

# Clotting Conundrums!



**Thomas DeLoughery, MD MACP FAWM**  
**Oregon Health & Sciences University**

**@bloodman**



GENERAL  
HEMATOLOGY

OHSU

# DISCLOSURE

Current Relevant Financial Relationship(s)

None

- **A potpourri of cases raising interesting issues...**

# #1

- **Seeing a 85 YO patient for iron deficiency**
- **You notice she has afib and is on just 2.5mg bid of apixaban because “fall risk” and “being old”**

# DOAC in Patients > 75

Outcomes	OR	CI
Bleeding	1.02	0.73-1.43
Stroke/embolism	0.65	0.48-0.87
VTE/Fatal PE	0.45	0.27-0.77
VTE/Fatal PE*	0.55	0.38 – 0.82

**N = 25,031 in 10 RCT**

**\*N = 3,665**

**JAGS 62:857, 2014, \*JAGS 2020**

# Anticoagulation and Falls

- **Most commonly cited reason not to anticoagulated older patients**
- **But what is the data?**

# Falls: Man-Son-Hing

- Elaborate decision analysis by Man-Son-Hing demonstrate that the average patient would have to fall **295 times** in one year for warfarin to be too dangerous to use.
- Retrospective review of hospital falls show only 1 SDH in 2500 falls

# Gage Study AJM 118:612

- **Patients at risk of falling and Afib had:**
  - Higher incidence of ICH (2.8% vs 1.1%/yr)
  - Higher risk of stroke (13.7% vs 6.9%/yr)
  - More stroke risk factors

# Gage

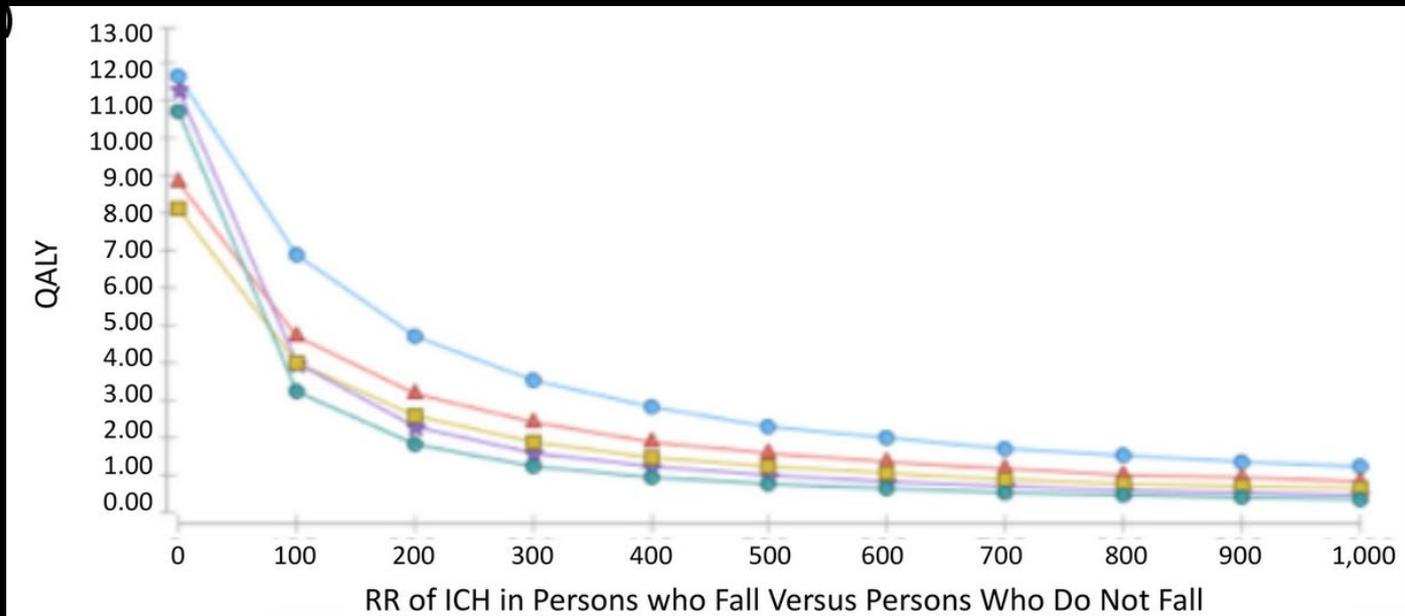
- Warfarin use in patients at risk of falls
  - Did not increase ICH rates
  - Did increase 30 day mortality (52% vs 33%)
- Warfarin for patients with CHADS2 > 2 reduced bad outcomes by 25%

# Donze

- **Prospective study of 515 patients on warfarin**
  - 60% at high risk of falls
- **No** higher risk of bleeding
- **0.6%/yr bleeds after falls**
- **Am J Med 125:773-778, 2012**

# Bond

- 2635 falls in 1861 inpatients
- Major bleeding
  - Warfarin vs nothing
    - 6% vs 11%;  $p = 0.01$
    - No difference with INR 3-5 vs normal
  - Aspirin vs nothing
    - OR 1.45% (1.1 -1.8)
  - Clopidogrel vs nothing
    - OR 2.2 ( 1.1 - 4.8)
- Thromb J. 2005; 3: 1.



