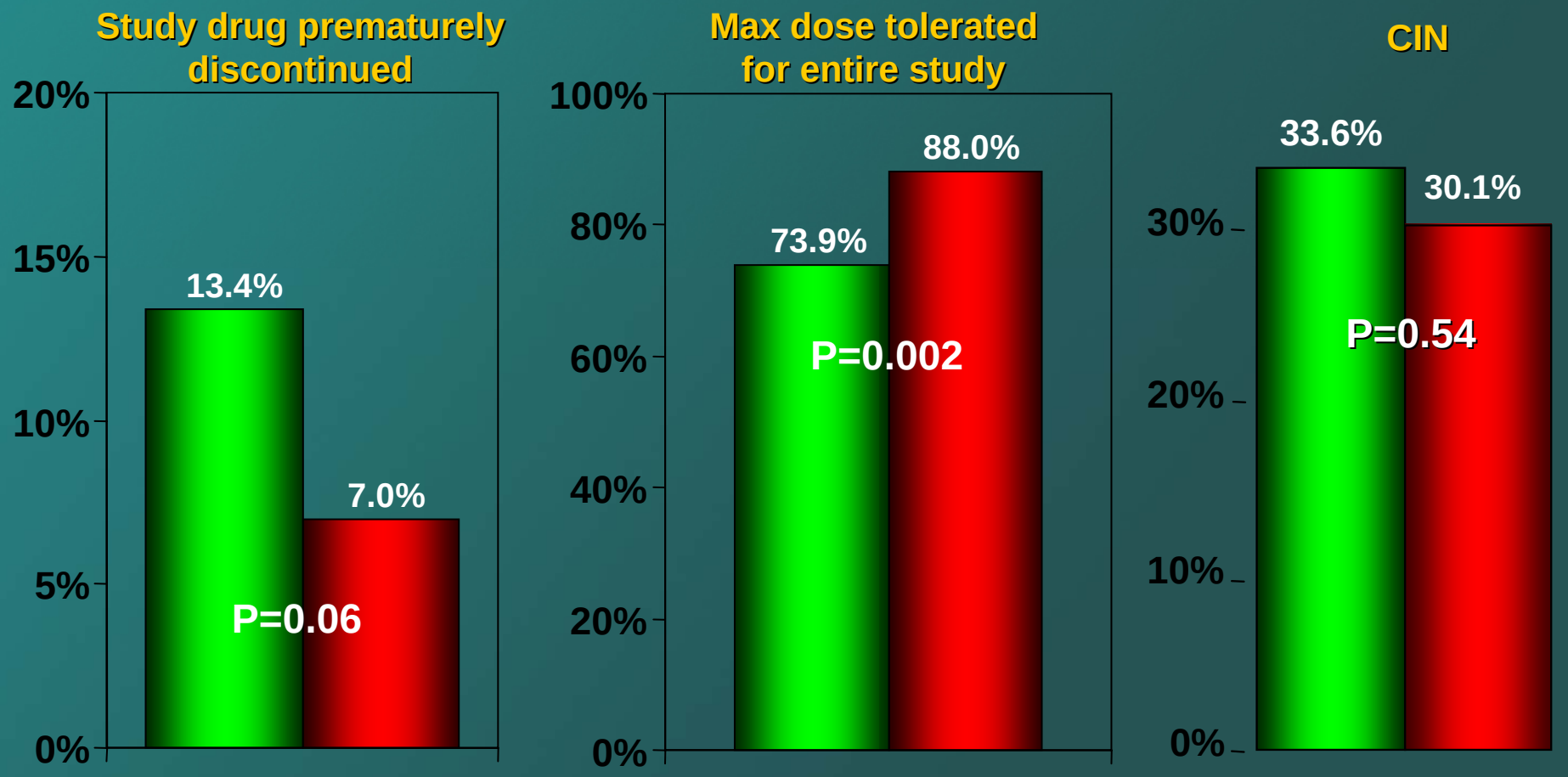
Fenoldopam
Cortex ↑
Medulla ↑

Endothelin
Cortex ↓
Medulla ↑

Specific DA-1 Agonist

The CONTRAST Trial

Fenoldopam vs. Placebo (315 pts): 0.05-0.10 mcg/kg/min

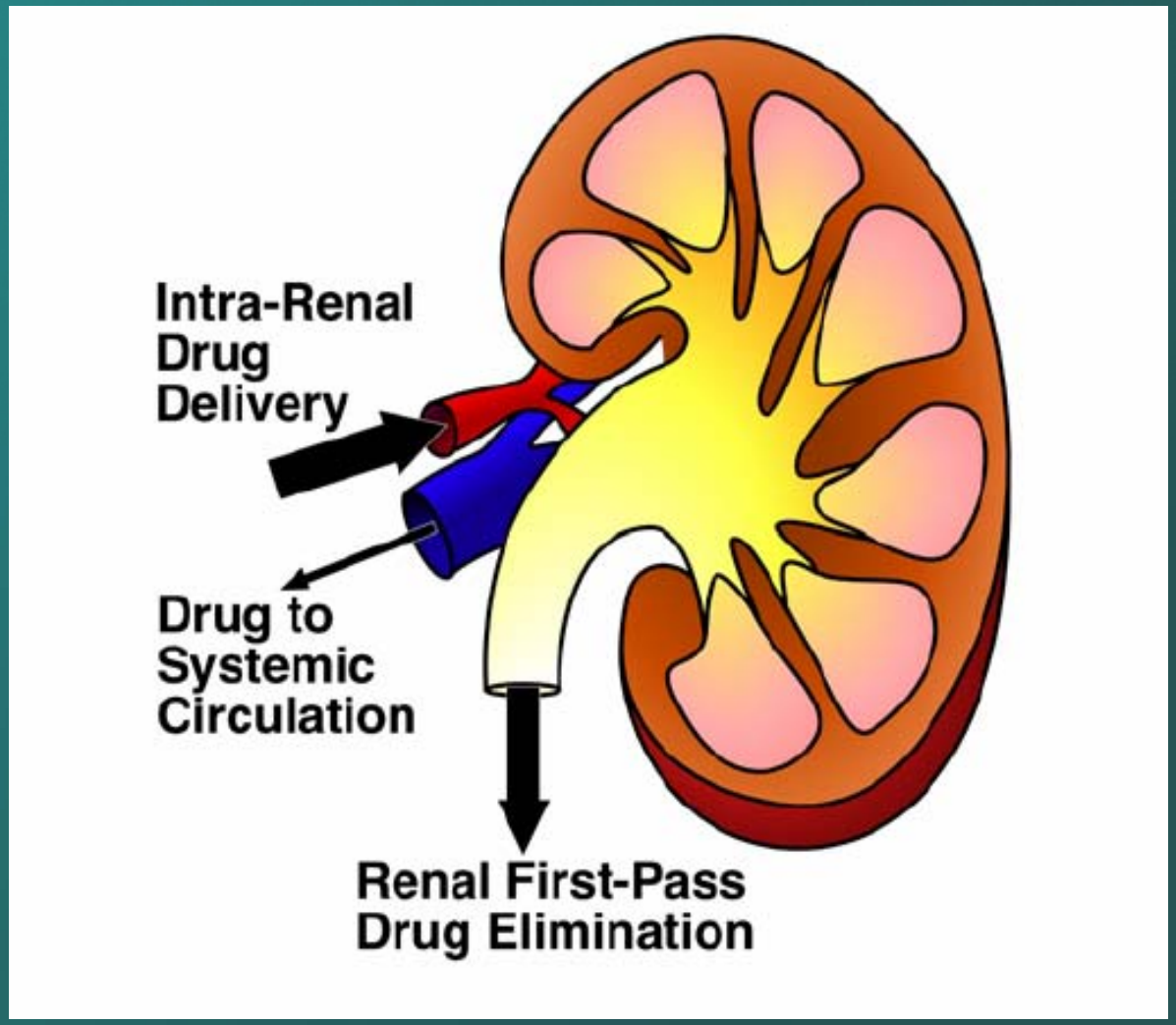


Columbia University Medical Center

Fenoldopam Placebo

