Anticoagulation FORUM | Webinar Lunch & Learn

The real world use of combined P-glycoprotein and moderate CYP3A4 inhibitors with rivaroxaban or apixaban increases bleeding

Thursday | February 27, 2020 | 12:00pm - 1:00pm EST

Guest Authors:

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Geoff Barnes, MD, MSc, FACC, FAHA, FSVM

Presenter:

Sara Vazquez, PharmD, BCPS, CACP

Moderator:

Diane Wirth, RN, MSN, ANP-BC, CACP

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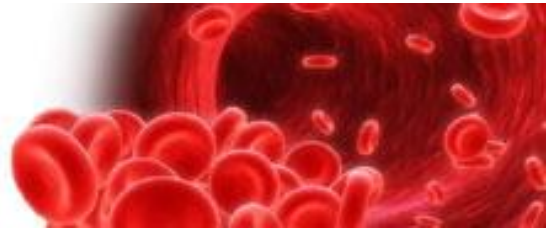

Presenters

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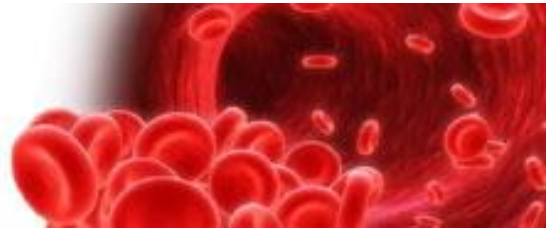

Disclosures-Sara Vazquez

- Editorial consultant for UptoDate® (WoltersKluwer)

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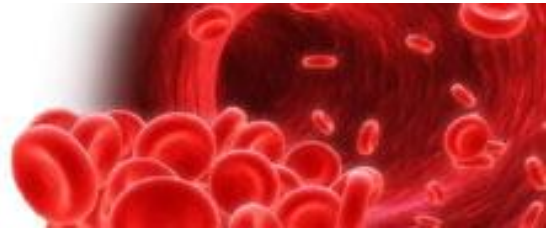

Background-DOAC DDIs

- All DOACs substrates for p-glycoprotein
- Rivaroxaban/apixaban **also** substrates for CYP3A4
  - Rivaroxaban 51% metabolized, mainly by CYP3A4/5 and CYP2J2
  - Apixaban 25% metabolized, mainly by CYP3A4

STRONG: ≥ 5-fold mean increase in a sensitive substrate AUC OR > 80% decrease in clearance in clinical study

MODERATE: ≥ 2-fold but <5-fold mean increase in a sensitive substrate AUC or ≥50% but < 80% decrease in clearance in clinical study

	Rivaroxaban	Apixaban
STRONG inhibitors	Avoid concomitant administration of riva with known combined p-gp and strong CYP3A4 inhibitors	For patients receiving apixa doses of 5 mg or 10 mg BID, reduce the dose by 50% when coadministered with drugs that are combined p-gp and strong CYP3A4 inhibitors. In patients already taking 2.5 mg BID, avoid coadministration of apixa with combined p-gp and strong CYP3A4 inhibitors.
MODERATE inhibitors	Riva should not be used in patients with CrCl 15 to < 80 mL/min who are receiving combined p-gp and moderate CYP3A inhibitors **unless the potential benefit justifies the potential risk**	**No guidance**

* Based on manufacturer labeling

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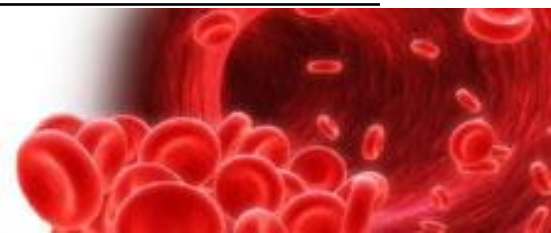
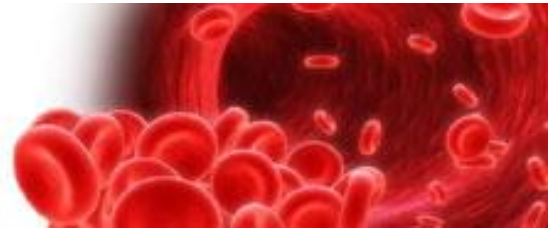


