ATRIAL FIBRILLATION

THINNING THE CONCERNS ABOUT THINNING (OR NOT THINNING) THE BLOOD

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DISCLOSURES

- I routinely consult for or am on retainer with the following industry entities:

gsk
MERCK
Pfizer
Lilly
Wyeth
Johnson & Johnson
janssen
Roche
SANOFI
Bristol-Myers Squibb
Takeda

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Just kidding

- I have no potential or real conflicts or dualities of interest, whether financial, relational, or otherwise.
- My only "disclosure" is that I am extremely passionate about evidence-based medicine (EBM) and shared decision-making (SDM). I also firmly believe it is imperative to remember patients are people, not just diagnoses or chief complaints.
- For anyone who cares, I am employed as follows:
  - Clinical Evidence Synthesizer, Principal Editor | Innovations and Evidence-Based Medicine Development, EBSCO Health
  - Inpatient internal medicine PA-C | Cone Health

What we'll cover today

At the end of this session, participants should be able to:

- Discuss two methods used to assist with stratification of thromboembolic and major bleeding risk in patients with nonvalvular atrial fibrillation
- Describe how shared decision-making can be implemented in making decisions about thromboembolic prophylaxis in nonvalvular atrial fibrillation
- Discuss key evidence surrounding the various antithromboembolic options in nonvalvular atrial fibrillation

What we won't cover today

- Management of the rhythm vs. rate portion of managing atrial fibrillation
  - This includes pulmonary vein isolation (AKA pulmonary vein isolation ablation, pulmonary vein antrum isolation, etc.)

Imagine…

- You have nonvalvular atrial fibrillation (nvAF)
- You have a few different treatment options to manage your risk of thromboembolism

Imagine…

- The major benefit of the various pharmacologic options is their ability to reduce a person's risk of thromboembolism (with the most feared event being an ischemic stroke)
- The major harm of the various pharmacologic options is their ability to increase a person's risk of major bleeding (bleeding → to a serious drop in hemoglobin and/or need for transfusion and/or hospitalization, etc.)

Imagine…

- There are other things to consider (e.g., cost of medication, inconvenience of taking medication daily, "nuisance" bleeding)

The key question:

What amount of benefit would you want for your risk of ischemic stroke before you would consider the medication to be "worth it" (in terms of the tradeoff with respect to the risk of major bleeding and the "other considerations")?

Imagine…

- Medication A reduces your 1-year risk of ischemic stroke by about 65%.
- Medication B reduces your 1-year risk of ischemic stroke by about 1.9%.
- Each carries a 1-year risk of major bleeding of about 2%. Cost is essentially the same (~$4/month).

Would you rather take Medication A or Medication B?

If Medication B were your only option, would you want to take it?

Imagine…

- Medication C reduces your 1-year risk of ischemic stroke by about 2.2% (0.3% greater reduction in risk compared to Medication B).
- 1-year risk of major bleeding with Medication C is about 1.9% (0.1% lower risk compared to Medication B).
- The cost of Medication C depends heavily on insurance. It could be comparable to Medication B (~$4/month), but for many, it costs more. It could be ~$10/month, ~$25/month, or higher. Without insurance, it may be ~$440 with a discount coupon (e.g., from GoodRx®).

