# Use of Cell Therapy and Biomedical Engineering in Vascular Access

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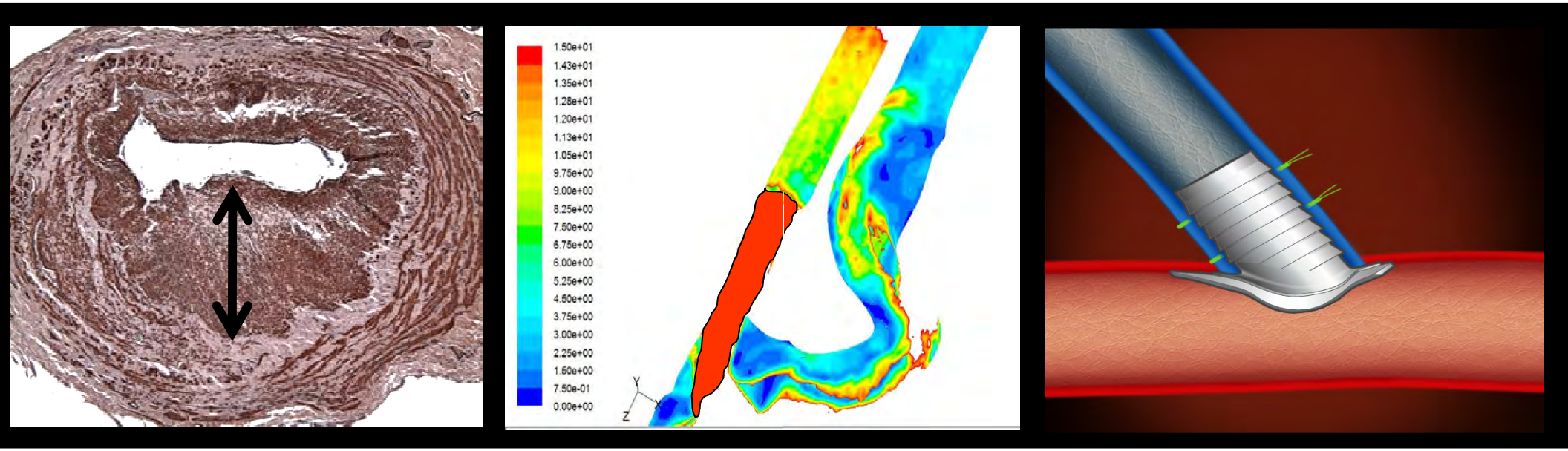


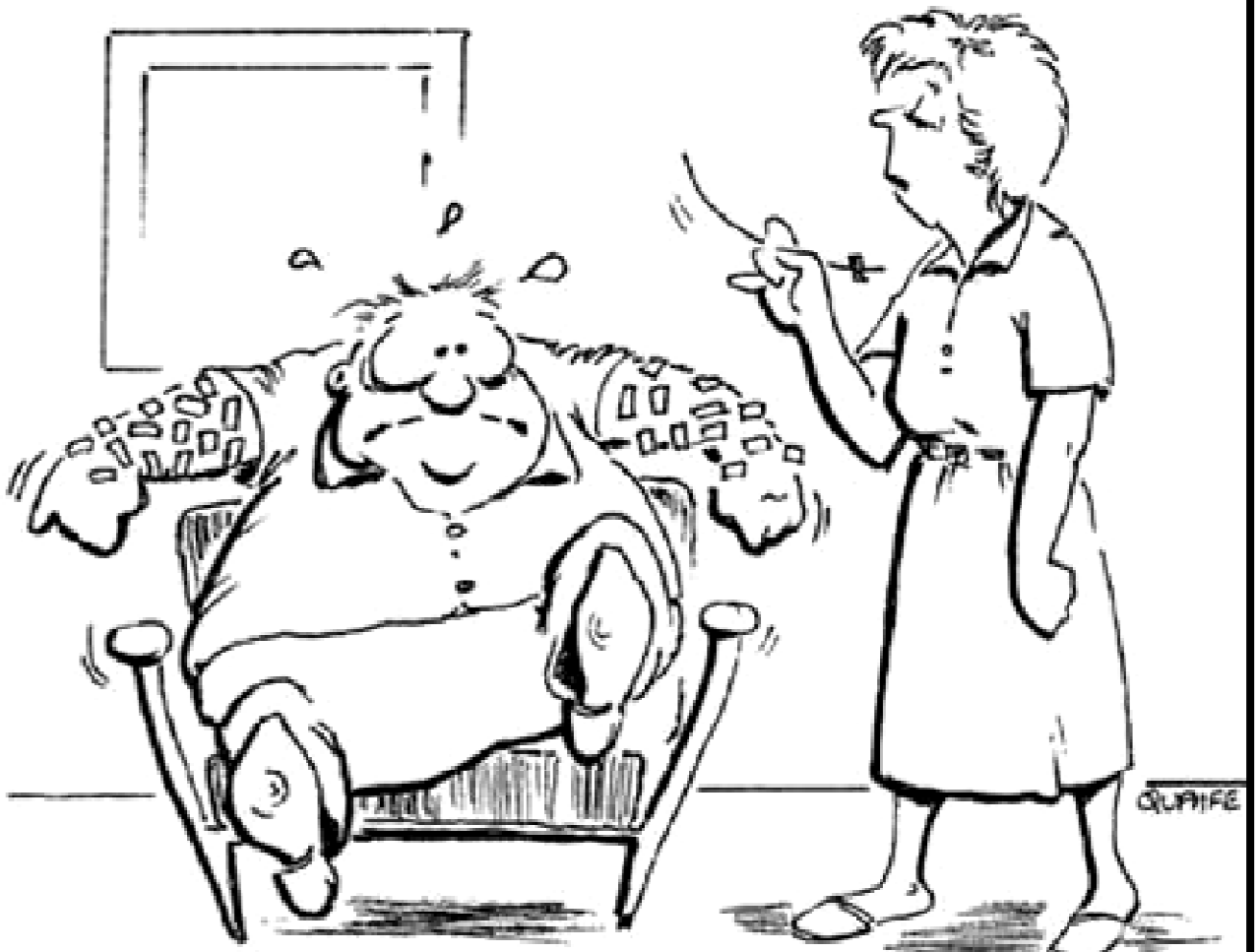
# Disclosures

- Off Label use: Optiflow
- Consultant/Advisory Board: Bioconnect, Pervasis, WL Gore, NanoVasc, Proteon, Shire, Medtronic
- Grant/Research Support: NIH, VA, Bioconnect, WL Gore, Proteon, Shire
- Clinical Trial Support: NIH, Pervasis, Proteon, WL Gore

# Outline

- Pathology and pathogenesis of dialysis vascular access dysfunction
- Interactions between hemodynamics and vascular biology (central to dialysis vascular access dysfunction)
- Novel therapies that target both hemodynamics and vascular biology
- Message for the future!!

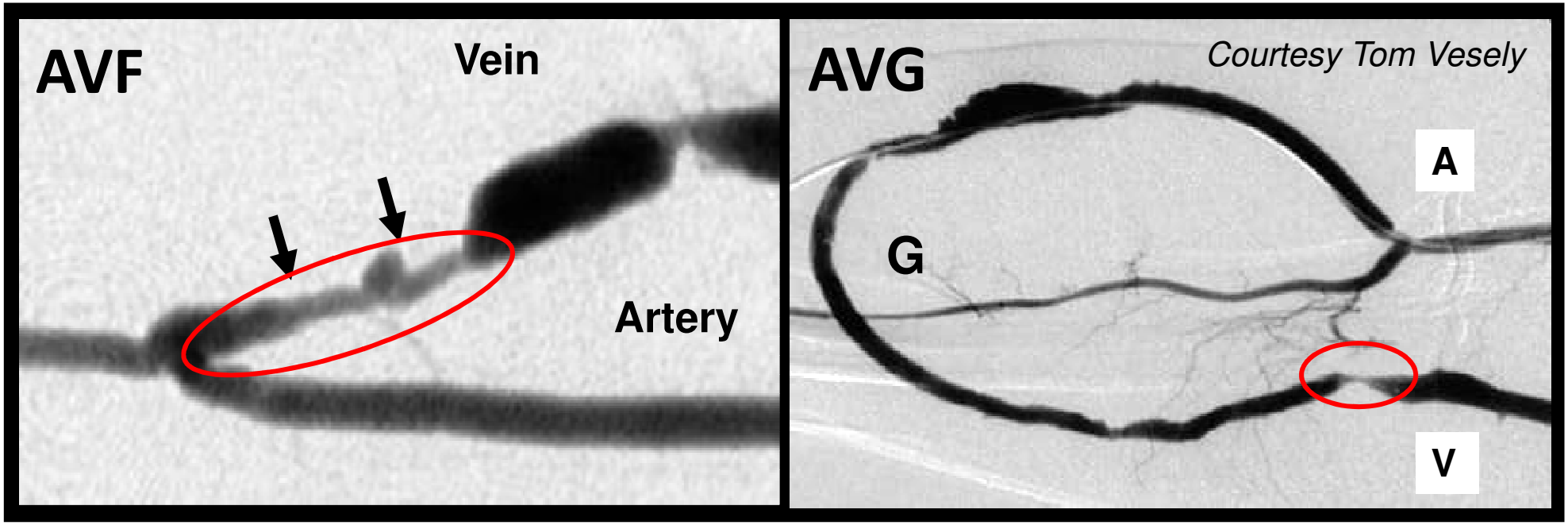
# A message for the present!!




