Updates from the 2023 ASH Meeting

Thursday | January 11, 2024 | 12:00pm ET

Anticoagulation FORUM

Moderators

Jean Connors, MD
Medical Director, Hemostatic Antithrombotic Stewardship
Medical Director, Anticoagulation Management Services
Hematology Division
Brigham and Women's Hospital / Dana-Farber Cancer Institute
Professor of Medicine
Harvard Medical School

Naomi Yates, PharmD, BCACP
Manager, Clinical Pharmacy Services
Outpatient Pharmacy Anticoagulation Service (OPAS)
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Presenters

Keith R. McCrae, MD
Director of Classical Hematology
Cleveland Clinic

Jordan Schaefer, MD, MSc, FACP
Associate Professor of Internal Medicine
Division of Hematology and Oncology
University of Michigan

Hope Pritchett Wilson, MD
Assistant Professor
Division of Pediatric Hematology and Oncology
University of Alabama at Birmingham

Agenda

Brief Overview of the ASH Meeting
Presenter: Jean Connors, MD

Use and outcomes of secondary anticoagulation in patients less than 21 years old following completion of a primary course of anticoagulation for treatment of acute provoked VTE: Findings from the multinational Kids-DOTT trial
Presenter: Hope Pritchett Wilson, MD; University of Alabama at Birmingham

How to Diagnose and Manage Antiphospholipid Syndrome
Presenter: Keith R. McCrae, MD; Cleveland Clinic

A Comparison of Bleeding Events Among Patients on Apixaban, Rivaroxaban, and Warfarin for Atrial Fibrillation and/or Venous Thromboembolism
Presenter: Jordan Schaefer, MD, MSc, FACP; University of Michigan

Scientific Program

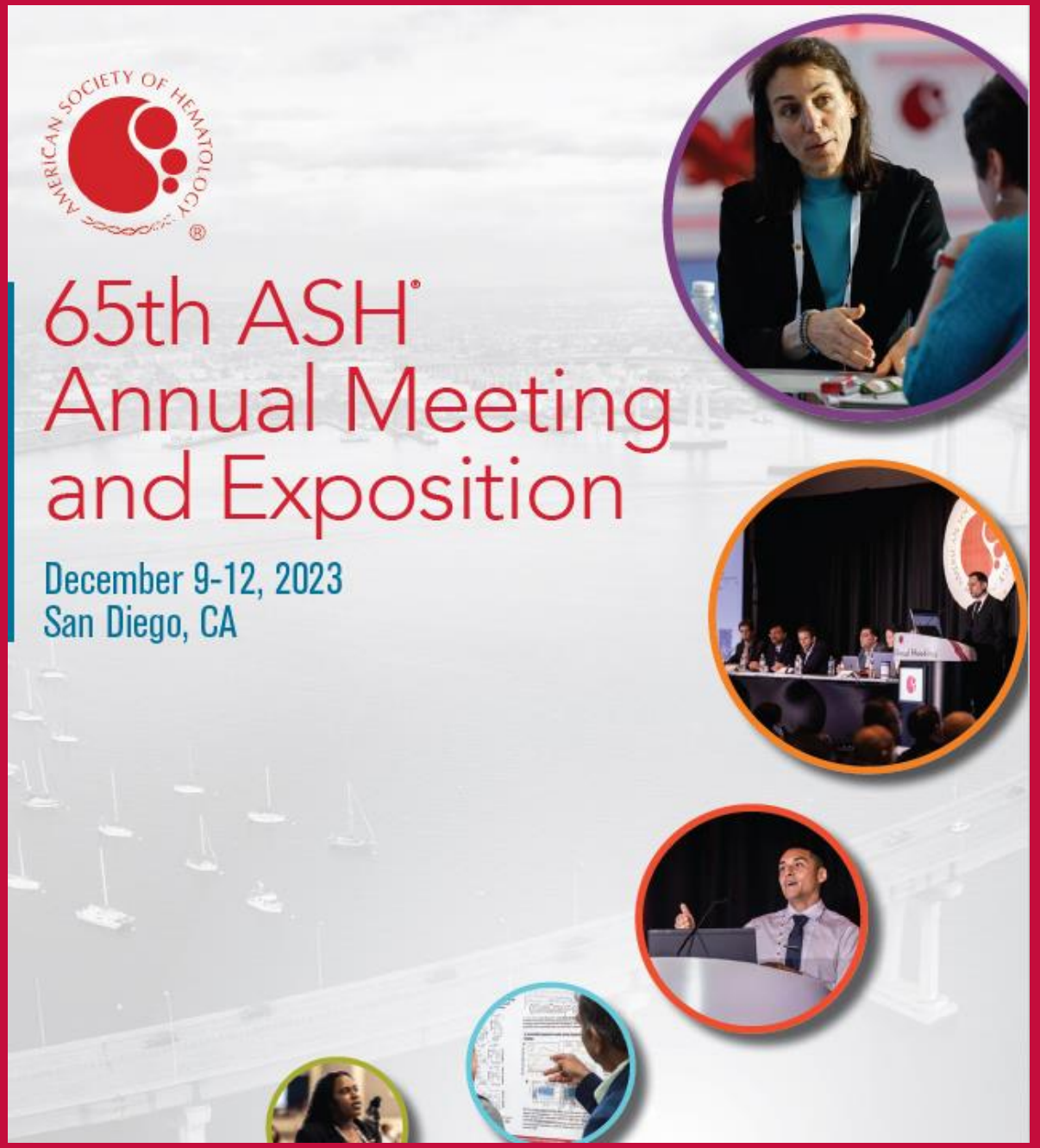
Education Program

General Sessions

Special Interest Sessions

Oral and Poster Sessions

Networking



Use and outcomes of secondary anticoagulation in patients <21 years old following completion of a primary course of anticoagulation for treatment of acute provoked VTE: Findings from the multinational Kids-DOTT trial

HP. WILSON[1], M. BETENSKY[2], A. MILLER[3], E. AMANKWAH[3,4], M.MOSHA[3], J. FARGO[5], A. MAHAJERIN[6], C. THORNBURG[7], C. TARANGO[8], S. ACHARYA[9], C. MALE[10], S. NARANG[11], S. SCHULMAN[12], N. GOLDENBERG[2,3,13]

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Children's of Alabama

Alabama Center for Childhood Cancer and Blood Disorders

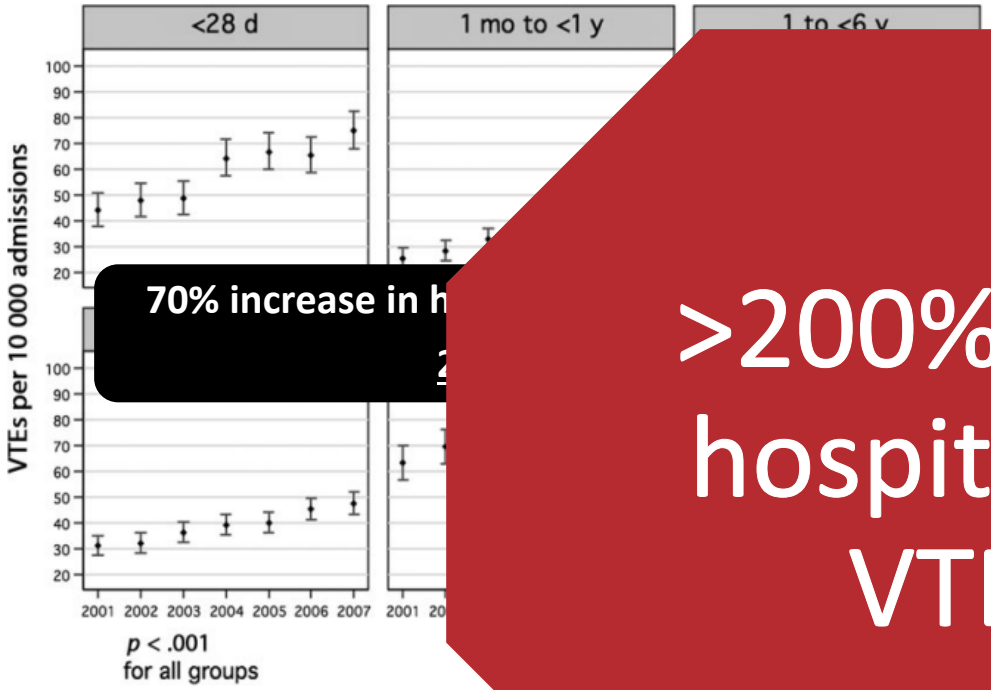
UAB MEDICINE

Hope P. Wilson, MD

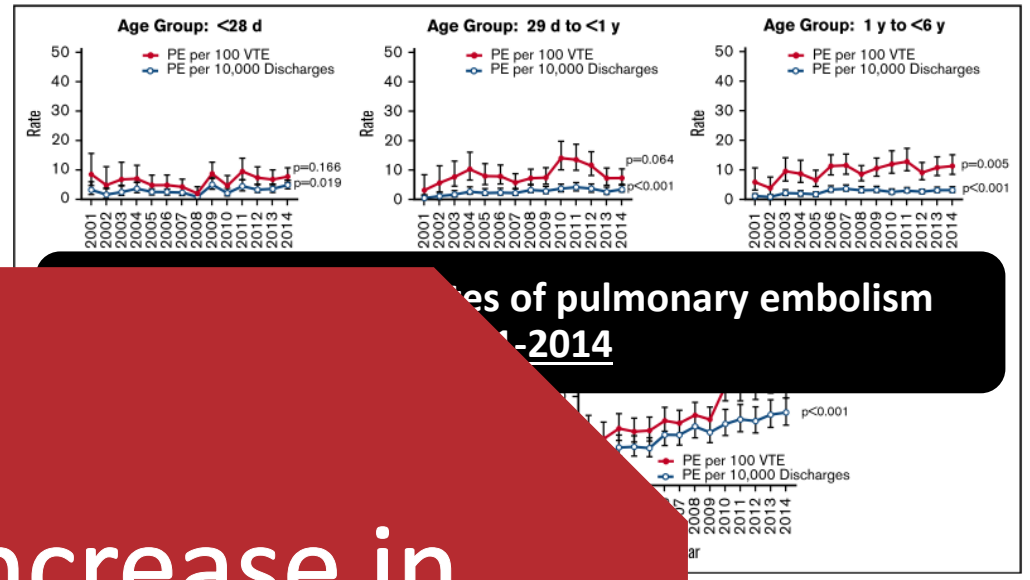
UAB Department of Pediatric Hematology/Oncology

January 11, 2024

Background



70% increase in h



es of pulmonary embolism
-2014

ired VTE rates

>200% increase in hospital-acquired VTE rates!!

Leslie Raffini, Yuan-Shung Huang, Char Witmer, Chris Feudtner; Dramatic Increase in Venous Thromboembolism in Children's Hospitals in the United States From 2001 to 2007. Pediatrics October 2009; 124 (4): 1001–1008. 10.1542/peds.2009-0768

Carpenter SL, Richardson T, Hall M. Increasing rate of pulmonary embolism diagnosed in hospitalized children in the United States from 2001 to 2014. Blood Adv. 2018 Jun 26;2(12):1403-1408. doi: 10.1182/bloodadvances.2017013292.

O'Brien SH, Stanek JR, Witmer CM, et al. The Continued Rise of Venous Thromboembolism Across US Children's Hospitals. Pediatrics. 2022;149(3):e2021054649

Background

Although the rate of venous thromboembolism (VTE) recurrence is low among pediatric patients with provoked VTE, children who have persistent prothrombotic risk factors, such as central venous catheters, thrombophilia and cancer after initial treatment have been shown to have increased risk for recurrent VTE.

