The Real HFM Story...Do Fistulas Mature, When, If and How Often?

Prabir Roy-Chaudhury MD, PhD, FRCP (Edin)
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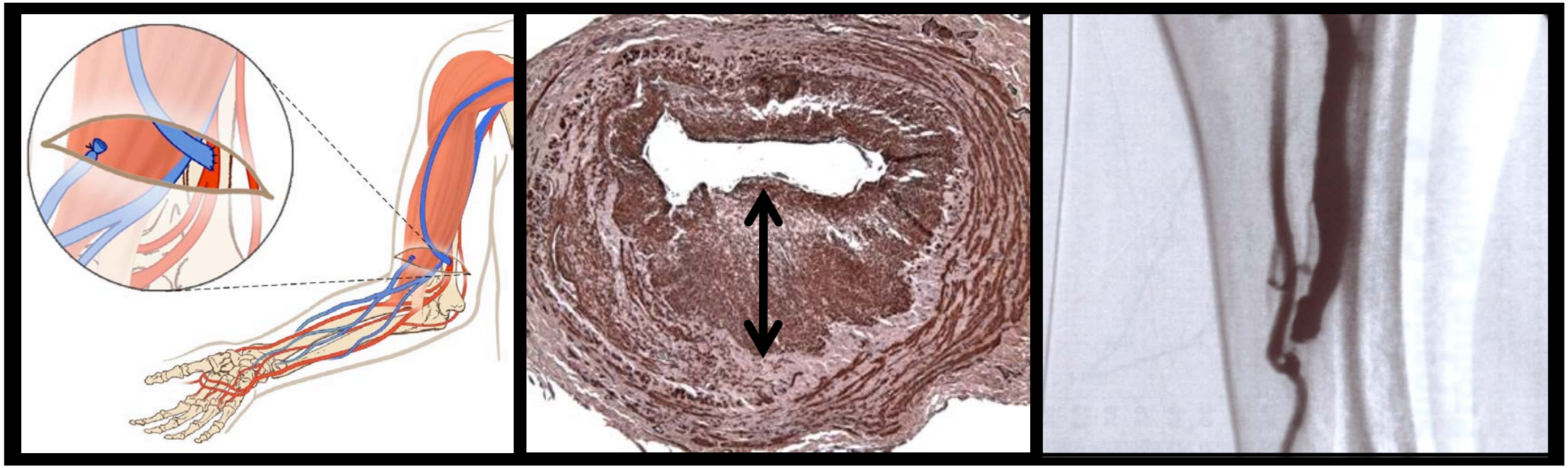
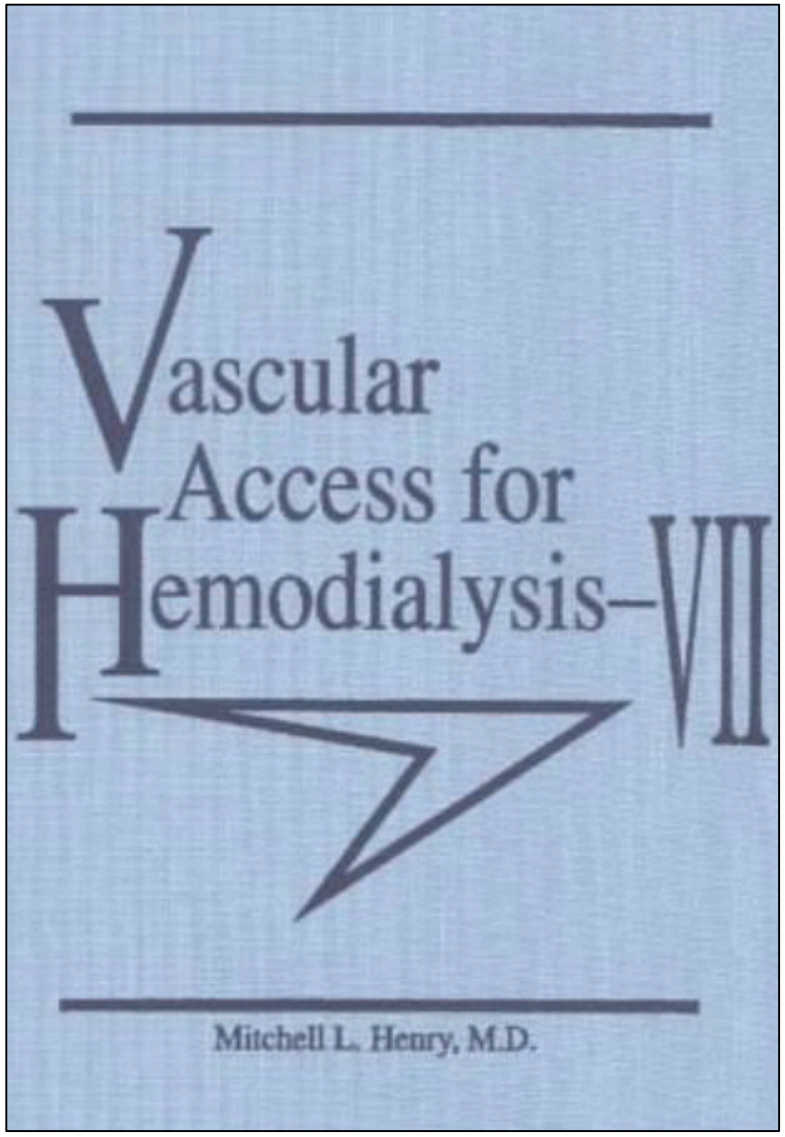


Disclosures

- Founder and Chief Scientific Officer of Inovasc
- Consultant/Advisory Board: WL Gore, Medtronic, Bard, Cormedix, TVA, Humacyte, Akebia, Relypsa

A distinct and personal honor



- **Good friend**
- **My first publication on vascular access**
- **Jump started my professional career**
- **Roy-Chaudhury P**, Whiting JF, Miller MA, Reaves A, Denman D, Munda R, First MR, Heffelfinger SC. Venous Neointimal Hyperplasia in PTFE Dialysis Grafts: A role for specific cell types, cytokines and native proteins. In Ferguson R and Henry M (eds), Vascular Access for Hemodialysis VI., Precept Press 1998, 45-56.

Outline

- Biological and clinical rationale for Hemodialysis Fistula Maturation Study (HFM)
- HFM study design
- Salient results
- Messages for the future (the good, the bad and the ugly!)

Biological and clinical rationale: Why HFM??

- Go back to an earlier NIH study (Dialysis Access Consortium)
- Examined the role of Clopidogrel in reducing AVF dysfunction
- Spectacularly successful study (reduction in 6 wk thrombosis from 19.5% to 12.2%)
- Dismal failure: no impact on AVF suitability for dialysis at 4-5 months
- 40% of AVFs in the control group were capable of supporting dialysis at 4-5 months post surgery!

Effect of Clopidogrel on Early Failure of Arteriovenous Fistulas for Hemodialysis

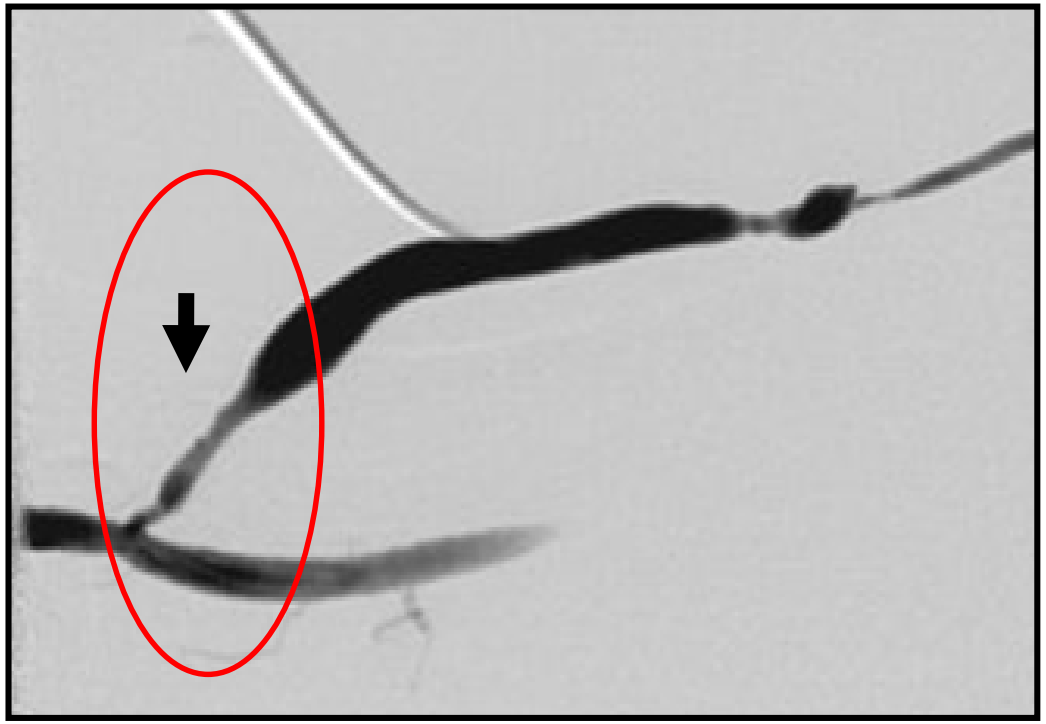
A Randomized Controlled Trial

AVF Thrombosis	No. (%) of Patients		
	Clopidogrel (n = 435)[a]	Placebo (n = 431)[a]	Relative Risk (95% Confidence Interval)[b]
Thrombosis at 6 wk (all patients)	53 (12.2)	84 (19.5)	0.63 (0.46-0.97)[c]
By location			
Forearm fistula	31 (12.9)	60 (24.7)	0.53 (0.36-0.77)
Upper arm fistula	22 (11.3)	24 (12.8)	0.89 (0.52-1.53)

AVF Suitability	No. (%) of Patients		
	Clopidogrel (n = 385)[a]	Placebo (n = 373)[a]	Relative Risk (95% Confidence Interval)[b]
Suitability failure (all patients)	238 (61.8)	222 (59.5)	1.05 (0.94-1.17)[c]
By location			
Forearm fistula	144 (66.9)	137 (64.0)	1.05 (0.92-1.20)
Upper arm fistula	94 (55.3)	85 (53.4)	1.05 (0.87-1.27)

Message from DAC to the community

- In order to develop better therapies for vascular access dysfunction we need to get a better handle on the mechanisms responsible AVF maturation failure



Goals

- To describe pre-operative predictors and post-operative indicators of maturation outcome
- To elucidate mechanisms of AVF maturation failure
- To identify potential targets for future therapeutic intervention

Design

- Prospective observational cohort study
- 7 centers; 602 participants
- Single stage AVF creation
- Pre-operative, intra-operative and post-operative data collection
- AVFs followed up till abandonment

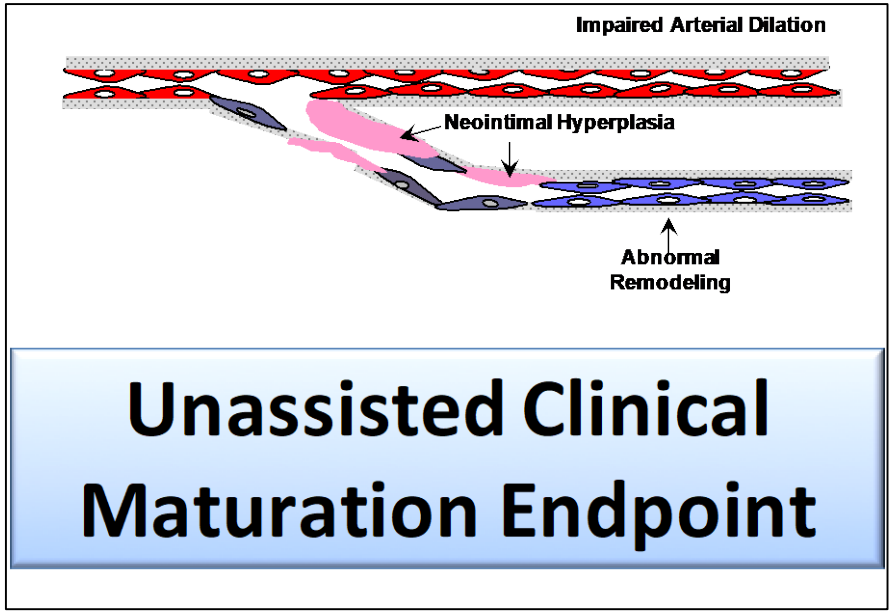
Unassisted clinical maturation endpoint (Primary endpoint)

