Update in VA

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Objectives

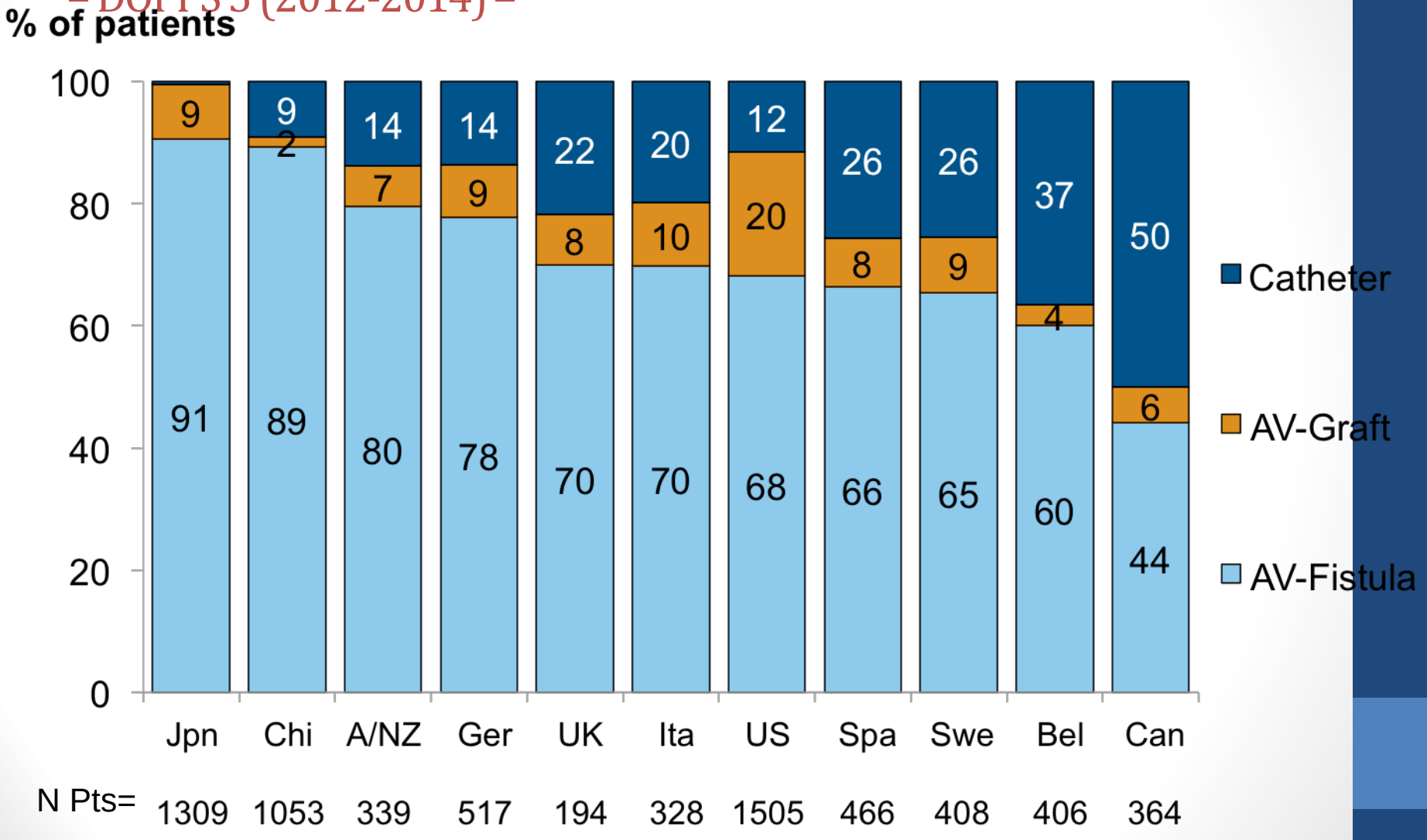
1. To review current VA scene Worldwide, Canada and BC
2. Understand the variability of AVF primary failure rates
3. Review physiology of AVF maturation
4. Review risk factors for AVF non-maturation
5. Novel approaches to maturation
6. Review upcoming important VA trials
7. Recognize impact of cannulation technique on AVF outcome
8. Questions

9. BC VA picture

Objective 1:
Vascular Access Scene

Prevalent Vascular Access Type

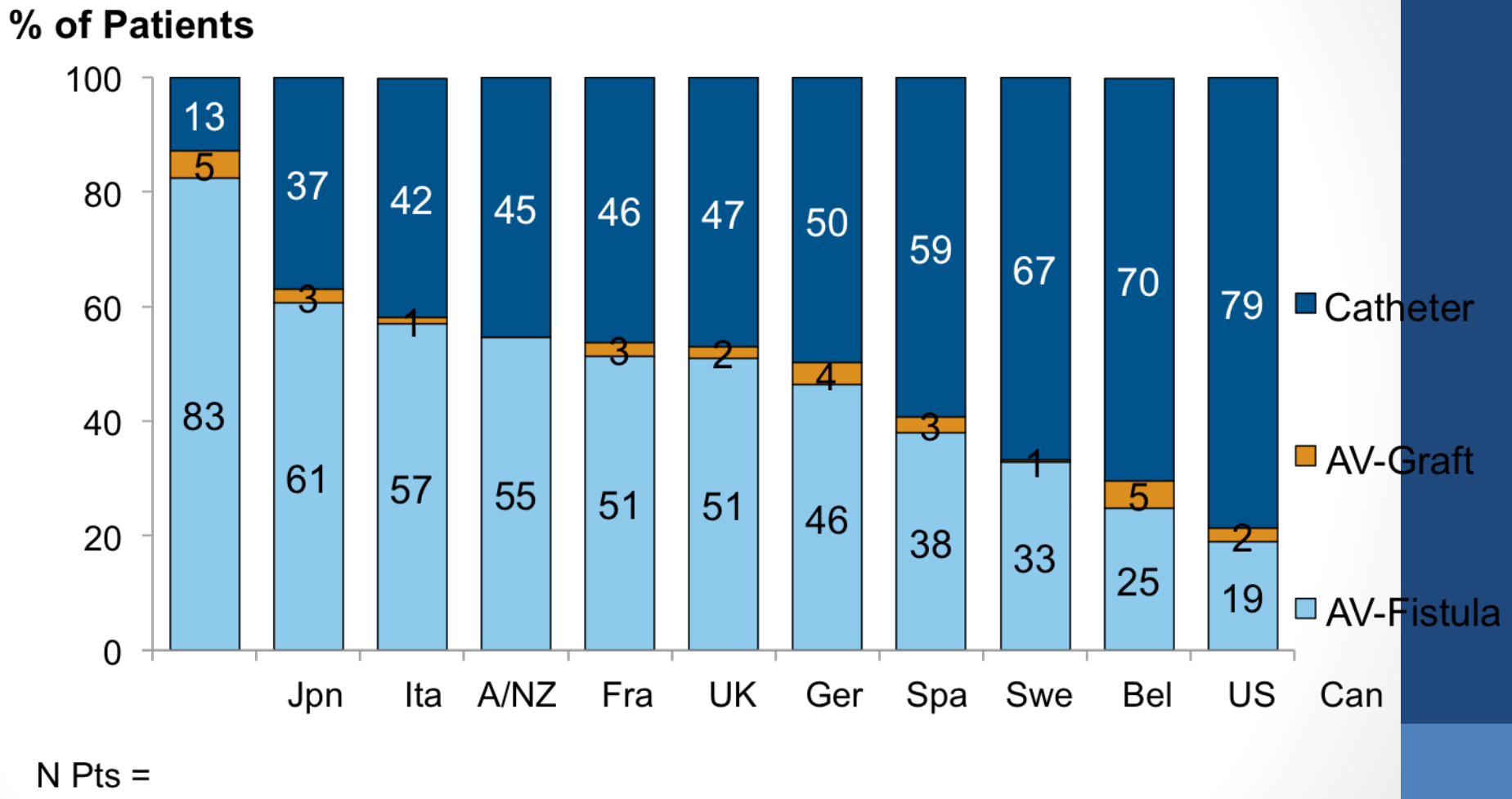
– DOPPS 5 (2012-2014) –



Initial prevalent cross-sections of DOPPS 5 (2012-2014) with vintage > 90 days; weighted by facility sampling fraction

