

Dare We DOAC??



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GENERAL
HEMATOLOGY

DISCLOSURE

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CAN WE LOOK FORWARD TO BETTER ANTICOAGULANTS
THAN HEPARIN AND DICUMAROL?

KARL PAUL LINK,
University of Wisconsin,
Madison, Wisc.

March 26, 1949

March 26, 1949

CHICAGO MEDICAL SOCIETY BULLETIN

Disadvantages of Warfarin

- Drug interactions
- Food interactions
- Variable² metabolism
- Frequent monitoring

DRUGS THAT INTERACT WITH WARFARIN

Abciximab	Corticotropin	Ibuprofen	Ofloxacin	Secobarbital
Acetaminophen	Cortisone	Ifosamide	Olsalazine	Sertaline
Alcohol (acute and chronic)	Coumadin	Indomethacin	Omeprazole	Simvastatin
Allopurinol	Cyclophosphamide	Influenza virus vaccine	Oxaprozol	Spironolactone
Aminodarone	Danazol	Itraconazole	Oxymetholone	Stanozolol
Aminoglutethimide	Dextran	Ketoprofen	Paraldehyde	Streptokinase
Amobarbital	Dextrothyroxine	Ketorolac	Paroxetine	Sucralfate
Anabolic steroids	Diazoxide	Levamisol	Penicillin G	Sulfamethazole
Aspirin	Diclofenac	Levothyroxine	Pentobarbital	Sulfamethoxazole
Azathioprine	Dicloxacillin	Liothyronine	Pentoxifylline	Sulfipyrazone
Butabarbital	Diflunisal	Lovastatin	Phenobarbital	Sulfipyrazone
Butalbital	Disulfiram	Mefenamic	Phenylbutazone	Sulfisoxazole
Carbamazepine	Doxycycline	Meprobamate	Phenytoin	Sulindac
Cefoperazone	Erythromycin	Methimazole	Piperacillin	Tamoxifen
Cefotetan	Ethacrynic acid	Methyldopa	Piroxicam	Tetracycline
Cefoxitin	Ethchlorvynol	Methylphenidate	Prednisone	Thyroid hormone
Ceftriaxone	Fenoprofen	Methylsallylate	Primidone	Ticacillin
Chenodiol	Fluconazole	Miconazole	Propafenone	Ticlopidine
Chloral hydrate	Fluorouracil	Metronidazole	Propoxyphene	t-PA
Chloramphenicol	Gemfibrozil	Miconazole	Propranolol	Tolbutamide
Chlorpropamide	Glucagon	Moricizine HCl	Propylthiouracil	Trazodone
Chlorthalidone	Glutethimide	Nafcillin	Phytonadione	Trimethoprim- sulfamethoxazole
Cholestyramine	Griseofulvin	Nalidixic acid	Quinidine	Urokinase
Cimetidine	Haloperidol	Naproxen	Quinine	Valproate
Ciprofloxacin	Halothane	Neomycin	Ranitidine	Vitamin C
Clarithromycin	Heparin	Norfloxacin	Rifampin	Vitamin E

Drug	Interaction	Effect
Abciximab	Antiplatelet agent	Increased risk of bleeding
Acetaminophen	Pain reliever	Increased risk of liver damage
Alcohol	Central nervous system depressant	Increased risk of bleeding and liver damage
Allopurinol	Gout medication	Increased risk of bleeding
Aminodarone	Antidepressant	Increased risk of bleeding
Aminoglutethimide	Antidepressant	Increased risk of bleeding
Amobarbital	Sedative	Increased risk of bleeding
Anabolic steroids	Hormone	Increased risk of bleeding
Aspirin	Pain reliever	Increased risk of bleeding
Azathioprine	Immunosuppressant	Increased risk of bleeding
Butabarbital	Sedative	Increased risk of bleeding
Butalbital	Sedative	Increased risk of bleeding
Carbamazepine	Antiepileptic drug	Increased risk of bleeding
Cefoperazone	Antibiotic	Increased risk of bleeding
Cefotetan	Antibiotic	Increased risk of bleeding
Cefoxitin	Antibiotic	Increased risk of bleeding
Ceftriaxone	Antibiotic	Increased risk of bleeding
Chenodiol	Bile acid sequestrant	Increased risk of bleeding
Chloral hydrate	Sedative	Increased risk of bleeding
Chloramphenicol	Antibiotic	Increased risk of bleeding
Chlorpropamide	Antidiabetic drug	Increased risk of bleeding
Chlorthalidone	Diuretic	Increased risk of bleeding
Cholestyramine	Bile acid sequestrant	Increased risk of bleeding
Cimetidine	Antacid	Increased risk of bleeding
Ciprofloxacin	Antibiotic	Increased risk of bleeding
Clarithromycin	Antibiotic	Increased risk of bleeding
Clofibrate	Lipid-lowering agent	Increased risk of bleeding
Corticotropin	Hormone	Increased risk of bleeding
Cortisone	Hormone	Increased risk of bleeding
Coumadin	Anticoagulant	Increased risk of bleeding
Cyclophosphamide	Chemotherapy	Increased risk of bleeding
Danazol	Hormone	Increased risk of bleeding
Dextran	Volume expander	Increased risk of bleeding
Dextrothyroxine	Thyroid medication	Increased risk of bleeding
Diazoxide	Antihypertensive	Increased risk of bleeding
Diclofenac	Pain reliever	Increased risk of bleeding
Dicloxacillin	Antibiotic	Increased risk of bleeding
Diflunisal	Pain reliever	Increased risk of bleeding
Disulfiram	Alcoholism medication	Increased risk of bleeding
Doxycycline	Antibiotic	Increased risk of bleeding
Erythromycin	Antibiotic	Increased risk of bleeding
Ethacrynic acid	Diuretic	Increased risk of bleeding
Ethchlorvynol	Sedative	Increased risk of bleeding
Fenoprofen	Pain reliever	Increased risk of bleeding
Fluconazole	Antifungal	Increased risk of bleeding
Fluorouracil	Chemotherapy	Increased risk of bleeding
Gemfibrozil	Lipid-lowering agent	Increased risk of bleeding
Glucagon	Antidiabetic drug	Increased risk of bleeding
Glutethimide	Sedative	Increased risk of bleeding
Griseofulvin	Antifungal	Increased risk of bleeding
Haloperidol	Antipsychotic	Increased risk of bleeding
Halothane	Anesthetic	Increased risk of bleeding
Heparin	Anticoagulant	Increased risk of bleeding
Ibuprofen	Pain reliever	Increased risk of bleeding
Ifosamide	Chemotherapy	Increased risk of bleeding
Indomethacin	Pain reliever	Increased risk of bleeding
Influenza virus vaccine	Vaccine	Increased risk of bleeding
Itraconazole	Antifungal	Increased risk of bleeding
Ketoprofen	Pain reliever	Increased risk of bleeding
Ketorolac	Pain reliever	Increased risk of bleeding
Levamisol	Antiparasitic	Increased risk of bleeding
Levothyroxine	Thyroid medication	Increased risk of bleeding
Liothyronine	Thyroid medication	Increased risk of bleeding
Lovastatin	Lipid-lowering agent	Increased risk of bleeding
Mefenamic	Pain reliever	Increased risk of bleeding
Meprobamate	Sedative	Increased risk of bleeding
Methimazole	Antithyroid	Increased risk of bleeding
Methyldopa	Antihypertensive	Increased risk of bleeding
Methylphenidate	Stimulant	Increased risk of bleeding
Methylsallylate	Pain reliever	Increased risk of bleeding
Miconazole	Antifungal	Increased risk of bleeding
Metronidazole	Antibiotic	Increased risk of bleeding
Miconazole	Antifungal	Increased risk of bleeding
Moricizine HCl	Antiarrhythmic	Increased risk of bleeding
Nafcillin	Antibiotic	Increased risk of bleeding
Nalidixic acid	Antibiotic	Increased risk of bleeding
Naproxen	Pain reliever	Increased risk of bleeding
Neomycin	Antibiotic	Increased risk of bleeding
Norfloxacin	Antibiotic	Increased risk of bleeding
Ofloxacin	Antibiotic	Increased risk of bleeding
Olsalazine	Antidiarrheal	Increased risk of bleeding
Omeprazole	Proton pump inhibitor	Increased risk of bleeding
Oxaprozol	Pain reliever	Increased risk of bleeding
Oxymetholone	Hormone	Increased risk of bleeding
Paraldehyde	Sedative	Increased risk of bleeding
Paroxetine	Antidepressant	Increased risk of bleeding
Penicillin G	Antibiotic	Increased risk of bleeding
Pentobarbital	Sedative	Increased risk of bleeding
Pentoxifylline	Antithrombotic	Increased risk of bleeding
Phenobarbital	Sedative	Increased risk of bleeding
Phenylbutazone	Pain reliever	Increased risk of bleeding
Phenytoin	Antiepileptic drug	Increased risk of bleeding
Piperacillin	Antibiotic	Increased risk of bleeding
Piroxicam	Pain reliever	Increased risk of bleeding
Prednisone	Hormone	Increased risk of bleeding
Primidone	Antiepileptic drug	Increased risk of bleeding
Propafenone	Antiarrhythmic	Increased risk of bleeding
Propoxyphene	Pain reliever	Increased risk of bleeding
Propranolol	Beta-blocker	Increased risk of bleeding
Propylthiouracil	Antithyroid	Increased risk of bleeding
Phytonadione	Vitamin K	Decreased risk of bleeding
Quinidine	Antiarrhythmic	Increased risk of bleeding
Quinine	Antimalarial	Increased risk of bleeding
Ranitidine	Antacid	Increased risk of bleeding
Rifampin	Antibiotic	Decreased risk of bleeding
Secobarbital	Sedative	Increased risk of bleeding
Sertaline	Antidepressant	Increased risk of bleeding
Simvastatin	Lipid-lowering agent	Increased risk of bleeding
Spironolactone	Diuretic	Increased risk of bleeding
Stanozolol	Hormone	Increased risk of bleeding
Streptokinase	Fibrinolytic	Increased risk of bleeding
Sucralfate	Antacid	Increased risk of bleeding
Sulfamethazole	Antibiotic	Increased risk of bleeding
Sulfamethoxazole	Antibiotic	Increased risk of bleeding
Sulfipyrazone	Pain reliever	Increased risk of bleeding
Sulfipyrazone	Pain reliever	Increased risk of bleeding
Sulfisoxazole	Antibiotic	Increased risk of bleeding
Sulindac	Pain reliever	Increased risk of bleeding
Tamoxifen	Anticancer drug	Increased risk of bleeding
Tetracycline	Antibiotic	Increased risk of bleeding
Thyroid hormone	Thyroid medication	Increased risk of bleeding
Ticacillin	Antibiotic	Increased risk of bleeding
Ticlopidine	Antiplatelet agent	Increased risk of bleeding
t-PA	Fibrinolytic	Increased risk of bleeding
Tolbutamide	Antidiabetic drug	Increased risk of bleeding
Trazodone	Antidepressant	Increased risk of bleeding
Trimethoprim-sulfamethoxazole	Antibiotic	Increased risk of bleeding
Urokinase	Fibrinolytic	Increased risk of bleeding
Valproate	Antiepileptic drug	Increased risk of bleeding
Vitamin C	Vitamin	Increased risk of bleeding
Vitamin E	Vitamin	Increased risk of bleeding

