

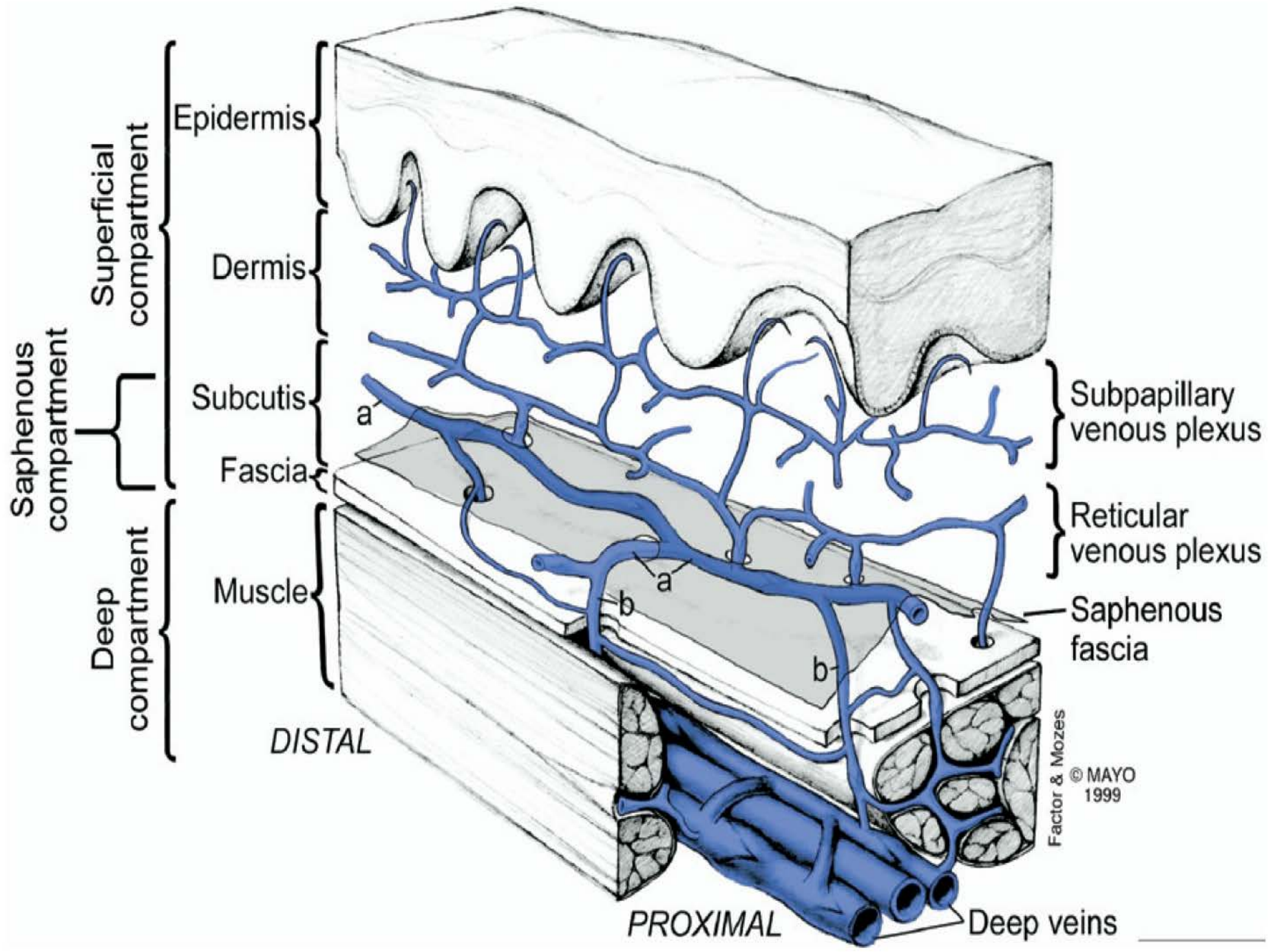
# THE EPIDEMIOLOGY OF CHRONIC VENOUS DISEASE

