Workshop Nefrologie Papendal
12 December 2018

De dialysefistel: snel maken, snel staken?

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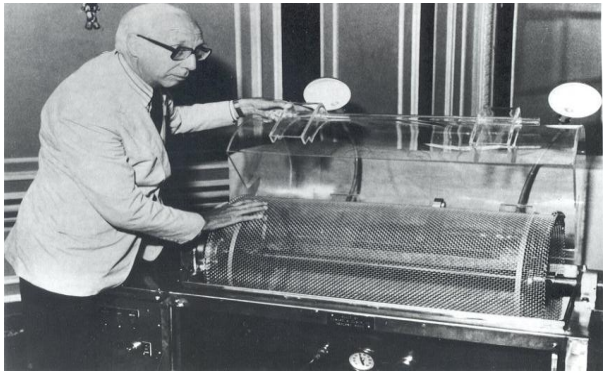
Disclosure belangen spreker

(potentiële) belangenverstrengeling	
Voor bijeenkomst mogelijk relevante relaties met bedrijven	Bedrijfsnamen
• Onderzoeksgeld • Honorarium of andere (financiële) vergoeding • Aandeelhouder • Andere relatie, namelijk …	• Enceladus Pharmaceuticals

History of hemodialysis and vascular access



Kolff

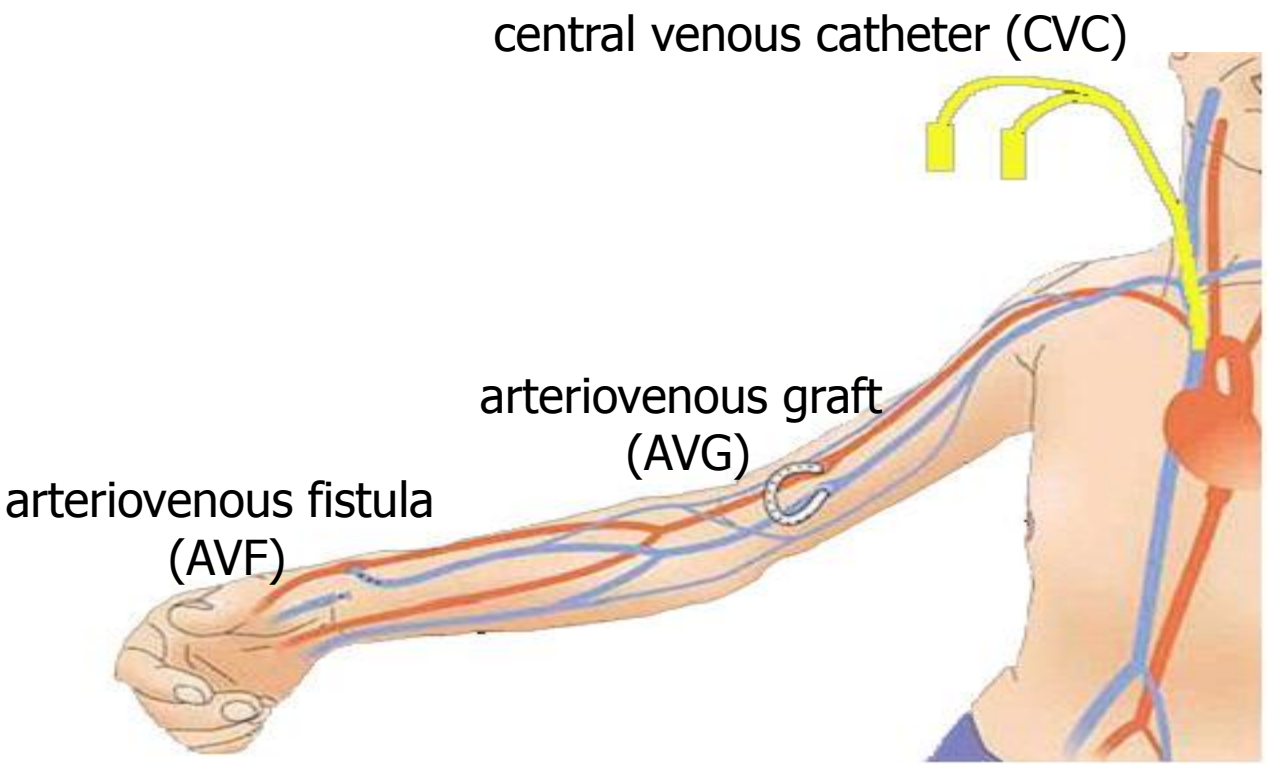
1943 1966 1985 2020

Brescia, Cimino, Appel

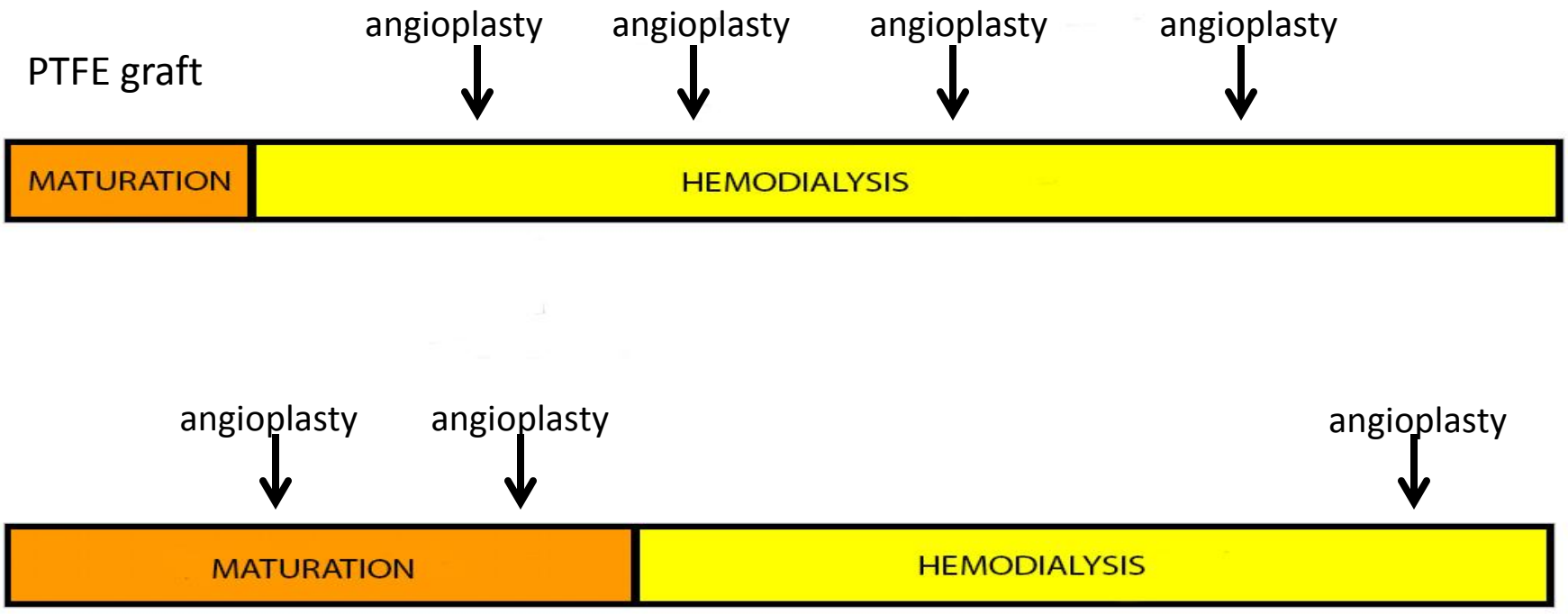
RCAVF: still the best option for most patients

…..but with a high burden for patients !

Current options for vascular access

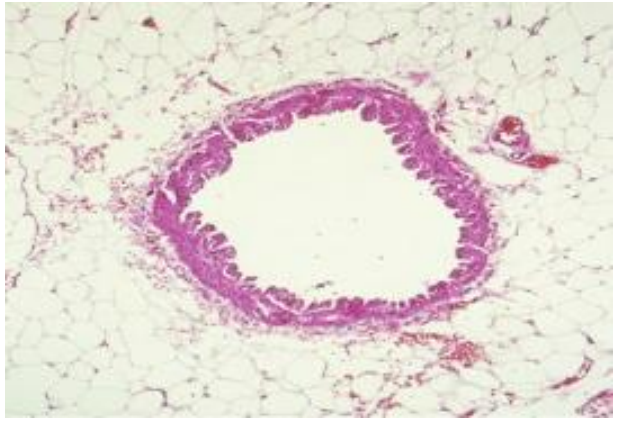


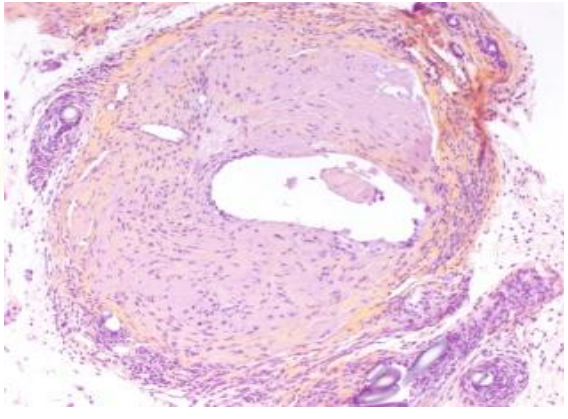
PTFE versus AVF interventions



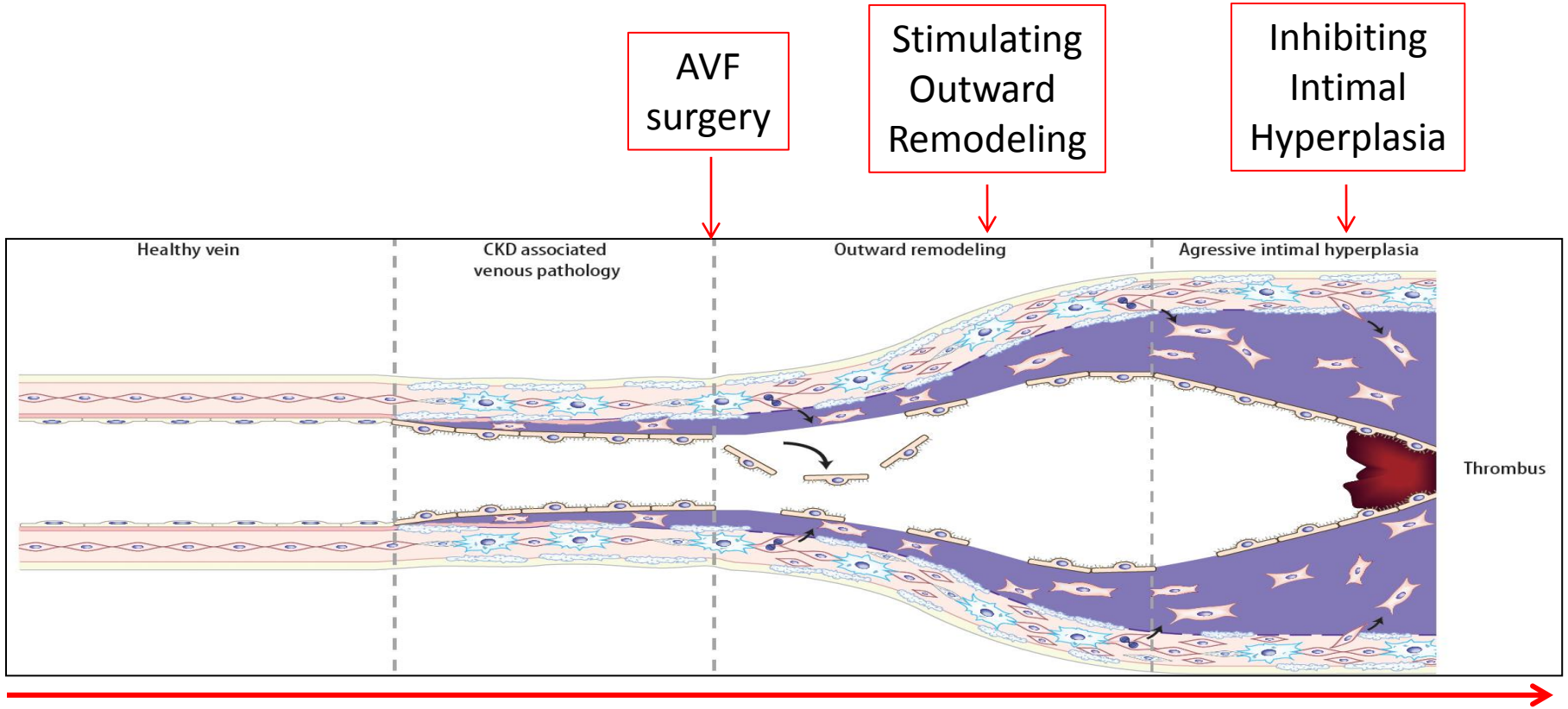
30-50 % of AVF fail to mature !

Improving AV-access durability remains a battle against nature





Vascular response upon AVF surgery



Journey of a cephalic vein in a hemodialysis patient

Rothuizen, Rotmans et al. NDT 2013

Determinants of AVF maturation

frequency of dialysis

genetic factors

Location of AVF

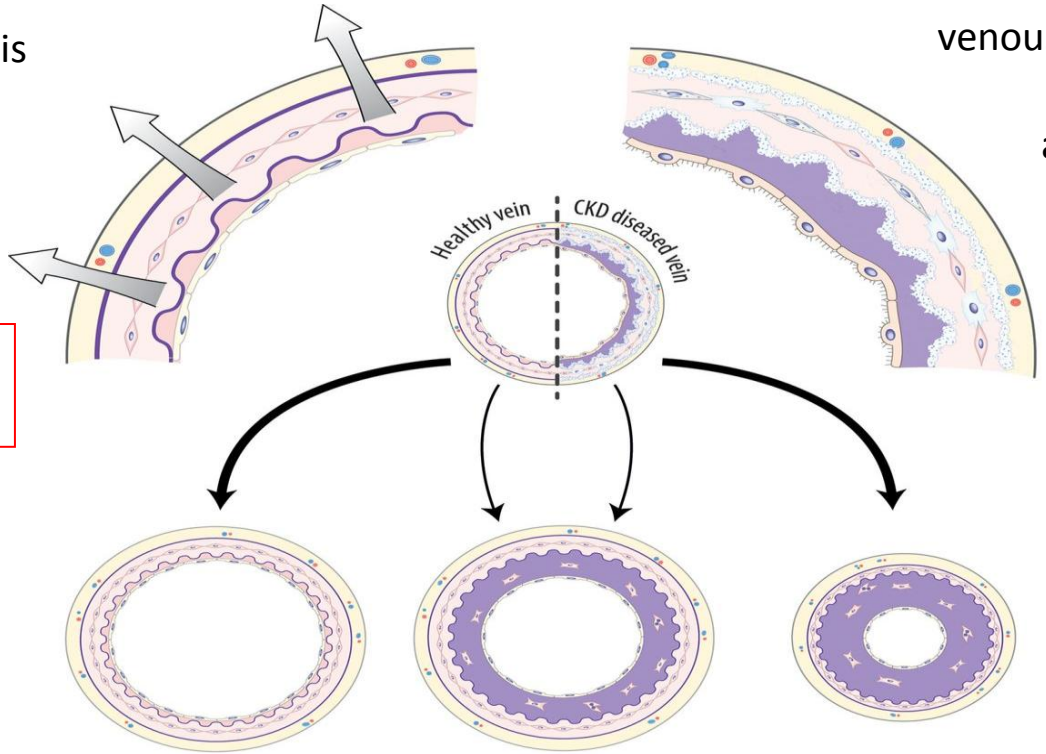
arterial and venous diameters

sex

leucocytosis

diabetes mellitus

intradialytic hypotension



venous distensibility

anemia

surgeon's experience

age

peripheral vascular disease

obesity

angle of anastomosis

previous catheter use

Rothuizen, Rotmans et al. NDT 2013

Non-maturation is an important limitation of AVFs

Retrospective, multicenter cohort study in the Netherlands (n = 1221)

