Apixaban compared with warfarin to prevent thrombosis in thrombotic antiphospholipid syndrome: a randomized trial

by Woller, S. et al. Blood Advances. 10/18/2021

ASTRO-APS: Apixaban in ThROmbotic AntiPhospholipid Syndrome

Presented by: Paramveer Singh, MD
Hematology and Medical Oncology Fellow
Karmanos Cancer Institute/Wayne State University, Detroit MI.
January 13, 2022

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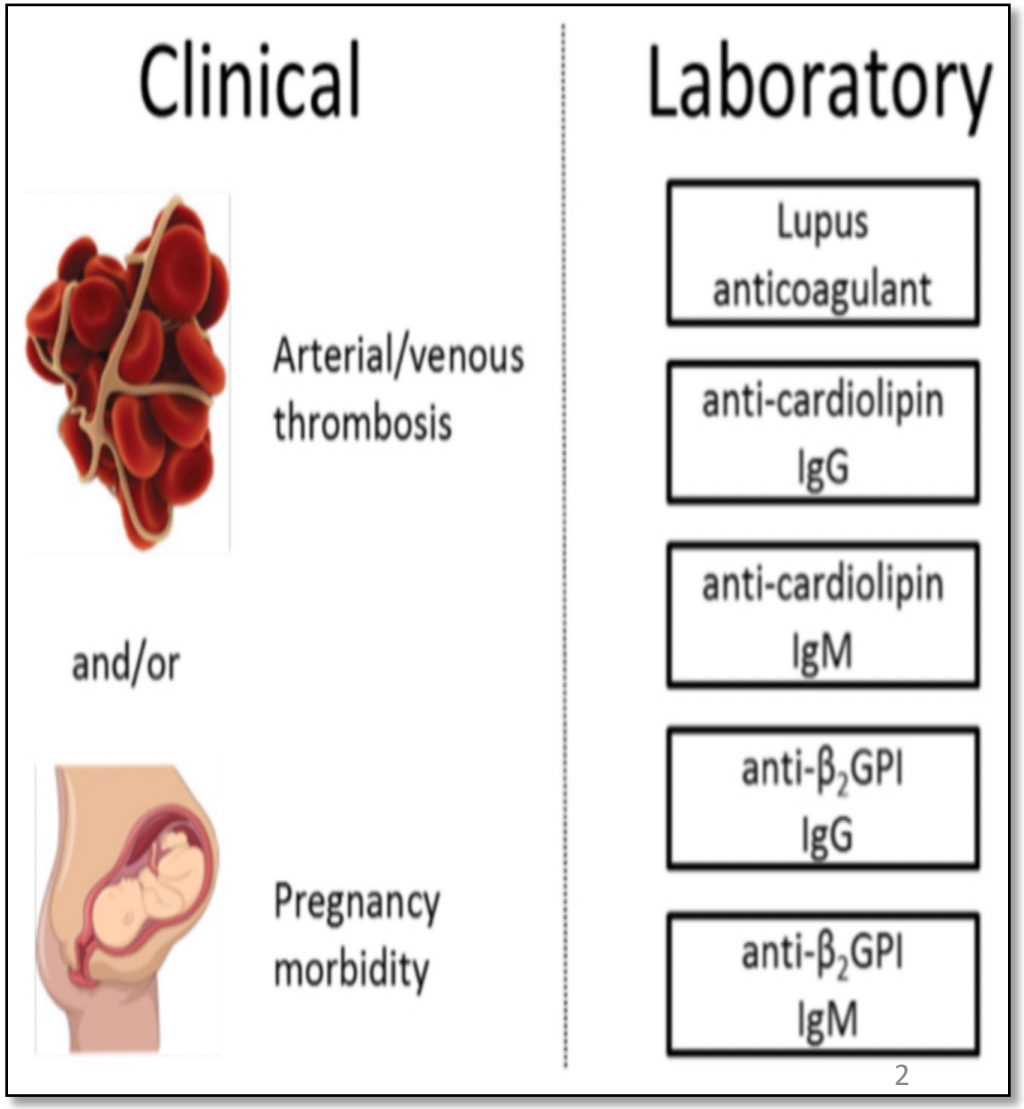
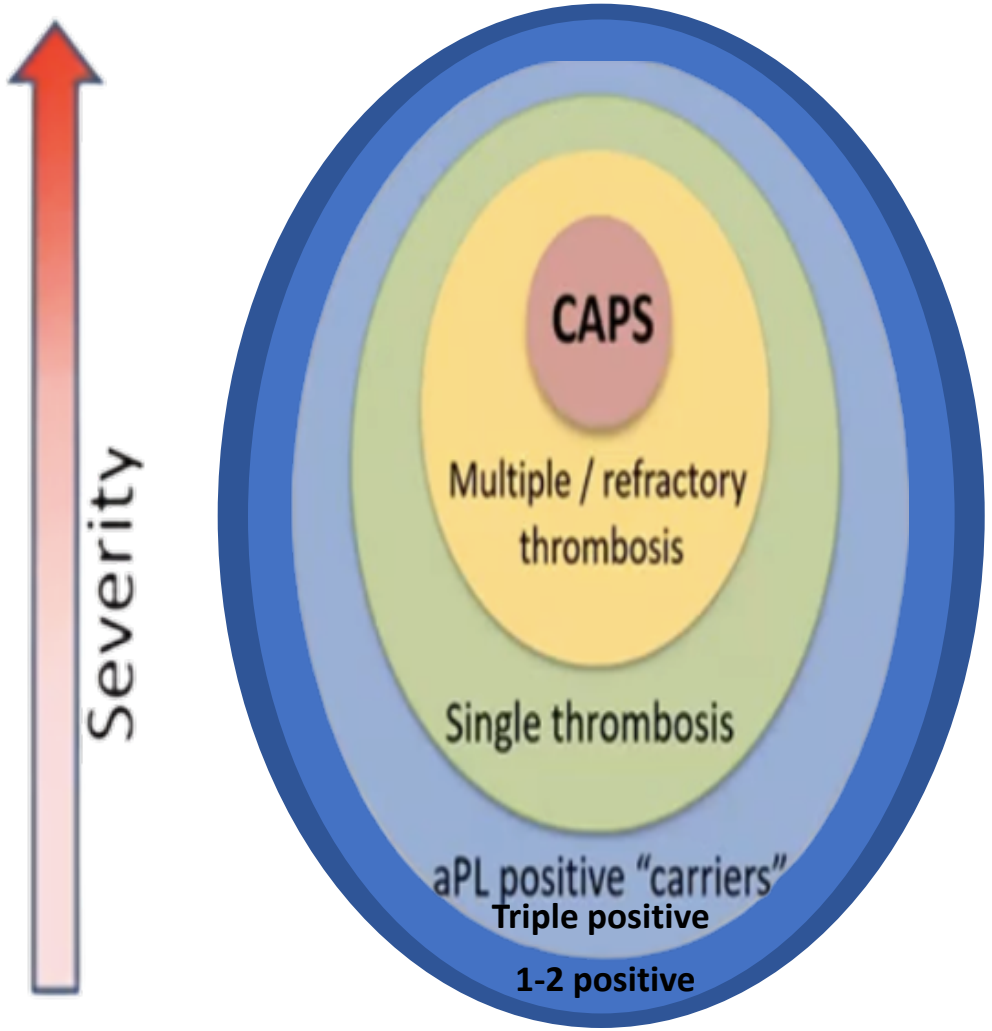
Background