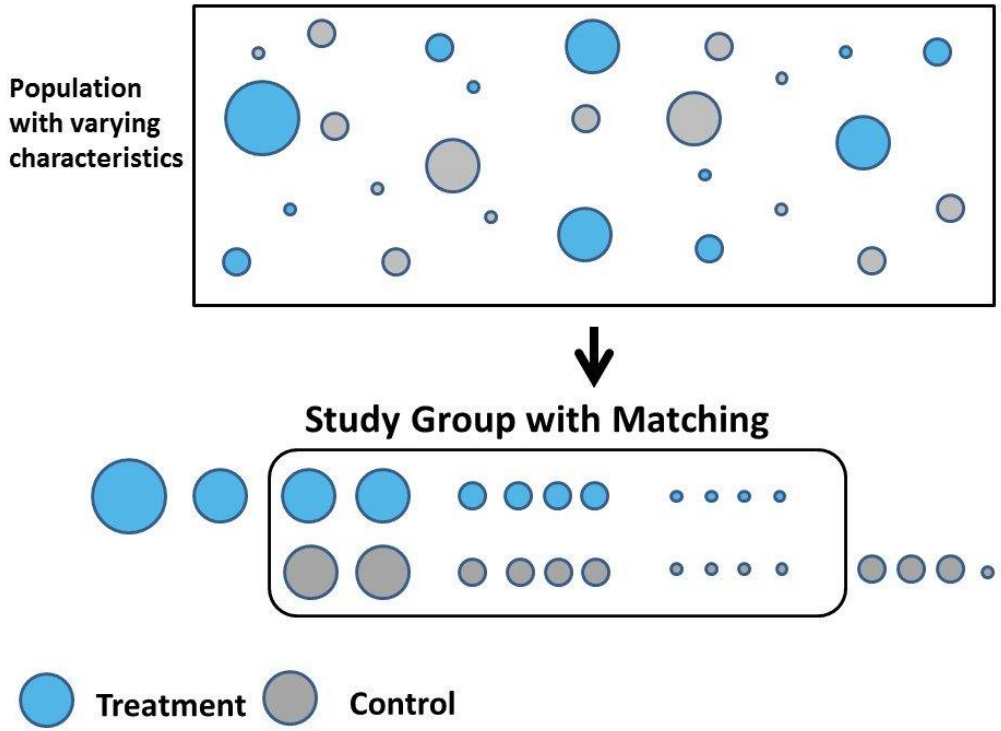
Clinical Dilemma:
What about the MODERATE dual inhibitors?

- How do you know if a drug is a strong/moderate/weak inhibitor?
- Data are mixed! For example…
  - Barlett JW, et al. Ann Pharmacother 2019 (same institution as this study) showed no difference in major or CRNMB in AF patients on rivaroxaban and diltiazem
  - Flaker G, et al. J Am Coll Cardiol 2014 (substudy of ARISTOTLE) showed no increase in bleeding in apixaban patients also taking amiodarone



Study Design

- Single-center (Michigan Medicine)
- Retrospective cohort study using propensity score matching



https://www.summitllc.us/propensity-score-matching

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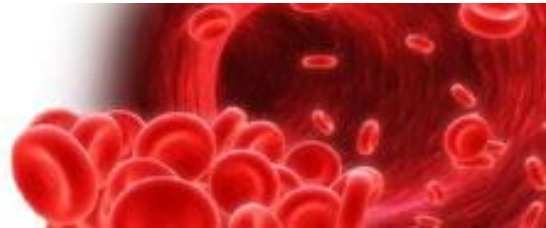
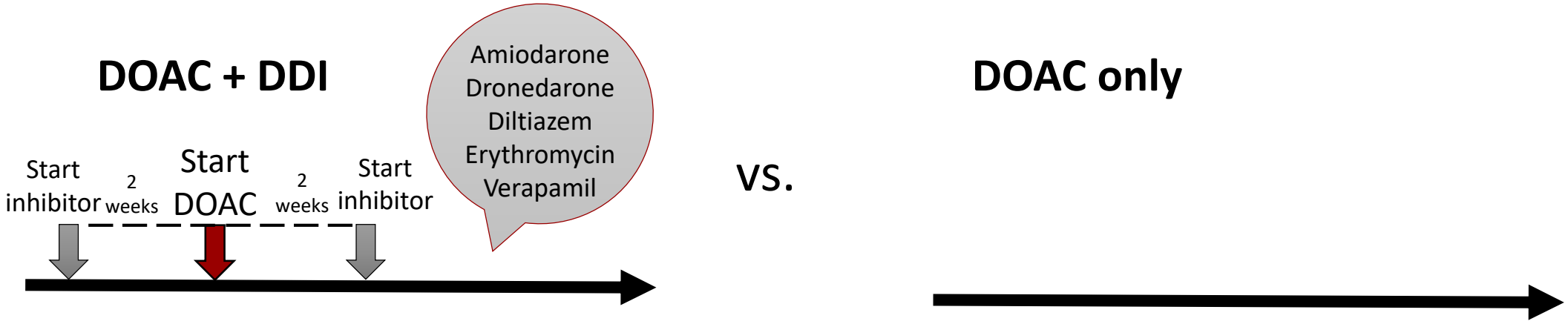