**Even patients at very high risk of ICH/falls benefit from anticoagulation in AF**

# Falls: Bottom Line

- Excess bleeding due to falls is markedly overstated
- Patients at risk of falls are those at risk of stroke
- Risk: benefit heavily in favor of treatment esp with DOACs
- Risk of falls is never an excuse to deny patients anticoagulation



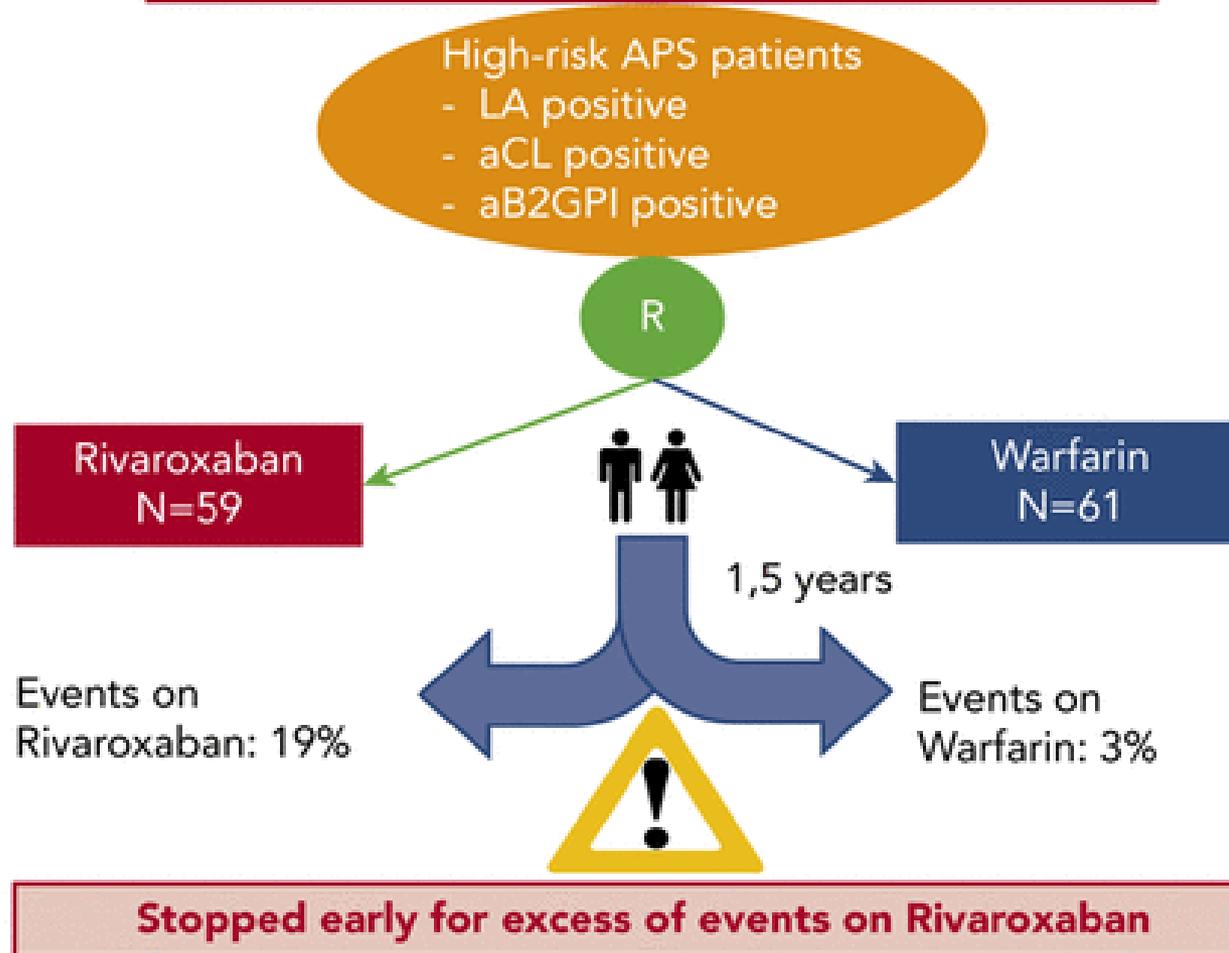
# #2

- eConsult
- Patient had FVL – can they be on a DOAC?

# Thrombophilia

- **Hereditary**
  - No concerns
- **Antiphospholipid Syndrome**
  - Not for triple positive
  - Not for arterial disease
  - Warfarin/LMWH standard

**TRAPS**  
**Randomized controlled trial of Rivaroxaban vs Warfarin in APS**





# #3

- **eConsult**
- **Patient with DVT**
- **Can they change to a DOAC?**
- **Weighs 145 KG**

# Weight

- **Is there a weight limit?**
- **Is this the same VTE and AF?**
- **What about bariatric surgery?**

# Weight

- **DOACs weight base**
- **Obesity**
  - **Atrial fibrillation: 140 kg**
    - **Check level if over 140 kg**
  - **Venous disease: ???**
- **Like with LMWH monitoring levels will allow greater use**

# DOAC –Obesity

- **New guidance no issues with rivaroxaban or apixaban (VTE)**
- **Bariatric**
  - **Gastric banding: Apixaban**
    - **Other check levels**
  - **Gastrectomy: Apixaban**
    - **Other check levels**
  - **RYGB: ?**
    - **Check levels**



# #4

- **Patient with new PE**
- **ED calls you because they are on dialysis**

# Renal: Standard Heparin

- Surprisingly little data!
- Some UFH renally cleared
- Limited data that aPTT underestimates heparin levels
- Increases risk of bleeding 3 fold

# Renal: Low Molecular Weight Heparin

- Renal clearance
- Need to dose adjust
  - Therapy: 1 mg/kg qDay
  - Prophylaxis: 20-30 mg/day
- If dosed right **NO** difference in bleeding compared to UFH

# UFH and LMWH

- **N = 624 with CrCl <60ml**
- **UFH major bleeding**
  - **26.3/1000 patient days**
- **Enoxaparin major bleeding**
  - **20.7/1000 patient days**
  - **Dose NOT renally adjusted!**