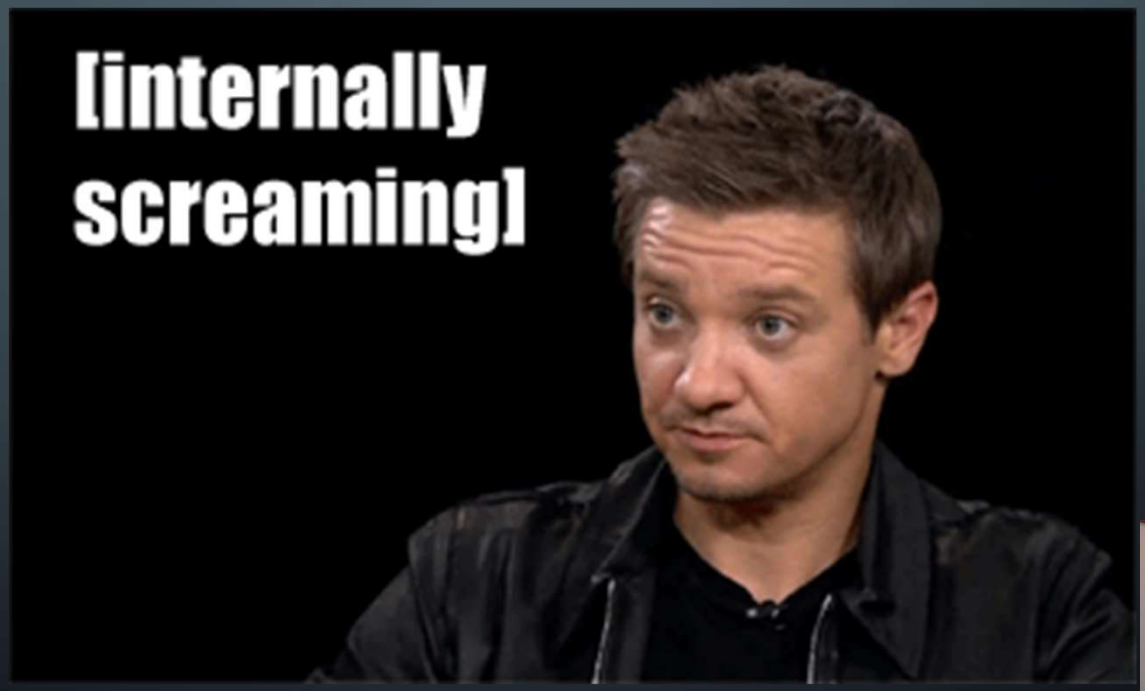
Would you rather take Medication B or Medication C?

Does your answer depend on the cost?

Managing thromboembolic risk in nvAF

(Worst possible approach)

Managing thromboembolic risk in nvAF



(Getting better)

Managing thromboembolic risk in nvAF

(Bingo … Well, kind of …)

Starting out: How risky are we talking here?

- Generally, the most-used and most-recommended tools for stratifying risk are:
  - $CHADS_2$ / CHA_2DS_2-VASc for thromboembolic risk
  - HAS-BLED for major bleeding risk
- Other methods exist, however
  - e.g., ATRIA, ABC, $HEMORR_2HAGES$
- Fortunately, $CHADS_2$ / CHA_2DS_2-VASc and HAS-BLED are backed by sufficient evidence (though others aren't bereft of evidential support)

(Borre et al. 2018, Sanders et al. 2018)

Starting out: How risky are we talking here?

- Some caveats
  - "All models are wrong, but some are useful." (George E. P. Box)
  - discrimination ← how well something categorizes people at higher risk vs. people at lower risk
  - calibration ← how well predicted risks match observed risks
- Ex: 78 yo woman w/ nvAF has a predicted 1-year risk of ischemic stroke of 14.15%. She is categorized as "high risk".
- Clinical judgment / gestalt (e.g., @ risk for falls?)

(Alba et al. 2017, Borre et al. 2018, McGinn et al. 2015, Sanders et al. 2018)

CHA_2DS_2-VASc & HAS-BLED

- CHA_2DS_2-VASc predicts 1-year risk of a thromboembolic event ***without treatment***
  - different tools provide different outcomes (e.g., thromboembolic composite vs. ischemic stroke)
- HAS-BLED predicts 1-year risk of major bleed ***on warfarin***
- Each has a maximum score of 9

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CHA_2DS_2-VASc

Unless otherwise stated, 1 point for each of the following comorbidities/risk factors:

- **C**ongestive heart failure
- **H**ypertension
- **A**ge:
  - ≥65 and ≤74 years
  - ≥75 years ← *2 points*
- **D**iabetes mellitus
- **S**troke or transient ischemic attack in past ← *2 points*
- **V**ascular disease
- **F**emale sex

HAS-BLED

1 point for each of the following comorbidities/risk factors:

- ***H***ypertension *that is uncontrolled* (>160 systolic)
- ***A***bnormal kidney or liver function (*1 point each*)
  - Kidney: chronic dialysis, transplant, Cr >2.26 mg/dL or 200 µmol/L
  - Liver: chronic hepatic disease or biochemical evidence of significant derangement (e.g., bilirubin >2x upper limit w/ AST/ALT/Alk phos. >3x the upper limit, and so forth)
- ***S***troke

HAS-BLED

1 point for each of the following comorbidities/risk factors:

- Prior major ***b***leeding or predisposition to bleeding
- ***L***abile INR (unstable/high INRs, time in therapeutic range <60%)
- ***E***lderly (age >65)
- ***D***rug/alcohol use (*1 point each*)
  - Drug: Medication usage predisposing to bleeding (e.g., aspirin, clopidogrel, NSAIDs)
  - Alcohol: ≥8 alcoholic drinks/week

Antithromboembolic management options

- No therapy
- Aspirin
- Warfarin
- Direct oral anticoagulants (DOACs; formerly novel oral anticoagulants / non-vitamin K oral anticoagulants / NOACs)
  - Apixaban
  - Dabigatran
  - Edoxaban
  - Rivaroxaban
- Left atrial appendage occlusion device (e.g., WATCHMAN®)

No therapy

- Should always be considered
- Benefits, risks, alternatives, *what happens if I do nothing?*
- For some, magnitude of possible benefit may not be large enough to offset things like the increased risk of bleeding (major or nuisance), copay / cost, or simply the hassle of taking (another) medication daily

Aspirin

- More guidelines are shying away from recommending aspirin as a therapeutic option (e.g., ESC 2016, ACCP 2018)
- The antithromboembolic effects of aspirin are less than warfarin, but aspirin may cause less major bleeding than warfarin

(Hart et al. 2007, Kirchhof et al. 2016, Lip et al. 2018, Sanders et al. 2018)

Aspirin

- aspirin vs. placebo/no treatment, for ischemic stroke: relative risk of 0.79 (95% CI 0.62 to 1.01)
  - if including other antiplatelet trials not limited to aspirin vs. placebo/no treatment *and* considering all strokes (not just ischemic): relative risk 0.78 (95% CI 0.65 to 0.94)
- How would you interpret the above findings?

(P.S. There's a reason I'm focusing on relative effect estimates here and for much of this talk.)

(Hart et al. 2007, Sanders et al. 2018)

Aspirin

- apixaban vs. aspirin in folks for whom warfarin was unsuitable
  - ischemic stroke and systemic embolism both better with apixaban (hazard ratios 0.37 [95% CI 0.25 to 0.55] and 0.15 [95% CI 0.03 to 0.68], respectively)
  - major bleeding with no clear difference (hazard ratio 1.13 [95% CI 0.74 to 1.75])
    - absolute rates 1.4% vs. 1.2% per year, respectively

(Connolly et al. 2011, Sanders et al. 2018)

Aspirin

- Stable, once/day dosing
- Inexpensive
- No blood tests

(Hart et al. 2007, Kirchhof et al. 2016, Lip et al. 2018)

Warfarin

- Often (previously?) considered "gold standard"
- Warfarin vs. placebo/control
  - ischemic stroke: relative risk of 0.35 (95% CI 0.24 to 0.54)
  - major bleeding: relative risk of 2.97 (95% CI 1.31 to 6.63) ← but can be estimated via risk prediction methods as well (e.g., HAS-BLED)

(Aguilar et al. 2005, Andersen et al. 2008, Hart et al. 2007, Sanders et al. 2018)

Warfarin

- Inexpensive (e.g., $4 list)
- Routine monitoring of INR
- Once/day dosing, but dose may fluctuate
- Consistency with dietary vitamin K

DOACs

- 4 are approved for use in nvAF (in order of approval date)
  - dabigatran
  - rivaroxaban
  - apixaban
  - edoxaban
- Pivotal trials for these agents were conducted as DOAC vs. warfarin