- Clinical manifestation of APS involves thrombosis, pregnancy morbidity, & persistence of characteristic antibodies.
- Indefinite anticoagulation is recommended.
- Warfarin is the preferred treatment.
- Apixaban is safe and effective of VTE.
- Apixaban not reported in RCTs in APS.



SPECTRUM OF APS SEVERITY



Timeline of pertinent clinical trials:

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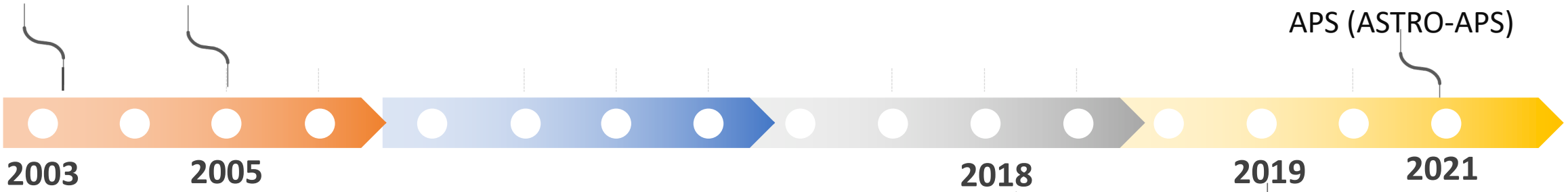
WARFARIN (INR 2-3) lower rate of recurrent thrombosis with than (INR 3-4).[1,2]



APIXABAN in thrombotic APS (ASTRO-APS)

RIVAROXABAN a/w higher arterial events in **HIGH-RISK APS**[3] and *Non-high-risk APS [4]

FDA WARNING 10/11/19: **DOACs not recommended for Triple Positive APS.**

1. Crowther, M. N Engl J Med 2003; 349:1133-1138
2. Finazzi, G. J Thromb Haemost 2005;3: 848–53 (WAPS)
3. Pengo V et al. Blood, 2018. Vol.132(13), p.1365-1371 (TRAPS)
4. Ordi-Ros et al. Ann Int Med. , 2019, Vol.171(10), p.685-694 (RAPS)

blood advances

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RESEARCH ARTICLE | OCTOBER 18, 2021

Apixaban compared with warfarin to prevent thrombosis in thrombotic antiphospholipid syndrome: a randomized trial

Scott C. Woller, Scott M Stevens, David Kaplan, Tzu-Fei Wang, D. Ware Branch, Danielle Groat, Emily L. Wilson, Brent Armbruster, Valerie T. Aston, James F. Lloyd, Matthew T. Rondina, C. Gregory Elliott

October 18, 2021

Trial Design

- Prospective
- Randomized
- Open label
- Active-controlled
- Pilot
- Multicenter
- Funding: Bristol-Myers-Squib-Pfizer Alliance

Trial Design:

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Wayne State University

KEY ELIGIBILITY CRITERIA

- KNOWN Thrombotic APS
- TAKING AC ≥ 6 months

- Requiring Clopidogrel.
- Prior thrombosis at INR >2
- Catastrophic APS
- Taking CYP3A4 and P-gp inducers e.g. Rifampin, Carbamazepin, Phenytoin

N=200

RANDOMIZE 1:1

APIXABAN
2.5 mg BID

WARFARIN
INR ≥ 2

WARFARIN
INR ≥2

End of study

Follow up = 12 months

OUTCOMES:

1°: Rate of thrombosis & vascular death
1°: Rate of bleeding
2°: Net clinical benefit

APS CLASSIFICATION:

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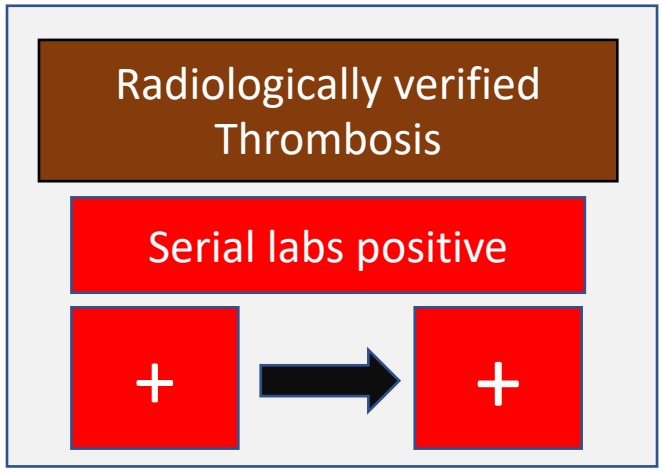
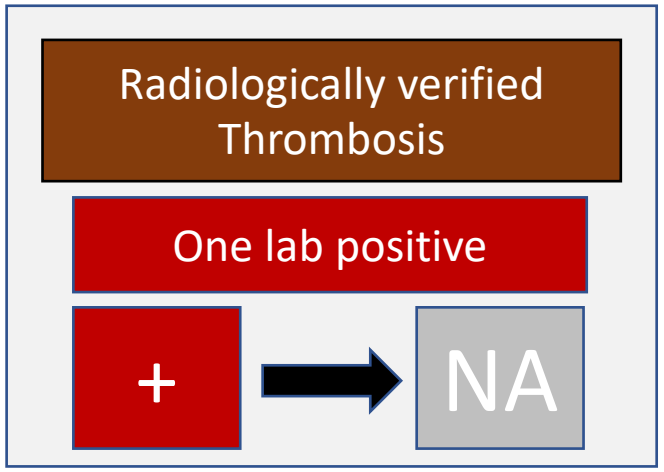
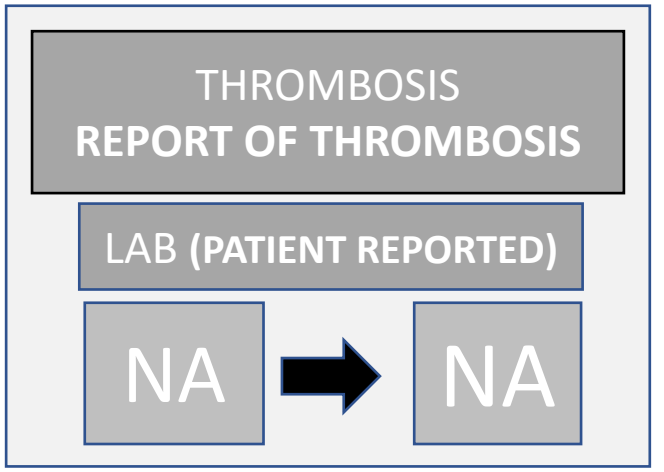
DEFINITE APS