Advantages of Old Anticoagulants

- **Familiarity**
- **No unexpected side effects**
- **Demonstrated use in multiple clinical areas**

CAUTION! KEEP OUT OF REACH OF CHILDREN
SEE BACK PANEL FOR ADDITIONAL CAUTIONS

98

Tyler's



Toss that
dirty trap
away!

cheese

Warfarin

flavored

**RAT & MOUSE
KILLER PELLETS**

ACTIVE INGREDIENTS: Warfarin (3-(*a*-dithienyl)-4-hydroxycoumarin) 0.025%
INERT INGREDIENTS: 99.975%
NET WEIGHT ONE POUND

Why DOAC?

- **Safer and same/better effectiveness**
- **Ease of use**
- **No food interactions**
- **Few drug interactions**
- **Simple management for procedures**

DOAC: Bleeding

- **Analysis of all phase III trials**
 - **Venous thrombosis therapy**
 - **Atrial fibrillation**
- **N = 102,607 patients**
- **Chai-Adisaksopha Blood. 2014**
Oct 9;124(15):2450-8

Results

- **Major Bleeding RR = 0.72**
 - NNT = 156
- **Fatal Bleeding RR = 0.78**
 - NNT = 454
- **ICH RR = 0.76**
 - NNT = 185
- **Total Bleeding RR = 0.76**
 - NNT = 18
- **GI bleeding RR = 0.94**

Thrombophilia

- **Hereditary**
 - **No concerns**
- **Antiphospholipid Syndrome**
 - **Not for triple positive**
 - **Not for arterial disease**

Pregnancy

- **NO!**
 - Will cross placenta
 - Secreted in breast milk
- **LMWH remains anticoagulants of choice**

History of GI Bleed

- Rivaroxaban (1.5 HR), edoxaban (HR 1.23) and dabigatran (1.6 HR) increase risk of bleeding but not apixaban (0.9 HR)



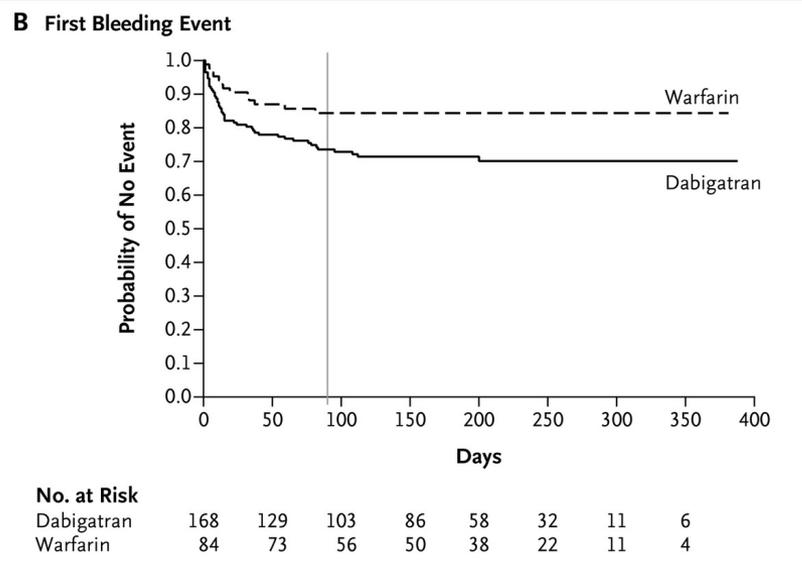
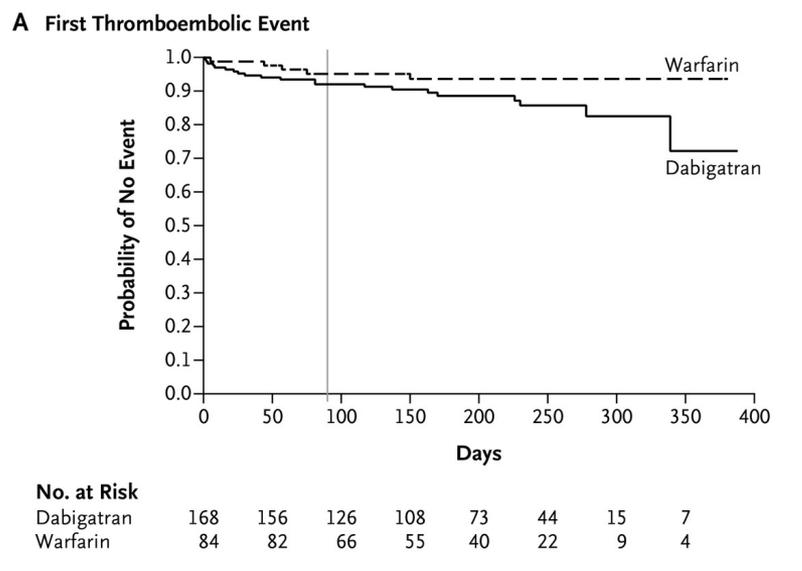
When NOT to use a DOAC

- Mechanical heart valves
- “Triple positive”
antiphospholipid antibody
syndrome
- Rheumatic valvular disease

Mechanical Valves

- **Several published and unpublished show higher rates of thrombosis**
- **Onyx apixaban trial shut down**
- **Bioprosthetic – no issues**

Valves: Kaplan–Meier Analysis of Event-free Survival.



Triple Positive APLA

- Both RCT and observational data show DOACs are inferior

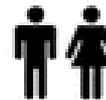
TRAPS
Randomized controlled trial of Rivaroxaban
vs Warfarin in APS

High-risk APS patients
- LA positive
- aCL positive
- aB2GPI positive

R

Rivaroxaban
N=59

Warfarin
N=61



1,5 years

Events on
Rivaroxaban: 19%

Events on
Warfarin: 3%



Stopped early for excess of events on Rivaroxaban

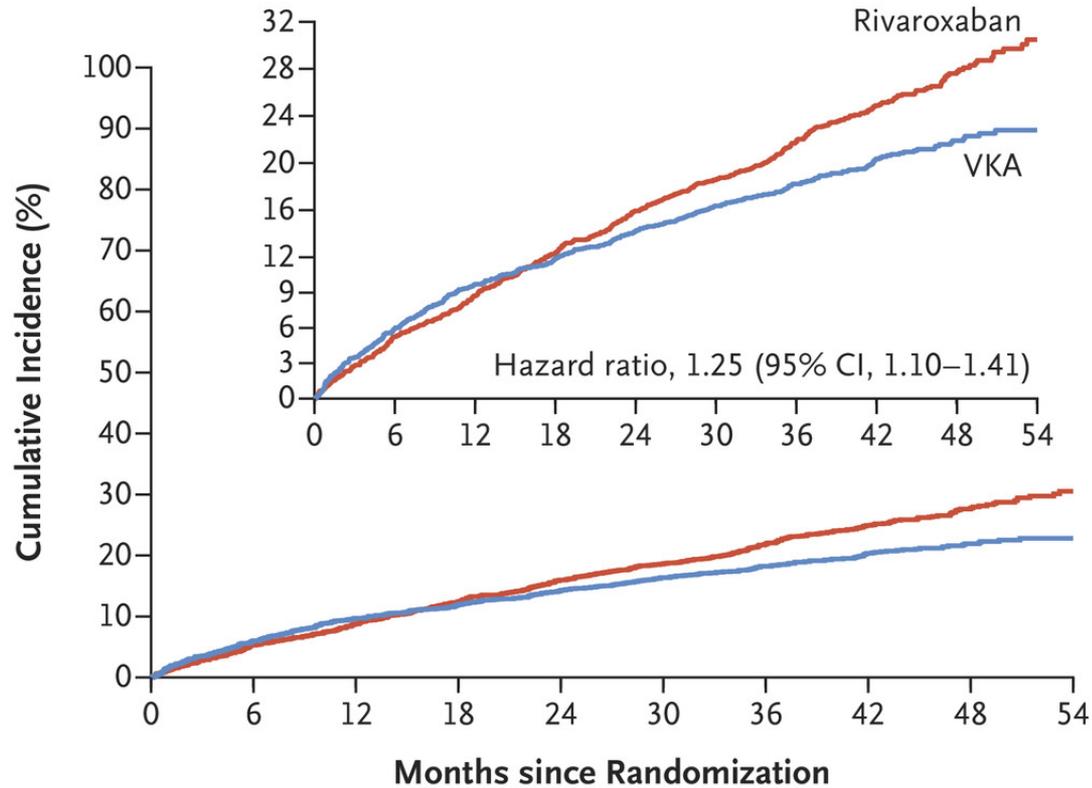
APLA and DOAC

- **No!**
 - Triple positive
 - Arterial disease
- **Maybe**
 - Double positive
- **Yes**
 - Single positive