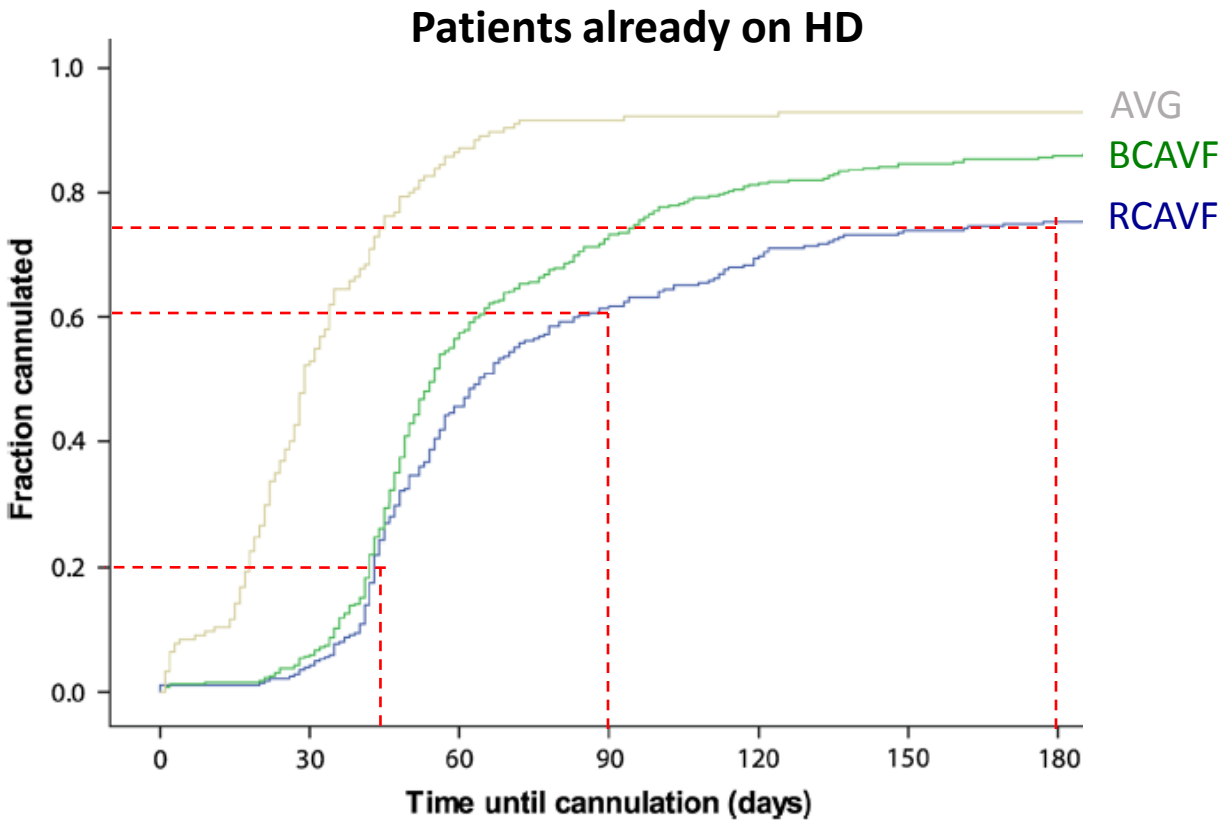
Timing of VA surgery for VA configurations

VA configuration (n) $n = 1605$	On HD at time of VA creation			First access for patient
	Yes	No but started within 3 months	No start after 3 months or never	
RCAVF (663)	44.8% (297)	16.6% (110)	38.6% (256)	89.9% (596)
BCAVF (547)	56.5% (309)	17.4% (95)	26.1% (143)	62.9% (344)
BBAVF (152)	76.3% (116)	8.6% (13)	15.1% (23)	46.1% (70)
AVG (243)	65.8% (160)	18.1% (44)	16.0% (39)	46.5% (113)

Voorzaat, Rotmans et al World J Surg 2017

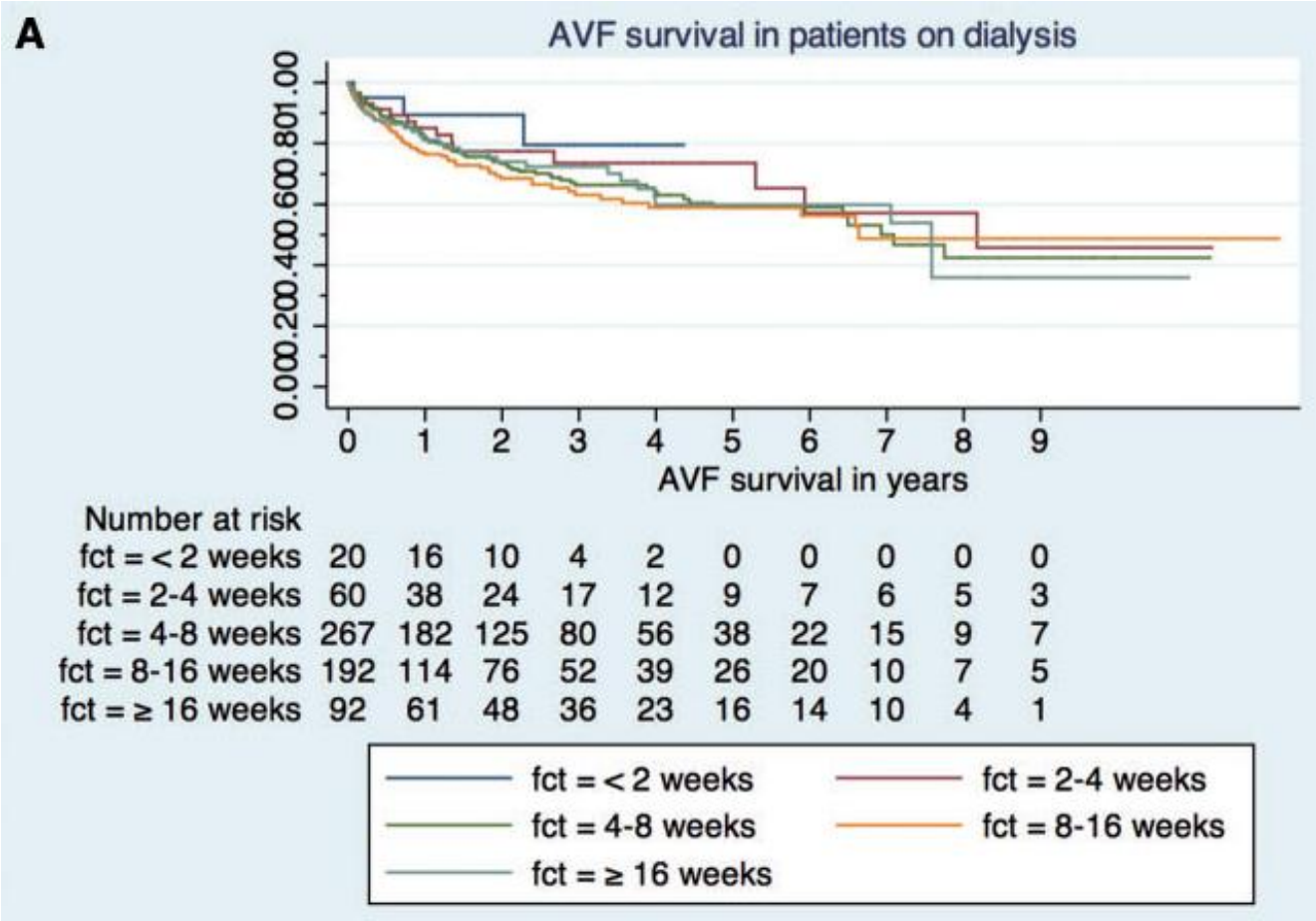
Non-maturation is an important limitation of AVFs

Retrospective, multicenter cohort study in the Netherlands (n = 1221)



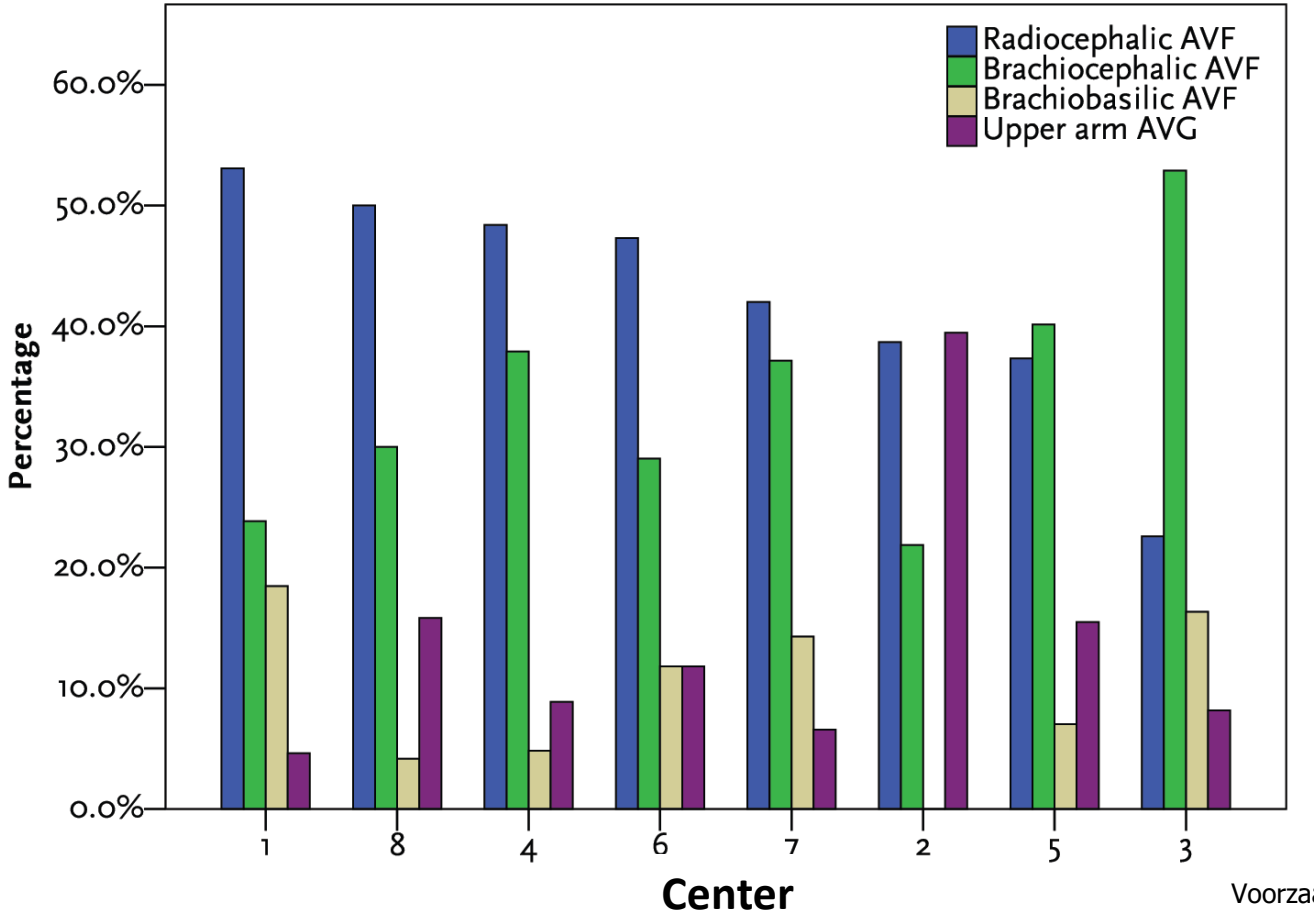
Voorzaat, Rotmans et al World J Surg 2017

Early cannulation of AVF might be safe



Wilmink et al NDT 2018

Large differences in VA configurations between centers



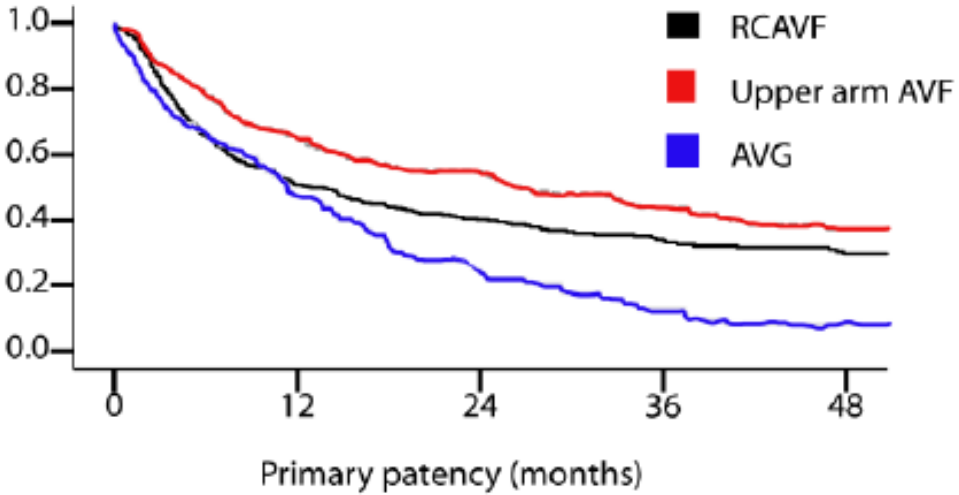
Voorzaat, Rotmans et al World J Surg 2017

Center effect of AVF unassisted maturation

Hospital	RCAVF	BB/BCAVF	AVG
1	50%	61%	75%
2	60%	76%	97%
3	62%	80%	90%
4	69%	78%	89%
5	48%	33%	73%
6	70%	70%	100%
7	59%	77%	95%
8	67%	74%	88%