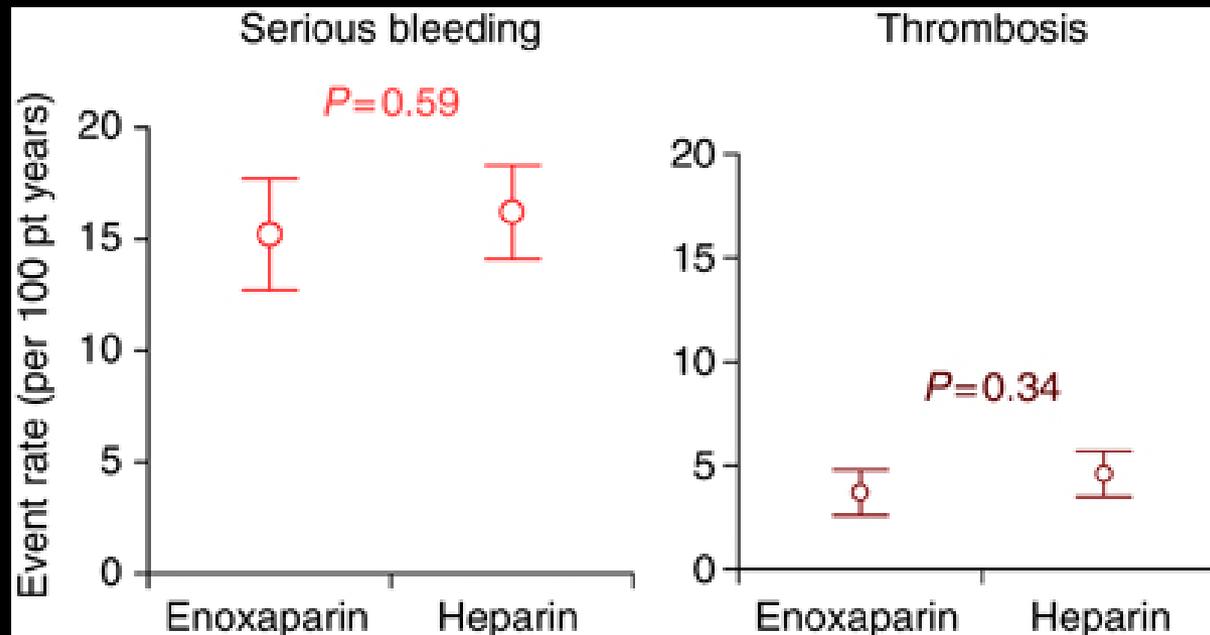
**Chest. 2004 Mar;125(3):856-63.**

# UFH and LMWH

	Mild 40-60	Mod 20-40	Severe <20
UFH	16.9	41.8	30.7
LMWH	12.4	22.5	33.2

Major bleeding /1000 patients days

Chest. 2004 Mar;125(3):856-63.



*Kidney International* (2013) 84, 555–561;

# But...

- **Study in CrCl 30-50 with 4x risk of bleeding**
  - **Especially bridging therapy**
- **Rec:**
  - **Caution with bridging therapy**
  - **Dose decrease for long term**
    - **0.8 mg/kg q 12**
    - **Follow levels**
- **Arch Int Med 2012 Dec 10;172(22):1713-8.**

# Warfarin

- **CYP 2C9 decreased by 30%**
- **Risk of bleeding 3 fold increased**
- **Increased incidence of erratic INR's**
  - **Supplement vitamin K**
  - **DOACs?**

# DOAC: Renal Disease

- **Renal Function**

- **All renally cleared:**

- **Apixaban – dose reduced to 2.5 mg bid if**
      - **Creatinine > 1.5 + age over 80 or weight < 60kg**
      - **Increasing dialysis data**
    - **Dabigatran – not for CrCl < 50**
    - **Rivaroxaban – 15mg CrCl 49-15**
      - **10mg for dialysis**
    - **Edoxaban –30mg/day if CrCl 15-50**