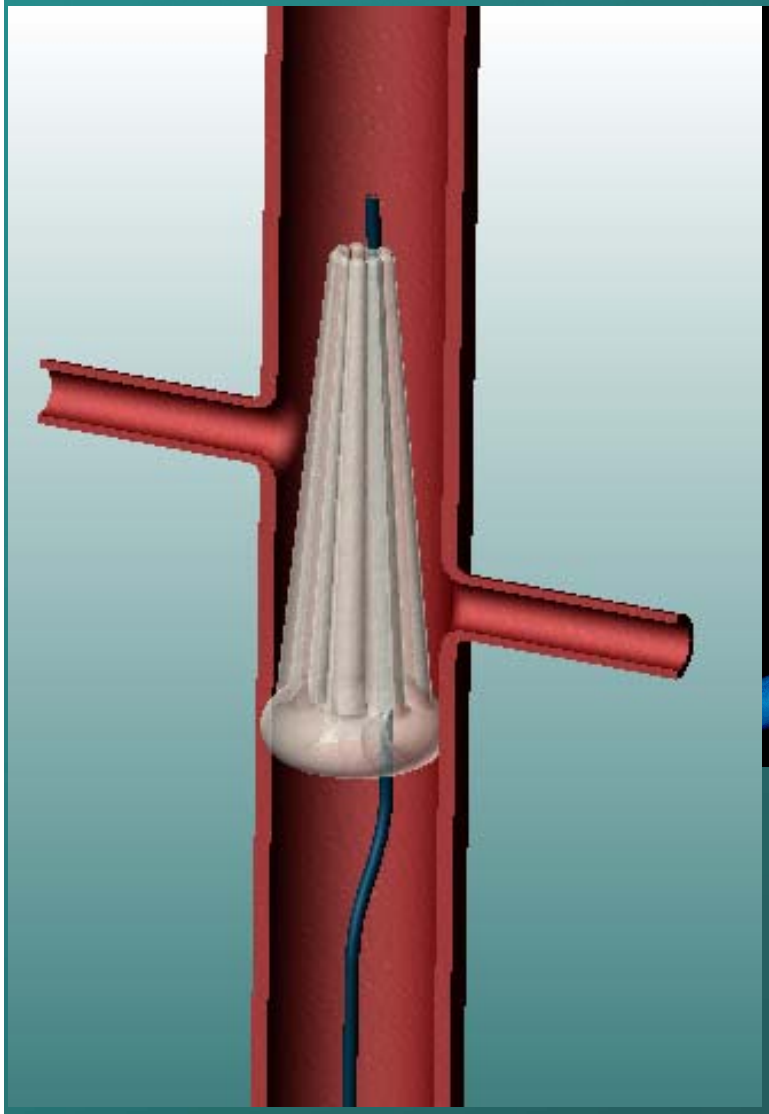
Cardiovascular Research Foundation

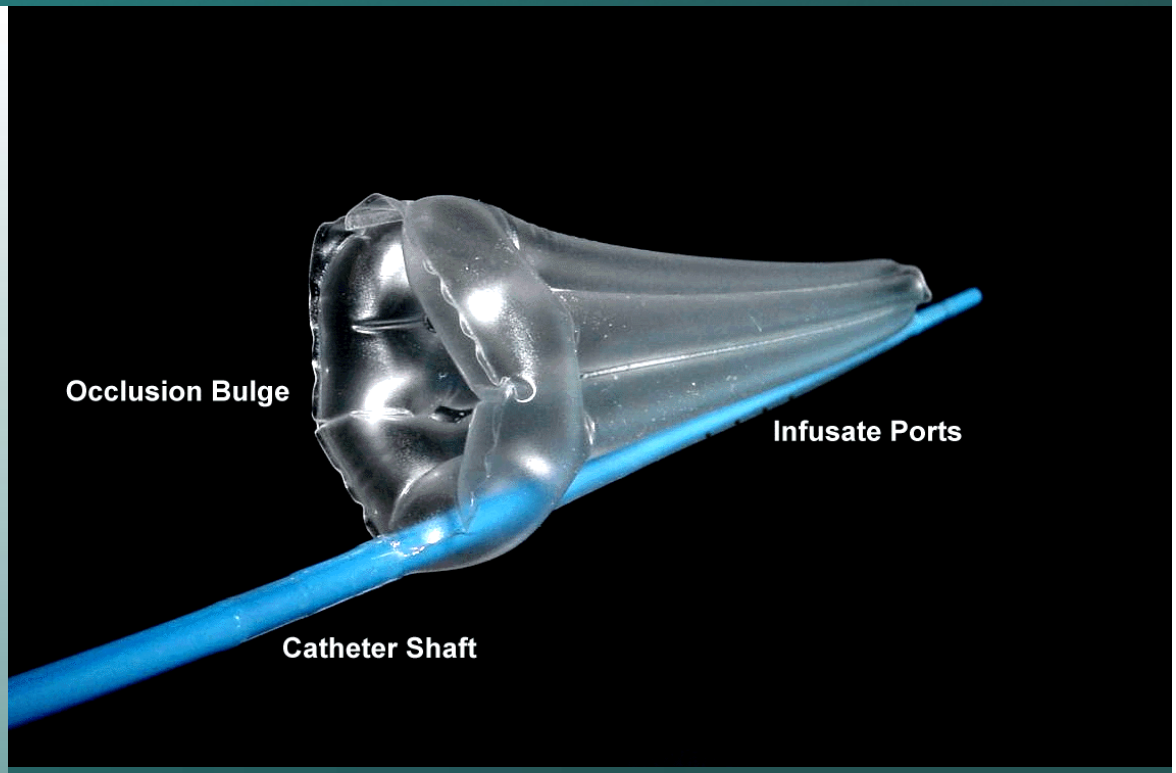
Targeted Renal Delivery



LIBRA MEDICAL

RenalGuard™ Catheter





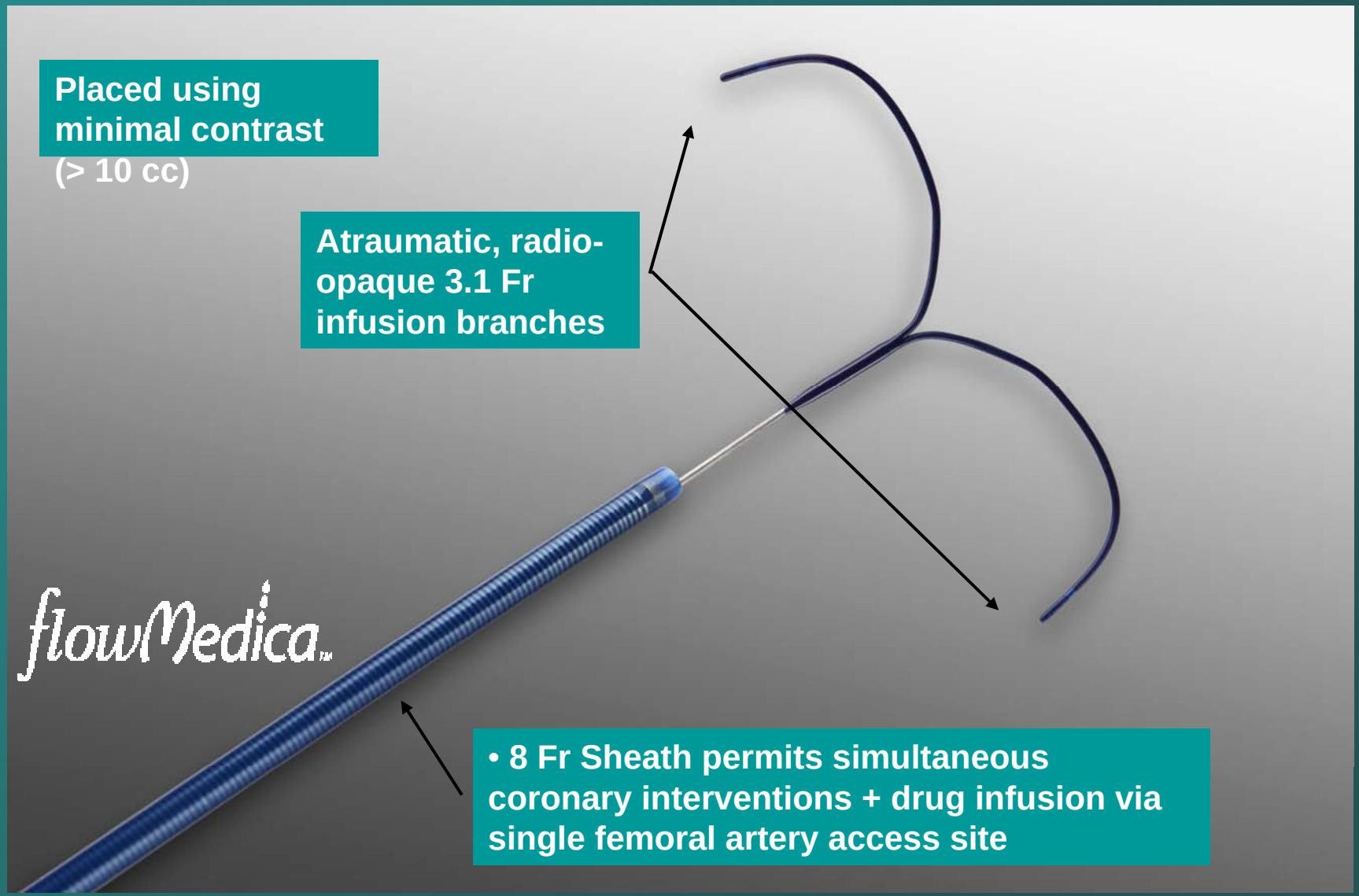
- Inner blood flow delivered to lower body
- Outer blood flow delivered to renal arteries combined with infusate