Voorzaat, Rotmans et al World J Surg 2017

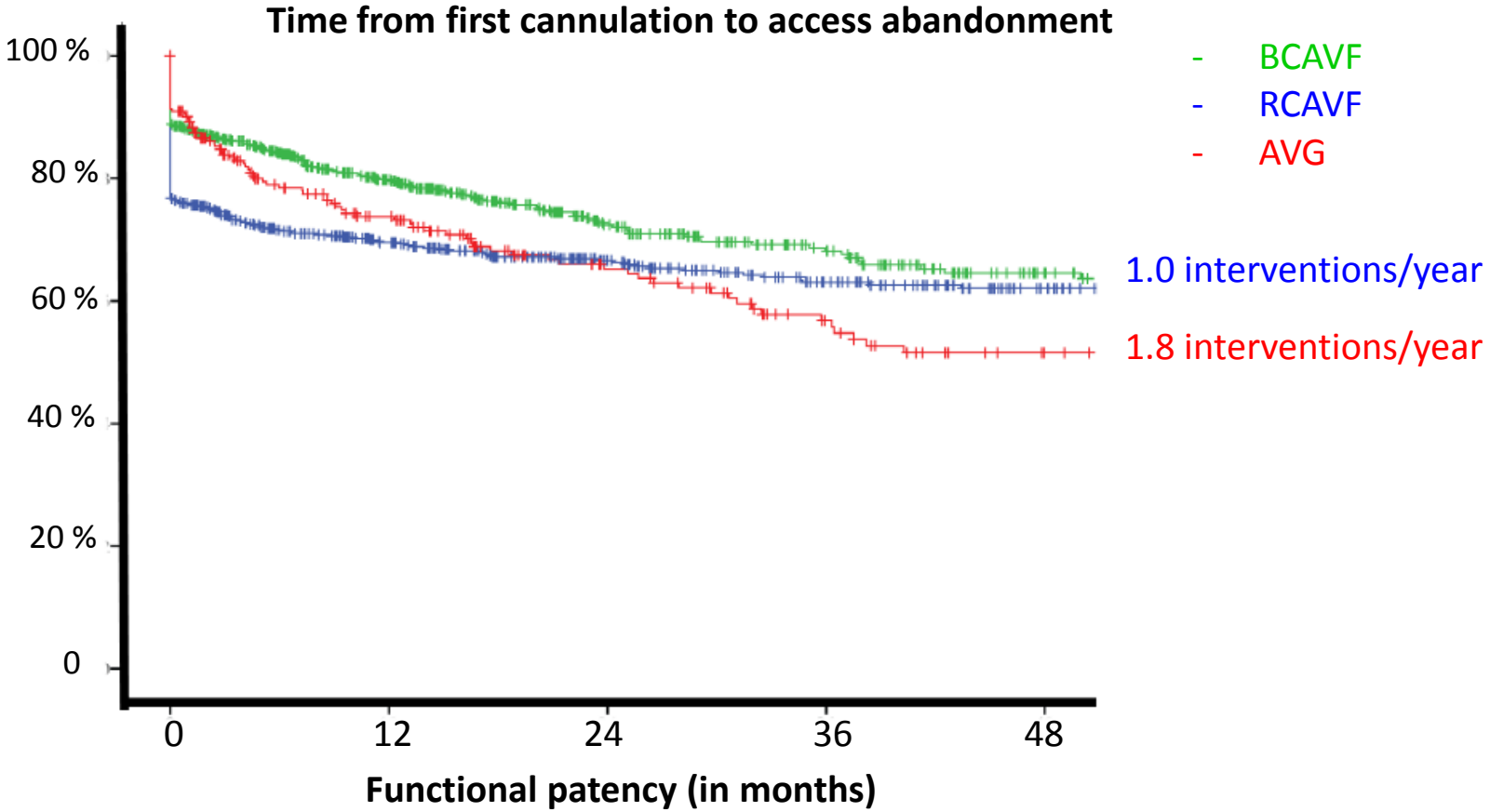
Primary patency of arteriovenous access conduits



Excluded non-maturated access

The Dutch Vascular Access Study Group. Unpublished

Functional patency is comparable between AVF and AVG

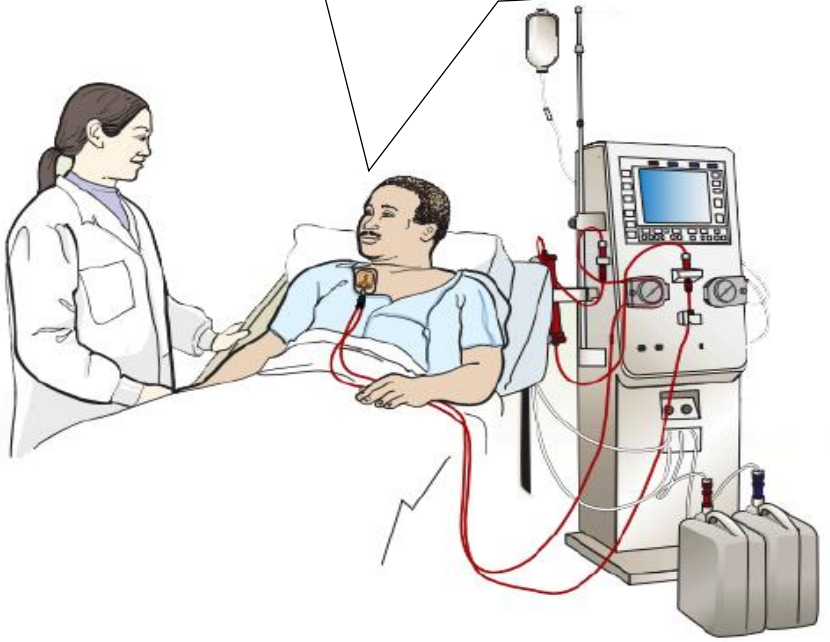


The Dutch Vascular Access Study Group. Submitted

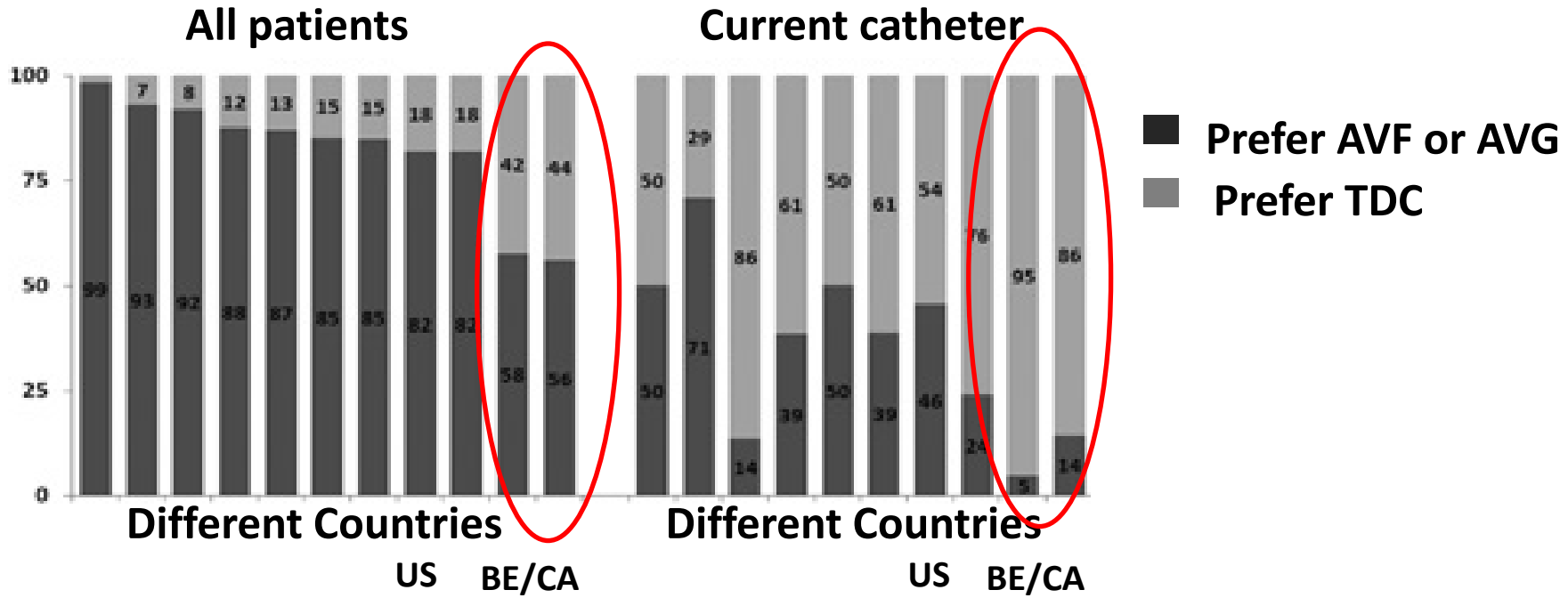
Sometimes different perspectives of doctors and patients

According to our guidelines, you need an AVF

I like my CVC, experienced no infections, How about maturation failure of AVFs?



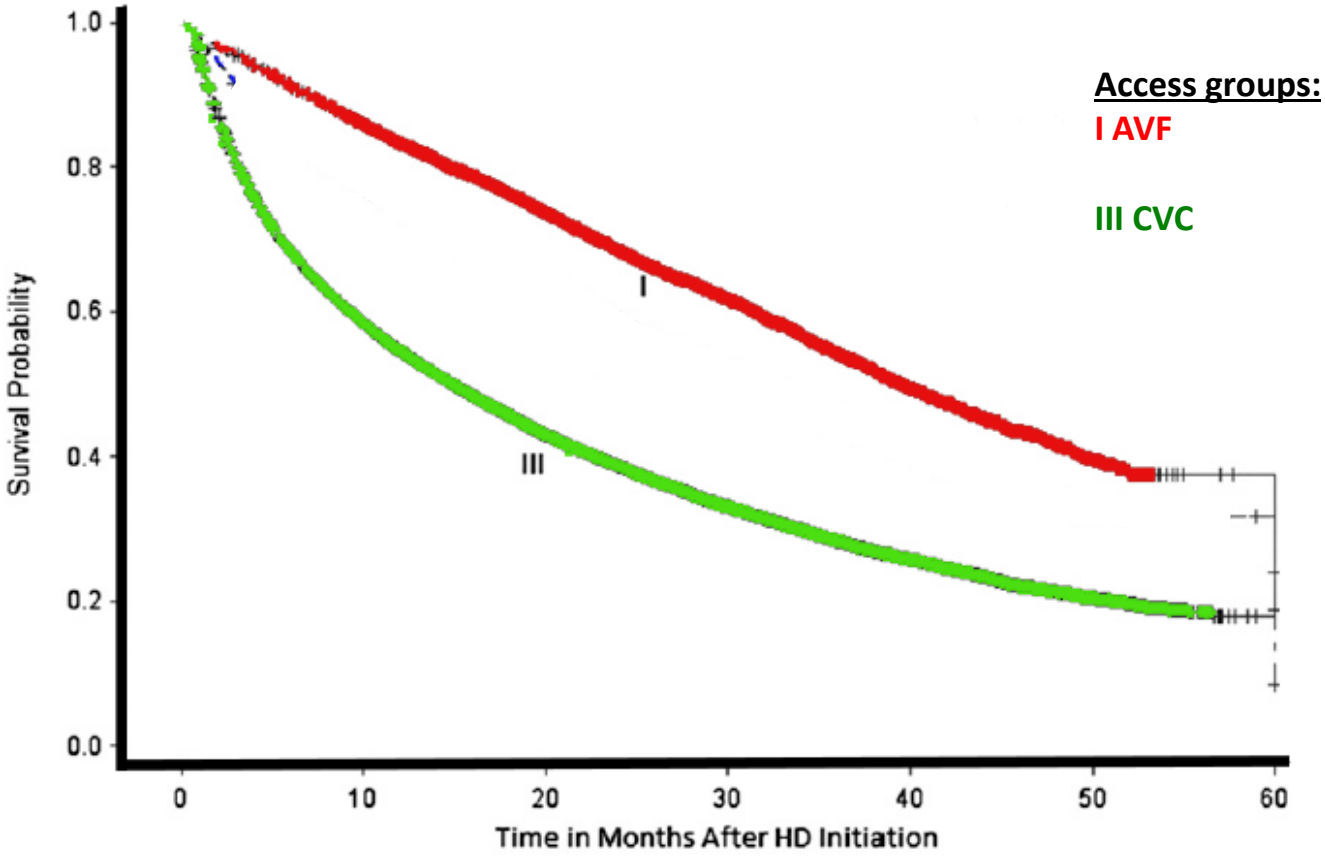
Patient preferences for vascular access



- Patient preferences for the type of vascular access varies across countries
  - Influenced by the history of current catheter use

Fissell et al. JVA 2013

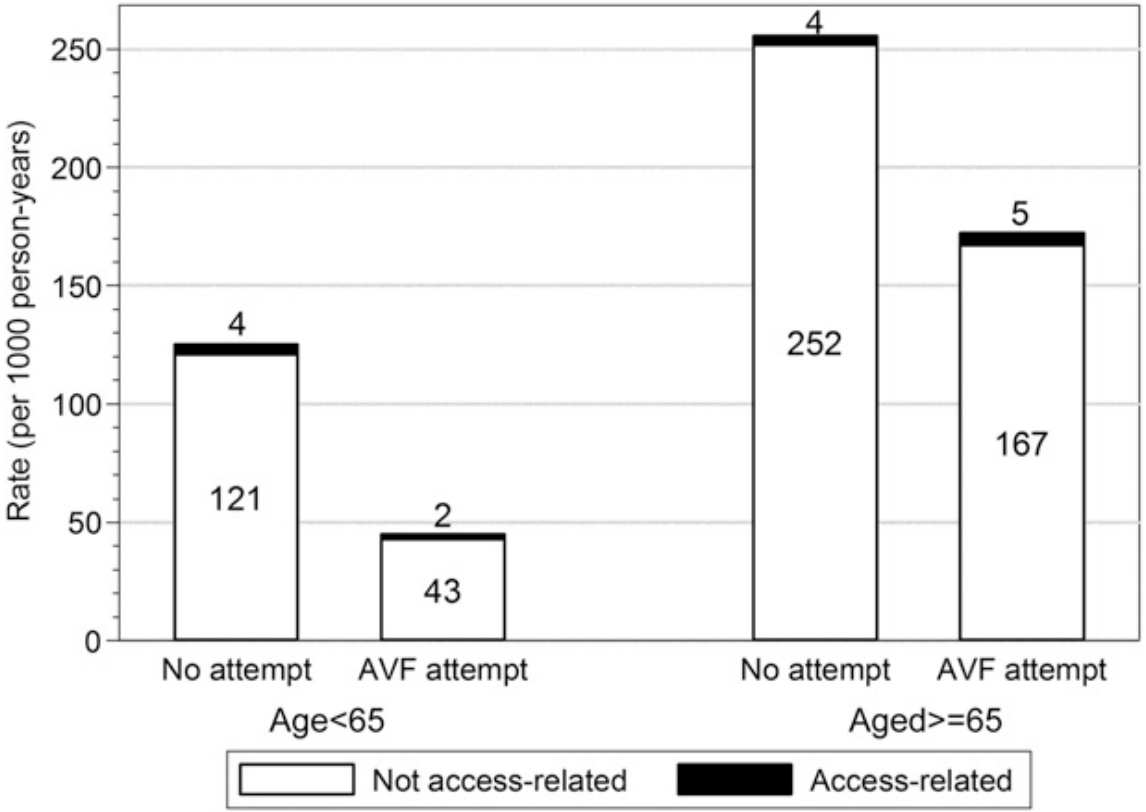
Increased mortality of patients with CVC mainly relates to patient factors