# Apixaban: Dialysis

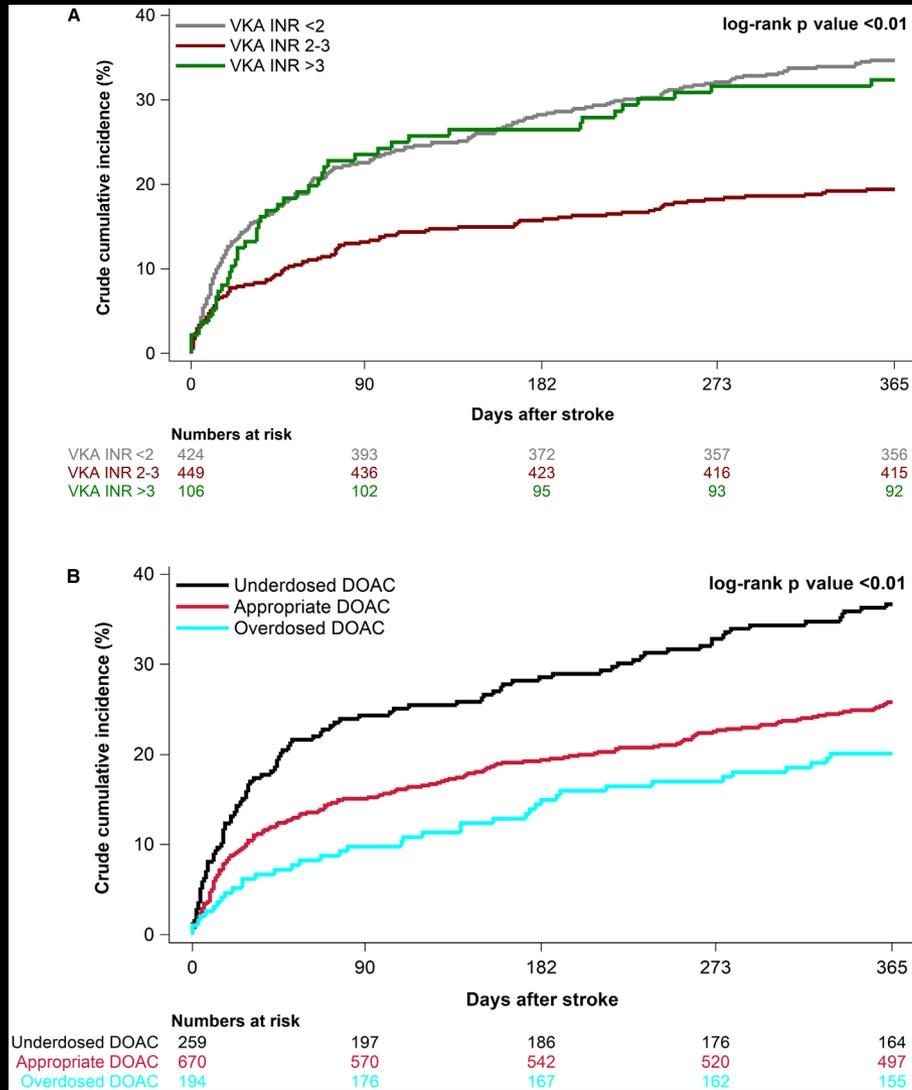
- Medicare dialysis patients
- Use of apixaban 5mg bid vs warf
  - Less bleeding
  - Less stroke
  - Less mortality
- Circulation. 2018;138:1519–1529

# Use Right Dose!

- Increasing data that under dosing DOACs lead to more thrombosis/stroke without change in bleeding risk
- Only dose adjust if indicated!

# Wrong Dosing

	Stroke/Systemic Embolism HR (95% CI)	Bleeding HR (95% CI)
Off-Label <u>UNDER</u> -dose	<b>↑ 22%</b> 1.22 (1.05-1.42)	<u>No difference</u> 0.95 (0.82-1.11)
Off-Label <u>OVER</u> -dose	<b>↑ 26%</b> 1.26 (1.11-1.43)	<b>↑ 30%</b> 1.30 (1.04-1.62)





# #5

- **While you are talking to the ED they have a patient with a new portal vein thrombosis**
- **“Too risky to anticoagulated liver disease right?”**

# Portland Portal Vein Protocol



# Portal Vein: Cirrhosis

- **Incidental**
  - **SMV negative – no treat**
  - **SMV involved - treat**
- **Symptomatic – treat**

# Noncirrhotics: Symptomatic

- **Provoked**
  - **Surgery**
  - **Infection, etc.**
    - **Treatment: 3 months**
    - **Work-up: not recommended**
- **Unprovoked**
  - **PNH, MPS, APLA**
  - **Indefinite anticoagulation**

# 2017 Meta-Analysis

- **8 studies with 353 patients**
- **Recanalization**
  - **71% vs 42%**
- **Complete recanalization**
  - **53% vs 33%**
- **PVT progression**
  - **9% vs 33%**
- **Bleeding**
  - **11% vs 11%**
- **Gastro 153:480, 2017**

# 2021 Update: DOAC & PVT

- **DOAC vs Warfarin**
  - Increased PVT recanalization – RR = 1.67
  - Decreased progression – RR = 0.14
- **Anticoagulation in PVT**
  - Increased PVT recanalization – OR 4.29
  - Decreased progression – OR 0.26
  - Bleeding slightly up – OR 1.16

# DOAC in PVT

- **Increasing data on safety in liver disease**
  - **Easier to use**
  - **Less bleeding**
- **Drug of choice: apixaban**
- **Exception Child C**
  - **Case by case basis**



# #6

- **Questioned emailed from a podcast listener**
- **“What do we do about breakthrough clots”**

# **“Break-Through” Clots**

- **DOACs are not perfect**
- **Neither are patients...**

# **“Break-Through” Clots**

## **1. Is it a breakthrough clot?**

- New PE in first week ~ 5%**
- DVT can grow on therapy**
- New: new vessel or limb involved**
- PE after 2 weeks**
  
- Olson SR, RPTH 2019**

# **“Break-Through” Clots**

- **2. Was patient taking med?**
  - **Ideal: levels sent**
  - **Ok: INR/PTT check**
  - **Check DOAC dose**
  - **Ask patient**
  - **Check pharmacy**

# **“Break-Through” Clots**

## **3. Treatment**

### **– LMWH**

- If breakthrough LMWH raise dose 25%**

### **– Warfarin**

- Compliance concerns**



# #7

- **Asked to see patient with GI bleed on warfarin**

# **Anticoagulation: When to Restart after a Bleed**

- **Very common problem**
- **Increasing data on subject**
- **Risk of rebleed varies with site of bleed and presence of anatomic lesions**

# Risk of Rebleeding

- **ICH/SDH: long term risk of recurrence ~2%**
  - Higher if cerebral amyloid angiopathy present (deep lobar bleeds)
- **Gastrointestinal**
  - Higher (10-20%?) especially if lesion present

# GI Bleeding

- 9 studies show restarting anticoagulation
  - Associated with **less** thrombosis
  - Associated with **less** mortality
  - Minimal increase in the risk of bleeding
  - Apixaban less bleeding
- Restart 7 days
  - All GI bleeding patients needs work-up