Rheumatic Afib

- 4565 patients
- Rivaroxaban
 - Higher rate of stroke
 - Higher rate of death
 - No difference bleeding
- Death – sudden death and CHF
- NEJM 387:978, 2022

Cumulative Incidence of the Composite of Stroke, Systemic Embolism, Myocardial Infarction, or Death from Vascular or Unknown Causes (Primary Outcome).



No. at Risk

Rivaroxaban	2275	2124	2023	1931	1838	1750	1356	876	451	144
VKA	2256	2100	2003	1944	1880	1809	1392	881	462	138

Elderly and DOACs

- **Data in Afib and DVT**
 - **Less bleeding**
 - **Relatively more effective**
 - **Beneficial across all ages**
 - **Beneficial in nursing home patients**

Frail-AF

- Frail > age 75 stable on warfarin
- Warfarin vs DOAC
- N = 1330
- HR bad outcome 1.69
 - Bleeding mainly GI/GU
- HR thrombosis NS
- Circulation 2023

Frail-AF

- **Why DOAC inferior?**
 - Warfarin patients long run-in
 - Warfarin patients seen more
- **Time in therapeutic range same/worse than key DOAC clinical trials**

Anticoagulation Clinics

- **Patients on warfarin frequently assessed**
- **May pick up other medical issues**
- **Assures compliance**

Warfarin vs DOAC

- **Still favor DOACs except**
 - **Mechanical valves**
 - **Triple and arterial APLA**
 - **Rheumatic valvular disease**
 - **Very stable older patients?**
 - **Frail/forgetful patients**

Costs!

- **BIG issue!**
- **Warfarin: \$4/month**
- **DOACs: \$5-800/month**



Can this patient be on a DOAC?

37 yo

Multiple thrombosis

Weight is 148 kg

Obesity

- **Obesity an increasing problem**
- **Heaviest patients in clinical trials
~ 120-130 kg**
- **Obese patients**
 - **Greater risk of thrombosis**
 - **Increasingly undergoing surgery
and hospital care**

ISTH Summary Guidance Statements: Use of DOACs in Patients With Obesity

**BMI \leq 40 kg/m² or
Weight \leq 120 kg:**

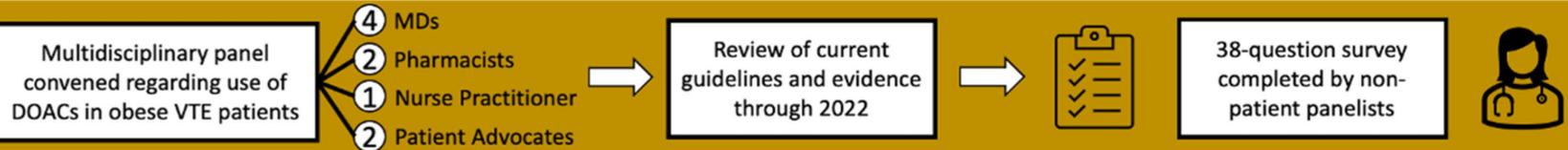
**BMI $>$ 40 kg/m² or
Weight $>$ 120 kg:**

VTE Treatment	VTE Prevention	VTE Treatment	VTE Prevention
 Use of Any DOAC is appropriate (Consistent with 2016 ISTH SSC recommendations)		✓ Rivaroxaban ✓ Apixaban Fewer supportive data for apixaban ✗ Dabigatran ✗ Edoxaban ✗ Betrixaban	✓ Rivaroxaban ✓ Apixaban Note limited indications for use ✗ Dabigatran ✗ Edoxaban ✗ Betrixaban
		OK VKA OK Wt-based LMWH OK Fondaparinux	
		✗ Do not regularly follow peak/trough DOAC levels ✗	
		✗ Do not use in acute setting after bariatric surgery	

BACKGROUND

- DOACs are often not used in obese and severely obese (BMI >40 kg/m² or weight > 120 kg) patients.
- Due to limited data, previous 2016 ISTH Guidance recommended NOT to use DOACs in severely obese patients.
- ISTH 2021 Guidance statement: "Okay to use apixaban and rivaroxaban in obese and severely obese VTE patients"

METHODS



Survey results noted the following:

Real-world practice is currently not consistent with UPDATED (2021) ISTH guidance



DOACs should be considered in all obese patients, regardless of BMI; however, data is limited in excessive obesity (BMI>50 kg/m²)



Peak and trough levels generally should not influence management decisions



Following bariatric surgery, do not use DOACs until at least 4 weeks post-operatively. Consider trough level to assure drug absorption



The efficacy of dose reduction for extended VTE prophylaxis is unclear in obesity/severe obesity

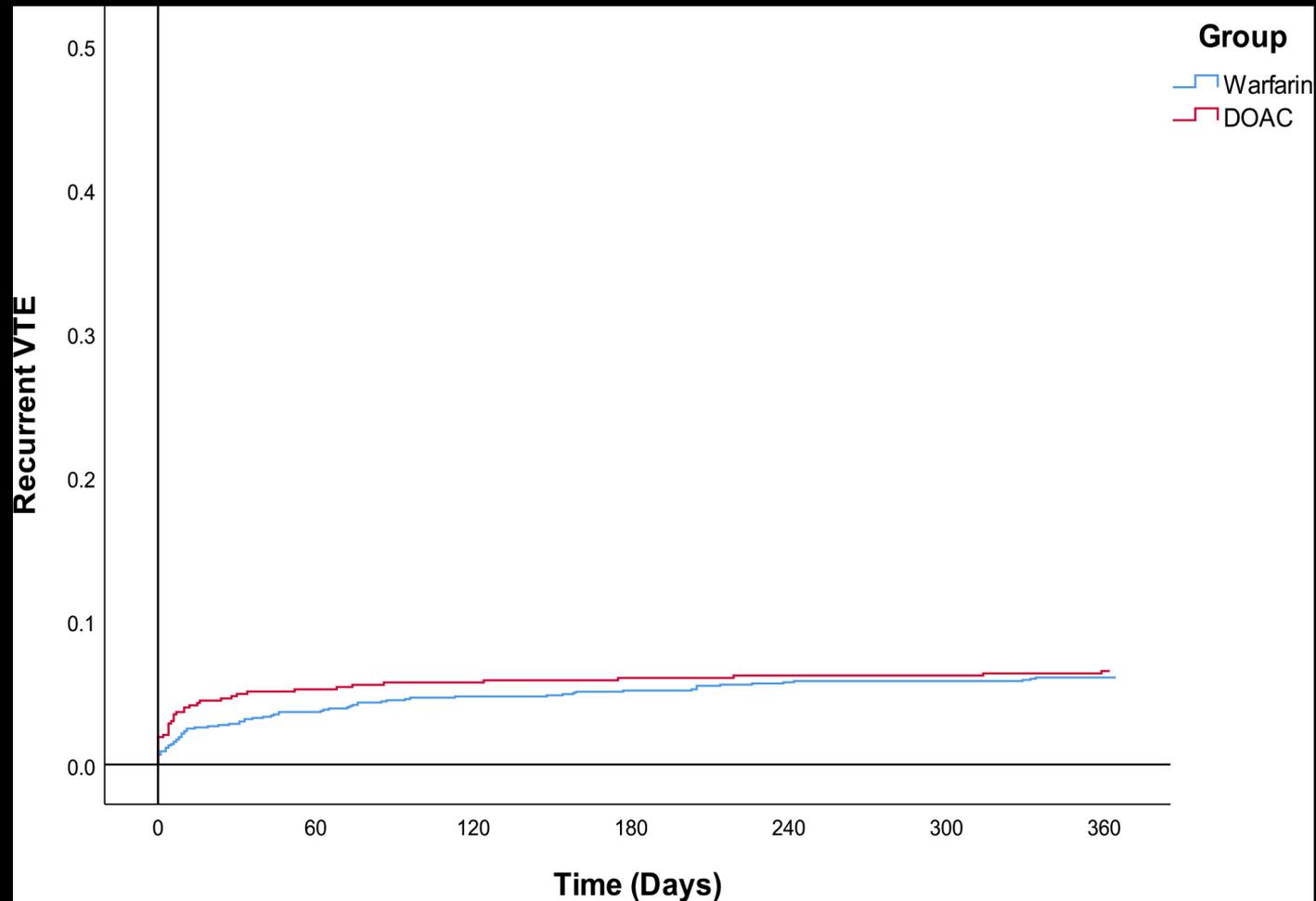


TAKE HOME MESSAGE

In 2022, for treatment of acute VTE, weight should not be a significant factor in deciding which anticoagulant to use.