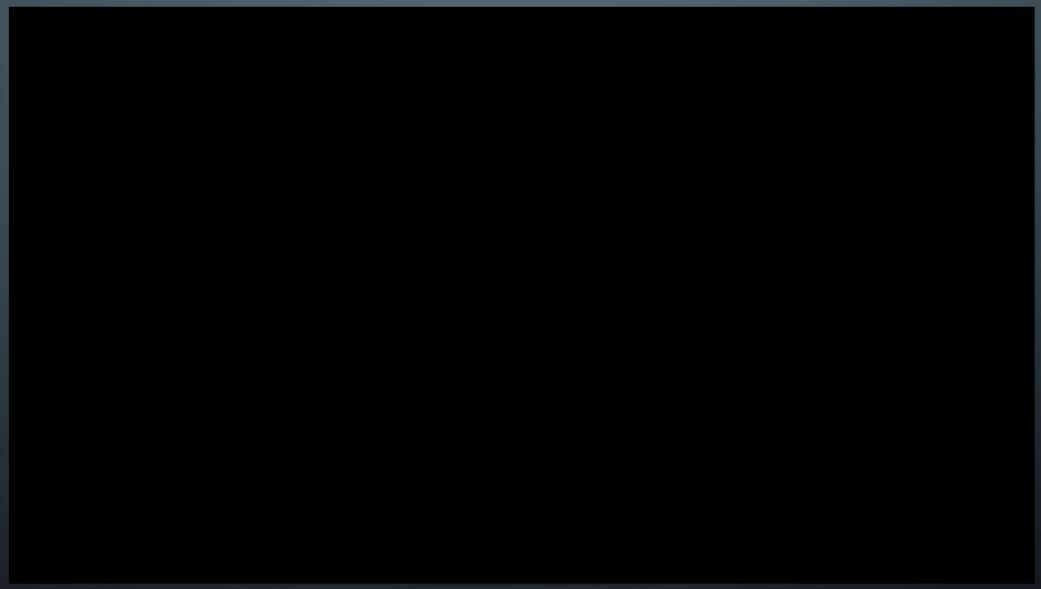
(Bruins et al. 2018, Connolly et al. 2009/2010/2014, Giugliano et al. 2013, Granger et al. 2011, Patel et al. 2011, Salazar et al. 2014)

DOACs

- Advantages
  - Set dosing schedule
  - No blood tests required

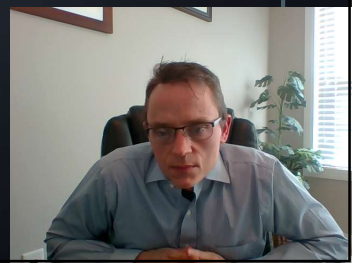
DOACs

- Advertisements



DOACs

- What were the claims about apixaban vs. warfarin?



DOACs

- Evidence?

DOAC vs. warfarin	Stroke	Ischemic or uncertain / unspecified stroke	Hemorrhagic stroke	Major bleeding
apixaban 5 mg BID	HR 0.79 (0.65 to 0.95)	HR 0.92 (0.74 to 1.13)	HR 0.51 (0.35 to 0.75)	HR 0.69 (0.60 to 0.80)

Parentheticals contain 95% confidence intervals for the hazard ratio; DOAC, direct oral anticoagulant; HR, hazard ratio

(Bruins et al. 2018, Granger et al. 2011)

DOACs

- Evidence?

DOAC vs. warfarin	Stroke	Ischemic or uncertain / unspecified stroke	Hemorrhagic stroke	Major bleeding
dabigatran 150 mg BID	RR 0.64 (0.51 to 0.81)	RR 0.76 (0.59 to 0.97)	RR 0.26 (0.14 to 0.49)	RR 0.94 (0.82 to 1.08)
rivaroxaban 20 mg qDay with evening meal	HR 0.85 (0.70 to 1.03)	Ischemic HR 0.94 (0.75 to 1.17) Unknown HR 0.65 (0.25 to 1.67)	HR 0.59 (0.37 to 0.93)	HR 1.04 (0.90 to 1.20)
apixaban 5 mg BID	HR 0.79 (0.65 to 0.95)	HR 0.92 (0.74 to 1.13)	HR 0.51 (0.35 to 0.75)	HR 0.69 (0.60 to 0.80)
edoxaban 60 mg qDay	HR 0.88 (0.75 to 1.03)	Ischemic HR 1.00 (0.83 to 1.19)	HR 0.54 (0.38 to 0.77)	HR 0.80 (0.71 to 0.91)

Parentheticals contain 95% confidence intervals for respective relative effect estimate (and there's a reason this table focuses on the relative effect estimates; DOAC, direct oral anticoagulant); HR, hazard ratio; RR, relative risk

(Bruins et al. 2018, Connolly et al. 2009/2010/2014, Giugliano et al. 2013, Granger et al. 2011, Patel et al. 2011, Salazar et al. 2014)

DOACs

- Consider the kidneys if using

	Adjustment considerations
dabigatran	**CrCl 30-50 mL/min**: **if** also taking **donedranone or ketoconazole**, **75 mg BID** **CrCl 15-30 mL/min***: **75 mg BID** ***unless*** taking **P-gp inhibitor** (e.g., amiodarone, verapamil), **then avoid use** **CrCl <15 mL/min***: should probably **avoid use**** **Dialysis***: should **avoid use** (dialyzable)**