Brown et al. JASN 2016

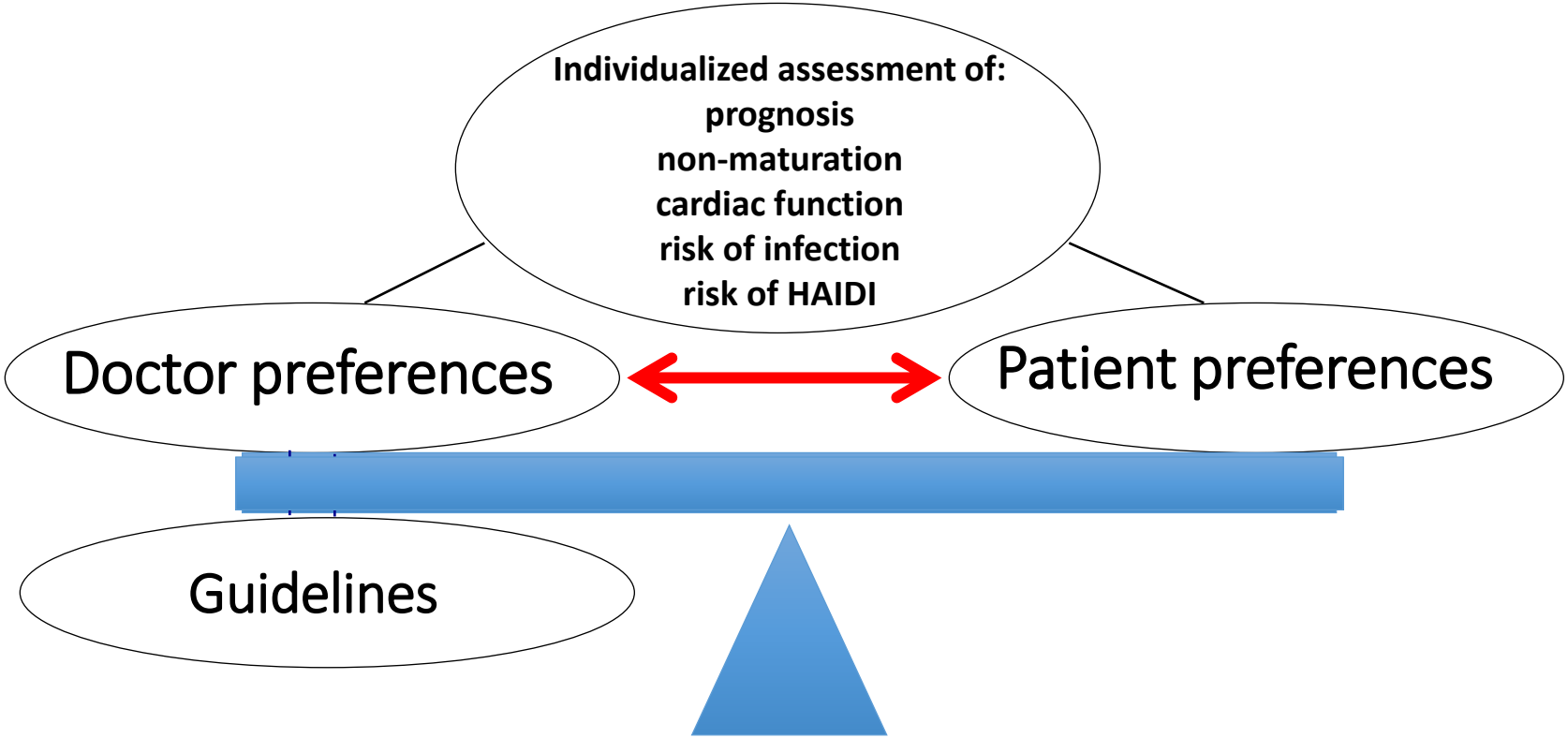
Vascular access-related mortality is low (2.3%)

Canadian retrospective cohort study of 3168 patients



Quinn et al. JASN 2016

Individualized shared decision about preferred vascular access



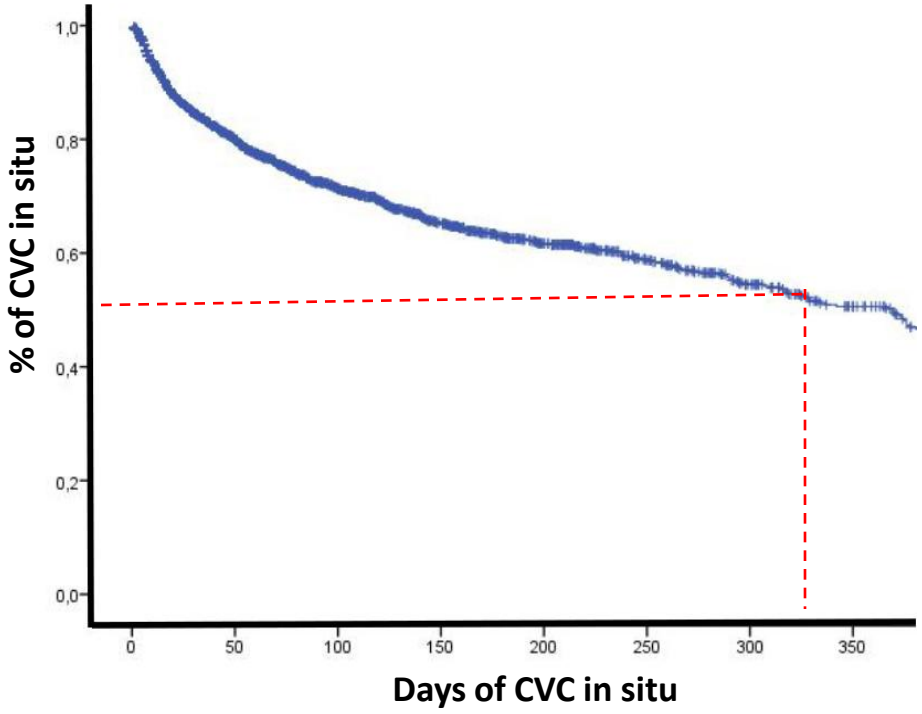
CVC functionality

Ducatho study (n= 1600 patients)

Retrospectieve, observational cohort study

12 HD centers in The Netherlands

Time to removal of CVC because of infection or patency problem



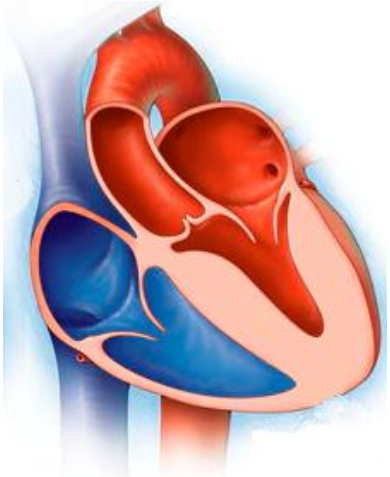
Van Oevelen, Rotmans, Meijvis, et al. Journal of Vasc Access 2018

RCT on optimal vascular access in eldery with prognosis < 2 years

Population	Patients of ≥70 years or older who have a life expectancy of ≤2 years (i.e. ≤50% chance of surviving 2 years) and who are expected to start hemodialysis within 3 months or who have started hemodialysis treatment with a central venous catheter in the past 3 months
Intervention	1. Placement of an arteriovenous graft 2. Placement of a permanent central venous catheter
Comparison	Creation of an autologous arteriovenous fistula (as suggested by current guidelines)
Outcome	Primary outcome: The number of interventions required for each person-year of hemodialysis treatment Secondary outcomes: Patient-reported outcome measures (KDQOL-36 measured every 3 months and SF-VAQ measured every month in the first year of the study), access-related health care costs, access-related complications, days in hospital, and mortality

….and what to do with the AVF after successful kidney transplantation ?

Do you know which of your transplant patients still have a functioning AVF ?



Risk of return to hemodialysis

LVH and associated morbidity

Case

Male, 42 years old.

IgA nephropathy

HD vintage 3 years

Living-related kidney transplantation 2 years ago

MM 0-1-0, no episodes of rejection

Creatinine clearance 60 ml/min, 0.2 g proteinuria

Brachiocephalic AVF 2200 ml/min

No cardiac symptoms

How do you approach the AVF?

a) Leave as it is

b) Banding

c) Elective surgical ligation

What is in the guidelines about VA after kidney transplantation ?

K-DOQI guidelines on vascular access:
Nothing

K-DOQI guidelines on transplantation:
Nothing

European best practice guideline on vascular access:
Nothing

European Society for Vascular Surgery guidelines on vascular access:
Routine closure of a functioning vascular access after successful kidney transplantation is not recommended

Survey on vascular access management after kidney Tx

8 International Nephrology and Vascular Surgery Societies participated

40-year-old male
Good kidney transplant prognosis:
2 years after living donor kidney transplantation, no rejection, eGFR: 50 mL/min/1.73 m^2
Cardiac status: **preserved left ventricular ejection fraction (50%)**
Current brachiocephalic AVF, left-sided, flow: **1000 mL/min**
Asymptomatic with regard to the AVF
Vein mapping right arm: suitable for both radiocephalic and brachiocephalic AVF creation

65-year old

LVEF 30%

2500 ml/ml

How do you approach the AVF?

Strong preference to maintain the AVF	Tendency to maintain the AVF	Tendency to ligate the AVF	Strong preference for AVF ligation

Voorzaat, Rotmans et al. J Vasc Access 2018

Survey on vascular access management after kidney Tx

585 respondents

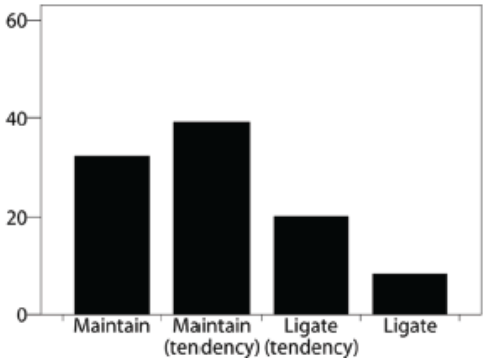
Specialty	Surgery	319 (54.5%)
	Nephrology	220 (37.6%)
	General nephrology	163 (27.9%)
	Interventional nephrology	57 (9.7%)
	Radiology	28 (4.8%)
	Other	18 (3.1%)
Affiliation	Academic hospital	326 (55.7%)
	Affiliated hospital	169 (28.9%)
	Other	90 (15.4%)
Years of experience		13 (7; 20)
VA treatment decisions in the past year		80 (27; 265)
Routine VA surveillance after kidney transplantation	Yes	169 (28.9%)
	No	384 (65.6%)
	Unknown	32 (5.5%)
Continent	Africa	7 (1.2%)
	Asia	49 (8.4%)
	Australia	28 (4.8%)
	Europe	372 (63.6%)
	North America	109 (18.6%)
	South America	20 (3.4%)

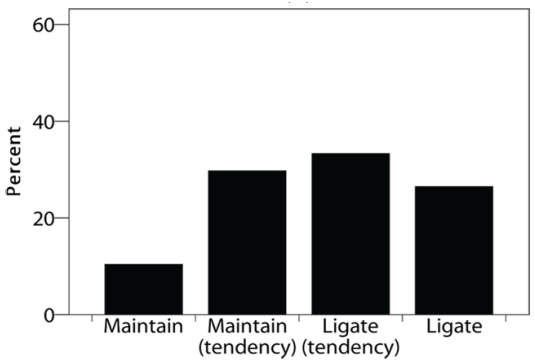
Voorzaat, Rotmans et al. J Vasc Access 2018

Survey on vascular access management after kidney Tx

No consensus on physicians' preferences

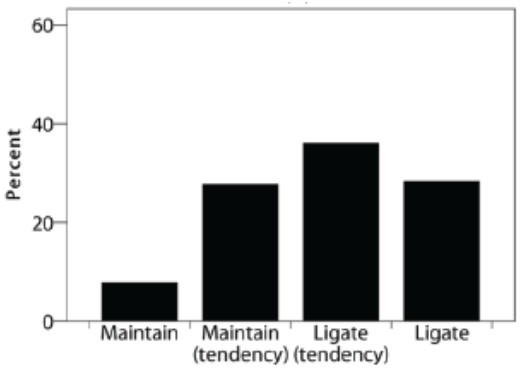
40 years age
Flow 1000 ml/min
LVEF 50%

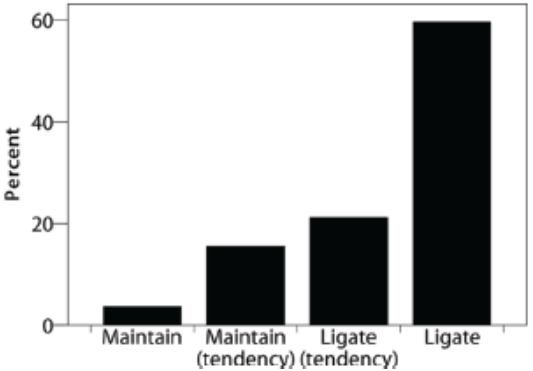




65 years age
Flow 2500 ml/min
LVEF 50%

65 years age
Flow 1000 ml/min
LVEF 30%



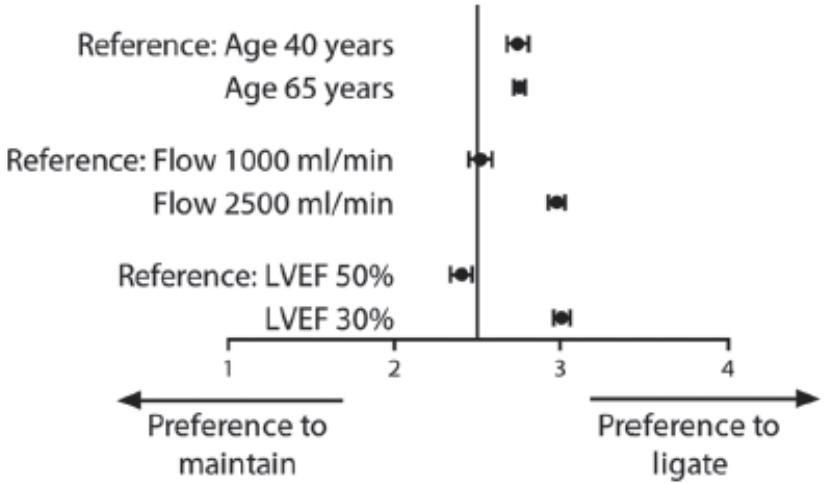


65 years age
Flow 2500 ml/min
LVEF 30%

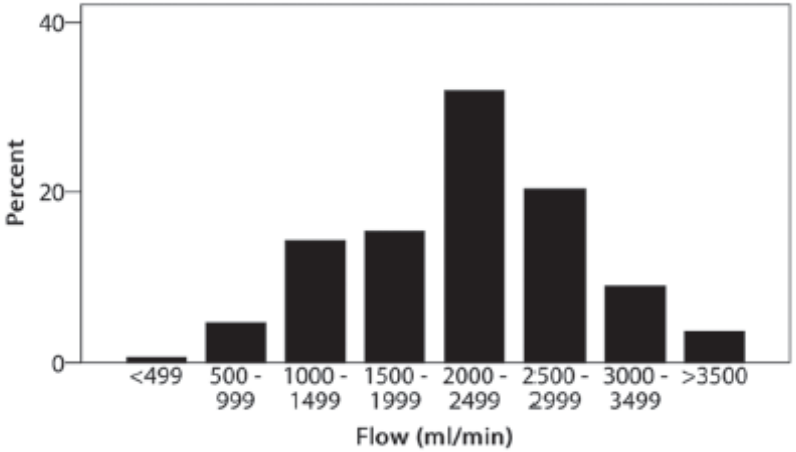
Voorzaat, Rotmans et al. J Vasc Access 2018

Survey on vascular access management after kidney Tx

Routine AVF surveillance after Tx was performed by 29% of physicians



Mean cutt-off 2038 ml/min



Reference is: 40 years
flow of 1000 mL/min,
preserved LVEF of 50%

Voorzaat, Rotmans et al. J Vasc Access 2018

Relevant questions on this issue

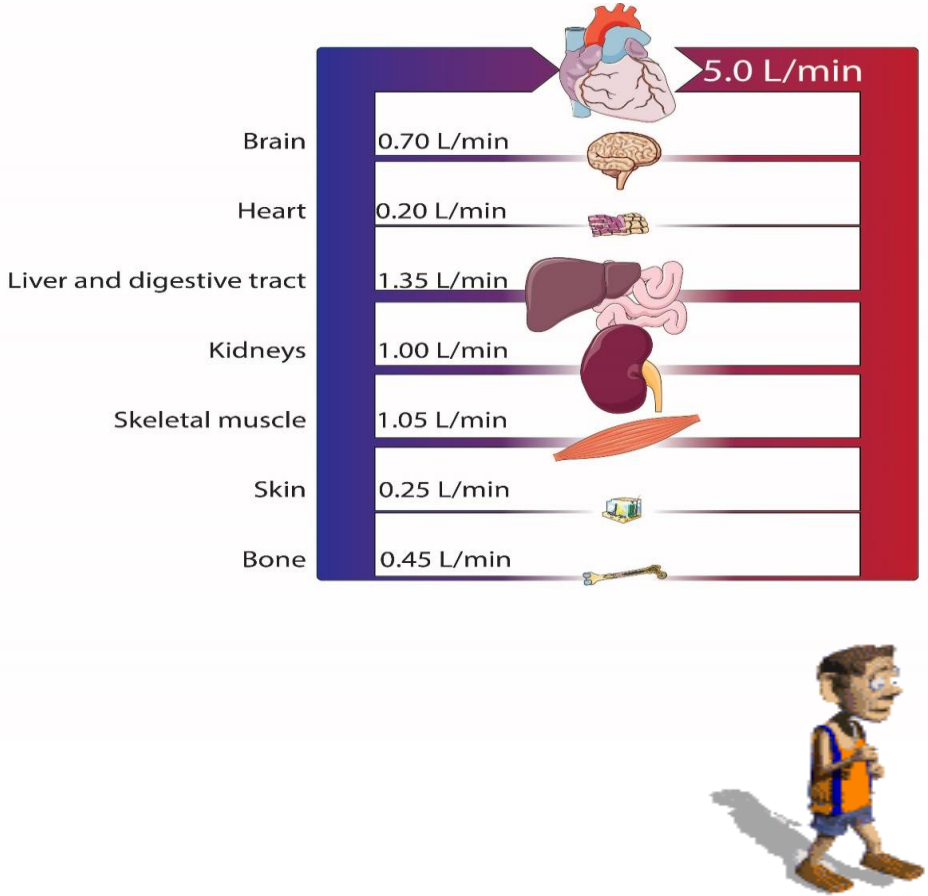
What is the cardiovascular burden of an AVF for transplant patients ?