Incident Vascular Access Type

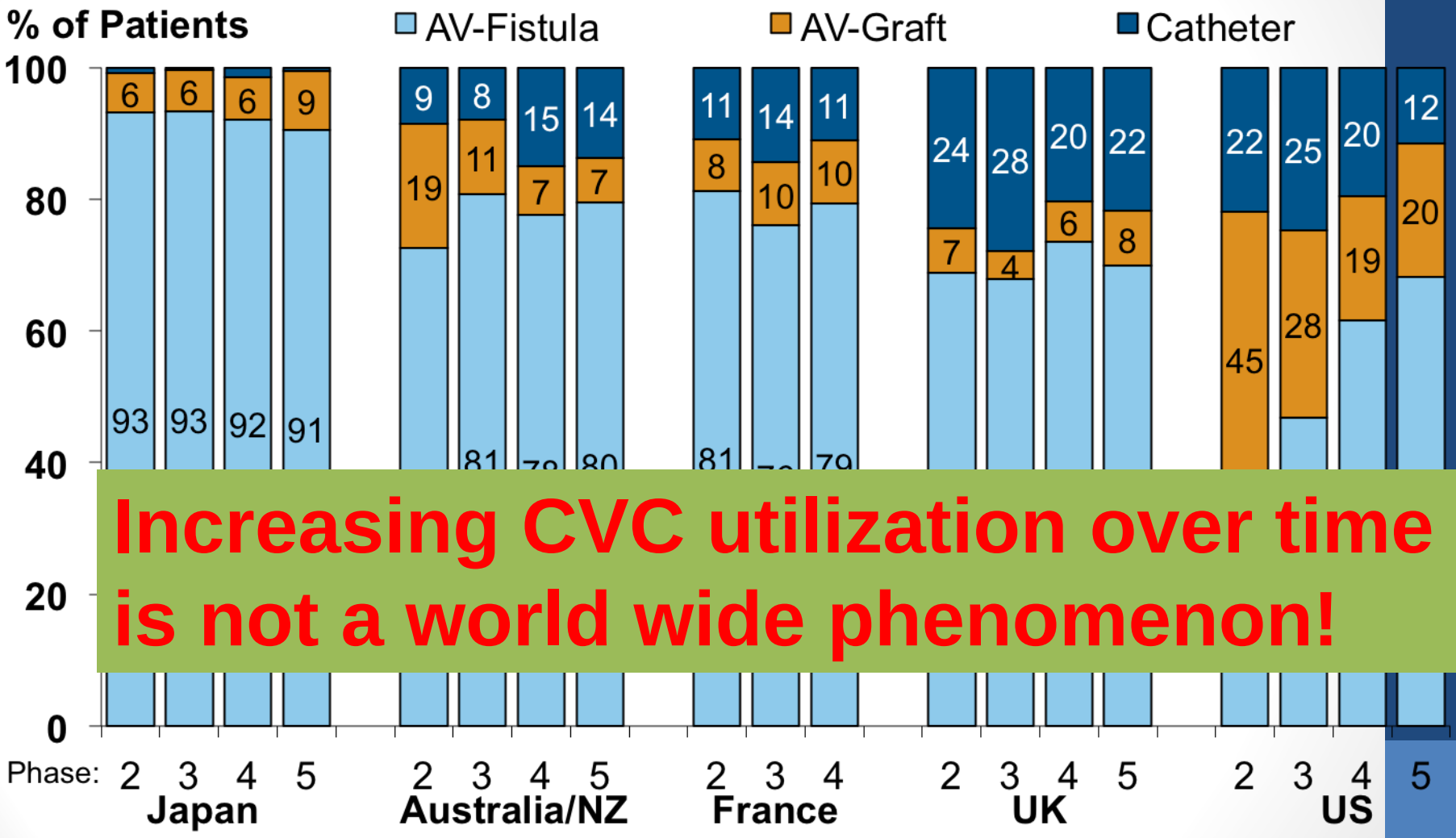
– DOPPS 5 (2012-2014) –



* Among patients on dialysis < 120 days at DOPPS enrollment; For patients missing data on access at dialysis start (42%), access at DOPPS enrollment was used (median [interquartile range] of days on dialysis at DOPPS enrollment was 69 [36-93] days for these patients)

Bieber et al. ASN Abstract (2013)

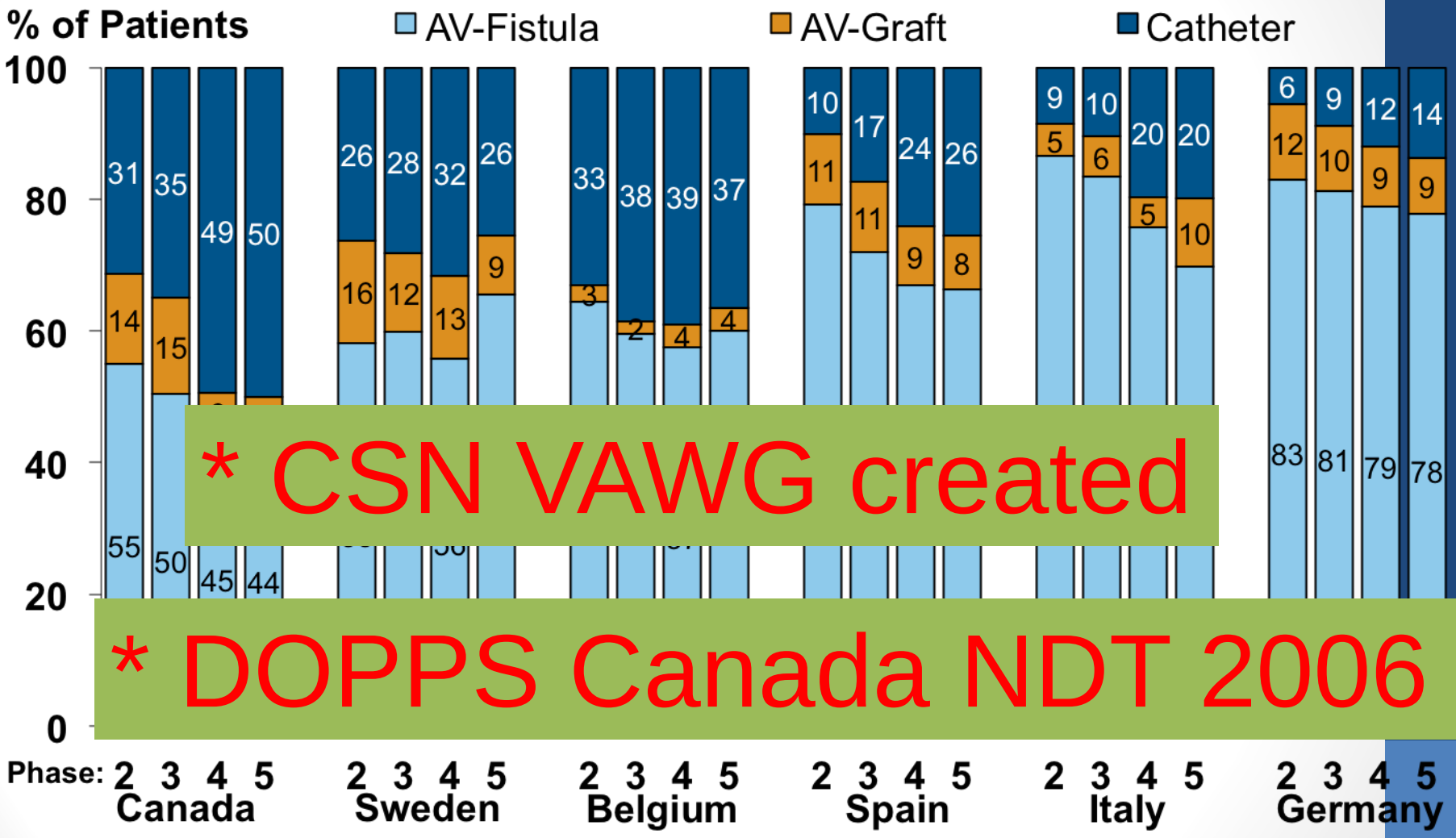
Distribution of VA Types in Countries with Stable or Increasing Fistula Use



Increasing CVC utilization over time is not a world wide phenomenon!

Prevalent cross-sections of patients on dialysis >90 days at time of study entry; weighted by facility sampling fraction; DOPPS 2 (2002-2004), DOPPS 3 (2005-2008), DOPPS 4 (2009-2011); DOPPS 5 (2012-2014)

VA Use in Countries with Decreasing Fistula Use & Increasing Catheter Use



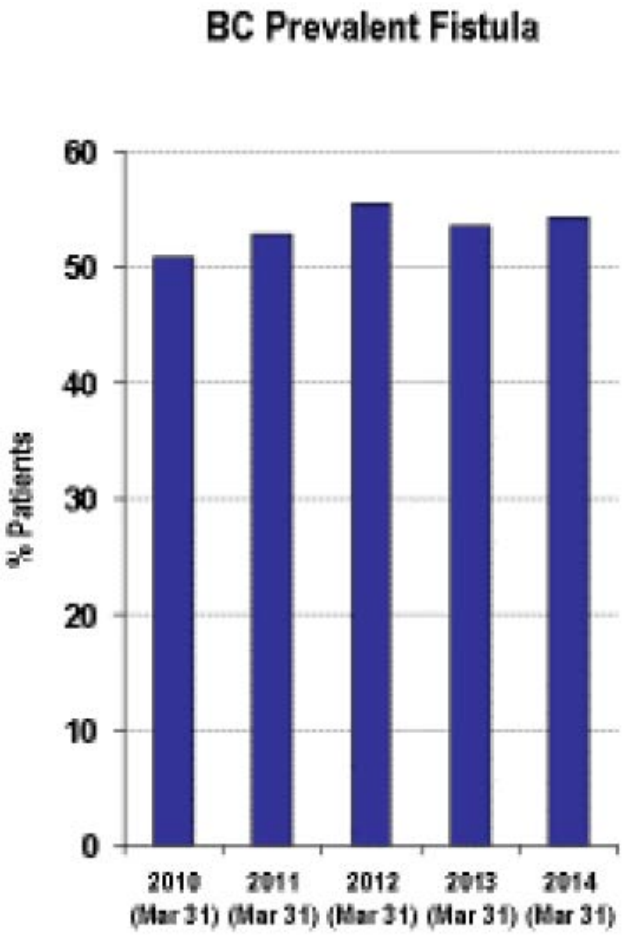
Prevalent cross-sections of patients on dialysis >90 days at time of study entry; weighted by facility sampling fraction; DOPPS 2 (2002-2004), DOPPS 3 (2005-2008), DOPPS 4 (2009-2011); DOPPS 5 (2012-2014)

VA Distribution – Alberta

Vascular Access: Follow-Up Hemodialysis Patients, 2010 to 2012
80016 FOOTHILLS MEDICAL CTR/SOUTHERN ALBERTA RENAL PROG