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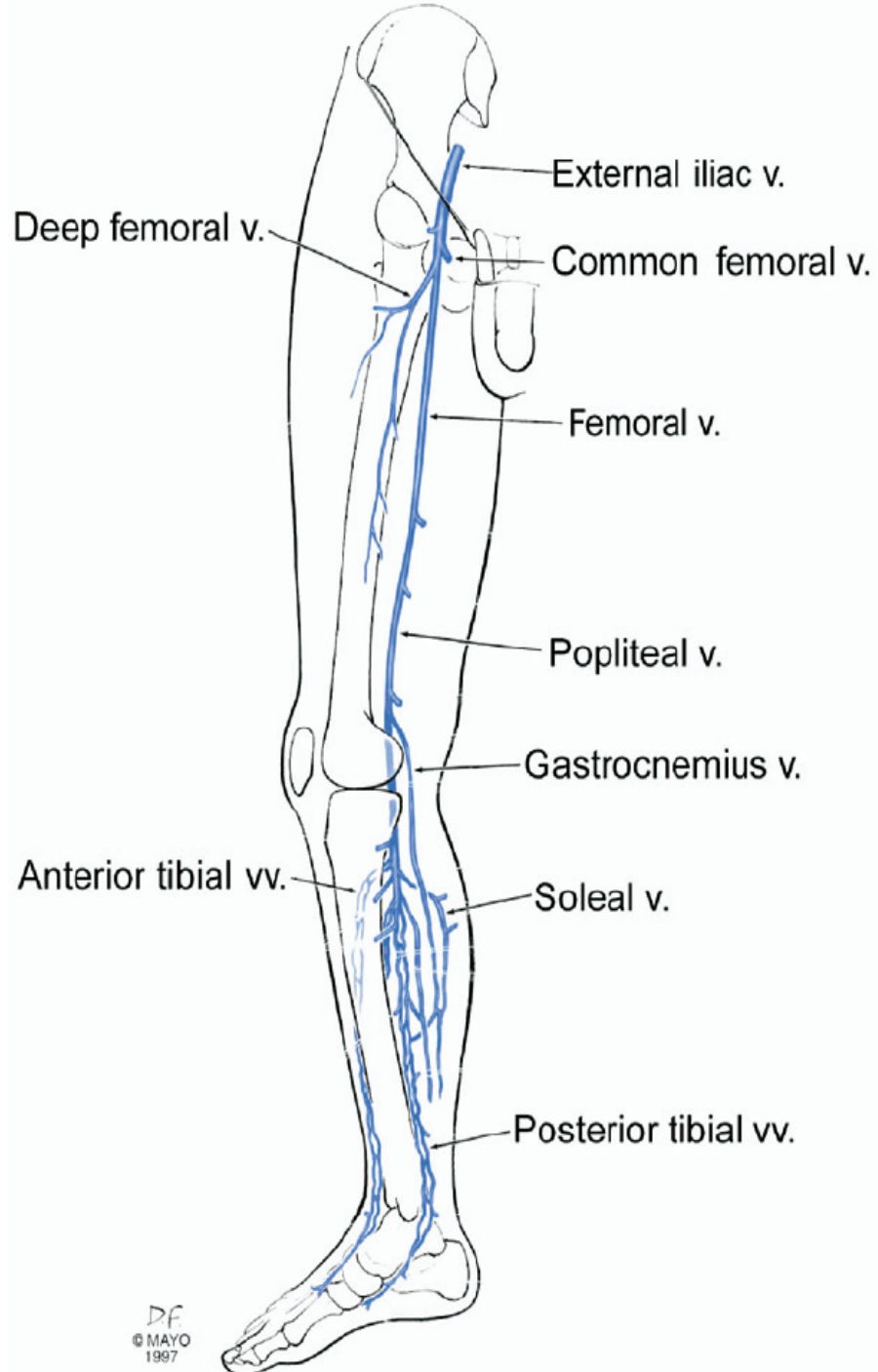
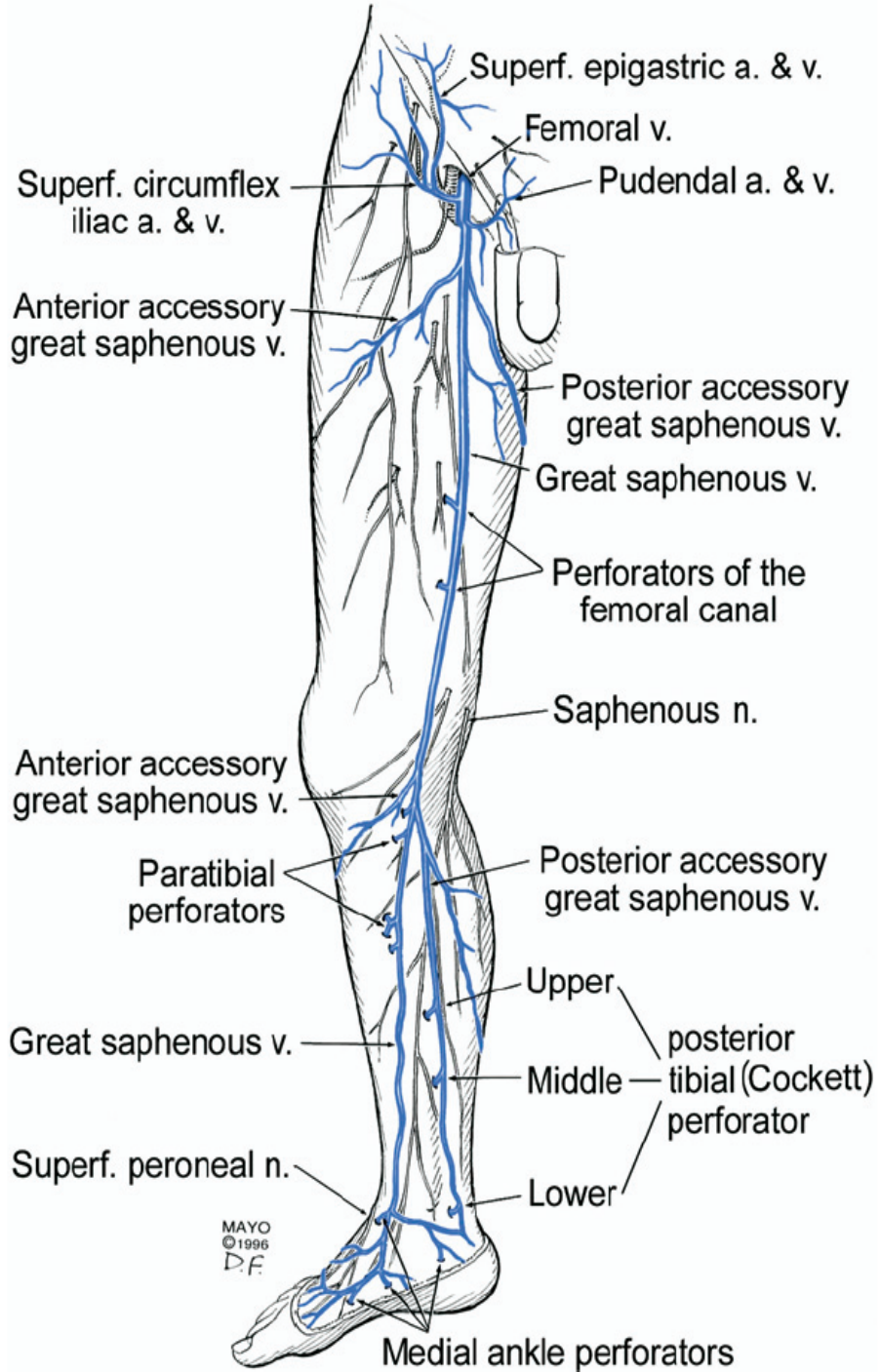
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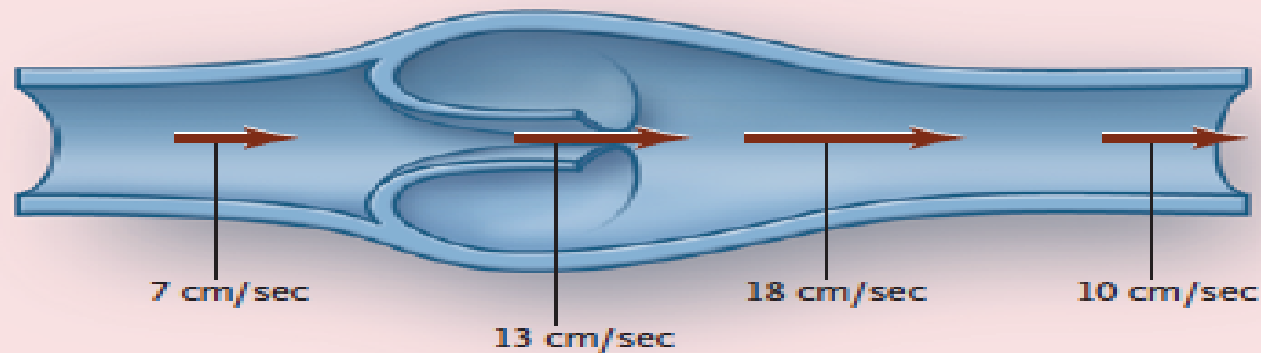
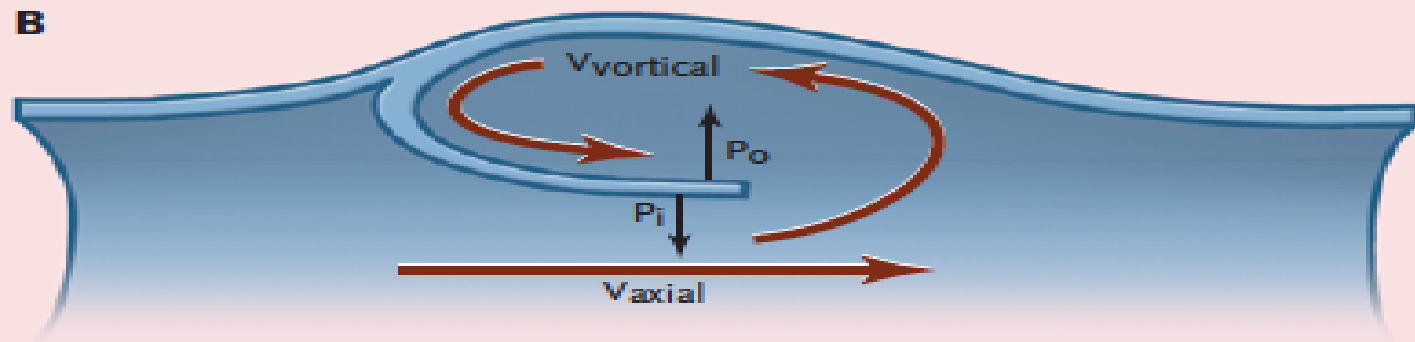
# Disclosures