Courtesy of Gad Keren

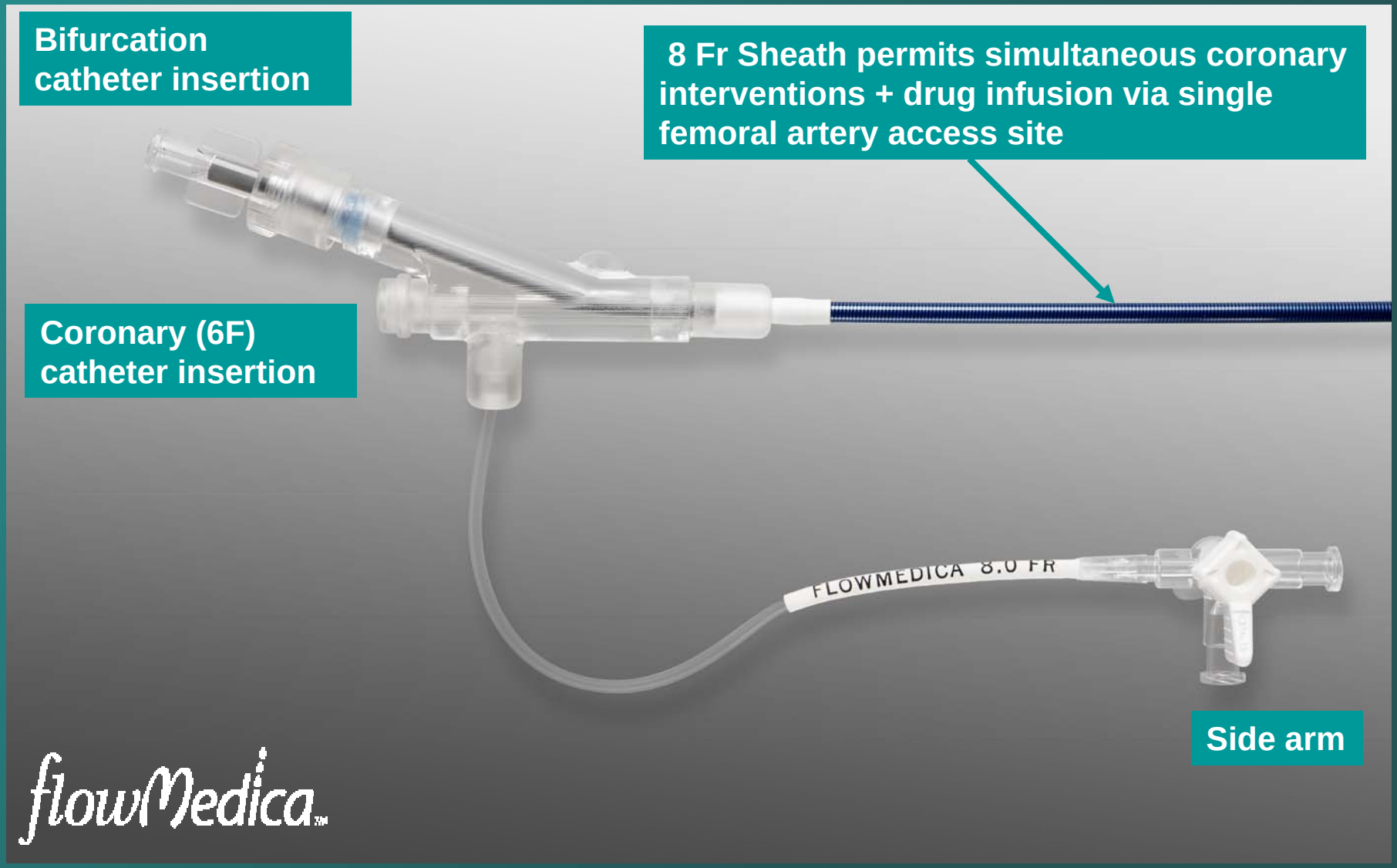
flowMedica™

FDA 510K
CE mark

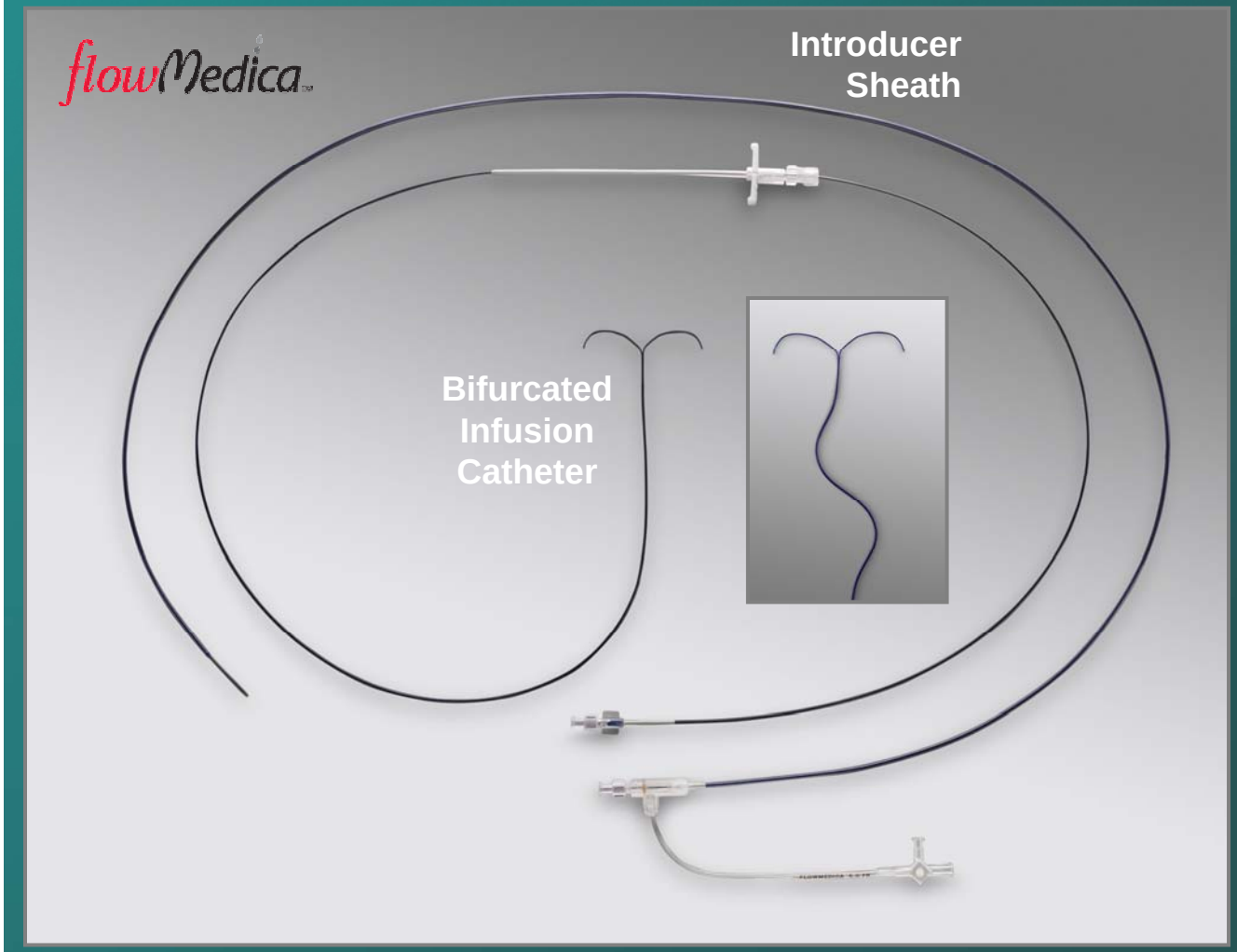
Distal


Placed using minimal contrast
(> 10 cc)
Atraumatic, radio-opaque 3.1 Fr infusion branches
flowMedica
• 8 Fr Sheath permits simultaneous coronary interventions + drug infusion via single femoral artery access site