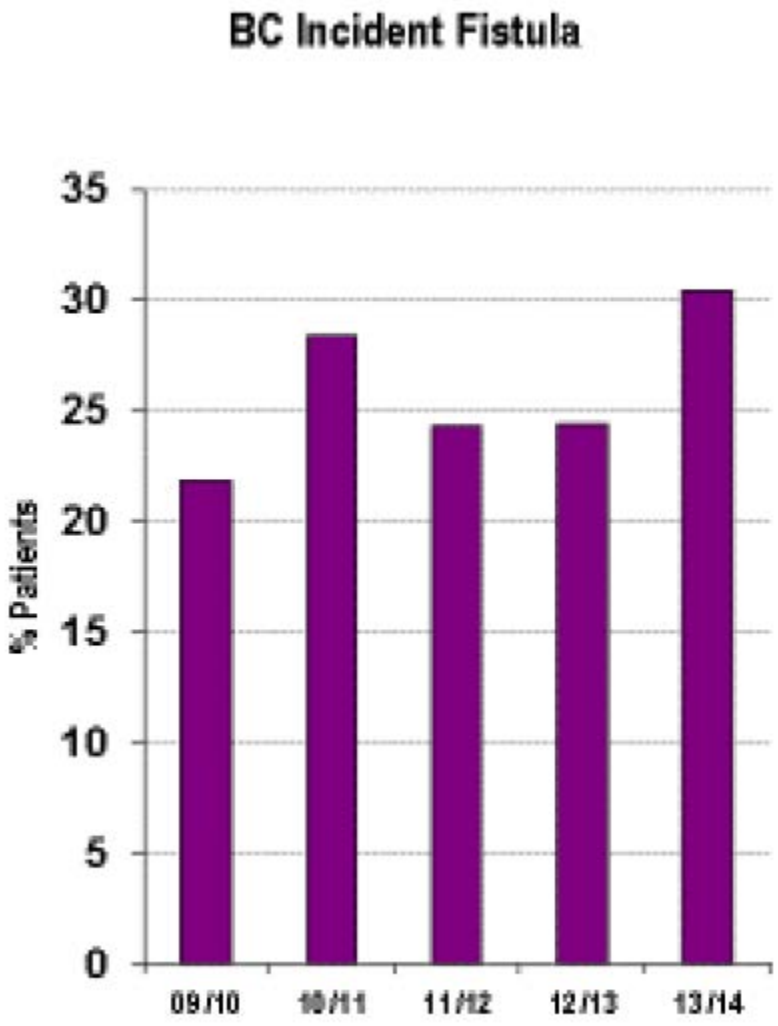
		Facility			Province			Canada		
		2010	2011	2012	2010	2011	2012	2010	2011	2012
Total Patients	*N*	391	391	418	1,538	1,585	723	16,291	16,440	14,632
Incident Vascular Access*	*N*	278	275	295	1,158	1,219	536	12,423	12,730	11,542
Catheter‡	*%*	55.5	55.8	55.7	55.6	57.9	59.2	57.6	59.1	61.0
AV Fistula	*%*	14.6	14.1	14.1	17.3	16.8	14.5	17.2	17.1	16.7
AV Graft	*%*	1.0	0.5	0.7	2.4	2.1	0.4	1.4	1.3	1.1
Unknown	*%*	28.9	29.7	29.4	24.7	23.1	25.9	23.7	22.6	21.1
Prevalent Vascular Access†	*N*	391	391	418	1,538	1,585	723	16,235	16,424	14,587
Catheter‡	*%*	38.6	27.6	29.9	40.8	37.2	29.0	50.3	50.8	51.5
AV Fistula	*%*	59.3	66.5	65.3	53.4	55.3	66.5	45.6	45.1	44.4
AV Graft	*%*	2.0	5.9	4.8	5.8	7.5	4.4	3.8	4.0	3.8
Unknown	*%*	0.0	0.0	0.0	0.0	0.0	0.0	0.3	0.1	0.3

VA Distribution – BC Picture



- More about this later…

VA BC Slides



- More about this later…

Objective 2
Variability of Fistula Failure Rates

Primary AVF failure

- Low AVF rates thought due to high primary failure rates

- Primary failure definitions not standardized
  - Early failure (thrombosis) or late failure (thrombosis or maturation failure)
  - immediate failure of AVF within 72 h of surgery, early dialysis suitability failure (3m), or late dialysis suitability failure (6m) (NAVAC definition)[4]

  - Lack of ability to supply dialysis with 2 needles for 6 – 12 consecutive HD sessions
  - Lack of ability to supply at least 75% of HD runs in 4 weeks with 2 needles
  - Inability to use on HD
  - Failure within 3 months of use

High Primary Failure Rate

Effect of Clopidogrel on Early Failure of Arteriovenous Fistulas for Hemodialysis

A Randomized Controlled Trial

Laura M. Dember, MD
Gerald J. Beck, PhD
Michael Allon, MD
James A. Delmez, MD
Bradley S. Dixon, MD
Arthur Greenberg, MD
Jonathan Himmelfarb, MD

Context The arteriovenous fistula is the preferred type of vascular access for hemodialysis because of lower thrombosis and infection rates and lower health care expenditures compared with synthetic grafts or central venous catheters. Early failure of fistulas due to thrombosis or inadequate maturation is a barrier to increasing the prevalence of fistulas among patients treated with hemodialysis. Small, inconclusive trials have suggested that antiplatelet agents may reduce thrombosis of new fistulas.

Objective To determine whether clopidogrel reduces early failure of hemodialysis fistulas.

Dember JAMA 2008

RCT Plavix on AVF thrombosis

- Pts (HD or within 6 months) eligible for AVF creation
- Plavix vs placebo day of AVF creation for 6 weeks
- Assessed at baseline, 6 weeks then monthly to assess fistula suitability for 5 months or 30 days of HD
- Planned 642 pts/ arm to achieve 30% ↓thrombosis rate

- Fistula Suitability:
  - failure to attain dialysis suitability (2 needles Qb ≥ 300 ml/min for 8/ 12 sessions:
  - or Use in 8 HD sessions:
  - overall failure 50% (48% plavix vs 52% placebo

Dember JAMA 2008

RCT Plavix vs Placebo on AVF thrombosis

- AVF Thrombosis (lack of bruit 6 weeks after creation)
  - 19% vs 12% plavix; P=0.018; RR 0.63

Table 3. Fistula Suitability Failure

	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)
By failure reason			
Fistula abandoned with no expectation of future use	115 (29.9)	134 (35.9)	0.85 (0.69-1.03)
Fistula not yet in use despite treatment with dialysis	57 (14.8)	47 (12.6)	1.17 (0.83-1.66)
Fistula in use during ascertainment period but failed to meet suitability criteria	66 (17.1)	41 (11.0)	1.56 (1.08-2.24)

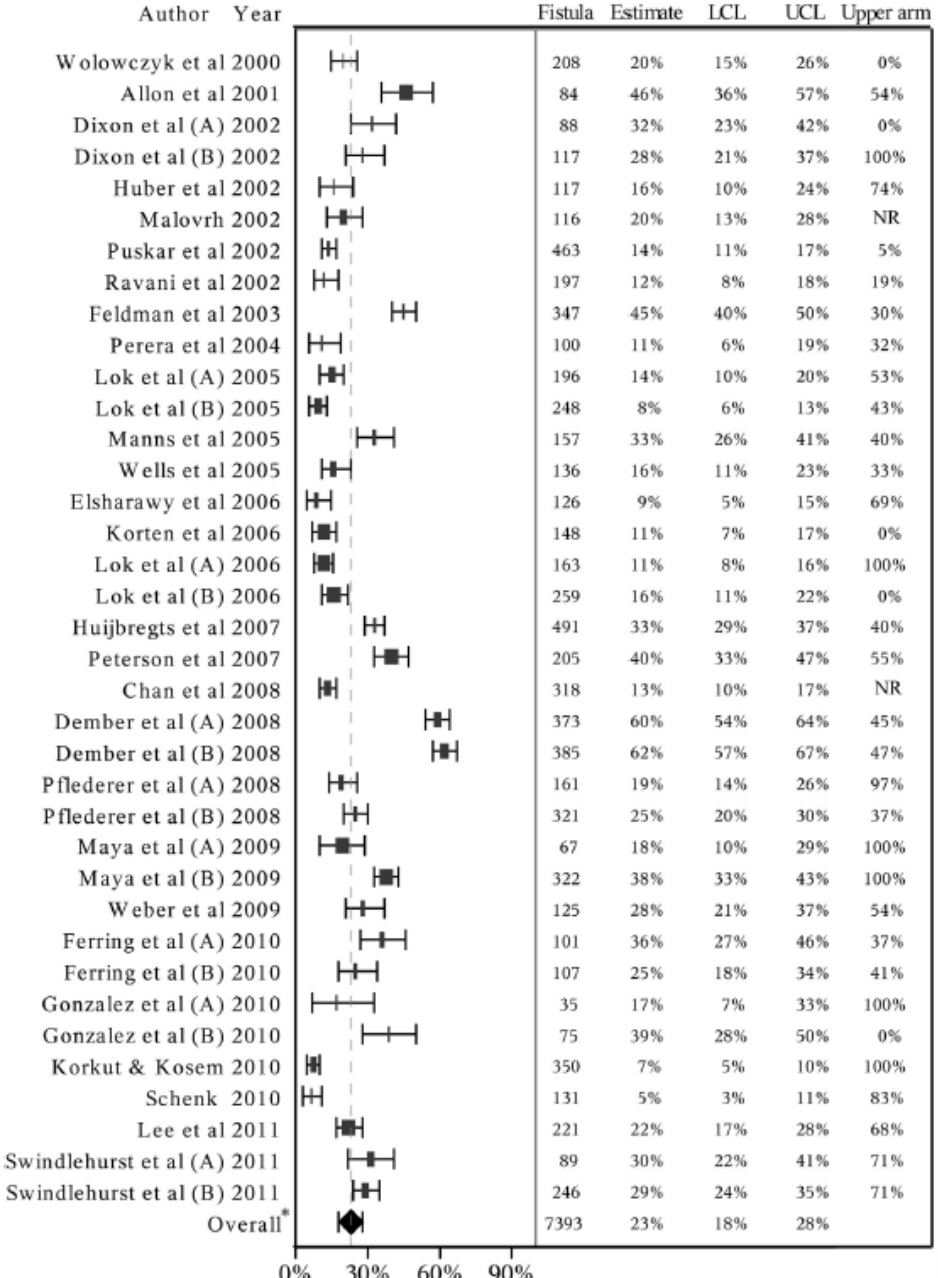
[a] Fifty-six of the 441 patients randomized to clopidogrel and 63 of the 436 patients randomized to placebo were not included because suitability was not ascertained (Figure).
[b] Relative risks were stratified for fistula location and center.
[c] $P = .40$.