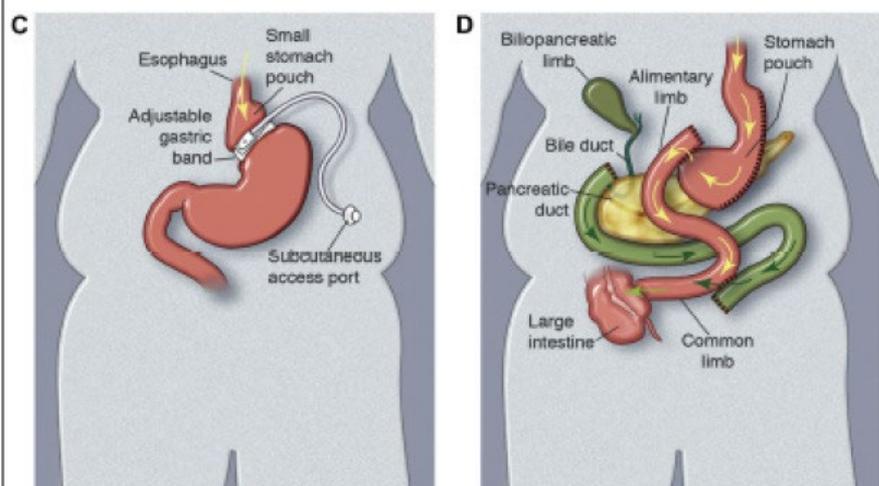
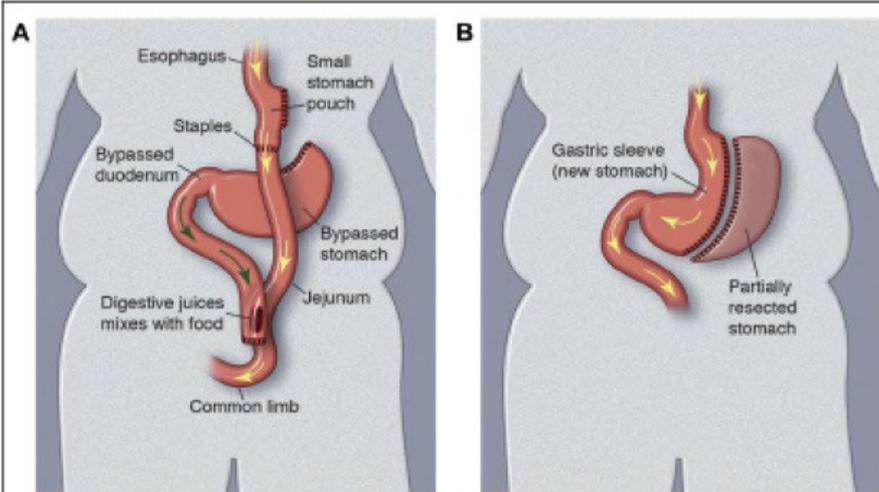
Abbreviations: DOAC=direct oral anticoagulant; VTE=venous thromboembolism; BMI=body mass index; ISTH=International Society of Thrombosis and Hemostasis

Effectiveness and Safety of Direct Oral Anticoagulants versus Warfarin in Obese Patients with Acute Venous Thromboembolism



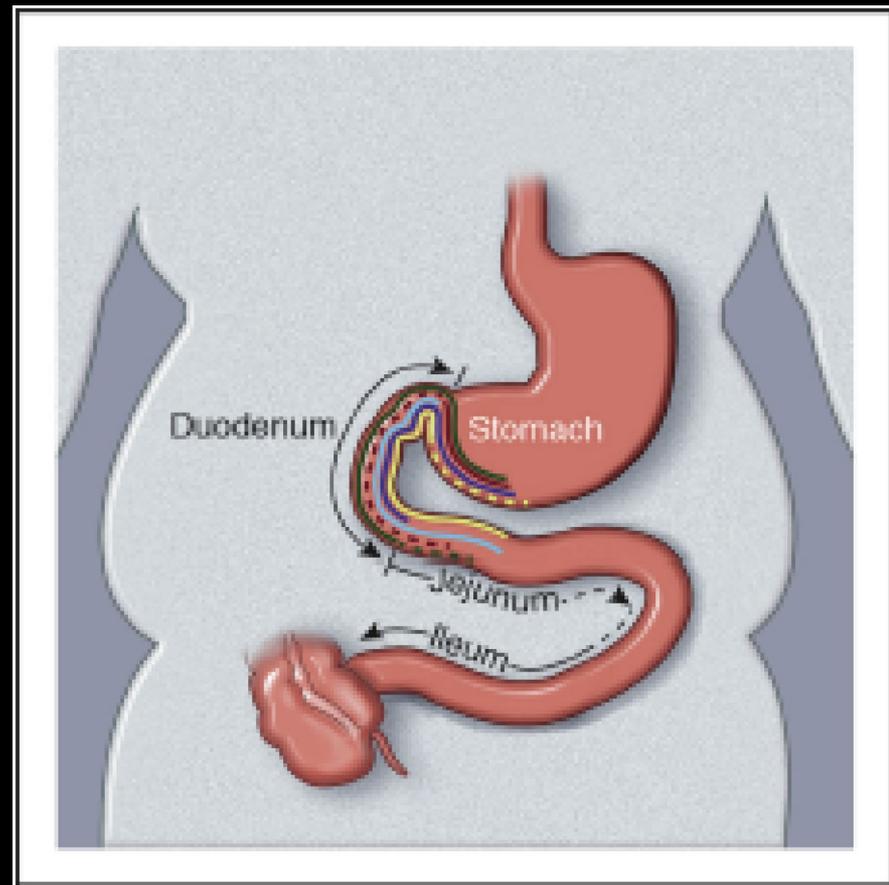
Weight

- **DOACs weight base**
- **Obesity**
 - **Atrial fibrillation: 140 kg**
 - **Ignore BMI**
 - **Venous disease: ???**
 - **Acute 140 kg**
 - **Chronic < 200 kg**
- **Like with LMWH monitoring levels will allow greater use**



Food path
 Bile and pancreatic secretions

J. Chouh



	Apixaban		Main absorption
	Dabigatran		Some absorption
	Edoxaban		
	Rivaroxaban		
	Warfarin		

J. Chouh

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**



Can this patient be on a DOAC?

- 48 yoM
- On dialysis due to lupus
- Stroke due to AF

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!**

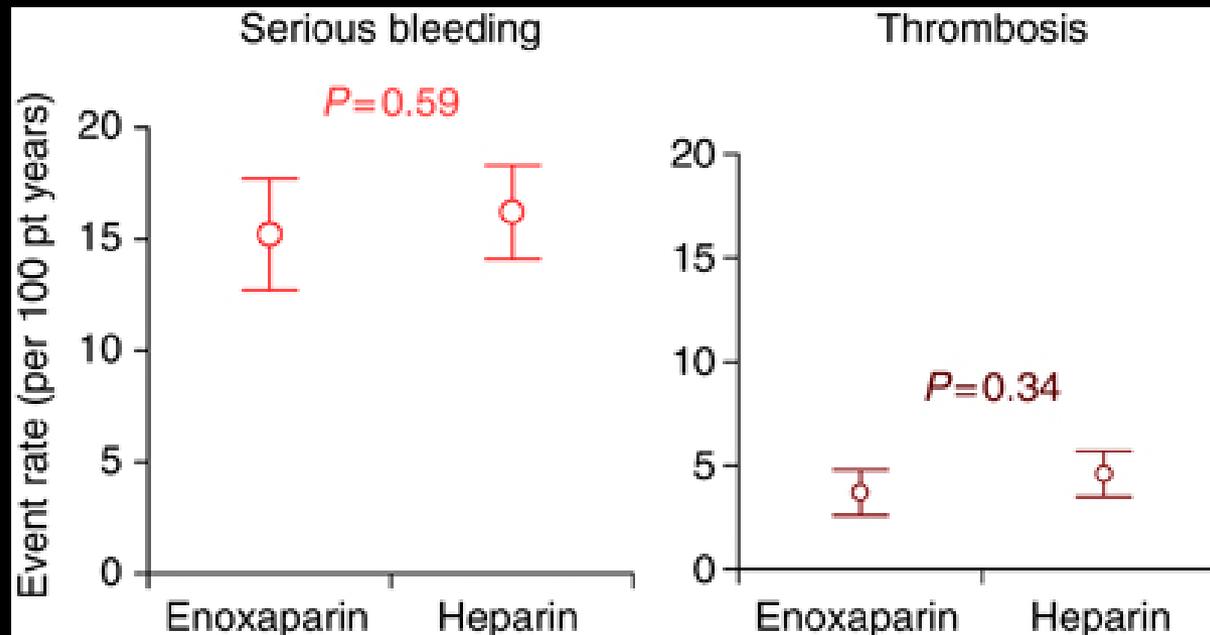
Chest. 2004 Mar;125(3):856-63.