*People with CrCl <30 mL/min were excluded from RE-LY trial; consider using another agent instead

Warfarin often recommended here ***if* going to anticoagulate, and some consider apixaban reasonable as well; for patients on dialysis, decision should be highly individualized, and some only recommend anticoagulation if thromboembolism risk is very high

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(Connolly et al. 2009/2010/2014, Guyatt et al. 2012, Ha et al. 2019, Herzog et al. 2011, January et al. 2014, January et al. 2019)

DOACs

- Consider the kidneys if using

	Adjustment considerations
rivaroxaban*	**CrCl 15-50 mL/min****: **15 mg qDay** **CrCl <15 mL/min****: should **avoid use***** **Dialysis****: should **avoid use** (not dialyzable)***

*Administer with evening meal
**People with CrCl <30 mL/min were excluded from ROCKET-AF trial; consider using another agent instead
Warfarin often recommended here ***if going to anticoagulate, and some consider apixaban reasonable as well; for patients on dialysis, decision should be highly individualized, and some only recommend anticoagulation if thromboembolism risk is very high

(Guyatt et al. 2012, Ha et al. 2019, Herzog et al. 2011, January et al. 2014, January et al. 2019, Patel et al. 2011)

DOACs

- Consider the kidneys if using

	Adjustment considerations
apixaban	**Cr <1.5 mg/dL***: **if ≥80 years** of age **and ≤60 kg**, **2.5 mg BID** **Cr >1.5 mg/dL***: **if ≥80 years** of age **or ≤60 kg**, **2.5 mg BID** **Severe or end-stage renal disease *not* requiring dialysis*: Can consider, but might consider 2.5 mg BID** **Dialysis***: **Can consider, but consider 2.5 mg BID** (not dialyzable / only slightly dialyzable)**

*People with Cr >2.5 mg/dL ***or*** CrCl <25 mL/min were excluded from ARISTOTLE trial; consider using another agent instead
Warfarin often recommended here ***if* going to anticoagulate, and some consider apixaban reasonable as well; for patients on dialysis, decision should be highly individualized, and some only recommend anticoagulation if thromboembolism risk is very high

(Granger et al. 2011, Guyatt et al. 2012, Ha et al. 2019, Herzog et al. 2011, January et al. 2014, January et al. 2019, Lip et al. 2018, Siontis et al. 2018, Wang et al. 2016)

DOACs

- Consider the kidneys if using

	Adjustment considerations
edoxaban	**CrCl >95 mL/minute**: **do not use (yes, >95 mL/min; that's not a typo)** **CrCl 15 to 50 mL/minute*: 30 mg qDay** **CrCl <15 mL/minute*:** should **avoid use**** **Dialysis***: should **avoid use** (not dialyzable)**

*People with CrCl <30 mL/min were excluded from ENGAGE AF-TIMI 48 trial; consider using another agent instead
Warfarin often recommended here ***if* going to anticoagulate, and some consider apixaban reasonable as well; for patients on dialysis, decision should be highly individualized, and some only recommend anticoagulation if thromboembolism risk is very high

(Giugliano et al. 2013, Guyatt et al. 2012, Ha et al. 2019, Herzog et al. 2011, January et al. 2014, January et al. 2019)

DOACs

- Hepatic function is important, too (but seems to get people in trouble less often)
  - dabigatran: no labeling adjustments/cautions; study in folks w/ moderate impairment didn't have consistent findings
  - rivaroxaban: use not recommended in Child-Pugh B or C (or any liver disease w/ coagulopathy)
  - apixaban: Child-Pugh B, use with caution; Child-Pugh C, use not recommended
  - edoxaban: use not recommended in Child-Pugh B and C

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(Food and Drug Administration 2019)

Quick aside: Anticoagulation reversal

- warfarin: vitamin K
- dabigatran: idarucizumab
- apixaban and rivaroxaban: andexanet alfa
- edoxaban: strictly speaking, no approved agent
  - edoxaban is a factor Xa inhibitor (as are apixaban and rivaroxaban)
  - andexanet alfa is a modified recombinant inactive form of human factor Xa (acts as a "decoy")
- ***However***, not necessarily your "first stop" when patient has bleeding
- Good sources below (also guidance for periprocedural management)

(Connolly et al. 2019, Doherty et al. 2017, Owusu et al. 2019, Pollack et al. 2017, Siegal et al. 2010, Tomaselli et al. 2017, Tornkvist et al. 2018, Verma et al. 2018)

Sooo…

- What does all this mean, and how can I put it to use?
- And why have I focused on presenting relative effect estimates here? Don't patients care more about the absolute risk of something happening?