Brandao LR et al. Safety of dabigatran etexilate for the secondary prevention of venous thromboembolism in children. *Blood. 2020;135(7):491-504.*

Goldenberg NA et al. Effect of Anticoagulant Therapy for 6 Weeks vs 3 Months on Recurrence and Bleeding Events in Patients Younger Than 21 Years of Age With Provoked Venous Thromboembolism: The Kids-DOTT Randomized Clinical Trial. *JAMA. 2022;327(2):129-37.*

Clark HH, Ballester L, Whitworth H, Raffini L, Witmer C. Prevention of recurrent thrombotic events in children with central venous catheter-associated venous thrombosis. *Blood. 2022;139(3):452-60.*

Limperger V, Kenet G, Goldenberg NA, Heller C, Holzhauer S, Junker R, et al. Impact of high-risk thrombophilia status on recurrence among children with a first non-central-venous-catheter-associated VTE: an observational multicentre cohort study. *Br J Haematol. 2016;175(1):133-40.*

Young G, Albisetti M, Bonduel M, Brandao L, Chan A, Friedrichs F, et al. Impact of inherited thrombophilia on venous thromboembolism in children: a systematic review and meta-analysis of observational studies. *Circulation. 2008;118(13):1373-82.*

JAMA | Original Investigation

Effect of Anticoagulant Therapy for 6 Weeks vs 3 Months on Recurrence and Bleeding Events in Patients Younger Than 21 Years of Age With Provoked Venous Thromboembolism

The Kids-DOTT Randomized Clinical Trial

Neil A. Goldenberg, MD, PhD; John M. Kittelson, PhD; Thomas C. Abshire, MD; Marc Bonaca, MD, MPH; James F. Casella, MD; Rita A. Dale, MS; Jonathan L. Halperin, MD; Frances Hamblin, MSHS; Craig M. Kessler, MD; Marilyn J. Manco-Johnson, MD; Robert F. Sidonio, MD, MSc; Alex C. Spyropoulos, MD; P. Gabriel Steg, MD; Alexander G. G. Turpie, MD; Sam Schulman, MD; for the Kids-DOTT Trial Investigators and the ATLAS Group

Goldenberg NA et al. Effect of Anticoagulant Therapy for 6 Weeks vs 3 Months on Recurrence and Bleeding Events in Patients Younger Than 21 Years of Age With Provoked Venous Thromboembolism: The Kids-DOTT Randomized Clinical Trial. JAMA. 2022;327(2):129-37.

Kids-DOTT

eTable 1. Inclusion and exclusion criteria

Inclusion Criteria

1. Children (birth to <21 years of age) with radiologically-confirmed acute deep venous thrombosis in the past 30 days
2. In the opinion of the investigator, the venous thrombosis was a provoked (i.e., non-spontaneous) event (e.g.: hospitalization; Central venous catheterization; infection; dehydration; surgery; trauma; immobility; use of estrogen-containing oral contraceptive pills; flare of autoimmune/rheumatologic condition).

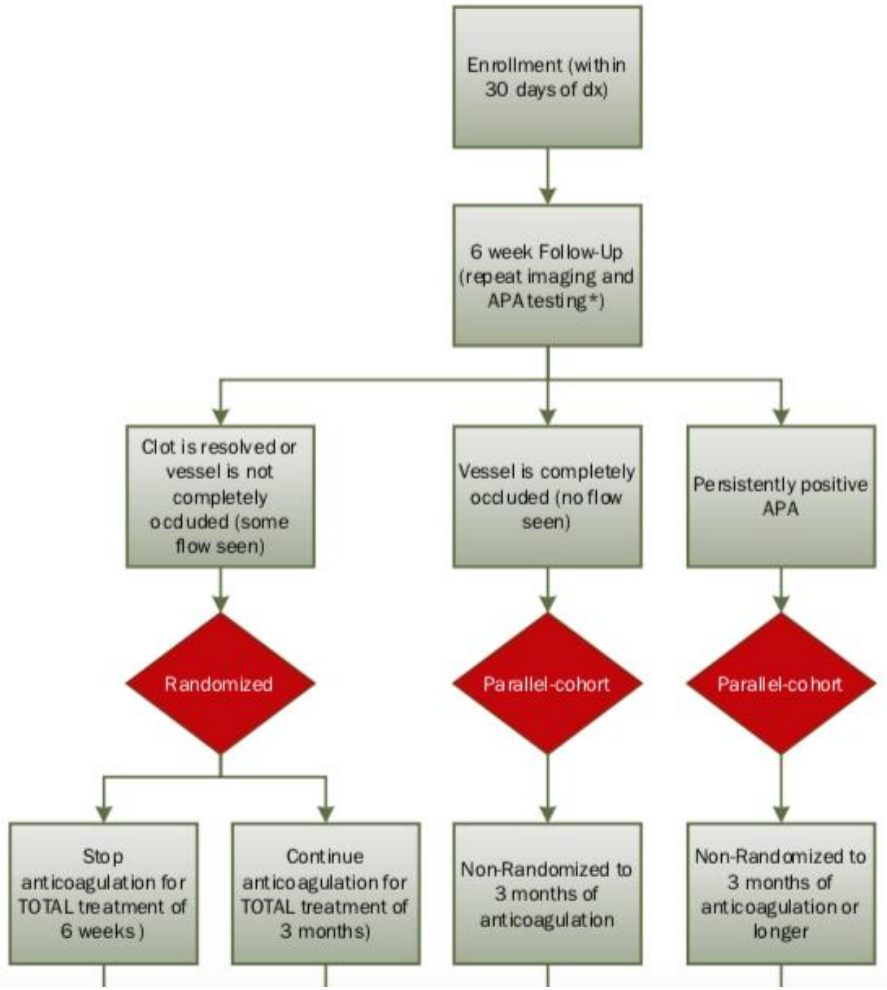
Exclusion Criteria

1. Prior episode of VTE
2. Malignancy that, in the opinion of the treating oncologist, is not in remission (note: remission may exist on or off anti-neoplastic therapy)
3. Systemic lupus erythematosus
4. Pulmonary embolism that is not accompanied by DVT or is more proximal than segmental branches of the pulmonary artery
5. Use of, or intent to use, thrombolytic therapy
6. Chronic anticoagulant at prophylactic dosing is being or will be administered beyond 6 months post VTE diagnosis
7. Moderate/severe anticoagulant deficiency (defined by any one of the following):
    a. protein C <20 IU/dL if patient is ≥3 months of age, or protein C below lower limit of detection if patient is <3 months of age;
    b. antithrombin <30 IU/dL if patient is ≥3 months of age, or antithrombin below lower limit of detection if patient is <3 months of age;
    c. protein S (free antigen or activity) <20 IU/dL.

NOTE regarding pregnancy and eligibility:

A patient who develops a DVT while pregnant who has no other provoking factor beyond the pregnancy will remain ineligible for this study.

Figure 1:
STUDY SCHEMA



Objective

To characterize the use and outcomes of secondary anticoagulation in patients <21 years old with provoked VTE, via the multinational Kids-DOTT trial

Methods

- Secondary analysis of patients enrolled in the Kids-DOTT trial who received secondary anticoagulation
- Definitions:
  - **Secondary anticoagulation** was defined as anticoagulant use beyond the initial treatment period of 6-12 weeks for the purpose of secondary VTE prevention, as captured in case report forms.
    - **Chronic-** anticoagulation began within 2 weeks of the prescribed treatment course
    - **Episodic**- anticoagulation began $\geq$ 2 weeks after end of prescribed treatment course

Preliminary Results

Table 1. Characteristics of patients in the Kids-DOTT study (including randomized population and parallel cohorts) who did versus did not receive secondary anticoagulation

Variable	Overall N=532[1]	No secondary anticoagulation N=514[1]	Secondary anticoagulation N=18[1]	p-value[2]
Age (years)				0.051
N	532	514	18	
Median	8 (1,15)	7.8 (1,15)	12.9 (7.6,15.5)	
Sex				0.8
Female	249/532 (47%)	240/514 (47%)	9/18 (50%)	
Male	283/532 (53%)	274/514 (53%)	9 /8 (50%)	
Race				0.4
American Indian or Alaskan Native	2/532 (0.4%)	2/514 (0.4%)	0/18 (0%)	
Asian	16/532 (3.0%)	16/514 (31%)	0/18 (0%)	
Black or African American	69/532 (13%)	66/514 (13%)	3/18 (17%)	
White or Caucasian	385/532 (72%)	373/514 (73%)	12/18 (67%)	
Multiple	6/532(11%)	5/514 (1.0%)	1/18 (5.6%)	
Other	13/532 (2.4%)	13/514 (2.5%)	0/18 (0%)	
Unknown/Not Reported	41/532 (7.7%)	39/514 (76%)	2/18 (11%)	
Index VTE Anatomical Site				**0.003**
Cerebral Sinovenous Thrombosis	75/532 (14%)	73/514 (14%)	2/18(11%)	
Lower Extremity DVT +/- PE	**242/532 (45%)**	**238/514 (46%)**	4/18 (22%)	
Renal Vein Thrombosis	2/532 (0.4%)	1/514 (0.2%)	1/18 (5.6%)	
Right Atrial Thrombosis	2/532 (0.4%)	2/514 (0.4%)	0/18 (0%)	
Splanchnic Vein Thrombosis	7/532(13%)	5/514 (1.0%)	2/18 (11%)	
Upper Extremity DVT +/- PE	157/532 (30%)	148/514 (29%)	**9/18 (50%)**	
Other VTE Site	46/532 (8.6%)	46/514 (89%)	0/18 (0%)	
Not Reported	1/532 (0 2%)	1/514 (0.2%)	0/18 (0%)	

[1] n/N (%)

[2] Mann-Whitney U test; Pearson's Chi-squared test; Fisher's exact test

- The median age was 12.9 (IQR 7.6, 15.5) and the majority (67%) were white.
- The most common index VTE anatomical site was upper extremity +/- PE in subjects who received secondary anticoagulation versus lower extremity +/- PE in those who received no secondary anticoagulation.

Preliminary Results

Table 2. Characteristics of secondary anticoagulation use in the Kids-DOTT study

Variable	n/N (%)
Agent used for secondary anticoagulation	
Vitamin K antagonist	2/18 (11%)
Low molecular weight heparin	14/18 (78%)
Unfractionated heparin	1/18 (5.6%)
Other	1/18 (5.6%)
Interval from end of treatment to start of secondary anticoagulation (days)	
N	11
Median (IQR)	116 (16,135)
Modality of secondary anticoagulation	
Chronic	3/11 (27%)
Episodic	8/11(73%)
Duration of secondary anticoagulation (days)	
N	17
Median (IQR)	20 (7,71)
Indication for secondary anticoagulation	
Central venous catheter	5/18 (28%)
Infection	3/18 (17%)
Trauma or surgery within previous 30 days	1/18 (5.6%)
Prothrombotic medication	0/18 (0%
Flare of autoimmune disease	0/18 (0%
Hospitalization within previous 30 days	0/18 (0%)
Congenital or acquired cardiac disease	0/18 (0%)
Persistent thrombus	0/18 (0%)
Other indication[1]	2/18 (11%)
Unknown indication	1/18 (5.6%)
Outcomes (*during/following course of secondary anticoagulation)	
Recurrent VTE	*0/18 (0%)
Clinically relevant bleeding	*0/18 (0%)

[1] melody valve replacement, renal transplant

- Low molecular weight heparin was the most frequently used anticoagulant at 78%.
- The most common indication for secondary anticoagulation was presence of central venous catheter.
- Of the 18 subjects receiving secondary anticoagulation, none had clinically relevant bleeding or recurrent VTE during or after course of secondary anticoagulation.

Conclusions

- The use of secondary anticoagulation is low among patients <21 years old with provoked VTE.
- Among those who received secondary anticoagulation for persistent or recurrent prothrombotic risk factors, the risks of recurrent VTE and clinically relevant bleeding are low.
- Focused study of use and outcomes of chronic and episodic secondary anticoagulation is warranted to inform future practice on secondary VTE prevention in children, adolescents, and young adults with a history of provoked VTE.