*Don't worry, I'll find a good site soon!!*

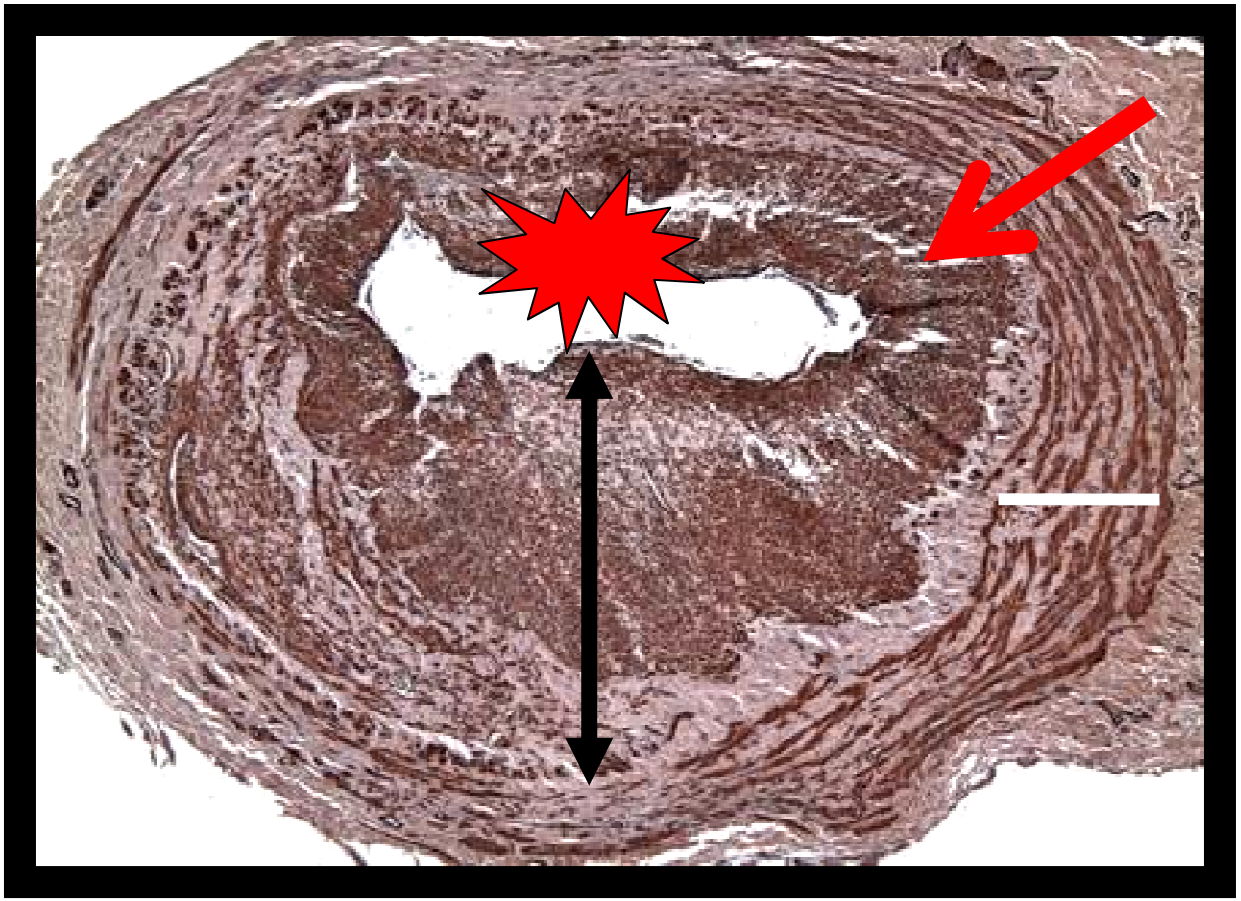
- **Current modalities and therapies for dialysis vascular access are not very effective**
- **Last real innovation in this field was the tunneled dialysis catheter (early 80's)**
- **Huge unmet clinical need that needs to be addressed**

# Radiological presentation of dialysis vascular access dysfunction




- Perianastomotic stenosis
- AVF non maturation
- Stenosis at the graft-vein anastomosis
- Graft thrombosis

# Histological presentation of dialysis vascular access dysfunction

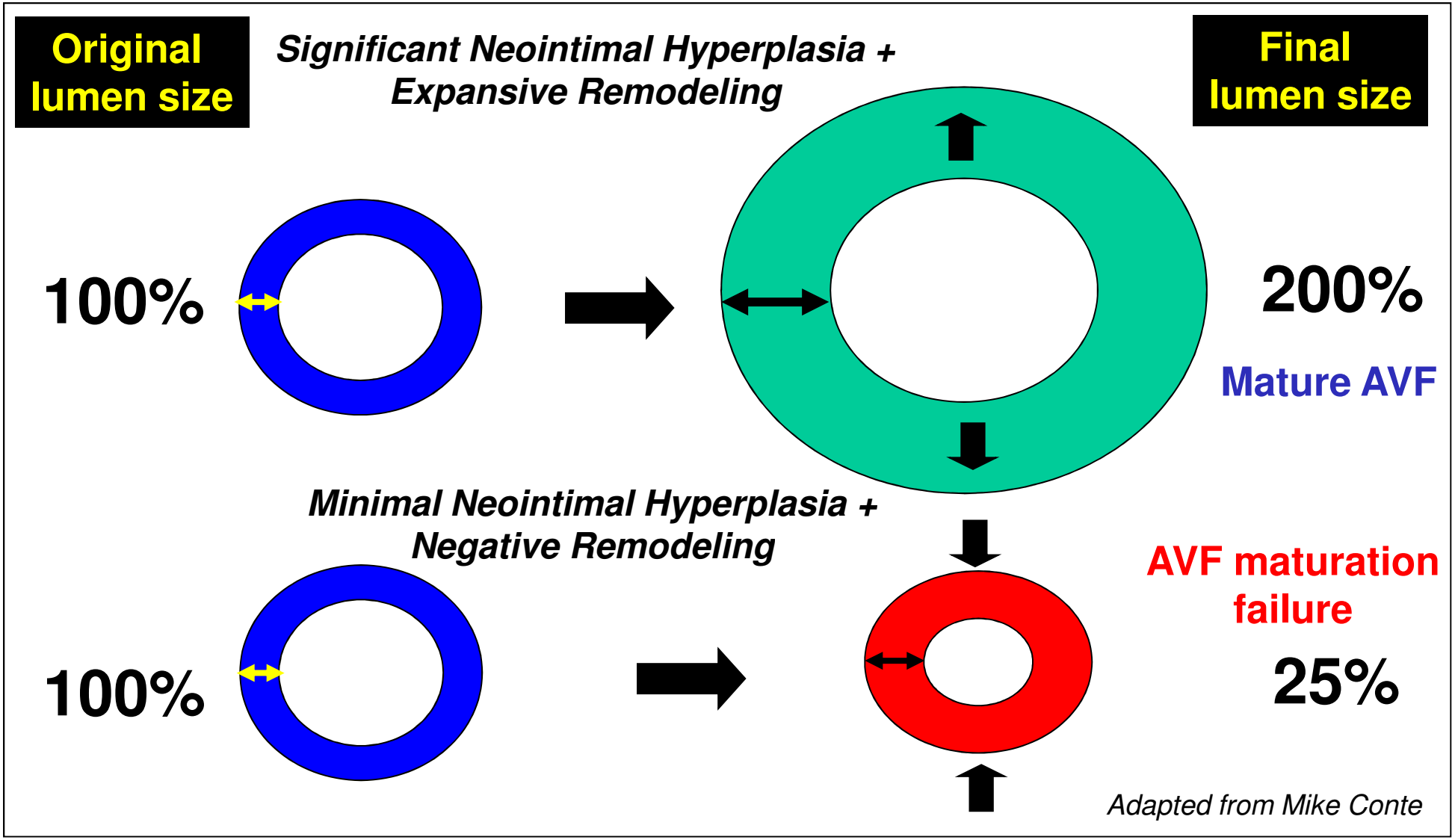


| | SMA | Vim | Des |
|---|---|---|---|
| SMCs | + | - | + |
| Myofib | + | + | - |
| Fib. | - | + | - |

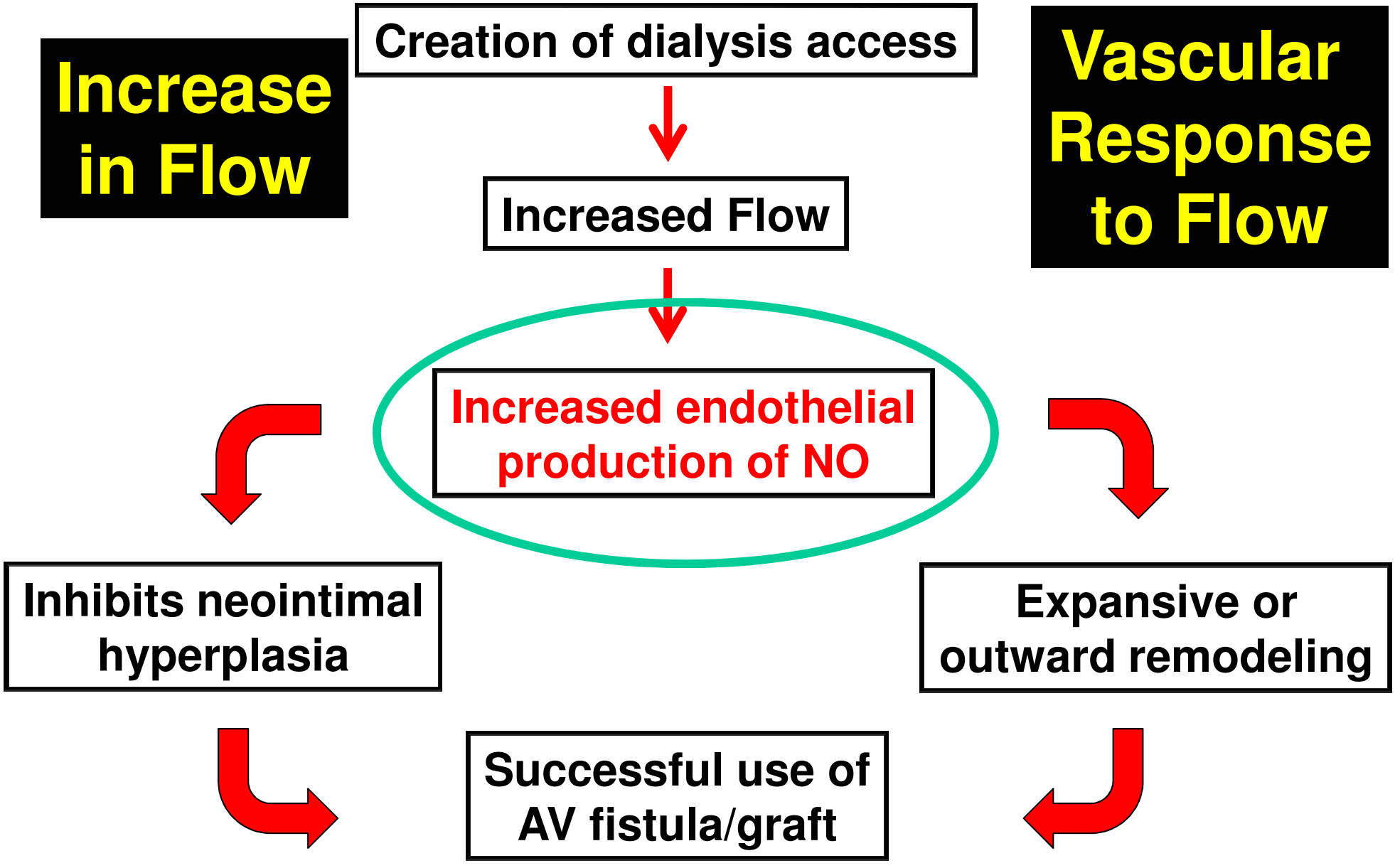
- Migrated in from the media and perhaps the adventitia
- Response to endothelial and smooth muscle cell injury