- **Use of the AVF with 2 needles for 75% of dialysis sessions within a 4 week period AND**
  - **4 consecutive sessions with a blood pump speed of > 300 ml/min**
  - **A measured spKt/V >1.4**

Conceptual level (identify predictors for clinical maturation in 4 domains)

Clinical Patient-Level Attributes

Vascular Anatomy and Blood Flow



Vascular Biology

Processes of Care

Adapted from Laura Dember ASN 2015

Procedures

Pre-Operative	• Ultrasound (“mapping”) • Vascular Function Testing – Brachial artery flow-mediated and nitroglycerin-mediated dilation – Arterial pulse wave velocity – Venous plethysmography • Blood Collection
Intra-Operative	• Surgical Details • Vein Sample Collection
Post-Operative	• Fistula ultrasound (1 day, 2 weeks, 6 weeks, pre-cannulation) • Blood collection (2 weeks) • Events (diagnostic and interventional procedures, fistula events, cannulations, infiltrations) • **FISTULA USE**

Courtesy Laura Dember ASN 2015

Cohort characteristics

Baseline Characteristic	Mean ± SD; N (%)
Age (yr)	55.2 ± 13.4
Male	422 (70%)
Female	180 (30%)
White	283 (47%)
Black	264 (44%)
BMI	30.4 ± 7.6
Current/Former Tobacco Use	330 (54.8%)
Diabetes	353 (59%)
Coronary Artery Disease	156 (26%)
Peripheral Artery Disease	91 (15%)
On dialysis	383 (64%)

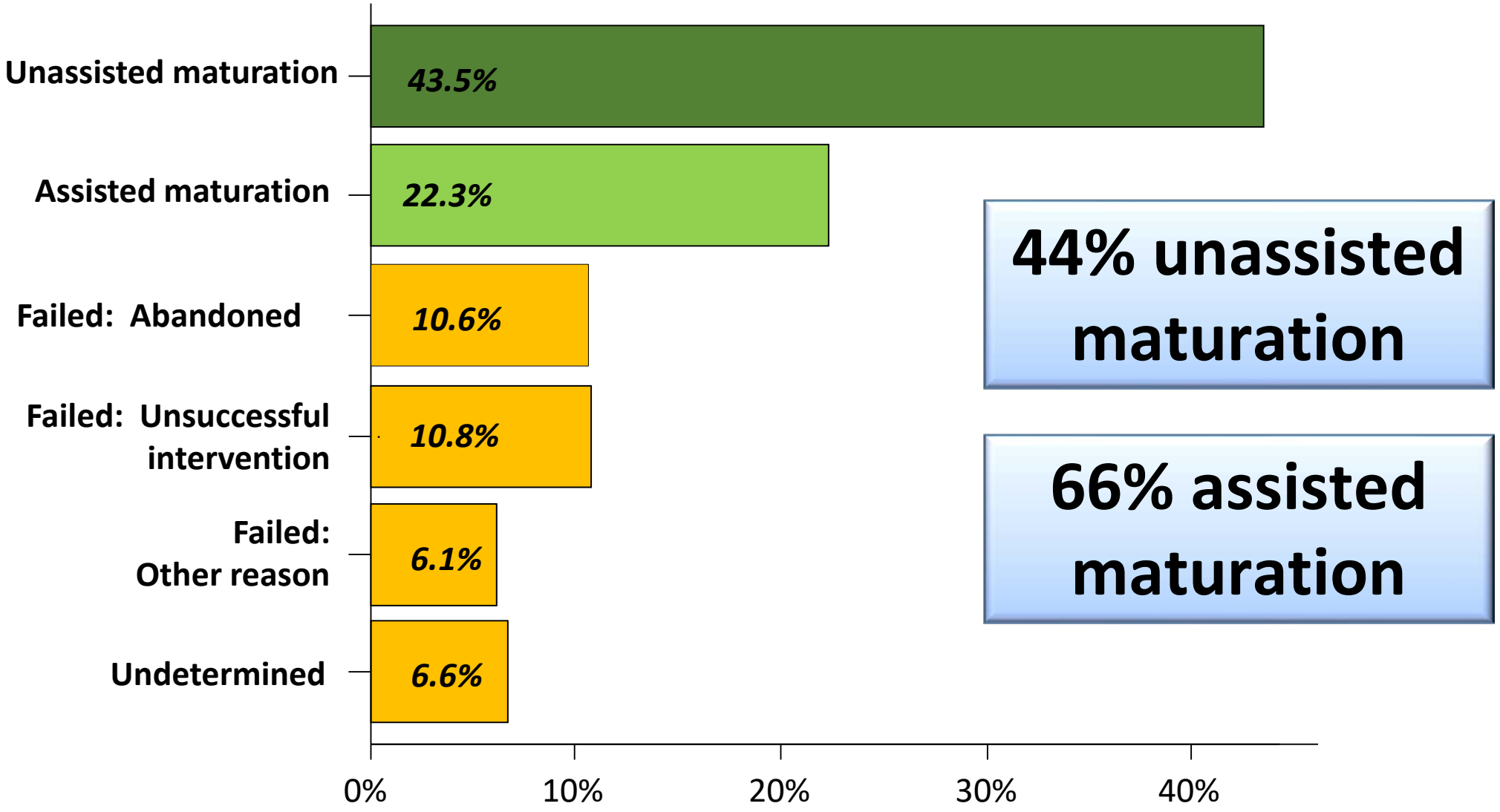
Courtesy Laura Dember ASN 2015

Fistula configurations

Forearm • Cephalic vein • Basilic vein	**143 (24%)** • 133 (22%) • 10 (2%)
Upper Arm • Cephalic vein • Basilic vein • Brachial vein	**459 (76%)** • 285 (47%) • 162 (27%) • 12 (2%)
Transposed vein	**184 (31%)**
Anastomosis length, mm **(10^{th}, 90^{th} percentile)**	**8.0 (4.0, 11.0)**