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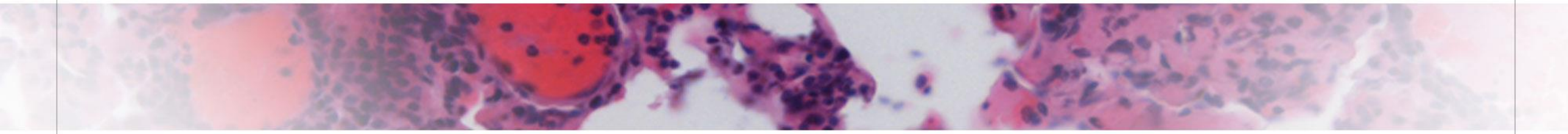

How to Diagnose and Manage Antiphospholipid Syndrome

Beyond Guidelines

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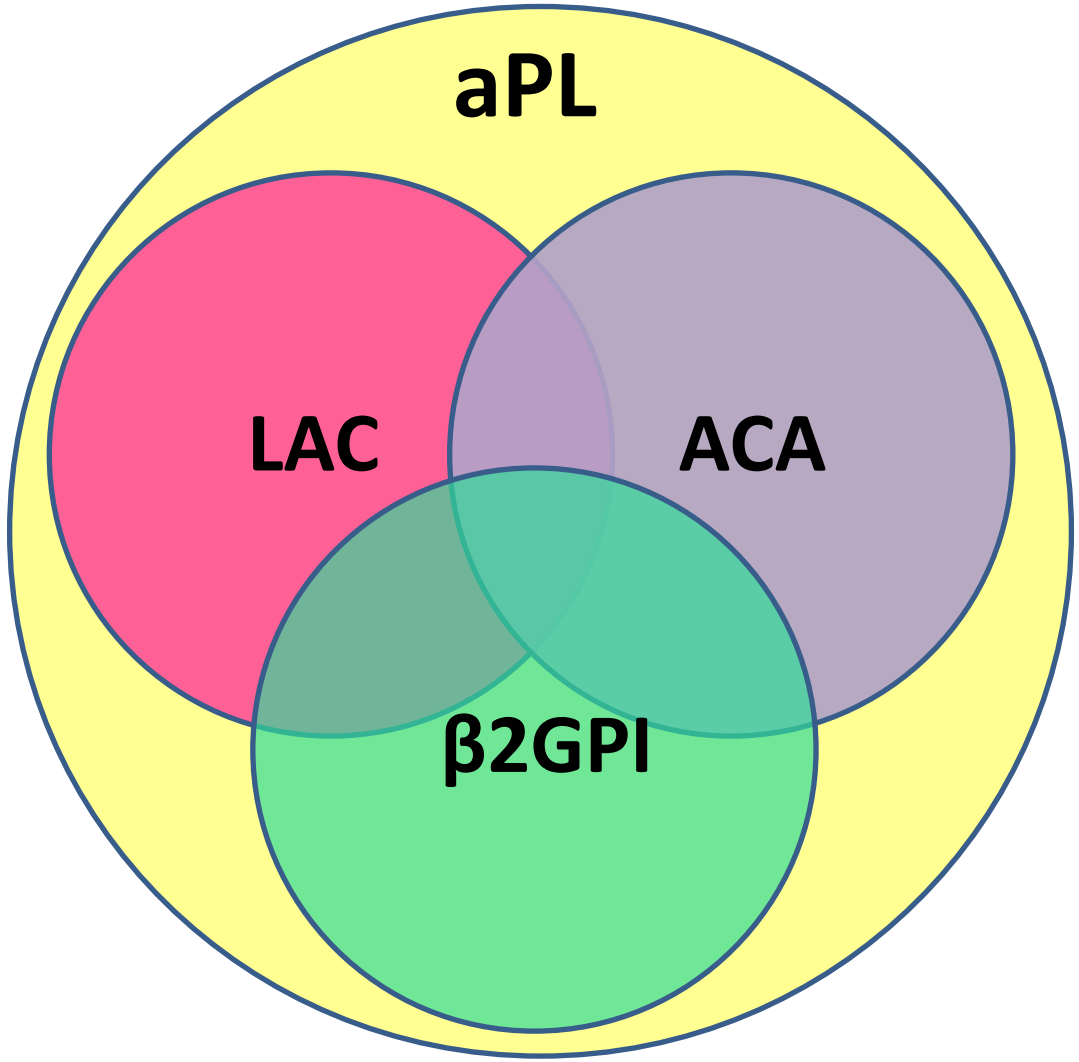
Antiphospholipid Antibodies (aPL)



- Heterogeneous antibody population with unique and overlapping specificities
- Primarily cofactor-dependent in humans: β2GPI, prothrombin, PS/PT, others
- May arise in response to viral peptides in animal models
- aPL are found in association with several autoimmune disorders, but most common in normal individuals (2-4%)
- APS prevalence ~50 cases/100,000

Case 1: Postoperative VTE/Isolated IgM aPL

- 77-year-old woman presents for an opinion concerning duration of anticoagulation
- Cervical discectomy and fusion six months previously
  - Not given anticoagulant prophylaxis
  - Sat in chair immediately after surgery, ambulatory and discharged the following day
- One week postop presented with R calf and chest discomfort; evaluation showed peroneal and soleal vein DVT and PE involving lobar, segmental and subsegmental arteries-placed on apixaban
- Seen in follow up by hematologist: anti-β2GPI IgM 87 SMU, aCL IgM 66 MPL
  - Switched to warfarin
  - aPL three months later: β2GPI IgM 106 SMU, aCL IgM 74 MPL
- Saw another hematologist after 6 months: recommended D/C anticoagulation

Revised “Sapporo” Criteria for APS

- *Clinical*
  - Vascular thrombosis—one or more clinical episodes
  - Pregnancy morbidity
    - Three or more consecutive spontaneous abortions before 10th week
    - One or more unexplained deaths beyond 10 weeks
    - One or more premature births at or before the 34th week of gestation because of eclampsia or severe preeclampsia or severe placental insufficiency
- *Laboratory*
  - LAC on 2 or more occasions at least 12 weeks apart, detected by ISTH guidelines
  - aCL antibody of IgG or IgM isotype in serum or plasma, in medium or high titer (>40 GPL or MPL, or the 99th percentile) on 2 or more occasions at least 12 weeks apart, measured by standardized ELISA
  - Anti-β_2GPI antibody of IgG or IgM isotype in serum or plasma (in titer > 99th percentile), present at two or more occasions, at least 12 weeks apart, measured by standardized ELISA

Definite APS requires at least one clinical and one laboratory criteria

Miyakis et al. JTH 4:295, 2006

EULAR 2023 APS Criteria (Ann Rheum Dis 82:1258, 2023)

Entry Criteria
At least one clinical criteria (D 1-6) PLUS a positive aPL test (LAC or moderate/high levels of ACA or anti-β2GPI (G or M) within 3 years

Clinical			
D1. Macrovascular (Venous thromboembolism)		D2. Macrovascular (Arterial Thrombosis)	
With high risk VTE profile	1	With high-risk CVD profile	4
Without high risk VTE profile	3	Without high-risk CVD profile	2
D3. Microvascular		D4. Obstetric	
Suspect livedo racemosa, livedoid vasculopathy, aPL nephropathy, pulmonary hemorrhage	2	≥ 3 Consecutive pre-fetal (≤ 10 wk) or fetal (10-16 wk) deaths	1
Established livedoid vasculopathy, aPL nephropathy, myocardial disease, pulmonary/adrenal hemorrhage	5	Fetal death (16-33 wk) in absence of PEC or PI with severe features	1
		PEC or PI (<3 4 wk) with severe features w/ or w/o fetal death	3
		PEC AND PI (< 34 wk) with severe features w/ or w/o fetal death	4
D5. Cardiac Valve		D6. Hematology	
Thickening	2	Thrombocytopenia (lowest 20-130 x 10^9/L)	2
Vegetation	4		
Laboratory			
D7. APL test by coagulation-based functional assay (LAC)		D8. aPL test by solid-phase assay (persistent)	
Positive LAC (single-one time)	1	Moderate or high positive IgM (aCL and/or aβ2GPI)	1
Positive LAC (persistent)	5	Moderate positive IgG (aCL and/or aβ2GPI)	4
		High positive IgG aCL or aβ2GPI	5
		High positive IgG aCL and aβ2GPI	7

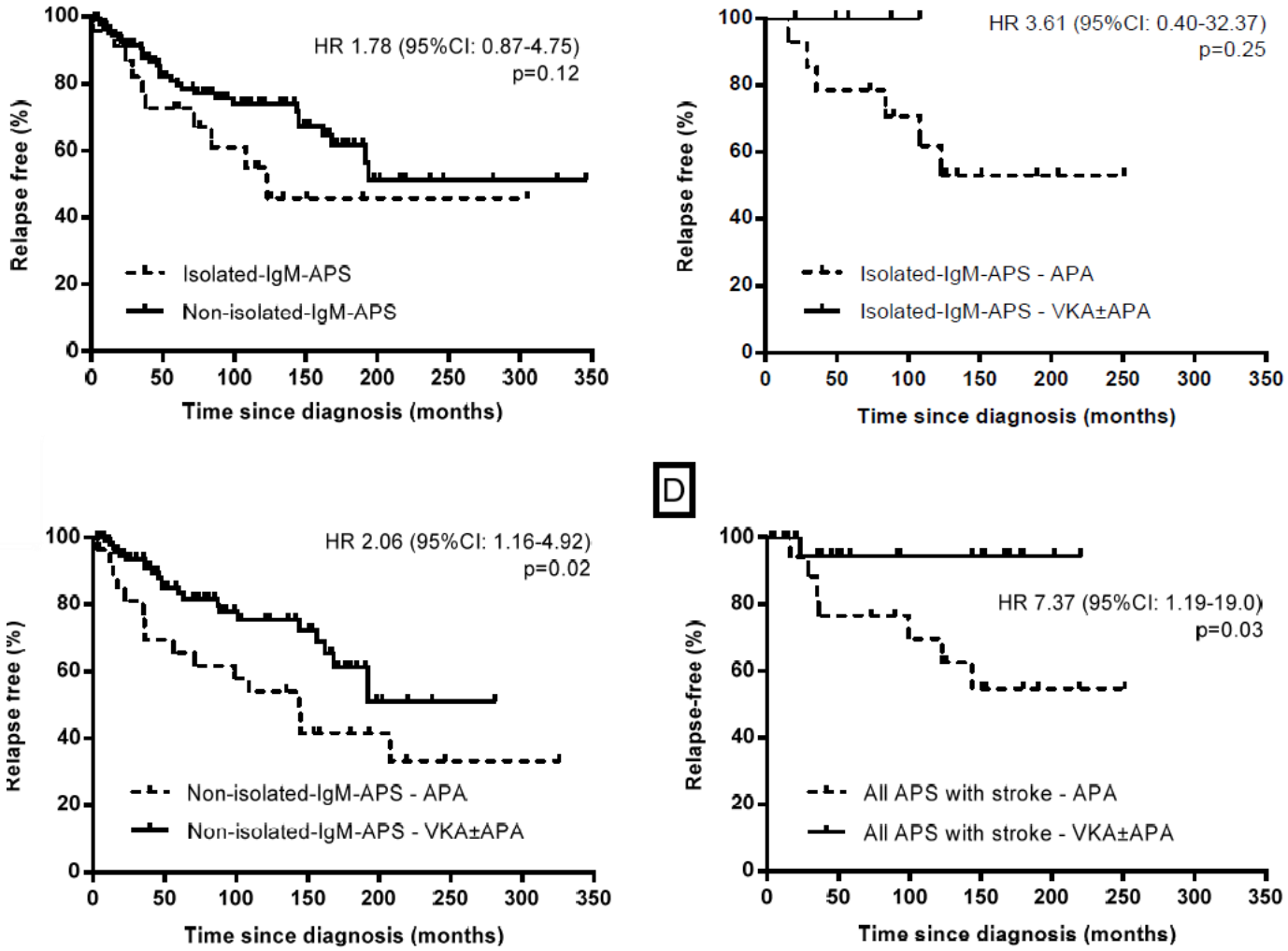
*Classify as APS (for research purposes) if at least **3 points each from clinical and laboratory domains***

Clinical Importance of IgM Isotype in APS?