*Roy-Chaudhury et al. AJKD 2007*

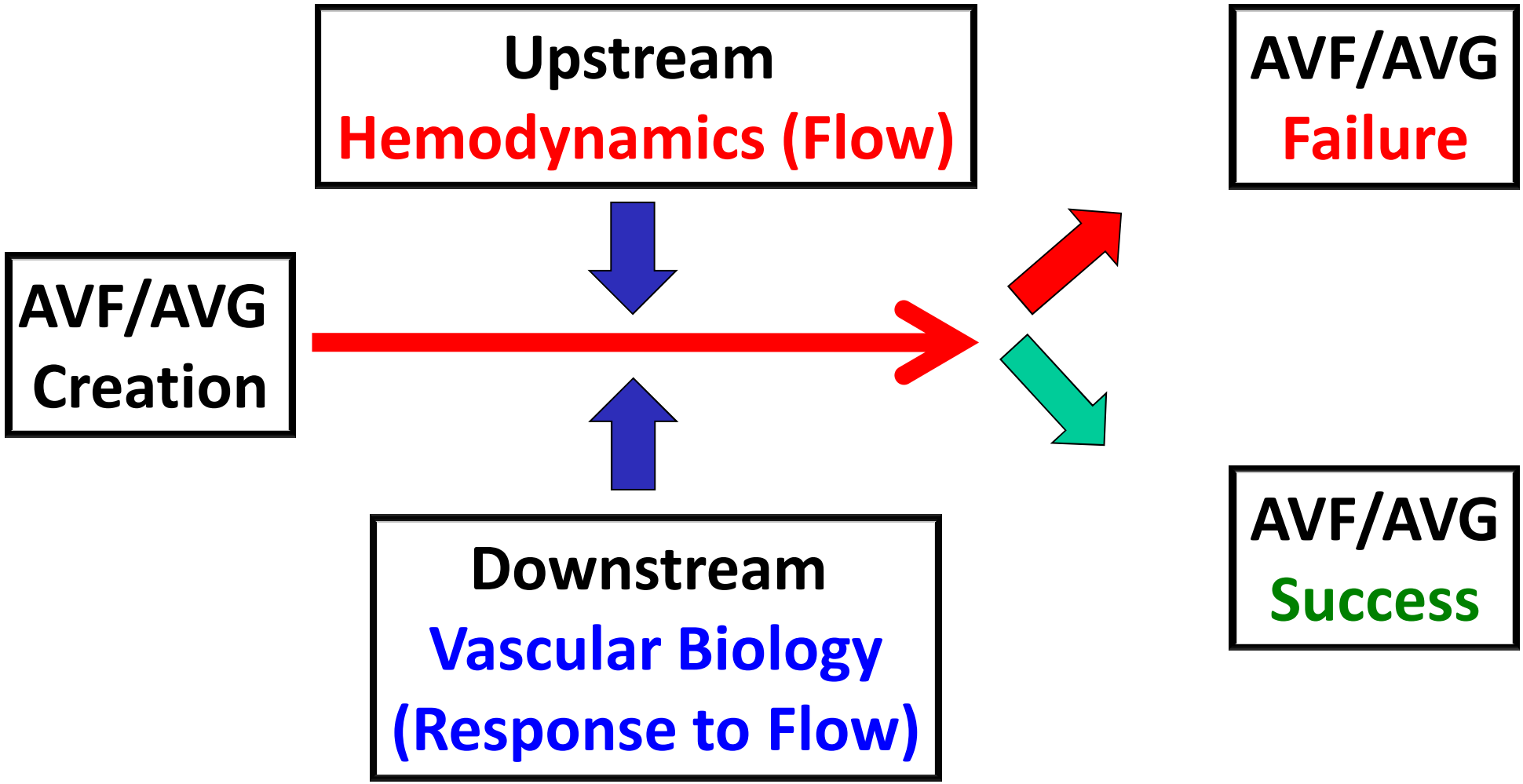
# Dialysis access stenosis is a balance between vascular remodeling and neointimal hyperplasia



# In an ideal world!!!

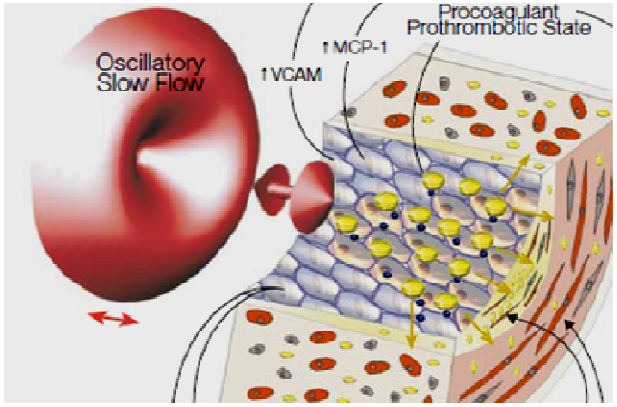


# Hemodynamic and vascular biology interactions



# Flow patterns and shear stress influence endothelial function

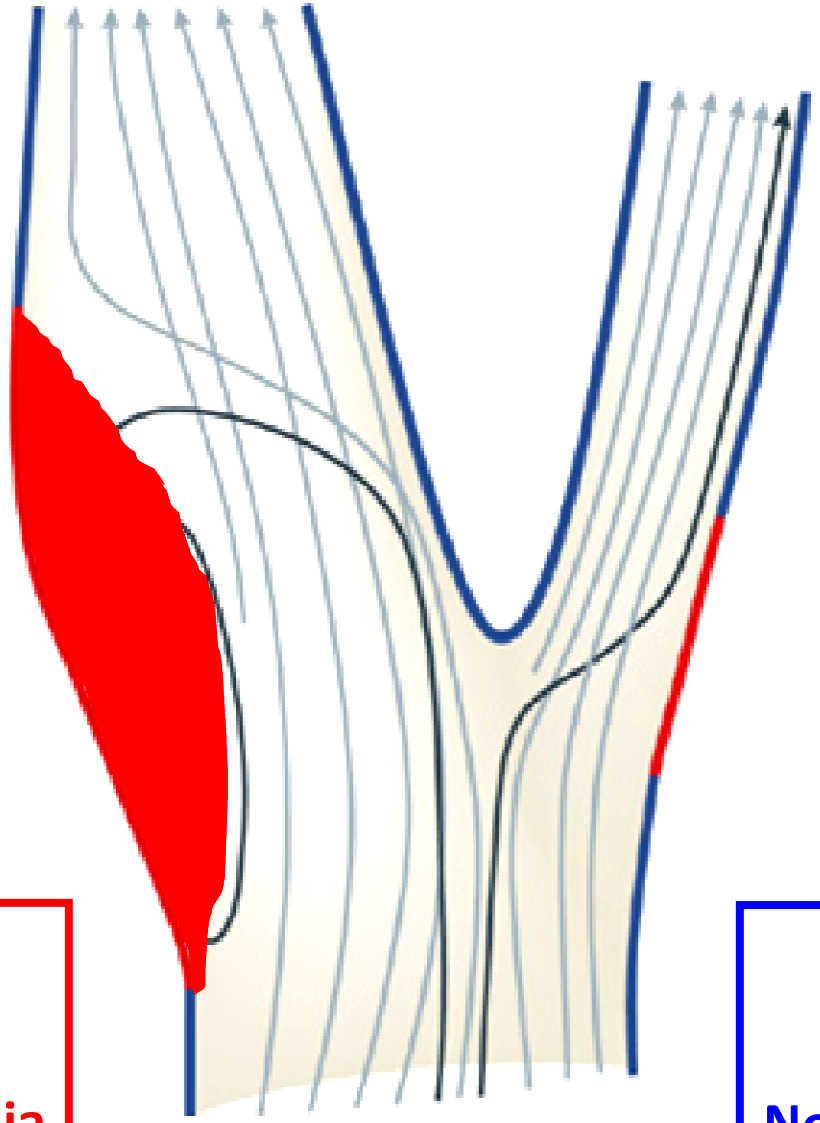
## Hemodynamics 101

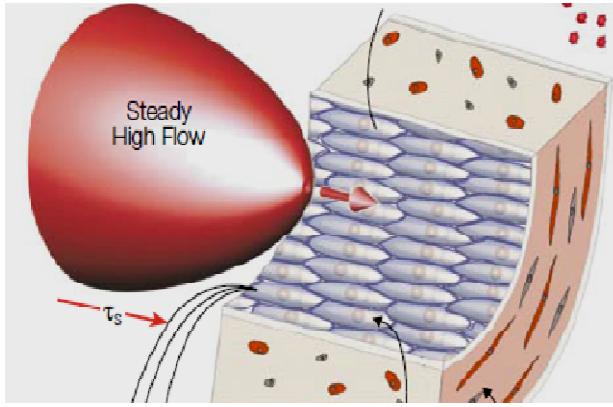



- **Non laminar flow with oscillatory shear (LOW)**
- **Endothelial activation**
- **Increased Oxidative Stress**
- **Inflammatory gene profile (VCAM-1)**

↓

**AVF/AVG**
**Inward remodeling**
**Neointimal hyperplasia**






- **Laminar flow with laminar shear (HIGH)**
- **Endothelial quiescence**
- **Minimal Oxidative Stress**
- **Non-Inflammatory gene profile (Nitric oxide)**