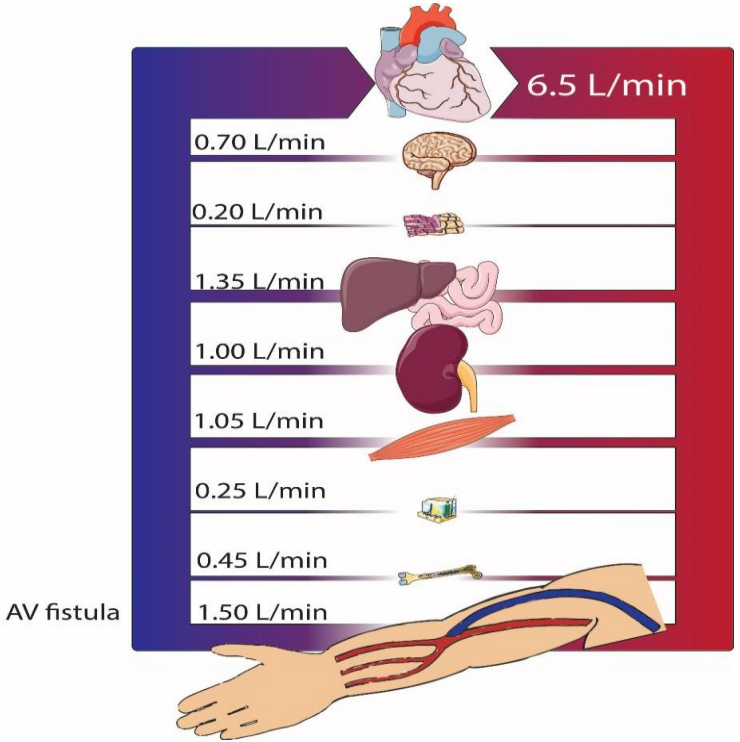
Could ligation or banding restore or prevent further damage to the heart?

What is the likelihood of spontaneous occlusion of the AVF after transplantation?

What are the changes that the transplant recipient will return to hemodialysis?

Effect of AVF on cardiac output

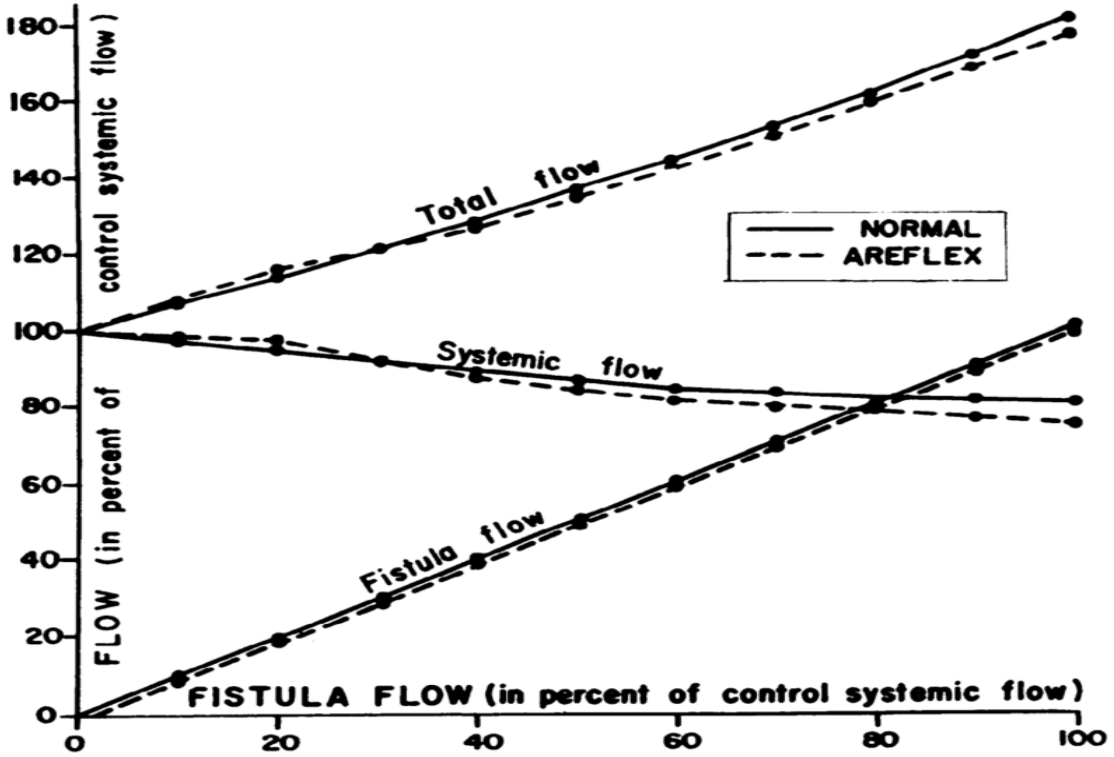




Voorzaat, Rotmans et al. J Vasc Access 2016

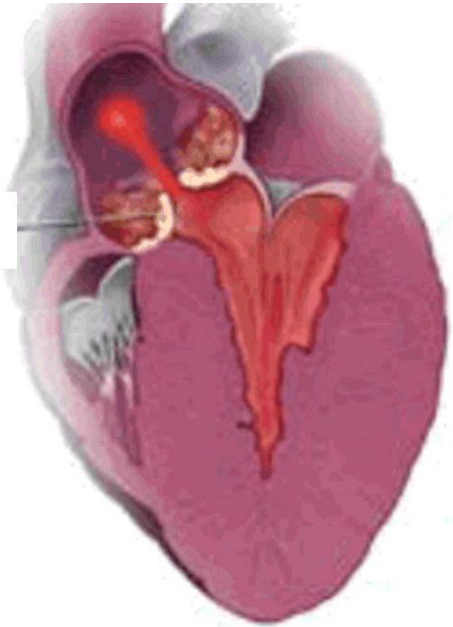
Acute cardiac adaptation

20 dogs with AVF



Guyton et al. Am J Physiol 1961

Cardiac effects of AVF in patients with ESRD

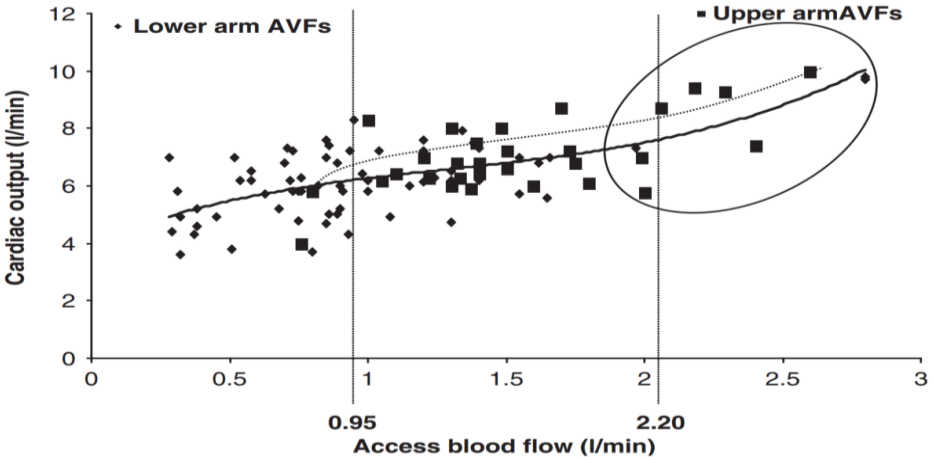


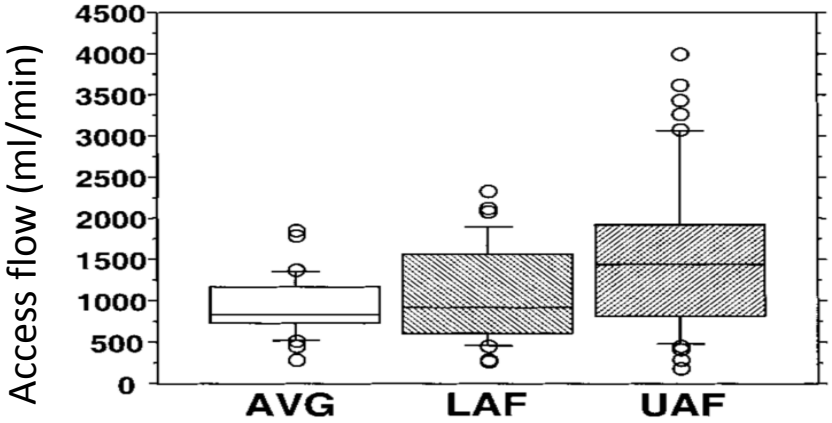
50 % has LVH

75 % has hypertension

50 % has conoary artery disease

Access flow and cardiac output



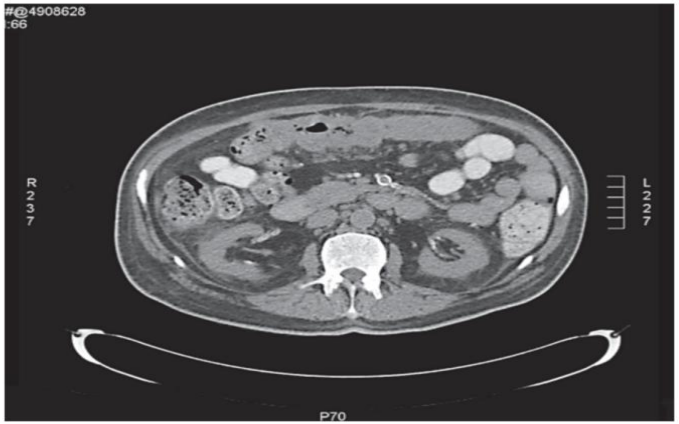


Basile, et al. Nephrol Dial Transplant 2008

Dixon, et al. Am J Kidney Dis 2002.

Systemic effects of AVF

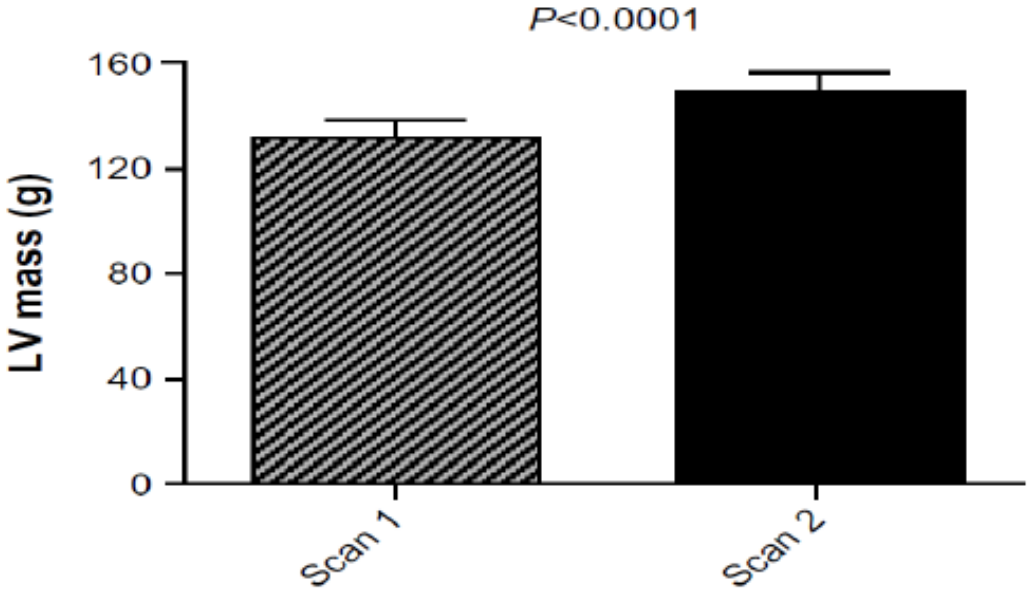
- “Global steal syndrome”
  - Reduced systemic blood flow
  - High of pseudo-normal cardiac output
- Often unrecognized: no wet symptoms
- Sometimes symptoms at contralateral arm
- Reversible after AVF ligation



Amerling, et al. Blood Purif 2011

Increased LV mass following AVF creation

MRI scan 1: pre-surgery; scan 2: + 6 months
Mean brachial artery flow: 1.158 ± 0.44 L/min