Tools to help?

- AnticoagEvaluator from the American College of Cardiology
- Based on SPARCtool from Peter Loewen
- Great idea and laudable effort
- However, importantly flawed, and until fixed, cannot be recommended

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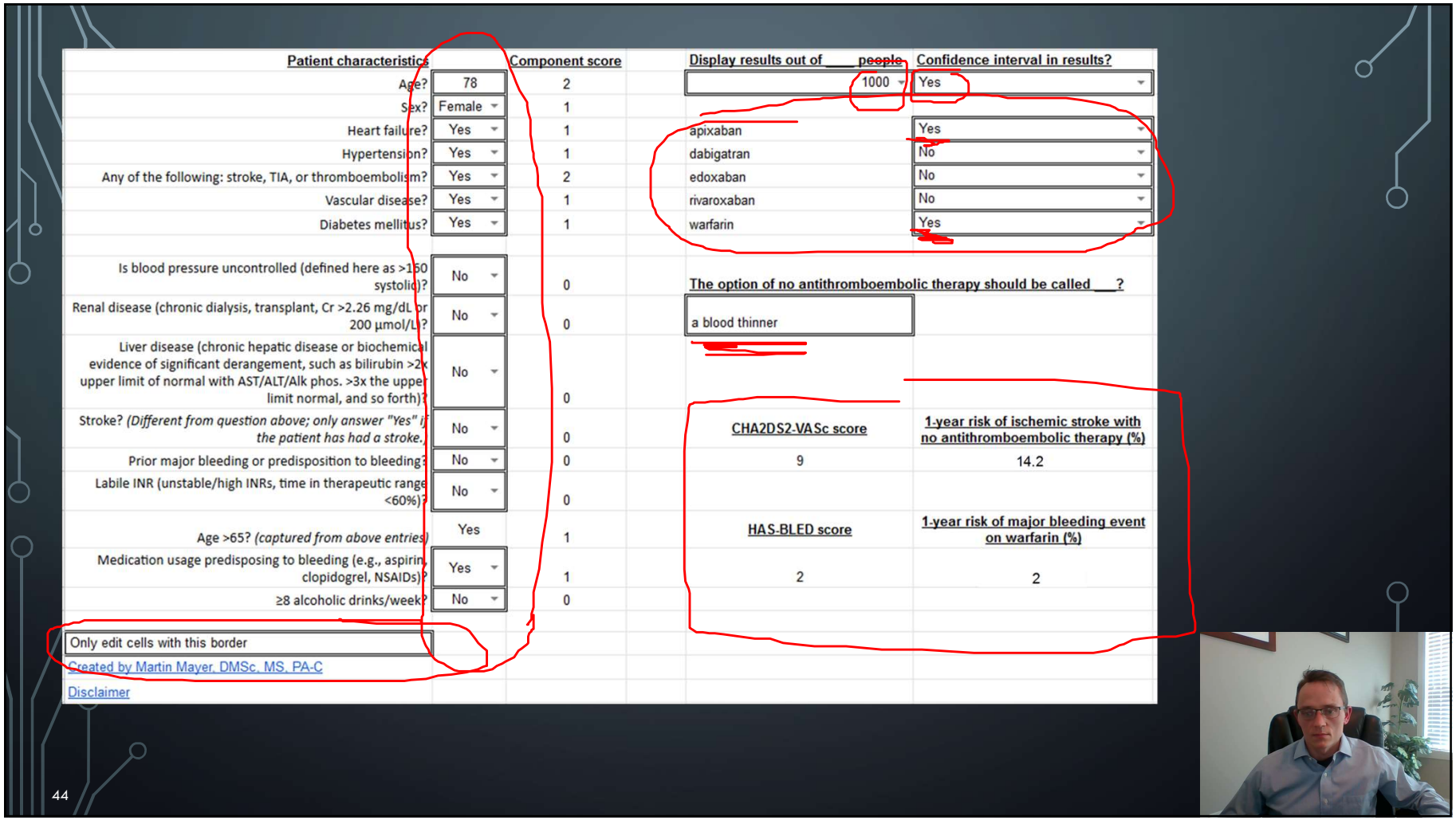
(Mayer 2019)

Tools to help?