What is a reasonable estimate of Primary Failure?

- Meta analysis AL Jashri (462 papers, 7400 AVF)
  - Pooled estimate of primary failure rate 23%
    - 28% lower arm and 23% for upper arm
    - 37% for elderly vs 27% non elderly ($p<0.001$)
  - Risk of primary failure decreased
    - with more recent publication date, more males and more upper arm AVFs

Al Jashri AJKD 2014

Variation in primary failure

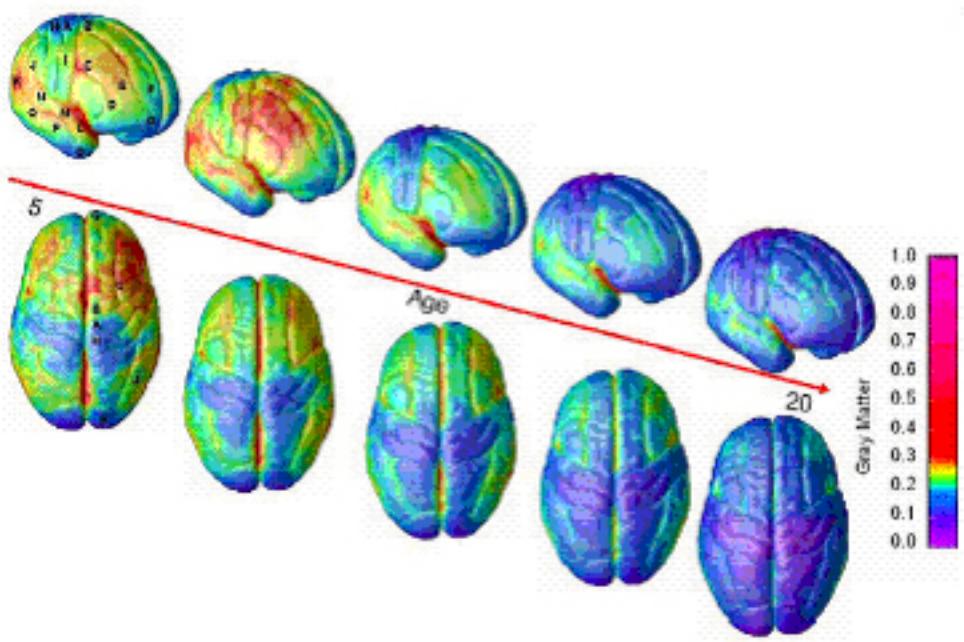


What is a reasonable estimate of AVF Patency?

- Primary patency (time to first intervention)
  - 67% at 1 year, 51 % at 2 years
  - Decrease in patency with more recent publications

- Secondary patency (time from access creation until abandon)
  - 82% at 1 year; 73% at 2 year
  - Improved patency rates more recently

Objective 3
Review physiology of maturation



NIMH 2004

What is Fistula Maturation? Physiology

- Anastamose artery to vein
  - immediate increase in blood flow
  - increase wall shear stress
  - Stimulates endothelial cells to release NO and other vasodilators

What is Fistula Maturation? Physiology

- ARCH STUDY (Caroli 2013):
  - flow & diameter consecutively over time

- Blood Flow
  - Baseline flow: 20 – 50 ml/min in artery
  - Post op day 1: 250 – 500 ml/min
  - Post op day 40: 500 – 2000ml/min

- Blood vessel dilation
  - Artery (radial) 2.5 mm → 3.5 mm → 4.5 mm (6 weeks)
  - Artery (brachial) 4mm → 4.5 mm → 5 mm
  - Vein (lower arm) 2.5 mm → 5 mm
  - Vein upper 3.3 mm → 6.4 mm

What is Fistula Maturation? Clinical

- Appropriate blood flow to supply dialysis?
  - Thrill+ (> 400ml/min); biphasic bruit
- Appropriate vessel diameter?
  - Palpable
- Appropriate depth under the skin?
  - palpable
- Appropriate straight length to allow rotation needle sites?
  - At least 10 cm
- Appropriate vessel wall strength?
  - Sense of vessel firmness

- **KDOQI Rules for Mature AVF – Rule of 6's**
  - By 6 weeks: 600 ml/min, 0.6 cm diameter, <0.6cm deep

Evidence for AVF maturation assessment

- HD AVF maturity: US Evaluation. Robbins ML, Radiol 2002
  - Retrospective observational study in 69 pts
  - Key study to showed that size and flow of AVF at 2 – 4 months predicted fistula maturation and adequacy for dialysis
  - No difference in flow or size from months 2 to 4 post op

  - Fistula with diameter **> 0.4 cm** were more likely suitable for HD
  - Fistula with flow **> 500 ml/min** more likely suitable for HD
  - Combining flow + diameter increased predictive value

  - Accuracy of experienced HD nurse predict fistula maturity using physical exam: 80%

Objective 4
Predictors of AVF maturation

AVF Failure: Patient Factors

- Age
- Gender (most studies but not all)
- PVD
- DM

Non Modifiable risk factors: Patient level

Nonmodifiable factor	*Level of best evidence*	*Best evidence suggests effect on patency*
Increased age	Meta-analysis[2]	Yes
Female sex	Meta-analysis[5]	No
Diabetes	Prospective series[6,7]	Yes
Hypotension	Prospective series[12,13]	Yes
Artery diameter	Meta-analysis[28]	Yes
Arteriosclerosis	Prospective series[29,30]	Yes
Arterial low	Prospective series[31-33]	Yes
Venous diameter	Meta-analysis[28]	Yes
Venous distensibility	Prospective eries[31,34]	Yes

Smith; J Vas Surgery 2012

Lok Prediction model

score	<2	2-3	3-7	>7
risk	low	mdm	high	Very high
Risk of non-maturation	24%	34%	50%	69%

- Risk score determined from: age, gender, DM, PVD
- When tested in other pt populations it did not do well

AVF Failure: Modifiable risk factors

Modifiable factor	*Level of best evidence*	*Best evidence suggests effect on patency*	*Limitations*
Smoking	Prospective series[8-11]	Yes	Negative effect on patency in smokers
Obesity (BMI >30)	Prospective series[14]	No	Evidence of effect seen in BMI >35
"Early" referral	Retrospective series[18]	Yes	No evidence of optimal timing of referral
Ultrasound imaging	RCT[19-21]	Yes	RCT evidence not applicable to majority of patients
Anastomosis type	RCT[36]	Yes	End to side (or functional end to side) preferred
Vascular staples/clips	Prospective series[37,38]	Yes	
Flow assessments	Prospective series[39,40]	Yes	Can be used as prognostic tool or prompt re-evaluation in
Antiplatelet therapy	Systematic review/RCT[41,42]	Yes/o	short-term benefit but paucity of data/largest trial found reduced thrombosis rate but no effect on cumulative patency
Systemic heparin use	RCT (see Table III)	No	Evidence suggests increased risk of bleeding with heparin given systemically
GTN patch therapy	Controlled experiment[44]	Potential for effect	Evidence of acute effect on AVF size and flow, no evidence of effects on patency
Far infrared therapy	RCT[45]	Yes	Single RCT evidence
Timing of first cannulation	Prospective observational study[46]	Yes	Cannulation before 14 days reduces patency rates
Cannulation technique	Cohort studies[50]	No	Limited data suggest shift in types of complications; no specific data regarding patency
Surveillance	Meta analysis[52,53]	No	AVF cumulative patency does not appear to be improved by surveillance

Smith; J Vas Surgery 2012

AVF Failure: Surgical Factors

- Degree of expertise
- Role of US mapping
- Technical details (clips vs sutures)
- Cephalic vein diameter
- Angle of anastamosis

AVF Failure: Surgical Factors

- Expertise: Surgeons with > 25 AVF creations during training (vs < 25) had 34% lower primary failure rates
- US mapping RCT (n= 218); (Ferring CJASN 2010)
  - Primary outcome (primary AVF failure): thrombosis + FTM
  - Significant reduction in Immediate thrombosis rate
  - trend to improved primary failure rate (21% vs 31%)
  - improved assisted primary survival 1 year 65% vs 80%
- Non-penetrating Clips vs sutures RCT (n=98)
  - Primary patency 1 year no difference (61% vs 69% clips)
  - Secondary patency improved (Zeebregts Br J Surgery 2004)
- Angle of anastamosis