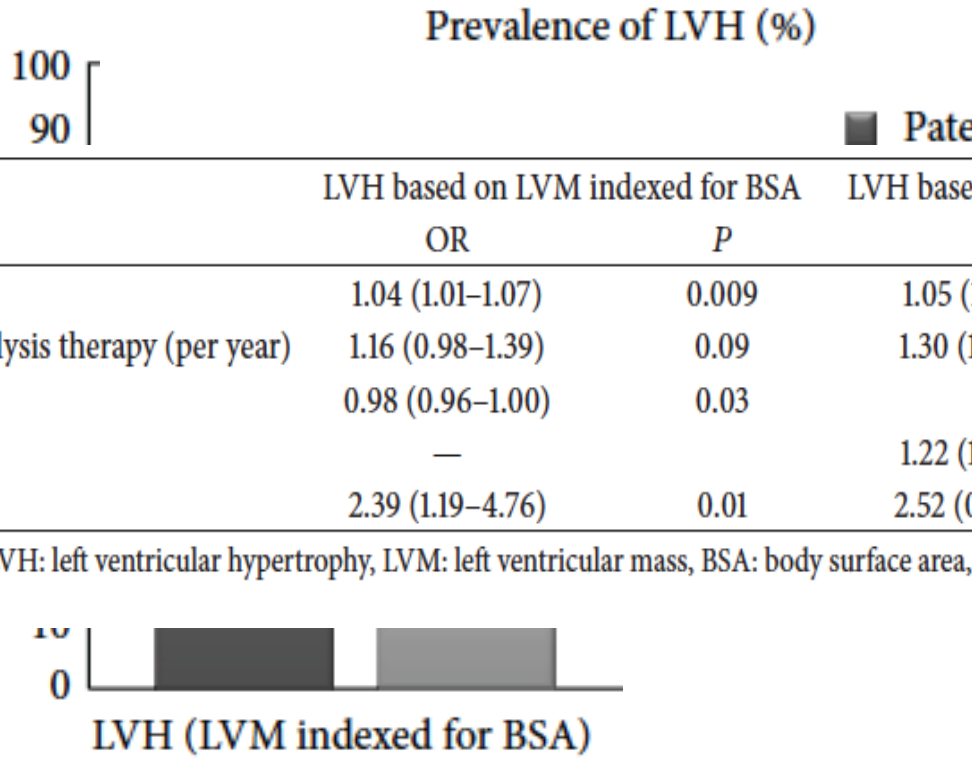
132 ± 32 g 149 ± 35 g

+13%

Dundon, et al. Int J Nephrol Renovasc Dis 2014

AVF is associated with LVH after kidney transplantation

162 transplant recipients, 67 with functioning AVF

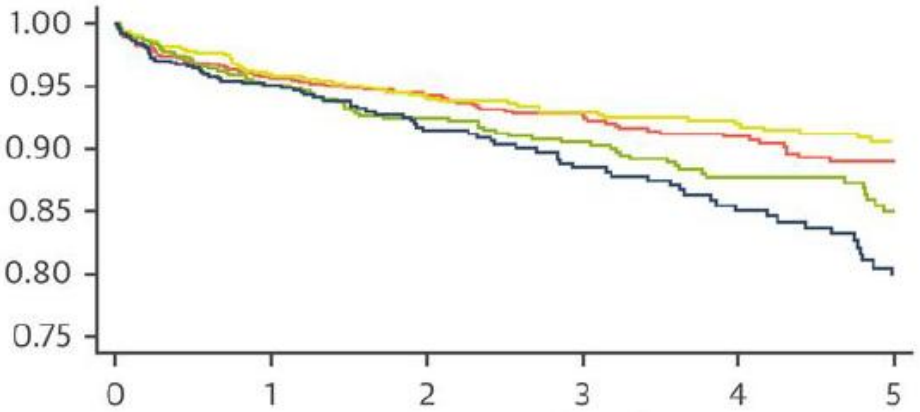


Independent variable	LVH based on LVM indexed for BSA		LVH based on LVM indexed for height$^{2.7}$	
	OR	*P*	OR	*P*
Age (per year)	1.04 (1.01–1.07)	0.009	1.05 (1.01–1.09)	0.02
Duration of pretransplant dialysis therapy (per year)	1.16 (0.98–1.39)	0.09	1.30 (1.00–1.69)	0.04
eGFR (per mL/min/1.73 m^2)	0.98 (0.96–1.00)	0.03	—	
BMI (per 1 kg/m^2)	—		1.22 (1.09–1.36)	<0.001
Patent vascular access	2.39 (1.19–4.76)	0.01	2.52 (0.99–6.47)	0.05

Data shown as means ± 95% CI. LVH: left ventricular hypertrophy, LVM: left ventricular mass, BSA: body surface area, eGFR: estimated glomerular filtration rate, and BMI: body mass index.

Kolonko et al. Biomed Res Int 2014

LV mass correlate with cardiovascular mortility

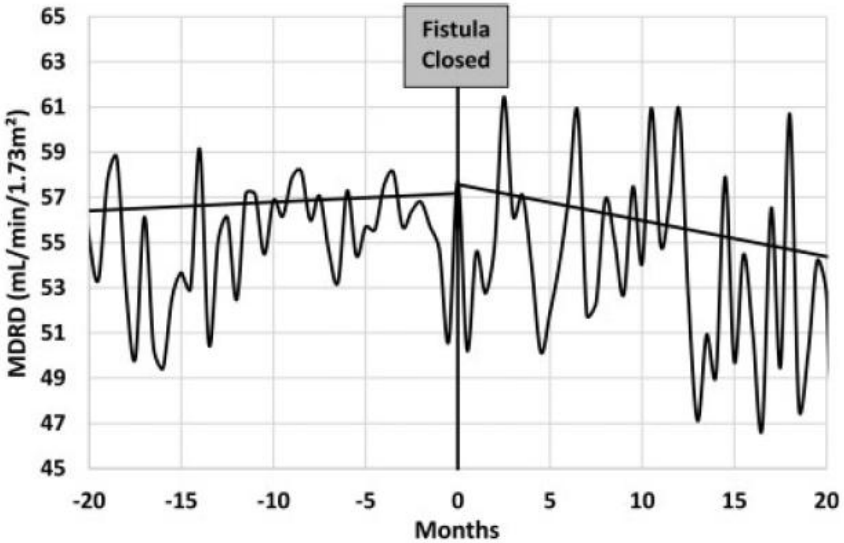


Number at risk						
Lowest Quartile	880	677	593	481	351	226
Second Quartile	916	673	575	474	360	246
Third Quartile	861	543	430	349	267	177
Highest Quartile	847	506	350	271	203	138

Ahmed Abdi-Ali et al. JIMG 2017

Conflicting data on effect of AVF ligation on renal allograft function

N = 200



Weekers et al NDT 2017

N = 300

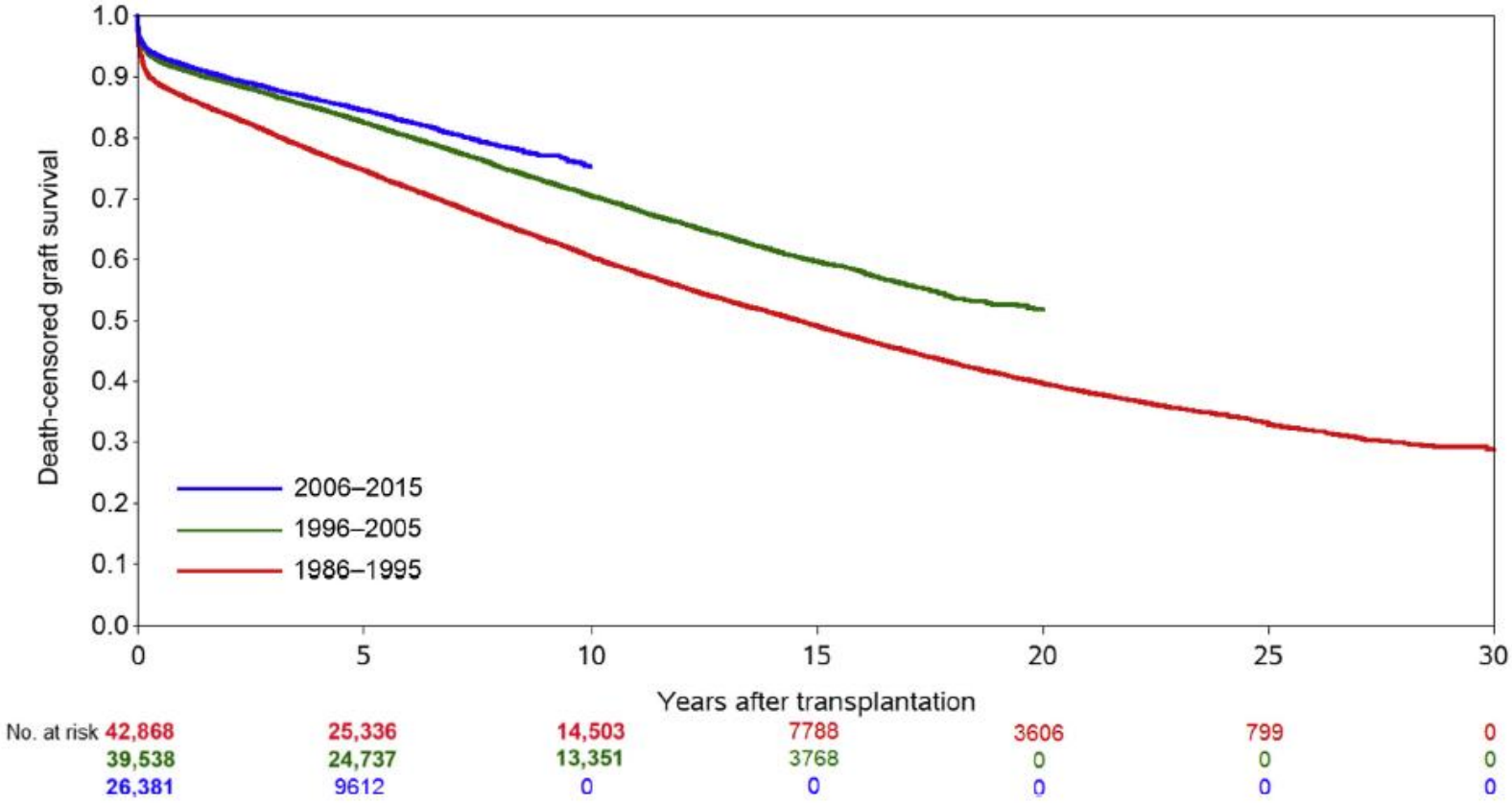
Variable	Arteriovenous Fistula at 1 Year		*P* Value
	Functional (n = 239)	Nonfunctional (n = 72)	
Serum creatinine (μmol/L)	110 ± 38	99 ± 30	.046
eGFR (mL/min/1.73 m²)	69 ± 21	74 ± 19	.047
eGFR <60 mL/min/1.73 m² (%)	36.8	23.6	.038
5-year graft survival rate (%)	60.0	75.0	.045

Data are mean ± SD or percentage.

Vakdic et al Transplant Proceedings 2010

Renal allograft survival anno 2018

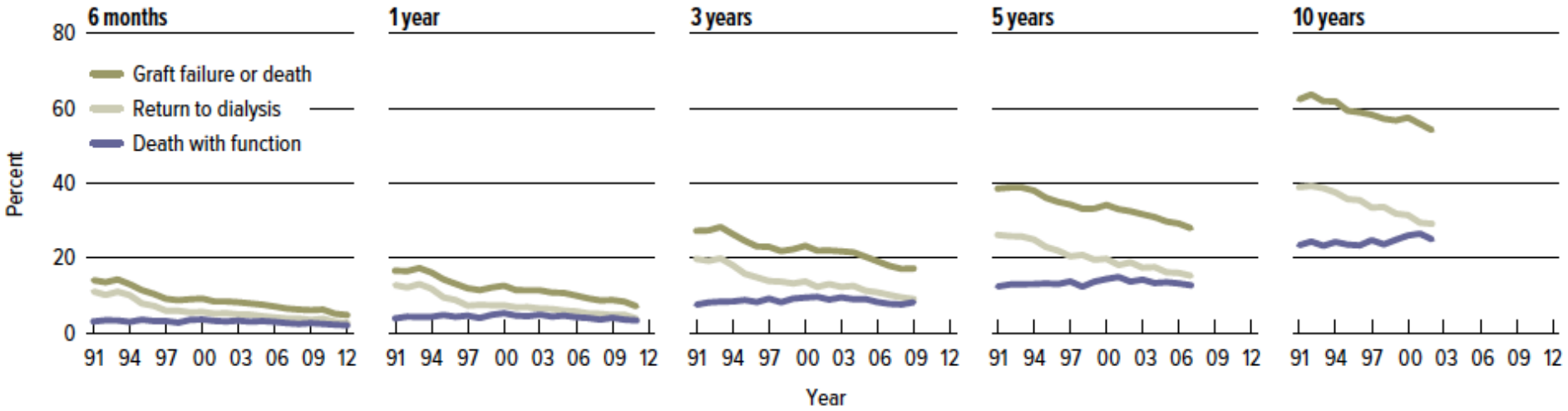
> 100.000 patients included



Coemans et al. Kidney Int 2018

Transplant patients die more often with functioning allograft

Outcomes among adult transplant recipients: deceased donors



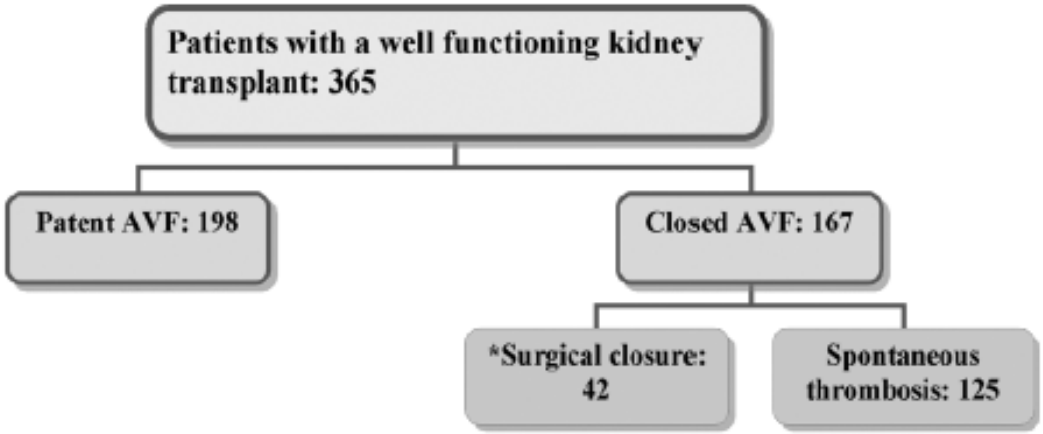
SRTS 2012

Change of still having a functional AVF at time of allograft failure

Long term fate of AVF after kidney transplantation

Retrospective study Italy 1994-2004

365 patients with well functioning kidney transplant and functioning AVF at time of transplant



*Causes of surgical closure aneurysm in 26 patients (61%), ischemic syndrome in nine patients (22%), infections in two patients (4%), oedema in two patients (4%), and an aesthetic reason in three patients (9%).

Manca et al JVA 2015

RCT on AVF ligation after succesfull kidney transplantation

- **Study Design**: Open-label, multi-centre, investigator-initiated randomised controlled trial

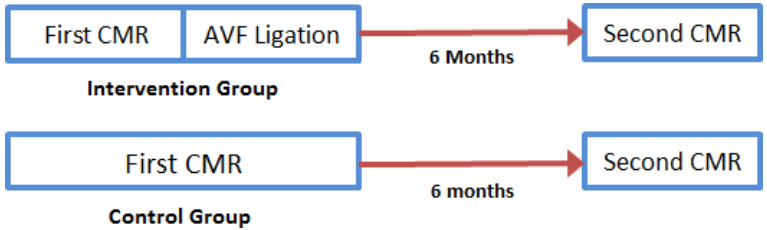
- **Inclusion Criteria**: Adult (≥ 18 years) renal transplant recipients
  ≥ 12 months post successful transplant
  stable kidney function
  a persistent functioning AVF
  deemed at low risk of graft failure

- **Exclusion Criteria**: Contraindication to MRI scan;
  anticipated to require hemodialysis within 24 months.

Stokes et al. Abstract AHA 2018

RCT on AVF ligation after successfull kidney transplantation

- **Procedure**:



63 participants.

- **Primary Outcome**: Change in LV mass at 6 months (MRI)
- **Secondary Outcomes**: Changes in atrial and ventricular volumes
  pulmonary artery velocity
  change in NT-pro BNP level.