# CNS Bleeding

- Risk of rebleeding 1-2%
- Higher if lobar bleed
  - Cerebral amyloid angiopathy
- Increasing data that is better to restart anticoagulation

# CNS Bleeding

Meta-analysis 10 studies

	Restart	Stop	HR
Death	18.7%	32.3%	0.51
Stroke	3.5%	7.0%	0.56
New ICH	6.7%	7.7%	NS

Thromb Res. 2017 Dec;160:97-104

# Aspirin after ICH

- **Not a substitute for anticoagulation**
  - **No affect on stroke rates**
  - **Increased risk of bleeding**
- **Nothing or anticoagulation**

# CNS Bleeding

- **Unless evidence of CAA restart anticoagulation**
- **Apixaban may be safer**
- **No concurrent antiplatelet therapy**
- **Restart 14-28 days**
- **RCT underway**



# #8

- **Long time patient of yours wants her enoxaparin refilled to bridge before her colonoscopy**

# Anticoagulation and Surgery

- **Millions of people on anticoagulation**
- **~10% yearly need procedures**
- **Common issue is peri-operative management**

# **Approaches to Warfarin Anticoagulation and Procedures**

- **Continue agents**
- **Stop drug**
- **Bridging therapy**

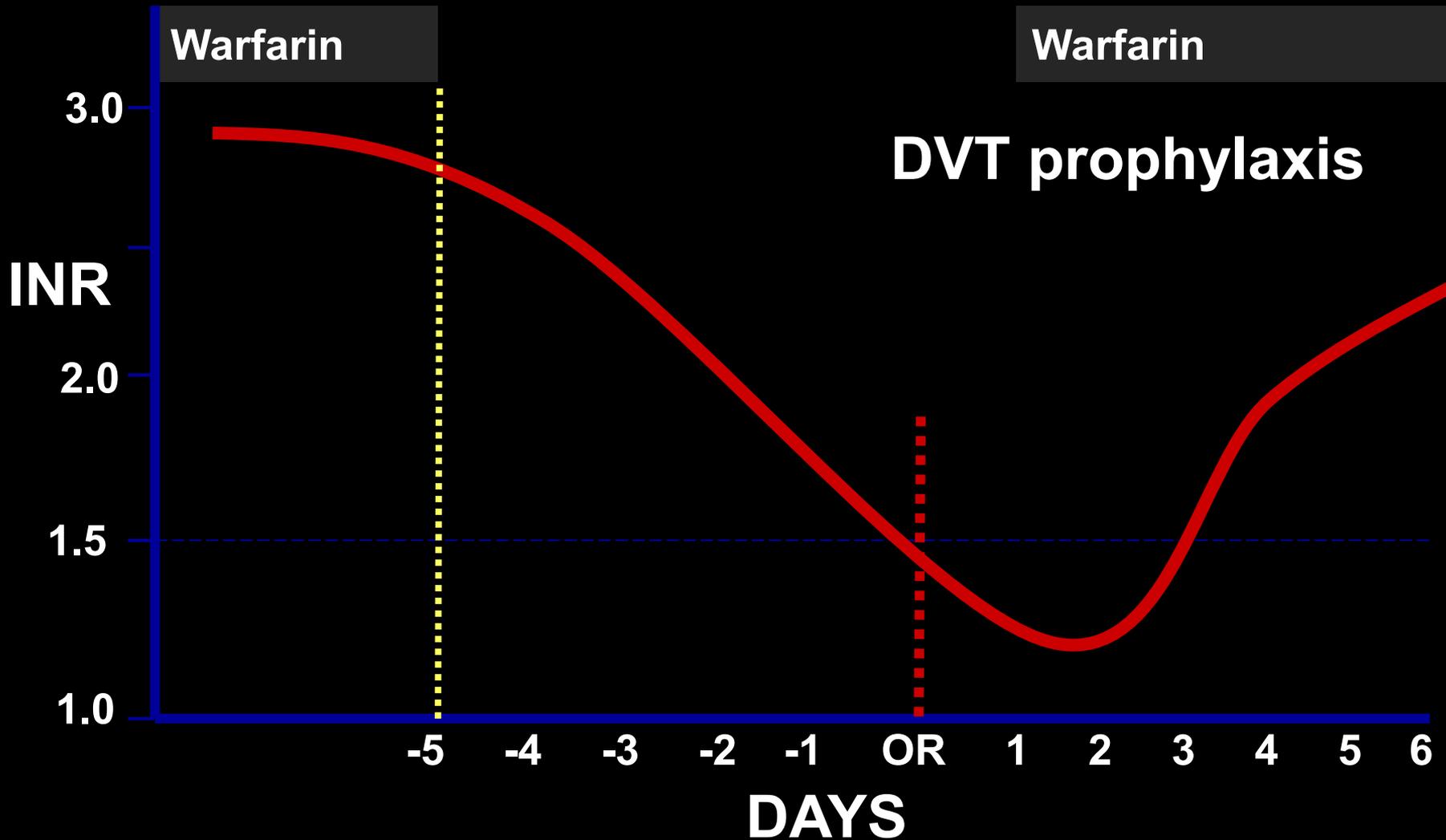
# Continue Warfarin

- **Recommended approach for low risk procedures**
  - Dental extractions
  - Cataracts
  - Simple endoscopy/colonoscopy
  - Pacemaker/ICD placement
  - Hip/Knee arthroplasty
- **Works best if INR < 3.0**

# Stop all Drugs

- Approach associated with least risk of bleeding but (in theory) highest risk of thrombosis
- Warfarin and antiplatelet agents must be stopped **5-7** days before procedure
- Can take 2-5 days to get INR back up
- Best approach for patients not at high risk of thrombosis