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?**

Apixaban: Renal Disease

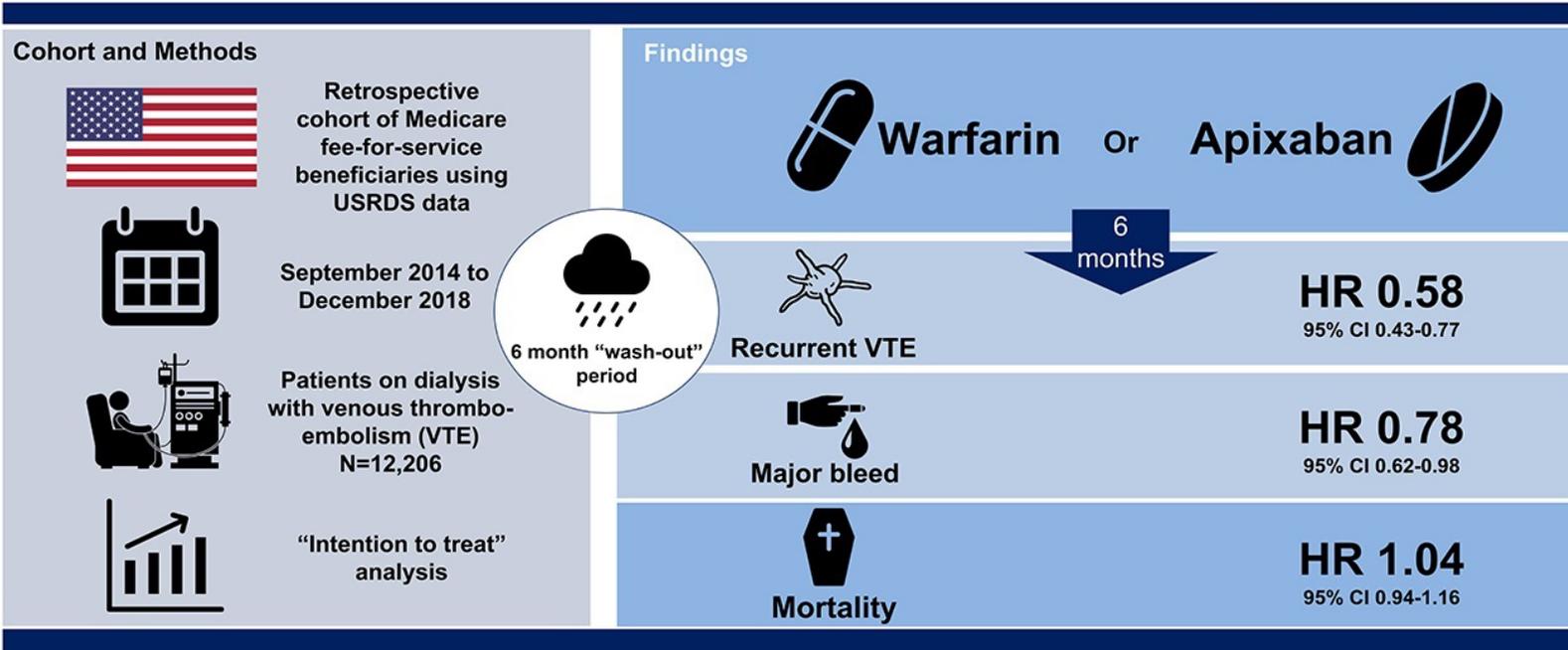
- **GRF < 50 mL/min**
 - **Stroke** **0.61** (0.39-0.94)
 - **Mortality** **0.78** (0.63-0.96)
 - **Bleeding** **0.48** (0.37-0.64)

 - Eur Heart J. 2012 Nov;33(22):2821-30

Apixaban: Dialysis

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

Apixaban versus warfarin for treatment of venous thromboembolism in patients receiving long-term dialysis



Conclusions: In a cohort of US dialysis patients with recent venous thromboembolism, apixaban was associated with lower risk of recurrent venous thromboembolism and major bleeding compared with warfarin. There was no difference in mortality.

James B. Wetmore, Charles A. Herzog, Heng Yan, et al. *Apixaban versus Warfarin for Treatment of Venous Thromboembolism in Patients Receiving Dialysis*. CJASN doi: 10.2215/CJN.14021021. Visual Abstract by Nayan Arora, MD