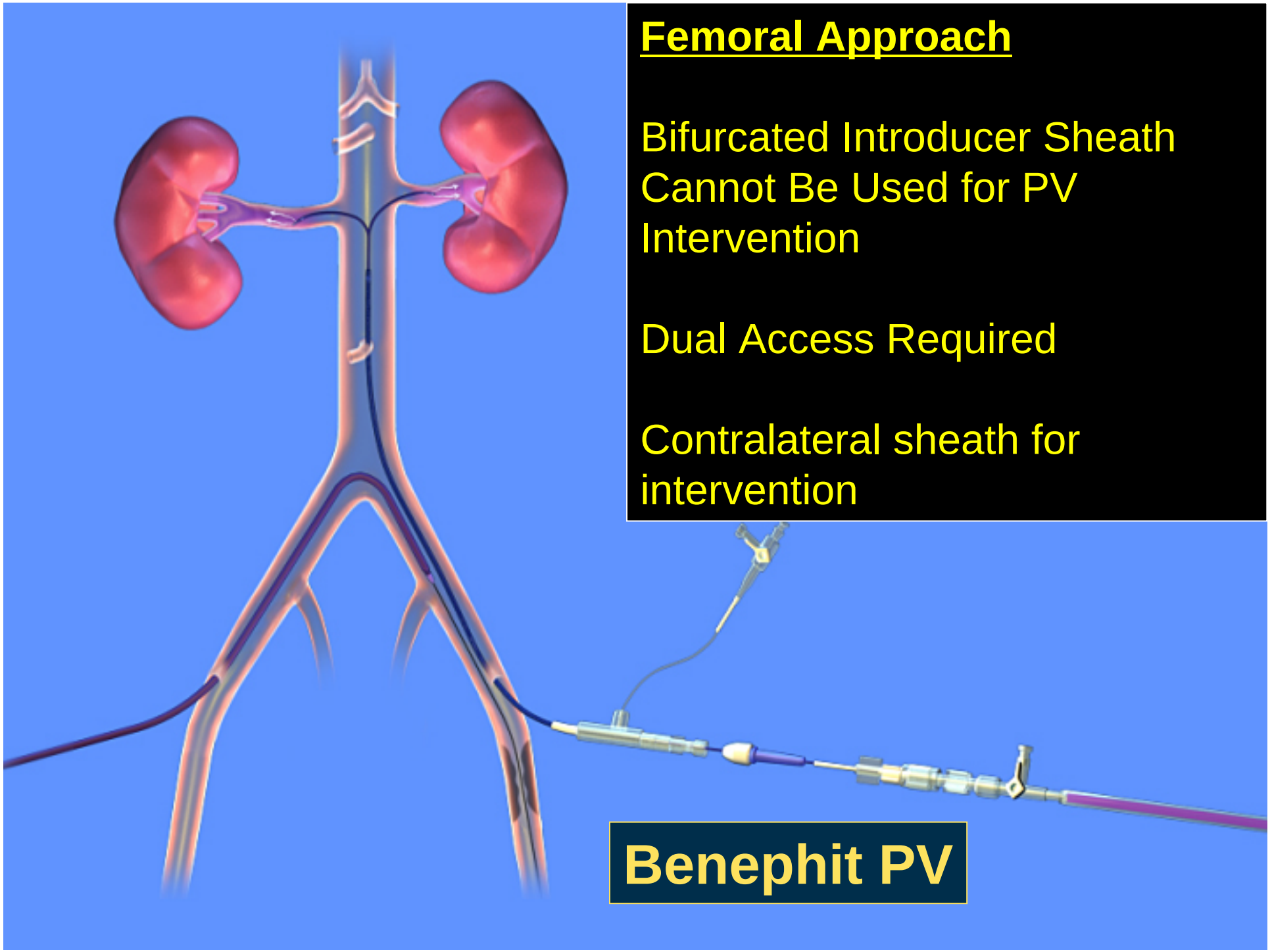
Proximal

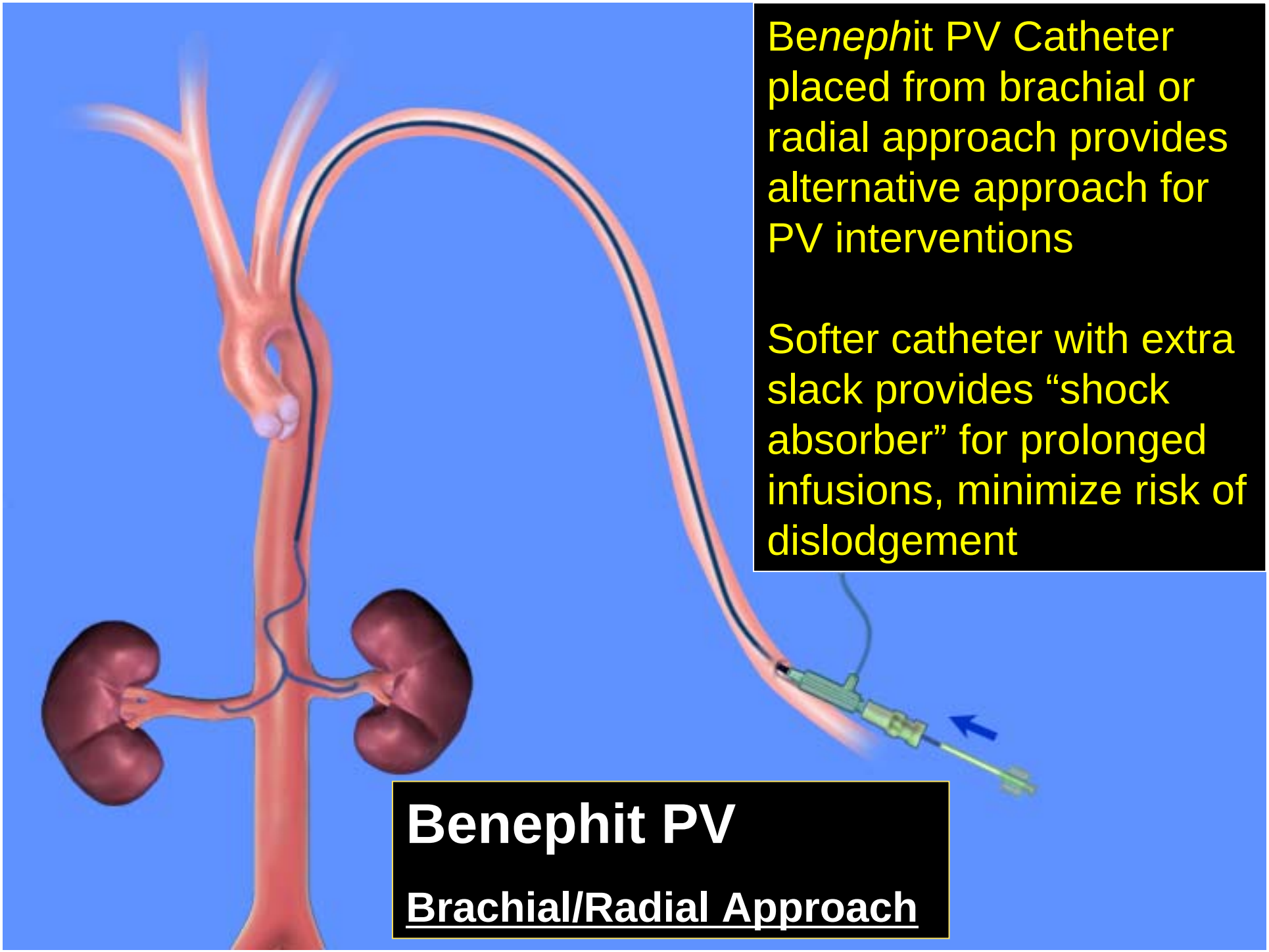

Bifurcation catheter insertion
8 Fr Sheath permits simultaneous coronary interventions + drug infusion via single femoral artery access site
Coronary (6F) catheter insertion
FLOWMEDICA 8.0 FR
Side arm
flowMedica

5F Benephit™ Delta Infusion System



- Flexible 5 Fr sheath
- Designed for extended indwell periods
- 3 system lengths for femoral, radial, and brachial access
- 'Floppy' distal section for improved stability and extended in dwell


Femoral Approach
Bifurcated Introducer Sheath Cannot Be Used for PV Intervention
Dual Access Required
Contralateral sheath for intervention
Benephit PV