LIKELY APS



HISTORICAL APS



Outcomes:

- Primary Clinical outcome
  - *Rate* of clinically overt thrombosis (arterial or venous) or vascular death
- Primary Safety outcome
  - *Rate* of occurrence of major and clinically relevant non-major bleeding
- Secondary outcome
  - Net clinical benefit (combined bleeding & thrombosis *rate*)

Trial oversight:

- Sponsors had no role in design or conduct of the study.
  - Data collection, analysis, interpretation, and manuscript preparation were independent of funding source.
- Independent panel of experts were blinded to the treatment allocation.
- Data & Safety Monitoring Board was internal.

Analysis Methods:

- Intention to treat population.
- Cox proportional-hazards model to assess difference in outcomes.
- Person-time and KM method used to evaluate outcome separately.
- Mann-Whitney U test used to compare satisfaction in two arms.

Trial Design: (modification 1 @ N =25)

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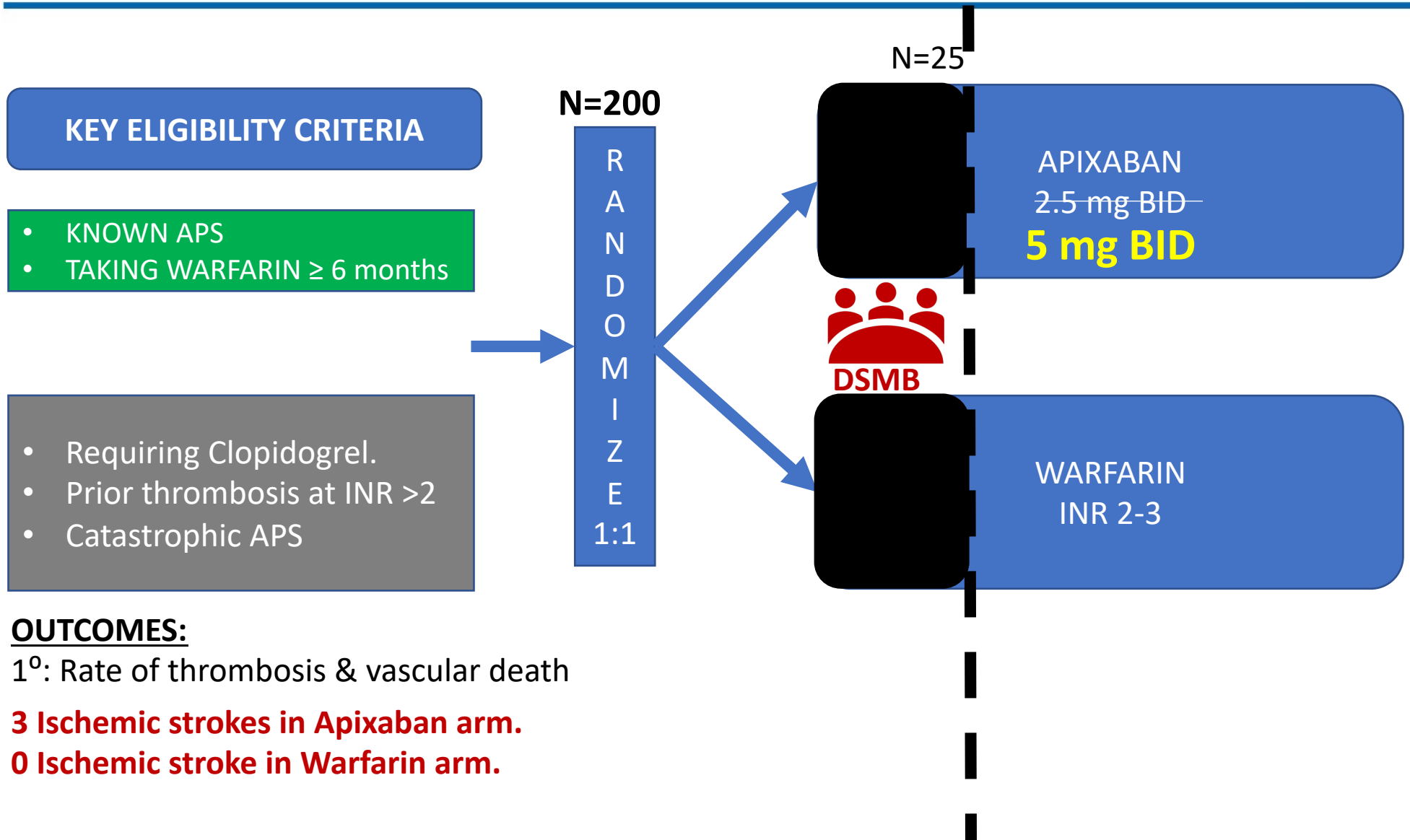

OUTCOMES:

1^{o}: Rate of thrombosis & vascular death

3 Ischemic strokes in Apixaban arm.

0 Ischemic stroke in Warfarin arm.

Trial Design: (modification 2 @ N =30)