CLINICAL JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

Renal Disease

- **Renal Function**

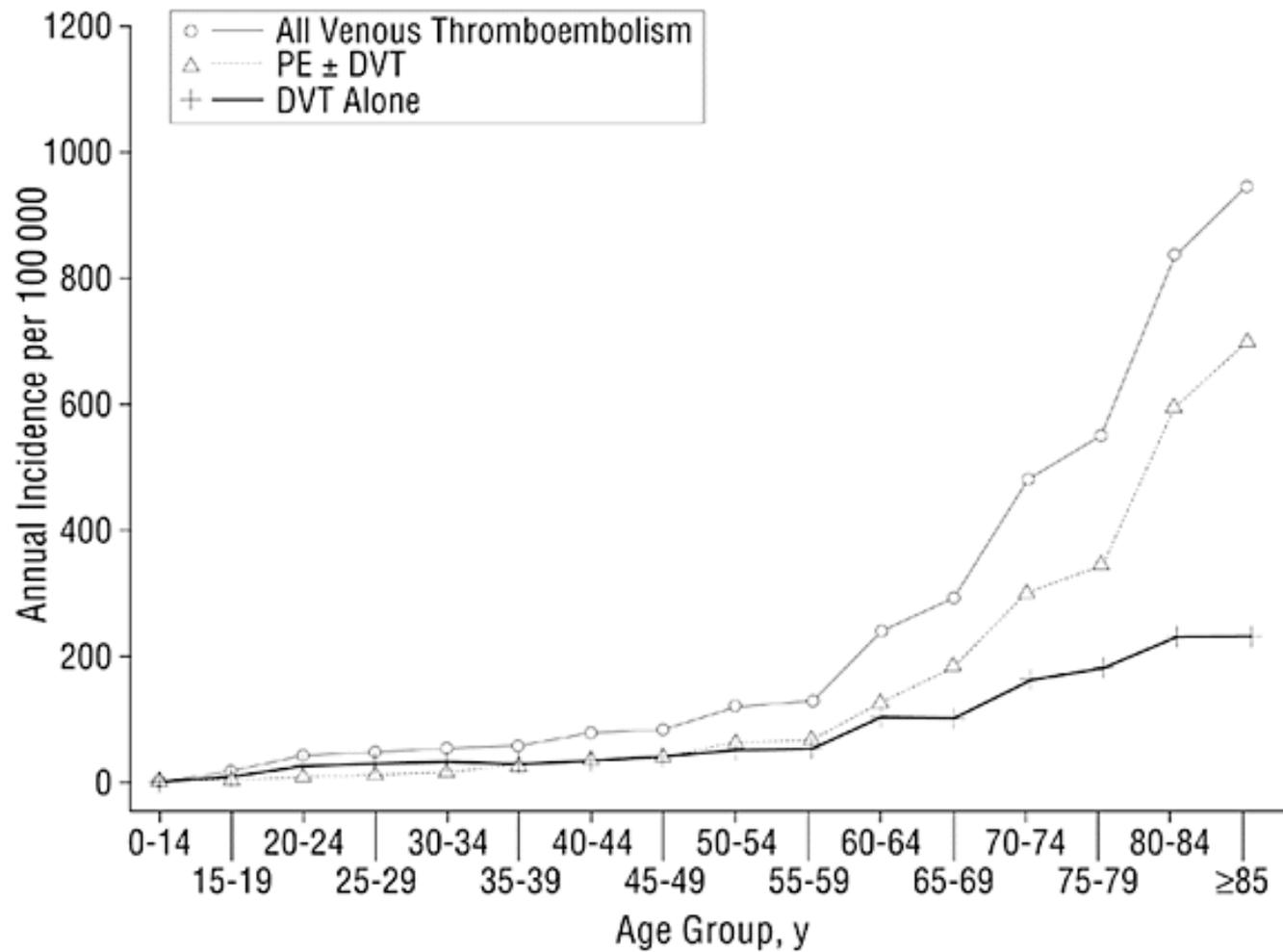
- **All renally cleared:**

- **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**

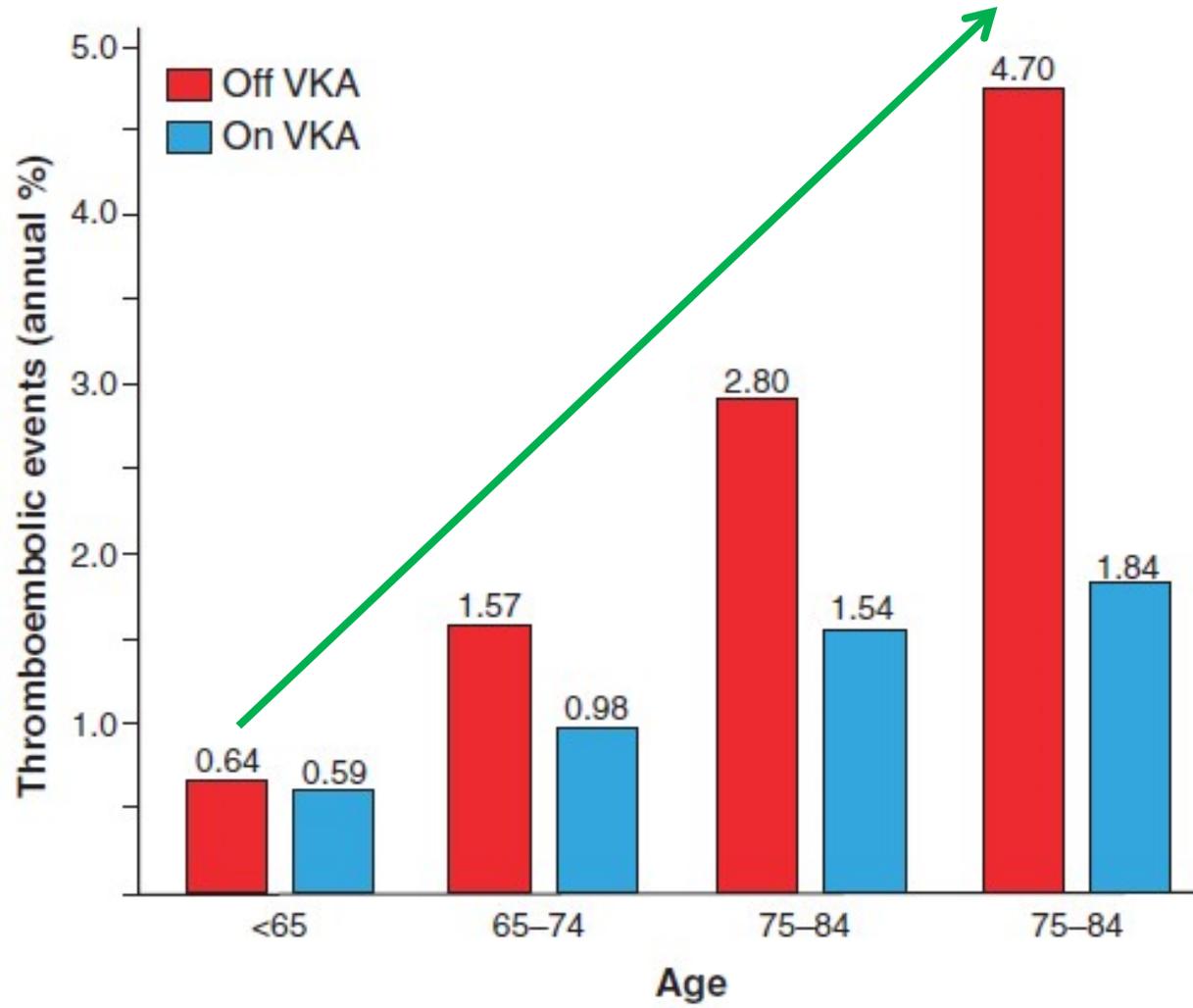


Can this patient be on a DOAC?

- 89 YoF
- Hx of AIHA
- Now with atrial fibrillation



Arch Intern Med. 1998;158:585-593



J Intern Med 2012; **271**: 15-24.

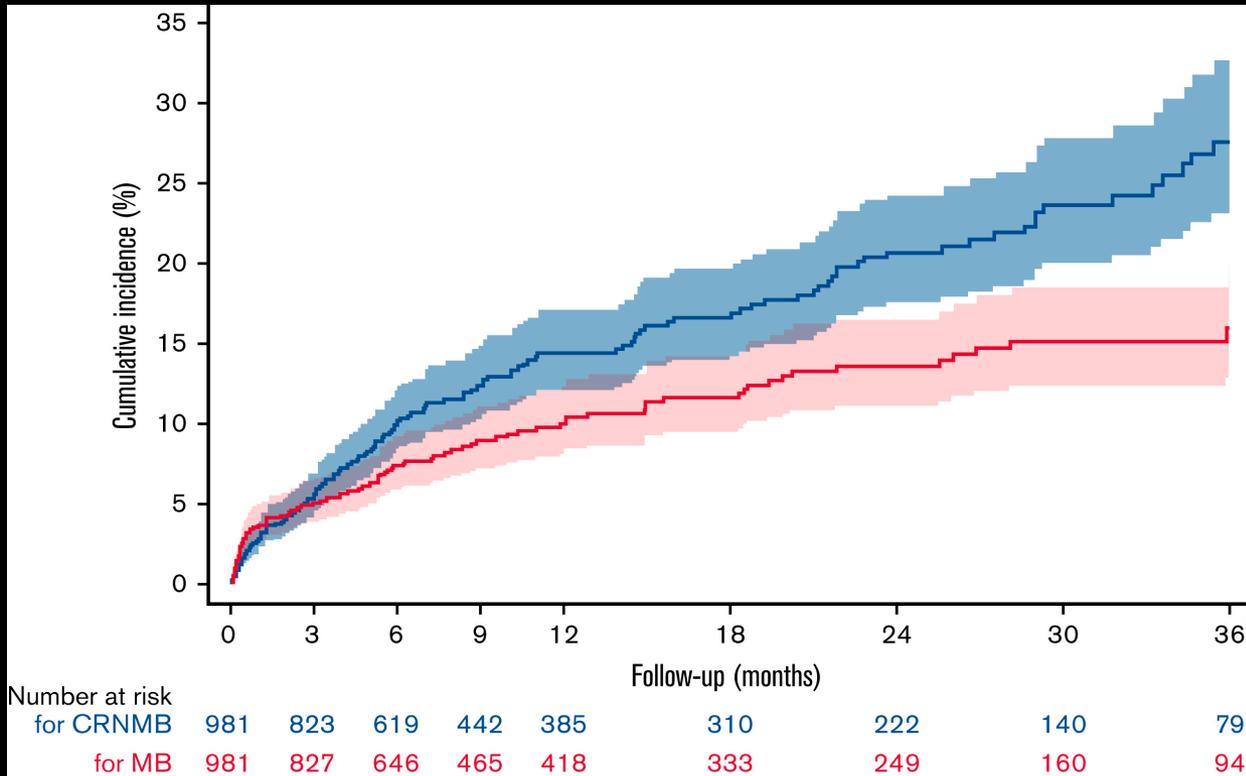
DOAC in Patients > 75

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



Elisa Ferrazzini, Marie Méan, Odile Stalder, Andreas Limacher, Nicolas Rodondi, Drahomir Aujesky, Incidence and clinical impact of bleeding events in older patients with acute venous thromboembolism, Blood Adv, 2023, Figure 1.

AF: Use Right Dose!

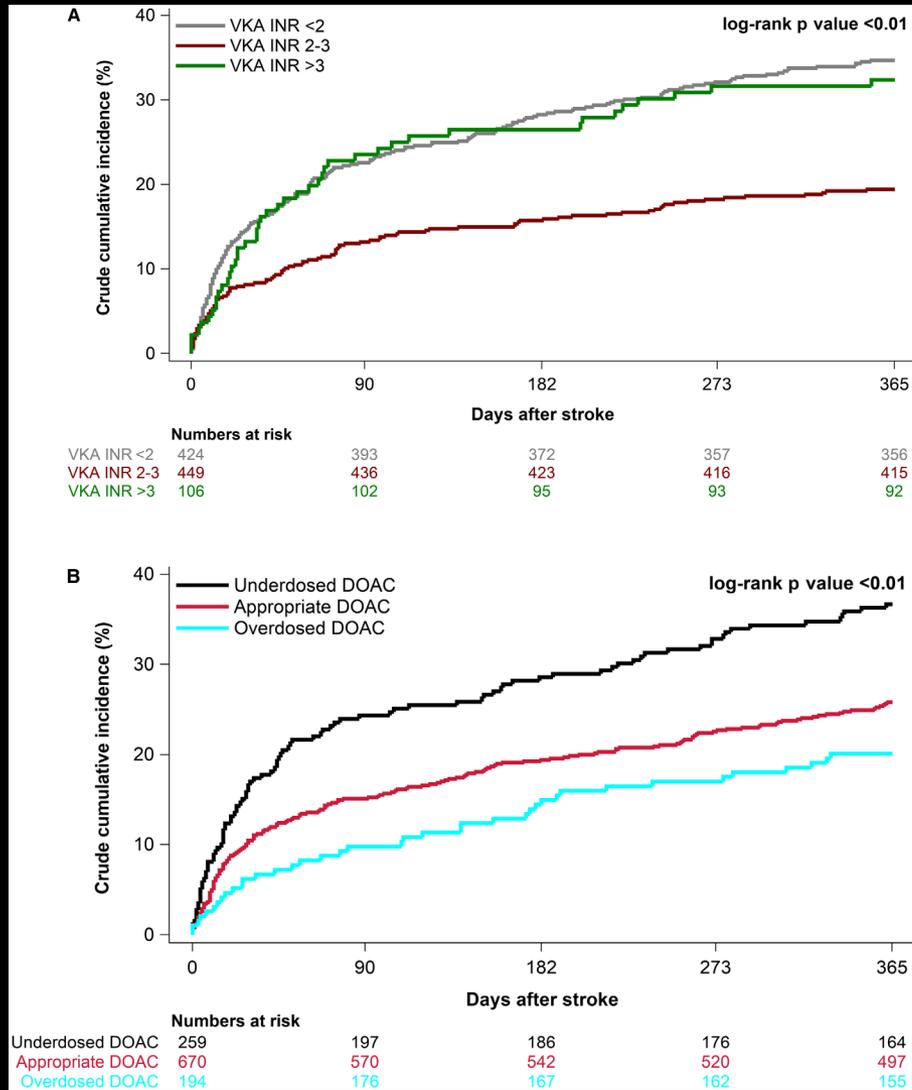
- Increasing data that under dosing DOACs lead to more thrombosis/stroke without change in bleeding
- Only dose adjust if indicated!
 - Apixaban 2 of 3
 - Age > 80
 - Creat > 1.5
 - Weight < 60