- Financial
  - Intercept Pharmaceuticals (Mild) – DSMB
  - Merck Pharmaceuticals (Mild) - Advisory Board
- Intellectual
  - None



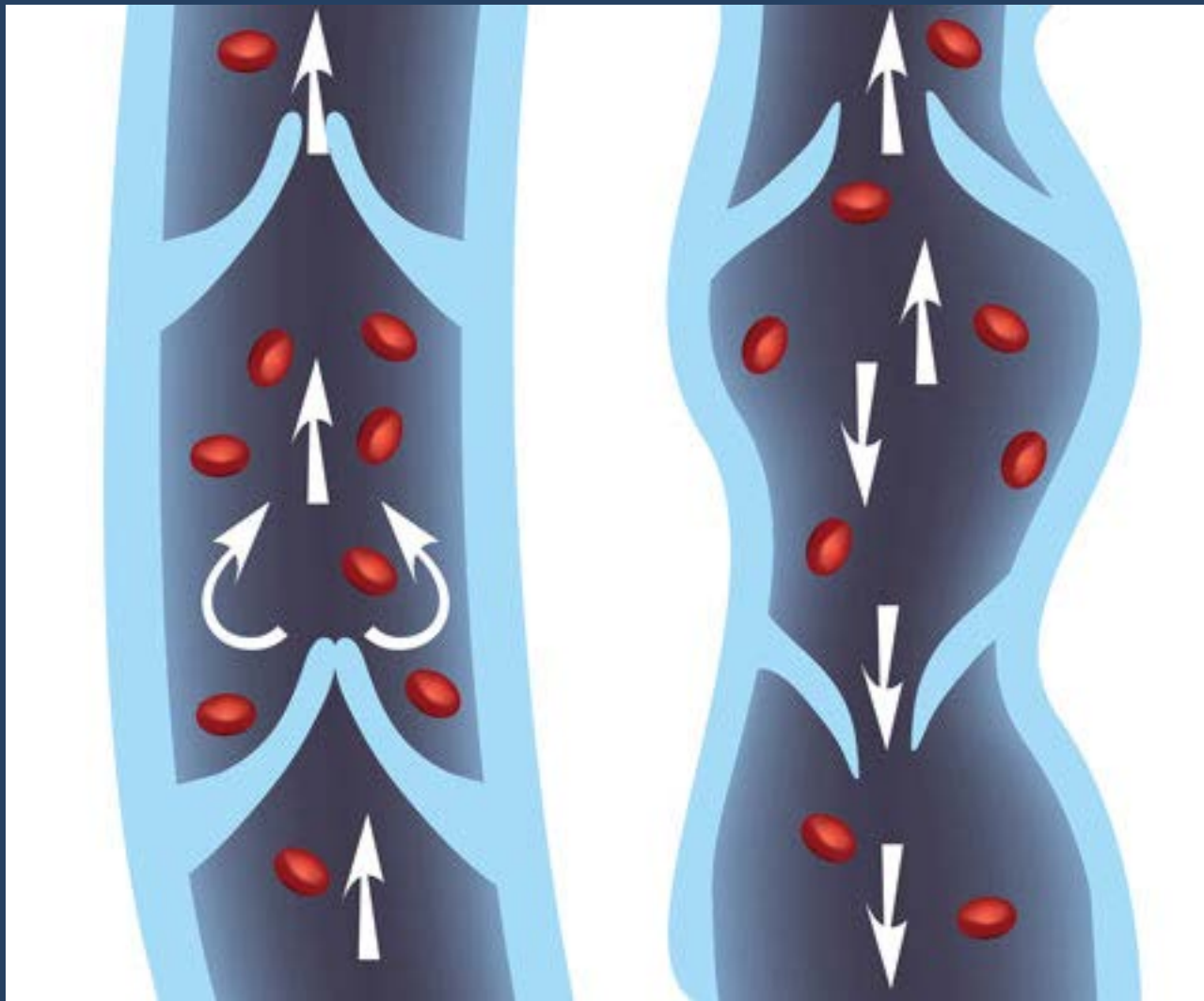
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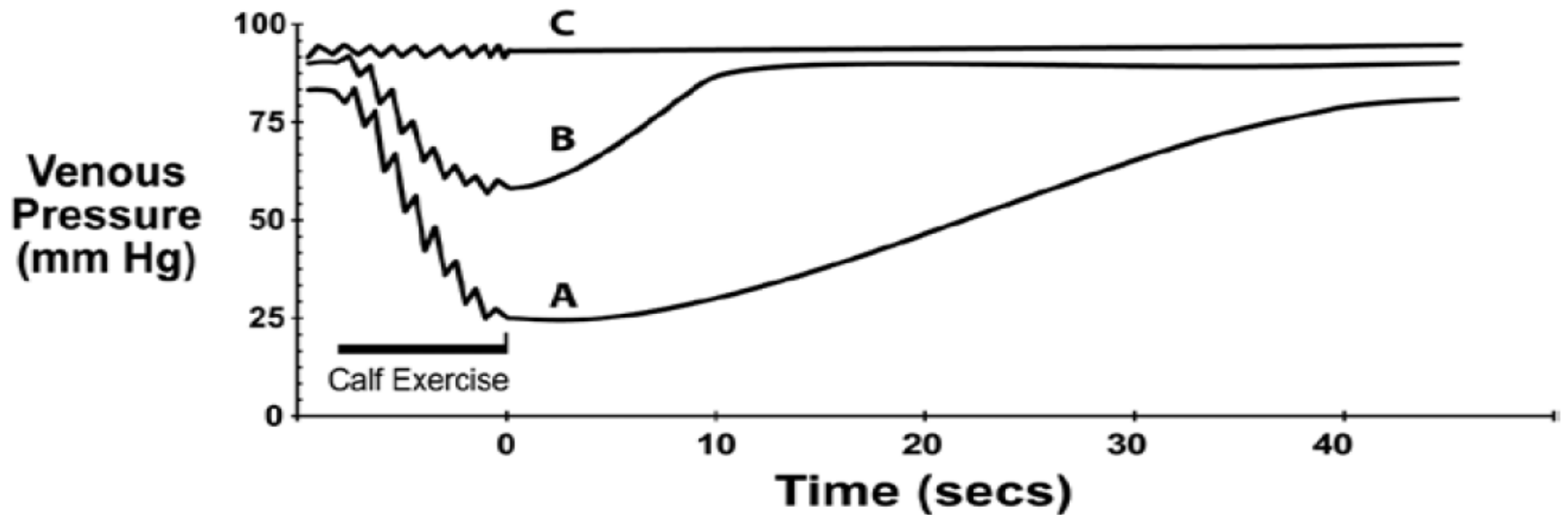