- **Del Ross et al, Thromb Res 136:883, 2015**; retrospective analysis of 106 patients
  - Overall thrombosis rate: VTE 41.5%, ATE 45.3%, PE 10.4%, microvascular 2.8%
  - Overall frequency of IgG and IgM antibodies did not differ (P = 0.88)
  - 13 patients (12.3%) positive for isolated IgM aPL (all positive for aCL and aβ2GPI)
    - All medium to high levels, and 100% persistent over mean follow up of 10.2 years
    - Higher incidence of cerebrovascular disease (46.1% vs 30.0%; NS)
    - Higher mean age at time of thrombosis (P = 0.002)
    - Higher incidence of retinal thrombosis (P = 0.005, OR 27.6)

- **Urbanski et al, Stroke 49:2770, 2018**; Retrospective analysis of 168 APS patients, mean follow up 92.5 months
  - 24 (14.3%) had isolated IgM (9 IgM aCL, 2 isolated IgM aβ2GPI)
  - IgM antibodies were persistent, and remained isolated in 70.8%
  - Stroke more frequently led to APS diagnosis in isolated IgM aPL patients (OR 3.1, 95% CI 1.3-11.5, P = 0.018)
  - Use of antiplatelet agents alone (APA) was more common in isolated IgM APS (14/20 vs 28/134; P < 0.0001)
    - In patients presenting with stroke, APA alone used in 9/10 isolated IgM vs 10/33 non-isolated IgM (P = 0.002)

Clinical Importance of IgM Isotype in APS? (Urbanski et al)

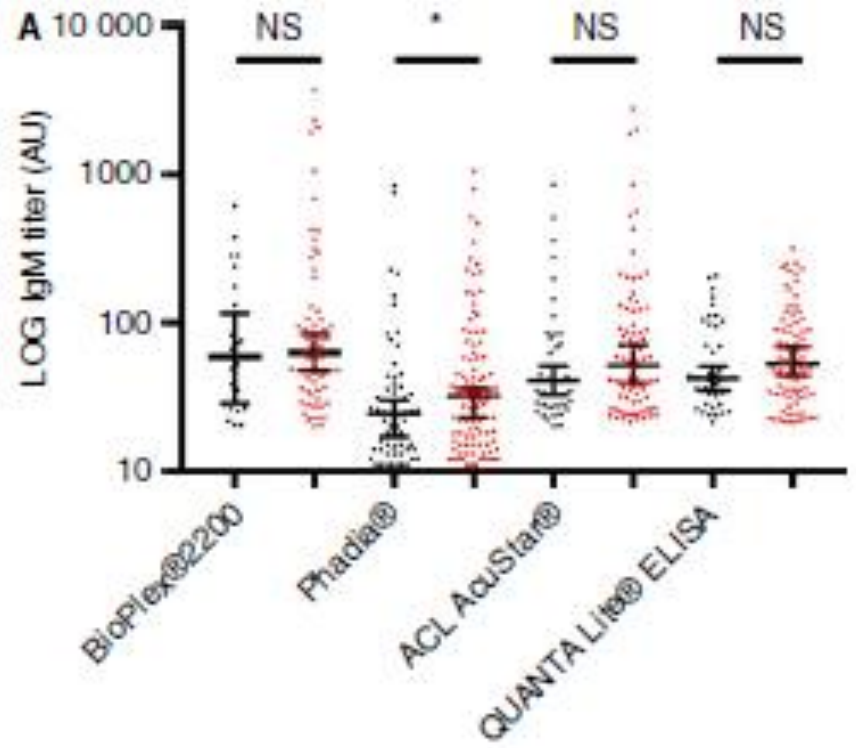


- No difference in relapse-free survival between IgM-APS and non-isolated IgM APS
- Decreased relapse (thrombosis) free survival in both isolated IgM-APS, non-isolated IgM APS and the pooled cohort in patients on APA alone vs APA + VKA

Urbanski et al, Stroke 49:2770, 2018

(Non)sense of Detecting IgM aCL and aβ2GPI in APS

- 1008 patients/8 European centers (259 APS thrombosis, 204 non-APS thrombosis)
- 3.5-4.5% of thrombotic APS patients had isolated IgM aCL or aβ2GPI antibodies
- 2.5% of patients classified as non-APS thrombosis had isolated IgM aCL or aβ2GPI positivity
- No significant difference between overall IgM aCL or aβ2GPI levels in patients versus controls in 3 of 4 assays
- IgM positivity was not associated with thrombosis in multivariate logistic regression analysis including age, sex, LAC, IgG and IgM
- IgM aPL were significantly associated with obstetric APS



Chayuoa et al JTH 18:169, 2020

Case 1: Summary

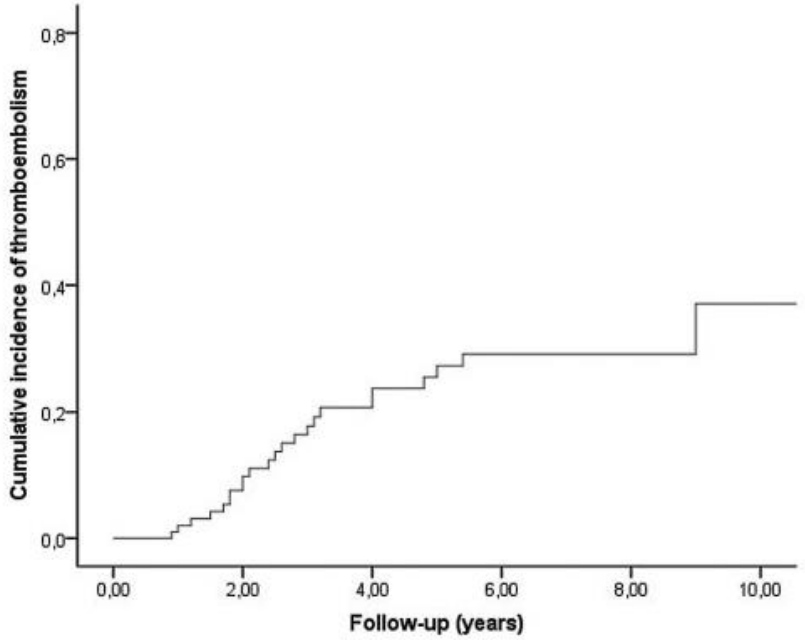
- Isolated IgM aPL are uncommon in APS
- There is insufficient data to consider isolated IgM aPL insignificant
- Using classification schemes for APS as diagnostic tools or therapeutic guides may be misleading
- Recommendations for this patient:
  - Continue warfarin anticoagulation
  - Periodic reassessment of aPL levels

Case 2: An Asymptomatic Patient with aPL

- 53-year-old man with medically intractable epilepsy for six years
- Strong family history of coronary artery disease.
- Imaging studies suggested an epileptic focus in the orbital/anterior-mesial temporal regions
- Distant history of antiphospholipid antibodies
- Antiphospholipid testing
  - Positive LAC (dilute Russel's viper venom time, hexagonal phospholipid assay)
  - aCL IgG and IgM each > 150 GPL/MPL units, aCL IgA 21.2 APL
  - anti-β2GPI IgG and IgM each >150 SGU/SMU
- *Does this patient require prophylactic anticoagulation?*

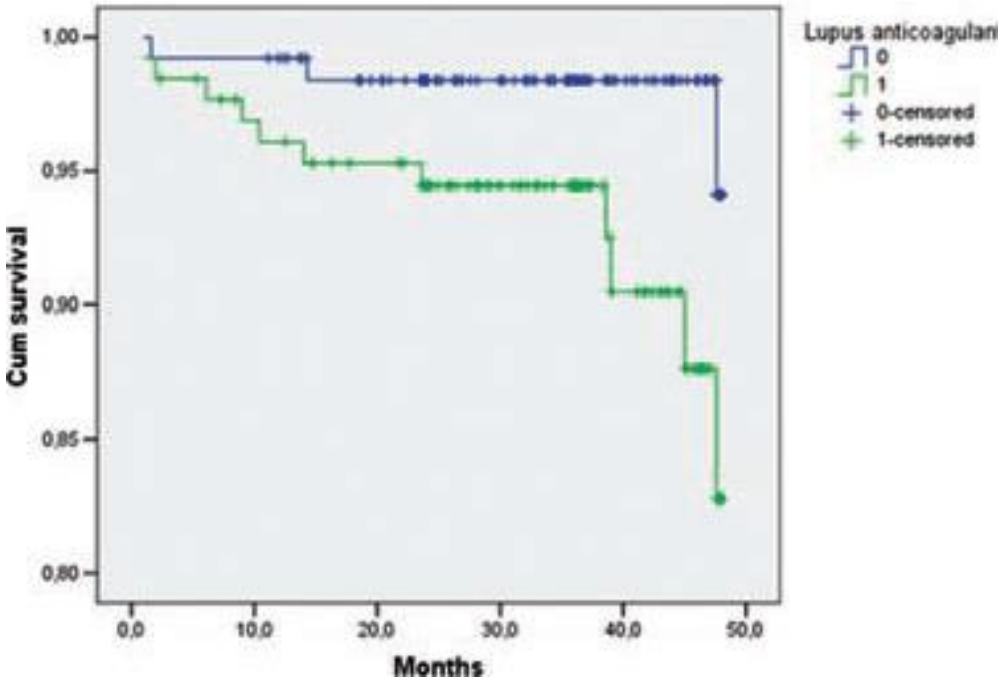
Absolute Risk of Thrombosis with aPL

Triple positive: 5.3%/year



Pengo et al. Blood 118:4714, 2011

Any aPL 1.86%/year



Ruffatti et al Ann Rheum Dis 70:1083, 2011

Aspirin did not reduce incidence of thrombosis

APLASA: Aspirin for Primary Thrombosis Prophylaxis

Table 3. Followup period and outcomes in the Antiphospholipid Antibody Acetylsalicylic Acid (APLASA) study and the observational study

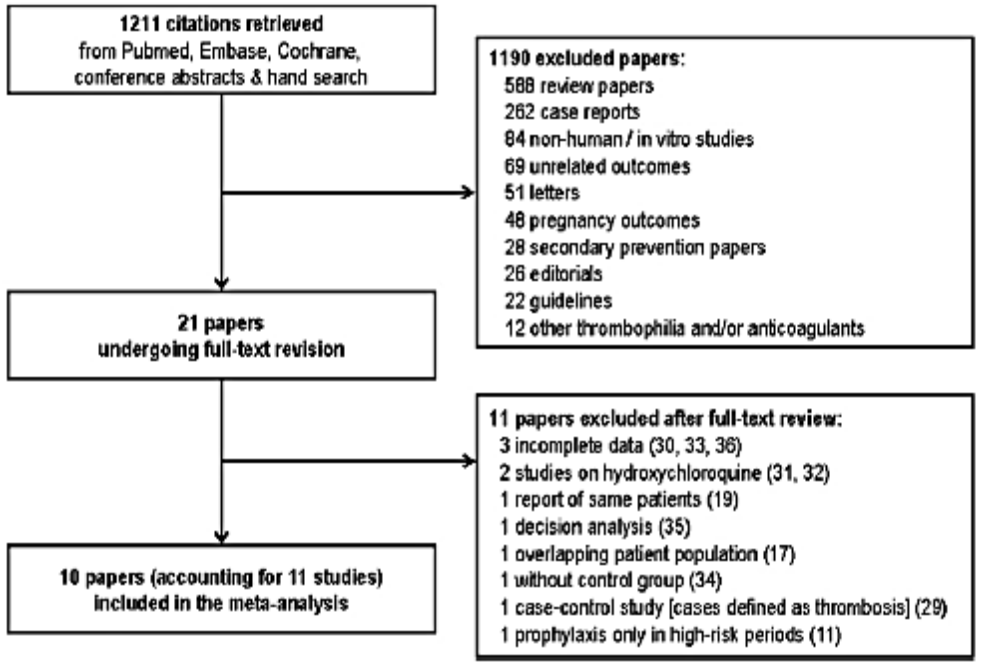
	APLASA study		Observational study	
	Aspirin (n = 48)	Placebo (n = 50)	Aspirin (n = 61)	No aspirin (n = 13)
Followup period				
Mean ± SD years	2.27 ± 0.91	2.33 ± 0.99	2.42 ± 0.79	2.63 ± 0.56
Patient-years	109.32	116.45	148.01	34.24
Primary outcomes, incidence rate per 100 patient-years	2.75	0	2.70	0
Secondary outcomes, incidence rate per 100 patient-years	1.83	0.86	0	0
Primary and secondary outcomes combined, incidence rate per 100 patient-years	4.57	0.86	2.70	0

