COMMON QUESTIONS!!

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GENERAL HEMATOLOGY
OHSU

DISCLOSURE

Relevant Financial Relationship(s)

Author: UpToDate (Iron def, anemia in pregnancy)

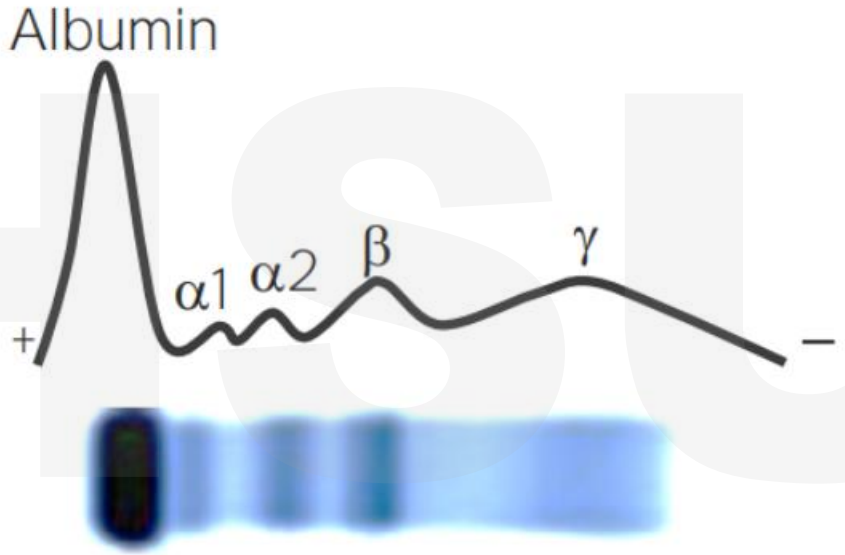
3 Common Questions

- What do I do with this SPEP result?
- What do I do with a high ferritin?
- How long do I anticoagulate?

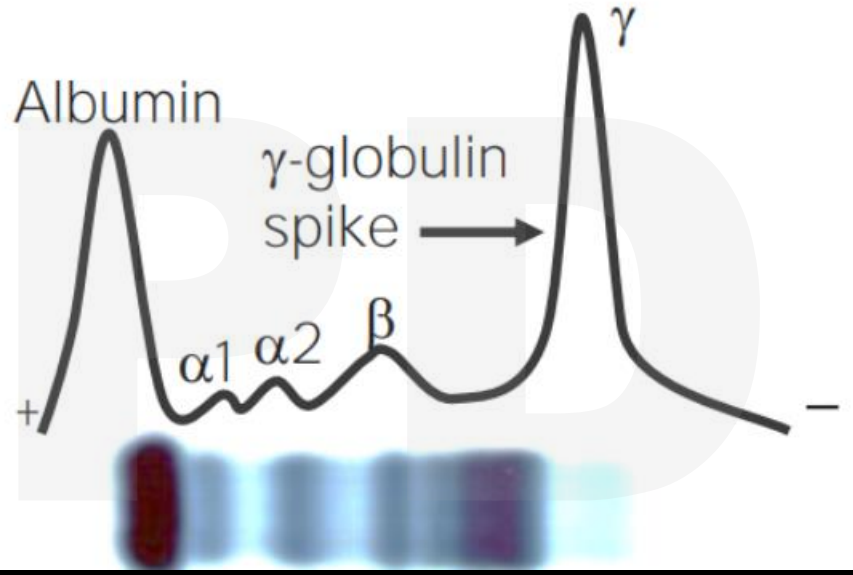
SPEP

- Very commonly ordered test
- Use to diagnosis multiple myeloma by finding monoclonal protein (MP)
- Can be affected by other illnesses

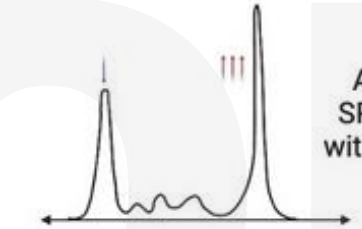
Normal serum, protein electrophoresis



Monoclonal gammopathy

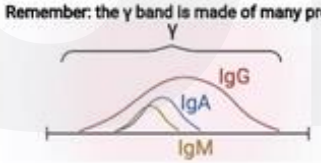


Immunofixation Electrophoresis (IFE)



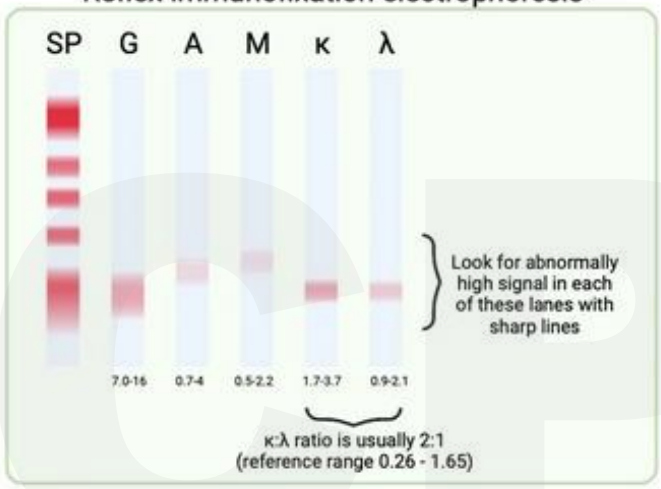
Abnormal SPEP/UPEP with "M-Spike"

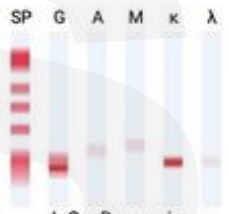
Remember: the γ band is made of many proteins

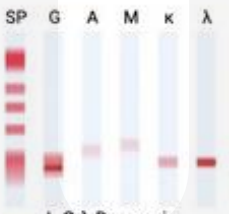


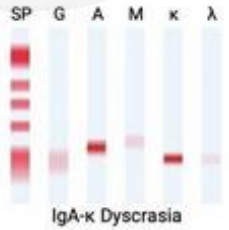
We don't know if this spike is due to IgM, IgA, IgD, IgE, κ or λ

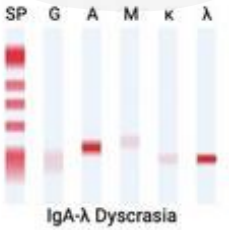
Reflex immunofixation electrophoresis

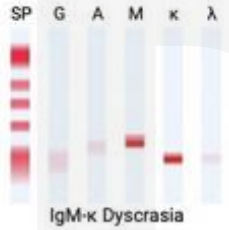


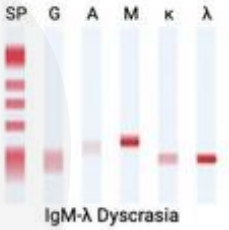












https://www.pathelective.com/micromeded/spep-ife

Common Issues

- Polyclonal gammopathy
  - Not malignant – inflammation, liver disease etc..
- Beta-gamma bridging
  - Liver disease, inflammation

MP SPEP

- MP SPEP are found in up to 5% of the population
- Increase with age
- Increasingly sensitive to small abnormalities

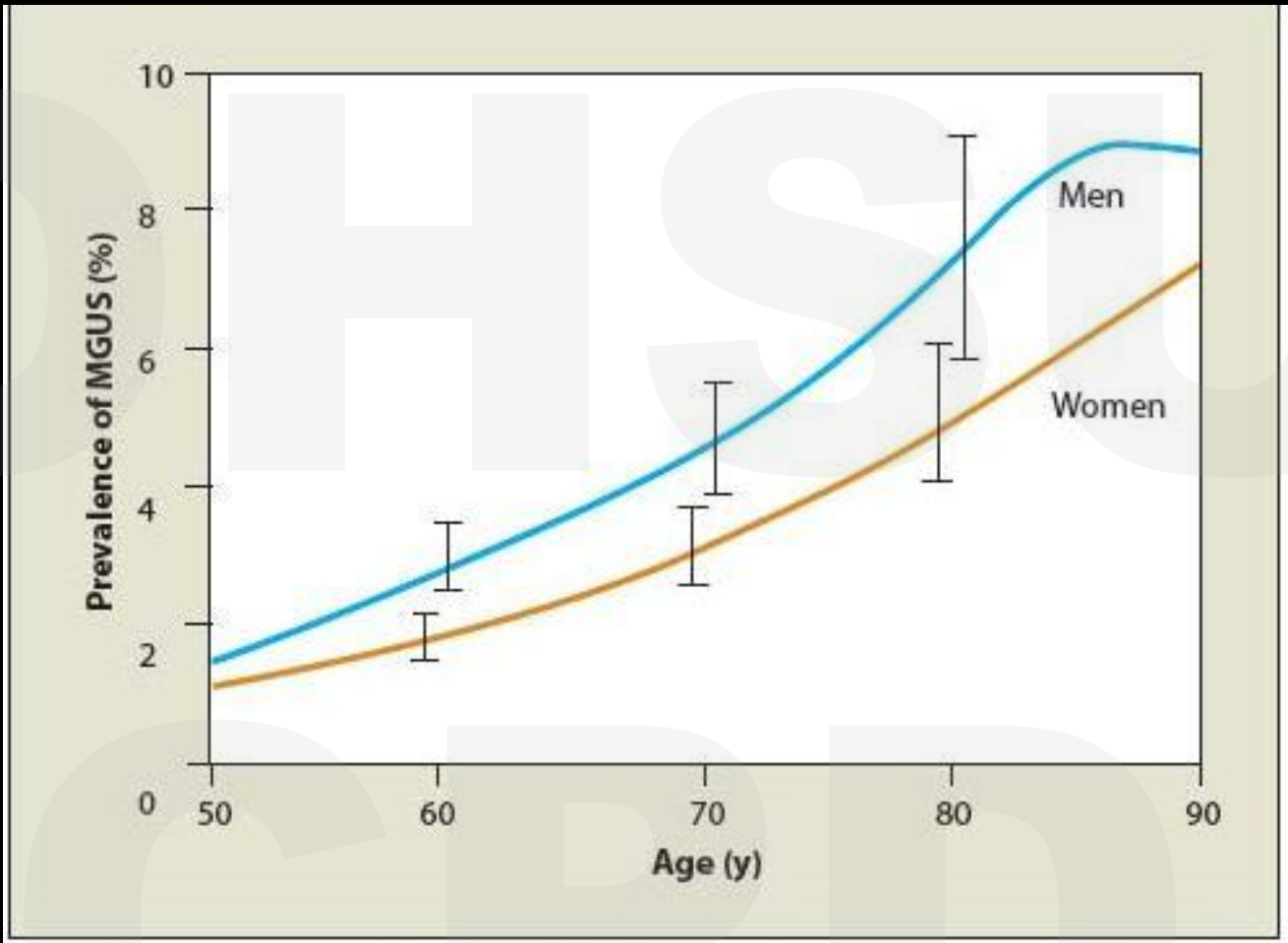
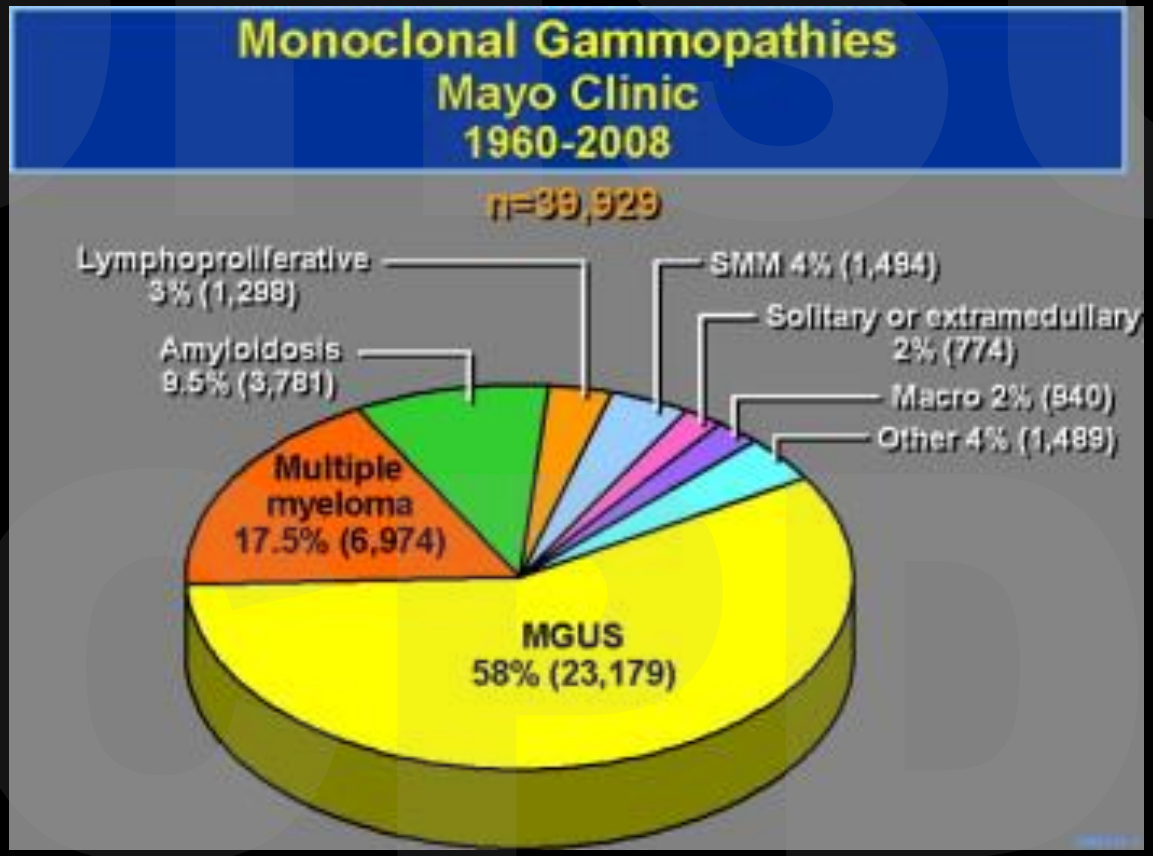