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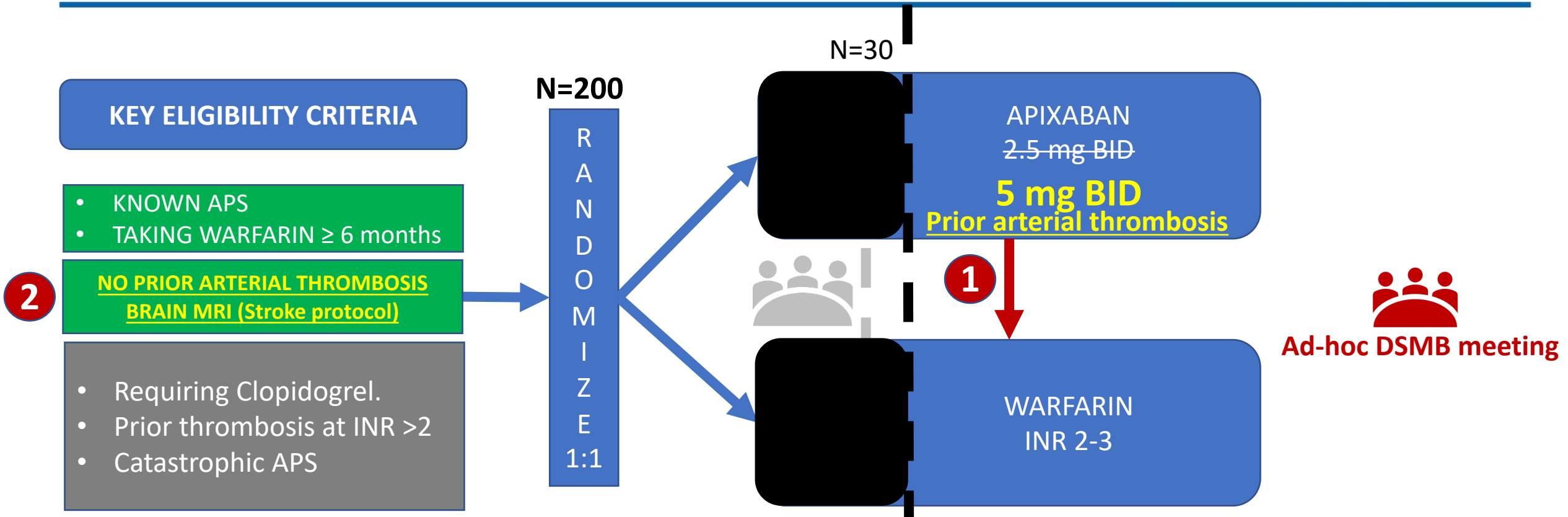


OUTCOMES:

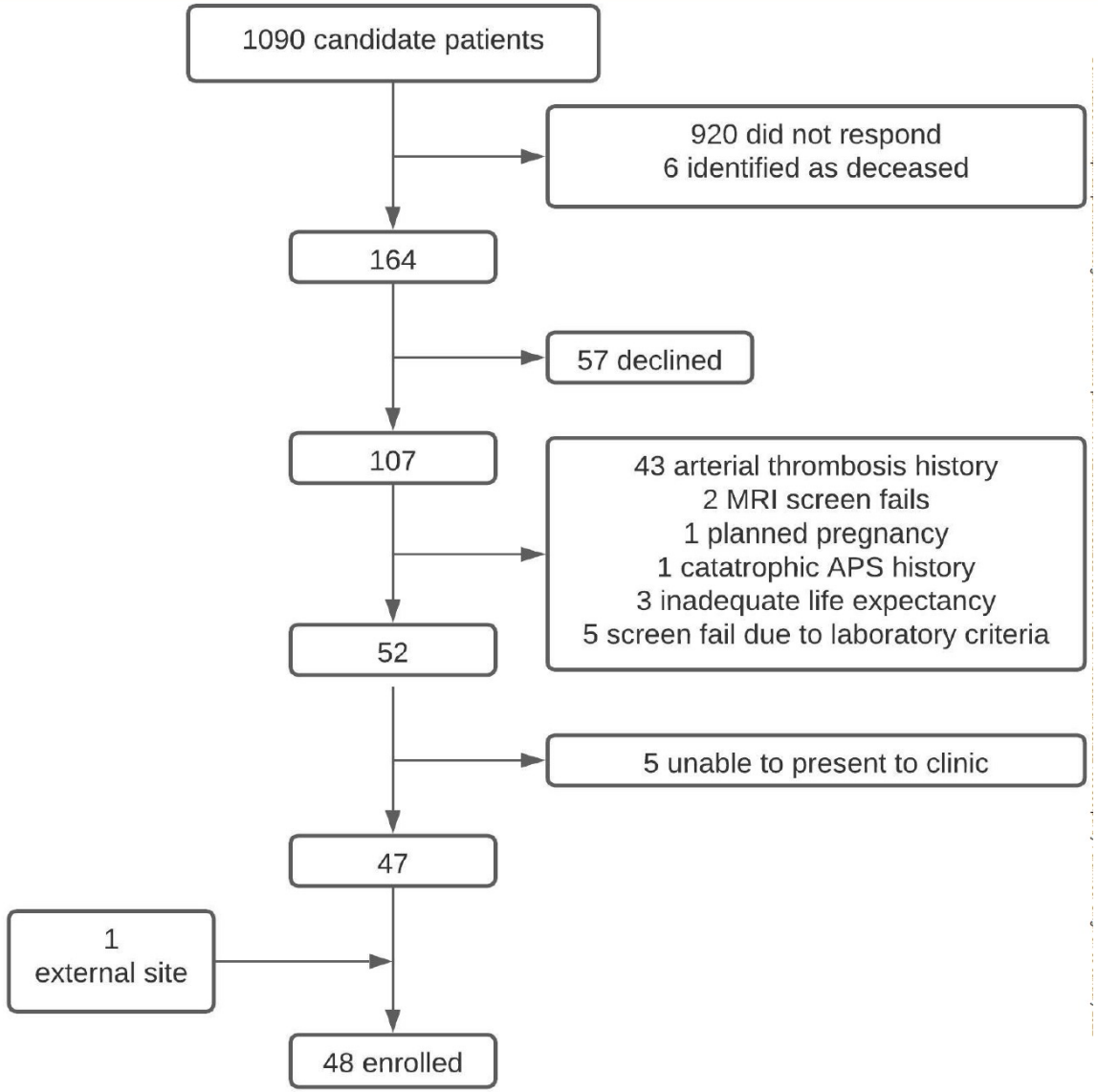
1^{o}: Rate of thrombosis & vascular death = 6:0

3 Ischemic strokes in Apixaban arm. ***INCREASED TO 6.***

0 Ischemic stroke in Warfarin arm.

Results

CONSORT DIAGRAM:



Results

- Due to inadequate accrual and resultant loss of funding, early termination at N = 48 instead of anticipated N=200.
- Enrolled over 4 years: 02/2015-03/2019.
- All participants had 12-month follow-up.