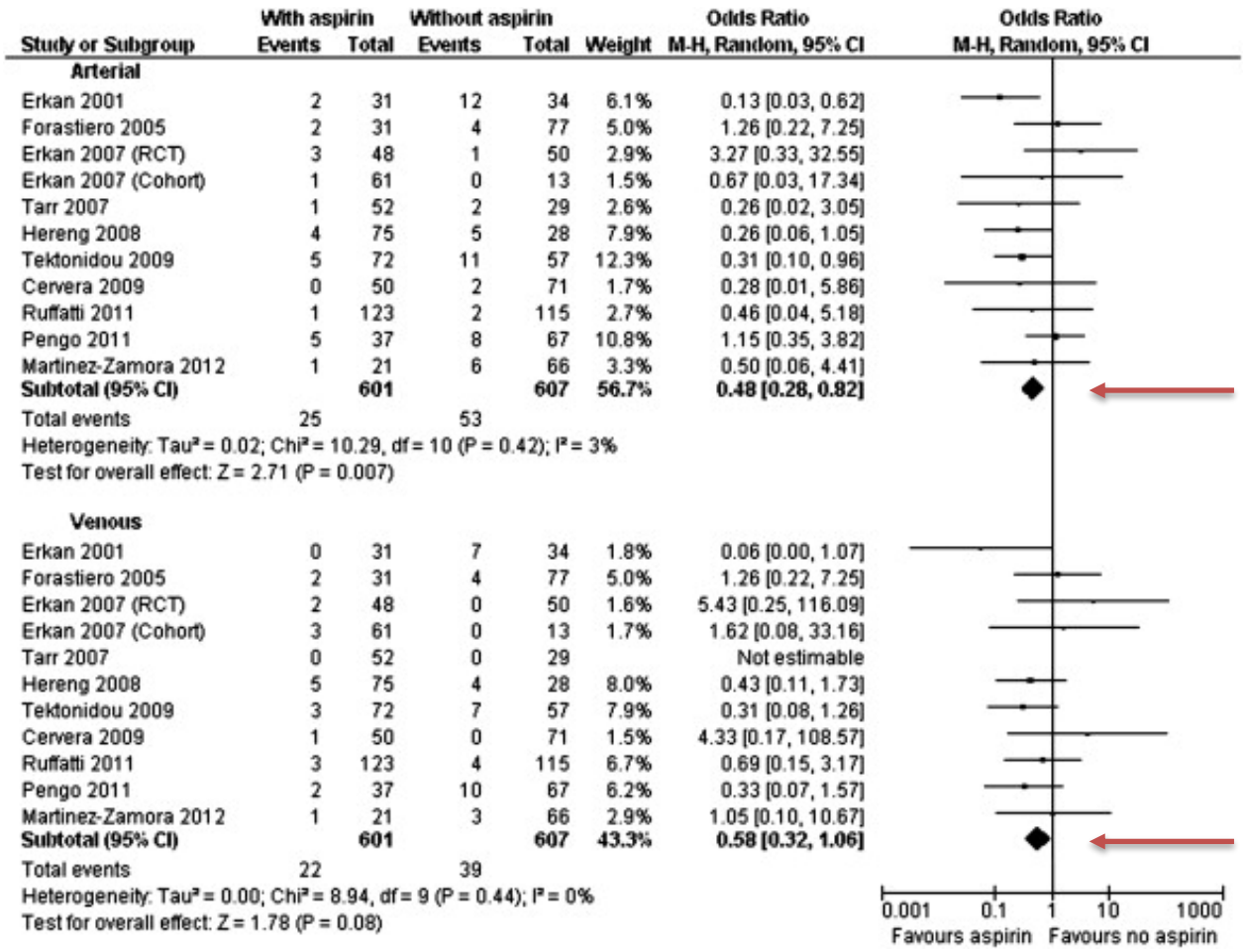
↔ HR 1.04 95% CI: 0.69-1.56

↔ HR 1.08 95% CI: 0.72-1.62

Erkan et al. Arthritis Rheum 56:2382, 2007

Aspirin for Primary Prevention: Meta-analysis





Arnaud et al, Autoimm Rev 13:281, 2014

EULAR Recommendations

In asymptomatic aPL carriers (not fulfilling any vascular or obstetric APS classification criteria) with a high-risk aPL profile with or without traditional risk factors, prophylactic treatment with low - dose aspirin (LDA) (75 – 100 mg daily) is recommended

Definitions of medium-high antiphospholipid antibody (aPL) titres, and of high-risk and low-risk aPL profile

- ***Medium-high aPL titres***
  - Anticardiolipin (aCL) antibody of IgG and/or IgM isotype in serum or plasma present in titres >40 IgG phospholipid (GPL) units or >40 IgM phospholipid (MPL) units, or >the 99th percentile, measured by a standardized ELISA.
  - Anti β2 glycoprotein I antibody of IgG and/or IgM isotype in serum or plasma in titre >the 99th percentile, measured by a standardized ELISA.
- ***High-risk aPL profile***
  - The presence (in 2 or more occasions at least 12 weeks apart) of lupus anticoagulant (measured according to ISTH guidelines), or of double (any combination of lupus anticoagulant, aCL antibodies or anti β2 glycoprotein I antibodies) or triple (all three subtypes) aPL positivity, or the presence of persistently high aPL titres
- ***Low-risk aPL profile***
  - Isolated aCL or anti β2 glycoprotein I antibodies at low-medium titres, particularly if transiently positive.

Tektonidou et al. Ann Rheum Dis 78:1296, 2019

Case 2: Summary

- This patient had “high-risk” aPL profile
- Despite this, he may have had aPL for many years without thrombosis, demonstrating the deficiencies in using aPL levels alone for risk stratification
- No significant secondary cardiovascular risk factors
- Our recommendations for this patient: consider low dose aspirin

Case 3: Direct FXa Inhibitor or VKA

- 36 year-old woman developed ileofemoral DVT six months previously
- No provoking factors or significant PMH. Not obese, no smoking
- Treated with apixaban in urgent care, and released
- Laboratory at 3 month follow up visit:
  - β2 glycoprotein 1 IgG 143 SGU, aCL IgG 56 GPL
  - Testing for LAC could not be completed due to FXa inhibitor treatment
- Referred for opinion about need further anticoagulation
- *Question—should she remain on apixaban or switch to warfarin*

Trial of Rivaroxaban vs Warfarin in High-Risk APS (TRAPS)

- Randomized, open label study: Rivaroxaban 20 mg/d vs warfarin (INR 2.0-3.0)
- Triple positive APL patients

Table 4. Adjudicated efficacy and safety outcomes

Outcome, n	"As treated" analysis				ITT analysis			
	Rivaroxaban (n = 59)	Warfarin (n = 61)	HR (95% CI)	P	Rivaroxaban (n = 59)	Warfarin (n = 61)	HR (95% CI)	P
Thromboembolic events, major bleeding, and vascular death	11 (19)	2 (3)	6.7 (1.5-30.5)	.01	13 (22)	2 (3)	7.4 (1.7-32.9)	.008
Arterial thrombosis Ischemic stroke Myocardial infarction	7 (12) 4 (7) 3 (5)	0 0 0	—	—	7 (12) 4 (7) 3 (5)	0 0 0	—	—
Venous thromboembolism	0	0			1 (2)	0		
Major bleeding	4 (7)	2 (3)	2.5 (0.5-13.6)	.3	4 (7)	2 (3)	2.3 (0.4-12.5)	.3
Death	0	0	—	—	1 (2)	0	—	—

Numbers in parentheses denote percentage with respect to total.
—, statistical analysis not applicable.

Pengo et al, Blood 132:1365, 2018

Recurrent Thrombosis/Stroke in APS: VKA vs Rivaroxaban

Study Population	Events, *n* (%)		Risk Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)‡	*P* Value
	Rivaroxaban Group (*n* = 95)	VKA Group (*n* = 95)†				
Per protocol, as treated						
All events	11 (11.6)	6 (6.3)	1.83 (0.71–4.76)	0.21	1.94 (0.72–5.24)	0.190
Arterial events§	10 (10.5)	3 (3.2)	3.33 (0.95–11.73)	0.060	3.52 (0.97–12.79)	0.060
Venous events§	2 (2.1)	3 (3.2)	0.67 (0.11–3.90)	0.65	0.70 (0.12–4.21)	0.70
Stroke	9 (9.5) ←	0 (0)	19.00 (1.12–321.9)	<0.001	19.97 (1.00–400.0)	0.050
Intention to treat						
All events	12 (12.6)	6 (6.3)	2.00 (0.78–5.11)	0.150	2.10 (0.79–5.59)	0.140
Arterial events	11 (11.6)	3 (3.2)	3.67 (1.06–12.73)	0.040	3.84 (1.07–13.76)	0.040
Venous events	2 (2.1)	3 (3.2)	0.67 (0.11–3.90)	0.65	0.70 (0.12–4.18)	0.69
Stroke	10 (10.5) ←	0 (0)	21.00 (1.25–353.3)	0.001	20.01 (1.12–431.8)	0.040

VKA = vitamin K antagonist.
* All analyses of thrombotic events were based on the first event in the safety population during treatment. Among patients who had a thrombotic event, 3 (50%) in the VKA group and 6 (54.5%) in the rivaroxaban group had additional conventional cardiovascular risk factors, and they were adherent to their treatment.
† Four thrombotic events in the VKA group occurred in patients with an international normalized ratio below target.
‡ Hazard ratios are for the rivaroxaban group compared with the VKA group.
§ One patient with catastrophic antiphospholipid antibody syndrome presented with arterial and venous events simultaneously.

Ordi-Ros et al, Ann Int Med 171:685 2019

Apixaban vs Warfarin in APS

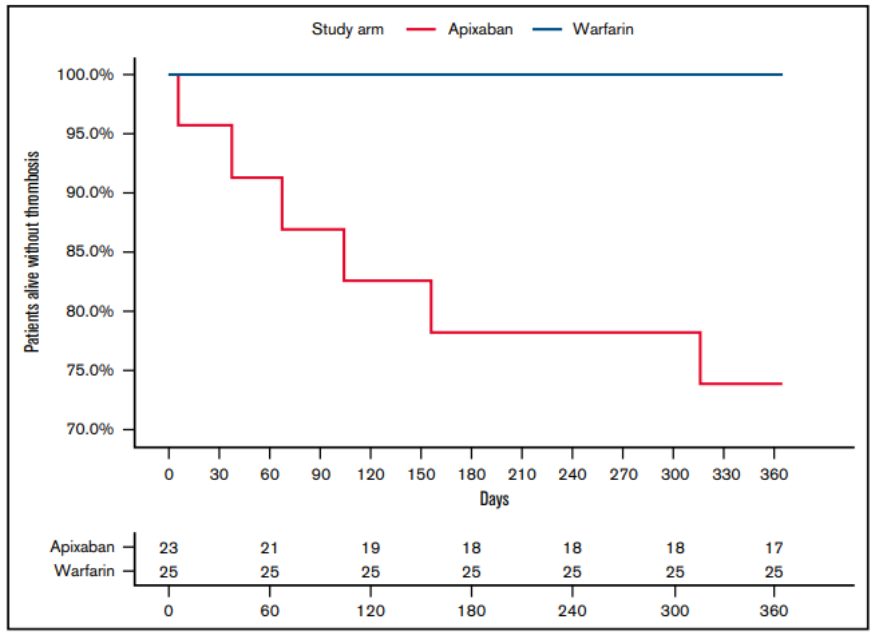


Table 2. Details for each participant that experienced a thrombotic or major bleed event during the study

ID	Age	Sex	BMI	Treatment	History	Positivity level*	Type	Event type	Days to event
24	40	Female	39.3	Apixaban	Stroke, DVT, PE, pregnancy loss	Single	Likely	Stroke	156
16	43	Female	36.9	Apixaban	DVT	Triple	Definite	Stroke	67
12	47	Female	19.4	Apixaban	Stroke, TIA, DVT, pregnancy loss	Double	Likely	Stroke	37
2	51	Female	25.5	Apixaban	Stroke, other arterial thrombosis, DVT, PE	Triple	Definite	Stroke	316
32	66	Male	39.3	Apixaban	DVT	N/A	Historical	Stroke	104
3	69	Female	23.2	Apixaban	Stroke, pregnancy loss	N/A	Historical	Stroke	6
27	62	Female	30.5	Warfarin	Stroke, DVT, PE	N/A	Historical	Major bleed†	319

BMI, body mass index; DVT, deep vein thrombosis; N/A, not applicable as historical APS; PE, pulmonary embolism; TIA, transient ischemic attack.
*Refers to whether the patient's laboratory markers denote single-, double-, or triple-positivity for antiphospholipid syndrome.
†Vaginal hemorrhage.