Be*neph*it PV Catheter placed from brachial or radial approach provides alternative approach for PV interventions
Softer catheter with extra slack provides “shock absorber” for prolonged infusions, minimize risk of dislodgement
Benephit PV
Brachial/Radial Approach

It is easy!

17 sec

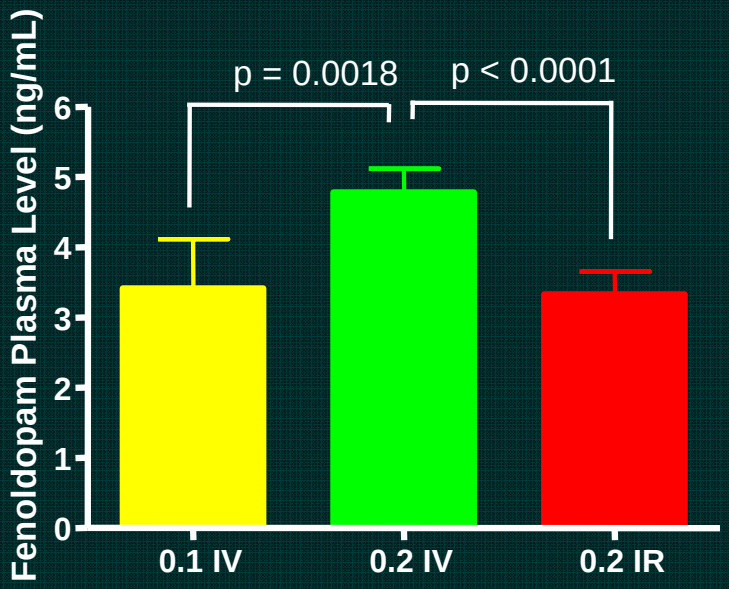
Placement Confirmation

0.5 ml

Less Systemic Exposure → Less Hypotension

FEN-1

Systemic Exposure to Fenoldopam

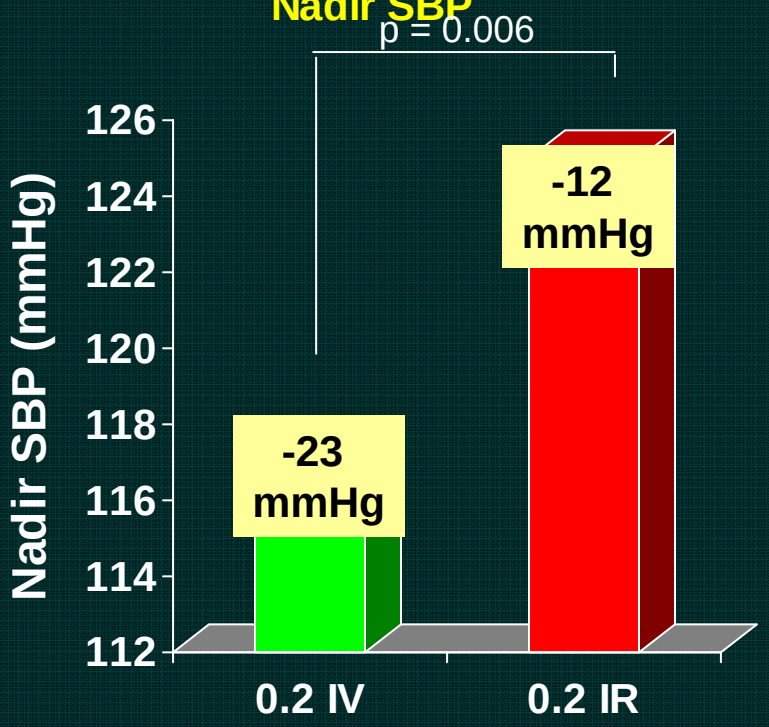


IV = Intravenous
IR = Intra-renal

Fenoldopam Dose (mcg/kg/min) and Route

Plasma levels drawn 30 minutes into infusion
n = 22 (all fenoldopam patients)

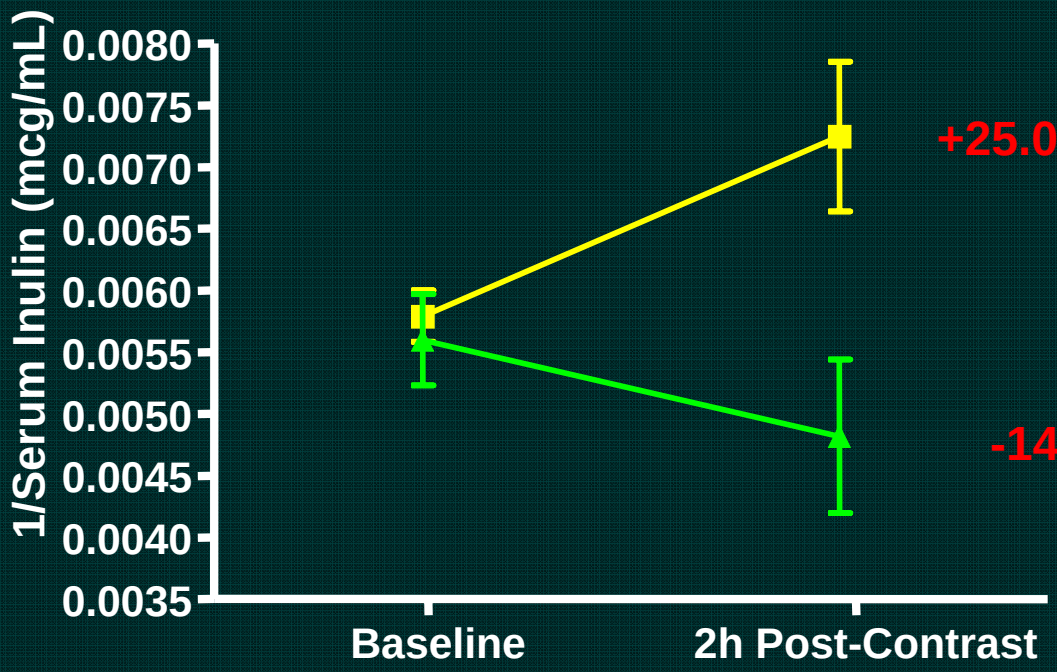
Nadir SBP



Fenoldopam Route and Dose (mcg/kg/min)