Inclusion Criteria

- ≥ age 18 years
- Routine care with Michigan Medicine
- Receiving **rivaroxaban** or **apixaban** for atrial fibrillation for a minimum duration of 3 months



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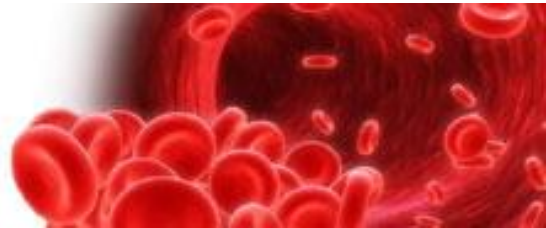

Exclusion Criteria

- Combined p-gp/CYP3A4 STRONG inhibitor or inducer
- Stage 5 CKD (CrCl <15 mL/min or requiring RRT)
- Patients were removed from the trial if the DOAC or inhibitor was discontinued or when primary outcome was met.

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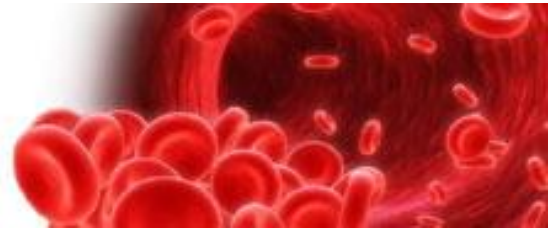

Outcomes

- Primary endpoint:
  - **Composite** of major bleeding, clinically relevant non-major bleeding (CRNMB), and minor bleeding
    - **Major bleeding**: clinically overt bleeding associated with fatal outcome and/or involvement of critical anatomical site and/or Hgb fall of ≥ 2 g/dL or leading to administration of ≥ 2 units of whole/RBCs
    - **CRNMB**: overt bleeding that does not meet major bleeding criteria but requires medical intervention, unscheduled contact with physicians (including telephone call to provider), temporary interruption of study drug, pain, and impairment of daily activities.
    - **Minor bleeding**: any bleeding that did not meet criteria for major or CRNMB

- Secondary endpoints:
  - Individual components of the composite outcome
  - Bleeding in patients with concomitant renal dysfunction