Woller, Blood Adv 6:1661, 2022

Case 3: Summary

- **FDA recommendation**: *Increased Risk of Thrombosis in Patients with Triple Positive Antiphospholipid Syndrome treated with Direct-acting oral anticoagulants (DOACs).* ***DOACs are not recommended for use in patients with triple-positive antiphospholipid syndrome (APS)****. For patients with APS (especially those who are triple positive [positive for lupus anticoagulant, anticardiolipin, and anti-beta 2-glycoprotein I antibodies]), treatment with DOACs has been associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy*
- Double positive? Single positive? LAC only? Prior venous thrombosis?
  - Data unclear
- If patient doing well on FXa inhibitors?
  - Unclear how long a thrombosis-free course of treatment is needed for reassurance
- This patient
  - Double positive (cannot R/O triple positive, since on FXa inhibitor)
  - Has been on FXa inhibitor for a relatively short time (~6 months)
  - Switch to warfarin was recommended

A Comparison of Bleeding Events Among Patients on Apixaban, Rivaroxaban, and Warfarin for Atrial Fibrillation and/or Venous Thromboembolism

Jordan Schaefer, MD, MSc

AC Forum Presentation, 1/11/24

Disclosures

- **Research Funding:** American Society of Hematology, Hemostasis Thrombosis Research Society Mentored Research Award (Supported by an educational grant from Takeda), NIH
- **Consultancy:** Pfizer

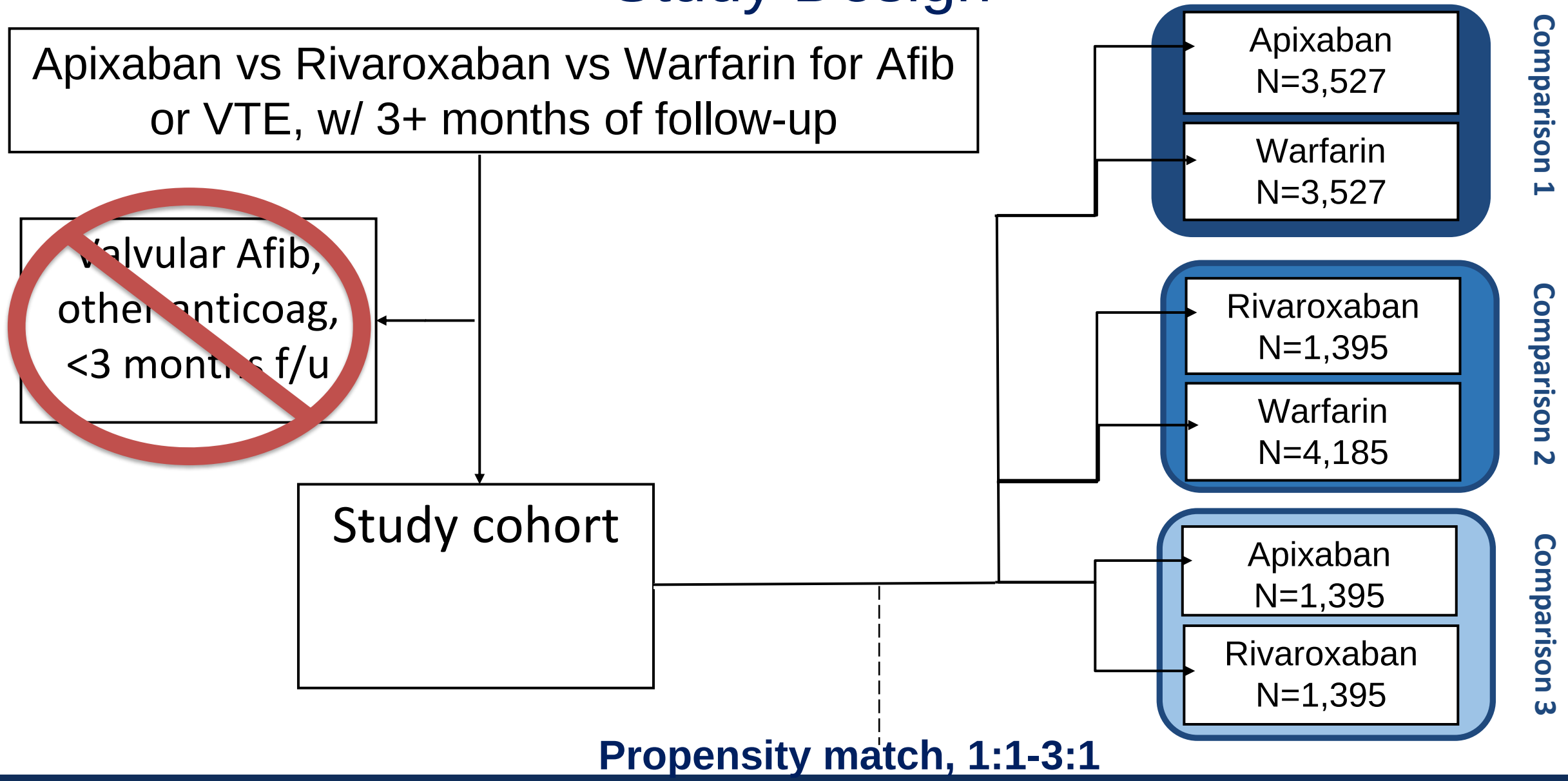
Objectives

- Apixaban, rivaroxaban, and warfarin are some of the most commonly used oral anticoagulants[1,2]
- Apixaban and rivaroxaban have been compared to warfarin for the indications of atrial fibrillation and venous thromboembolism[3-6]
  - Limited direct comparative efficacy studies
  - Limited data in a non-trial setting
- We sought to compare patient characteristics and outcomes with use of these three anticoagulants

Methods-Michigan Anticoagulation Quality Improvement Initiative

- Warfarin registry
  - 6 clinics
- DOAC registry
  - 4 clinics
- Enrollment:
  - Jan 2009 – June 2023
- Data collection:
  - Trained abstractors
  - Predefined forms
  - Random chart audits

Study Design



Methods-Propensity Match

- Demographics
  - Age, sex, BMI, alcohol/tobacco use
- Indication
  - Atrial fibrillation, venous thromboembolism
- Co-morbidities
- Coagulation History
  - History of recent bleeding (≤ 30 days)
  - Remote bleeding (>30 days)
  - History of systemic embolism
  - History of stroke/TIA
  - History of venous thromboembolism
  - History of gastrointestinal bleeding
  - Myocardial infarction
- Medications
  - Aspirin dose
  - Estrogen
  - Antiplatelet therapy
  - NSAIDs
- Duration of follow-up
- HAS-BLED (modified)
- Charlson Co-morbidity index

Data Analysis

- Patients followed from enrollment until:
  - Lost to follow-up
  - Anticoagulation clinic discharge
  - End of study
  - Death
- Event rates compared by Poisson regression

Outcomes

- Thrombosis
  - Stroke/TIA
  - Pulmonary embolism
  - Deep vein thrombosis
  - Other thrombosis
- Bleeding
  - Major bleeding
    - Fatal
    - Life threatening
    - Intracranial or intraspinal
  - Non-major
- Emergency room visits
- Hospitalizations
- Blood transfusion
- Death

Results-Patient Characteristics

13,435 patients

3,536 on apixaban, 1,395 on rivaroxaban, 8,504 on warfarin

Mean ± SD age: 67 ± 15 years

51.1% male

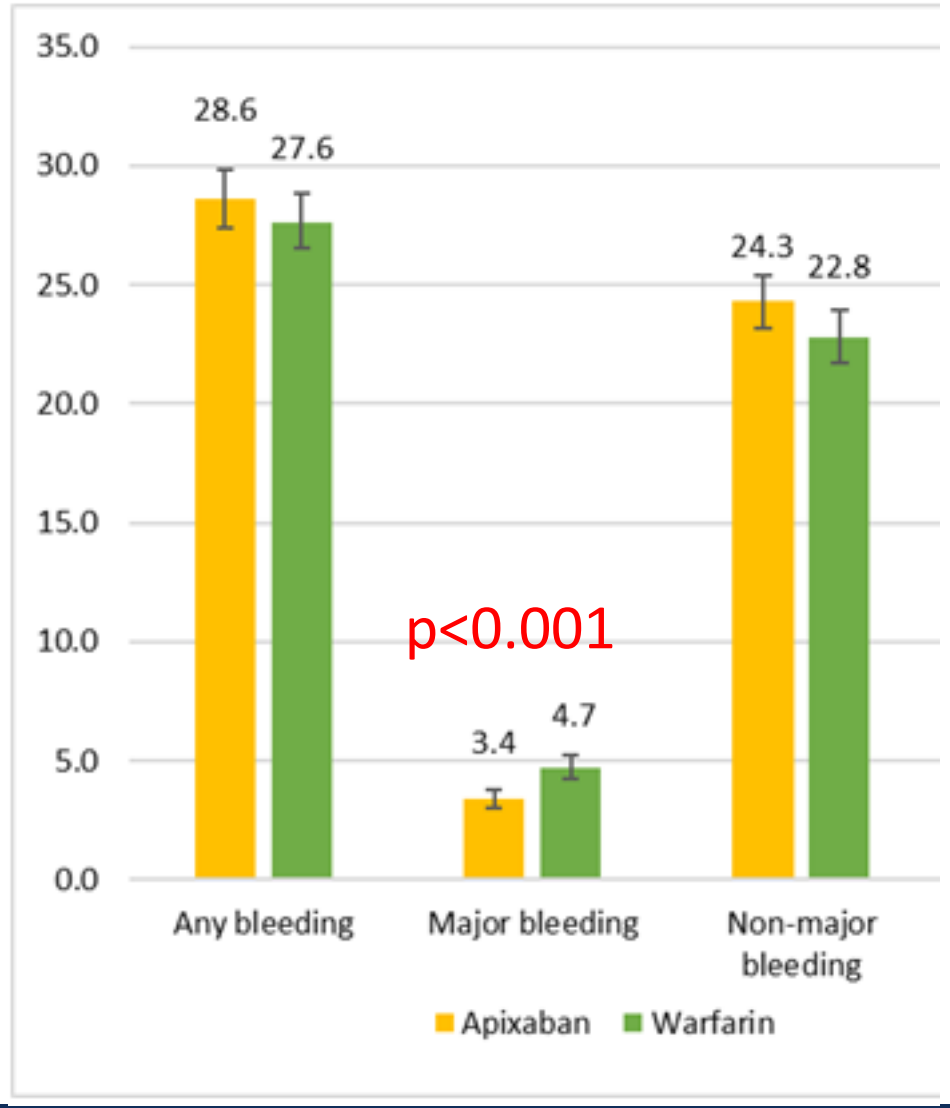
Results

Table 1: Patient Characteristics Before Matching[a]			
Anticoagulant	Apixaban N=3,536	Rivaroxaban N=1,395	Warfarin N=8,504
DOAC dose[b] (%)			
Reduced dose	18.3	10.0	/
Standard dose	81.7	90.0	/
Aspirin (%)	33.5	29.4	39.0
Demographics			
Age, y mean (sd)	70.5 (13.2)	64.8 (15.1)	65.4 (15.4)
Male (%)	50.0	49.9	51.8
BMI > 30 kg/m2 (%)	49.2	50.3	48.5
Alcohol or drug use	6.1	7.2	4.9
Current tobacco use	7.2	9.3	8.0
Former tobacco use	37.7	35.1	32.1