**A****B**

**Figure 3. Velocity of Blood Flow through a Venous Valve (Panel A) and Forces Acting on a Venous Valve Leaflet (Panel B).**

In Panel A, the reduced cross-sectional area between the valve leaflets produces a proximally directed jet of increased axial velocity. In Panel B, axial flow between the leaflets generates a pressure ( $P_o$ ) that tends to keep the leaflet in the open position, and vortical flow in the valve pocket generates a pressure ( $P_i$ ) that tends to close the leaflet. These pressures depend on the respective flow velocities ( $V_{vortical}$  and  $V_{axial}$ ); pressure is inversely related to velocity. (Adapted from Lurie et al.<sup>49</sup> with the permission of the publisher.)





**Figure 1.** Illustrative ambulatory foot venous pressure measurements during exercise and at rest over time in the standing position. **A**, Normal venous pressure. The resting standing venous pressure is  $\approx 80$  to  $90$  mm Hg. The pressure drops to  $\approx 20$  to  $30$  mm Hg (or  $>50\%$  decrease) with calf exercise. The return in pressure is gradual, with refill taking  $>20$  seconds. **B**, Abnormal venous pressure with venous reflux. The resting standing pressure is usually higher than normal. The drop in pressure with exercise is blunted ( $<50\%$  decrease). The return in venous pressure to the resting level is rapid because of a short refill time ( $<20$  seconds). **C**, Abnormal venous pressure with venous obstruction. Resting standing venous pressure is usually higher than normal. There is minimal-to-no drop in pressure with exercise.

# Symptoms

- Aching
- Heaviness
- Leg Fullness
- Nocturnal Leg Cramps
- Itching
- Tingling/Burning
- Restless legs