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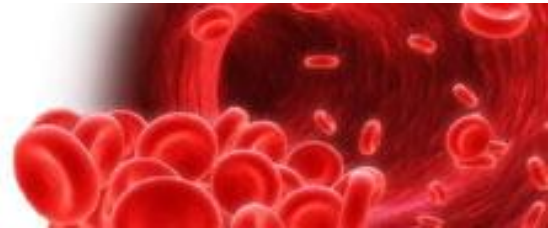
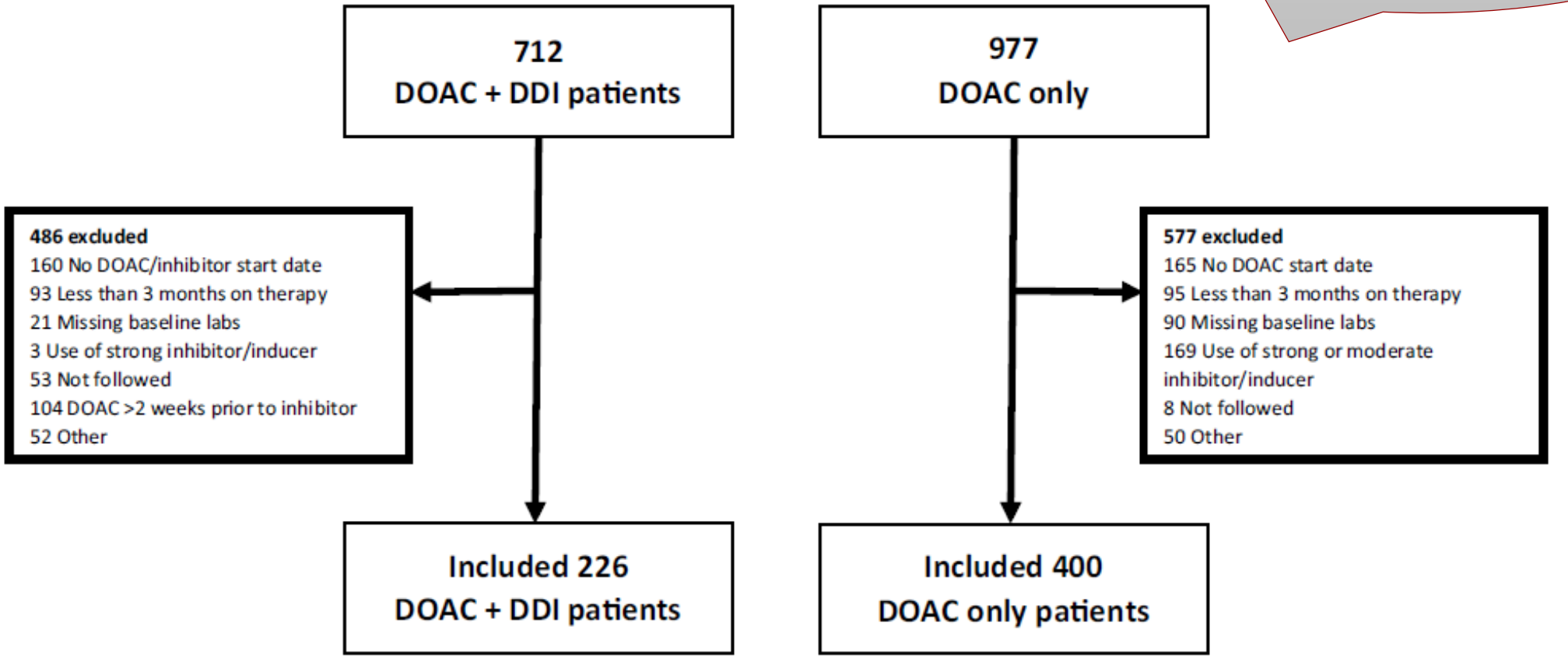


Results

712 + 977 = 1,689 AF DOAC patients
712 / 1,689 = **42%** **of patients had one of these DDIs present!**



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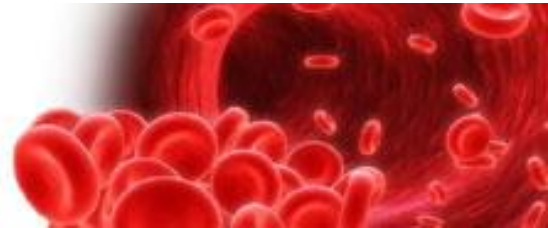

Baseline characteristics (AFTER PM)