# Holding Anticoagulation



# Bridging



# Bridging

- **Covering the patient with LMWH while off warfarin**
- **Increasing data**
  - **Increases risk of bleeding**
  - **No decrease in thrombosis**
- **Shift away from aggressive bridging**



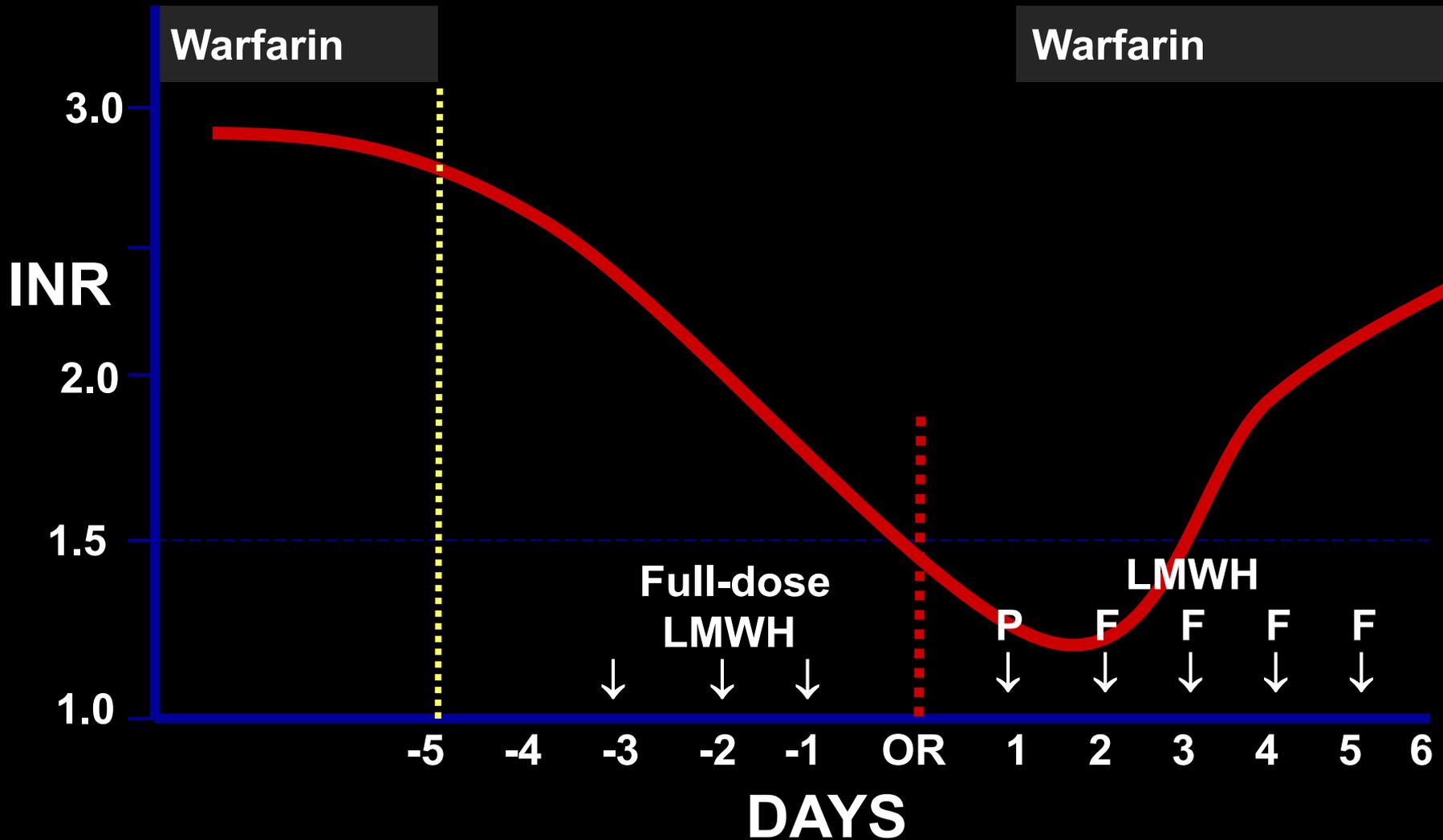
### Restarting LMWH

Simple procedure – after procedure

Complex – Prophylactic 24-48 hrs

- Therapeutic **48** hrs or more

# Bridging Therapy

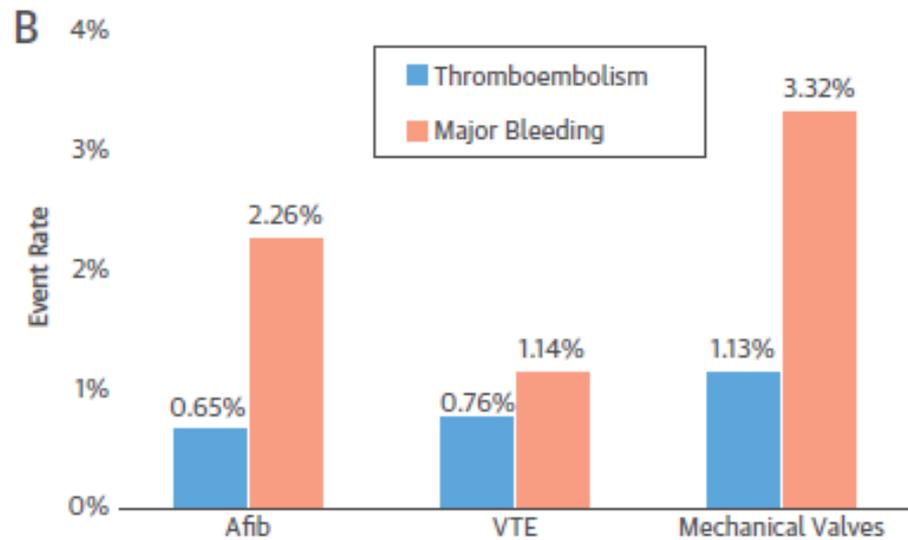
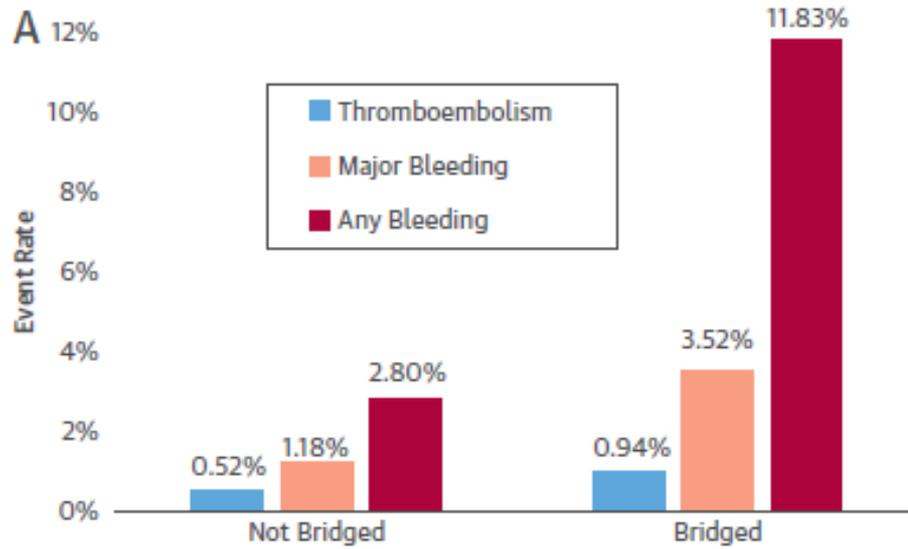


**But Does Bridging Work?**

# 2012 Meta-Analysis

- N = 12,278 patients in 34 studies
- Bleeding **5.4** (3.00-9.74)
- Major bleeding **3.6** (1.52-8.50)
- Thrombosis **0.8** (0.42-1.54)
- Circulation 126:1630, 2012

**FIGURE 1** Rates of Periprocedural Thromboembolism and Bleeding



# Bridge Trial

- **N = 1884**
- **Atrial fibrillation CHAD2  $\geq$  1**
- **Excluded:**
  - **Mechanical valves**
  - **Stroke, arterial or venous thrombosis last 12 weeks**
- **NEJM 373:823, 2015**

# Bridge Trial

	No Bridge	Bridge
Arterial Thrombosis	4 (0.4)	3 (0.3)
Venous thrombosis	0 (0)	2 (0.2)
MI	7 (0.8)	14 (1.6)
Major Bleeding	12 (1.3)	<b>29 (3.2)</b>

# Bottom Line

- Bridging associated with **harm** and no reduction in thrombosis
- Only highest risk patients should be bridged

# Who to Bridge: Valves

- **Valves**
  - **Mitral valve replacement**
  - **Multiple valves**
  - **Non-bileaflet aortic valve**
  - **Bileaflet AVR with other risk factors**

# **Who to Bridge: Atrial Fibrillation**

- **Atrial fibrillation**