DOACs

- **Doses established by clinic trials**
- **Biggest errors**
 - **Rivaroxaban (venous disease)**
 - Continuing 15mg bid too long
 - Going to 15mg daily instead of 20mg
 - **Apixaban (atrial fibrillation)**
 - **Wrongly going to 2.5 mg bid**
 - Renal disease
 - Older patient

Wrong Dosing

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



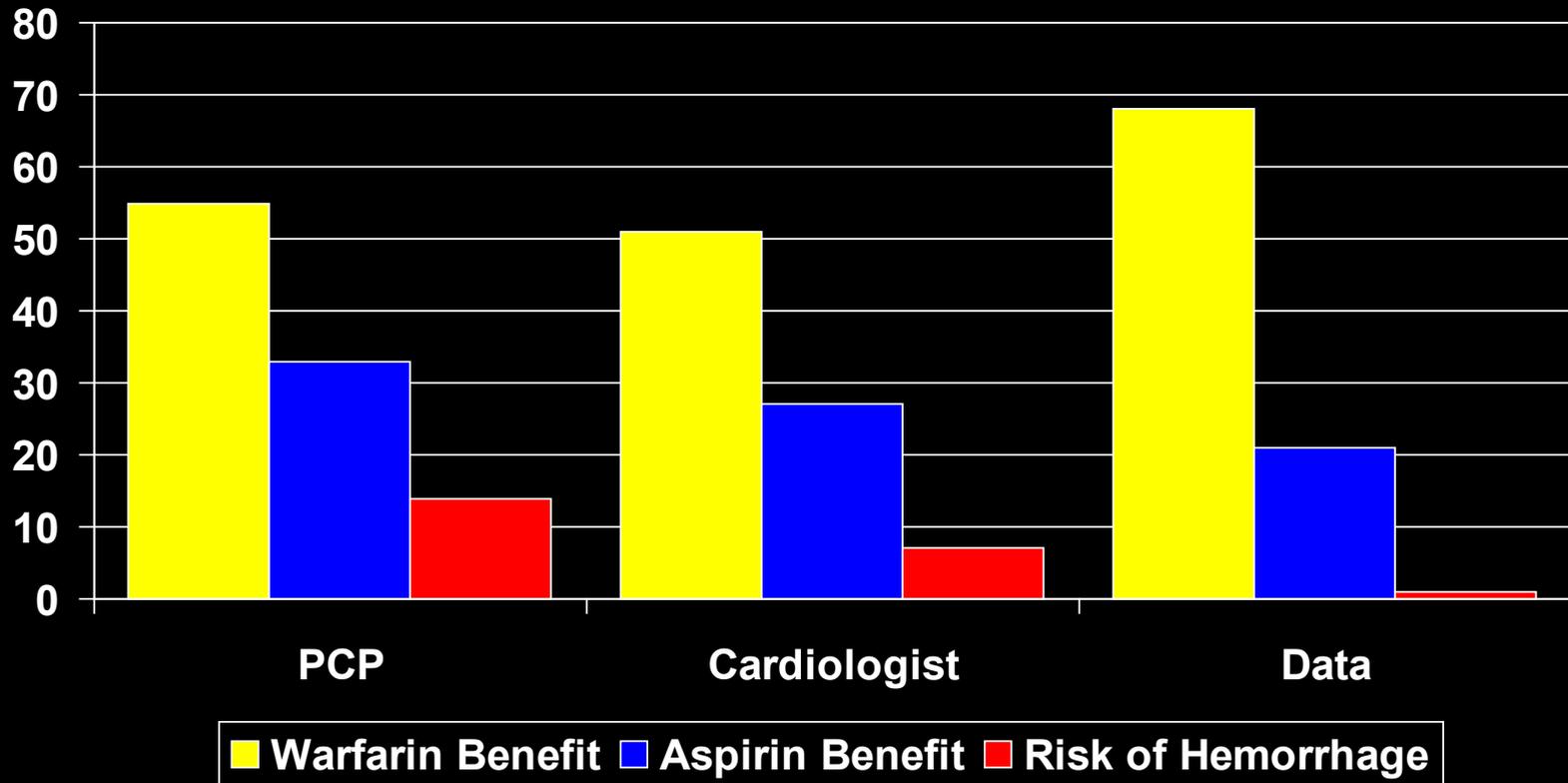
Use Right Dose!

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

Scared Doctors

- **Doctors consistently overestimate risk of bleeding and underestimate benefit of warfarin**
 - **Fear of causing damage**
 - **Remembering vivid cases**

Scared Doctors





Can this patient be on a DOAC?

- 45 YoM
- Child B cirrhosis
- New portal vein thrombosis after surgery

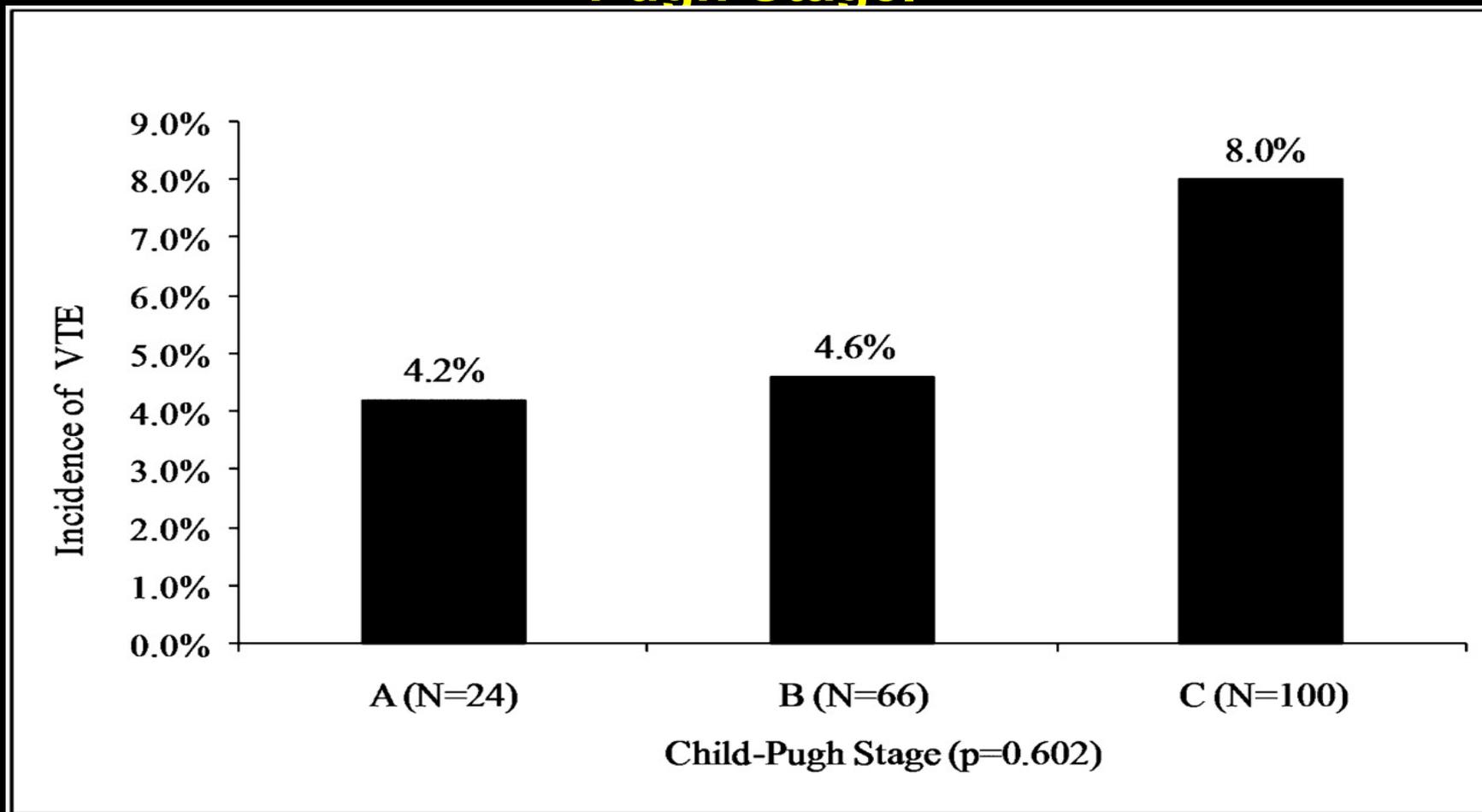
Liver Disease

- **Multiple defects in coagulation**
 - Decreased synthesis of factors
 - Decreased platelets
 - Decreased platelet function
- **But does not lead to bleeding diathesis in most patients**