Table 1 Baseline characteristics of patients

Characteristic	DDI group (unmatched) n = 226	Control (unmatched) n = 400	p-value	DDI group (matched) n = 213	Control (matched) n = 213	p-value
Age: year	68.2 ± 11.5	69.8 ± 12.7	0.114	68.6 ± 11.5	67.7 ± 14.0	0.428
Female sex: no. (%)	93 (41.2)	163 (40.8)	0.922	91 (42.7)	93 (43.7)	0.845
Race or ethnic group: no. (%)						
White	199 (88)	355 (88.8)	0.856	188 (88.3)	195 (91.6)	0.619
Black	16 (7.1)	23 (5.8)	–	14 (6.6)	12 (5.6)	–
Asian	6 (2.7)	14 (3.5)	–	6 (2.8)	3 (1.4)	–
Other	5 (2.2)	8 (2)	–	5 (2.4)	3 (1.4)	–
Height: m	1.7 ± 0.1	1.7 ± 0.1	0.306	1.7 ± 0.12	1.7 ± 0.13	0.181
Weight: kg	90.9 ± 23.7	90.5 ± 23.1	0.847	89.6 ± 22.8	92.5 ± 24.8	0.207
Systolic blood pressure: mmHg	129 ± 20	126 ± 19	0.081	128 ± 19	128 ± 19	0.793
Diastolic blood pressure: mmHg	72 ± 12	70 ± 11	0.1	71 ± 12	71 ± 11	0.967
SCr: g/dL	0.96 ± 0.29	0.97 ± 0.46	0.756	0.96 ± 0.29	0.97 ± 0.54	0.948
Hgb: mg/dL	13.5 ± 1.9	13.5 ± 2.0	0.924	13.4 ± 1.9	13.6 ± 2.0	0.50
Prior Stroke or TIA: no. (%)	22 (9.7)	65 (16.3)	0.024	20 (9.4)	21 (9.9)	0.87
Heart failure: no. (%)	58 (25.7)	102 (25.5)	0.964	53 (24.9)	56 (26.3)	0.74
Hypertension: no. (%)	166 (73.5)	285 (71.3)	0.556	155 (72.8)	155 (72.8)	1.00
Diabetes: no. (%)	39 (17.3)	99 (24.8)	0.030	38 (17.8)	41 (19.3)	0.708
Vascular disease: no. (%)	43 (19)	122 (30.5)	0.002	42 (19.7)	41 (19.3)	0.903
CHA2DS2-VASc	3.0 ± 1.7	3.3 ± 1.8	0.024	3.0 ± 1.7	3.0 ± 1.7	0.84
Liver disease: no. (%)	5 (2.2)	37 (9.3)	0.001	5 (2.4)	4 (1.9)	1.00
COPD: no. (%)	28 (12.4)	57 (14.3)	0.514	27 (12.7)	29 (13.6)	0.774
Anemia: no. (%)	26 (11.5)	77 (19.3)	0.012	26 (12.2)	27 (12.7)	0.883
Drug use history: no. (%)	5 (2.2)	8 (2)	1.000	4 (1.9)	4 (1.9)	1.000
Alcohol consumption: no. (%)	19 (8.4)	8 (2)	<0.001	8 (3.8)	7 (3.3)	0.793
Surgery or trauma in past 6 months: no. (%)	37 (16.4)	35 (8.8)	0.004	32 (15)	26 (12.2)	0.397
Alternative anticoagulation use in past 6 months: no. (%)	52 (23.1)	89 (22.3)	0.827	50 (23.5)	44 (20.7)	0.483

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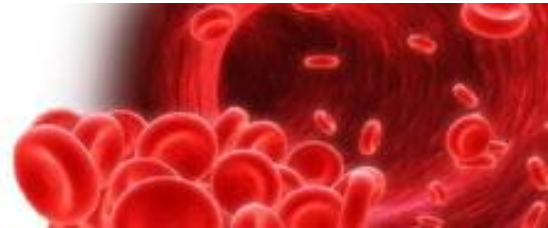

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Aspirin	34 (15.1)	91 (22.8)	0.021	34 (16)	33 (15.5)	0.894
P2Y12 inhibitor	3 (1.3)	5 (1.3)	1.0000	3 (1.4)	3 (1.4)	1.000
Chronic NSAID	6 (2.7)	18 (4.5)	0.248	4 (1.9)	9 (4.2)	0.159
Chronic steroid	6 (2.7)	18 (4.5)	0.248	6 (2.8)	9 (4.2)	0.43
Rivaroxaban: no. (%)	115 (50.9)	200 (50)	0.832	108 (50.7)	101 (47.4)	0.498
Apixaban: no. (%)	111 (49.1)	200 (50)	0.832	105 (49.3)	112 (52.6)	0.498
Inhibitor: no. (%)						
Diltiazem	157 (69.5)	–	–	145 (68.1)	–	–
Verapamil	12 (5.3)	–	–	12 (5.7)	–	–
Amiodarone	58 (25.7)	–	–	57 (26.8)	–	–
Dronedarone	5 (2.2)	–	–	5 (2.3)	–	–
Erythromycin	0 (0)	–	–	0 (0)	–	–
Multiple	6 (2.7)	–	–	6 (2.8)		