  - **Mechanical valves**
  - **Recent (< 12 weeks) stroke, arterial or venous thrombosis**
  - **Rheumatic Valvular disease**
  - **CHADS 5-6??**

# **Who to Bridge: Venous Thrombosis**

- **Venous Thrombosis**
  - **Thrombus within 3 months**
    - **One month IVC filter?**
  - **Cancer and thrombosis**
  - **Virulent thrombophilia**

# Indication for Warfarin

**Bridge?**

**Mechanical Valve**

**Atrial  
Fibrillation**

**Venous  
Thrombosis**

**YES**

**Mitral  
Older valve  
Non-Bileaflet Aortic  
Bileaflet Aortic + stroke  
risk factors**

**Mechanical or  
rheumatic valve  
Recent event**

**VTE last 3  
months  
Severe  
thrombophilia  
Cancer**

**NO**

**Bileaflet Valve and NO  
stroke risk factors**

**All other atrial  
fibrillation**

**VTE > 3 months  
ago, no other  
major risk  
factors**

# Factors Which Increase Risk for Bleeding

- **Pre-procedure**
  - **Trough LMWH level too high**
    - **Need to stop q12 LMWH 24 hours before and q24 maybe 36-48%**
    - **Too aggressive LMWH in patients with renal disease**
- **Post-procedure**
  - **Starting therapeutic LMWH too soon!!**
    - **Need 48 hours or more**
- **Do not use fondaparinux**

# Post-Op

- **PERIOP-2**
- **N = 1471**
- **Randomized (all restarted warfarin)**
  - **No LMWH after surgery**
  - **LMWH bridging until INR at goal**
- **BMJ 2021**

# Post-Op

- **Thrombosis**
  - NB: 1.2%   B: 1.0%
- **Major Bleeding**
  - NB: 2%   B: 1.3%
- **No benefit of post-op aggressive bridging**