**B**







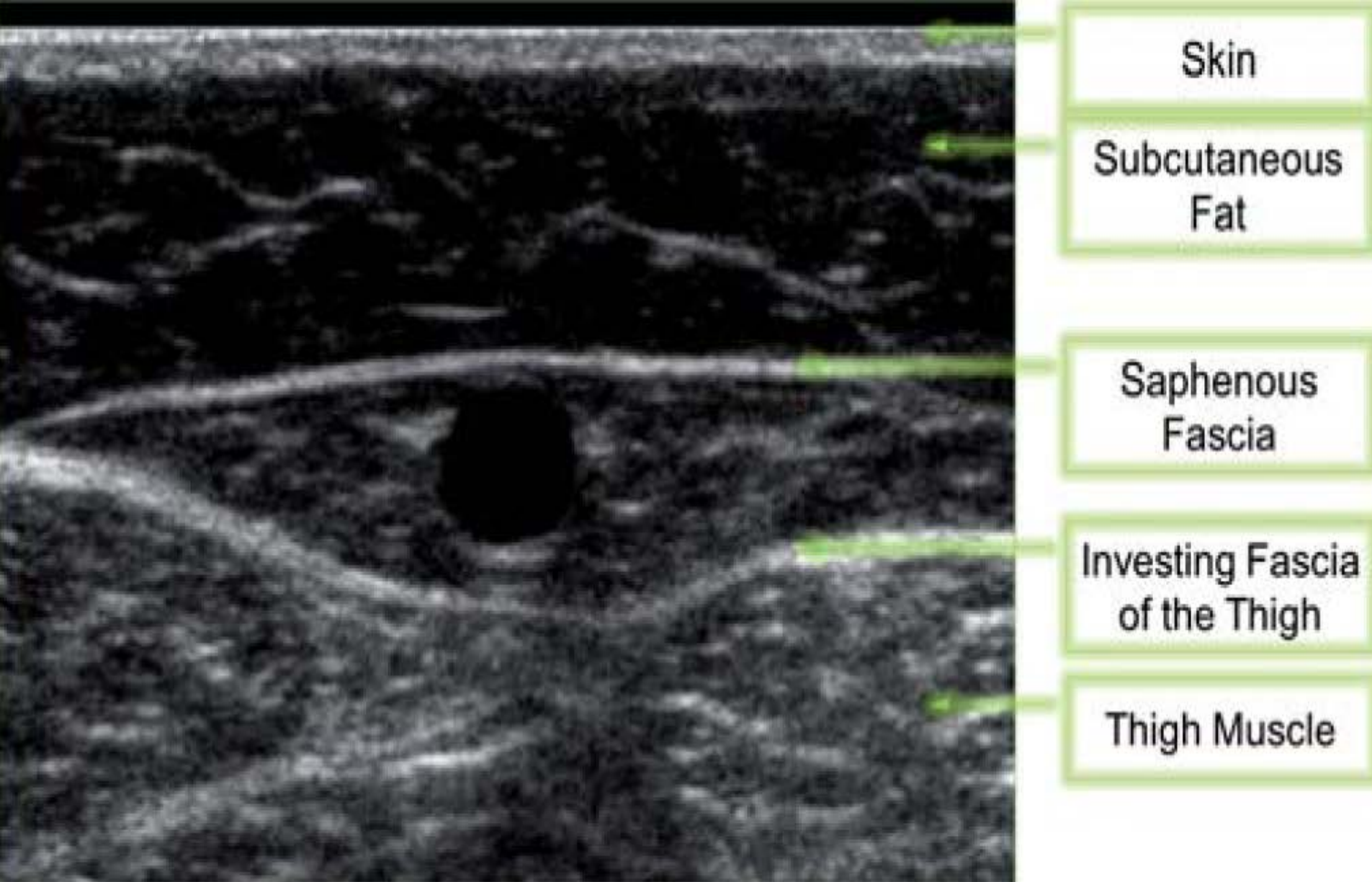






**Table 1.** Revised Clinical Classification of Chronic Venous Disease of the Leg.\*

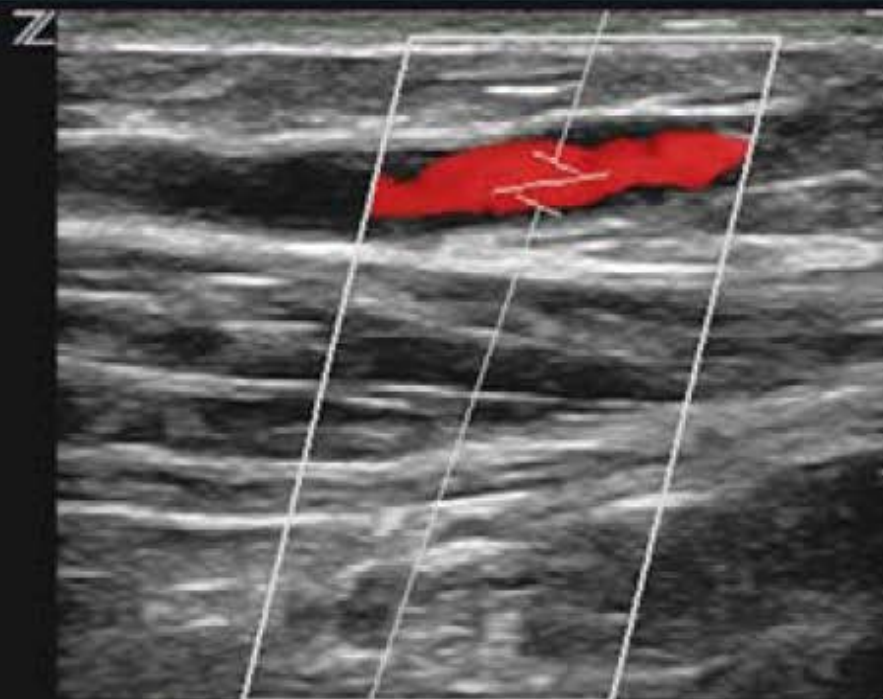
Class	Definition	Comments
C <sub>0</sub>	No visible or palpable signs of venous disease	
C <sub>1</sub>	Telangiectases, reticular veins, malleolar flare	Telangiectases defined by dilated intradermal venules <1 mm diameter Reticular veins defined by dilated, nonpalpable, subdermal veins ≤3 mm in diameter
C <sub>2</sub>	Varicose veins	Dilated, palpable, subcutaneous veins generally >3 mm in diameter
C <sub>3</sub>	Edema without skin changes	
C <sub>4</sub>	Skin changes ascribed to venous disease	
C <sub>4A</sub>		Pigmentation, venous eczema, or both
C <sub>4B</sub>		Lipodermatosclerosis, atrophie blanche, or both
C <sub>5</sub>	Skin changes with healed ulceration	
C <sub>6</sub>	Skin changes with active ulceration	



**Fig. 10:** The Saphenous Fascial Envelope. The normal fascial envelope of the GSV.

+ 5.0  
RIGHT  
GSV DIST

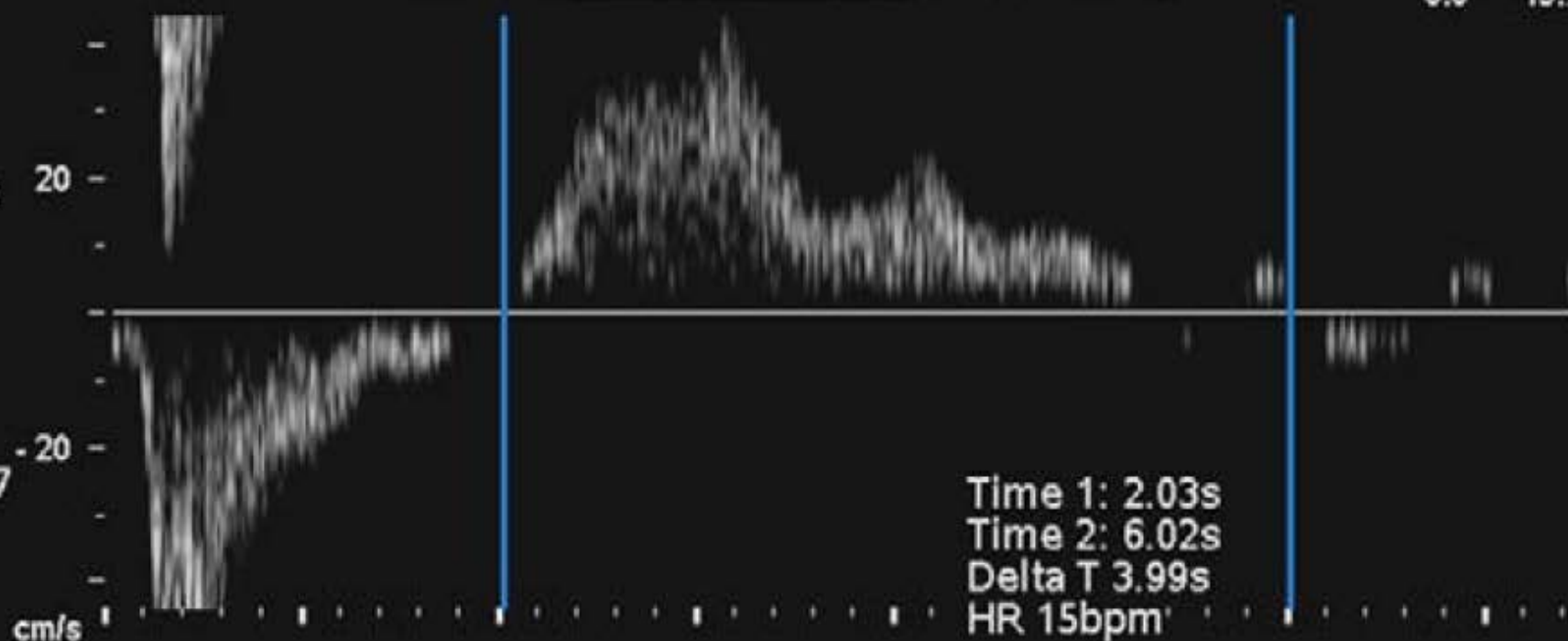
- 5.0  
cm/s  
5.5MHz  
M3/P1  
G10/E1  
WF M