Primary failure:
Effect of anastamosis angle

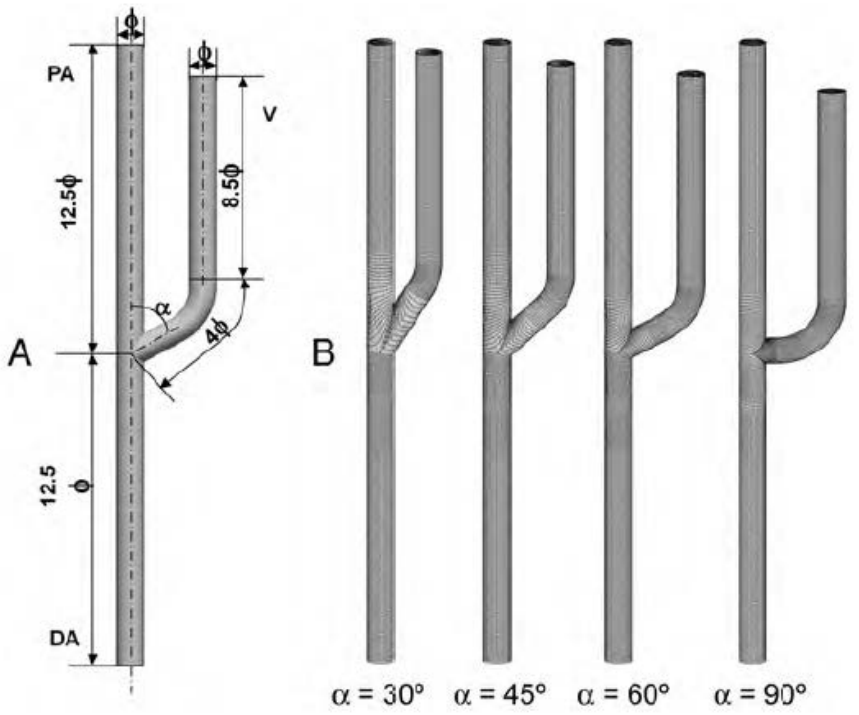
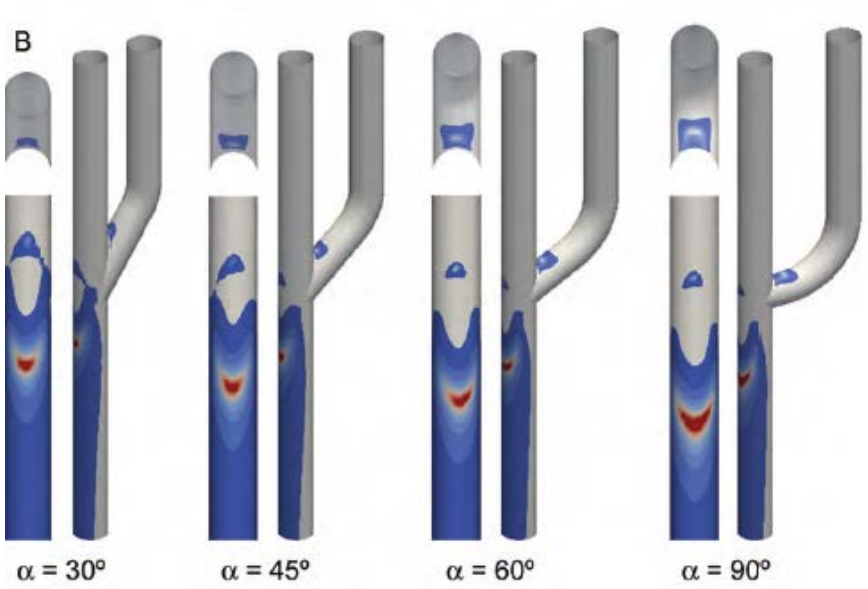


FIGURE 2: (A) Parametric model of 'side-to-end' radial-cephalic anastomosis used for the generation of meshes for numerical analyses. (B) The 3D meshes created with an anastomosis angle of 30°, 45°, 60° and 90°, respectively. V, vein (cephalic); PA, proximal artery; DA, distal artery; α, anastomotic angle; ϕ, diameter.

Ene-Iordache NDT 2013

Primary failure: Effect of anastamosis angle



- For side to end RCF AVF get altered flow at inner wall of the swing segment of vein and at arterial section of the anastamosis
- Less alteration of flow dynamics with smaller angles (30)
- Less neointimal hyperplasia and stenosis

Novel Predictors of Fistula Maturation – Patient factors

- Endothelial function reflects vessel health
- Flow mediated dilation (FMD) of Brachial artery is an established marker of endothelial function
  - Occlude brachial artery x 5 minutes, cause tissue ischemia and realease of vasodilators
  - Corresponding increase in hyperemia
  - Increase in brachial artery diameter correlated to degree of CAD, cardiac risk and mortality in cardiac patients

- Peripheral arterial tonometry (PAT) measures the blood flow at the finger tip; reflects microvascular endothelial function

Can endothelial function predict fistula maturation?

- 25 CKD pts had FMD pre AVF creation;
  - positive correlation between FMD baseline and change in diameter of artery and vein at 3 months post op [Owens et al JVA 2010]

- 28 CKD pts had FMD, PAT, PWV testing prior to AVF creation
  - CKD pts had impaired values compared to normal healthy pts
  - PAT (microvascular endothelial function) was predictive of AVF successful maturation (MacRAe submitted ASAIO)

Objective 5.
Novel Approaches to Maturation

Traditional Methods to promote maturation

- Surgical
  - Revision of AVF (redo anastamosis, superficialization)
  - ligation of collateral / accessory vein
- Radiology
  - PTA of stenosis (inflow, para-anastamotic or central vein)
  - coil embolization of collateral/ accessory vein

How successful are these interventions?

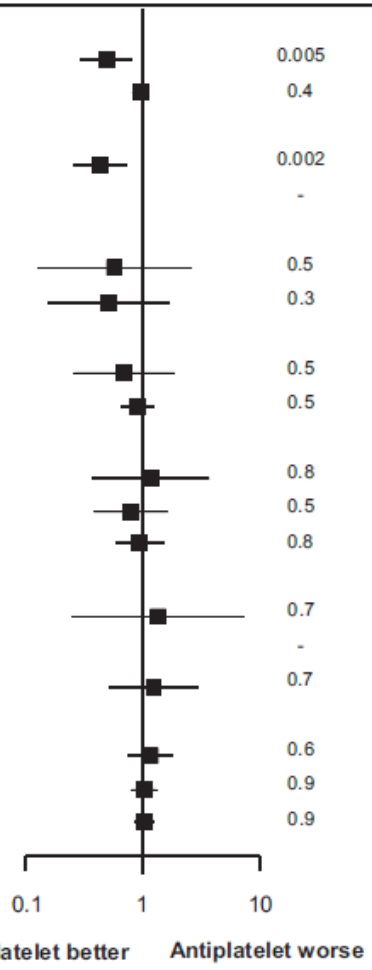
- Meta analysis of interventions for non maturing AVF (AVF that is between 4 – 24 weeks post op that is unsuitable for HD)
- Caveat: mostly poor quality studies, lack control group, definitions (?)

- 1 year primary patency 50%
- 1 year secondary patency of 75%
- Overall 9.3% complication rate
  - 5.5 % hematoma
  - 2.2% venous rupture
  - 1% steal

Vermoolen J Vasc Surgery 2009

Antiplatelets to promote maturation

Outcome	Studies	Events/Total: Antiplatelet	Events/Total: Control	Relative risk (95% CI)	Relative risk (95% CI)	P value for effect	I^2 (%)
Dialysis vascular access failure (thrombosis or loss of patency)							
Fistula	6	67/622	121/620	0.49 (0.30 to 0.81)		0.005	29
Graft	3	193/508	181/448	0.94 (0.80 to 1.10)		0.4	0
Early thrombosis (before 8 weeks)							
Fistula	5	61/553	116/552	0.43 (0.26 to 0.73)		0.002	25
Graft	-	-	-	-		-	-
Failure to attain suitability for dialysis							
Fistula	2	240/404	230/390	0.57 (0.13 to 2.51)		0.5	79
Graft	1	4/321	8/328	0.51 (0.16 to 1.68)		0.3	-
Need for access intervention							
Fistula	1	7/435	10/431	0.69 (0.26 to 1.83)		0.5	-
Graft	1	93/321	103/328	0.89 (0.64 to 1.25)		0.5	-
Major bleeding							
Fistula	3	6/505	5/500	1.15 (0.37 to 3.61)		0.8	0
Graft	2	19/405	13/352	0.79 (0.39 to 1.64)		0.5	0
All trials combined	11	39/1983	32/1947	0.93 (0.58 to 1.49)		0.8	0
Minor bleeding							
Fistula	2	6/64	4/64	1.33 (0.25 to 7.14)		0.7	34
Graft	-	-	-	-		-	-
All trials combined	4	11/118	9/119	1.22 (0.51 to 2.91)		0.7	0
Withdrawal from antiplatelet treatment							
Fistula	2	39/449	34/446	1.14 (0.74 to 1.78)		0.6	0
Graft	3	106/508	94/448	1.01 (0.67 to 1.54)		0.9	48
All trials combined	8	167/1014	154/959	1.01 (0.84 to 1.20)		0.9	0



Palmer AJKD 2013

Pharmacologic approach to promote maturation

- **Transdermal triglycerin nitrate**
  - may increase blood flow in new created AVF

- Demonstrated increased AVF diameter and flow a few hours after topical application vs control, no long term studies

Akin, World J surgery 2002;26; 1256-9

Infra red therapy (FIR) to promote maturation

- Improves endothelial function in coronary arteries (like heat) by upregulating eNOS→ dilation