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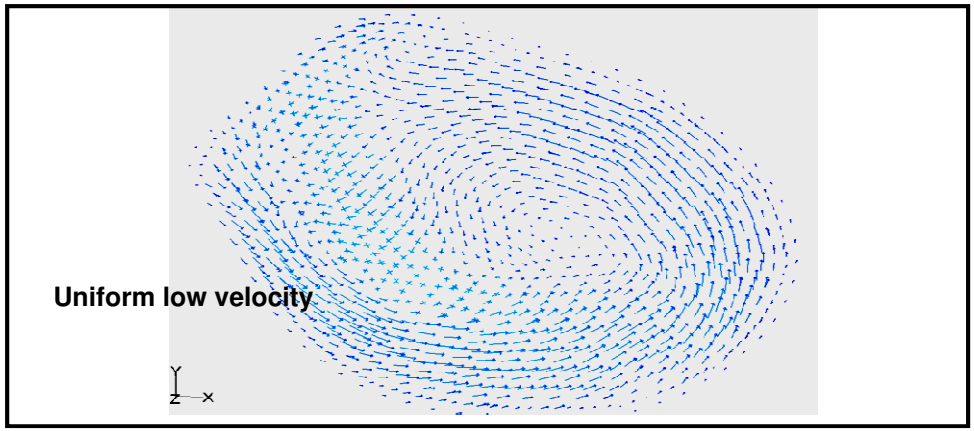
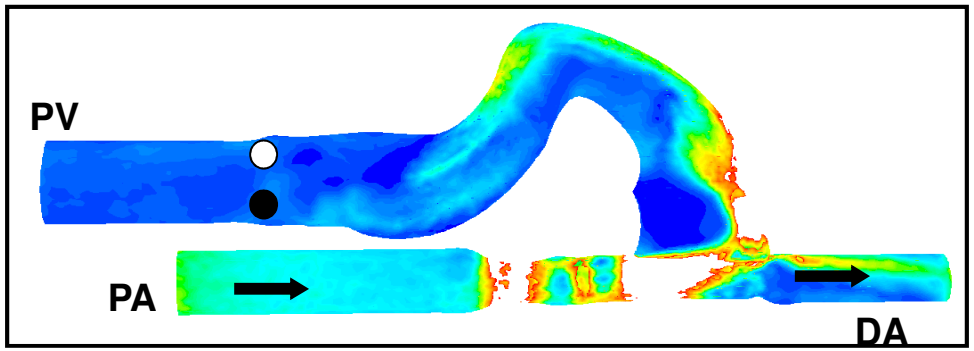
**AVF/AVG**
**Expansive remodeling**
**No neointimal hyperplasia**

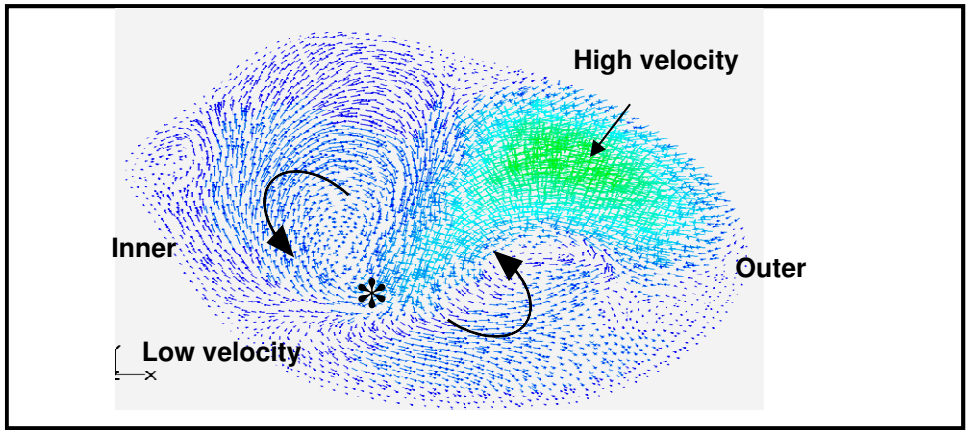
# Surgical configuration influences shear stress profiles