Vasc/REFLUX  
L8-3/7.0MHz  
DR55/M3/P2  
G78/E2/100%  
MI1.1 TIs0.5  
3.0 cm  
10 Hz  
ZSI 0

0.0 15.7

PW  
A 60°  
3.5MHz  
G34  
WF M  
DR30  
M2  
Min  
SVD 0.7  
SV2



# The San Diego Population Study

## Baseline Prevalence

- NHLBI R01 study of chronic peripheral venous disease (CPVD) and peripheral arterial disease (PAD) in a defined multi-ethnic population
- 4 primary aims for CPVD component
  - CPVD prevalence by age, sex, and ethnicity
  - Risk factors for CPVD
  - Symptoms in CPVD
  - Quality of life in CPVD

# The San Diego Population Study

## Baseline Prevalence

- 2404 participants (4808 legs), 2/3 women, aged 29-91 years
- 59.7% NHW, 14.7% Hispanic, 13.4% African-American, 12.2% Asian
- Questionnaire about previous superficial or deep venous thrombosis (SVT and DVT)
- Standardized visual examination of legs, with 4 hierarchic visual categories – normal, telangectasias/spider veins (TSV), varicose veins (VV), trophic changes (TCS)
- Standardized duplex ultrasound examination of legs, with 3 hierarchic functional categories – normal, superficial functional disease (SFD), deep functional disease (DFD). “Functional” is either reflux or obstruction.

**Table 1a. Visible and Functional Chronic Venous Disease by Strata of Sex, Age, and Ethnicity**

		Study Cohort		Visible Disease, %				Functional Disease, %		
		N	%	NL	TSV	VV	TCS	NL	SVD	DVD
All subjects		2404	(100.0)	18.2	51.3	24.2	6.3	70.9	19.4	9.7
Men		824	(34.3)	33.1	43.1	15.9	7.9	74.4	13.6	12.0
Women		1580	(65.7)	10.4	55.6	28.5	5.4	69.1	22.5	8.5
Age, yrs	<50	603	(25.1)	30.4	48.9	18.4	2.3	80.6	11.8	7.6
	50-59	650	(27.0)	21.7	52.9	21.2	4.2	76.8	15.1	8.2
	60-69	596	(24.8)	12.2	52.0	27.2	8.6	64.9	24.2	10.9
	70+	555	(23.1)	7.2	51.4	30.8	10.6	59.8	27.8	12.4
Ethnicity	NHW	1436	(59.7)	13.6	54.2	25.3	7.0	68.3	20.5	11.2
	Hispanic	353	(14.7)	18.7	49.6	27.2	4.5	70.5	23.2	6.2
	Afr. Am.	323	(13.4)	27.2	45.8	20.7	6.2	76.8	16.4	6.8
	Asian	292	2.2)	30.1	45.6	19.2	5.1	77.4	13.0	9.6

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	Asian	292	2.2)	30.1	45.6	19.2	5.1	77.4	13.0	9.6

## Visible and Functional Chronic Venous Disease in 4808 legs of 2404 persons

		Functional Disease					
		Normal	SVD	DVD	Total		
Visible Disease		N (%)*	N (%)	N (%)	N (%)		
Normal		1024	5	39	1068		
		(21.3)	(0.1)	(0.8)	(22.2)		
TSV		2525	24	87	2636		
		(52.5)	(0.5)	(1.8)	(54.8)	Plus TSV	
VV		185	582	107	874	782/874=	
		(3.9)	(12.1)	(2.2)	(18.2)	89.5%	Plus VV
TCS		58	117	55	230	212/230 =	
		(1.2)	(2.4)	(1.1)	(4.8)	92.2%	70.4%
Total		3792	728	288	4808		
		(78.9)	(15.1)	(6.0)	(100.0)		
		Plus SVD					
		140/288 =					
		48.6%					

**TABLE 5. Age-adjusted prevalence (%) of edema, history of superficial thrombotic events, and history of deep thrombotic events, by visible and functional disease, San Diego, California, 1994–1998**

	Normal	Superficial functional disease	Deep functional disease
<b>Edema</b>			
Normal	1.7†	0.6	6.6
Spider veins	1.8	14.9*	10.5*
Varicose veins	3.9	7.4*	15.6*
Trophic changes	40.8*	30.0*	48.2*
<b>Superficial events</b>			
Normal	0.6†	0.0	5.3*
Spider veins	0.4	10.0*	0.0
Varicose veins	1.2	4.1*	1.2
Trophic changes	0.2	4.9*	11.3*
<b>Deep events</b>			
Normal	1.3†	0.0	5.4
Spider veins	1.7	0.0	5.4*
Varicose veins	3.0	2.4	6.6*
Trophic changes	7.7*	7.6*	24.6*

\*  $p < 0.005$ .

† Reference group.

# Risk factors for Moderate Venous Disease (VV or SFD, no TCS or DFD)

Criqui et al J Vasc Surg 2007;46:331-7

**Table III.** Risk factors for moderate venous disease (vs normal) in men and women\*

<i>Variable</i>	<i>Men</i>		<i>Women</i>	
	<i>Point estimate</i>	<i>95% CI</i>	<i>Point estimate</i>	<i>95% CI</i>
Age (10 years)	1.59	1.26, 2.00	1.43	1.25, 1.64
African-American	0.64	0.25, 1.60	0.84	0.57, 1.24
Asian	0.55	0.23, 1.29	0.90	0.57, 1.42
Hispanic	1.48	0.74, 2.94	1.21	0.85, 1.70
Venous disease, family history	2.87	1.81, 4.55	2.34	1.77, 3.10
Hernia surgery	1.85	1.09, 3.14	1.81	1.04, 1.34
Hypertension	0.58	0.34, 0.98	0.64	0.47, 0.87
CVD history	0.22	0.08, 0.66	—	—
Current				
Walking (per hr)	1.14	1.05, 1.24	—	—
Move after sitting	0.31	0.13, 0.79	—	—
Adult sitting (per hour)	—	—	0.92	0.87, 0.96
Weight (10 kg)	—	—	1.32	1.12, 1.56
Births (n)	NA	NA	1.14	1.05, 1.23
Waist circumference (10 cm)	—	—	0.83	0.69, 1.00
Oophorectomy	NA	NA	1.37	1.00, 1.87
Flat feet	—	—	1.39	0.97, 2.00

CI, Confidence interval; CVD, cardiovascular disease; NA, not applicable.