Figure 1: Prevalence of MGUS According to Age—The bars represent 95% confidence intervals. Ages greater than 90 years have been collapsed to 90 years. MGUS = monoclonal gammopathy of undetermined significance. From Kyle RA et al. N Engl J Med. 2006.[9]

MP SPEP - DDX


Monoclonal Gammopathies
Mayo Clinic
1960-2008
n=89,929
Lymphoproliferative
3% (1,298)
Amyloidosis
9.5% (3,781)
SMM 4% (1,494)
Solitary or extramedullary
2% (774)
Macro 2% (940)
Other 4% (1,489)
Multiple
myeloma
17.5% (6,974)
MGUS
58% (23,179)

MGUS

- Monoclonal gammopathy of uncertain significance
  - IgG < 3 grams/dl
  - IgM < 1- 1.5 gm/dl
  - IgA < 1 gm/dl
  - And no end organ damage

CRAB Signs

- hyperCalcium
- Renal disease
- Anemia
- Bone
  - Skeletal survey or MRI **NOT** bone scan

MP SPEP – Work Up

- CBC, calcium renal function
- Skeletal survey*
- Marrow if
  - Unexplained anemia
  - High protein level or IgA
  - End organ damage
- Serum light chains

Serum Free Light Chains

- Overproduction of light chain (kappa or lambda)
- High ratios worrisome
  - Light chain myeloma
  - Risk factor for progression in MGUS

sFL –Burn Points

- Ratio – not levels – is key
  - Levels can be raised by inflammation, liver disease, renal failure, etc
- Needs to be serum not urine
- Labs reference ranges wrong

Light Chain

- Reference intervals derived from small group (282 blood donors)
- Study of 42,000 patients suggest better ranges
  - Decreased LC-MGUS by 82
  - None of the 1006 LC-MGUS progress in 4.6 years
- JAMA Onc 11:753, 2025

Old vs New

- Old ratio: 0.26-1.65
- New: 0.44-2.16
  - > 70: 0.46 – 2.59 (3.33 renal disease)
- > 8.0 risk factor for progression

MGUS - Progression

- Overall about 0.5 -1%/yr to myeloma
- If IgG < 1.5 gm/dl and light chains normal – 2% lifetime risk

Table 5 Risk-Stratification Models to Predict Progression of Monoclonal Gammopathy of Undetermined Significance to Myeloma or Related Disorders

	Number (%) of patients	Risk of Progression at 20 Years (%)		
		Relative	Absolute Risk	Competing Risk
Serum M protein < 1.5 g/dL, IgG subtype, and normal FLC ratio	449	1	5	2
One risk factor abnormal	420	5.4	21	10
Two risk factors abnormal	226	10.1	37	18
Three risk factors abnormal (serum M protein ≥ 1.5 g/dl, IgM or IgA subtype, abnormal FLC ratio)	53	20.8	58	27

FLC = free light chain. This research was originally published in Blood (Rajkumar SV et al. Blood. 2005.[35]) and subsequently modified.

Are We Doing too many SPEPS??

- Increasing data many older disease associations are not valid
- SPEP for many condition needs to be move back to second line work-up

"Gamma Gap"

- Total protein – albumin
  - If too high ? M-protein
- Shown to not be helpful in diagnosis myeloma
- I ignore

PLoS One. 2020 Jan 15;15(1):e0224977.

Osteoporosis

- Prospective study showed no relationship
- MGUS actually had higher bone mass!
- Bld Advanc 1:2790, 2017

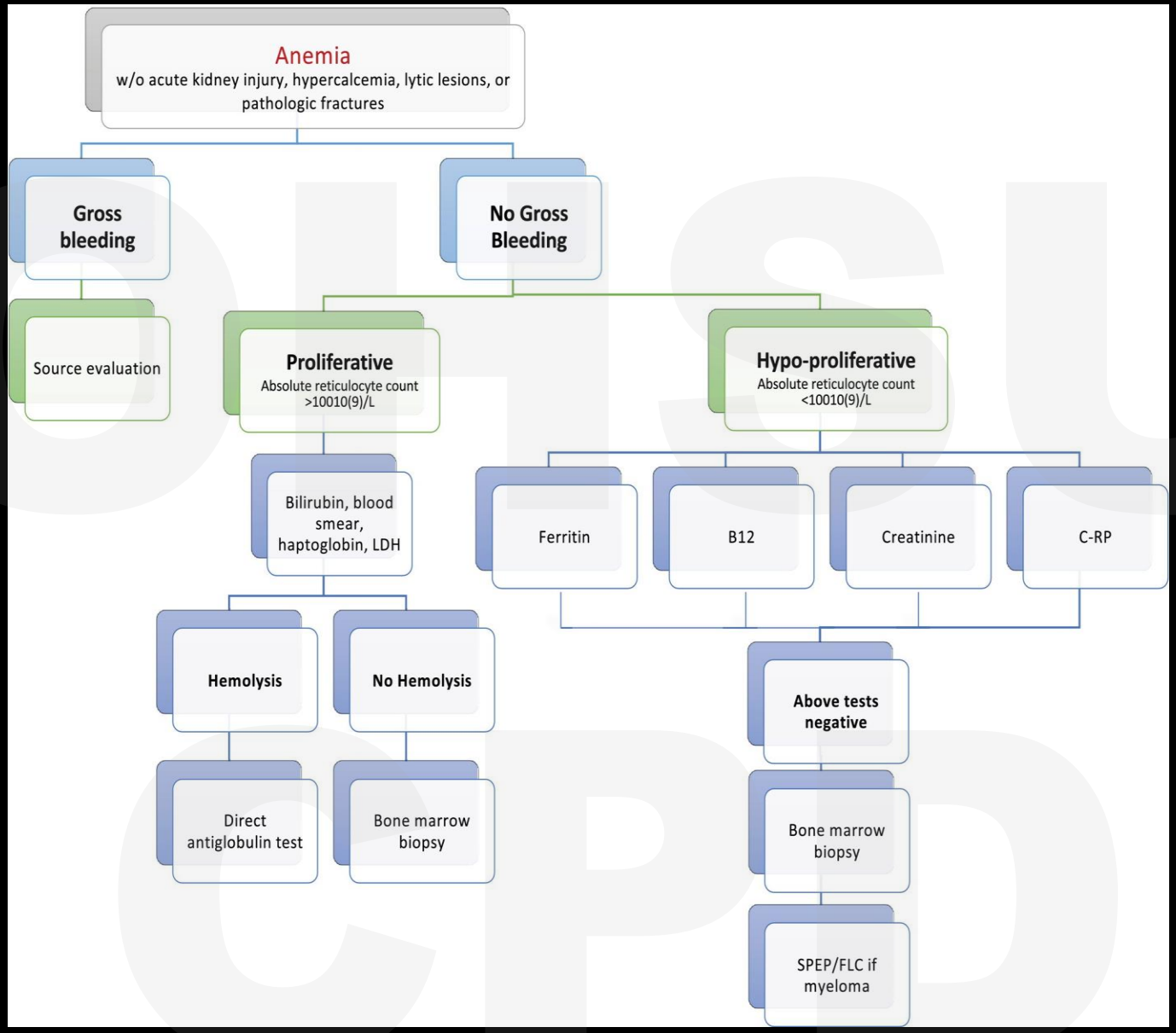
Autoimmune Disease

- Study of 75,000 – 10,000 with autoimmune disease showed no association

- Ann Intern Med. 2024 Jun;177(6):711-718

Anemia

- Review of 265 anemic patients who had SPEPs
- 32 (11.8) with MP
- $10,000 in health care cost the next year
- Maybe MP led to anemia in one patient



American J Hematol, Volume: 101, Issue: 1, Pages: 152-155, First published: 23 October 2025, DOI: (10.1002/ajh.70102)

Neuropathies

- Several classic associations
- SPEP always first line test
- 1399 patients with neuropathy tested with SPEP
  - 10% positive
  - MP neuropathy 2 patients (0.8%)
- J Gen Intern Med. 2025

Neuropathy

- Check for common causes (diabetes, alcohol etc..)
- Check SPEP if CRAB signs or EMG suggestive of MP related issues

High Iron Labs: What to Do

- High iron saturations
- High ferritins

High Iron Saturation

- Can be influence by oral iron
- Need to repeat fasting for 5-9 hours

High Iron Saturations

- Hemolysis
  - Release of heme iron
- Iron overload
  - Genetic
  - Acquired
- Don’t get too worked up if ferritin is normal

Ferritin

- Elevated levels
  - Inflammation
  - Liver disease
    - Fatty liver
  - Iron overload

Inflammation

- Ferritin acute phase reactant
- Can be > 1000 ng/dl
- Testing
  - High ferritin
  - High CRP
  - Low iron saturation

Being a Guy

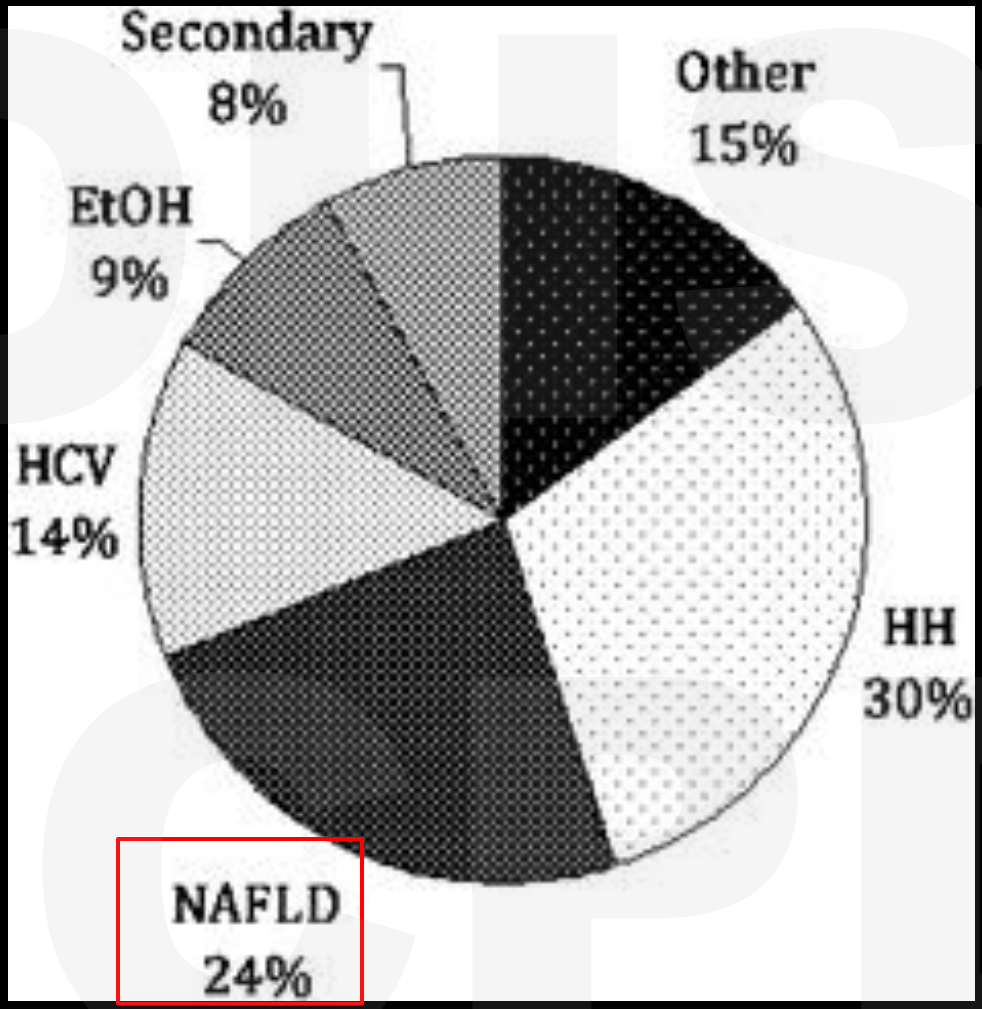
- Ferritins can range up to 4-500 ng/dl

Liver Disease

- Ferritin released from damage hepatocytes
- Acute liver disease
  - Very high levels
- Chronic liver disease
  - Up if liver function test up