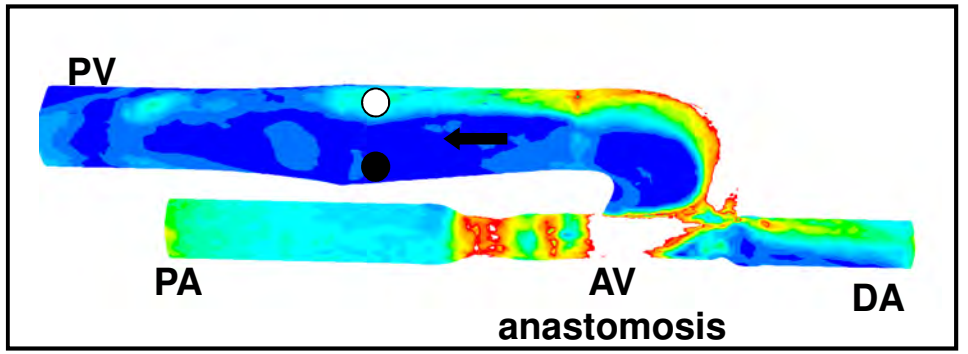
## Curved




## Straight

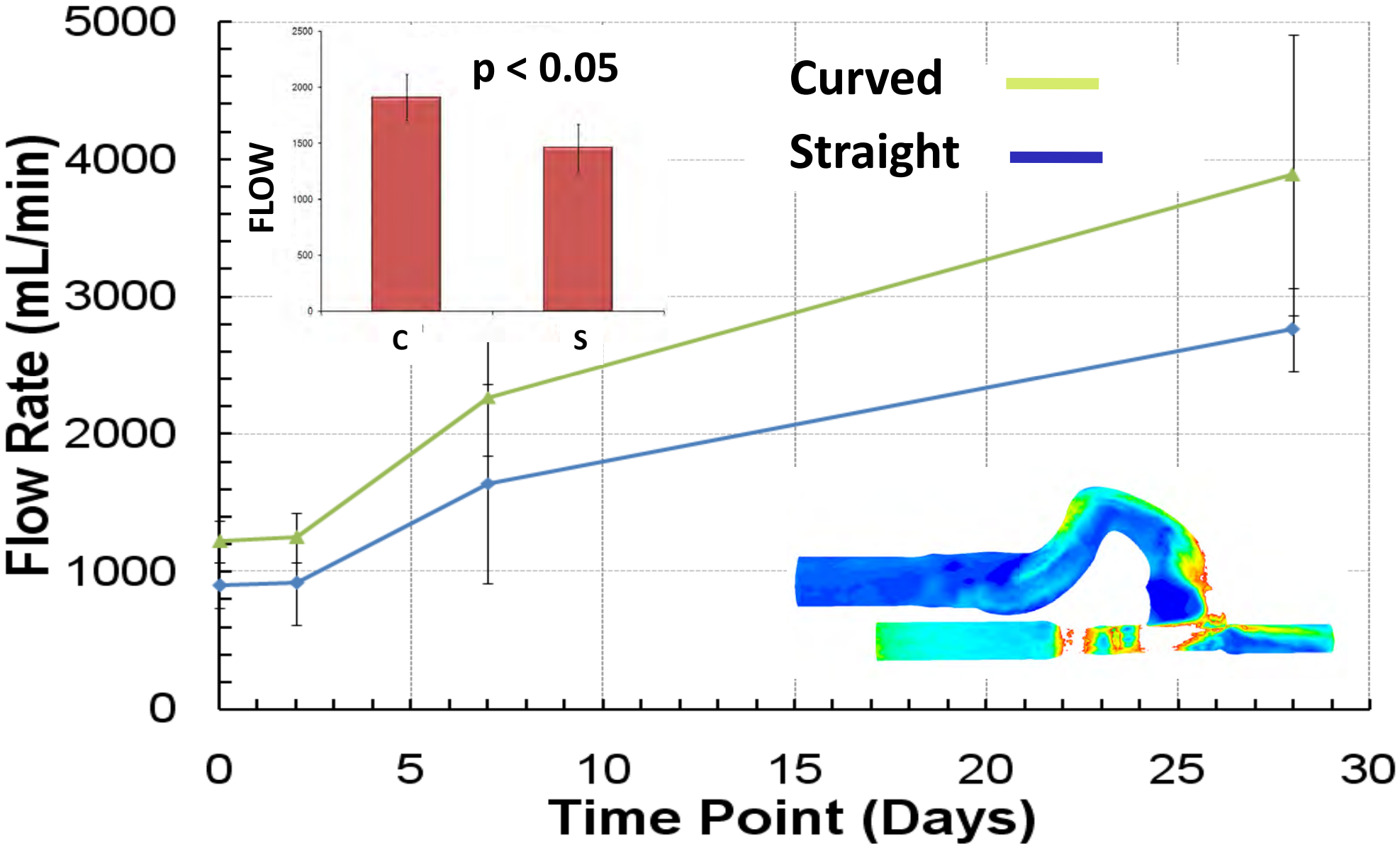


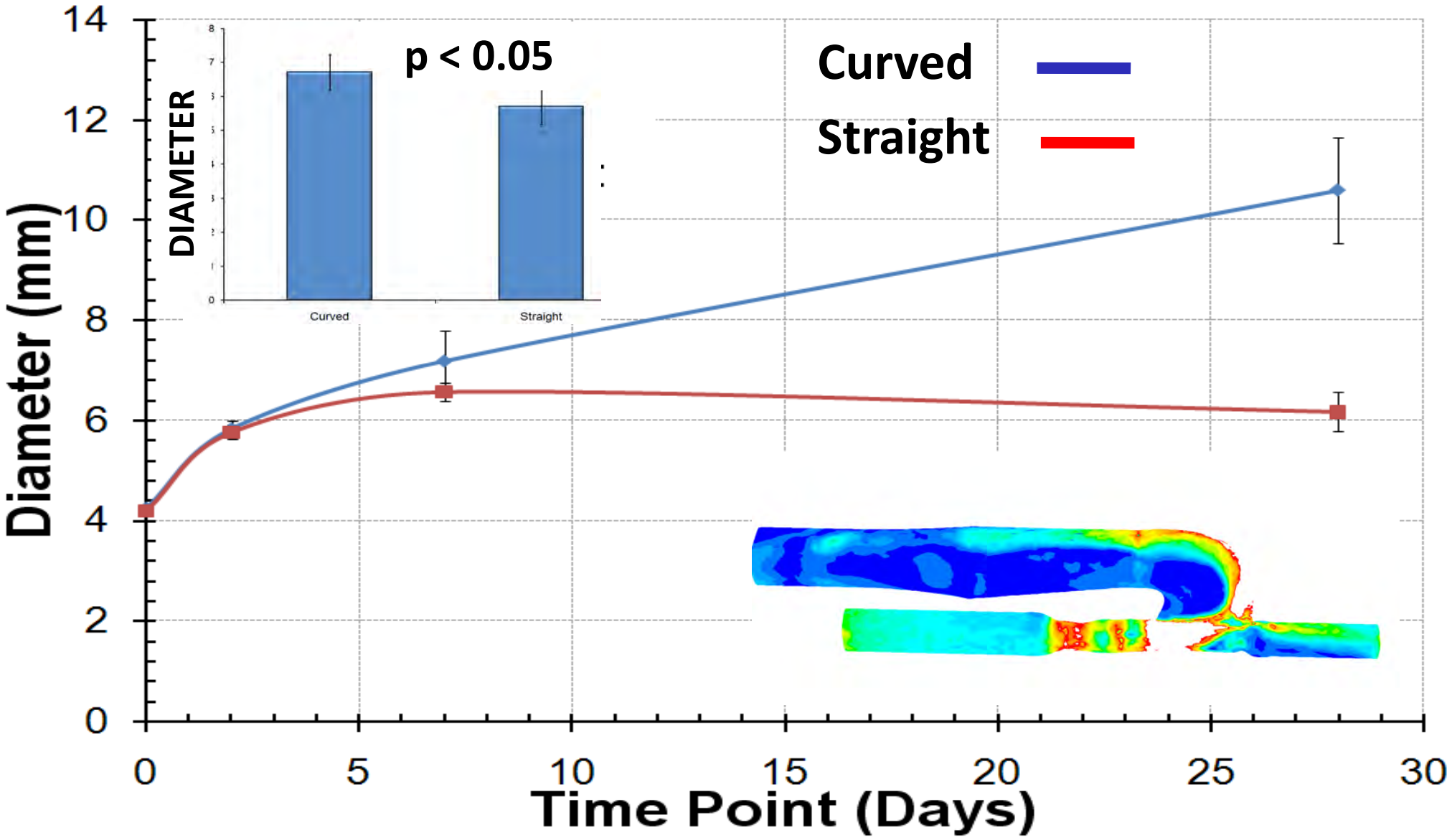


*Krishnamoorthy et al. Kidney International 2008*

# Blood flow is greater in the curved configuration



# Diameter is greater in the curved configuration



# Anatomy, Shear and Stenosis!

**Optimize** surgical configuration for AVFs and PTFE grafts using surgical devices

↓

**Ideal** flow patterns and shear stress profile in AVFs and PTFE grafts

↓

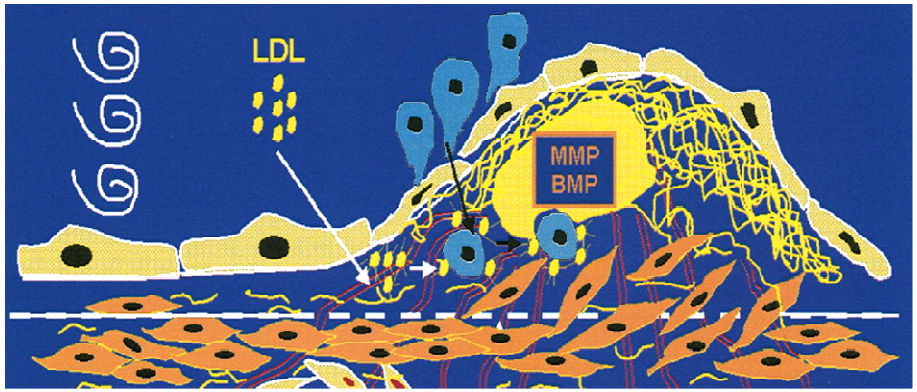
**Reduce AVF and PTFE graft stenosis**

# Intrinsic Endothelial (dys)function

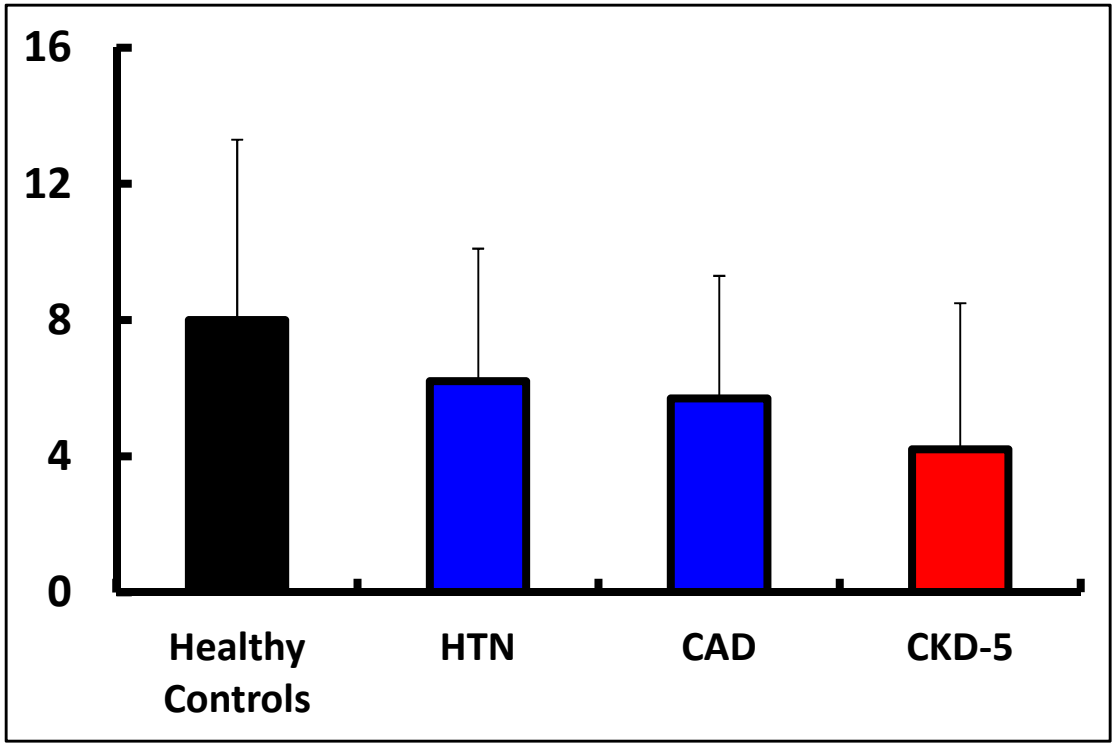
- Hemodynamic forces can influence endothelial response = YES

- Intrinsic function or (dys)function the baseline endothelial cell and how this influences its response to shear stress alterations??