\*Multivariable entry into model 0.3, exit 0.1.

# Risk factors for Severe Venous Disease (TCS or DFD)

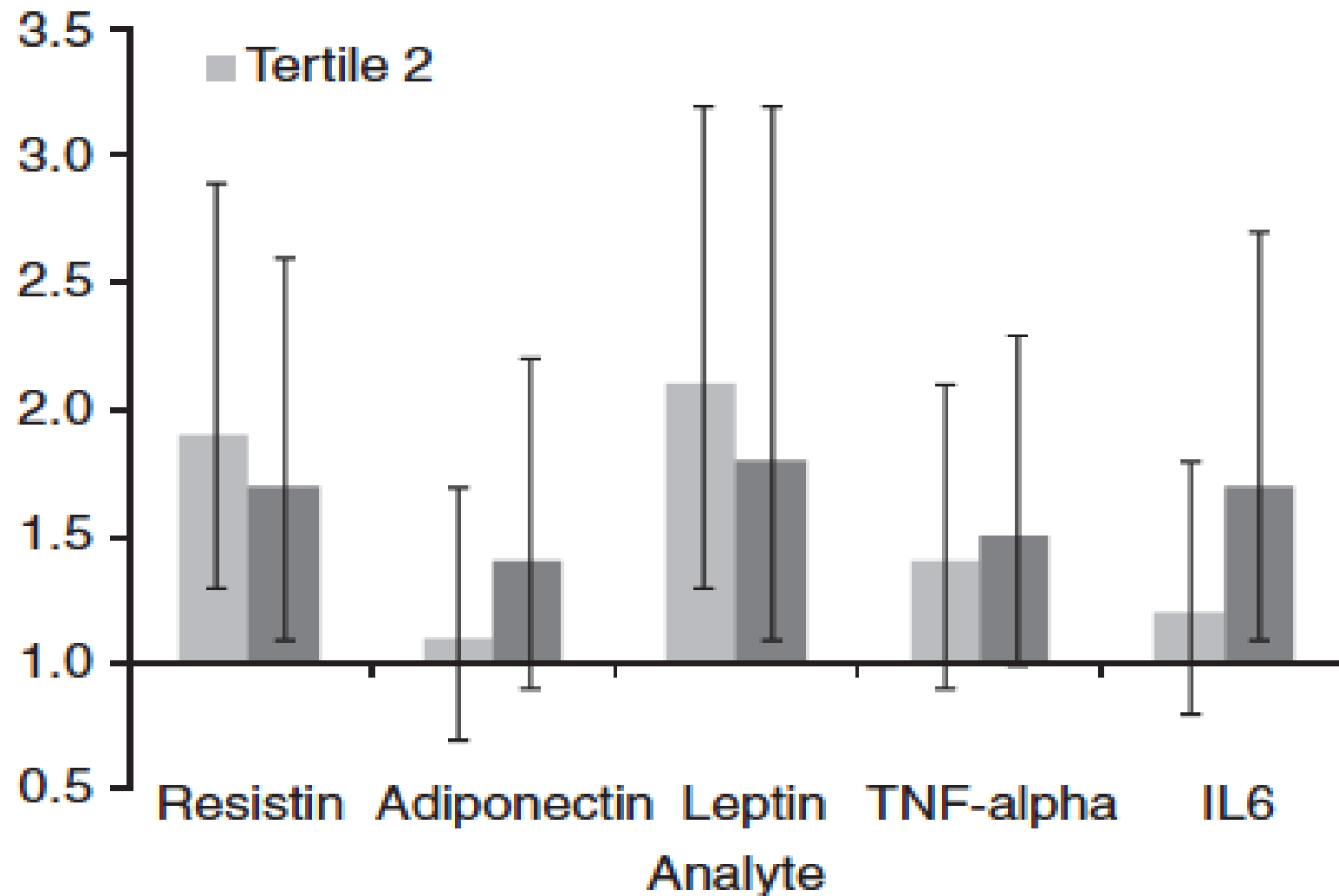
Criqui et al J Vasc Surg 2007;46:331-7

**Table IV.** Risk factors for severe venous disease (vs. normal) in men and women\*

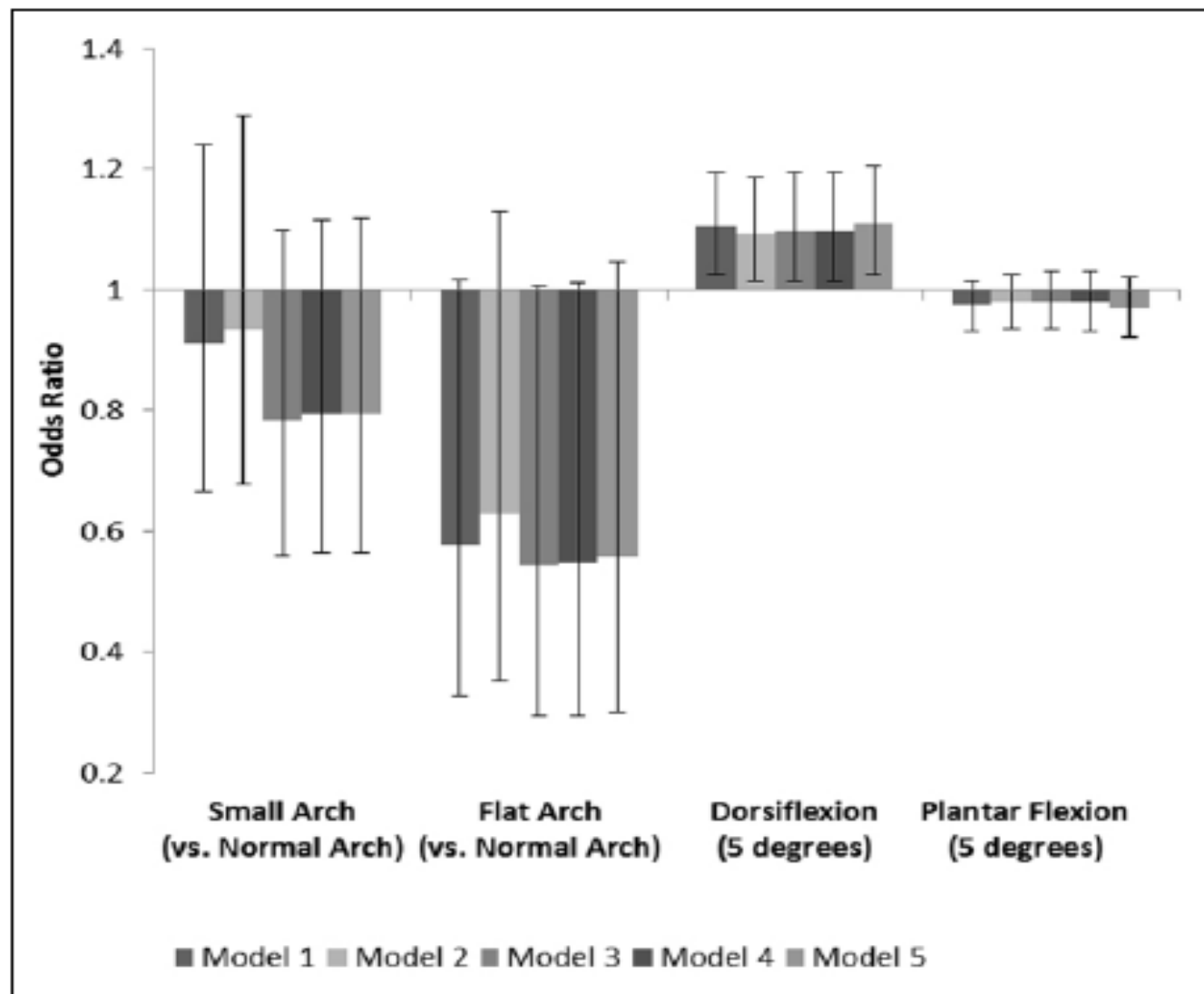
<i>Variable</i>	<i>Men</i>		<i>Women</i>	
	<i>Point estimate</i>	<i>95% CI</i>	<i>Point estimate</i>	<i>95% CI</i>
Age (10 years)	1.41	1.17, 1.70	1.43	1.21, 1.68
African American	0.63	0.30, 1.35	0.44	0.26, 0.77
Asian	1.50	0.81, 2.75	0.99	0.57, 1.74
Hispanic	0.63	0.28, 1.39	0.71	0.42, 1.19
Venous disease, family history	2.13	1.44, 3.16	1.92	1.33, 2.77
Waist circumference (10 cm)	1.37	1.15, 1.63	1.24	1.11, 1.39
Laborer	3.24	1.21, 8.67	—	—
DBP (10 mm/Hg)	0.80	0.67, 0.97	—	—
Current cigarettes (20/day)	2.24	1.11, 4.54	—	—
Flat feet	1.63	0.97, 2.75	—	—
Flat arch (vs normal)	—	—	3.28	1.83, 5.89
Current standing (per hr)	—	—	1.14	1.05, 1.24
Small arch (vs normal)	—	—	1.84	1.25, 2.71
Leg injury	—	—	1.67	1.14, 2.44
Births (n)	NA	NA	1.14	1.03, 1.27
CVD history	—	—	2.02	1.14, 3.56

*CI*, Confidence interval; *DBP*, diastolic blood pressure; *CVD*, cardiovascular disease; NA, not applicable.

\*Multivariable entry into model 0.3, exit 0.1.



**Fig. 2.** Odds for increasing severity of chronic venous disease in a model simultaneously including multiple adipokines. Adjusted for age, sex, race and body mass index. Comparing tertiles 2 and 3 with tertile 1 (separately).



**Figure 1.** Odds ratio of the progression of venous disease compared to the stable group. (*Model 1*: unadjusted; *Model 2*: age, sex, and ethnicity; *Model 3*: *Model 2* + covariates (history of cardiovascular disease, occupation, hernia surgery, supine for surgical procedure, current time spent lying, current time spent standing, history of hypertension); *Model 4*: *Model 3* + family history of venous disease, smoking history, and BMI; *Model 5*: *Model 4* + dorsiflexion (for weight-bearing arch measurements) or weight-bearing arch measurements (for dorsiflexion and plantar flexion)).

Association of unweighted and weighted genetic risk scores with moderate + severe venous disease<sup>a</sup>.