- Mine: tiny.cc/afibtool



Patient characteristics		Component score
Age?	78	2
Sex?	Female	1
Heart failure?	Yes	1
Hypertension?	Yes	1
Any of the following: stroke, TIA, or thromboembolism?	Yes	2
Vascular disease?	Yes	1
Diabetes mellitus?	Yes	1
Is blood pressure uncontrolled (defined here as >160 systolic)?	No	0
Renal disease (chronic dialysis, transplant, Cr >2.26 mg/dL or 200 µmol/L)?	No	0
Liver disease (chronic hepatic disease or biochemical evidence of significant derangement, such as bilirubin >2x upper limit of normal with AST/ALT/Alk phos. >3x the upper limit normal, and so forth)?	No	0
Stroke? *(Different from question above; only answer "Yes" if the patient has had a stroke.)*	No	0
Prior major bleeding or predisposition to bleeding?	No	0
Labile INR (unstable/high INRs, time in therapeutic range <60%)?	No	0
Age >65? *(captured from above entries)*	Yes	1
Medication usage predisposing to bleeding (e.g., aspirin, clopidogrel, NSAIDs)?	Yes	1
≥8 alcoholic drinks/week?	No	0

Only edit cells with this border

Created by Martin Mayer, DMSc, MS, PA-C

Disclaimer

Display results out of ____ people	Confidence interval in results?
1000	Yes

apixaban	Yes
dabigatran	No
edoxaban	No
rivaroxaban	No
warfarin	Yes

The option of no antithromboembolic therapy should be called ___?

a blood thinner

CHA2DS2-VASc score	1-year risk of ischemic stroke with no antithromboembolic therapy (%)
9	14.2

HAS-BLED score	1-year risk of major bleeding event on warfarin (%)
2	2

	no blood thinner	***apixaban***	***warfarin***
Stroke due to blood being blocked from the brain	Out of 1000 people like you, 142 may have a stroke due to blood being blocked from the brain in the next year.	Out of 1000 people like you, 43 may have a stroke due to blood being blocked from the brain in the next year. (That number may be as low as 26 to as high as 73.)	Out of 1000 people like you, 50 may have a stroke due to blood being blocked from the brain in the next year. (That number may be as low as 34 to as high as 76.)
	This also means that 858 will not have this happen.	This also means that 957 will not have this happen. (That number may be as low as 927 to as high as 974.)	This also means that 950 will not have this happen. (That number may be as low as 924 to as high as 966.)
Major bleeding	Out of 1000 people like you, 7 may have major bleeding in the next year. (That number may be as low as 3 to as high as 15.)	Out of 1000 people like you, 14 may have major bleeding in the next year. (That number may be as low as 12 to as high as 16.)	Out of 1000 people like you, 20 may have major bleeding in the next year.
	This also means that 993 will not have this happen. (That number may be as low as 985 to as high as 997.)	This also means that 986 will not have this happen. (That number may be as low as 984 to as high as 988.)	This also means that 980 will not have this happen.

(Technical note: Irrespective of a user's selection, confidence intervals will not be displayed for the outcomes of ischemic stroke with no antithromboembolic therapy or major hemorrhagic event with warfarin, as these values are based on the CHA2DS2-VASc and HAS-BLED scores, respectively.)

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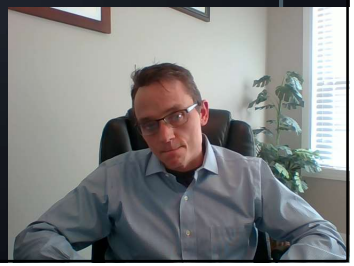

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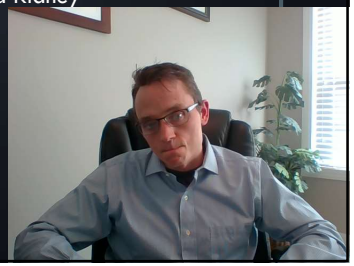

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