Courtesy Laura Dember ASN 2015

Unassisted clinical maturation

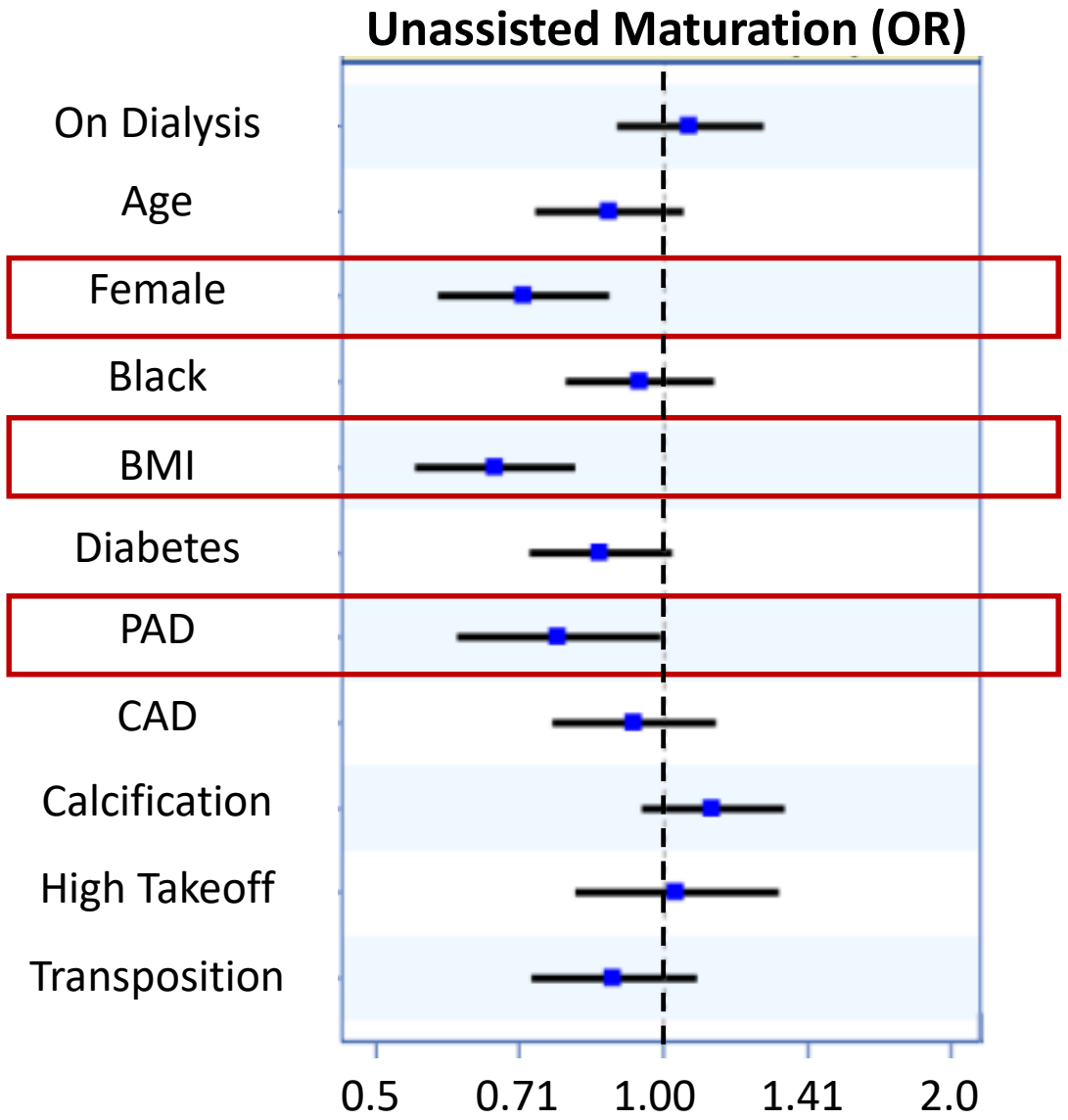


44% unassisted maturation

66% assisted maturation

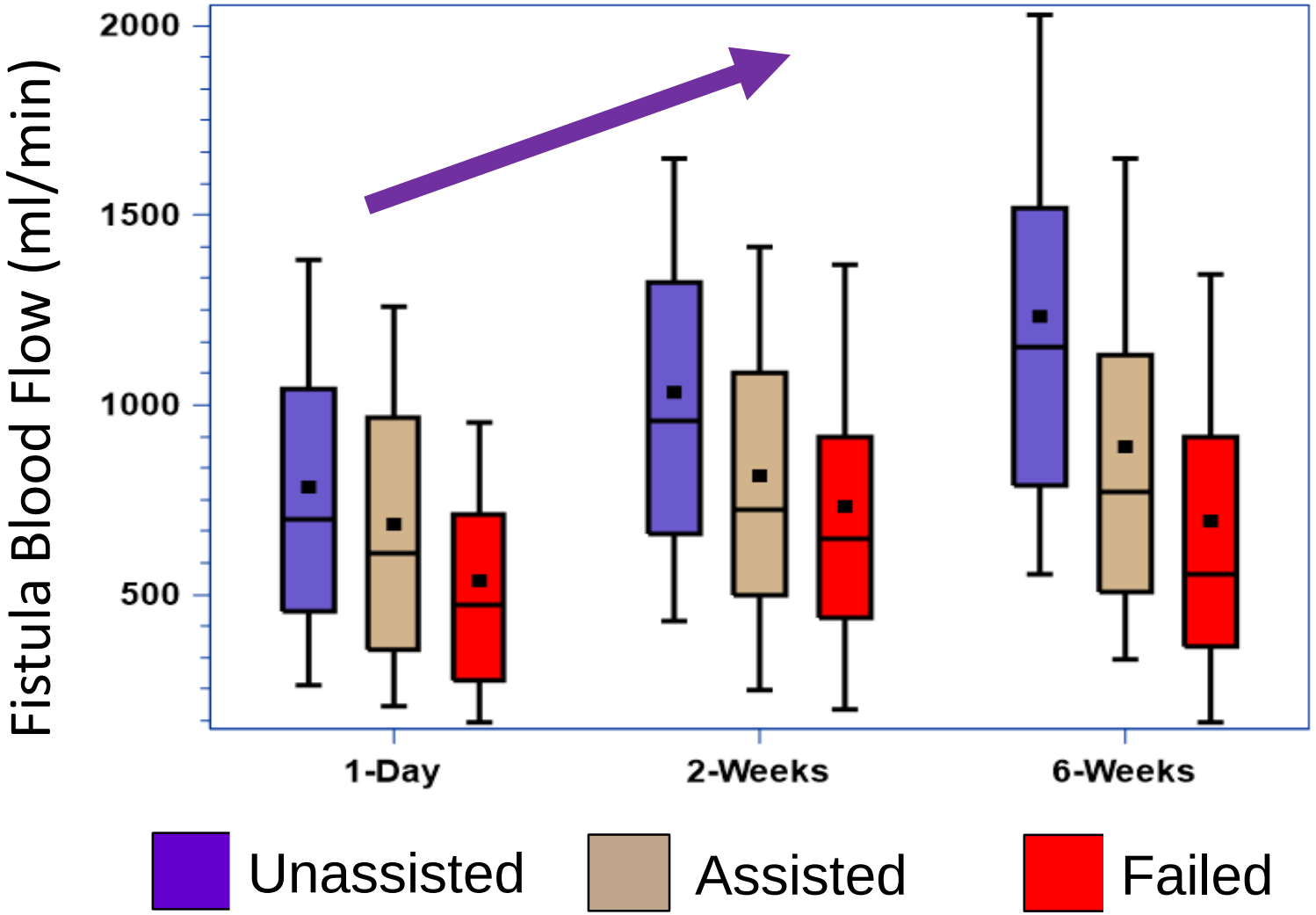
Courtesy Laura Dember ASN 2015

Clinical patient level attributes: no surprises



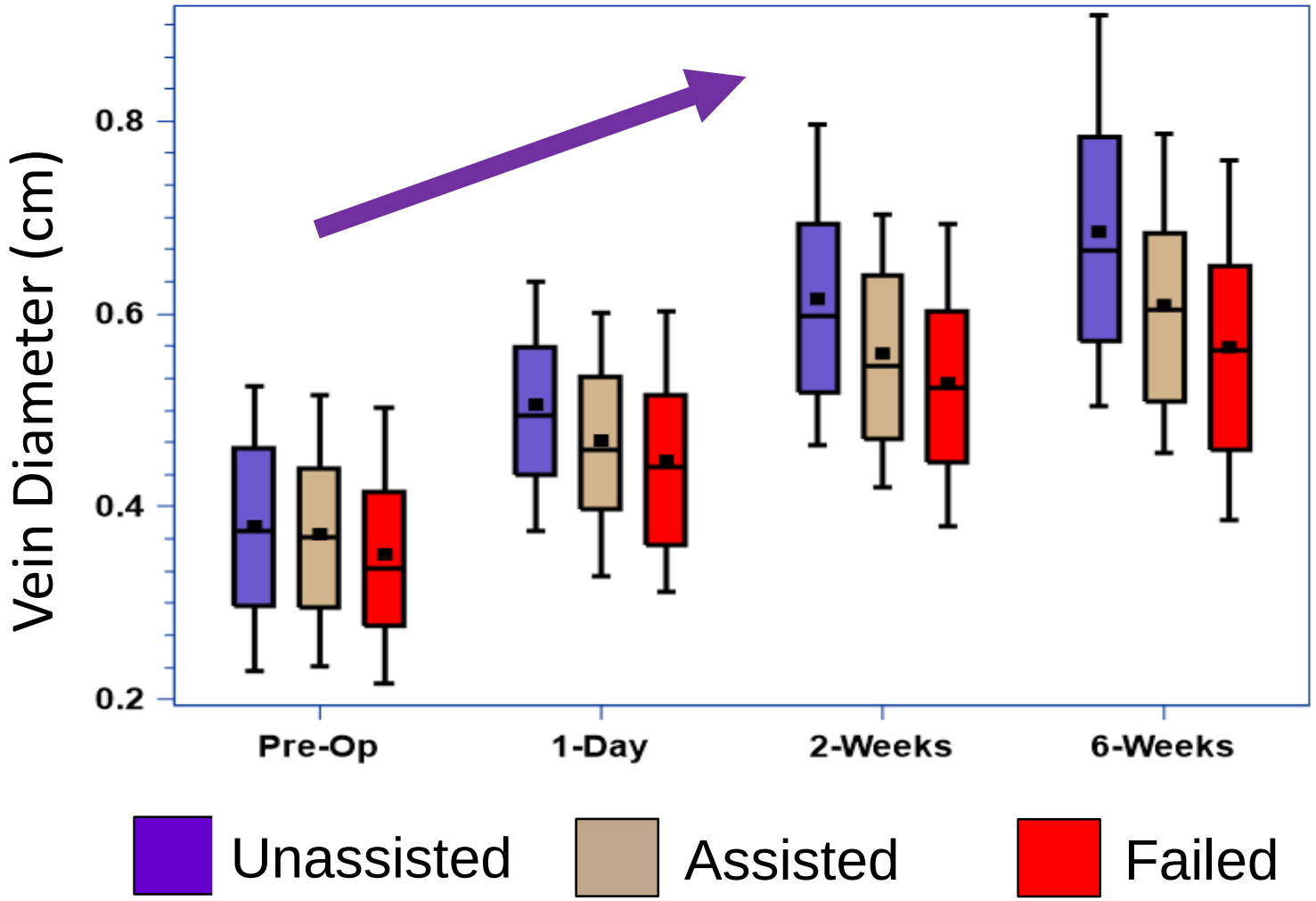
Courtesy Laura Dember ASN 2015

Vascular anatomy and blood flow (FLOW)



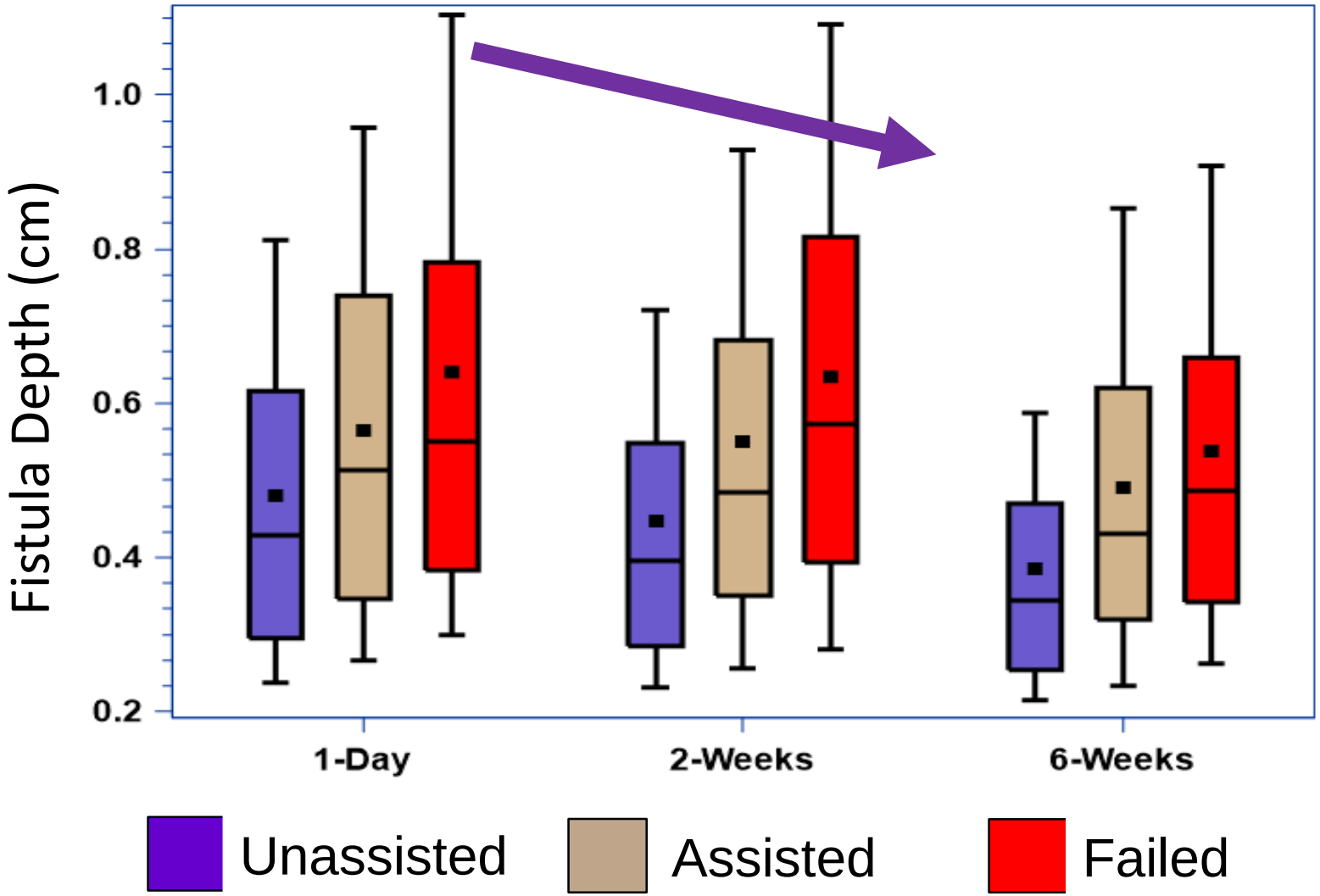
Courtesy Laura Dember ASN 2015

Vascular anatomy and blood flow (DIAMETER)