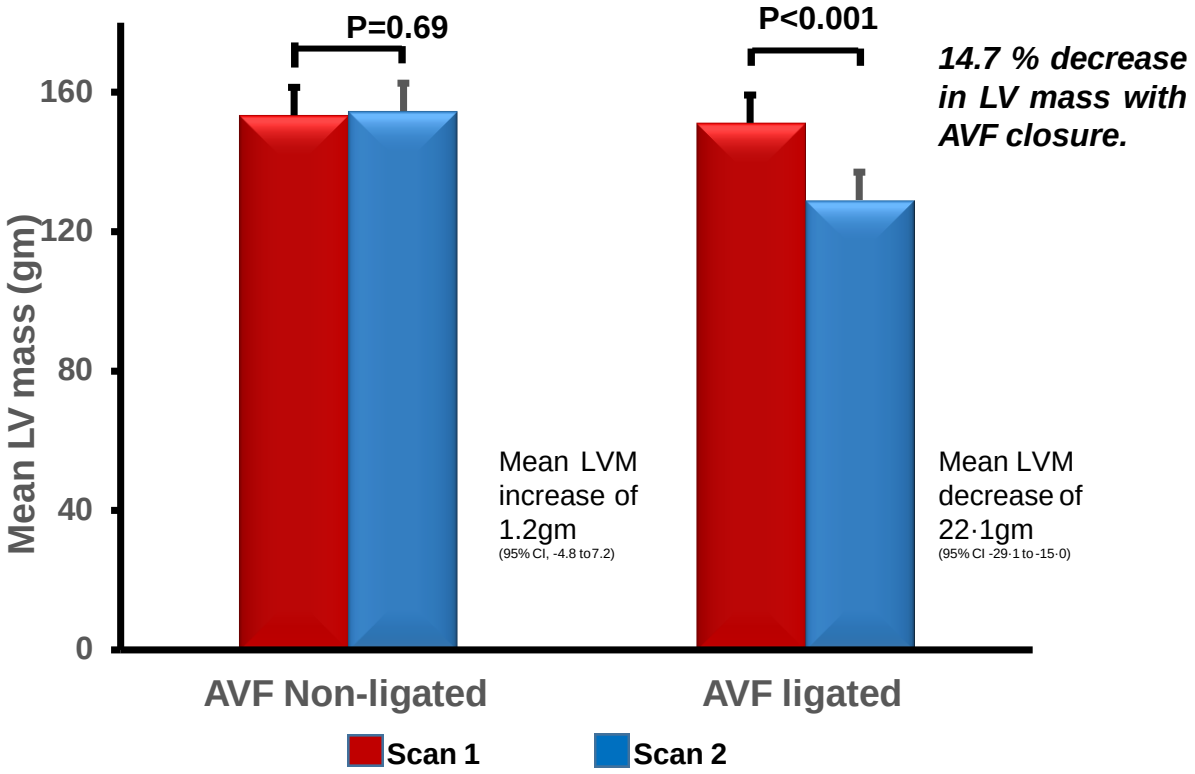
Stokes et al. Abstract AHA 2018

Baseline characteristics

Variable	All Participants	AVF ligation arm	Control arm	P value
N	63	32	31	
Age (years)	59.9 ± 10.6	59.3 ± 11.8	60.4 ± 9.5	0.70
Males {n , (%)}	42 (67)	20 (62.5)	22 (70.9)	0.25
AVF creation to first scan (months)	126.5 ± 92.4	113.3 ± 86.5	138.7 ± 99.4	0.32
Transplantation until first scan (months)	103.8 ± 86.0	92.3 ± 71.7	115.0 ± 97.9	0.34
Diabetes mellitus, n (%)	18 (28.5)	9 (28.1)	9 (29)	0.83
Hypertension, n (%)	48 (76.1)	25 (78.1)	23 (71.8)	0.25
Smoking, n (%)	16 (25.3)	7 (21.8)	9 (29)	0.32
Peripheral Vascular Disease, n (%)	4 (6.3)	2 (6.2)	2 (6.4)	0.83
Prior ischaemic heart disease, n (%)	6 (9.5)	4 (12.5)	2 (6.4)	0.36
Location of AVF, n (%) • Forearm AVF • Upper arm AVF	 30 (47.6) 33 (52.3)	 14 (43.7) 18 (56.2)	 16 (51.6) 15 (48.3)	0.59

Data are mean ± SD

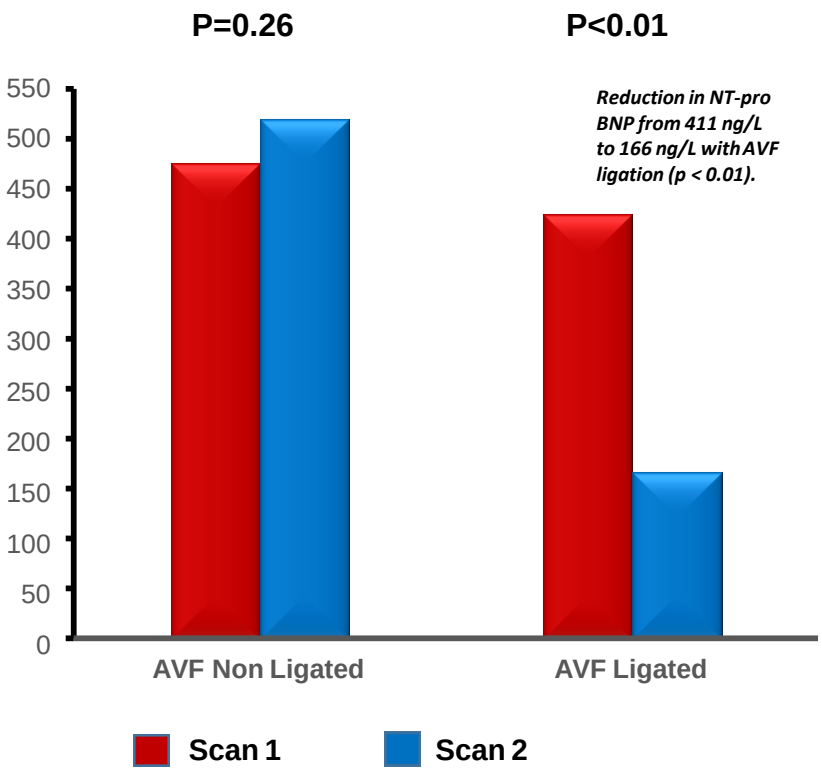
AVF ligation result in reduction in LV mass



Indexed to BSA, the LV mass reduction was 11·8 gm/m² (95 % CI 15·2 to 7·8, p<0.001)

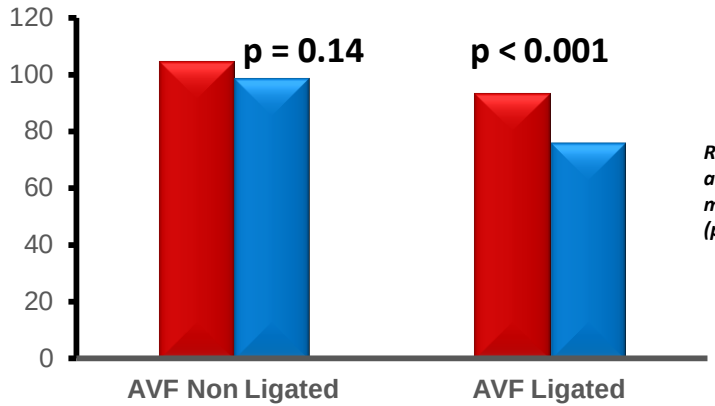
Secondary endpoints

NT-pro BNP Level



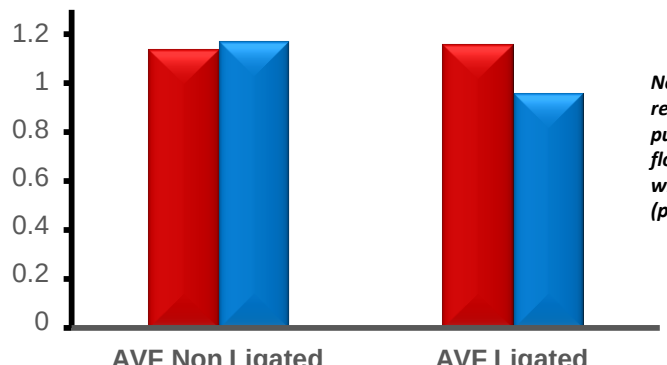
Reduction in NT-pro BNP from 411 ng/L to 166 ng/L with AVF ligation (p < 0.01).

Left Atrial Volume (ml)



Reduction in left atrial volume by 17.5 ml with AVF ligation (p<0.001)

Pulmonary Artery peak velocity (m/sec)



Non-significant reduction in peak pulmonary artery flow by 0.19m/sec with AVF ligation (p=0.07).

Relevant questions on this issue

What is the cardiovascular burden of an AVF for the patient ?

Higher cardiac output, left ventricular hypertrophy

Lower blood pressure, effect on eGFR unclear

Could ligation or banding restore or prevent further damage to the heart?

Cardiac parameters: yes. Cardiovascular events, mortality: unknown

What is the likelihood of spontaneous occlusion of the AVF after transplantation?

± 50%

What are the changes that the transplant recipient will return to hemodialysis?

Differs between patient and donor characteristics

Median death censored graft survival > 10 years

Recipients getting older and die more often with functioning allograft

Conclusions

- Arteriovenous fistulas are non-physiological
- Forearm fistula first, but the most appropriate VA depends on the patient's prognosis, co-morbidities and preferences
- AVF ligation results in a significant reduction in LV mass in Tx recipients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Pilot RCT on CVC versus AVF in elderly patients

Open Access Protocol

BMJ Open

ACCESS HD pilot: A randomised feasibility trial Comparing Catheters with fistulas in Elderly patientS Starting haemodialysis

- multi-center, parallel-arm, and open label.
- feasibility and safety of randomizing elderly patients (> 65 years) with end-stage kidney failure starting hemodialysis with a tunneled/non-tunneled catheter to one of the following vascular access strategies:
  - (a) attempt at fistula creation (intervention),
  - (b) continued use of a catheter (comparator).
- Estimated Enrollment: 100 patients
- Study Started in May 2016

Quinn et al. BMJ Open 2016; 6:e013081

Disappointing results of systemic interventions to promote AVF maturation

Fish oil or aspirin

No reduction in AVF failure at 12 mnths

JAMA Internal Medicine | Original Investigation 2017

Effect of Fish Oil Supplementation and Aspirin Use on Arteriovenous Fistula Failure in Patients Requiring Hemodialysis

A Randomized Clinical Trial

Ashley B. Irish, MD; Andrea K. Viecelli, MD; Carmel M. Hawley, MD, MMedSci; Lai-Seong Hooi, MD; Elaine M. Pascoe, MBiostat; Peta-Anne Paul-Brent, BSc; Sunil V. Badve, MD; Trevor A. Mori, PhD; Alan Cass, MD, PhD; Peter G. Kerr, MD, PhD; David Voss, MD; Loke-Meng Ong, MD; Kevan R. Polkinghorne, MD, PhD; for the Omega-3 Fatty Acids (Fish Oils) and Aspirin in Vascular Access Outcomes in Renal Disease (FAVOURED) Study Collaborative Group

Clopidogrel

Reduced early thrombosis does not increase in suitability for dialysis

Effect of Clopidogrel on Early Failure of Arteriovenous Fistulas for Hemodialysis: A Randomized Controlled Trial

Laura M. Dember; Gerald J. Beck; Michael Allon; et al.

JAMA. 2008;299(18):2164-2171 (doi:10.1001/jama.299.18.2164)

Colecalciferol

No improved AVF maturation at 6 mnths

J Vasc Access 2014; 15 (2): 88-94

DOI: 10.5301/jva.5000187

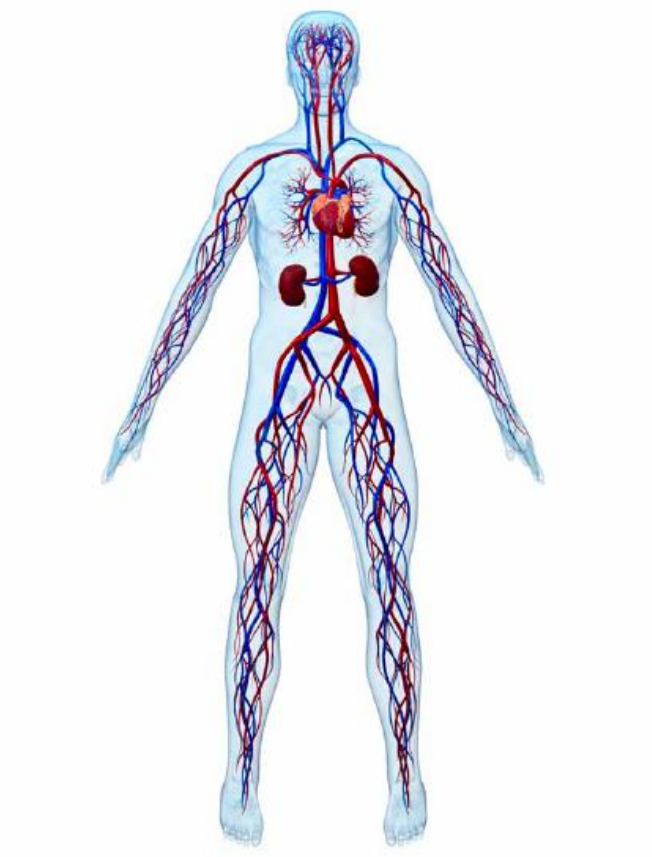
ORIGINAL ARTICLE

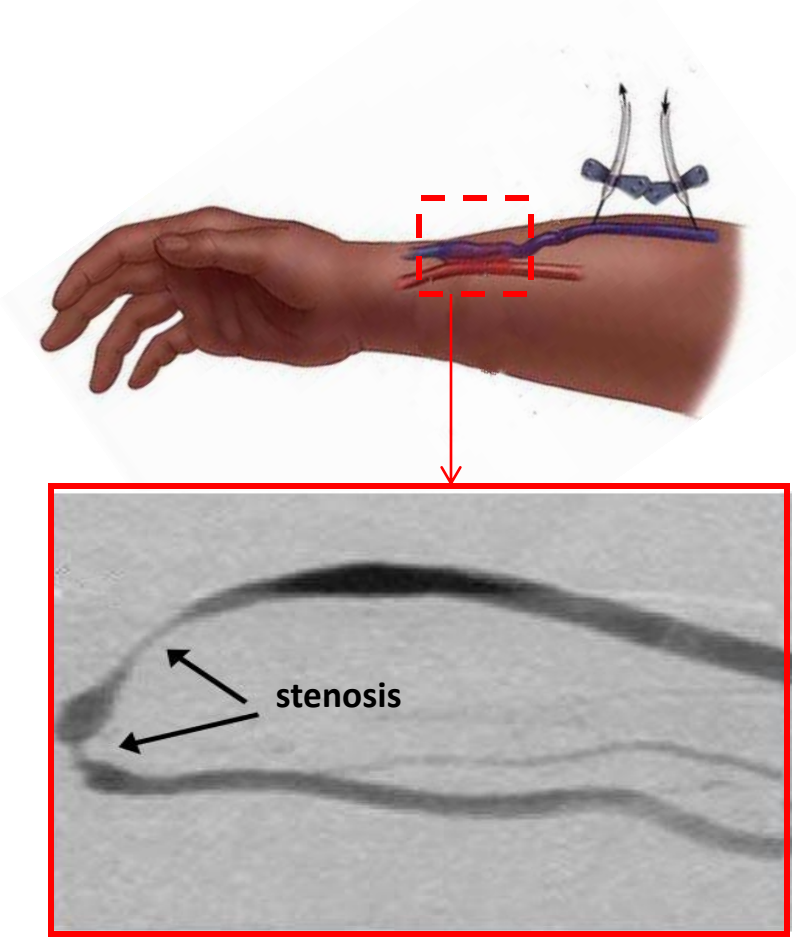
Very high-dose cholecalciferol and arteriovenous fistula maturation in ESRD: a randomized, double-blind, placebo-controlled pilot study

Haimanot Wasse[1], Rong Huang[1], Qi Long[2], Yize Zhao[2], Salman Singapuri[1], William McKinnon[3], George Skardasis[3], Vin Tangpricha[4]

Wrong target or insufficient local drug concentration?