Thrombosis Risk

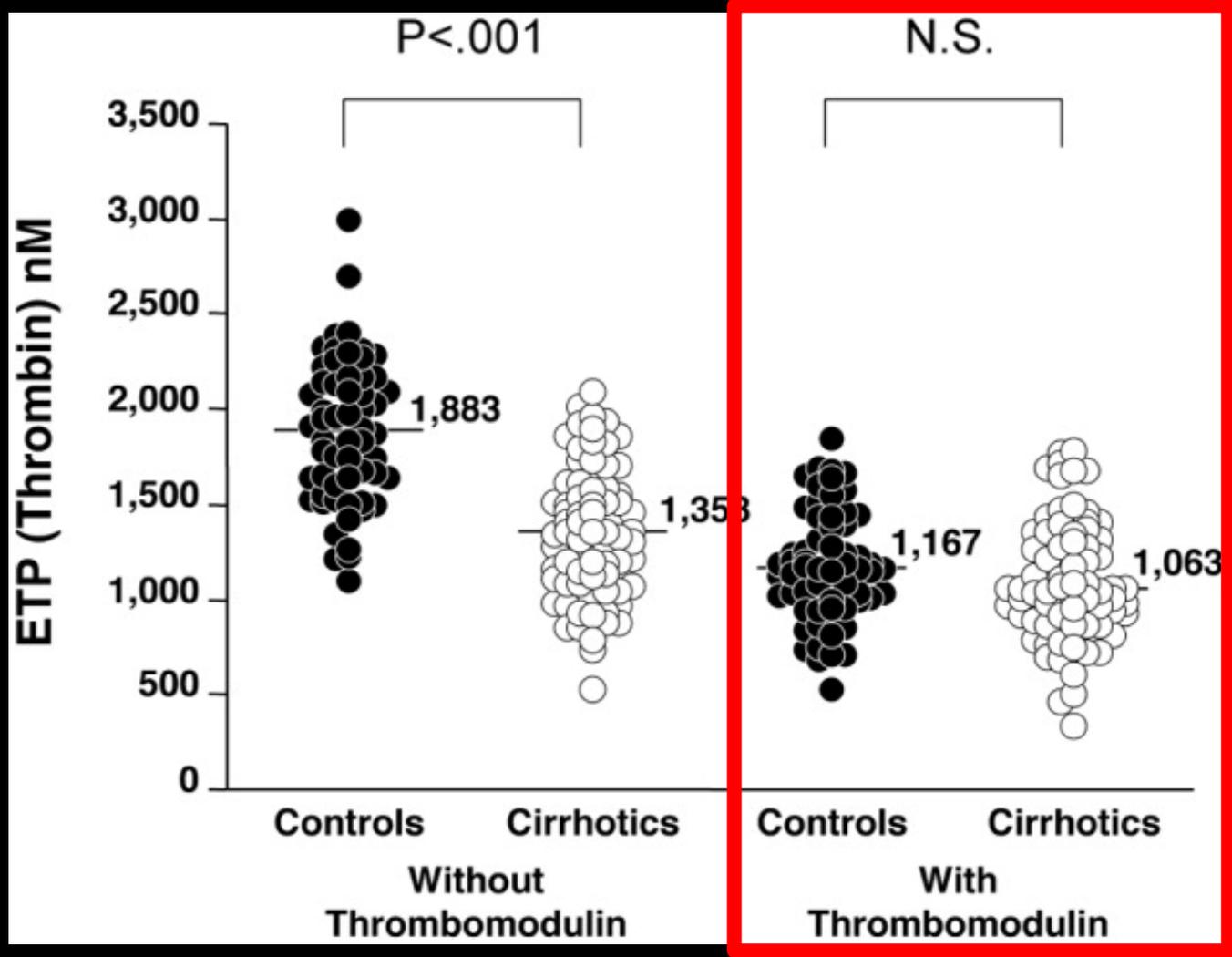
- **2 hospital case-control studies**
 - **0.5-1%**
 - **No different than controls**
- **Danish population case-control**
 - **Relative risk of DVT doubled with cirrhosis and with non-cirrhotic liver disease**

Incidence of venous thromboembolism based on Child-Pugh Stage.



Hemostasis in Liver Disease

- **Levels of natural anticoagulants and inhibitors of coagulation also reduced**
- **Coagulation is “rebalanced”**
 - **Thrombin generation is normal**



Hepatology 44:440-445, 2006

Bleeding in Liver Disease

- **Mechanical lesion**
 - **Varies**
 - **Ulcers**
- **Severe thrombocytopenia**
- **Fulminant liver failure**

Bottom Line

- **Patients with liver disease are not protected from thrombosis**
- **Routine tests of hemostasis overestimate the bleeding risk**



Portal Vein Thrombosis

- **Very common finding**
 - **With screening for hepatomas**
 - **After surgery**
- **Increasing guidance**

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**

Meta-Analysis: Anticoagulation

- **PTV improvement: 3.6 (2.6-5.2)**
- **PTV recanalization: 3.7 (2.5-5.7)**
- **PTV progression: 0.4 (0.2-0.6)**
- **Mortality: 0.5 (0.3-0.7)**
- **Bleeding: 0.8 (0.4-1.7)**

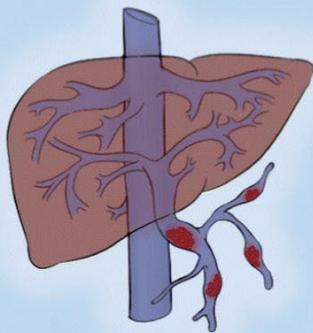
- **J Clin Exp Hep 13:404, 2023**

DOAC in Liver Disease

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

Direct Oral Anticoagulants for the Treatment of Splanchnic Vein Thrombosis

Systematic Review and Meta-analysis



Non-cirrhotic patients
N=489

Cirrhotic patients
N=394



DOAC

*Apixaban n=34
Dabigatran n=62
Edoxaban n=20
Rivaroxaban n=144



VKA

Recanalization

Non-Cirrhotic patients: OR = 4.33; 95% CI: 2.4, 7.83

Cirrhotic patients: OR = 3.90; 95% CI: 0.96, 15.87

ISTH Bleeding

Non-Cirrhotic patients: OR = 0.12; 95% CI: 0.02, 0.69

Cirrhotic patients: OR = 0.46; 95% CI: 0.07, 3.20



LWMH

Recanalization

Non-Cirrhotic patients: OR = 1.43; 95% CI: 0.76, 2.71

Cirrhotic patients: OR = 2.03; 95% CI: 0.66, 6.22

ISTH Bleeding

Non-Cirrhotic patients: OR = 0.13; 95% CI: 0.03, 0.62

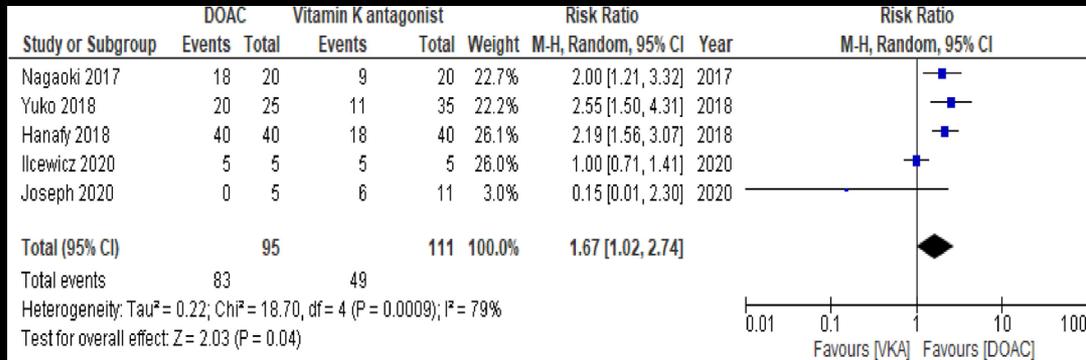
Cirrhotic patients: OR = 0.73; 95% CI: 0.17, 3.1

*Not all included studies reported specific DOAC used

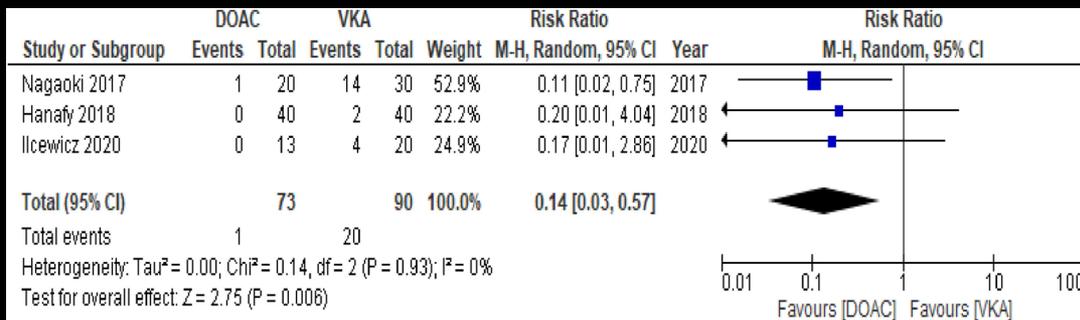
Throm Res 229:209, 2023

DOAC vs Warf

- **10,209 on anticoagulation**
- **Stroke**
 - Apixaban 1.4/100 ptyr
 - Rivaroxaban 2.6/100 ptyr
 - Warfarin 4.4/100 ptyr
- **Major bleeding**
 - Apixaban 6.5/100 ptyr
 - Rivaroxaban 9.1/100 ptyr
 - Warfarin 15.0/100 ptyr
- **Circ 147:782, 2023**



Portal vein recanalization



Portal vein thrombus progression



Major Bleeding

Liver Disease

- **DOAC prefers in most patients**
- **Strong data to treat portal vein thrombosis with DOAC**

Dare we DOAC?

- **Yes! Except:**
 - **Mechanical heart valves**
 - **“Triple positive” antiphospholipid antibody syndrome**
 - **Rheumatic valvular disease**
 - **Stable frail elderly**