GFR - 2 hours Following Contrast & drug

FEN-1



* p <0.05, FEN vs. PLC

IR = Intra-Renal
IV = Intravenous

FEN = Fenoldopam (n = 22)

PLC = Placebo (n = 11)

Numbers in parentheses indicate % change from baseline

Be-RITe! Registry

- An observational, multi-center, post-market, customer preference study
- Includes all patients
  (*coronary*, *peripheral*)
  "real world" usage
- **Objectives:**
  - Usage patterns of the Be*neph*it® Infusion Systems
    - patient characteristics
    - adjunctive procedures
    - infused agents
  - Safety
  - Collect user-interface information

Be-RITe! Registry: Enrolling Sites

26 operators from 13 centers

Cardiovascular Institute of the South	David Allie
Florida Hospital	Barry Weinstock
Columbia University Medical Center	Giora Weisz
Scripps Clinics	Paul Teirstein,
Stanford Medical Center	William Fearon
Ospedale Luigi Sacco, Milan, Italy	Paulo Danna
University of North Carolina	Mauricio Cohen
Providence Heart and Vascular Institute	Naveen Sachdev
North Florida Regional Medical Center	Bret Wiechmann
Toyohashi Heart Center, Japan	Y. Kinoshita
Brigham and Women hospital	Campbell Rogers
Dartmouth Hitchcock Medical Center	Craig Thompson
Brotman Medical Center	Hooman Madyoon

Be-RITe! Registry: patient Characteristics (n=403)

Risk factor	N=403
Age (Years) (% > 75)	71.7 ± 9.7 (51%)
Female / Male	35% / 65%
Baseline Cr (mg/dL)	2.0 ± 0.7
Creatinine Clearance, Crockroft Gault (<60ml/min)	44.3 ± 22.1 (85%)
Congestive Heart Failure	21.3%
Diabetes Mellitus	56.6%
Hypertension	76.7%
History of myocardial infarction	40.6%
Non-renal peripheral vascular disease	59.4%
Anemia (HCT< 39/36%)	75%
Contrast volume (ml)	*152 ± 86*

Be-RITe! : Device Performance

Bilateral renal artery cannulation	93%
Time to cannulation [min]	2.0±1.7

Major Reasons for Cannulation Failure

- Tortuous Iliac/ distal aorta
- Renal artery position
- Renal artery stenosis

Benephit: Strong Safety Profile

4 pts 1.0% (n=403)

- **Groin hematoma (2)**
- **Right upper renal artery dissection (1)**
  - Patient with dual accessory renal arteries (3mm each)
  - Upper renal artery cannulated
  - Rx: 3mm sirlomus stent x 2 with no residual dissection and perforation, SCr 2.1 -> 1.8 mg/dL post-procedure
- **"Mild hypotension" (1)**
  - BP declined to 87/50 mmHg following temporary dislodgment of the renal catheter and presumed systemic administration
  - Rx: Neosynephrine + IV fluid bolus with recovery of BP in 9 minutes Fenoldopam held x 2 minutes. Catheter replaced into renal arteries

Be-RITe! Registry: IR drug treatment

Fenoldopam Mesylate (0.05-0.8mcg/kg/min; mean 0.35 mcg/kg/min)	90.8%
Sodium Bicarbonate (1-2 ml/kg/hr; mean 1.6 ml/kg/hr; 1M-154mEq)	6.5%
Alprostadil (40 ng/kg/min)	2.7%
Total TRT duration [min]	162±244

*Numeric data is expressed as mean ± standard deviation. No patient received multiple agents via TRT.

Be-RITe! Registry:
IR Fenoldopam Analysis

Inclusion Criteria

- High risk to develop CIN
- Coronary / peripheral percutaneous procedure
- IR Fenoldopam
- Follow-up for ≥ 48h

n=217

Mehran's CIN risk score

Risk Factors	Integer Score
Hypotension	5
IABP	5
CHF	5
Age >75 years	4
Anemia	3
Diabetes	3
Contrast media volume	1 for each 100 cc^3
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OR	
eGFR <60ml/min/1.73 m^2	2 for 40 – 60 4 for 20 – 40 6 for < 20

eGFR < 60ml/min/1.73 m^2 = 186 x $(SCr)^{-1.154}$ x $(Age)^{-0.203}$ X (0.742 if female) x (1.210 if African American)

Calculate

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≥ 16	57.3%	12.6%

Mehran et al. *JACC* 2004;44:1393-1399.