“Non Alcoholic Steatohepatitis”

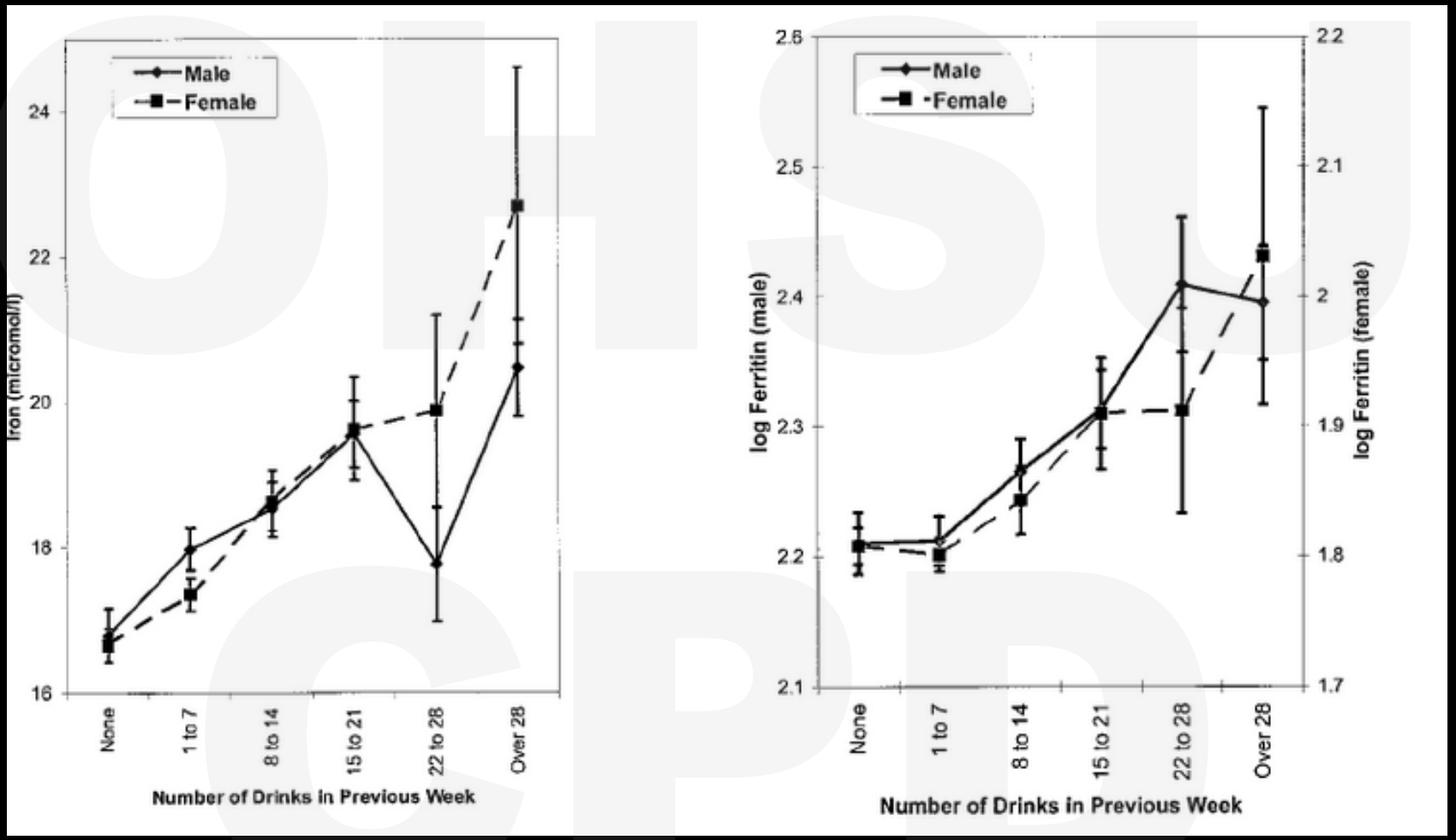
- Common in
  - Diabetes
  - Obesity
- High ferritins
  - Usually normal to low saturations
- Phlebotomy not helpful



Dever JB, Digestive Diseases and Sciences, Dig Dis Sci. 2010 Mar;55(3):803-7.

Alcohol

- Significant alcohol use can raise ferritin
  - Liver toxicity?
  - Increase iron absorption
- Can be seen with > 2 drinks/day
  - > 2 beers, > 10 oz wine, > 3 oz hard stuff

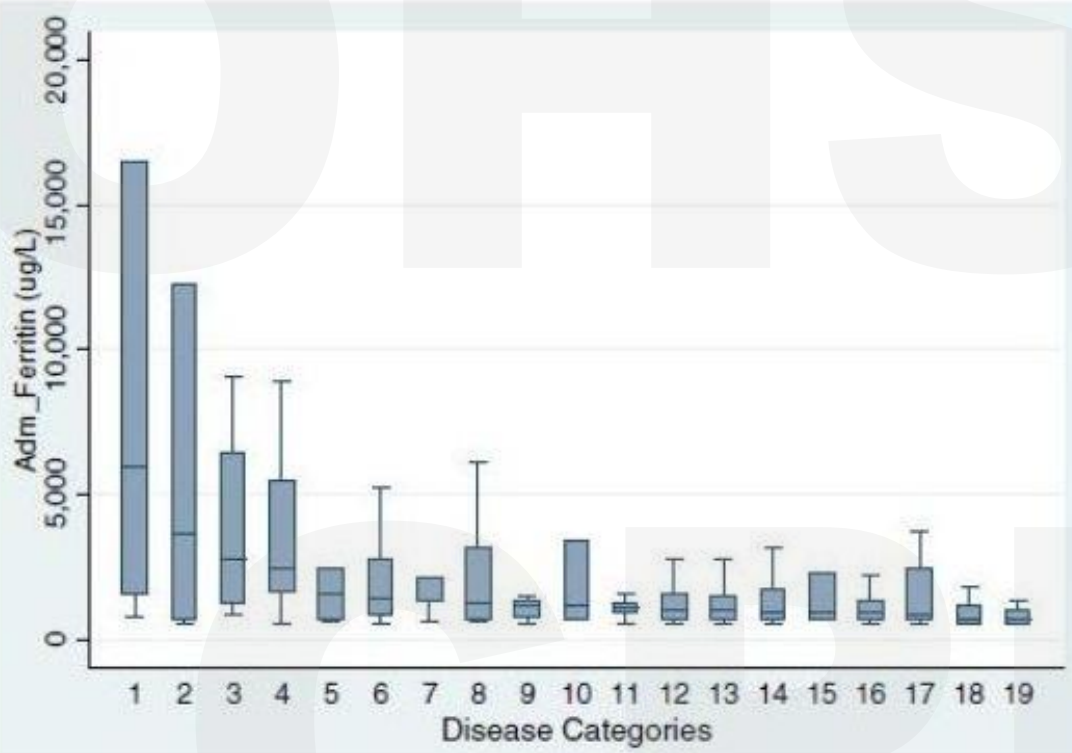


Alcohol Clin Exp Res. 2001 Jul;25(7):1037-45.

Iron Overload and Hemolysis

- Occurs frequently in congenital hemolytic anemia
  - Not associated with transfusion
- Associated with increase iron absorption
- Seen in all congenital hemolytic anemias
- Seen also in alpha-thal traits

Distribution of **initial** ferritin values from different disease categories



Disease Categories
1-HLH
2-Unknown
3-Shock
4-Stem cell transplant
5-Heart disease
6-Chronic transfusion
7-Immunodeficiency
8-Liver disease
9-Cystic fibrosis
10- Bone marrow failure
11-Prematurity
12-Malignancy
13-Viral infection
14-Bacterial infection
15-Solid organ transplant
16-Trauma
17-Autoimmune disease
18-Hemoglobinopathy
19-Renal disease

The unknown group includes 10 patients (only two were evaluated for HLH)

Allen, C. E., X. Yu, et al. (2008). "Highly elevated ferritin levels and the diagnosis of hemophagocytic lymphohistiocytosis." Pediatr Blood Cancer 50(6): 1227-35.

Ferritin > 50,000

- Renal failure (73%)
- Liver injury (61%)
- Infection (52%)
- Heme malignancies (36%)
- Rheumatological (20%)
- HLH (19%)
- Iron overload (13%)
- None (2%)

Work Up of High Ferritins

- First line
  - Saturation
    - > 50% -worrisome for iron overload
    - < 20% - inflammation
- CMP
- Alcohol history
- Hbg A1C
- Reticulocyte count

Iron Overload

- Genetic testing
- End organ damage
  - Liver MRI if ferritin > 800-1000 and sats high but negative genetic tests

Genetic Hemochromatosis

- At 4 kinds of defects
- Types 1 and 4 more common
- Mutations much more common than disease

HH Type 1

- Autosomal Recessive
- Carrier frequency - 1 in 10
- Homozygotes ~ 1 in 200 Caucasians
  - 1-21% symptomatic
- Clinical manifestation
  - 5:1 males:females
  - Late onset - > 40 years
  - Defects in HFE gene
  - Liver, joints, endocrine

Genetics

- Classic C282Y homozygous
  - Men ~ 20% penetrance
  - Women ~ 1%
- H63D
  - Not a true mutation and testing no longer recommended

Rarer types

- HH Type 2-4
  - 2/3 younger and severe
  - Type 4 not as severe
- Uncertain if worth screening for