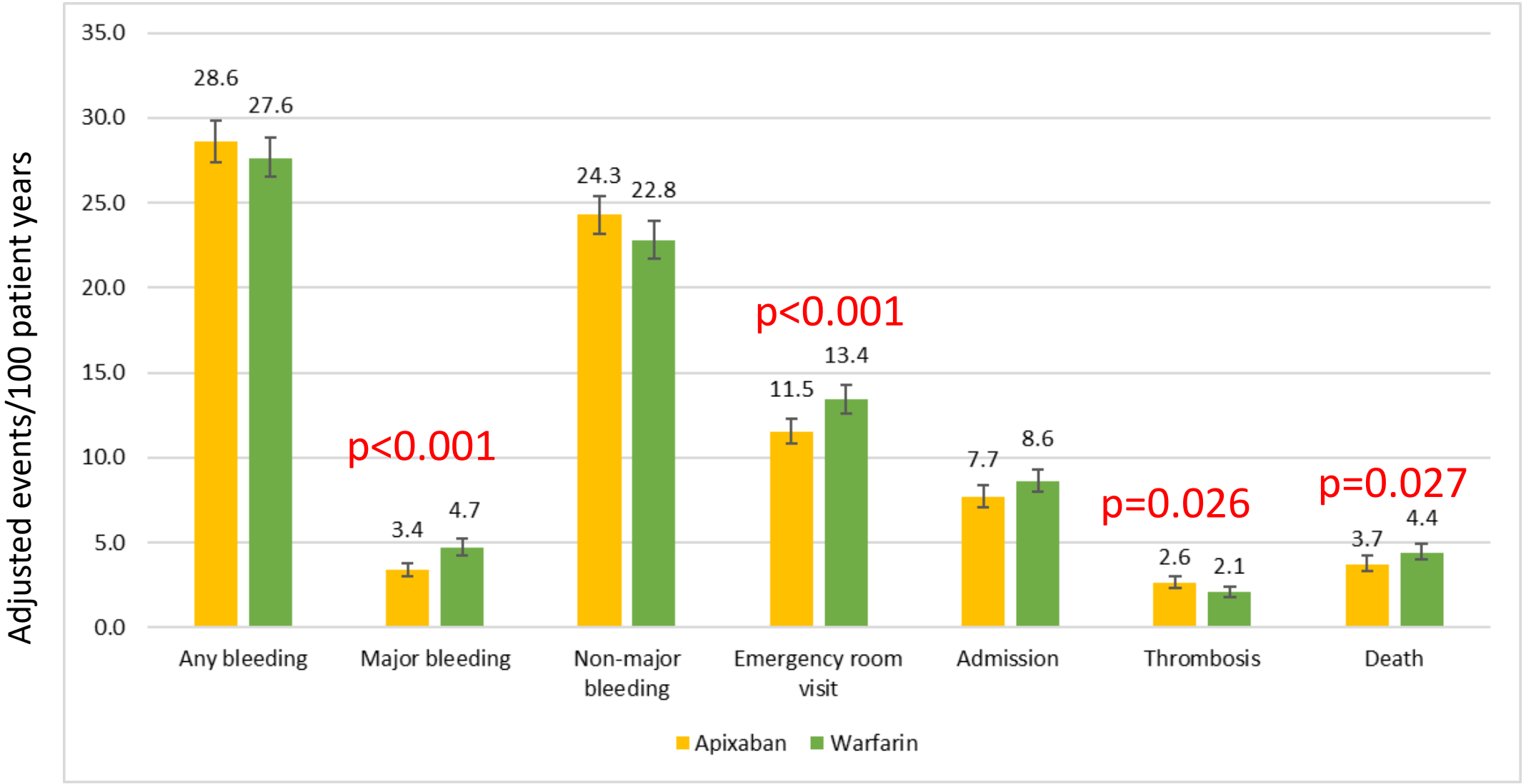
Results

Table 1: Patient Characteristics Before Matching[a]			
Anticoagulant	Apixaban N=3,536	Rivaroxaban N=1,395	Warfarin N=8,504
Indication (%)			
AF/Aflutter	71.0	48.9	54.1
DVT/PE	29.9	52.3	47.3
Both	0.8	1.2	1.4
TTR (warfarin) mean (sd)	/	/	60% (20%)
Other mean (sd)			
Follow-up Months	27 (24.1)	26.5 (27.1)	28.9 (33.6)
Modified HAS-BLED[c]	2.7 (1.4)	2.2 (1.4)	2.5 (1.4)
Charlson Comorbidity Index	4.8 (2.1)	4.0 (2.2)	4.5 (2.5)

Results


Adjusted events/100 patient years
35.0
30.0
25.0
20.0
15.0
10.0
5.0
0.0
28.6
27.6
3.4
4.7
24.3
22.8
p<0.001
Any bleeding
Major bleeding
Non-major bleeding
Apixaban
Warfarin

Results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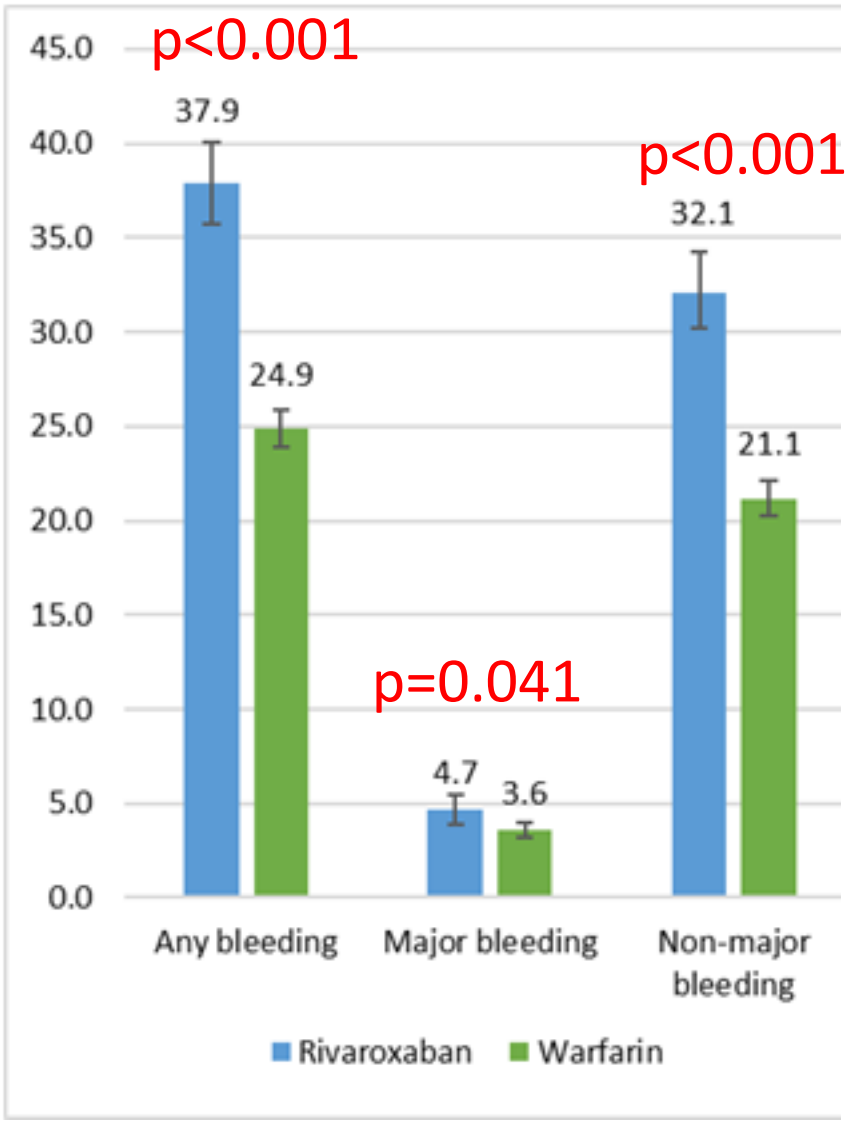
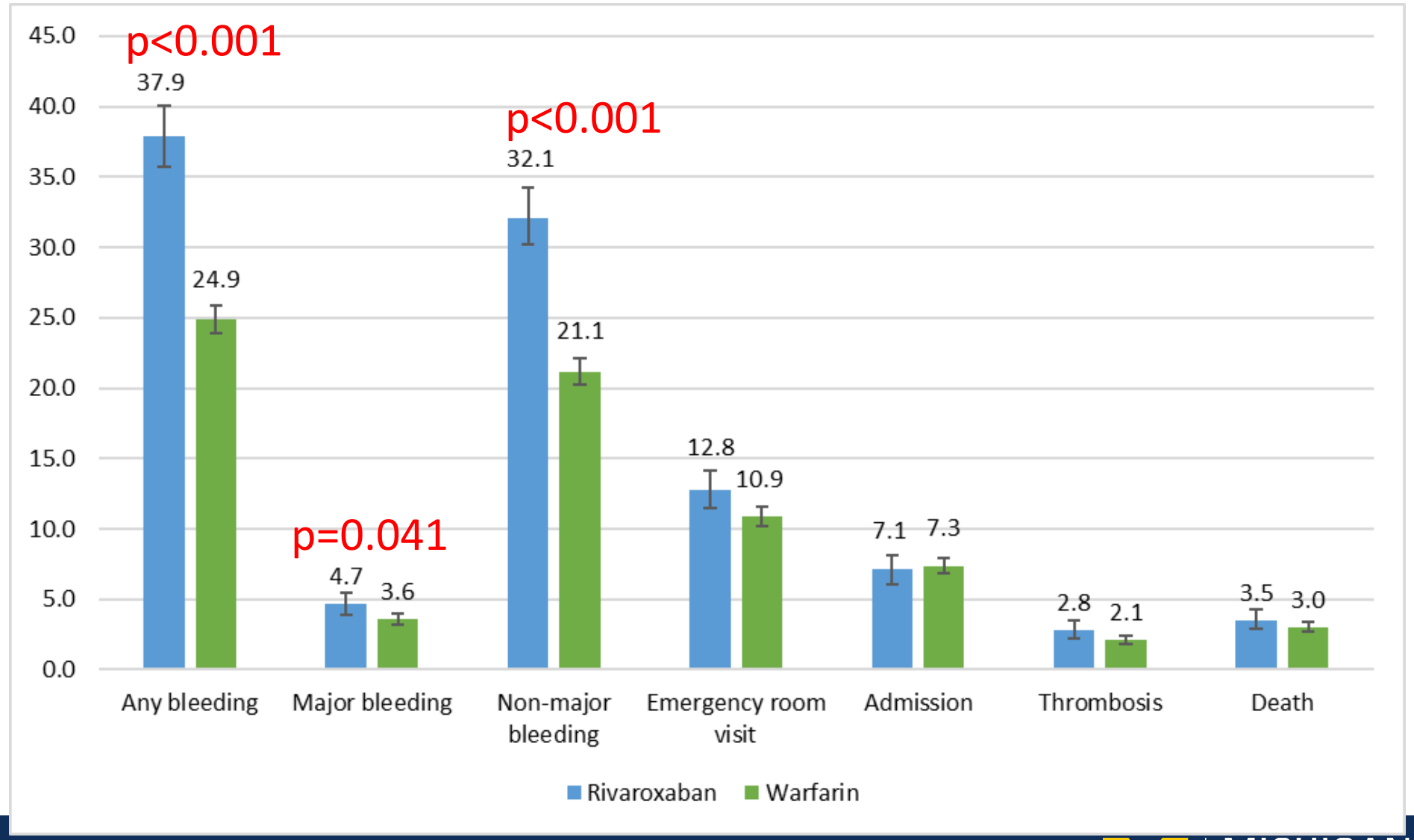
20.0
15.0
10.0
5.0
0.0
28.6
27.6
3.4
4.7
24.3
22.8
11.5
13.4
7.7
8.6
2.6
2.1
3.7
4.4
p<0.001
p<0.001
p=0.026
p=0.027
Any bleeding
Major bleeding
Non-major bleeding
Emergency room visit
Admission
Thrombosis
Death
Apixaban
Warfarin