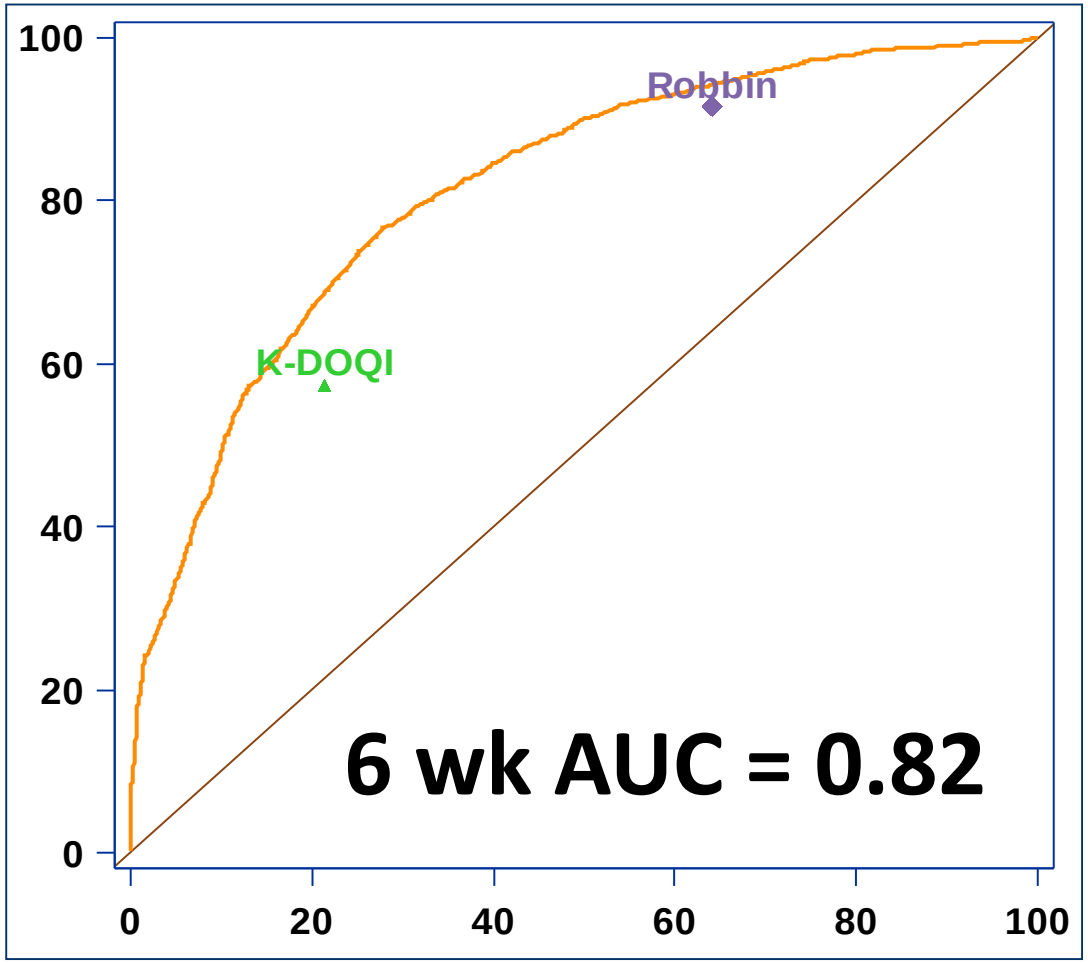
Courtesy Laura Dember ASN 2015

Vascular anatomy and blood flow (DEPTH)



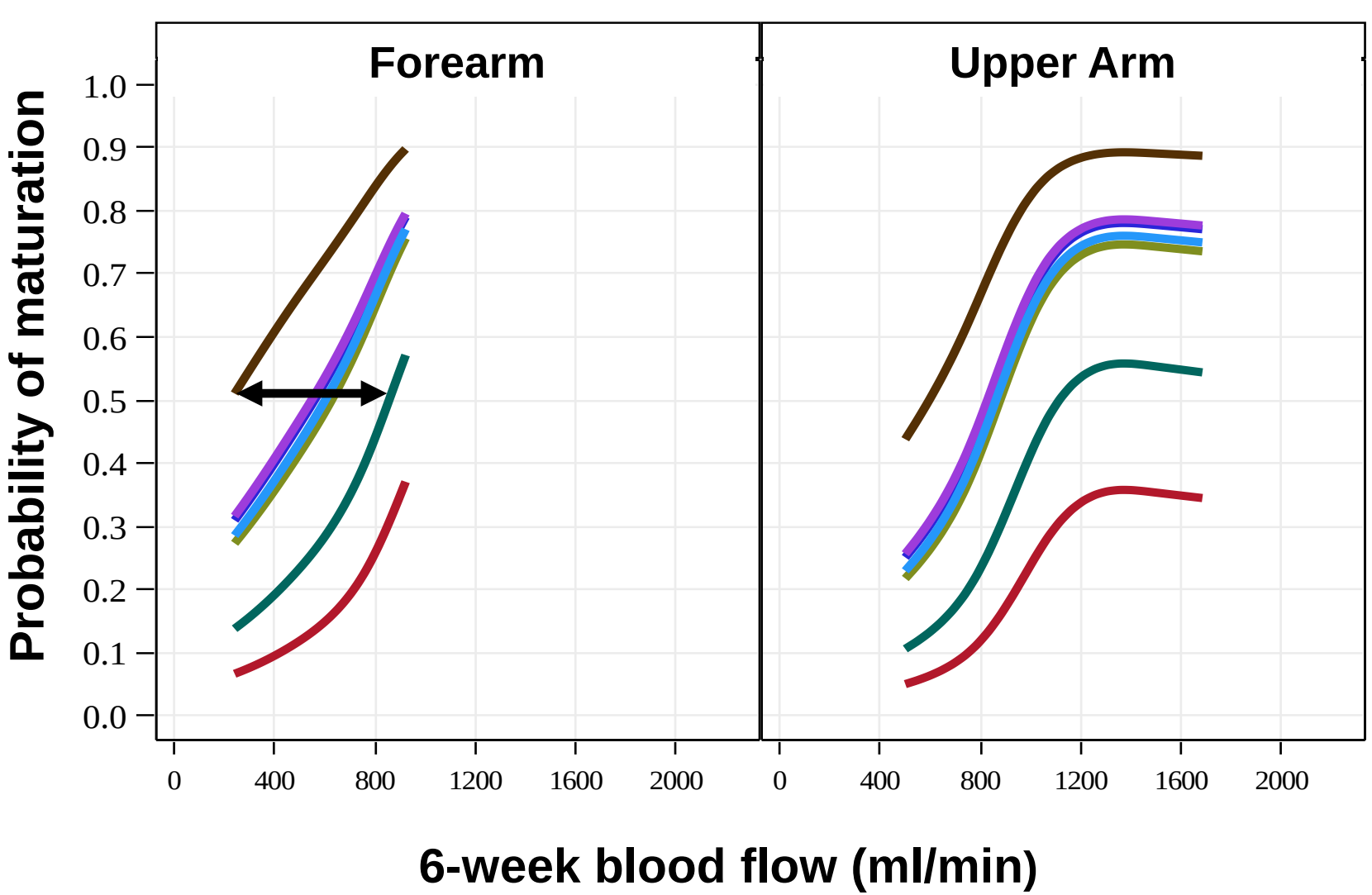
Courtesy Laura Dember ASN 2015

Independent Clinical Center effect



- Over and above these findings
- Correcting for independent effects of case mix, location, stenosis, accessory veins or arterial diameter
- Independent clinical center effect

Independent clinical center effect



- Controlling for case mix, AVF location, 6 week vein diameter and depth
- Probability of unassisted clinical maturation for an AVF with a Qb of 800 in the green center is the same as that of an AVF with a Qb of 400 in the brown center
- Beyond biological or clinical parameters

Courtesy Laura Dember ASN 2015

Why is there a center effect?

Relationships Between Clinical Processes and Arteriovenous Fistula Cannulation and Maturation: A Multicenter Prospective Cohort Study

AJKD 2018

Michael Allon, Peter B. Imrey, Alfred K. Cheung, Milena Radeva, Charles E. Alpers, Gerald J. Beck, Laura M. Dember, Alik Farber, Tom Greene, Jonathan Himmelfarb, Thomas S. Huber, James S. Kaufman, John W. Kusek, Prabir Roy-Chaudhury, Michelle L. Robbin, Miguel A. Vazquez, and Harold I. Feldman, on behalf of the Hemodialysis Fistula Maturation (HFM) Study Group

- **PREDICTORS: Post-operative care processes and complications**
- **OUTCOMES: Attempted cannulation, successful cannulation, unassisted maturation, overall clinical maturation**

Attempted cannulation

	OR (95% CI)	*P*
Process of care Factors		
Timing of surgeon's earliest visit, 2 wk vs 2-4 wk	0.21 (0.06-0.70)	0.01
Surgeon has regular 2nd follow-up visit, vs no 2nd visit	0.39 (0.15-0.97)	0.04
Surgeon's routine use of postoperative ultrasound, vs no or selective use	0.28 (0.14-0.55)	<0.001
Week 6 vs earlier routine postoperative ultrasound examination	0.72 (0.54-0.96)	0.03
Transposed AVF	0.55 (0.27-1.10)	0.09
Surgeon's routine no. of postoperative ultrasounds, 1 vs ≥2	1.18 (0.75-1.85)	0.5
Dedicated (active) vascular access coordinator	1.24 (0.64-2.39)	0.5
AVF complications/procedures		
No. of precannulation nonstudy ultrasounds, vs none	0.69 (0.48-0.99)	0.04
Invasive diagnostic or rescue procedure before 1st cannulation, vs none	0.51 (0.27-0.98)	0.04

Less is More!

Unassisted maturation

	OR (95% CI)	*P*
Process of care factors		
Dedicated (active) vascular access coordinator, vs none	1.91 (1.17-3.12)	0.01
No. of precannulation nonstudy ultrasounds before unassisted maturation determination, per attempt	0.42 (0.26-0.68)	<0.001
No. of cannulation attempts to achieve successful cannulation, per attempt	0.90 (0.83-0.98)	0.02
Transposed AVF	1.45 (0.84-2.44)	0.2
Surgeon's routine use of postoperative ultrasound, vs no or selective use	0.68 (0.42-1.09)	0.1
Initial cannulator experience, per year	1.06 (0.53-2.50)	0.9
Size of largest needle in first cannulation attempt, per increase in gauge	0.55 (0.21-1.45)	0.2
Dialysis unit, written protocol for initial cannulation procedure	1.59 (0.90-2.78)	0.1
Dialysis unit, no. of stations, per additional station	1.01 (0.98-1.04)	0.6
Dialysis unit weekly maintenance HD patients, per 25 patients	1.05 (0.98-1.12)	0.2
AVF complications/procedures		
Any infiltration between successful cannulation and maturation determination, vs none	2.44 (1.16-5.12)	0.01
Any infiltration before successful cannulation and maturation determination	1.30 (0.76-2.17)	0.3
No. of infiltrations before successful cannulation and maturation determination, per infiltration	0.83 (0.57-1.19)	0.3

Mixed Messages!

- Unassisted maturation will be highest in a center with a vascular access coordinator, that does not do ultrasound pre-cannulation, and which has a lot of infiltrations!