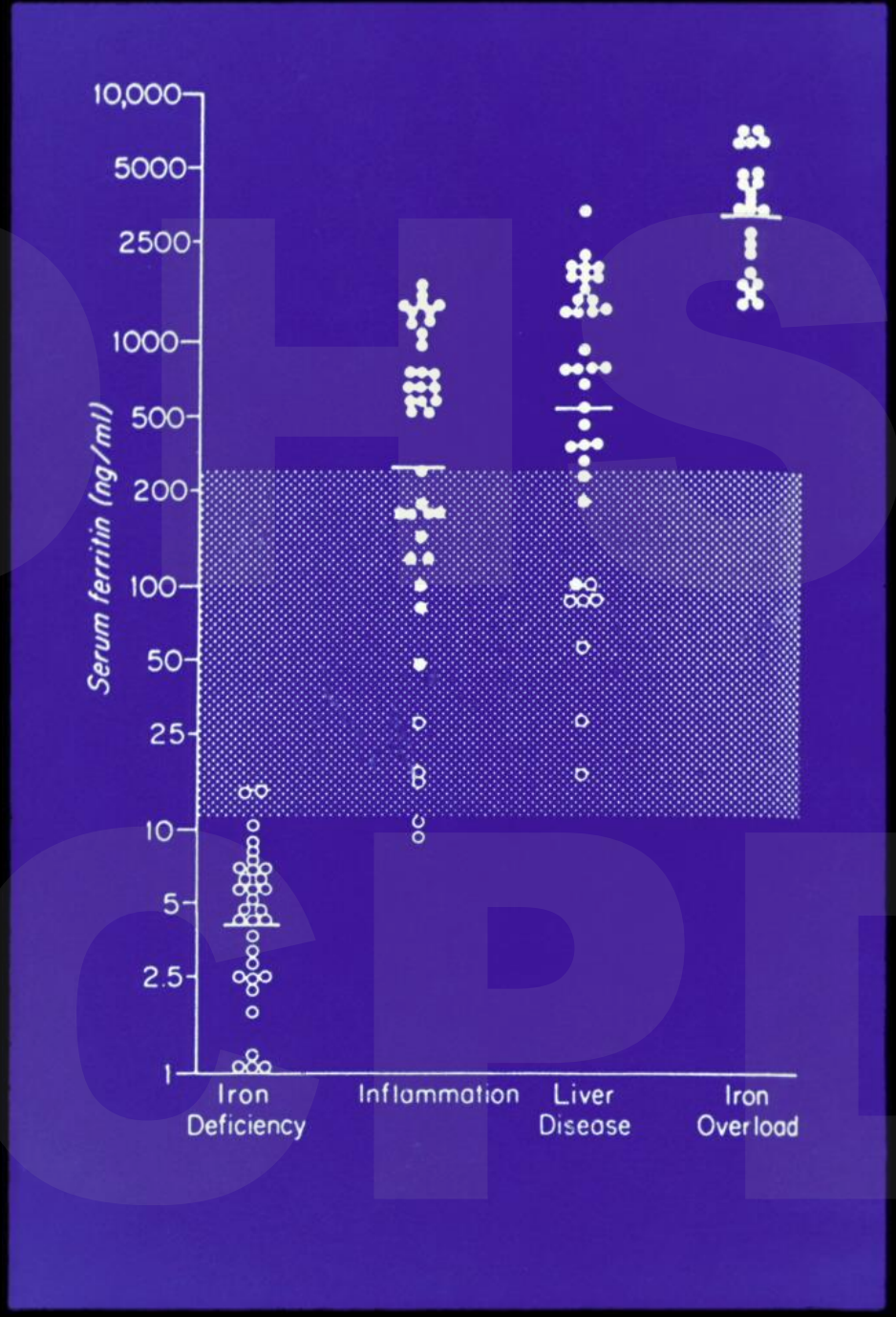
Hemochromatosis NOS

- ~ 20% negative HFE
  - High ferritin
  - Tissue iron overload
- Phlebotomy

How to Measure Iron

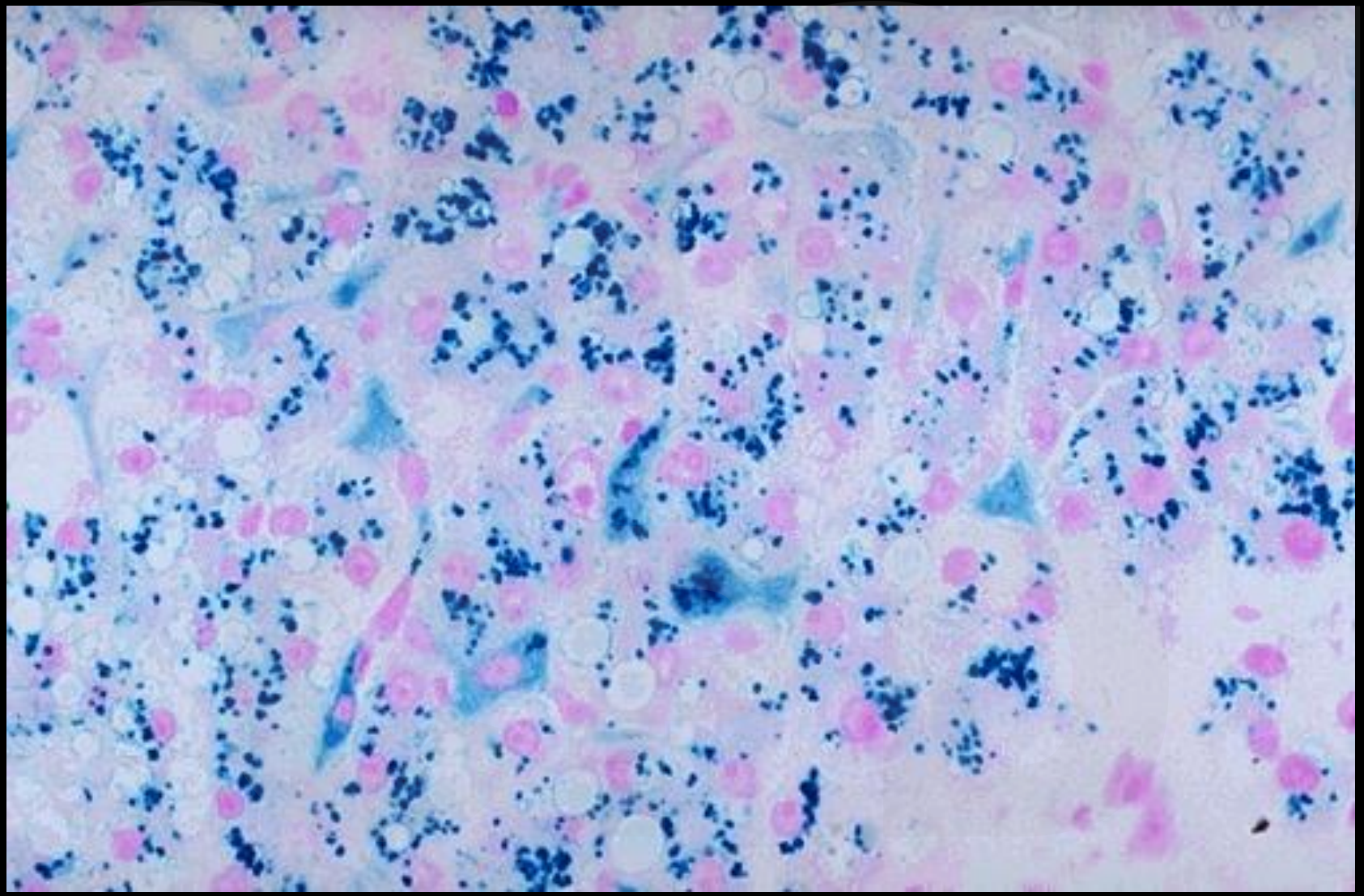
Ferritin

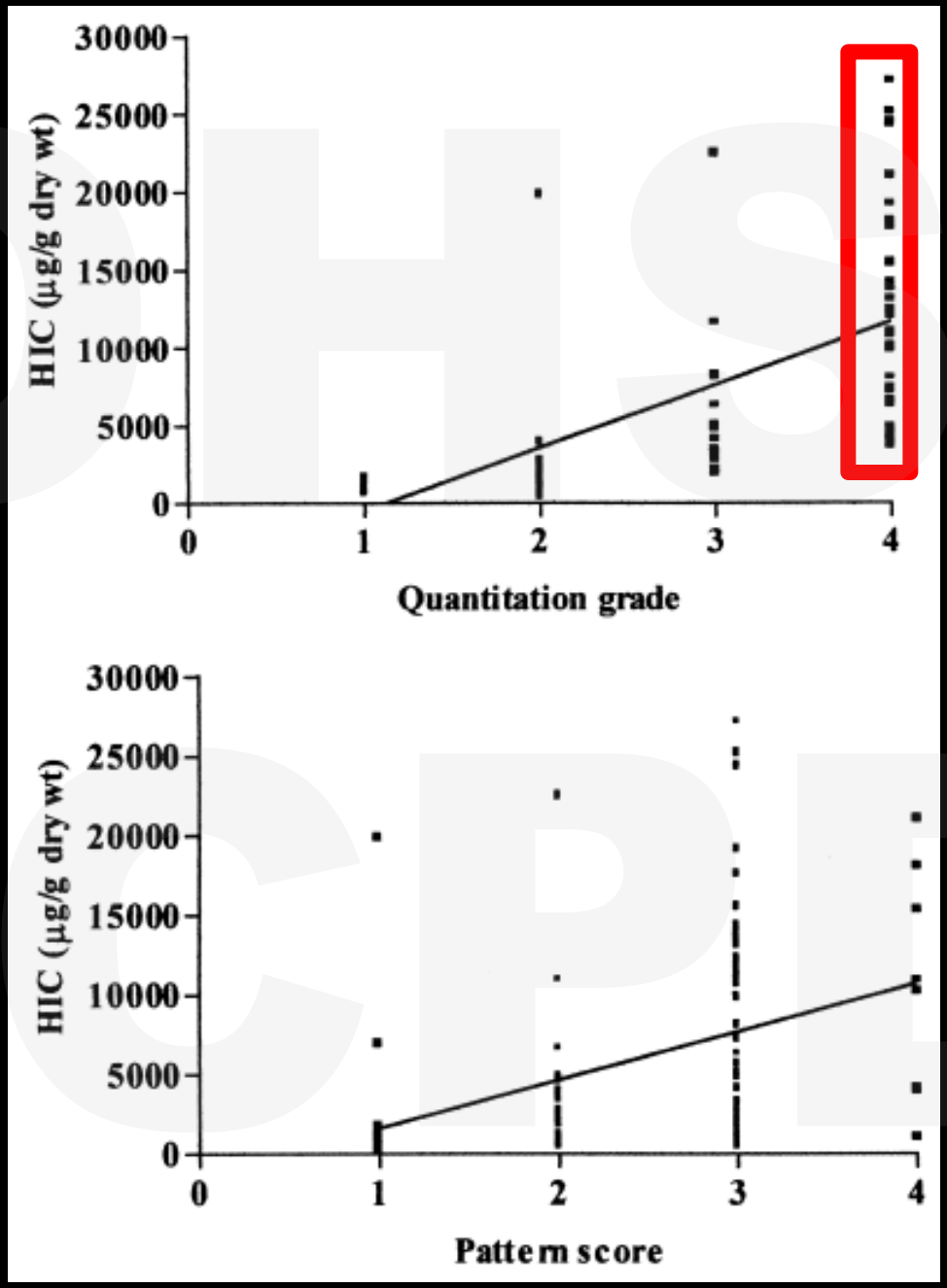
- Great for iron deficiency
- High levels worrisome for iron overload
- No relationship with high iron and amount of tissue iron


10,000
5000
2500
1000
500
200
100
50
25
10
5
2.5
1
Serum ferritin (ng/ml)
Iron Deficiency
Inflammation
Liver Disease
Iron Overload

Biopsy

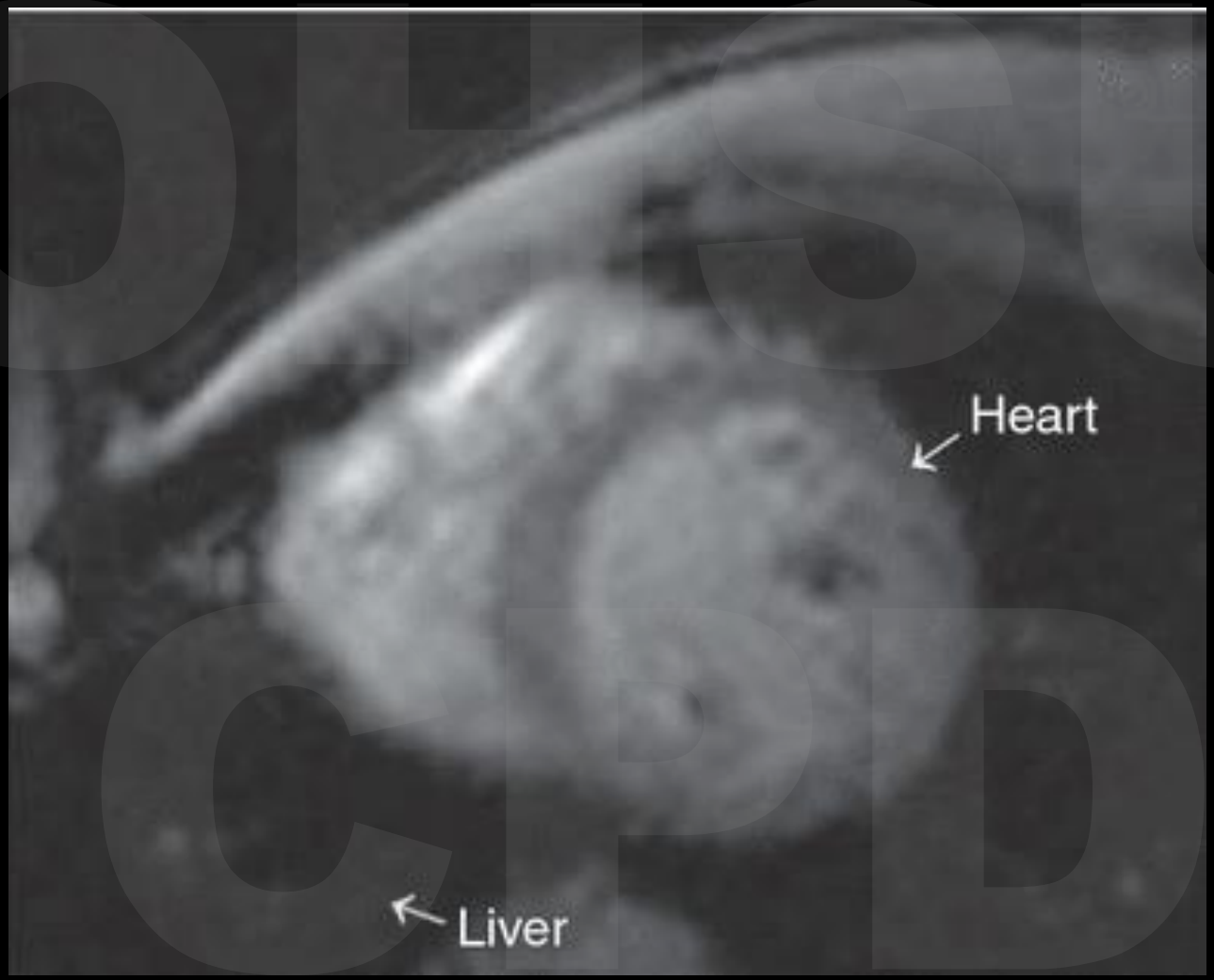
- Liver
  - Iron stain – quantitative
  - Tissue iron concentration key
- Cardiac – biopsy
- Marrow biopsy
  - Not helpful
    - Low in hemochromatosis!