Systemic versus local therapy to promote AVF maturation



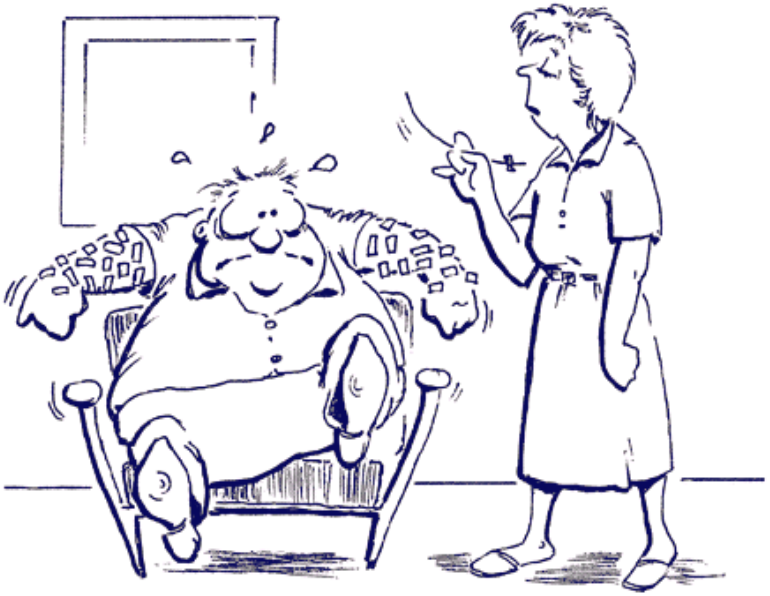


Clinical trials with (local) intervention to promote AVF maturation

Intervention to promote AVF maturation	Current status of clinical trial
Endothelial cell application	Trial stopped prematurely
NO availability (nitroglycerin)	Trial stopped prematurely
Recombinant elastase (PATENCY-2 trial)	Recruitment completed
Thrombin-receptor antagoist (Vorapaxar)	Recruitment completed
Liposomal prednisolone	Recruitment completed
VasQ external support device	Ongoing
Sirolimus eluting collagen implant	Ongoing
Adipose-derived mesenchymal stem cell application	Ongoing
Atorvastatin	Ongoing
Pre-operatieve forearm exercise	Ongoing

Patient-centered vascular access priorities

- Cannulation issues
- Pain
- Fewer procedures
- Wait times after pulling needles
- Physical disfigurement



Sounds like a preference for catheters or rapid and effective AVF maturation

Stimulation flow induced outward remodeling

JVA
ISSN 1129-7298
CLINICAL TRIAL PROTOCOL

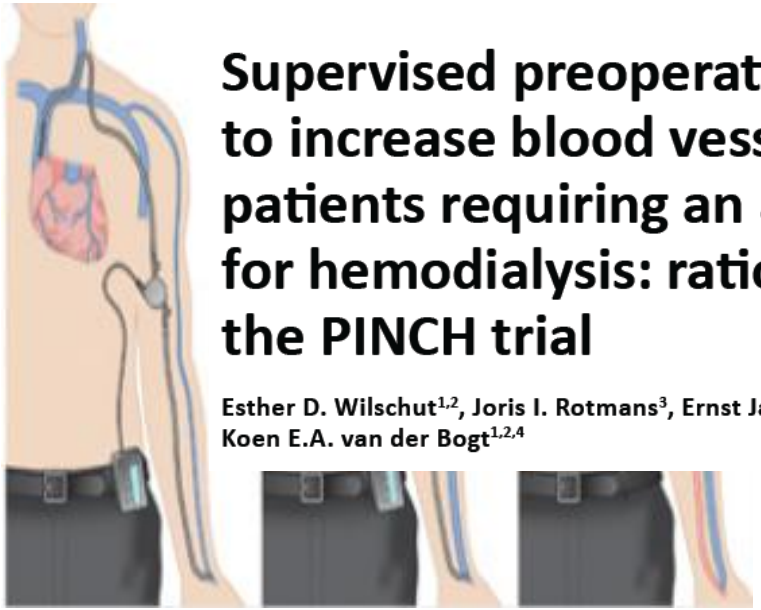
JVA The Journal of Vascular Access

The Journal of Vascular Access
2018, Vol. 19(1) 84–88

DOI: 10.5301/jva.5000826
journals.sagepub.com/home/jva
SAGE

Supervised preoperative forearm exercise to increase blood vessel diameter in patients requiring an arteriovenous access for hemodialysis: rationale and design of the PINCH trial

Esther D. Wilschut[1,2], Joris I. Rotmans[3], Ernst Jan Bos[4], Daniëlle van Zoest[5], Daniël Eefting[1,2], Jaap F. Hamming[2], Koen E.A. van der Bogt[1,2,4]



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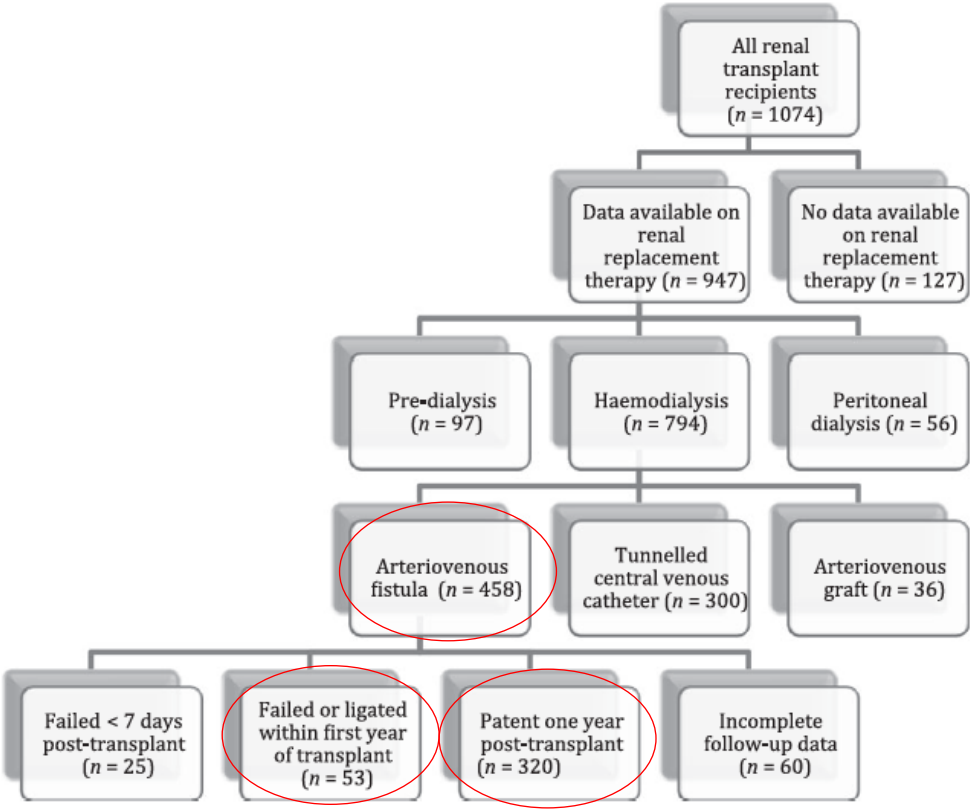
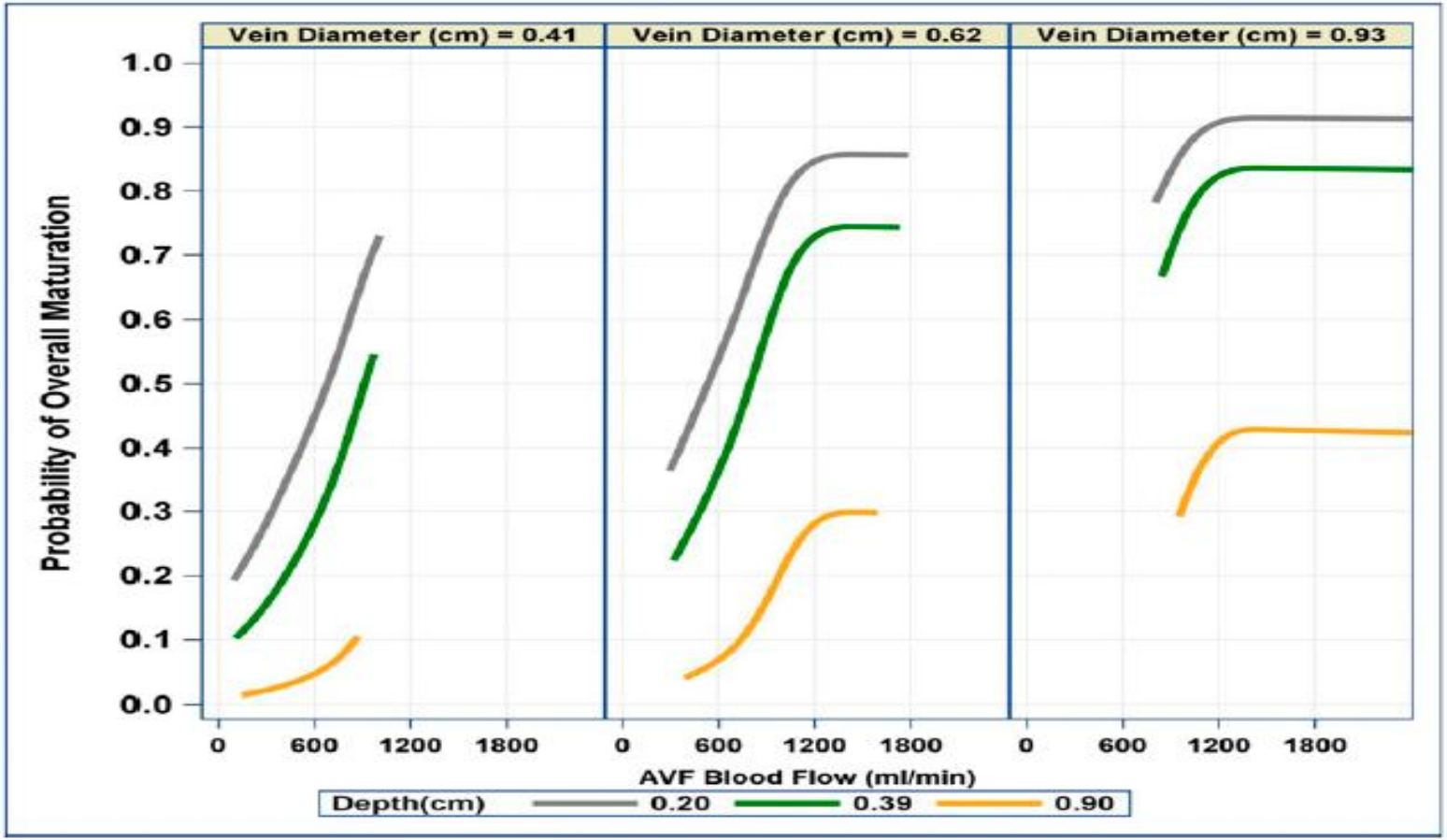
Change of still having a functional AVF at time of allograft failure?

Short term fate of AVF after kidney transplantation



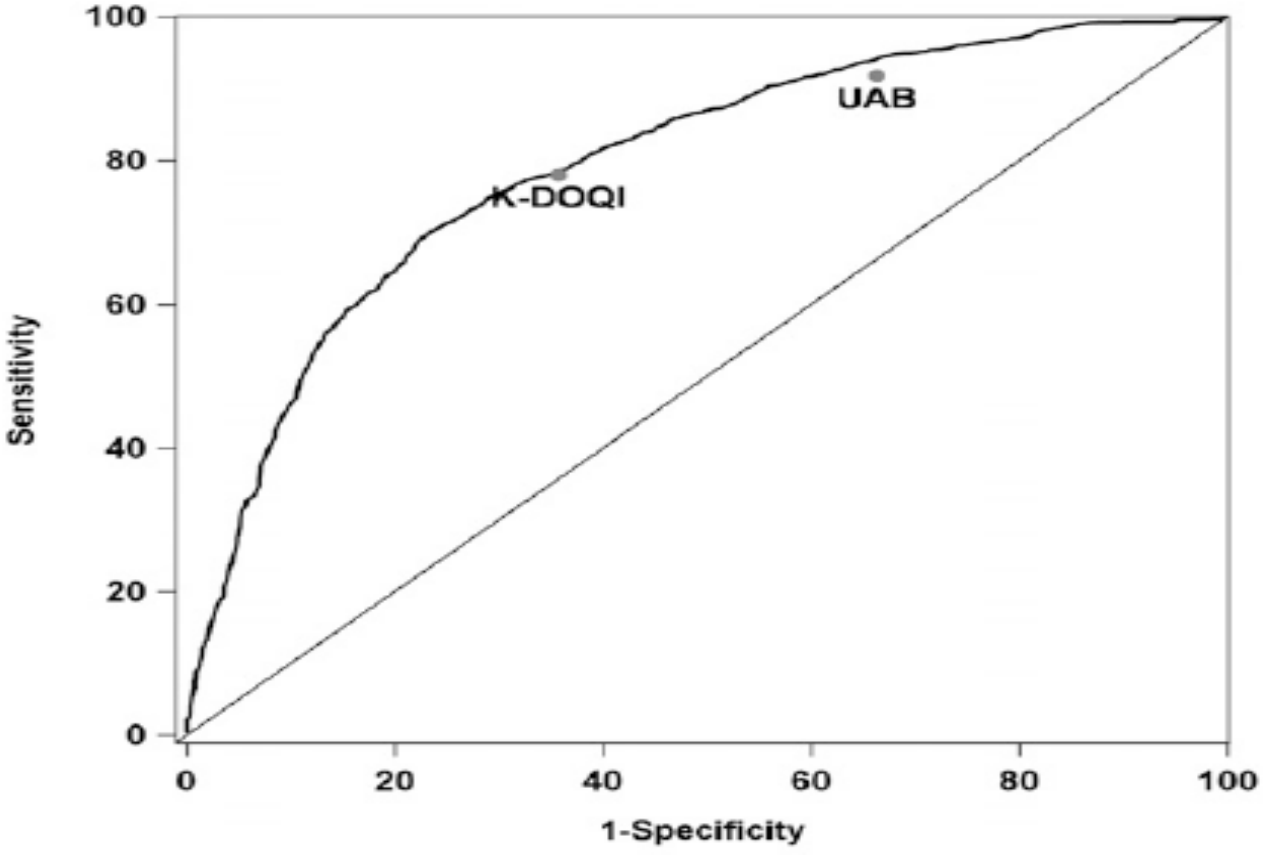
Aitkin and Kingsmore.Transplant International 2014

Prediction of clinical AVF maturation



Robbin et al. JASN 2018

Prediction of clinical AVF maturation



UAB
4 mm
500 ml/min

K-DOQI
6 mm
600 ml/min

Robbin et al. JASN 2018