Biology (vascular function tests): not much there

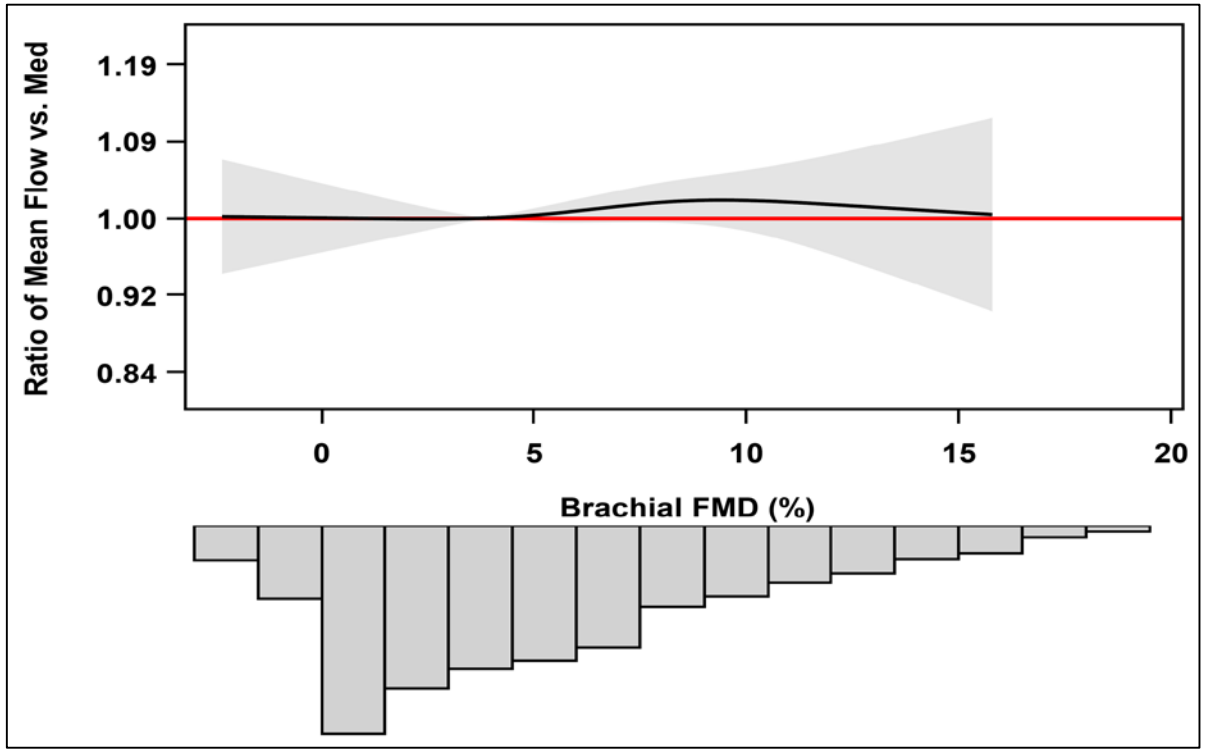
ORIGINAL RESEARCH

JAMA 2017

American Heart Association | American Stroke Association

Vascular Function at Baseline in the Hemodialysis Fistula Maturation Study

Laura M. Dember, MD; Peter B. Imrey, PhD; Mai-Ann Duess, BS; Naomi M. Hamburg, MD, MS; Brett Larive, MS; Milena Radeva, MS; Jonathan Himmelfarb, MD; Larry W. Kraiss, MD; John W. Kusek, PhD; Prabir Roy-Chaudhury, MD, PhD; Christi M. Terry, PhD; Miguel A. Vazquez, MD; Wanpen Vongpatanasin, MD; Gerald J. Beck, PhD; Joseph A. Vita, MD;* Hemodialysis Fistula Maturation Study Group†

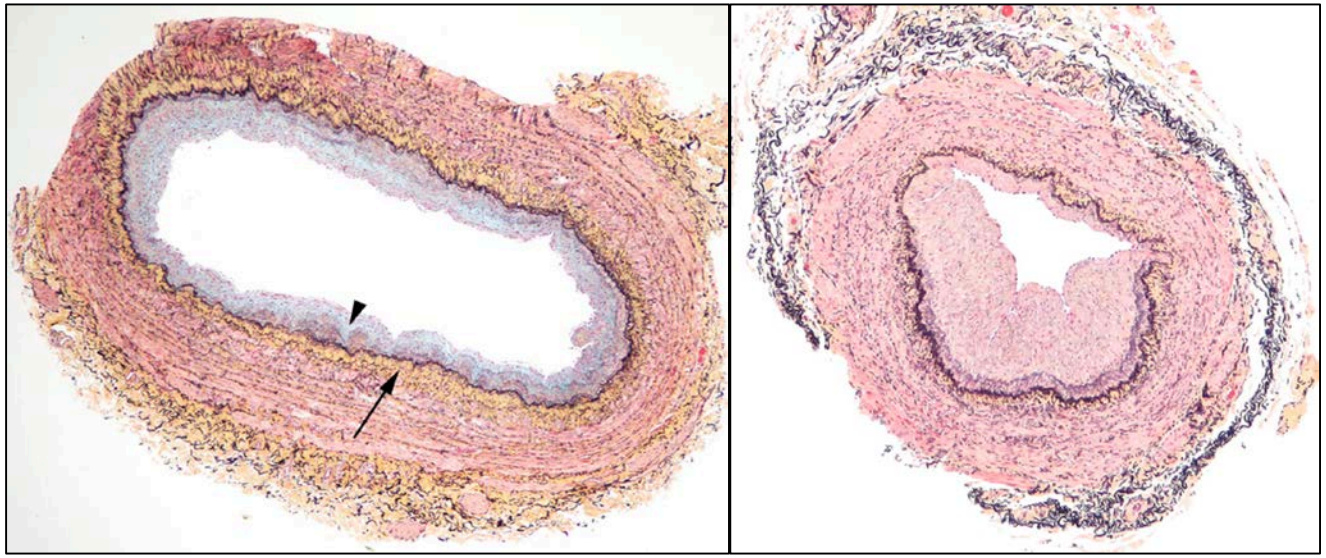


- For every 10% increase in FMD
- 10.4% increase in AVF flow

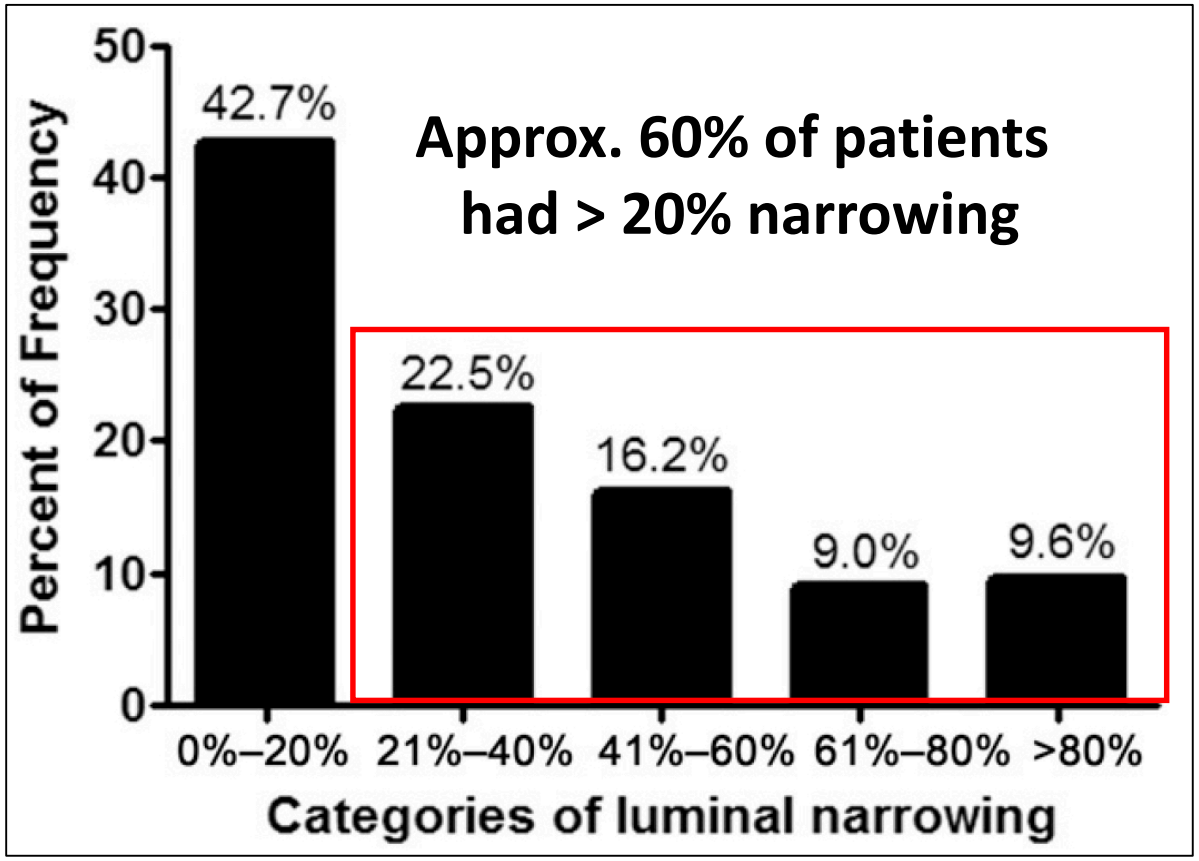
Biology (pre-operative neointimal hyperplasia)

Histopathology of Veins Obtained at Hemodialysis Arteriovenous Fistula Creation Surgery *JASN 2018*

Charles E. Alpers,* Peter B. Imrey,†‡ Kelly L. Hudkins,* Tomasz A. Wietecha,* Milena Radeva,† Michael Allon,§ Alfred K. Cheung,‖¶** Laura M. Dember,†††‡‡ Prabir Roy-Chaudhury,§§‖‖ Yan-Ting Shiu,‖¶¶ Christi M. Terry,‖¶¶ Alik Farber,*** Gerald J. Beck,†‡ Harold I. Feldman,†††‡‡ John W. Kusek,††† Jonathan Himmelfarb,‡‡‡ and the Hemodialysis Fistula Maturation Study Group



Minimal NH Maximal NH



- Neointimal hyperplasia (NH) was common
- The amount of NH was variable
- Minimal impact of NH on flow and none on maturation

Biology: post-operative stenosis associated with maturation failure

Intimal Hyperplasia, Stenosis, and Arteriovenous Fistula Maturation Failure in the Hemodialysis Fistula Maturation Study

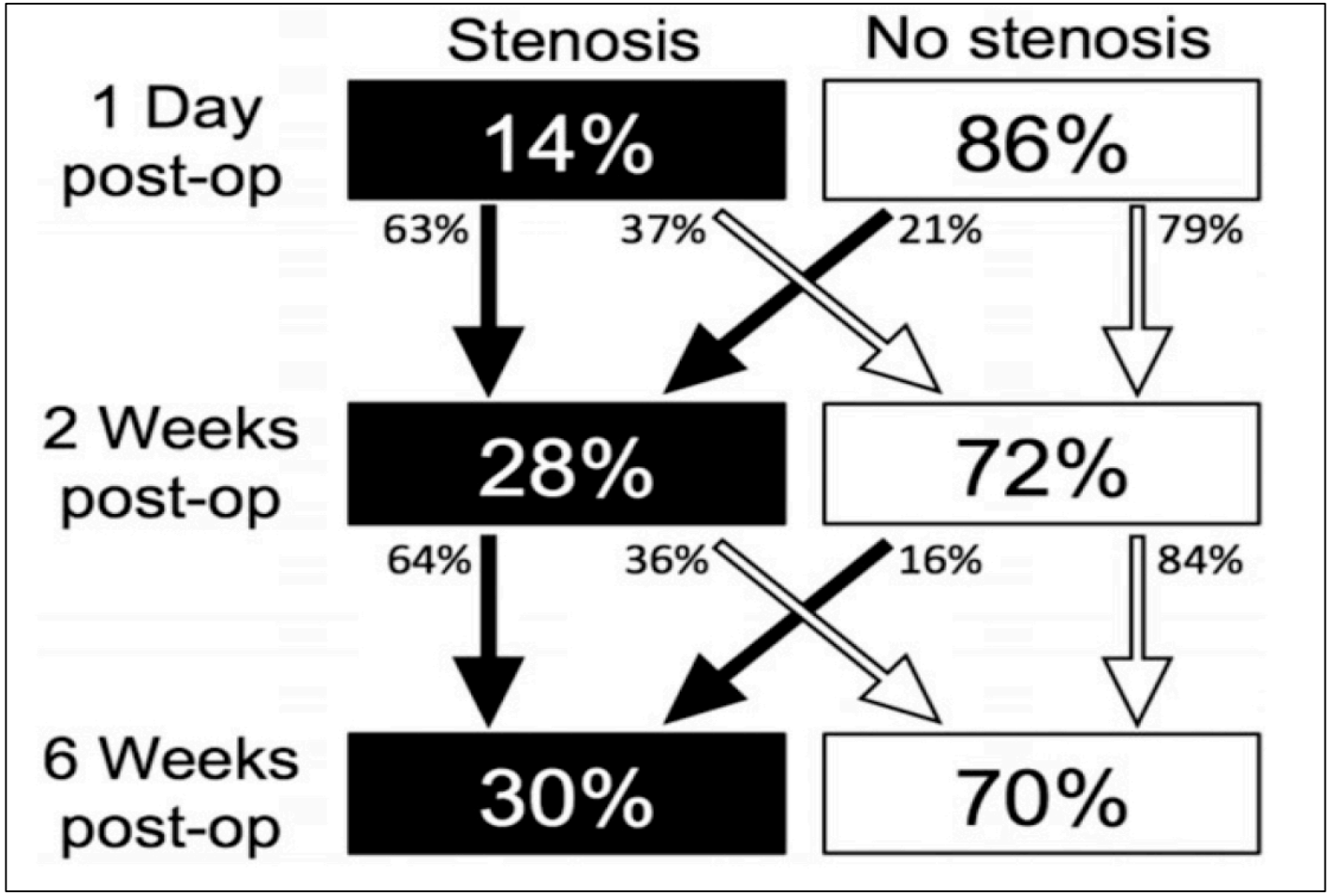
JASN 2018

Alfred K. Cheung,*†‡ Peter B. Imrey,§‖ Charles E. Alpers,¶ Michelle L. Robbin,** Milena Radeva,‖ Brett Larive,‖ Yan-Ting Shiu,* Michael Allon,†† Laura M. Dember,‡‡§§‖‖ Tom Greene,¶¶ Jonathan Himmelfarb,*** Prabir Roy-Chaudhury,†††‡‡‡ Christi M. Terry,* Miguel A. Vazquez,§§§ John W. Kusek,‖‖‖ and Harold I. Feldman,‡‡§§‖‖¶¶¶ and Hemodialysis Fistula Maturation Study Group