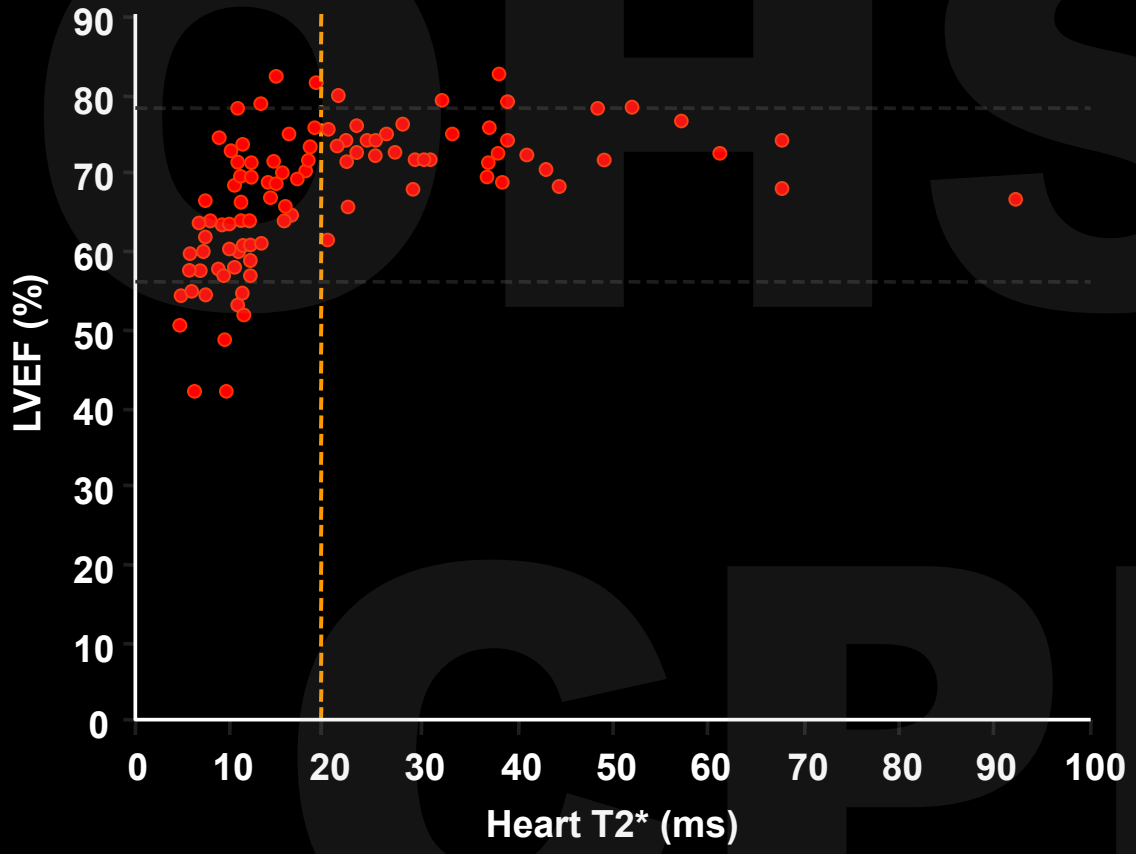

HIC (µg/g dry wt)
30000
25000
20000
15000
10000
5000
0
0
1
2
3
4
Quantitation grade
HIC (µg/g dry wt)
30000
25000
20000
15000
10000
5000
0
0
1
2
3
4
Pattern score

MRI

- Liver
  - Correlation with T2* scan and iron load
  - Now the go-to test
- Cardiac MRI
  - Rapidly becoming gold standard


Heart
Liver

T2* MRI—New Standard for Cardiac Iron

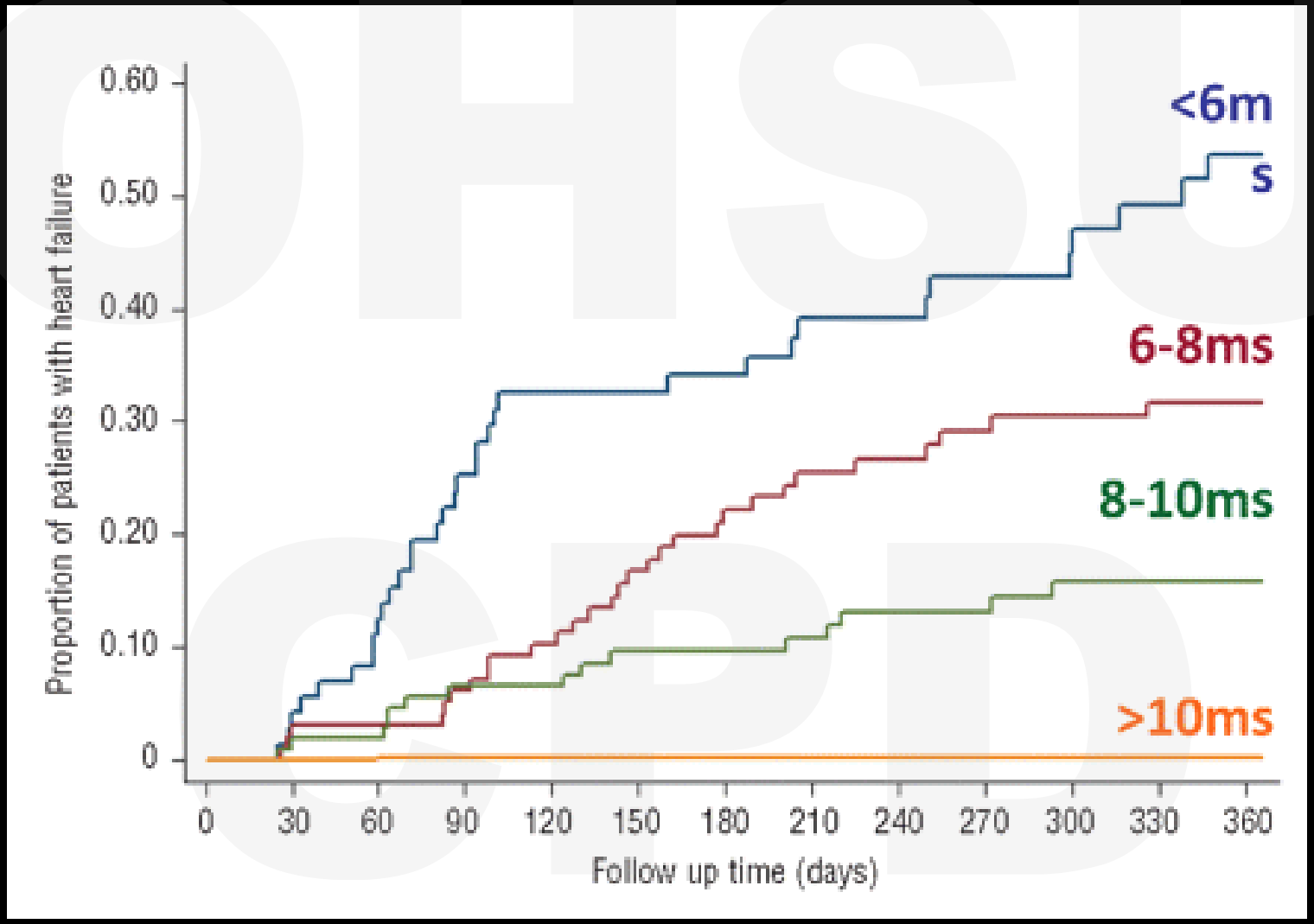


Relationship between myocardial T2* values and left ventricular ejection fraction (LVEF). Below a myocardial T2* of 20 ms, there was a progressive and significant decline in LVEF ($R = 0.61$, $P < .0001$).

Reprinted from Anderson LJ, et

Cardiac T2* value of 37 in a normal heart

Cardiac T2* value of 4 in a significantly iron overloaded heart


Proportion of patients with heart failure
0.60
0.50
0.40
0.30
0.20
0.10
0
<6ms
6-8ms
8-10ms
>10ms
0
30
60
90
120
150
180
210
240
270
300
330
360
Follow up time (days)

Therapy

- Inflammation
  - Primary cause
- Steatohepatitis
  - Lipid and diabetes control
  - No benefit phlebotomy
- Alcohol
  - Decrease drinking
- Iron overload
  - Phlebotomy

Therapy: Hemochromatosis

- Phlebotomy
  - Weekly in symptomatic patients
  - Weekly to biweekly in carriers if ferritin > 300
- Goals
  - Ferritins < 50
- Iron overload in congenital anemias
  - Phlebotomy if tolerated

Goals of Therapy

- No end organ damage
  - Full life expectancy
- Liver cirrhosis
  - Minimal improvement
  - Screen for hepatoma

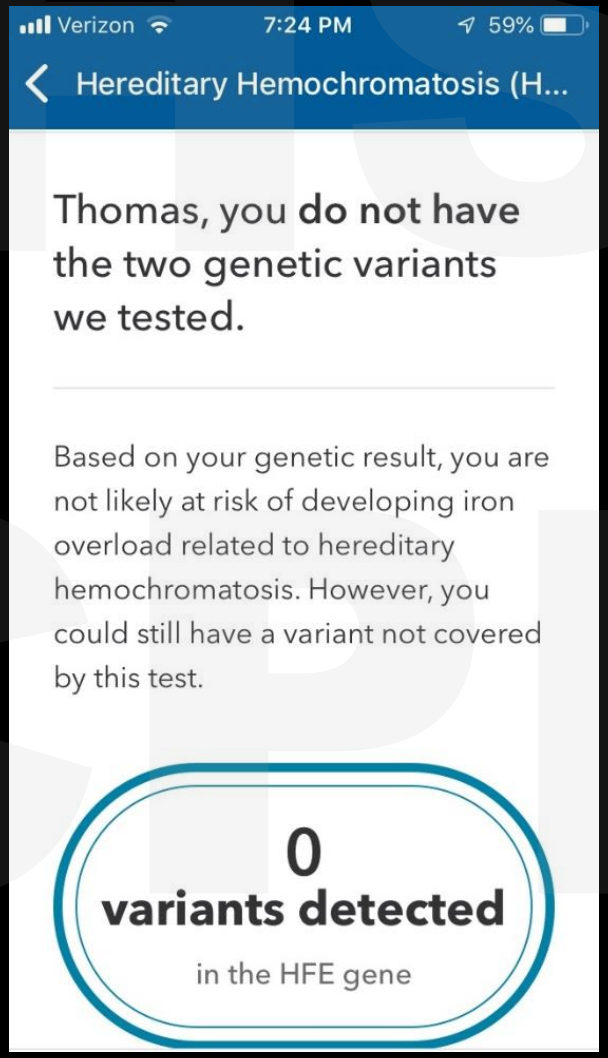
Goals of Therapy

- Cardiac
  - Reversal
- Diabetes
  - Some improvement
- Joints
  - Usually no improvement

Erythrocytosis

- Carries of HFE mutations can have erythrocytosis
  - Not due to higher iron levels
- Both homozygous and heterozygous
- HFE mutations overrepresented in athletes

23&Me


Verizon
7:24 PM
59%
Hereditary Hemochromatosis (H...
Thomas, you do not have the two genetic variants we tested.
Based on your genetic result, you are not likely at risk of developing iron overload related to hereditary hemochromatosis. However, you could still have a variant not covered by this test.
0
variants detected
in the HFE gene

Work-Up

- Repeat genetics
- Ferritin
  - > 300:phlebotomy
  - < 300: yearly ferritins
  - < 50: ok to treat iron deficiency
- Family screening

How Long to Treat Venous Thrombosis?