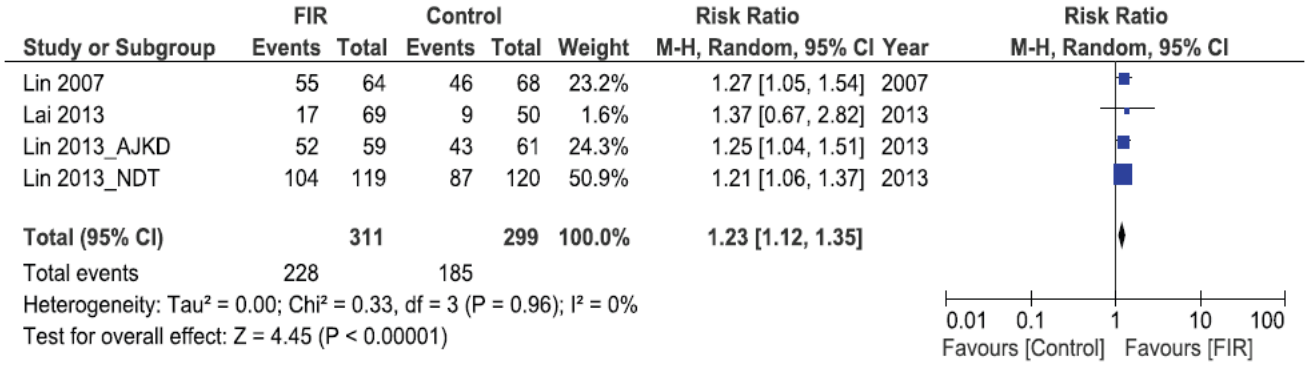
- Improved pain regulation in phantom limb
- Activate fibroblasts for better wound healing
- Stimulate autonomic nervous system in HD pts

- Improved NO formation, decreased inflammation, improve endothelial function

- Apply 20 - 30 cm above AVF for 40 minutes 3x week

Infra red therapy to promote maturation

- Meta-analysis of 4 RCT studies
  - 3/ 4 studies included pts on HD with previous AVF
  - 1 study newly formed AVF not on HD
  - 666 pts, 340 pts with FIR
  - Primary AVF patency (unassisted)at 12 months improved



Study or Subgroup	FIR Events	FIR Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Lin 2007	55	64	46	68	23.2%	1.27 [1.05, 1.54]	2007
Lai 2013	17	69	9	50	1.6%	1.37 [0.67, 2.82]	2013
Lin 2013_AJKD	52	59	43	61	24.3%	1.25 [1.04, 1.51]	2013
Lin 2013_NDT	104	119	87	120	50.9%	1.21 [1.06, 1.37]	2013
Total (95% CI)		**311**		**299**	**100.0%**	**1.23 [1.12, 1.35]**	
Total events	228		185				

Heterogeneity: Tau² = 0.00; Chi² = 0.33, df = 3 (P = 0.96); I² = 0%
Test for overall effect: Z = 4.45 (P < 0.00001)

Figure 2. Forest Plot showing Primary AVFs patency at 12 months.
doi:10.1371/journal.pone.0104931.g002

Bashar Plos One 2014

Infrared therapy for failing AVF/ AVG

- AVF or AVG with history of 2 or more angioplasties,

- Randomly assigned to FIR vs regular radiation therapy
- Excluded those with multiple lesions that were outside the territory of the radiation field, endovascular stent

- 40 minutes 3 x per week either before, during or after hd
- FIR placed 25 cm above the site of the major lesion
- Secondary patency at 12 months following procedure significantly improved

Lai Eur J Vas Surg 2013

Exercise
Promotion of maturation

- Exercise Pre AVF creation (AM J Med Sci 2003 Leaf DA)
  - 5 pts, GFR 30 l/min x 6 weeks forearm exercise training
  - Baseline US measurement cephalic vein in active arm (non dominant) and control arm
  - Exercise increased vein by 0.06 cm
- Exercise After AVF creation (ASAIO J 2003; Oder TF)
  - Effect of hand exercises on the diameter of AVF
  - 23 pts with new AVF
  - Measured cephalic vein pre and post hand ball squeezing x 5 minutes
  - AVF diameter increased in 20/23 pts; mean change 9.3% $p<0.001$

Regional nerve block Promotion of maturation

- Axillary block
  - Annals vascular surgery 2007; Laskowski IA
  - 26 pts and measured distal cephalic veins pre and post axillary block
  - Cephalic vein diameter increased from 0.29 to 0.34 cm (p=0.008)
- Supraclavicular Brachial plexus block
  - JVA 2011; Reynolds TS
  - 34 pts had baseline vein measurements pre and post block
  - Lower cephalic vein increased by 34%; upper cephalic vein 24%
  - Basilic vein increased 31%; brachial vein 8%
  - Primary patency 83% of the 23 pts with follow up

Regional nerve block Promotion of maturation

- Infraclavicular brachial plexus block vs local anaesthetic RCT
  - 60 pts; for planned RCF AVF
  - measured radial artery flow pre and post anaesthetic
  - AVF flow higher at 3 hours, 7 days and 8 weeks in IB

Variable[a]	*Group IB* (*n* = 30)	*Group C* (*n* = 30)	P
Radial artery flow, mL/min			
Before anesthesia	38 ± 5.6	37.6 ± 6.9	.26
After anesthesia	56 ± 8.6	40.7 ± 6.11	.0001
Fistula flow, mL/min			
At 3 hours	69.6 ± 7.9	44.8 ± 13.8	.0001
At 7 days	210.6 ± 30.9	129 ± 36.1	.0001
At 8 weeks	680.6 ± 96.7	405.3 ± 76.2	.0001
Thrill presence	28 (100)	27 (90)	.31

Group C, Control; *Group IB*, infraclavicular block.
[a]Data are presented as mean ± standard deviation, or No. (%).

Sahin J Vas Surgery 2011

Objective 7
Upcoming VA trials

Does Brachial plexus block lead to better AVF patency?

- RCT underway brachial plexus block vs local
  - Primary outcome: Primary patency at 3 months
  - Secondary outcomes
    - primary patency 12m,
    - secondary patency 1, 3, 12 m;
    - diameter vein,
    - flow at first hd session

Macfarlane Au, Trials 2013

Ongoing trial
Antiplatelets & Fish Oil to promote maturation

- RCT low dose ASA 100 mg/d and /or4 g fish oil in 1200 pts (Fish oil and Aspirin in Vascular Access Outcomes in Renal Disease study : **FAVOUReD stduy**
- Assume 25% failure rate at 3 months; 1200 pts needed
  - Start 1 day pre op x 3 months
  - Primary outcome: unassisted patency of AVF at 3 months
  - Secondary outcome:
    - functional patency at 6m (ability to use for HD without the need for an alternative access) and 12m;
    - primary patency
    - Assisted patency (time creation until abandonment)
  - Active and recruiting since 2009

Impact of Fish Oil on AVG

- 200 pts randomized to placebo vs 4 g fish oil on day 7 post AVG creation

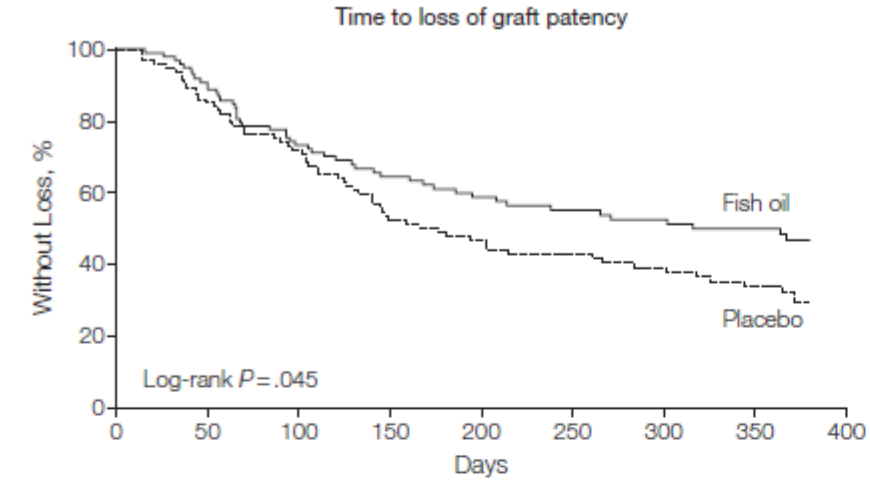
- Primary outcome: percentage of AVG that thrombosed
  - 48% vs 62 % RR 0.78; p=0.06

BUT

- Thrombosis: 1.71 vs 3.41/ 1000 days; p<0.001
- Interventions 2.82 vs 4.92/ 1000 days; p<0.001

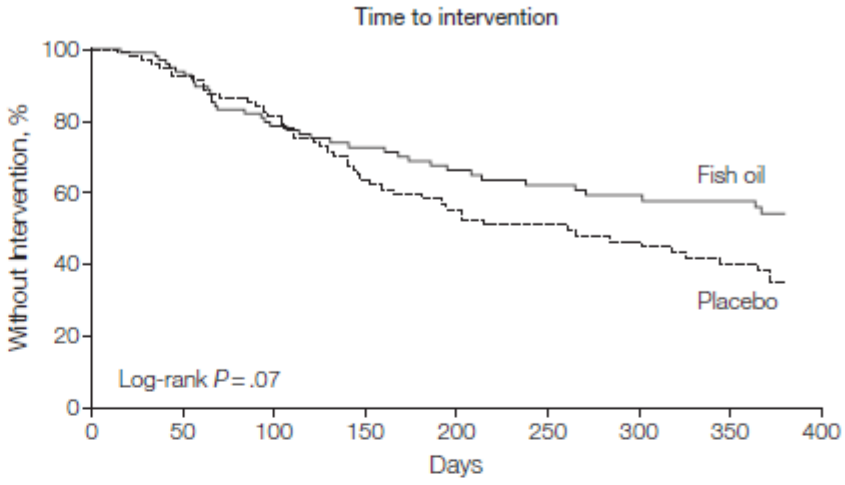
Lok JAMA 2012

Figure 3. Kaplan-Meier Estimates of Time to First Loss of Native Graft Patency, Thrombosis, Intervention, and Cardiovascular Event