Results


Adjusted events/100 patient years
45.0
40.0
35.0
30.0
25.0
20.0
15.0
10.0
5.0
0.0
p<0.001
37.9
24.9
p=0.041
4.7
3.6
p<0.001
32.1
21.1
Any bleeding
Major bleeding
Non-major bleeding
Rivaroxaban
Warfarin

Results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5.0
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24.9
p=0.041
4.7
3.6
p<0.001
32.1
21.1
12.8
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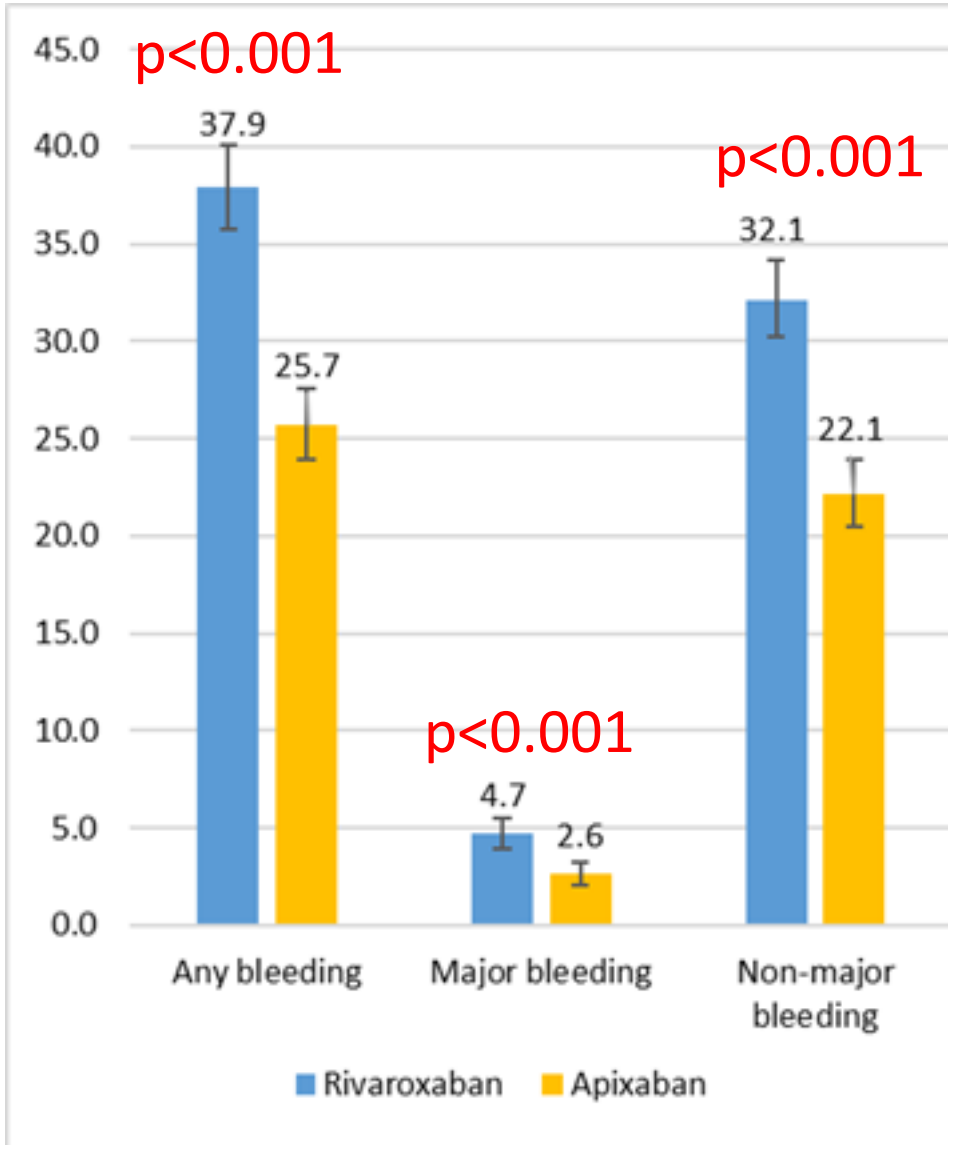
7.1
7.3
2.8
2.1
3.5
3.0
Any bleeding
Major bleeding
Non-major bleeding
Emergency room visit
Admission
Thrombosis
Death
Rivaroxaban
Warfarin

Results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10.0
5.0
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p<0.001
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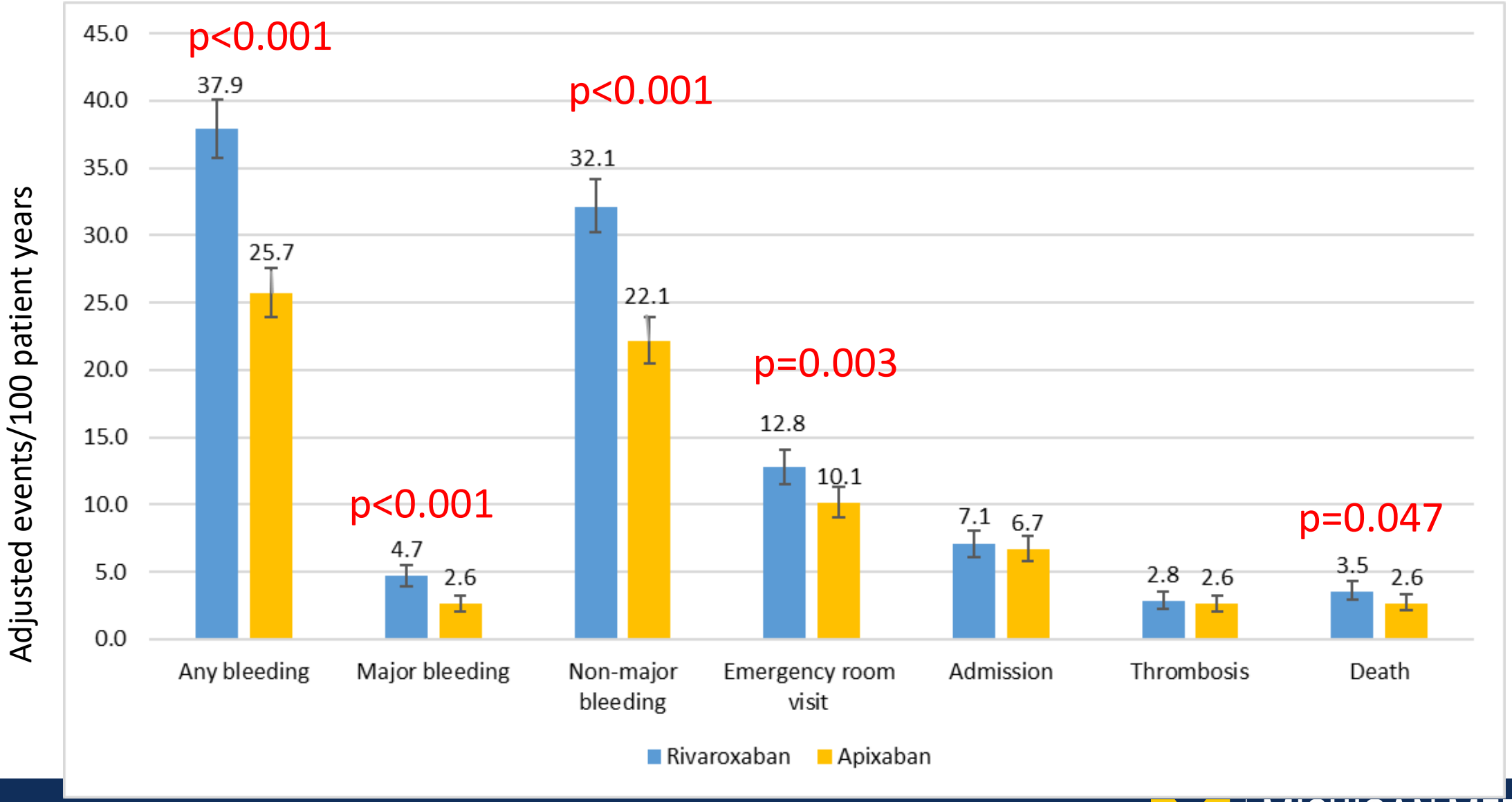
p<0.001
4.7
2.6
p<0.001
32.1
22.1
Any bleeding
Major bleeding
Non-major bleeding
Rivaroxaban
Apixaban

Results


Adjusted events/100 patient years
45.0
40.0
35.0
30.0
25.0
20.0
15.0
10.0
5.0
0.0
p<0.001
37.9
25.7
p<0.001
4.7
2.6
p<0.001
32.1
22.1
p=0.003
12.8
10.1
7.1
6.7
2.8
2.6
p=0.047
3.5
2.6
Any bleeding
Major bleeding
Non-major bleeding
Emergency room visit
Admission
Thrombosis
Death
Rivaroxaban
Apixaban

Strengths/Limitations

- Strengths
  - Large, robust data set
  - Bleeding/thrombosis outcomes
  - Real-world data
- Limitations
  - Observational data, selection bias potential
  - Potentially underpowered
  - Geographically limited
  - Data on MI may not be well captured
  - No data on adherence

Conclusions

- For patients on oral anticoagulation for AF and/or VTE
  - Bleeding was highest with rivaroxaban, followed by warfarin, and then apixaban.
  - Thrombosis was higher with apixaban compared to warfarin, seemingly largely driven by “other” thrombotic events.
  - Thrombotic event rates were otherwise similar between apixaban, rivaroxaban, and warfarin.
  - We observed apixaban to be associated with lower mortality than rivaroxaban and warfarin.
    - While these findings should be confirmed with randomized studies, they may have implications for anticoagulant selection.

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Acknowledgements

Spectrum Health
Michael McNamara, MD
Musa Dahu, MD
Mary Jo Deyoung, RN
Deborah Haney, RN
Barb Dobbs, RN

Memorial Healthcare
Sharon Sampson, PharmD
Derek Linskey, PharmD

Beaumont Hospital
Mona Ali, PharmD
Aaron Berman, MD

University of Michigan
Geoffrey Barnes, MD, MSc
Suman Sood, MD, MSCE
Naina Chipalkatti, MD
James Froehlich, MD, MPH
Xiaokui Gu, MD, MA
Xiaowen Kong, MA
Eva Kline-Rogers, RN, MS
Brian Haymart, RN, MS
Tina Alexandris-Souphis, RN
Josh Errickson, PhD
Deborah Decamillo, RN

Huron Valley Sinai
Jay Kozlowski, MD

Henry Ford Hospital
Greg Krol, MD
Scott Kaatz, DO, MSc
Stacy Ellsworth, RN
Noelle Ryan, PharmD
Beverly Stallings, RN

Funding: Blue Cross Blue Shield of Michigan

MAQI² Michigan Anticoagulation Quality Improvement Initiative

MICHIGAN MEDICINE UNIVERSITY OF MICHIGAN

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