# Post-Op

- **Restart warfarin**
- **Prophylactic LMWH if in hospital**



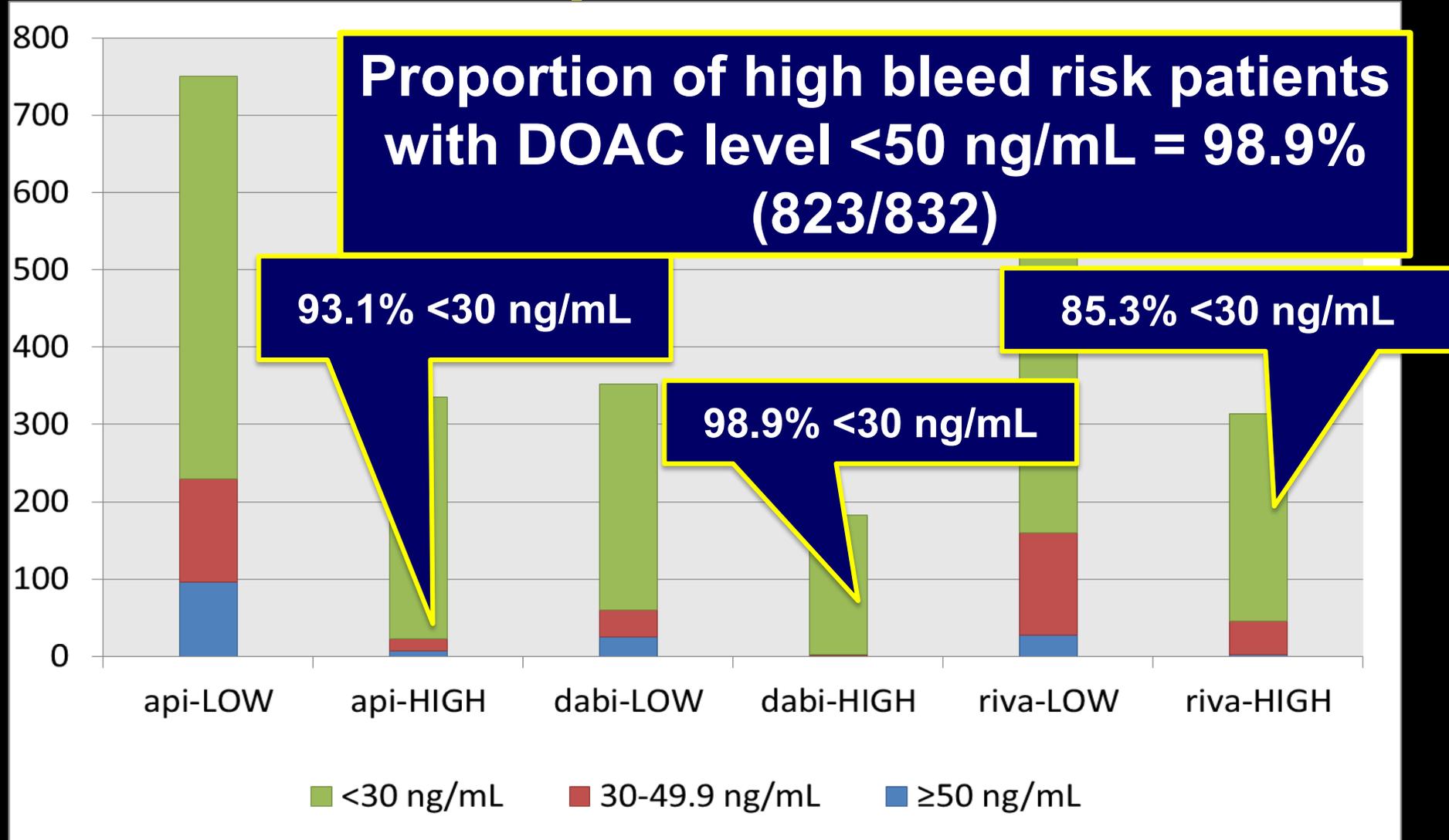
# DOACs and Surgery

- Protocol based on drug, renal function and surgery
- **Minor**
  - Endoscopy
  - Dermatologic surgery
- **Major**
  - Abdomen or thoracic surgery
- **NEVER** need bridging

# DOACs and Surgery

Drug	Surgery	CrCl	-4	-3	-2	-1	Surgery
Apix	Major				Hold	Hold	Hold
	Minor					Hold	Hold
Dabig	Major	>50			Hold	Hold	Hold
		<50	Hold	Hold	Hold	Hold	Hold
	Minor	>50				Hold	Hold
		<50		Hold	Hold	Hold	Hold
Rivarox	Major				Hold	Hold	Hold
	Minor					Hold	Hold

# Residual Preoperative DOAC Levels



# DOACs: Post Surgery

- **Treat like LMWH**
- **Simple – restart next day**
- **Complex**
  - **Prophylactic dose**
  - **Full dose 48 hours or more**





## Summary of RCT Results (>80% LMWH)

Trial	COVID patient population	Anticoagulant Dose Comparisons (LMWH)	Primary Outcome Results
Perepu et al.	~2/3 ICU ↑D-dimer	Intermediate vs. prophylactic	No difference
INSPIRATION	ICU patients	Intermediate vs. prophylactic	No difference
Multiplatform RCT	ICU stratum	Therapeutic vs prophylactic/interm	Prophylactic-dose better
Multiplatform RCT	non-ICU stratum	Therapeutic vs prophylactic/interm	Therapeutic-dose better
ACTION	non-ICU ↑D-dimer	Therapeutic vs prophylactic ( <i>DOAC</i> )	No difference
HEP-COVID	~2/3 non-ICU, ↑D-dimer	Therapeutic vs prophylactic/interm	Therapeutic-dose better
RAPID	non-ICU ↑D-dimer	Therapeutic vs prophylactic	Therapeutic-dose better

# COVID

- **Mild – no anticoagulation**
- **Hospitalization on oxygen – therapeutic LMWH**
- **ICU – prophylactic LMWH**
- **Discharge – consider prophylaxis in high risk patients**