# ESRD and CKD are states of massive endothelial dysfunction!!



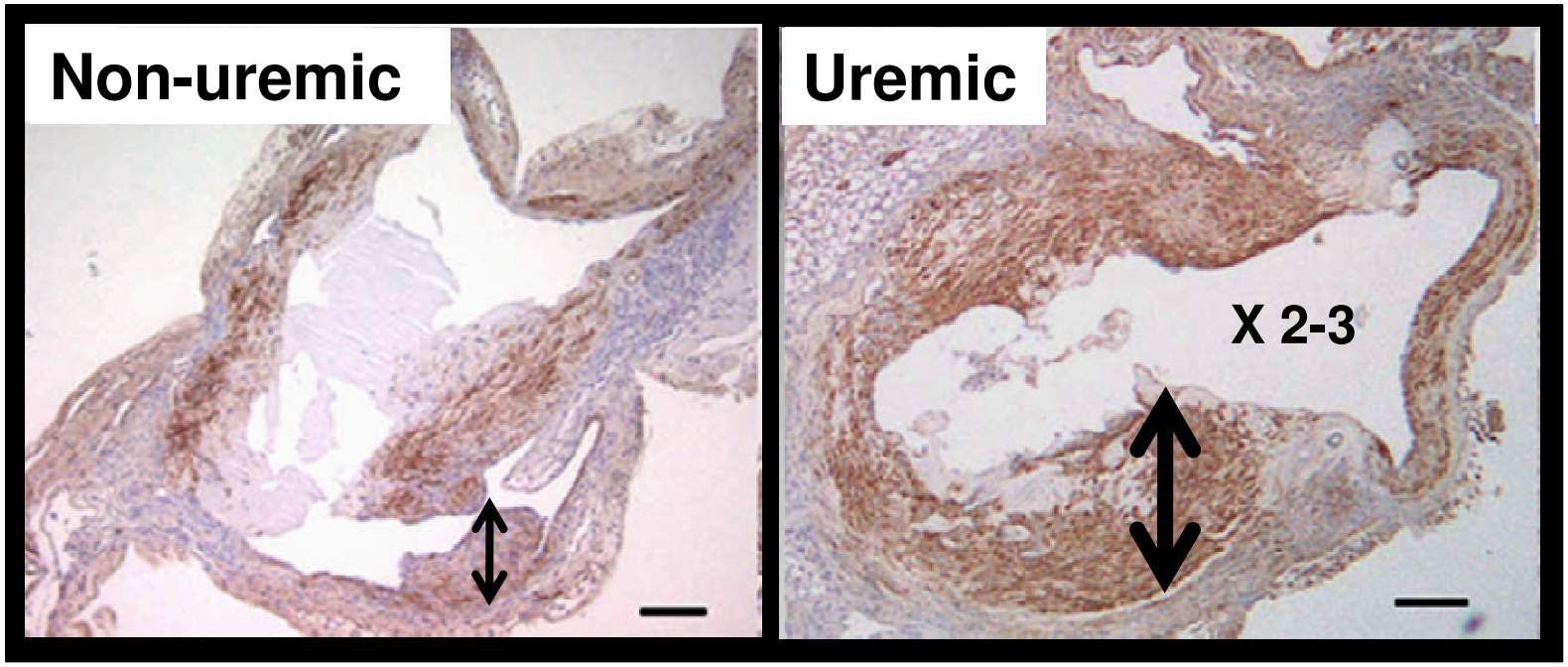

- Uremia
- Oxidative stress
- Inflammation

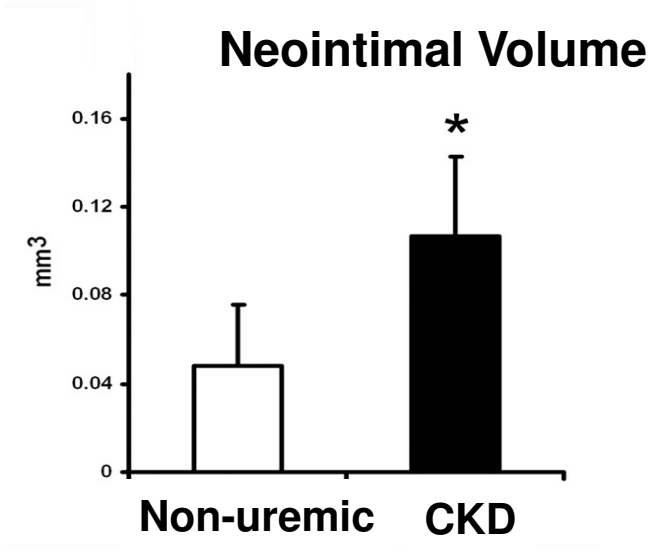


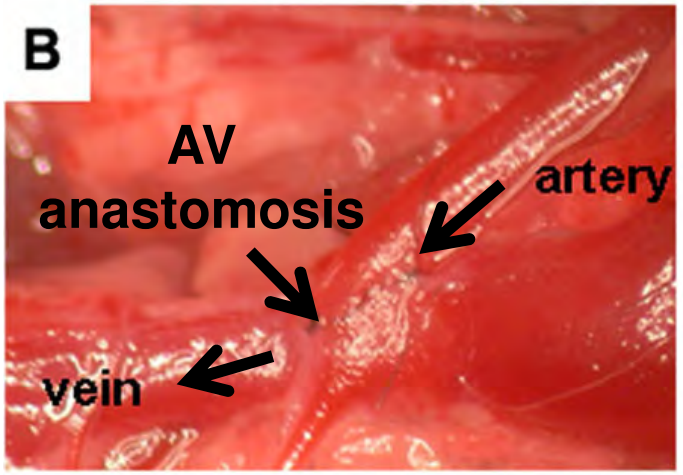

- Reduction in flow mediated dilation *(marker of endothelial function)*

*Kopel et al. F-PO1696, ASN 2009*

# Uremic mice have increased AV fistula stenosis

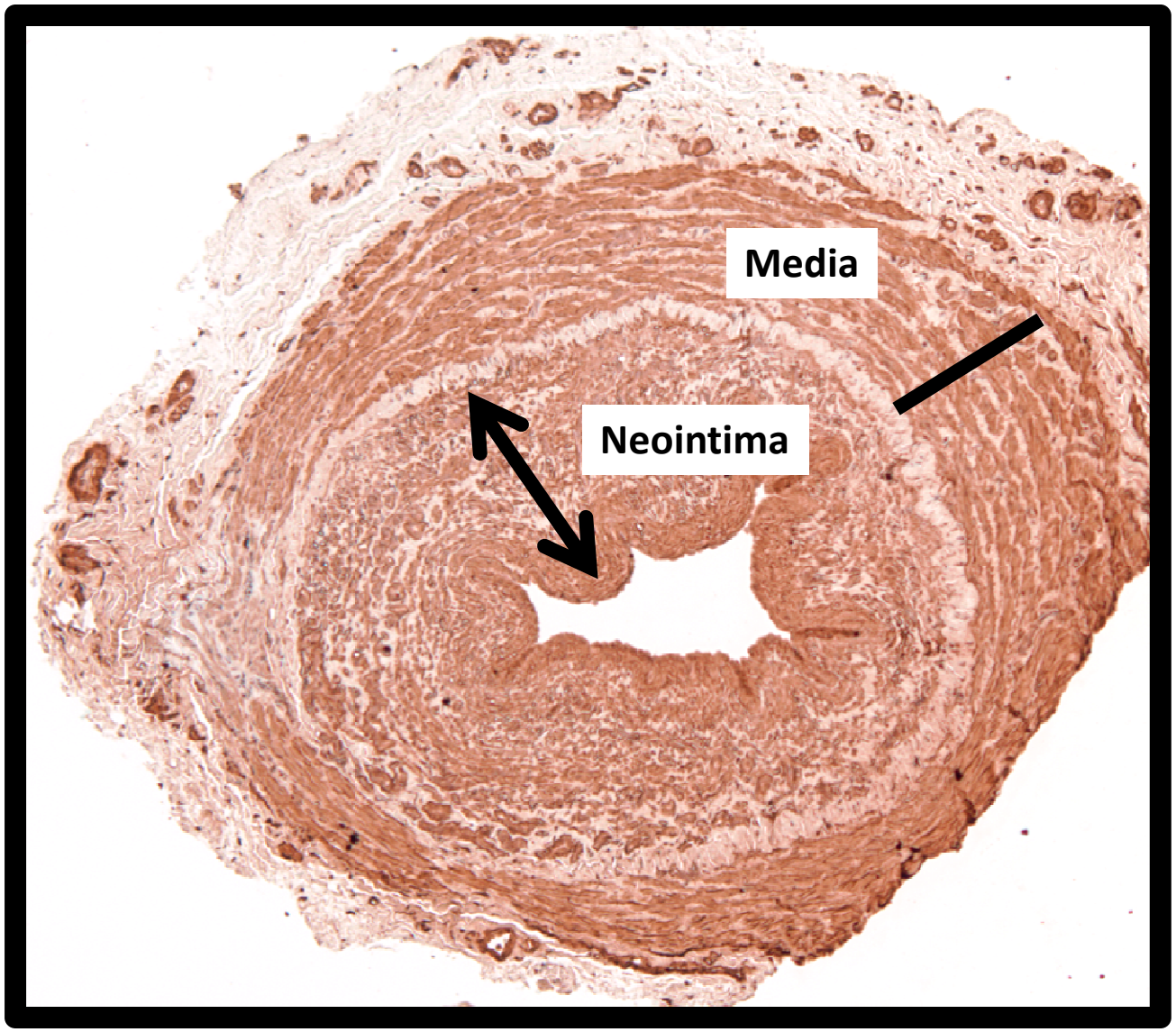



*Choi et al.*
*JASN. 2008*

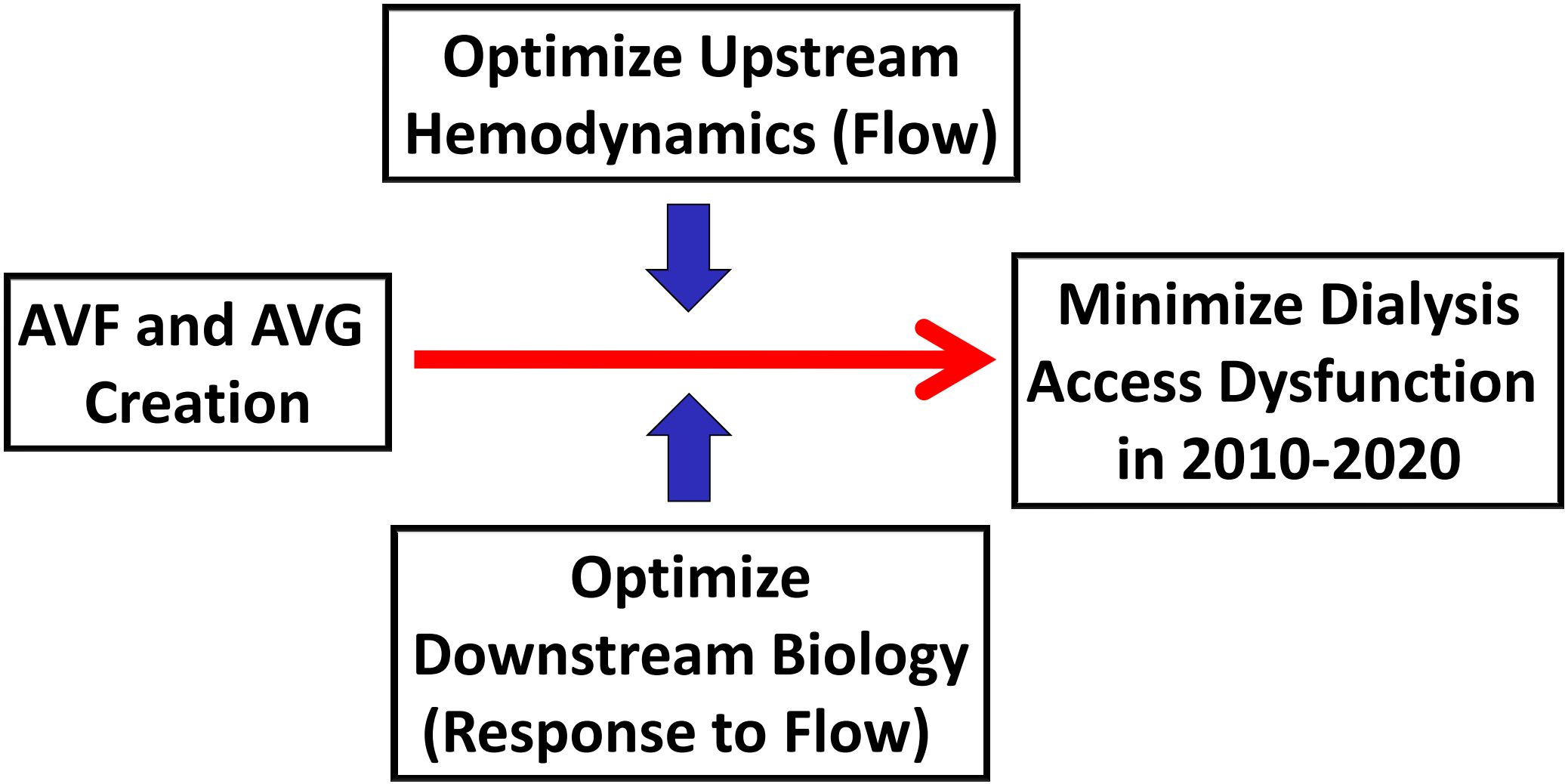
# Uremia and oxidative stress can result in neointimal hyperplasia independent of hemodynamics




| | |
|---|---|
| % Stenosis | 46.6 ± 9.3 |
| I/M Area Ratio | 0.24 ± 0.07 |
| Average IM Thickness | 0.34 ± 0.12 |
| Maximal IM Thickness | 1.16 ± 0.30 |