Duration of Therapy

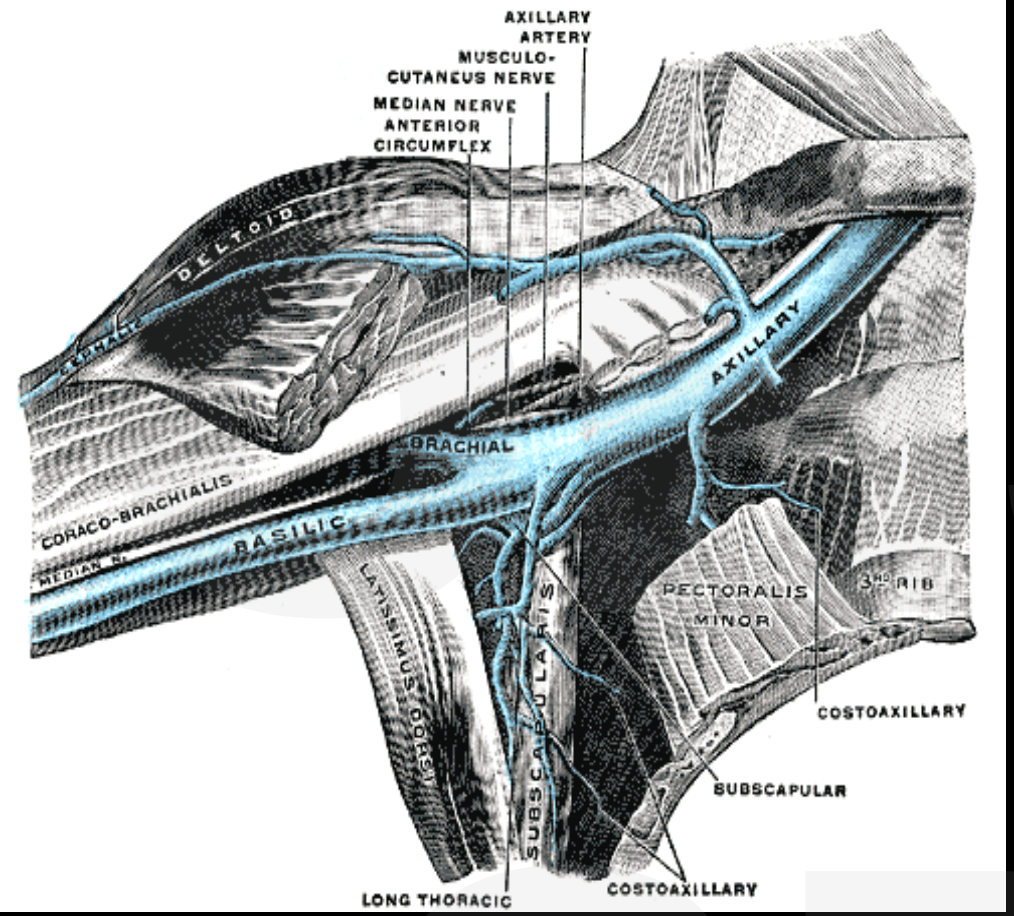
Idiopathic versus provoked thrombosis is **the biggest** determinant of risk of recurrent thrombosis

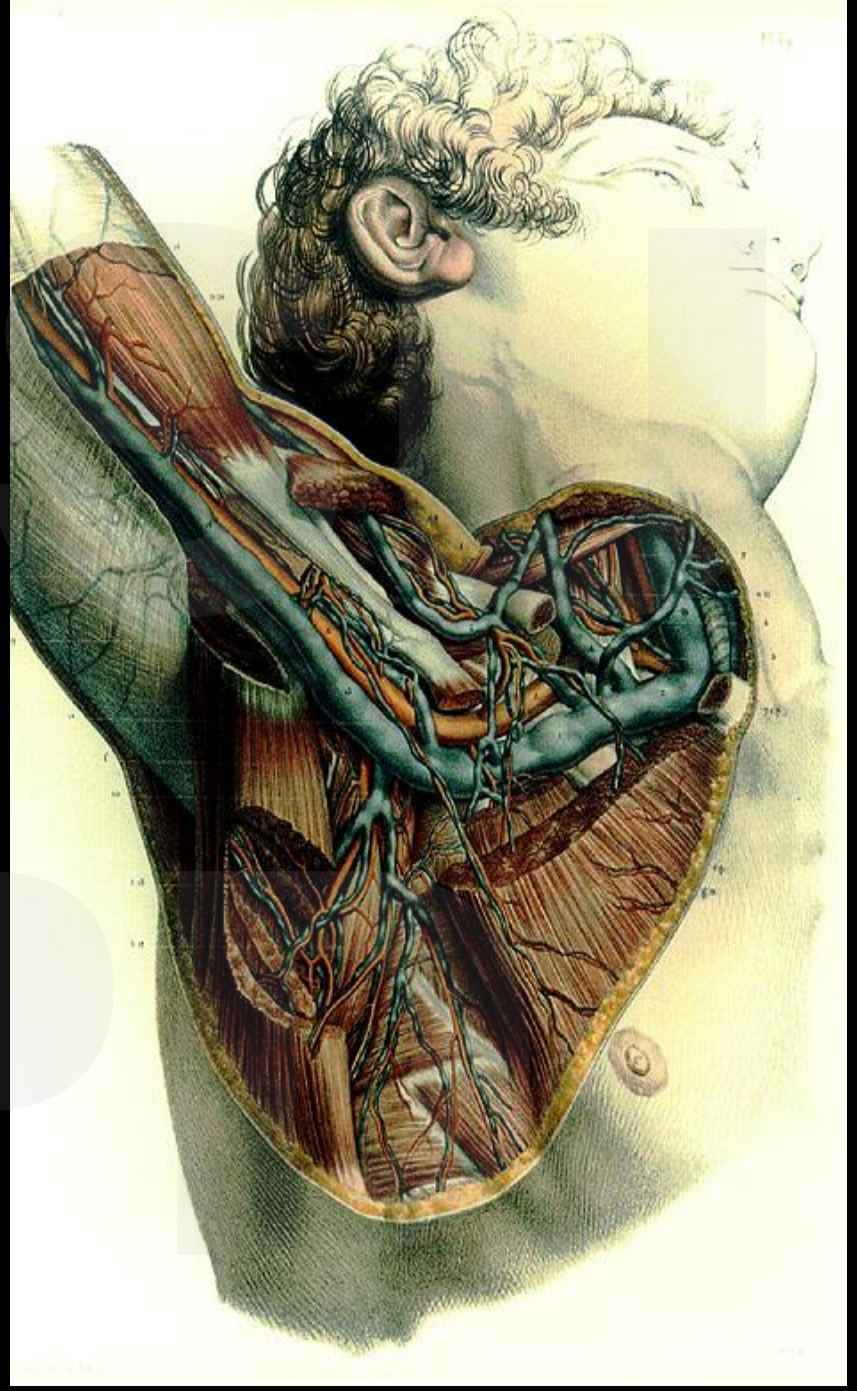
Duration of Therapy

- Not all thrombosis are the same
- Can stratify patients by:
  - Site of thrombosis
  - Circumstances of thrombosis
    - Most important!

Upper Extremity Thrombosis

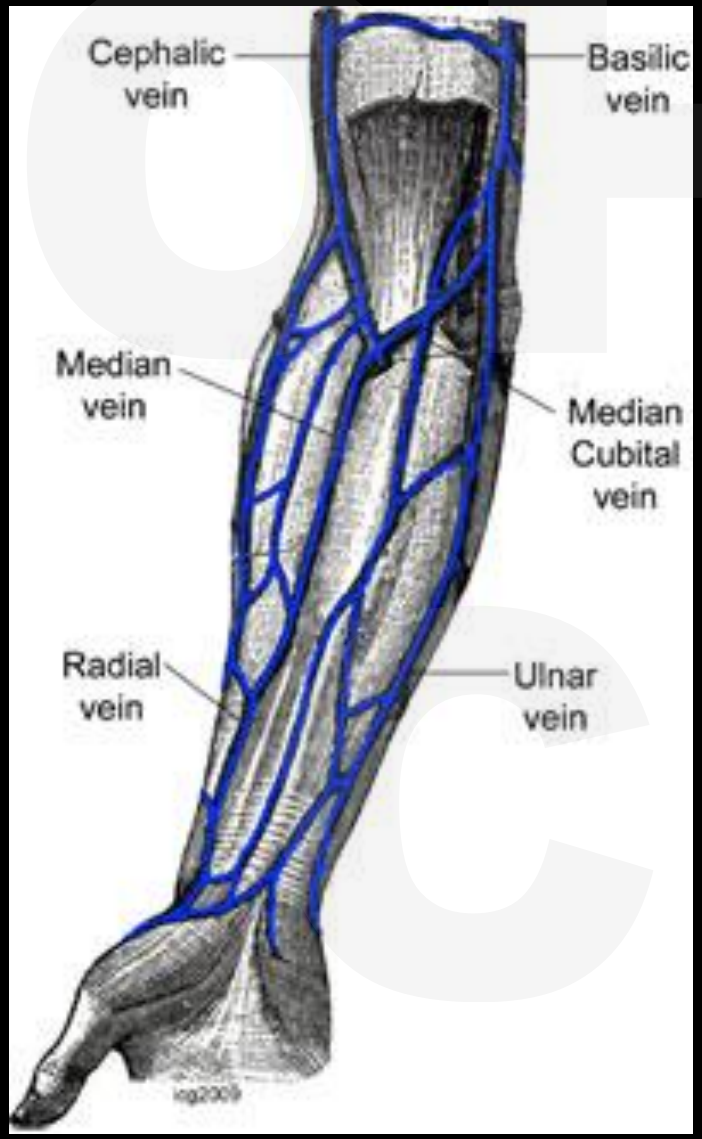
- Mechanical defects
  - Catheter
    - PICC 3-5%
  - Local venous trauma
- Prophylaxis ineffective
- Low risk of serious sequela

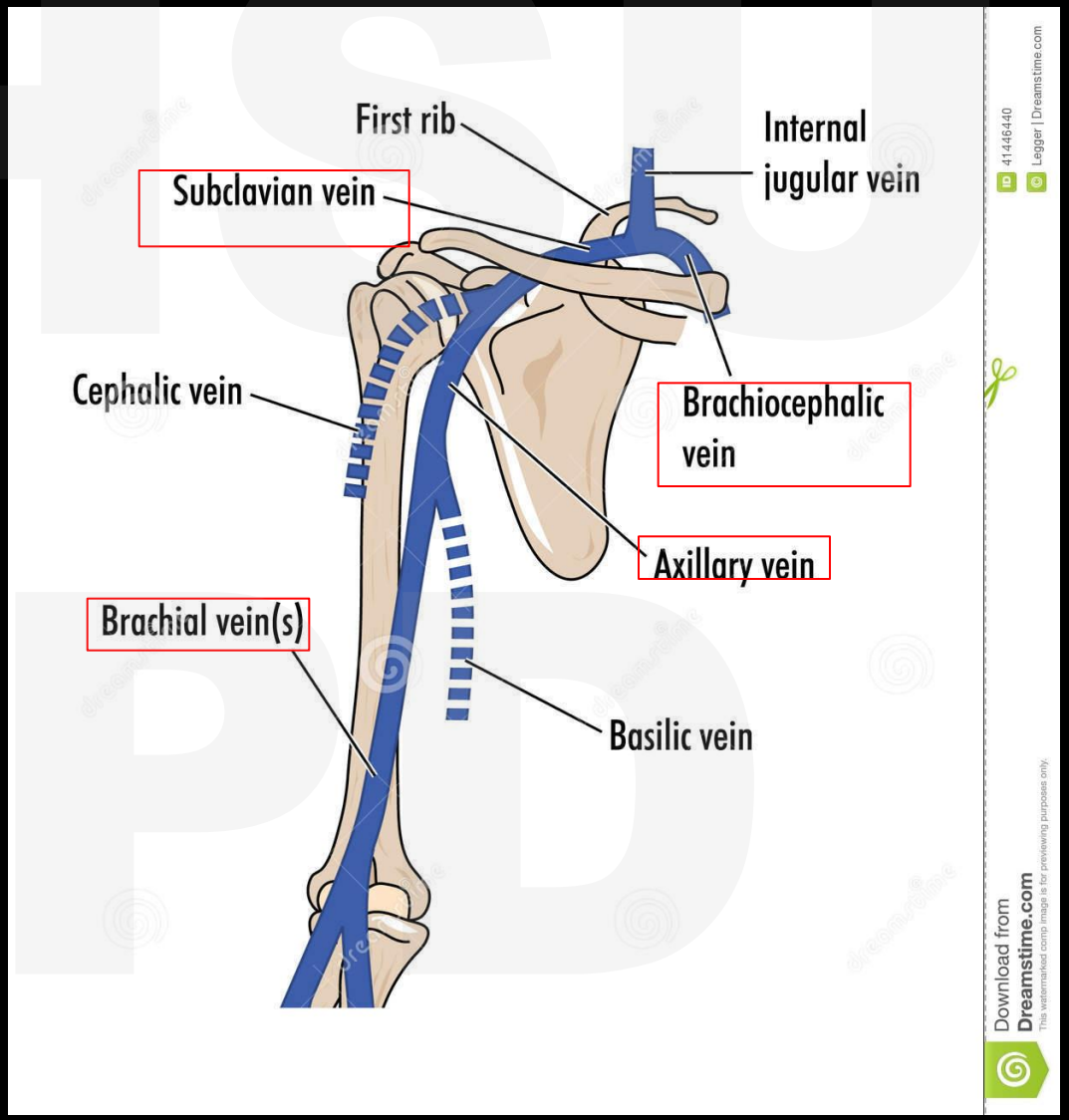

AXILLARY ARTERY
MUSCULO-CUTANEUS NERVE
MEDIAN NERVE
ANTERIOR CIRCUMFLEX
CEPHALIC
DELTOID
AXILLARY
BRACHIAL
CORACO-BRACHIALIS
BASILIC
MEDIAN N.
LATISSIMUS DORSI
SUBSCAPULARIS
PECTORALIS MINOR
3RD RIB
COSTOAXILLARY
SUBSCAPULAR
LONG THORACIC
COSTOAXILLARY