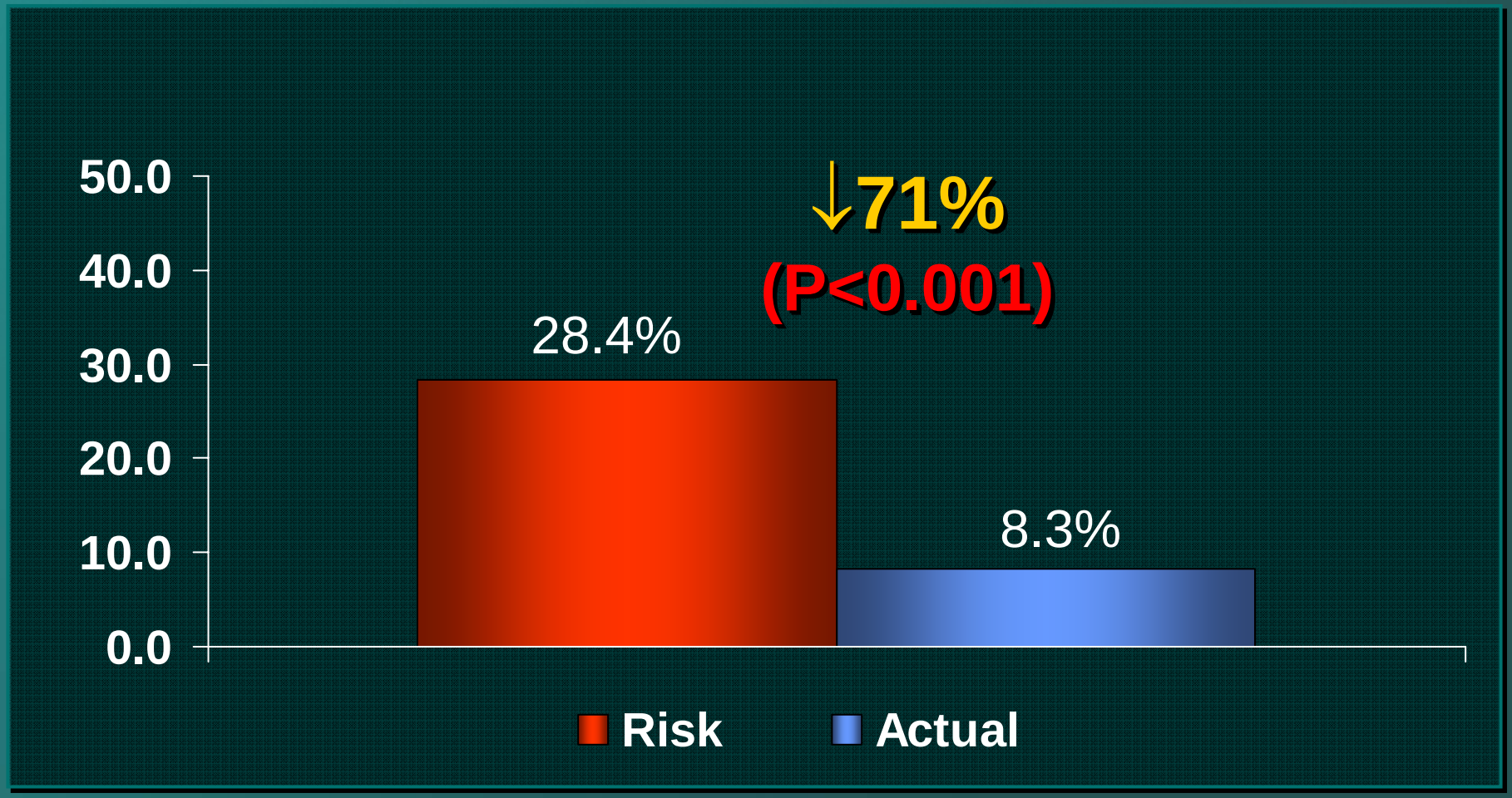
Be-RITe! Registry

Patients with IR fenoldopam followed for 48h *(n=217)*

Type	Integer Score	Rate
Hypotension	5	1.9%
IABP	5	0.9%
CHF	5	16.6%
Cr >1.5 or CrCl<60	4	95.9%
Age > 75yr	4	54.8%
Diabetes	3	64.5%
Anemia	3	92.6%
Mean Contrast Vol.	1 per 100ml	152±86 ml

Acute Renal failure @ 48 h

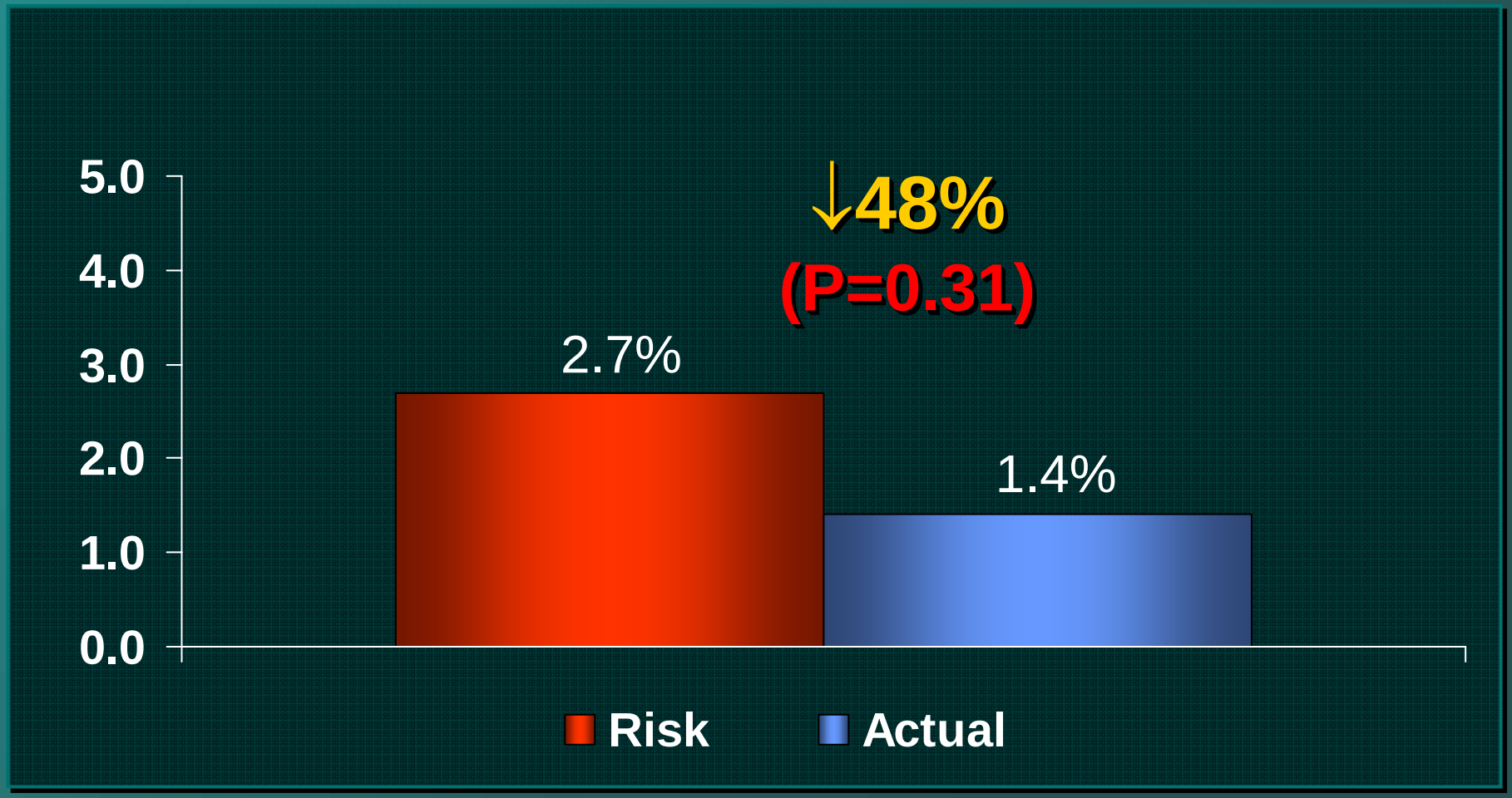
Patients with IR fenoldopam followed for 48h (n=217)



CIN Definition: Rise in serum Cr by either 25% or 0.5 mg/dl from baseline within 48 hours