*Lee et al. NDT 2011*

# Hemodynamic and vascular biology interactions: *a challenge and an opportunity*



# Optimizing upstream hemodynamics and downstream biology using LOCAL therapy

## Upstream Hemodynamics

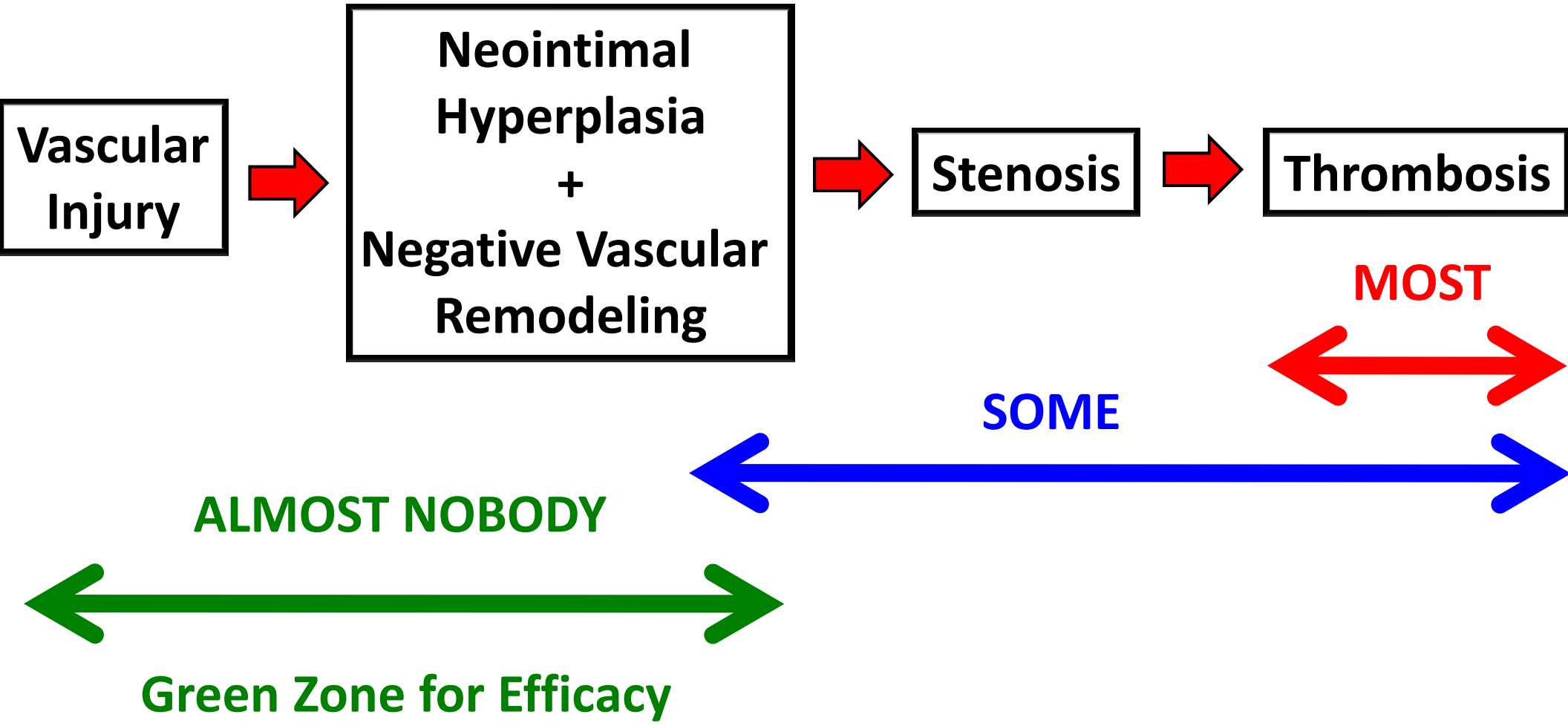
- DEVICE 1: Optiflow
- DEVICE 2: Hybrid
- DEVICE 3: Spiral Flow

## Downstream Biology

- CELL therapy *(Vascugel)*
- DRUG therapy *(Elastase)*
- VESSEL therapy

# Why have we been so unsuccessful??

## Hemodynamics and Vascular Biology



# Excellent results as compared to historical controls

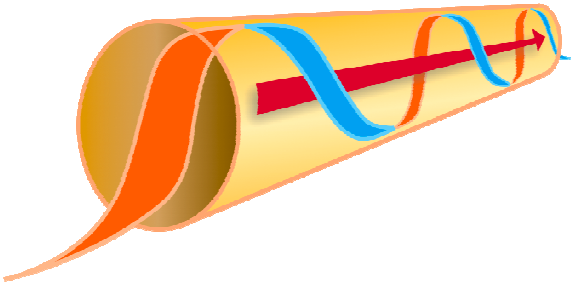
- 60 patient European study in Hungary and Greece
- Good data on an interim analysis (29 patients)

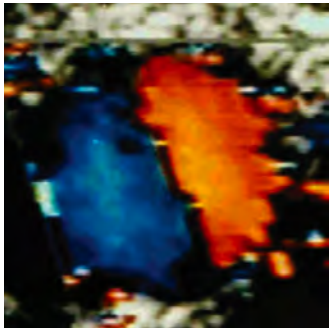
| Effectiveness | 14d patency | 42d patency | 90d patency |
|---|---|---|---|
| **Europe Study (on-going f/u)** | 100% (25/25) | **92%** (22/24) | **83%** (19/23) |
| **Literature Control** | n/a | 80% (DAC) | 68% (Falk, 2006) |
| Safety (n=41) | | | |
| 3 technical failures requiring device removal | | | |

**Watch this SPACE!!!**

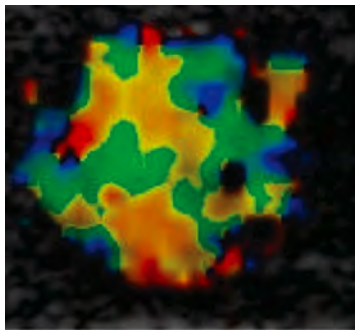
# Inducing Spiral Laminar Flow (Tayside Flow)

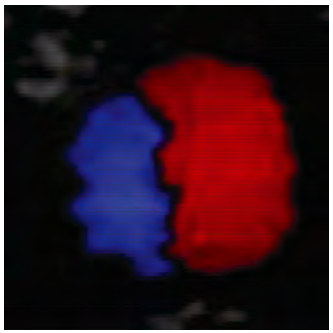
NORMAL

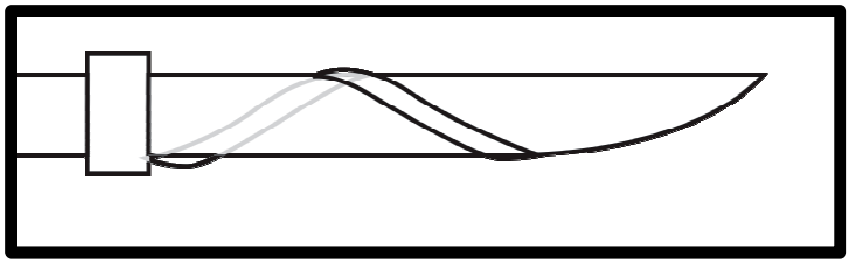




GRAFT

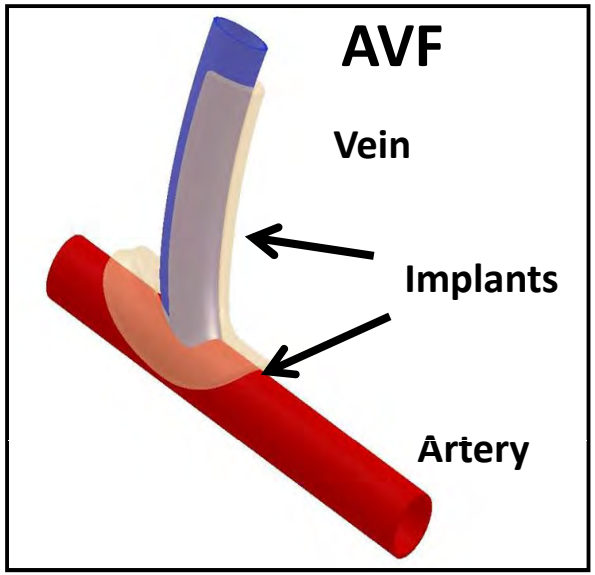


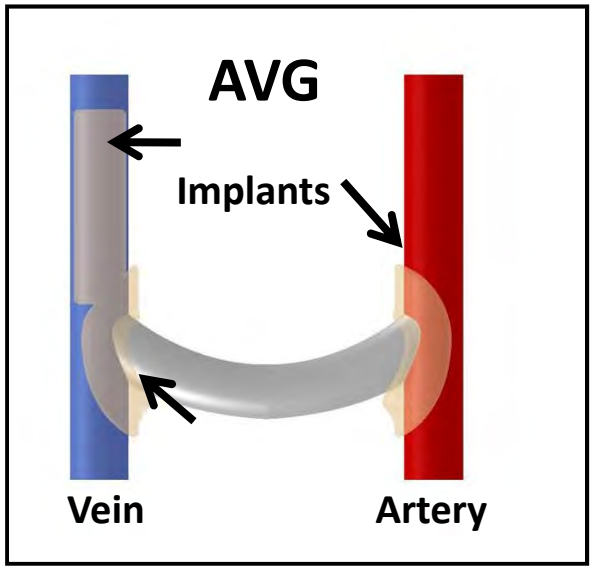


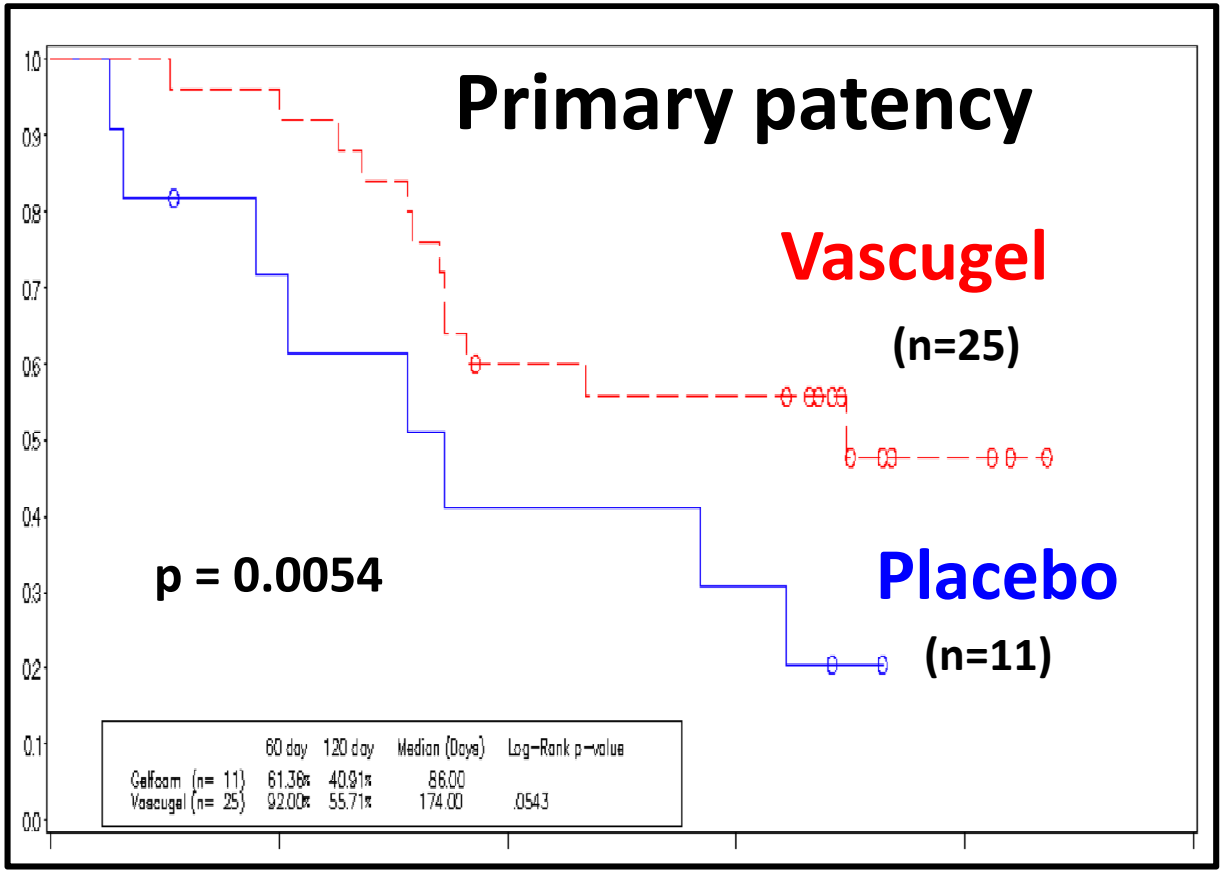


- Normal blood flow is spiral
- Turbulent blood flow at the outlet of a graft
- Spiral connector at the end of the graft converts turbulent flow into spiral flow
- Interesting concept but no clinical data at present
- SLOT technique (Shenoy)