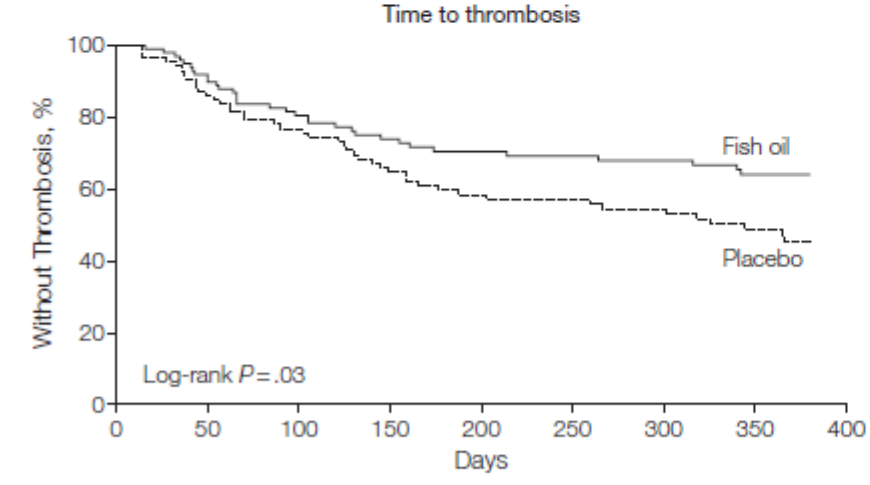
o. at risk

Fish oil	99	89	69	57	49	44	40	37
Placebo	97	79	64	46	38	34	30	25



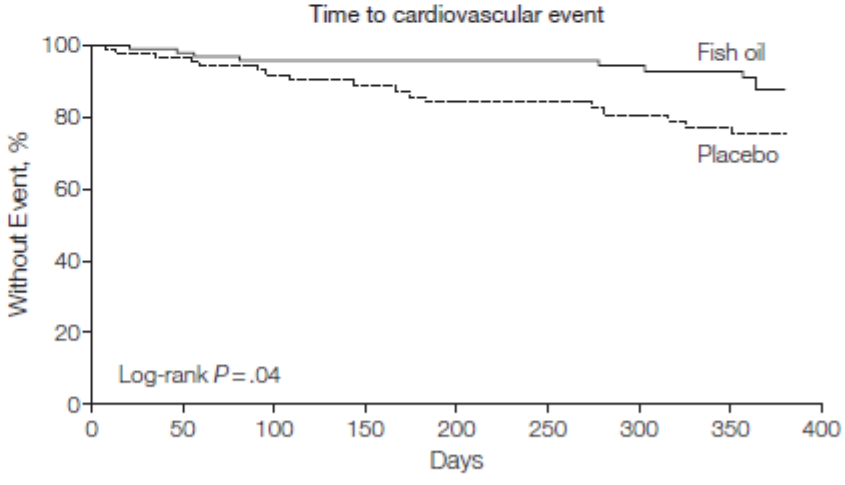
No. at risk

Fish oil	99	90	69	57	49	44	40	37
Placebo	97	81	66	48	38	34	30	25



o. at risk

Fish oil	99	90	75	65	59	56	52	47
Placebo	97	78	65	52	44	42	39	34



No. at risk

Fish oil	99	93	82	74	70	67	62	58
Placebo	97	81	68	58	51	50	47	44

Median time to primary unassisted patency was 354 days in the fish oil group and 176 days in the placebo group. Intervention indicates radiological or surgical intervention to maintain graft patency.

Results to be presented at ASN HD Fistula maturation Trial

- **Hemodialysis Fistula Maturation (HFM)Trial**
  - Prospective multicentre cohort; 600 pts followed over 4 years
  - Primary outcome: unassisted maturation:
    - successful use of AVF for dialysis for 4 weeks without maturation enhancing procedures
  - Secondary outcome: assisted maturation, US based maturation, fistula procedures, fistula abandonment, CVC use
  - Measurements:
    - pre – op artery and vein diameter,
    - FMD and NTG mediated dilation brachial artery; PWV (carotid fem and carotid radial)
    - Vein tissue samples
    - US post op day 1, 2 week, 6 weeks

Ongoing Trial
Endovascular creation of AVF

- Novel Endovascular Access Trial (NEAT)
  - Safety study to assess endovascular approach to making AVF
  - 6 month follow up study; planned 70 pts
  - Primary outcome: number of pts with adverse event
  - Secondary outcome: percent of fistula that can provide HD over a 4 week period
  - Status: recruiting; pts entered into study

Upcoming Trials

- The **ACCESS** Pilot Trial: **A** clinical trial **C**omparing **C**atheters to fistulas in **E**lderly patients **S**tarting dialysi**S**
  - 40 pts > 65yrs on HD with CVC deemed eligible for AVF randomized to AVF creation vs remain on CVC
  - 30 month study; 6 m F/U
    - Primary outcome feasibility to recruit
    - Secondary outcomes: adverse events, reasons for exclusion/ refusal
  - Status: not yet started

Upcoming Trials: Implanted devices & maturation

- Vascugel implant
  - cultured human aortic endothelial cells in a gel matrix
  - Implanted at time of AVF creation to determine if improves time to maturation

- Optiflow anastamotic connector device implanted at time of AVF creation

Upcoming Trials: Exercise & Fistula maturation

- RCT Effect of **8 week Handgrip exercise** on fistula maturation
  - Primary outcome vein diameter at 3 months
  - N= 30 pts (UK)

- RCT Effect of **exercise** and improved **NO** availability
  - Placebo vs hand grip training (15 min 2x/ day) vs 15 mg NTG paste vs NO + exercise
  - Intervention starts 4 weeks post AVF creation x 4 weeks
  - Primary outcome fistula maturation at 3 months

Upcoming Trials
Buttonhole Cannulation at Home

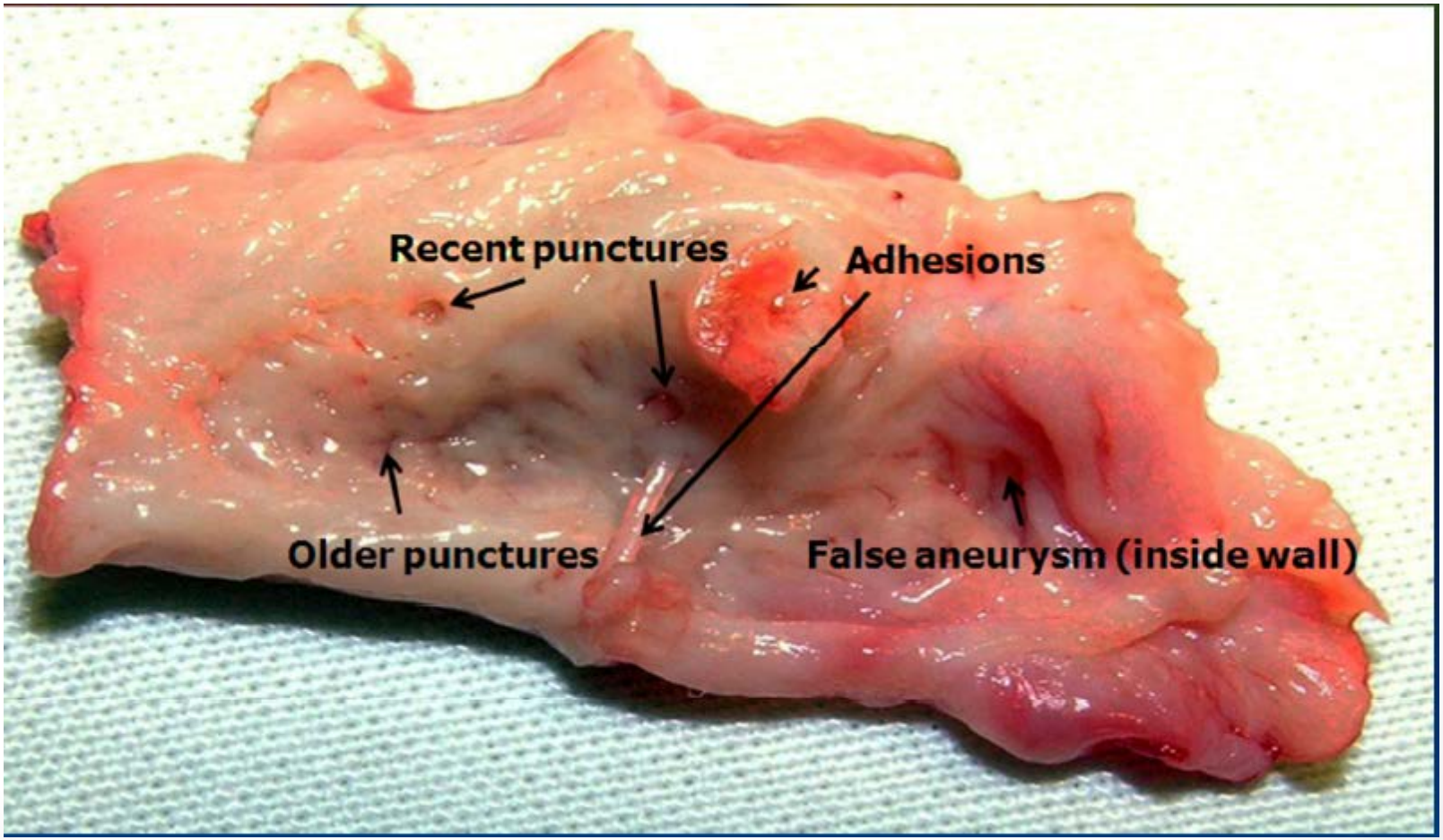
Buttonhole vs Step Ladder Cannulation in High Dose Hemodialysis. Pilot Study