Upper Extremity Thrombosis

- Therapy: PICC Catheter
  - Key is removing catheter
  - No new one for at least 10 days
  - Benefit of anticoagulation uncertain
    - 25% rate of bleeding
  - Remember many are superficial thrombosis





Upper Extremity Thrombosis

- Therapy: Non-PICC Catheter
  - Line can be removed
    - –Assess need for anticoagulation
    - –Substantial rate of bleeding
      - » 5% major bleeding
  - Line cannot be removed
    - –3 months anticoagulation
    - –High rates of serious bleeding

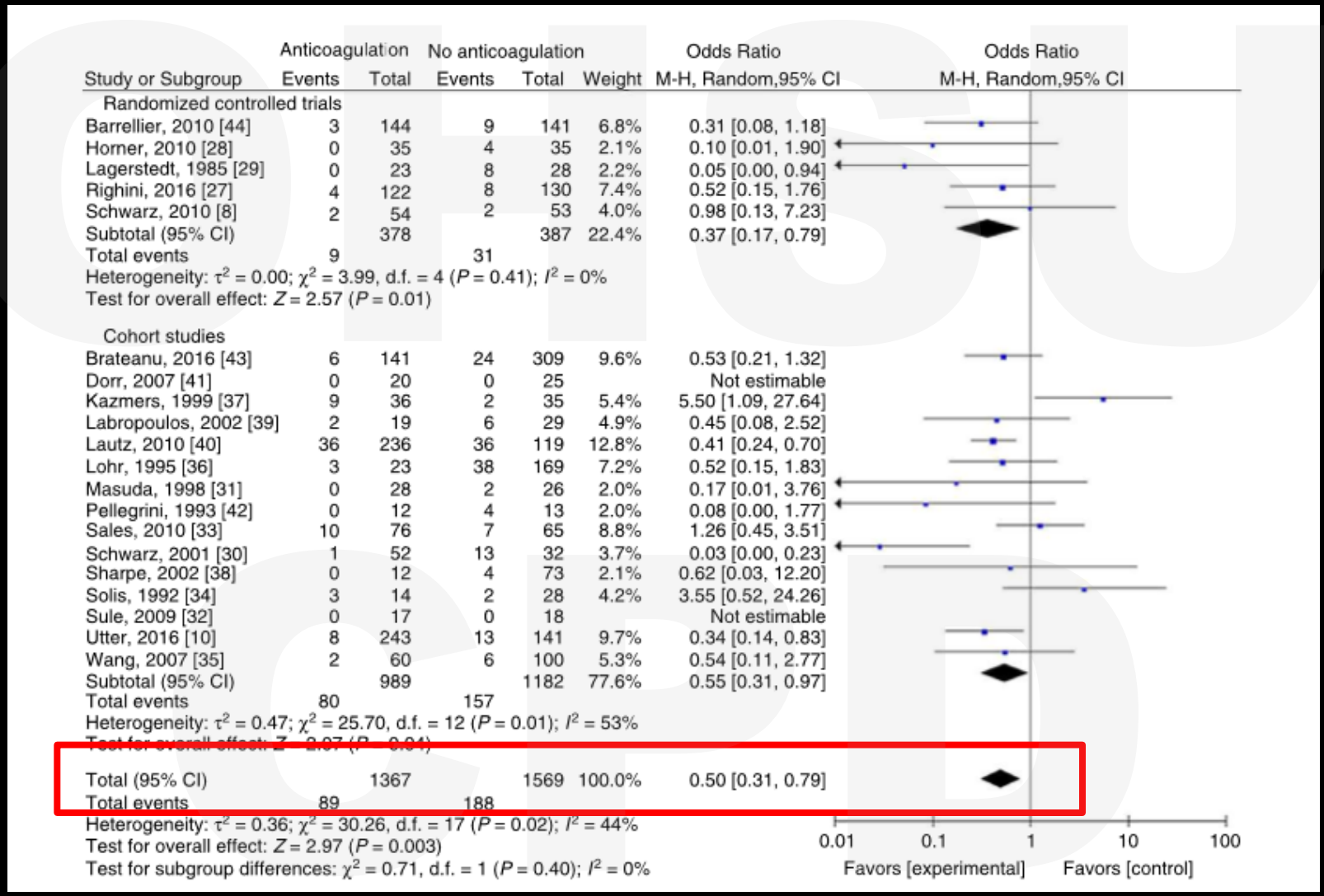
Upper Extremity Thrombosis

- "Spontaneous"
  - 3 months anticoagulation
  - Look for underlying vascular defects
  - Consider thrombolytic therapy
    - ~75% with underlying lesions

Calf Vein Thrombosis

- High risk of progression
  - Up to 10% progression
  - PE rate 2-3%
- **12 weeks** therapy for most patients

Calf Vein Thrombosis Therapy



Study or Subgroup	Anticoagulation Events	Total	No anticoagulation Events	Total	Weight	Odds Ratio M-H, Random,95% CI
Randomized controlled trials						
Barrellier, 2010 [44]	3	144	9	141	6.8%	0.31 [0.08, 1.18]
Horner, 2010 [28]	0	35	4	35	2.1%	0.10 [0.01, 1.90]
Lagerstedt, 1985 [29]	0	23	8	28	2.2%	0.05 [0.00, 0.94]
Righini, 2016 [27]	4	122	8	130	7.4%	0.52 [0.15, 1.76]
Schwarz, 2010 [8]	2	54	2	53	4.0%	0.98 [0.13, 7.23]
Subtotal (95% CI)		378		387	22.4%	0.37 [0.17, 0.79]
Total events	9		31			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 3.99$, d.f. = 4 ($P = 0.41$); $I^2 = 0\%$						
Test for overall effect: $Z = 2.57$ ($P = 0.01$)						
Cohort studies						
Brateanu, 2016 [43]	6	141	24	309	9.6%	0.53 [0.21, 1.32]
Dorr, 2007 [41]	0	20	0	25		Not estimable
Kazmers, 1999 [37]	9	36	2	35	5.4%	5.50 [1.09, 27.64]
Labropoulos, 2002 [39]	2	19	6	29	4.9%	0.45 [0.08, 2.52]
Lautz, 2010 [40]	36	236	36	119	12.8%	0.41 [0.24, 0.70]
Lohr, 1995 [36]	3	23	38	169	7.2%	0.52 [0.15, 1.83]
Masuda, 1998 [31]	0	28	2	26	2.0%	0.17 [0.01, 3.76]
Pellegrini, 1993 [42]	0	12	4	13	2.0%	0.08 [0.00, 1.77]
Sales, 2010 [33]	10	76	7	65	8.8%	1.26 [0.45, 3.51]
Schwarz, 2001 [30]	1	52	13	32	3.7%	0.03 [0.00, 0.23]
Sharpe, 2002 [38]	0	12	4	73	2.1%	0.62 [0.03, 12.20]
Solis, 1992 [34]	3	14	2	28	4.2%	3.55 [0.52, 24.26]
Sule, 2009 [32]	0	17	0	18		Not estimable
Utter, 2016 [10]	8	243	13	141	9.7%	0.34 [0.14, 0.83]
Wang, 2007 [35]	2	60	6	100	5.3%	0.54 [0.11, 2.77]
Subtotal (95% CI)		989		1182	77.6%	0.55 [0.31, 0.97]
Total events	80		157			
Heterogeneity: $\tau^2 = 0.47$; $\chi^2 = 25.70$, d.f. = 12 ($P = 0.01$); $I^2 = 53\%$						
Test for overall effect: $Z = 2.07$ ($P = 0.04$)						
Total (95% CI)		1367		1569	100.0%	0.50 [0.31, 0.79]
Total events	89		188			
Heterogeneity: $\tau^2 = 0.36$; $\chi^2 = 30.26$, d.f. = 17 ($P = 0.02$); $I^2 = 44\%$						
Test for overall effect: $Z = 2.97$ ($P = 0.003$)						
Test for subgroup differences: $\chi^2 = 0.71$, d.f. = 1 ($P = 0.40$); $I^2 = 0\%$						

Journal of Thrombosis and Haemostasis, **15**: 1142–1154

Calf Vein Thrombosis Therapy

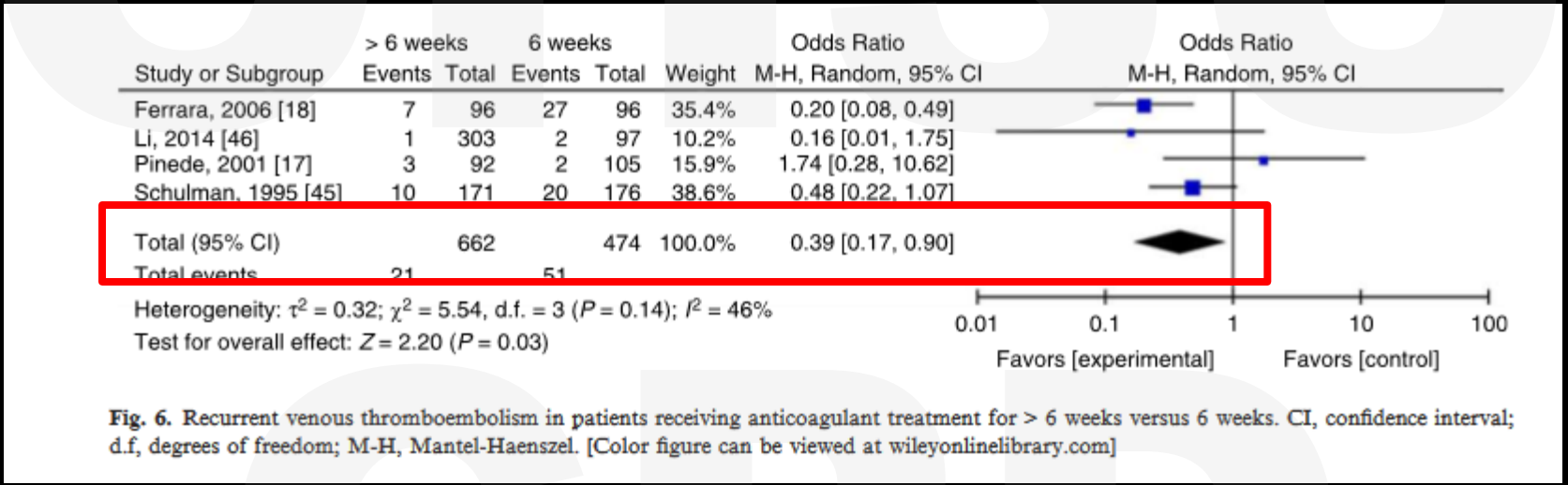


Fig. 6. Recurrent venous thromboembolism in patients receiving anticoagulant treatment for > 6 weeks versus 6 weeks. CI, confidence interval; d.f, degrees of freedom; M-H, Mantel-Haenszel. [Color figure can be viewed at wileyonlinelibrary.com]

Journal of Thrombosis and Haemostasis, **15**: 1142–1154

Distal DVT Trial

- Rivaroxaban 6 vs 12 weeks
- N = 400
- rDVT 6: 15% 12:8%
- No major bleeding
- BMJ. 2022 11 23; 379:e072623