# Perivascular endothelial cell implants (Vascugel) improve patency in diabetics



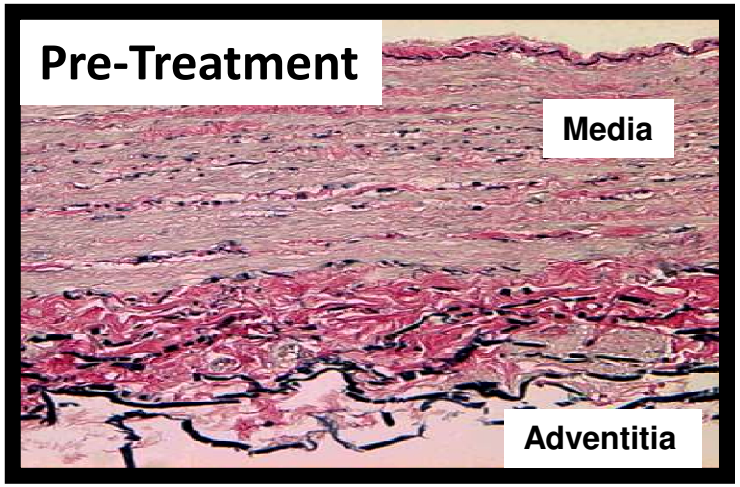



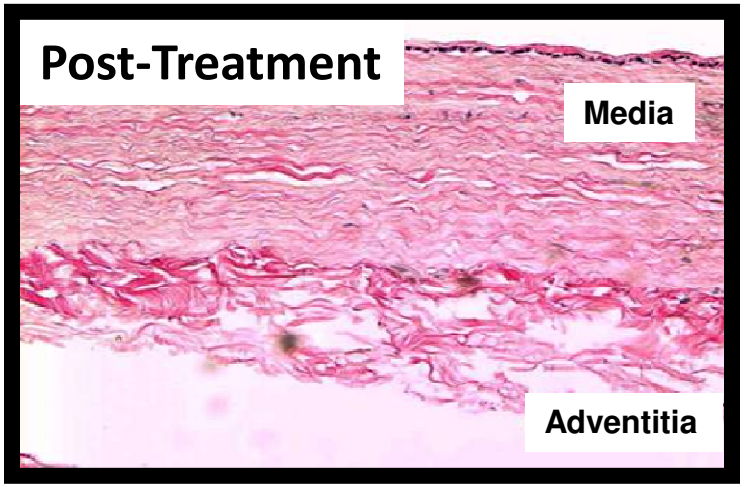




*Roy-Chaudhury et al. ASN 2009, PO-1576*

# Perivascular elastase administration (DRUG THERAPY)

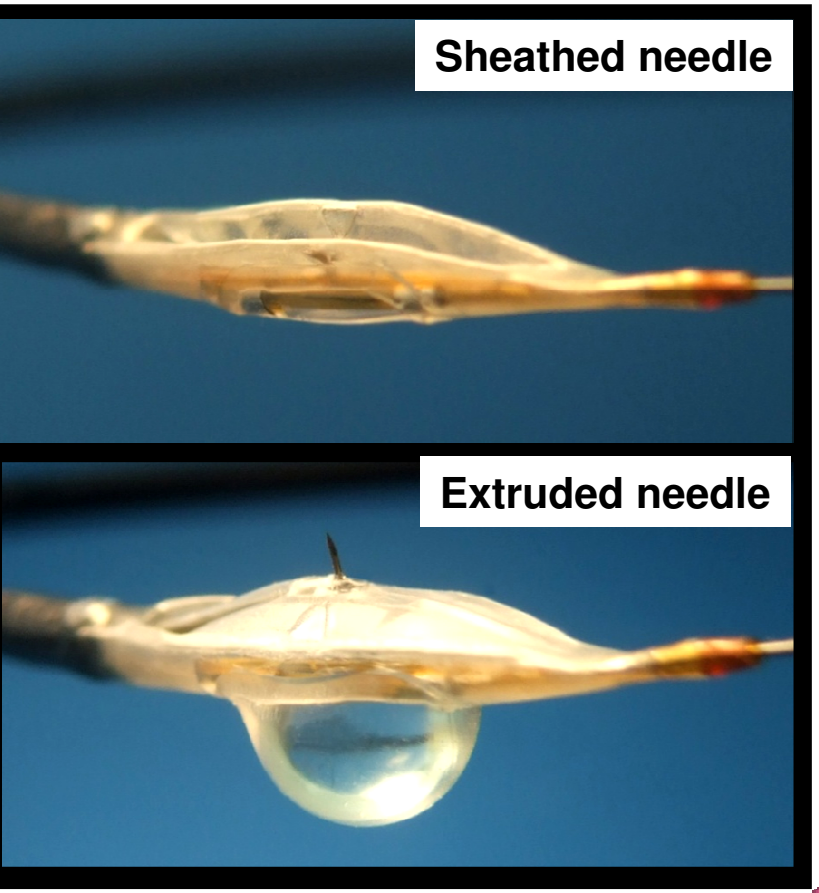
- Recombinant elastase
- Applied to the adventitia
- Destroys the elastin in the vessel wall
- Results in a permanent increase in vessel calibre



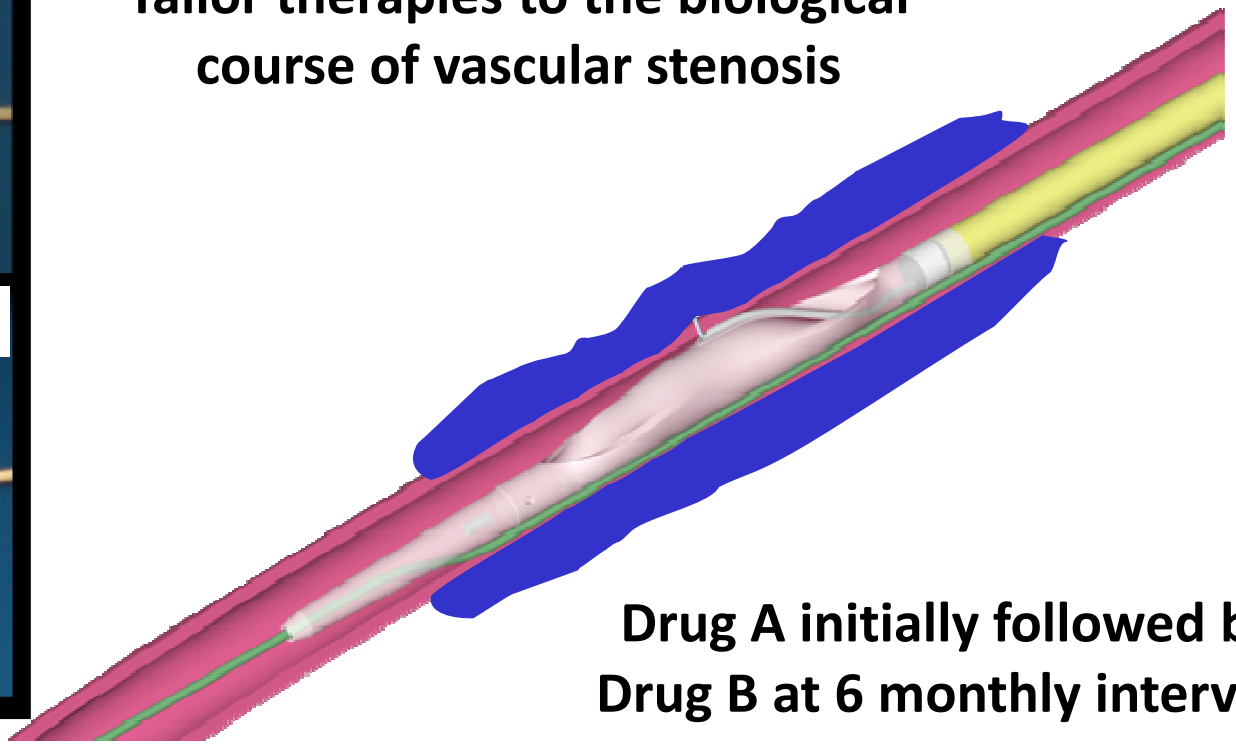



# Abluminal (perivascular) drug delivery

- Endovascular device such as the “Bullfrog” micro-infusion catheter (Mercator-Med)




Tailor therapies to the biological course of vascular stenosis



Drug A initially followed by Drug B at 6 monthly intervals

# A Message for the Future!!

- **Get away from the "one size fits all" paradigm**

# Individualize Vascular Access Care

- Stratify patients based on clinical and biological parameters
- Offer them the dialysis access that is best suited for them
- Individualize vascular access care through the use of novel technologies

# Individualize Vascular Access Care using Novel Technologies

- 25 yr old with large veins and good endothelial function = AVF
- 50 yr old with average veins and moderate endothelial function = AVF "plus"
- 70 yr old with small veins and poor endothelial function = Graft "plus"
- 80 yr old with no veins, poor endothelial function and multiple co-morbidities = Catheter "plus"

"PLUS" = better anatomical configuration, local enhancement of vascular dilation, local anti-proliferative drug therapy, anti-infective and anti-thrombotic coatings

# Technology can Change Existing Clinical Paradigms!!

- **Catheter without infection, thrombosis or central stenosis**
- ***from* Fistula First to Catheter First and Last!!**

# We Live in Exciting Times for Dialysis Access Stenosis!!

## It was the best of times…

- Advances in molecular pathogenesis
- Genomics and proteomics
- Advances in biomaterials and delivery technology

## It was the worst of times…

- Huge clinical problem
- Growing population
- Elderly and clinically complex patients
- No effective therapies

**SOLUTION**