- **Significant association of post-operative stenosis on US at 1d, 2wk and 6wk with unassisted and overall maturation failure**

Postoperative Ultrasound Time Point and Ultrasound Adjustment[a]	Unassisted Maturation Failure			Overall Maturation Failure		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Week 6[b]						
Preoperative ultrasound measures	1.98	1.25 to 3.12	0.004	1.98	1.26 to 3.13	0.004
Concurrent ultrasound measures	1.19	0.67 to 2.08	0.55	1.24	0.73 to 2.11	0.42
Week 2						
Preoperative ultrasound measures	1.47	0.96 to 2.25	0.08	1.66	1.04 to 2.65	0.04
Concurrent ultrasound measures	0.89	0.54 to 1.45	0.64	1.12	0.67 to 1.88	0.66
Day 1						
Preoperative ultrasound measures	1.86	1.09 to 3.18	0.02	2.24	1.27 to 3.93	0.005
Concurrent ultrasound measures	1.14	0.65 to 2.00	0.66	1.43	0.78 to 2.61	0.25

Biology: post-operative stenosis is dynamic!



- Post-operative stenosis was DYNAMIC!
- Many patients with early stenosis (1d or 2wk) did not continue to have stenosis at 6wk
- Maybe we don't need to rush in and fix every early stenosis (2 wk data only)

Intimal Hyperplasia, Stenosis, and Arteriovenous Fistula Maturation Failure in the Hemodialysis Fistula Maturation Study

JASN 2018

Alfred K. Cheung,*†‡ Peter B. Imrey,§‖ Charles E. Alpers,¶ Michelle L. Robbin,** Milena Radeva,‖ Brett Larive,‖ Yan-Ting Shiu,* Michael Allon,†† Laura M. Dember,‡‡§§‖‖ Tom Greene,¶¶ Jonathan Himmelfarb,*** Prabir Roy-Chaudhury,†††‡‡‡ Christi M. Terry,* Miguel A. Vazquez,§§§ John W. Kusek,‖‖‖ and Harold I. Feldman,‡‡§§‖‖¶¶¶
and Hemodialysis Fistula Maturation Study Group

What does one make of all this?

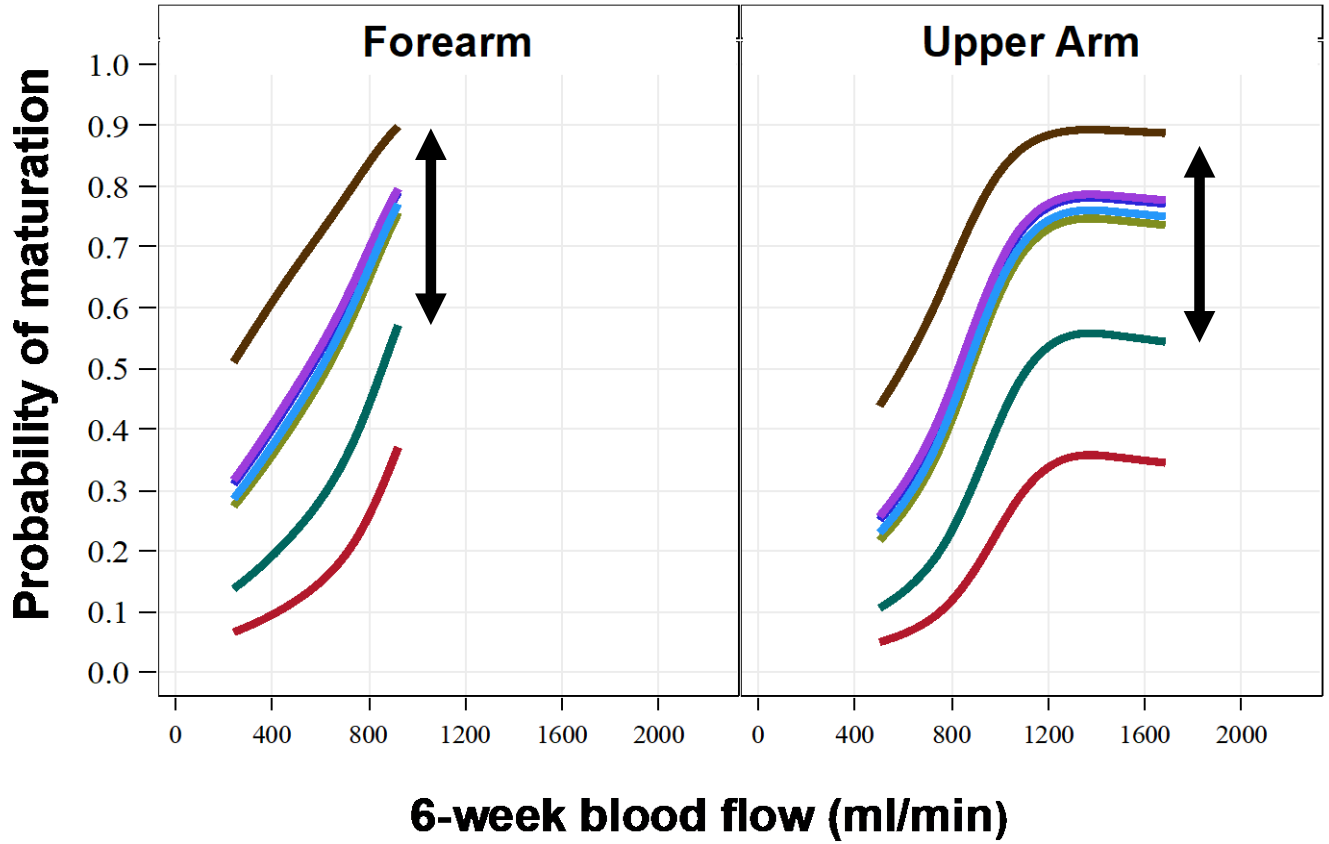
- What HFM tells us (the GOOD)
- What HFM does not tell us (the BAD)
- What HFM or its successors need to tell us (the UGLY)

What HFM tells us (the GOOD; sort of…)

- USA
- 2018
- Place 100 AVFs (3:1; upper arm to lower arm ratio)
- 33 will never be able to support adequate hemodialysis despite aggressive intervention
- Removes uncertainty about the role of a lack of maturation enhancing interventions in the DAC study

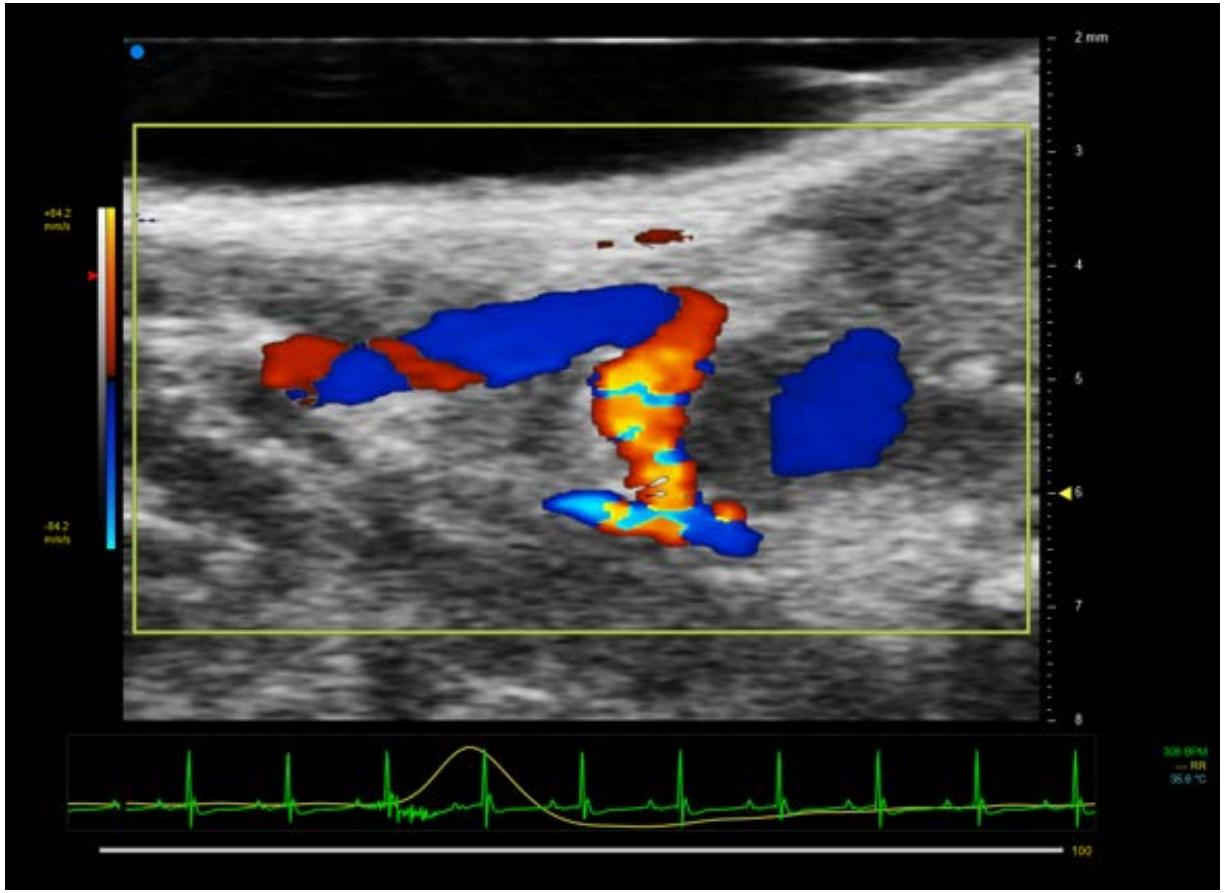
What HFM tells us: Process of Care is important

- Process of Care is important
- It is NOT intuitive
- It is almost certainly influenced by unique local attributes
- This is an area that is ripe for additional study and intervention
- Clearly suited for real world evidence generation



What HFM tells us: Post-op ultrasound is important (perhaps…)