	Unweighted 33-SNP GRS <sup>b</sup> OR (95% CI)	p	Weighted 33-SNP GRS <sup>b</sup> OR (95% CI)	p	Unweighted 5-SNP GRS <sup>b</sup> OR (95% CI)	p	Weighted 5-SNP GRS <sup>b</sup> OR (95% CI)	p
Whites	1.45 (1.26, 1.67)	<0.001	1.41 (1.23, 1.63)	<0.001	1.41 (1.22, 1.64)	<0.001	1.41 (1.22, 1.62)	<0.001
African-Americans	1.74 (1.18, 2.55)	0.005	1.55 (1.06, 2.26)	0.025	1.37 (0.96, 1.95)	0.08	1.31 (0.92, 1.87)	0.13
Hispanics	1.80 (1.30, 2.51)	<0.001	1.63 (1.18, 2.27)	0.003	2.15 (1.52, 3.04)	<0.001	1.75 (1.28, 2.40)	<0.001
Asians	1.88 (1.30, 2.73)	0.001	1.56 (1.09, 2.22)	0.01	1.88 (1.27, 2.79)	0.002	1.61 (1.10, 2.34)	0.01

<sup>a</sup> In race/ethnicity-stratified models adjusted for age, sex, weight, waist, ever smoking, time sitting, time walking, regular movement, hypertension, flat feet, previous leg injury, previous hernia surgery.

<sup>b</sup> Per standard deviation increment of the GRS; the 33 SNP is based on all genotyped SNPs, while the 5-SNP GRS is based on the top 5 associated SNPs within each race/ethnic group.

## **The San Diego Population Study Baseline Prevalence – Conclusions 1**

- CPVD increased with age, and was more common in NHW than in Hispanics, African-Americans, or Asian-Americans
- TSV, VV, and SFD were more common in women; TCS and DFD more common in men
- Visible and functional disease were highly concordant (92%), but 8% of legs were discordant, and 25% of limbs with TCS had no functional disease
- SVT, DVT, and edema increased dramatically with TCS and DFD, but also occurred in their absence
- In multivariate analysis, both moderate and severe venous disease were related to age and a family history of venous disease in both sexes

# **The San Diego Population Study**

## **Baseline Prevalence – Conclusions 2**

- In both sexes, moderate venous disease was related to previous hernia surgery and normotension, and severe venous disease to waist circumference and flat feet
- For moderate venous disease, CVD hx was protective in men, and weight, # of births, and oophorectomy history were positively associated in women
- For severe venous disease, working as a laborer and cigarettes per day showed positive associations in men. In women, prolonged standing, prior leg injury, # of births, and CVD hx showed positive associations.