Key Baseline Characteristics

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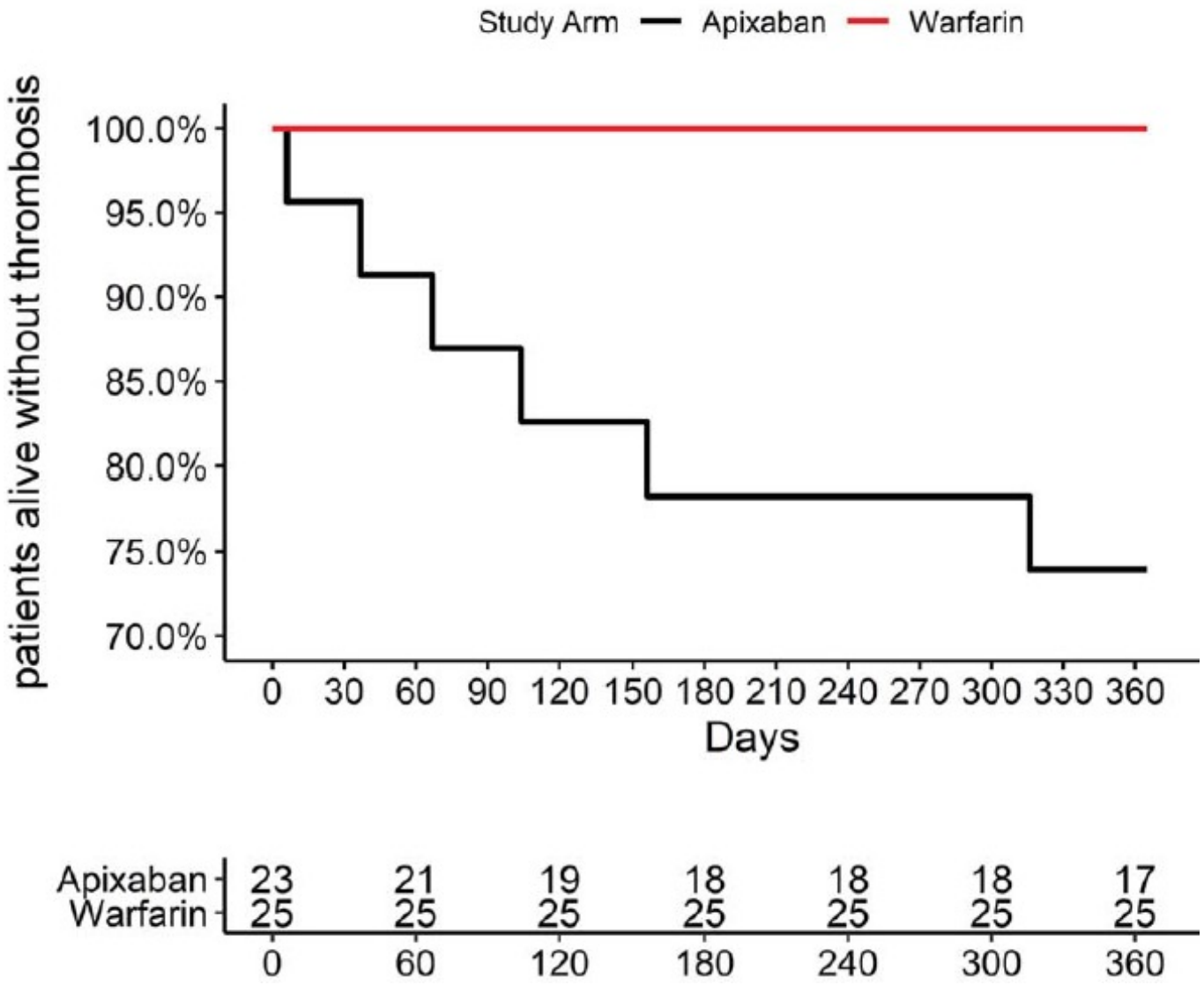
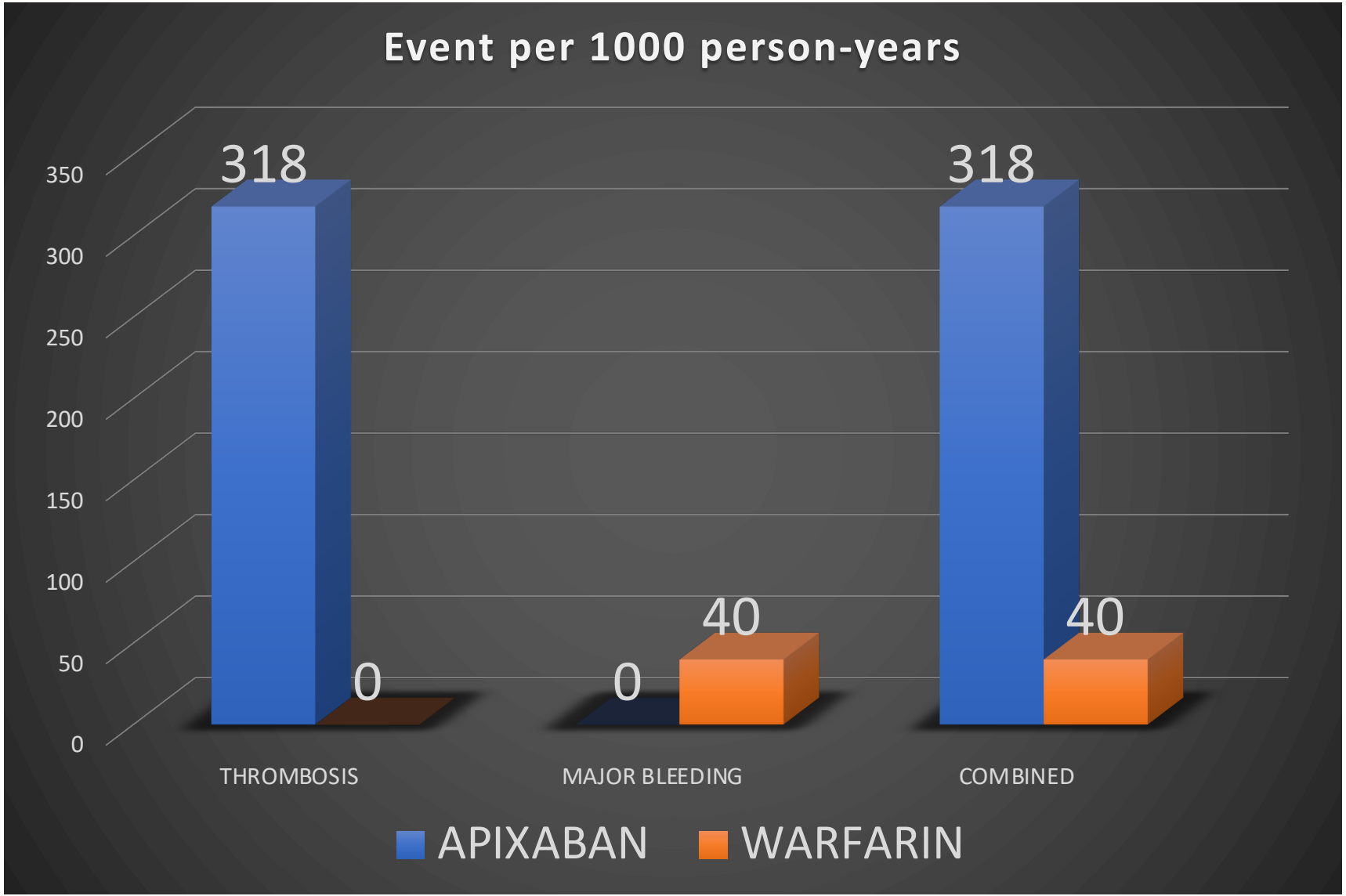
Baseline Characteristic	All: N=48	Apixaban (N=23)	Warfarin (N=25)
Female in %	83.3	83	84
Age, mean	47	46	48.5
BMI kg/m2	32	31	32
D-dimer in mean	569	412	713
Labs Positivity: (in %) Triple/Double/Single	29/12.5/25	30/17/22	28/8/28
APS status: (in %) Definite/Likely/Historical	42/25/33	35/35/30	48/16/36
Labs positive: in % LA/ACA IgG, IgM/B2Gp1 IgG, IgM	42/37.5,23/35,12.5	48/39, 26/43.5,17	36/36,20/28,8
Prior thrombotic event: in % Arterial(MI , Stroke) Venous(DVT/PE) Pregnancy	100 35(4.2/25) 79(71/37.5) 25	100 26(4.3/22) 87(74/48) 30	100 44(4/28) 72(68/28) 20
Key Risk factors and comorbidities: Smoking/HTN/DM/SLE/OCP	21/15/17/15/4	17/13/17/9/9	24/16/16/20/0
Adherence in %		97	60