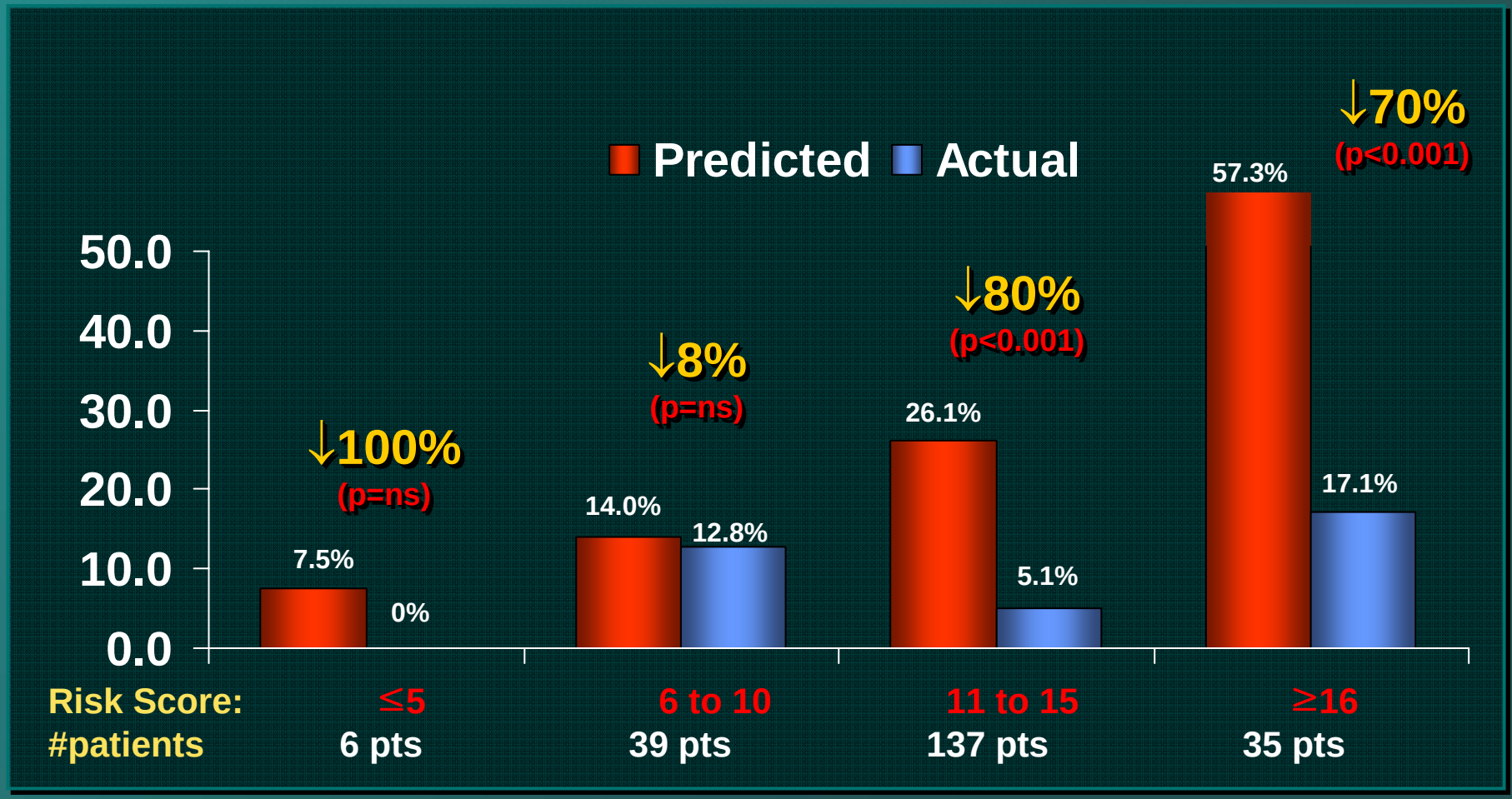
Dialysis

Patients with IR fenoldopam followed for 48h (n=217)



Acute Renal failure @ 48 h

Patients with IR fenoldopam followed for 48h (n=217)



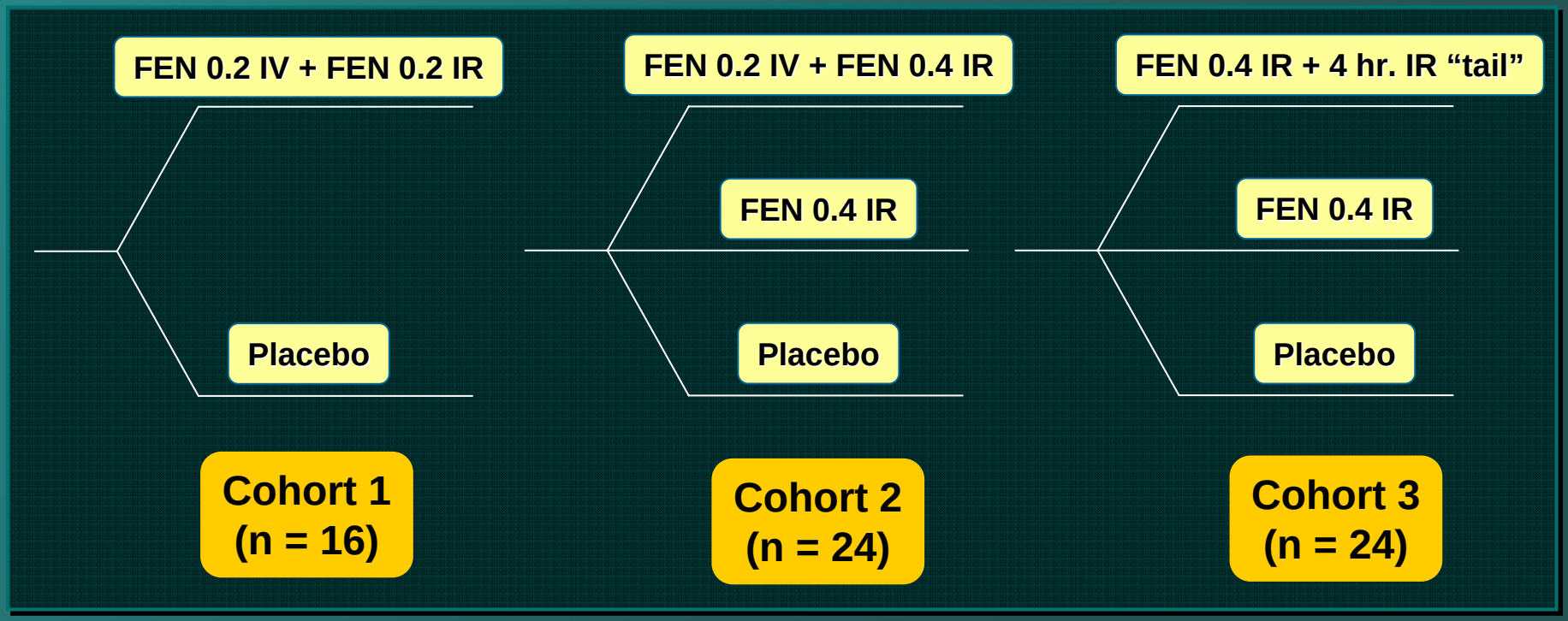
CIN Definition: Rise in serum Cr by either 25% or 0.5 mg/dl from baseline within 48 hours

TIFFANY: Study Design

Angiography / PCI

Diabetes Mellitus

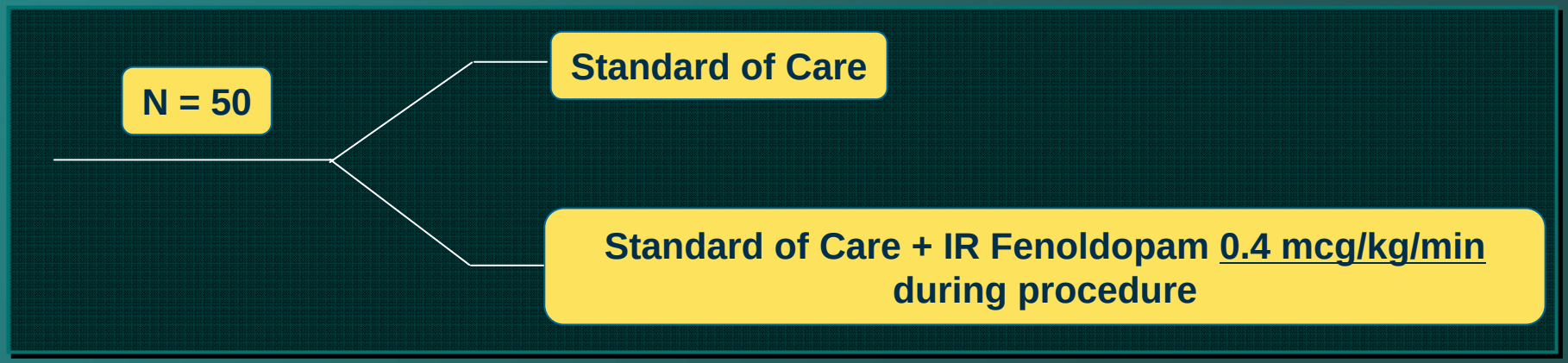
CrCL ≤ 35 cc/min or serum Cr ≥ 2.0 mg/dL



Randomization within each cohort is 1:1 or 1:1:1

PATRICIA: Study Design

- ✓ **Peripheral vascular angiographic interventional procedure**
- ✓ **Anticipated contrast volume > 80ml**
- ✓ **CrCL ≤ 50 cc/min or serum Cr ≥ 2.0 mg/dL**



Standard of Care:

- NaHCO3 3 cc/kg/hr IV intra-procedure, 1 cc/kg/hr IV post x 6hrs
- Saline 1.5 cc/kg/hr x 8hrs post NaHCO3
- Mucomyst 600 mg pre-procedure
- 600 mg po BID x 2 dose post-procedure
- Use of iodixanol (Visipaque)

Randomized Clinical Trial

Conclusions

1. Simultaneous bilateral renal artery cannulation with the FlowMedica Benephit bifurcated catheter is feasible, and safe

2. Targeted intra-renal infusion of Fenoldopam during angiography/PCI is associated with 25% increase in GFR

3. Intra-renal delivery of fenoldopam has resulted in 71% reduction in the incidence of CIN, as compared to predicted by the Mehran's risk score (8.3% vs. 28.4%)

4. Additional randomized clinical trials are ongoing to verify that intra-renal Fenoldopam can prevent CIN