- Primary Objective: To determine feasibility of
  - randomizing Home HD patients to SL versus BH cannulation
  - coordinating multiple Canadian sites

- Secondary Objectives:
  - home HD training time
  - reduced overall cost,
  - AVF complications of infection, radiologic/surgical interventions, re-trains for needle insertion difficulties, hematoma, aneurysm formation, missed insertions,
  - Pain with needling

Zimmerman; NCT01962025

And just a few words on…. Impact of Needling



M Rawa MD, from Lynda Ball Cannulation Talk

Needle Technique and AVF Survival

- Technique may impact AVF survival
  - blood vessel puncture incites local trauma and thrombus formation, venous neointimal hyperplasia
  - Repeated puncture results in weakness and aneurysm
  - 26% of needle infiltration result in AVF thrombosis*
- Area wall, rope ladder and buttonhole techniques

*Lee AJKD 2006

Impact of the Needle

- Flow Dynamics
  - Needle changes wall shear stress to turbulent flow
  - Alters the fluid dynamics for up to 10 cm downstream of needle
  - Turbulent flow associated with
    - Decreased NO production and NO release from endothelial cells
    - Denuding of endothelium (↓# Endo cells)
- Inflammation and trauma
  - Needle incites inflammation and thrombus formation
  - Smaller is better?
- Velocity
  - Velocity of blood through a smaller needle is higher→ ? More shear stress with smaller needles

Role of Needle Direction - Venous

- Venous needle recommended to be in same direction of blood flow (antegrade)
  - To minimize hematoma formation
  - To reduce tendency for pseudoaneurysm upon needle withdrawal
- Needle with back eye no effect in this position

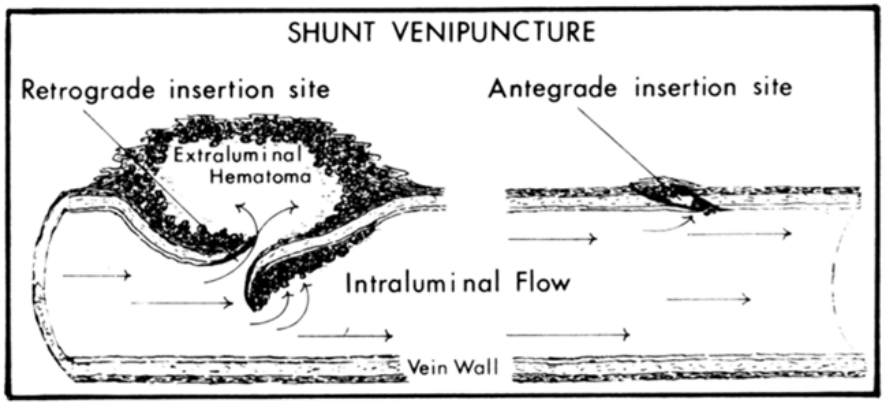
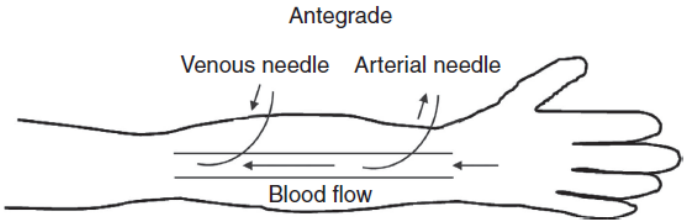
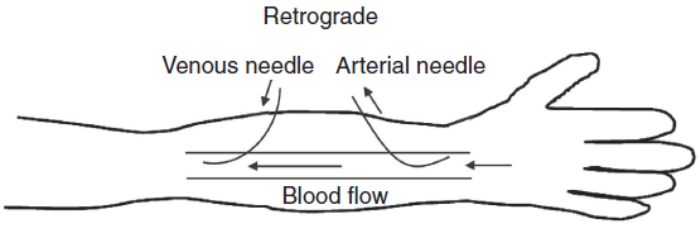


Figure 1. Potential sequelae of antegrade and retrograde puncture of an arterialized vein.

Role of Needle Direction Arterial

?





- Antegrade
  - High amount of flow enters the back eye of the needle
  - Lots of oscillatory shear near the needle: risk of IH and stenosis near arterial tip
- Retrograde
  - Flow is much smoother with less oscillating shear

Fulker et al. 2014

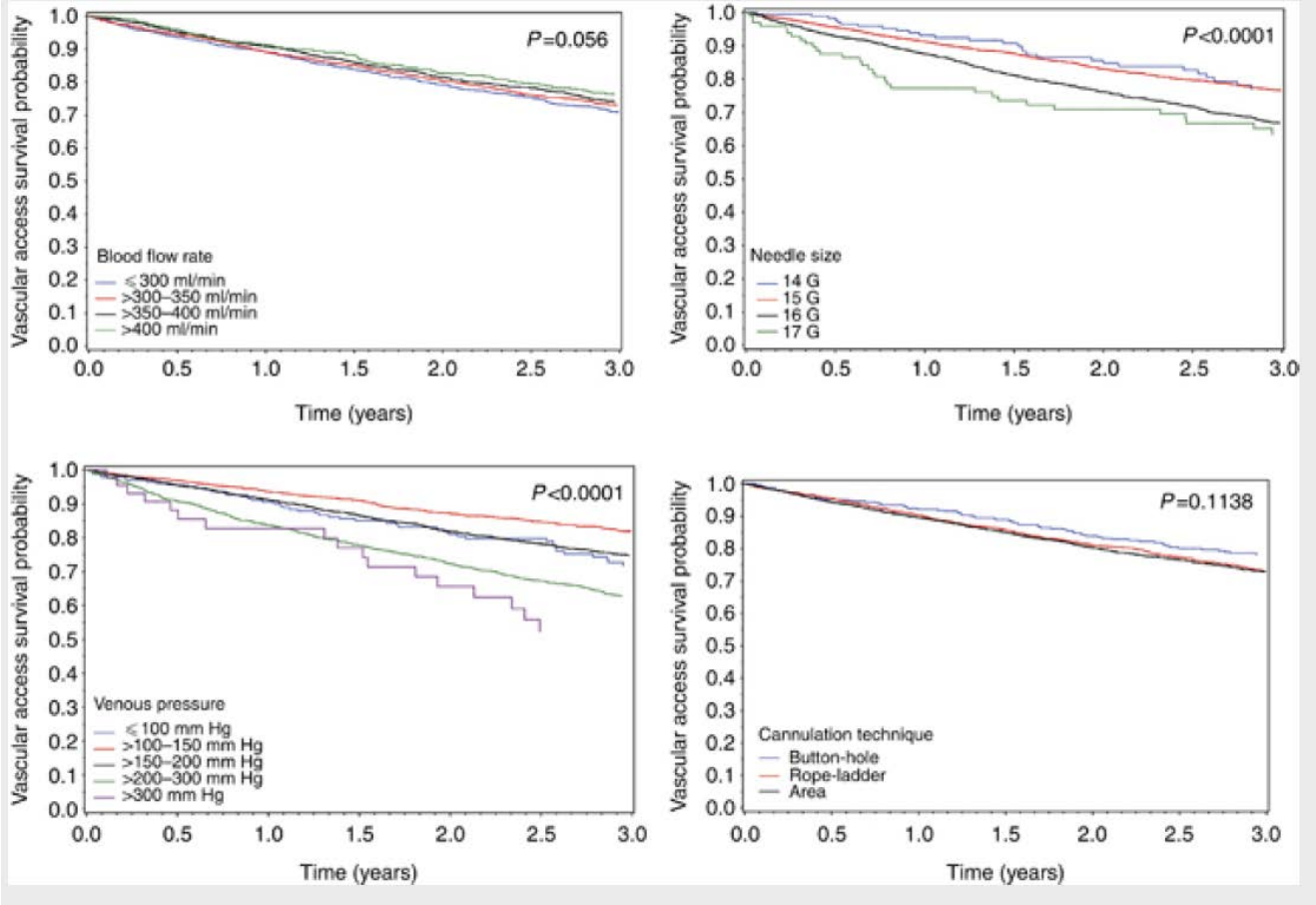
Cannulation Technique and Access Survival

Observational study 7000 pts with VA cannulation data obtained in April 2009 and VA outcomes assessed in 2012

- Qb: Median Qb 300 ml/min;
  - Poland 54% had Qb <300; Italy 40% had Qb>400 ml/min
- Needle size and orientation:
  - 15G used in 63% of pts; 16G in32%
  - Arterial puncture antegrade direction for 57% of pts (99% in poland)
- Cannulation technique:
  - **Area wall** 66%; 28 % rope ladder and 6% BH
- Primary outcome: Access failure by 12 months

Parisotto KI 2014

Access survival curves



- Conclusions limited by the observational design
- Hypothesis generating : impact of Qb, needle size and pressure limits

Parisotto KI 2014

Recognizing the impact of Cannulation Factors on Access Failure

- Cannulation technqiue: needle type, size
- Blood pump speed
- Pressure limits

Summary

- The rate of fistula failure after creation seems to widely varies
- Fistula flow rates increase immediately after creation
- ASA at time of AVF creation will reduce the thrombosis rate
- Fish oil for AVG at time of creation will reduce intervention rates and improve time to thrombosis

Summary

- Surgical factors are important determinants of AVF success
  - Smaller Angle of anastamosis has better flow characteristics
  - Brachial plexus blocks associated with vein dilation and increased artery flow
- Surgical and radiology Interventions should be attempted to promote maturation
- Important VA trials on the way……..

Thank You!

Questions?