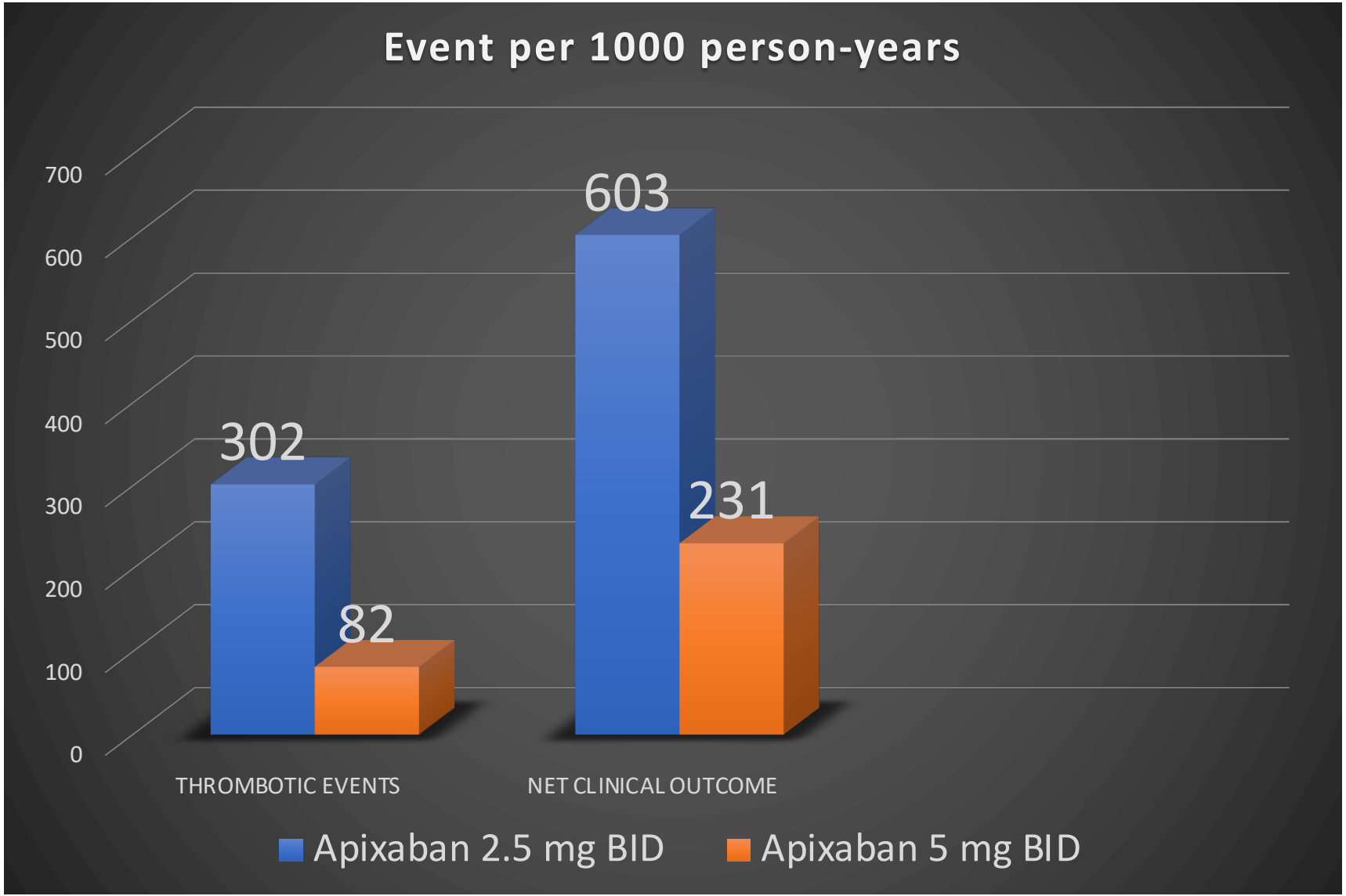
Kaplan–Meier Event Rate For Thrombosis:



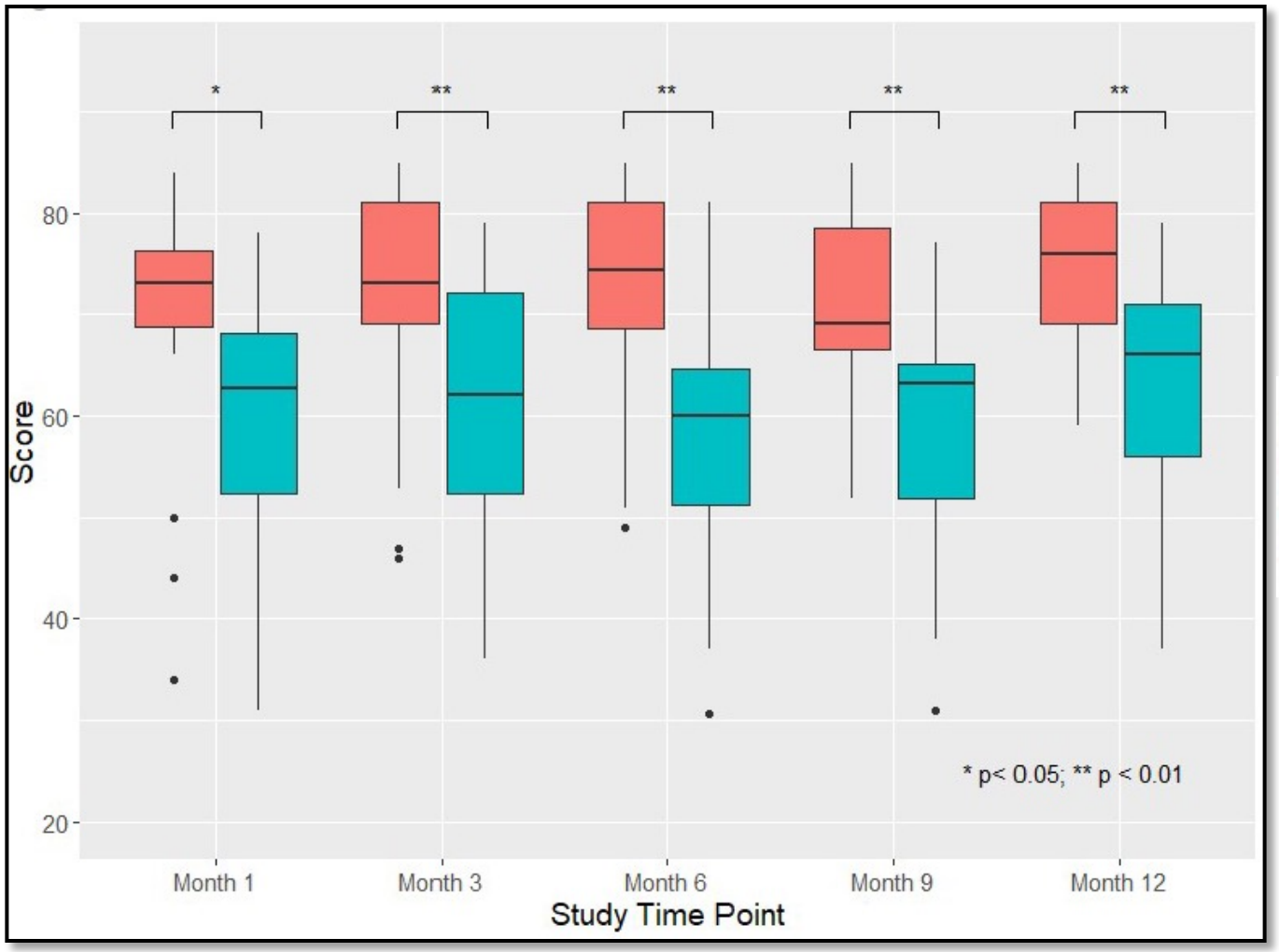
Outcomes using Person Time Analysis:



Outcomes using Person Time Analysis:



Patient Satisfaction Assessment:



Apixaban

Warfarin

LEGEND:

- **Midline = median**
- **Box = IQR**
- **Whiskers = 1.5 times IQR**
- **Dots = outliers**

"Patients on apixaban had significantly higher scores"

Details Of Thrombotic Events (N=6):