Duration of Therapy: Proximal DVT

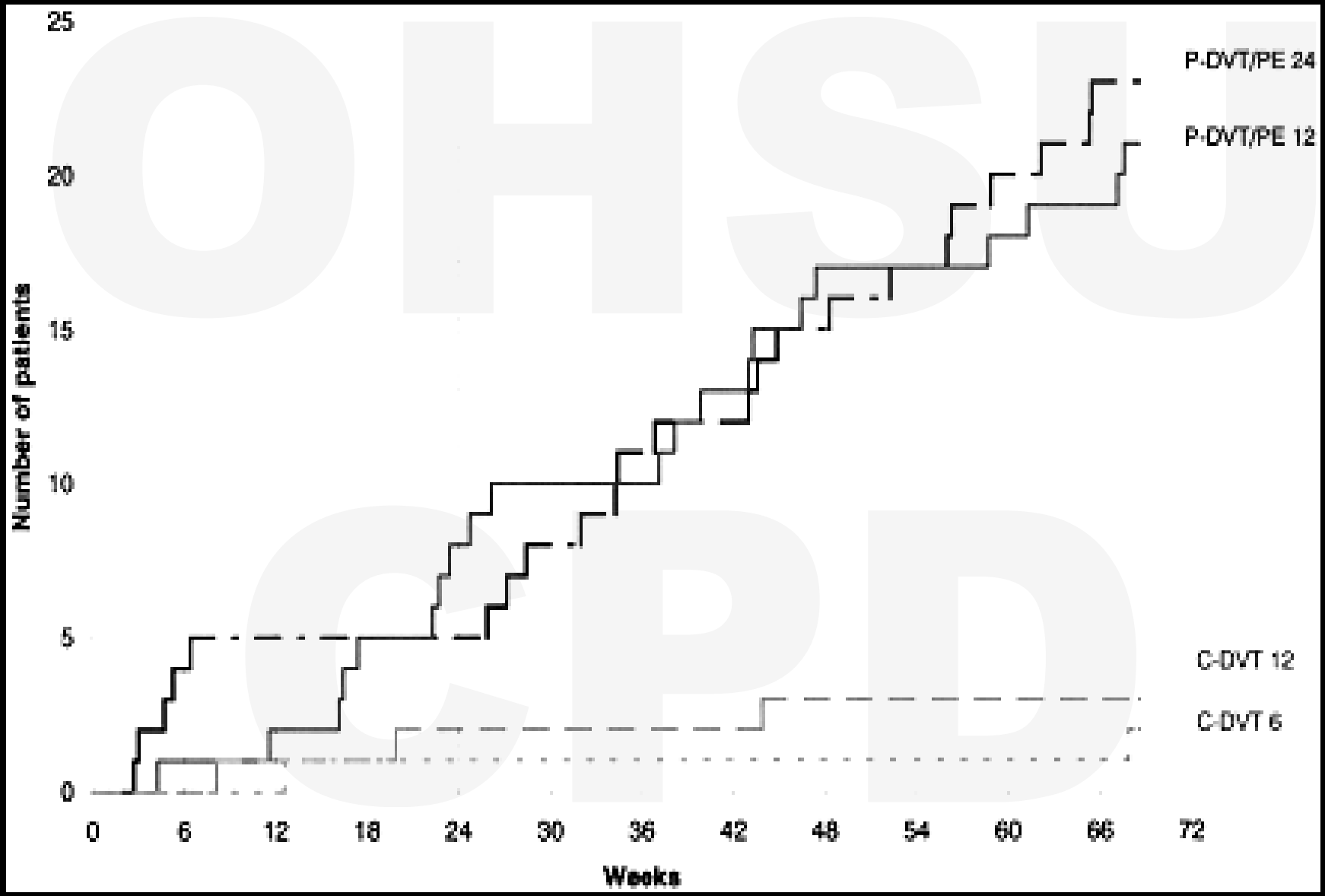
- 3 months
  - Provoked DVT
    - Especially estrogen related
- No benefit with 6 months except more bleeding
- Obtain scan at end of therapy for new baseline
  - J Thromb Haemost. 2011 Dec;9(12):2406-10

Residual Thrombosis

- 3 months – 80.5%
- 6 months - 61%
- 12 months – 42%
- 24 months – 31%
- 36 months – 27%

Prandoni Annals IM 2002

Proximal DVT



Circulation, May 2001; 103: 2453 - 2460.

What is Provoked??

- Major
  - Limb fracture
  - Major trauma
  - Big surgery
  - Estrogen
    - Pregnancy
    - Estrogen-containing contraception
    - HRT
  - Travel

1st Idiopathic VTE

- High rates (30-40%) of recurrence off anticoagulation
- Multiple RCTs show benefit of long term anticoagulation
  - Marked increase in recurrence when stopping anticoagulation

BMJ 2019 Meta-analysis

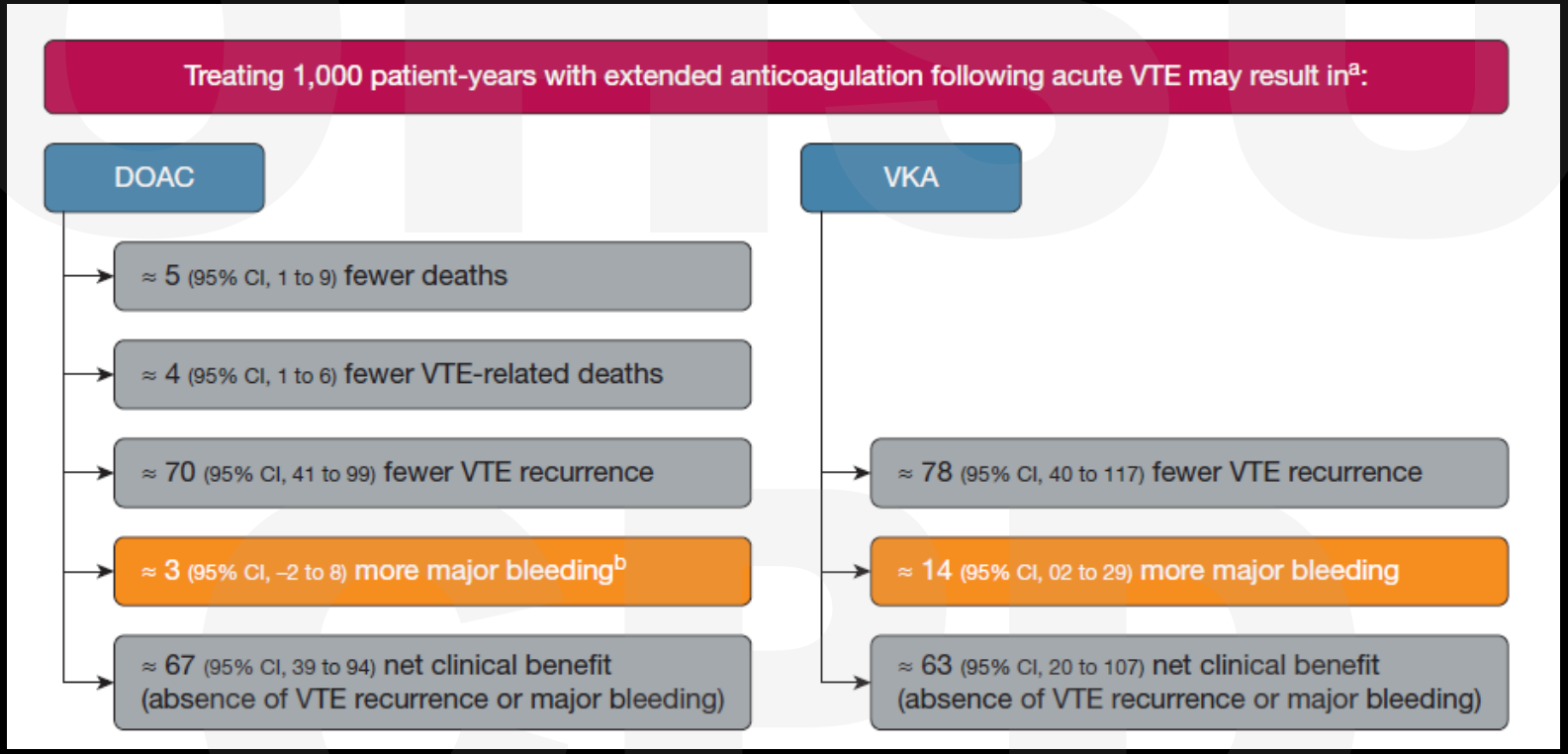
Year	Risk	Cumulative Incidence
1 Year	10.3%	-
2 year	6.3%	16%
3-5 years	3.8%/year	25% 5 years
6-10 years	3.1/year	36% 10 years

Case fatality rate for recurrence 4%

Distal thrombosis 1/10th of risk

BMJ 2019: 366:4364

Extended Therapy



Chest 155:1199-1216, 2019

Two Phases of VTE Therapy

- Active phase (3 months)
  - Prevents reactivation of initial thrombosis
- Secondary prevention (> 3 months)
  - Prevents new thrombosis
  - Need to identify patients who will benefit

- J Thromb Haemo 2012: 10: 507–5

D-Dimers

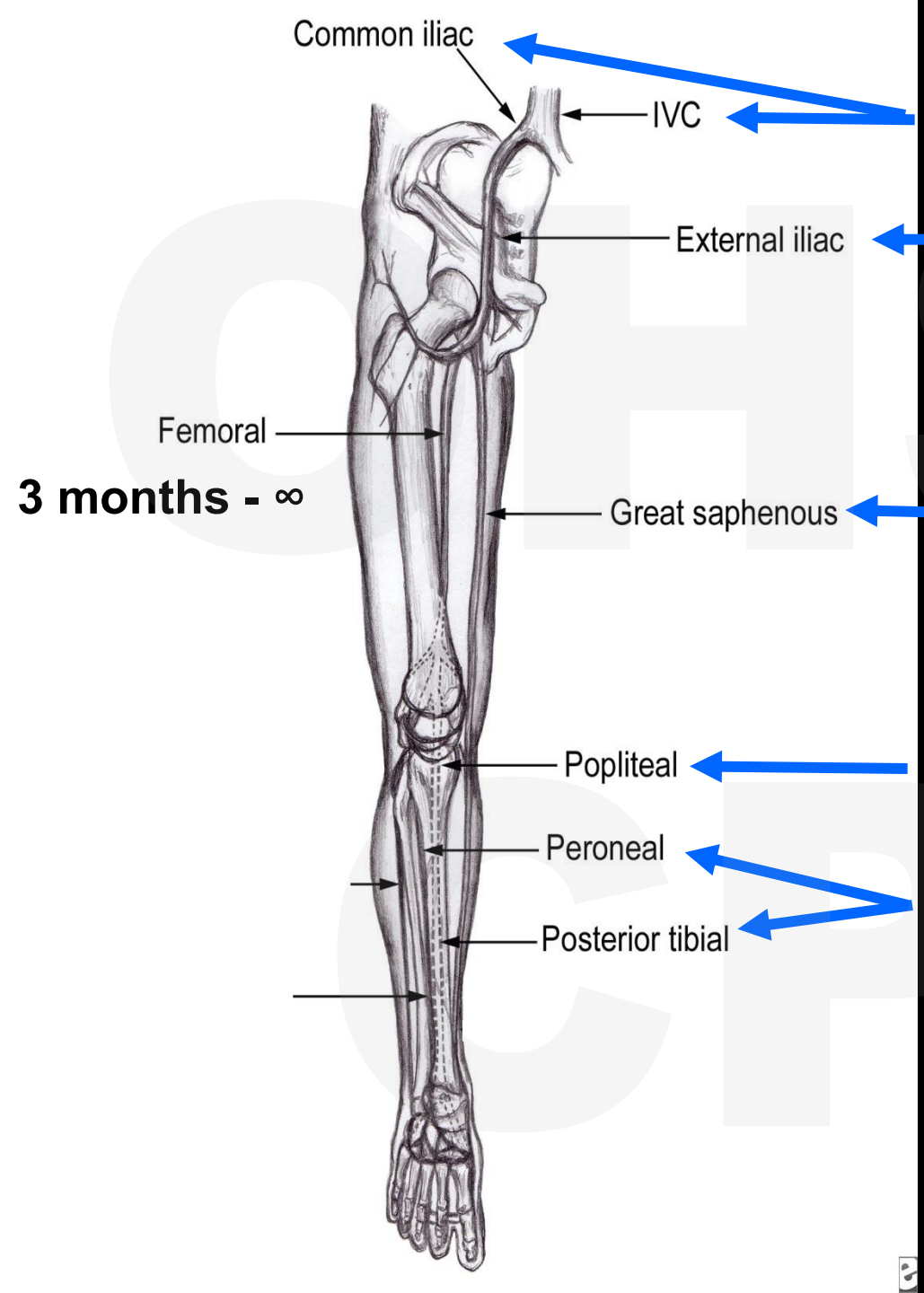
- D-dimers checked off therapy to predict risk
- Meta-analysis
  - 7 studies
  - Positive D-Dimer: 10%/yr
  - Negative D-Dimer: 2.9 - 4.0%/yr
- Unclear if repeat testing helps
- Most recent study showed high rates of recurrence with negative D-dimer 5%/yr

Idiopathic VTE

- No good prediction rules
  - Negative D-dimer - NOT predictive
  - Thrombus resolution – NOT predictive
- Still need better prediction rules!
- Safer anticoagulants is shifting balance toward longer treatment

Duration of Therapy

- Indefinite
  - >1 DVT (except upper ext)
  - Acquired hypercoagulable states
  - Idiopathic unusual site
  - Idiopathic severe pulmonary embolism
- 3 months
  - Provoked pulmonary embolism



3 months - ∞

3 months - ∞

3 months - ∞

14 days
(prophylactic dose)

3 months - ∞

3 months


OHSU

What about Hypercoagulable States?

Hypercoagulable State

- Clear risk factor for 1st VTE
- No evidence with classic genetic states predict recurrence
- Multiple guidelines against checking in provoked thrombosis

Thrombophilia Work-Ups

- Don’t screen for genetic causes
  - For provoked thrombosis
  - Arterial thrombosis
  - Upper extremity thrombosis
- ~$1200

3 Common Questions

- What do I do with this SPEP result?
- What do I do with a high ferritin?
- How long do I anticoagulate?