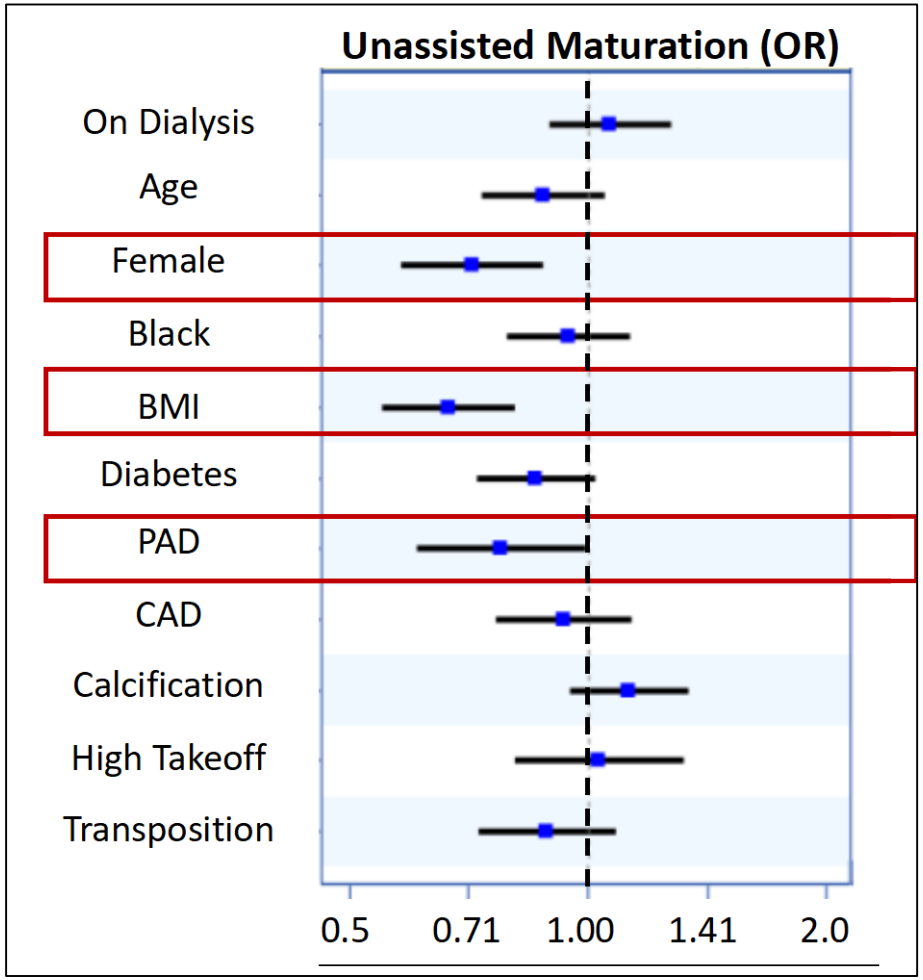
- Single or serial ultrasound post AVF creation for flow, diameter or depth can be a powerful predictor for ultimate AVF maturation
- Its negative impact on maturation processes of care needs to be further dissected!



What the HFM does not tell us (the BAD)

No pre-operative predictors!

- Does not give us a set of pre-operative predictors that will allow us to stratify patients into high and low risk categories
- Nothing new in the clinical predictors that came out of HFM
- Disappointing that the pre-operative vascular function testing did not predict AVF maturation



What HFM or its successors need to tell us or "Where do we go from here?"

- HFM study has given us an extremely rich dataset
- HFM data will play into national and international guidelines
- As a community we need to have a system where datasets such as the HFM can feed into available real time decision support tools
- Vascular Access Procedure Selection App

Establishing patient-specific criteria for selecting the optimal upper extremity vascular access procedure

Karen Woo, MD[a], Jesus Ulloa, MD[b], Michael Allon, MD[c], Christopher G. Carsten III, MD[d], Eric S. Chemla, MD[e], Mitchell L. Henry, MD[f], Thomas S. Huber, MD[g], Jeffrey H. Lawson, MD[h], Charmaine E. Lok, MD[i], Eric K. Peden, MD[j], Larry Scher, MD[k], Anton Sidawy, MD[l], Melinda Maggard-Gibbons, MD[m], and David Cull, MD[d]

VESS14.

Early Validation of a Tool to Standardize Vascular Access Procedure Selection for Hemodialysis

Joseph-Vincent V. Blas,[1] Christopher G. Carsten III,[1] John Dooley,[1] Karen Woo,[2] Lily Fatula,[1] Alyssa A. Adkins,[1] Carlyn M. Atwood,[1] David Cull[1]. [1]Greenville Health System, Greenville, SC; [2]University of California Los Angeles School of Medicine, Los Angeles, Calif

What HFM or its successors need to tell us: Mechanisms

- **We are still scratching at the surface in terms of exploring the biological dataset from HFM**
- **Hope is that a deeper dive into the archived blood samples and tissues from HFM will identify**
  - ***Additional pre-operative predictors***
  - ***Reveal mechanistic pathways for AVF maturation failure that could then be targeted with new drugs or devices***

Individualizing Vascular Access Care

- Get away from the one size fits all construct that we currently work under
- Truly want to place the right access in the right patient at the right time!
- Stratify patients based not just on clinical, but also on biological and process of care parameters
- Offer them the vascular access that is best suited to them

One Size Fits All Store!

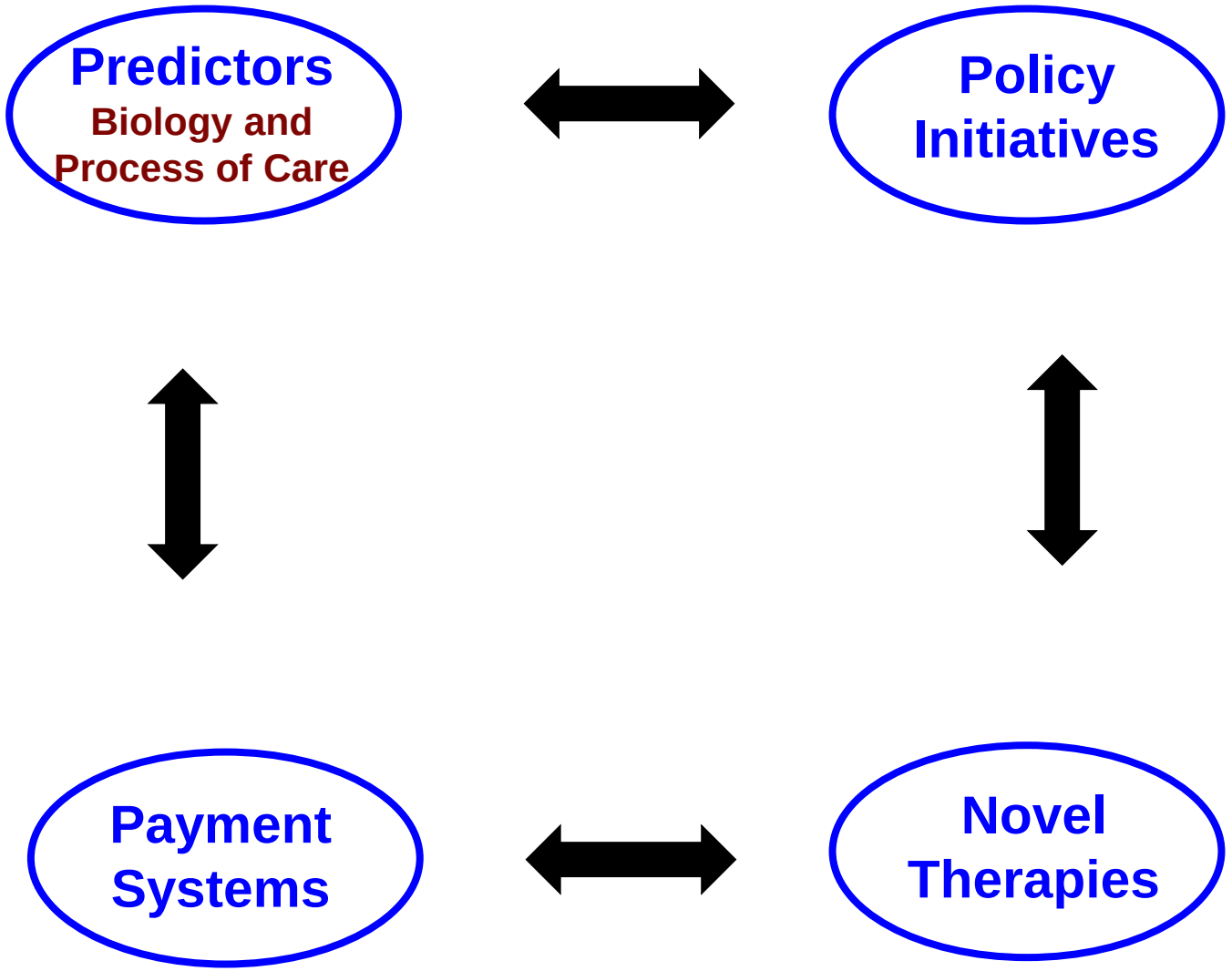
Individualizing Vascular Access Care

- **Best way to develop such an individualized approach is through the use of future novel therapies (pipeline or which emerge from the HFM dataset)**
  - Low Risk = Standard AVF
  - Moderate Risk = AVF + drug/device or a bioengineered vessel or a graft that lasts for 5 years
  - High Risk = Coated catheter!

- Humacyte
- Vascular Therapies
- Proteon
- Laminate
- TVA
- Avenu
- Innavasc
- WL Gore
- Bard
- Medtronic

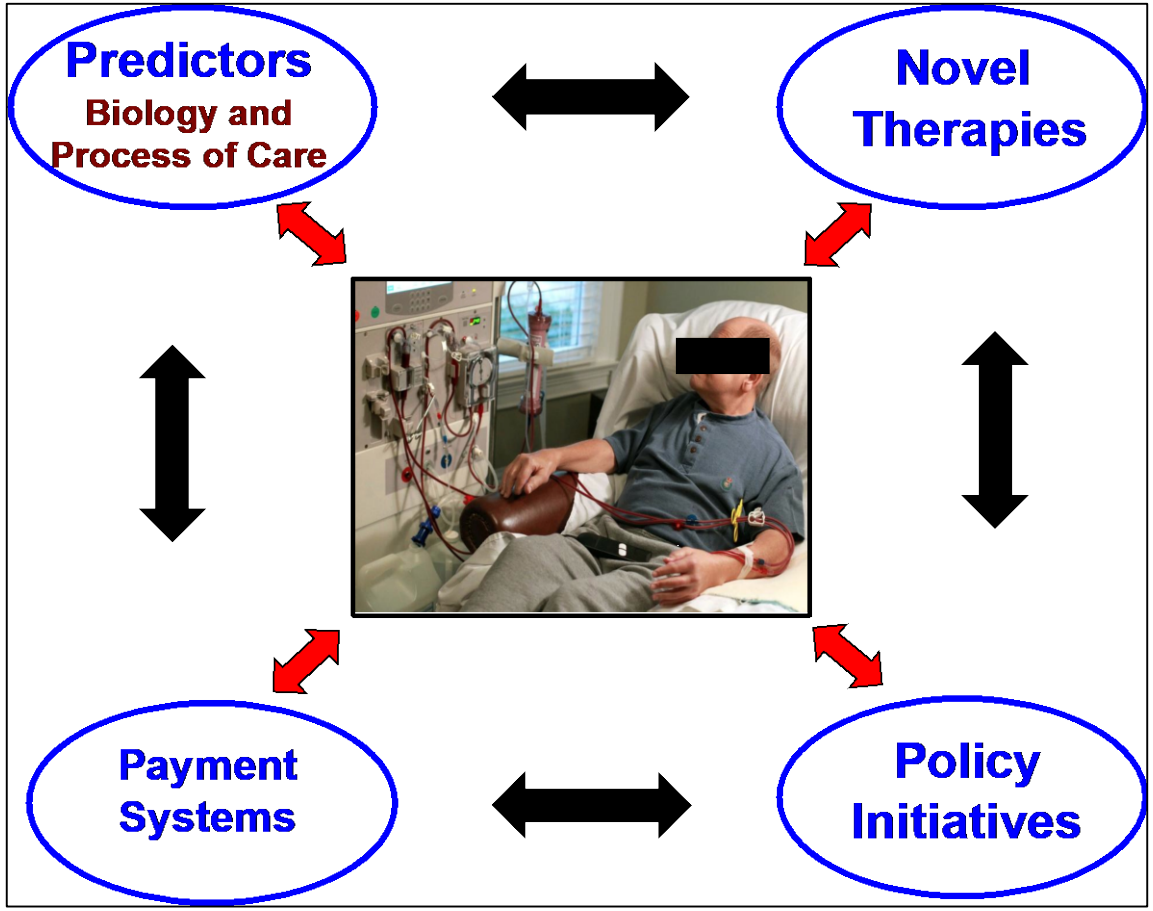
Sweet Spot for Vascular Access (Tangibles)