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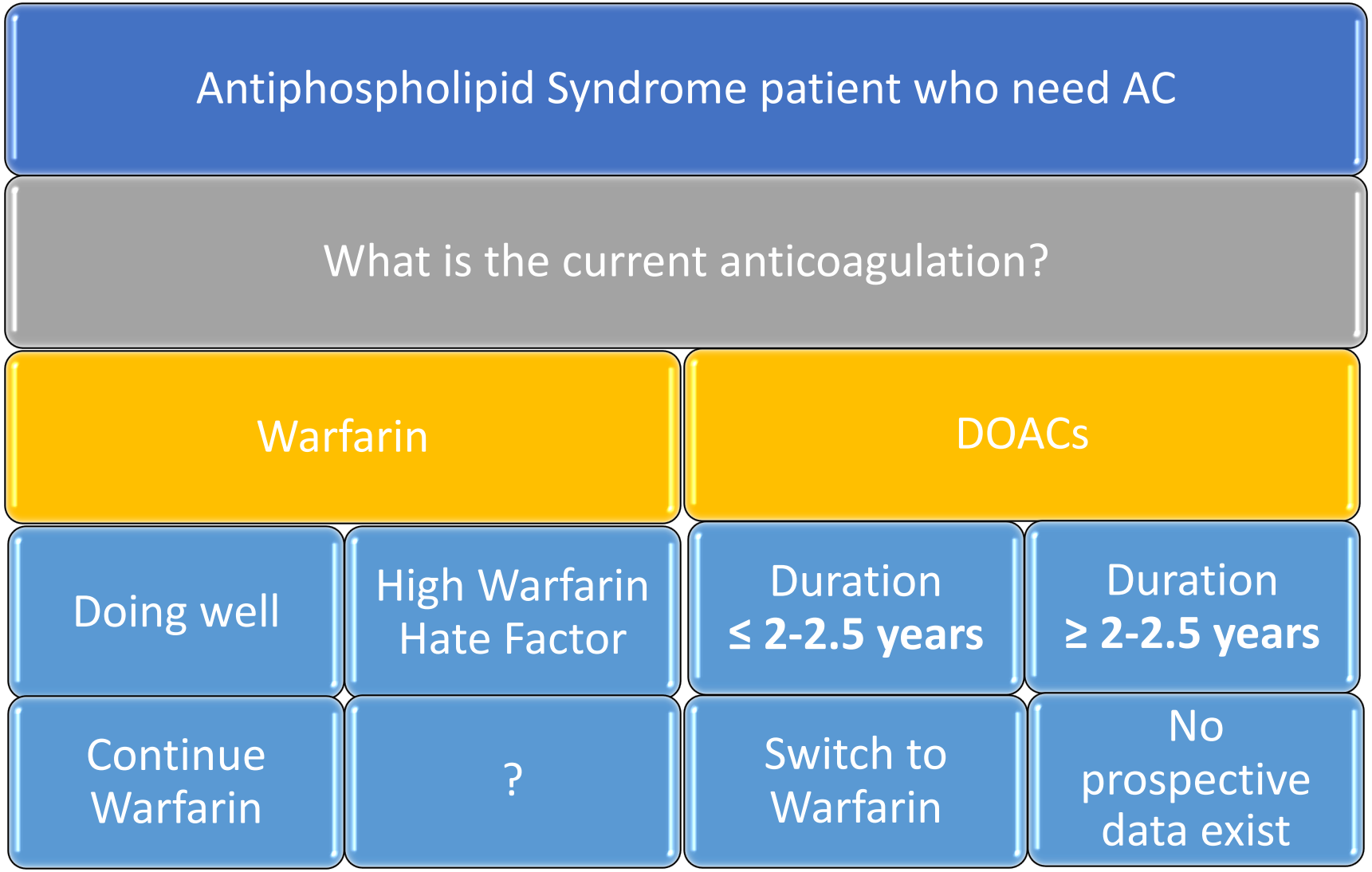
ID	Age	Sex	BMI	Treatment	History	Positivity	Type	Event	Lesions on MRI	Days to event	LA	CA IgG	CA IgM	B2gp1 IgG	B2gp1 IgM
24	40	F	39.3	Apixaban	Stroke, DVT, PE, pregnancy loss	Single	Likely	Stroke	Single	156	X				
16	43	F	36.9	Apixaban	DVT	Triple	Definite	Stroke	Multiple	67	X	X	X	X	X
12	47	F	19.4	Apixaban	Stroke, TIA, DVT, pregnancy loss	Double	Likely	Stroke	Multiple	37	X	X		X	
2	51	F	25.5	Apixaban	Stroke, other arterial thrombosis, DVT, PE	Triple	Definite	Stroke	Single	316		X	X	X	X
32	66	M	39.3	Apixaban	DVT	N/A^	Historical	Stroke	Multiple	104					
3	69	F	23.2	Apixaban	Stroke, pregnancy loss	N/A^	Historical	Stroke	Single	6					

Discussion:

- Apixaban, like rivaroxaban, not equitable substitute for warfarin.
- Limitations: protocol modification, early termination, small sample.
- Subjects were NOT treatment naïve, were switched from prior AC.
- Even a brief non-adherence may increase risk due to short half life.

Incorporating into practice:

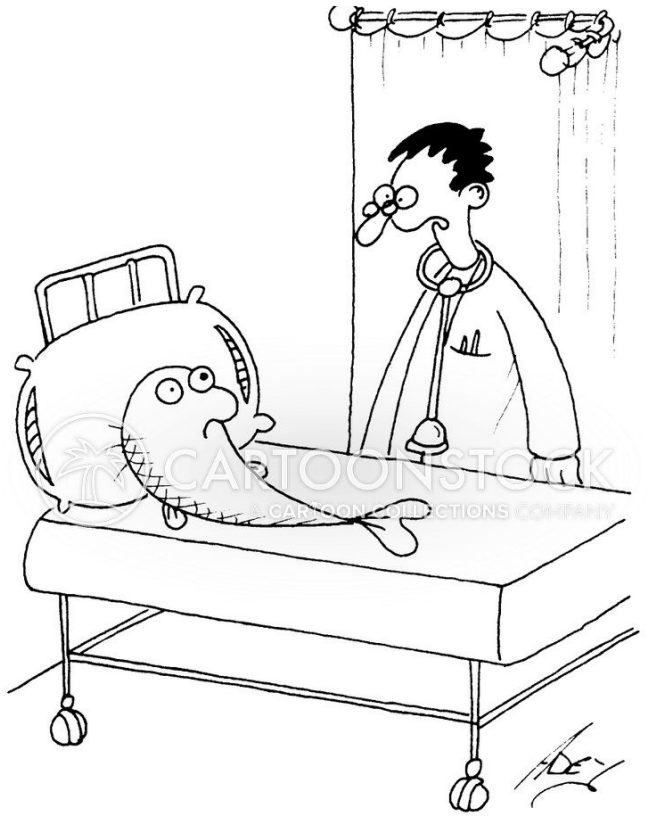


Moll, S. The Hematologist (2020) 17 (1)

Thank you!

Acknowledgements!

- Dr Gerald A Soff, MD
- Dr Vijendra Singh, MD



"I'm afraid you have deep vein thrombosis, Mr. Sardine."

https://www.cartoonstock.com/cartoon?searchID=CS257861