- Rich datasets (HFM) that continue to be interrogated
- Interest from federal agencies in a Vascular Access Database
- **Kidney Health Initiative:** focused on creating more streamlined product development pathways
- **Kidney Innovation Accelerator:** fund innovative products
- Large number of novel therapies in the pipeline
- Bundled payment systems that might incentivize innovation



Sweet Spot for Vascular Access (Intangibles)

- Reap the benefits of this powerful substrate for innovation for our patients
- Important that we come together as a TEAM
- Patients
- Health Care Professionals (Surgeons, nephrologists, radiologists, technicians, nurses, coordinators, administrators)
- Industry partners
- Federal agencies



With Thanks…

Clinical Centers

- Boston U. – L Dember
- U. Cincinnati – P Roy-Chaudhury
- U. Florida – T Huber
- U.T. Southwestern – M Vazquez
- U. Utah – A Cheung
- U. Washington – J Himmelfarb
- UAB Birmingham – M Allon

Data Coordinating Center

- Cleveland Clinic – G Beck

Ultrasound Core

- UAB – M Robbin

Vascular Function Core

- BU – J Vita

Histopathology Core

- U. Washington – C Alpers

Steering Committee Chair

- H Feldman

NIDDK

- J Kusek

HFM

Hemodialysis Fistula Maturation Study

Division of Nephrology

University of Arizona

Summary

- Continue to have a high rate of AVF maturation failure
- AVF flow, diameter and depth are key predictors of unassisted clinical maturation
- Presence of a center effect
- Rich repository of biological data which when combined with the clinical dataset will allow us to develop a future precision medicine approach to vascular access at a population health level

Demographics

Baseline Characteristic	Mean ± SD; N (%)
Age (yr)	55.2 ± 13.4
Male	422 (70%)
Female	180 (30%)
White	283 (47%)
Black	264 (44%)
BMI	30.4 ± 7.6
Current/Former Tobacco Use	330 (54.8%)
Diabetes	353 (59%)
Coronary Artery Disease	156 (26%)
Peripheral Artery Disease	91 (15%)
On dialysis	383 (64%)

Effect of Clopidogrel on Early Failure of Arteriovenous Fistulas for Hemodialysis

A Randomized Controlled Trial

AVF Thrombosis

	No. (%) of Patients		
	Clopidogrel (n = 435)[a]	Placebo (n = 431)[a]	Relative Risk (95% Confidence Interval)[b]
Thrombosis at 6 wk (all patients)	53 (12.2)	84 (19.5)	0.63 (0.46-0.97)[c]
By location			
Forearm fistula	31 (12.9)	60 (24.7)	0.53 (0.36-0.77)
Upper arm fistula	22 (11.3)	24 (12.8)	0.89 (0.52-1.53)

	No. (%) of Patients		
	Clopidogrel (n = 385)[a]	Placebo (n = 373)[a]	Relative Risk (95% Confidence Interval)[b]
Suitability failure (all patients)	238 (61.8)	222 (59.5)	1.05 (0.94-1.17)[c]
By location			
Forearm fistula	144 (66.9)	137 (64.0)	1.05 (0.92-1.20)
Upper arm fistula	94 (55.3)	85 (53.4)	1.05 (0.87-1.27)

Independent clinical center effect

Factor	Unassisted maturation		All maturation	
	Cumulative AUC	P-value for increment	Cumulative AUC	P-value for increment
Location Flow Diameter Depth	0.818	<0.001	0.793	<0.001
Case-mix	0.821	n.s.	0.801	n.s.
Clinical center	0.849	<0.001	0.825	<0.001

Courtesy Laura Dember

Why is there a center effect?

- Not just the surgeon
- Approach to maturation-facilitating interventions (type, intensity, operators)
- Intensity of follow-up
- Cannulation timing
- Cannulation personnel
- Cannulation-associated events (e.g., infiltration)
- Dialysis unit characteristics

Independent clinical center effect

Factor	Unassisted maturation		All maturation	
	Cumulative AUC	P-value for increment	Cumulative AUC	P-value for increment
Location Flow Diameter Depth	0.818	<0.001	0.793	<0.001
Case-mix	0.821	n.s.	0.801	n.s.
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Courtesy Laura Dember

Biology (neointimal hyperplasia)

Histopathology of Veins Obtained at Hemodialysis Arteriovenous Fistula Creation Surgery

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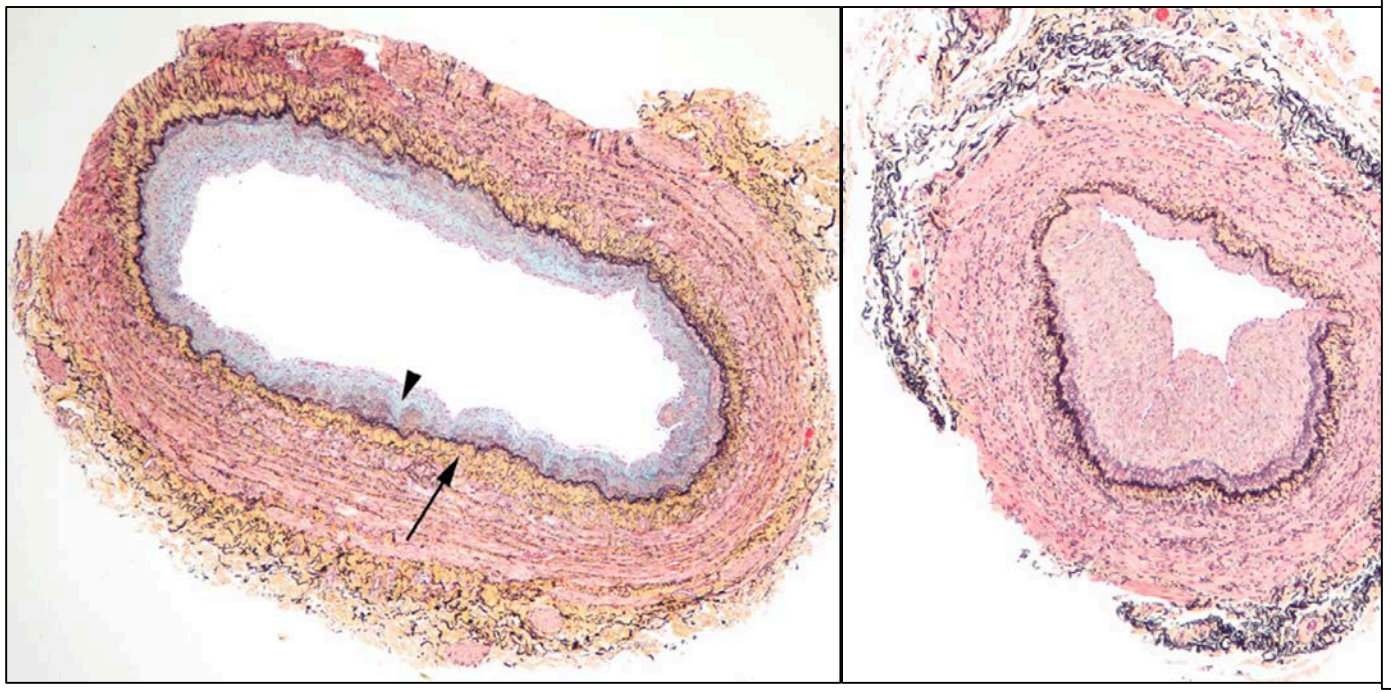

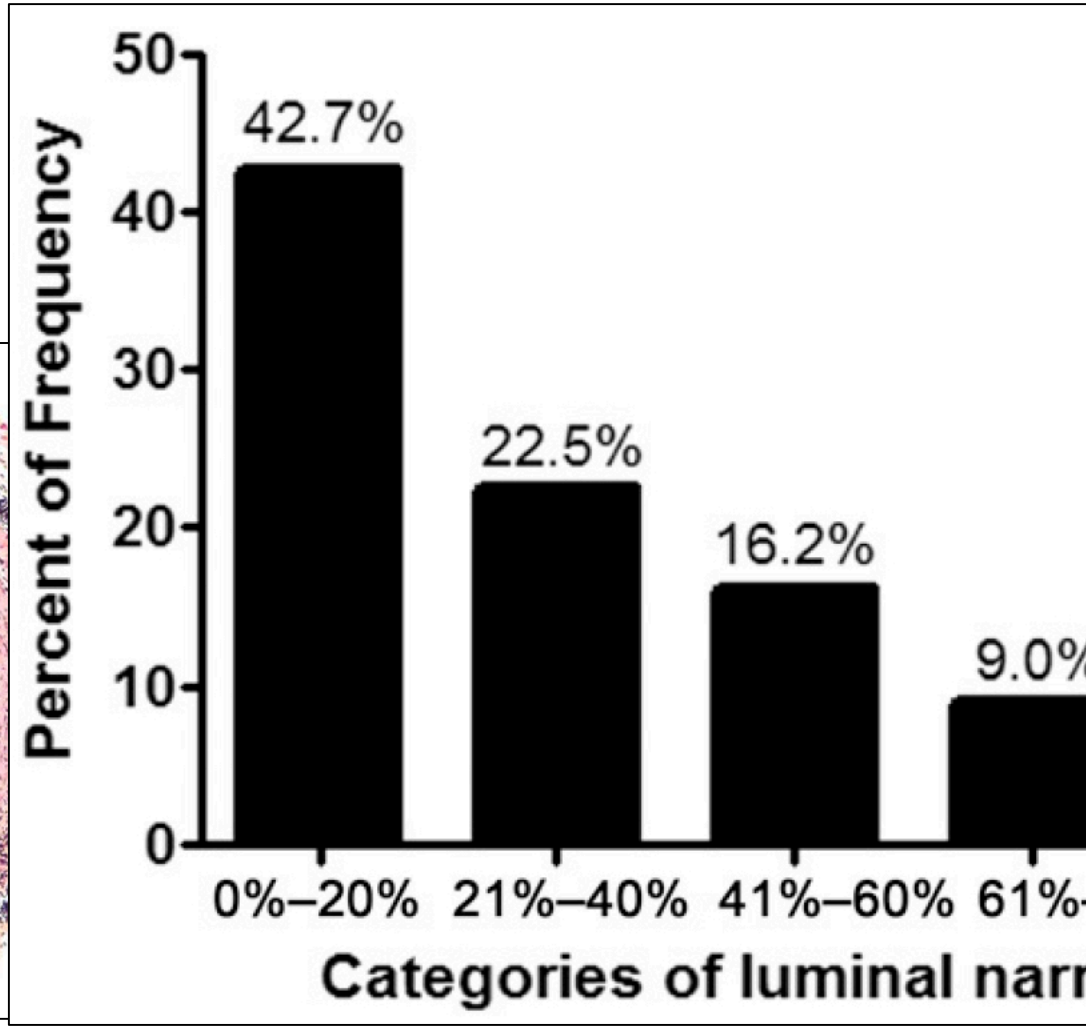

- For every 10% increase in

What HFM tells us (the GOOD; sort of…)

- Many of you this seems too low
- Remember that there was a significant center effect
- If you are at VASA you are probably functioning like the brown center so green seems very bad
- In the real world some people may be functioning like the red center