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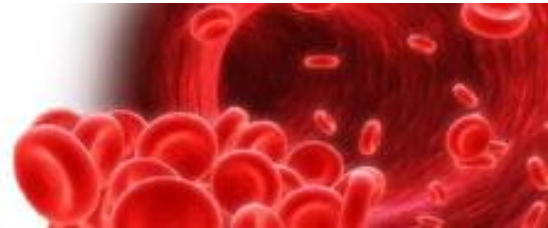
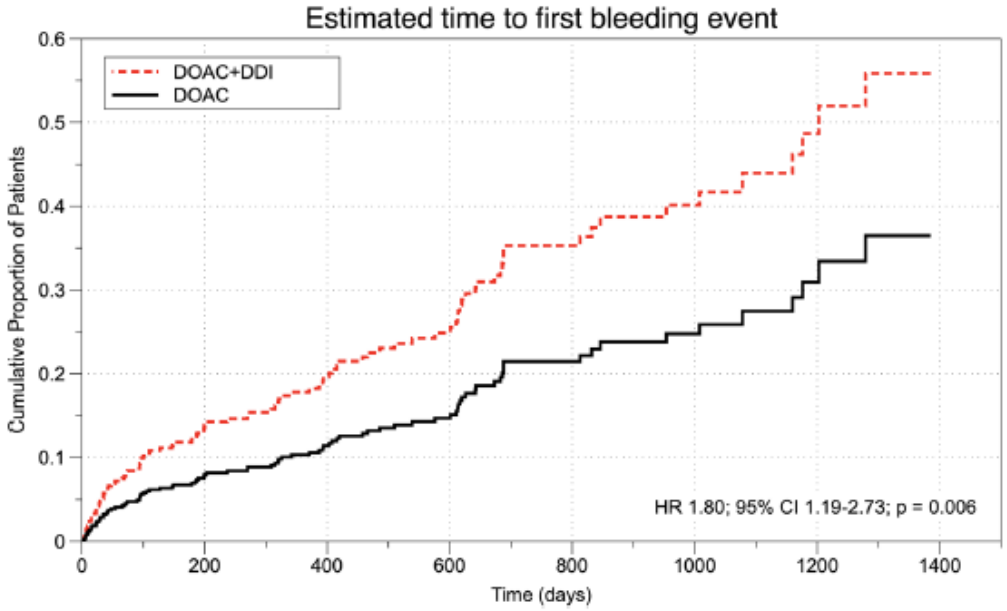


Results-Primary/Secondary Outcomes

	DOAC+DDI (n=213)	DOAC alone (n=213)	Hazard ratio (95% CI)
Any bleeding	56 (26.3%)	37 (17.4%)	1.8 (1.19-2.73) p=0.006
Major bleeding	5 (2.3%)	4 (1.9%)	
Clinically relevant nonmajor bleeding	32 (15%)	22 (10.3%)	
Minor bleeding	19 (8.9%)	11 (5.2%)	



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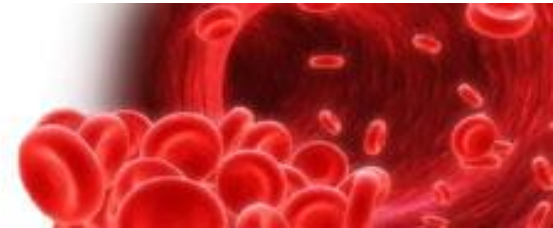

Results

33 riva
23 apixa

	Any bleeding n=56	No bleeding n=157
Diltiazem	42 (75%)	103 (65.6%)
Verapamil	1 (1.8%)	11 (7%)
Amiodarone	16 (28.6%)	41 (26.1%)
Dronedarone	1 (1.8%)	4 (2.6%)
Multiple inhibitors	4 (7.1%)	2 (1.3%) ★ p=0.043

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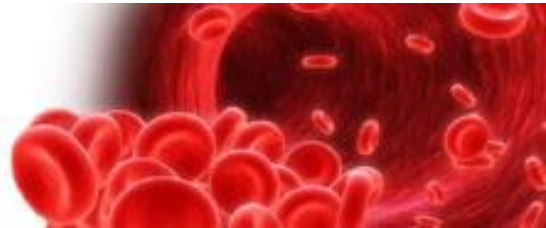

Strengths/Limitations

Strengths

- Addressed **clinical outcomes** from a potential DDI in a systematic manner
  - Propensity score matching
  - Start date and Duration of DOAC and interacting drug matched

Limitations

- Inclusion of minor bleeding as part of the composite outcome
- Diltiazem may not have p-gp inhibitor activity
- Single-center
- Unable to assess concomitant factors like age, renal function

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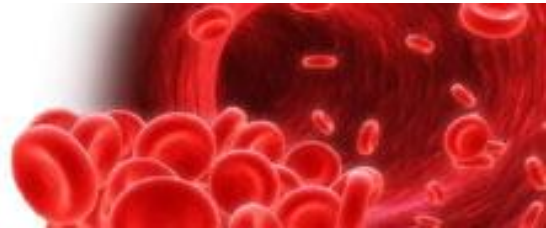

Conclusions

- In this small, single-center study…
  - Incidence of DOAC DDIs was frequent, major bleeding was not
  - Bleeding of any kind was higher in AF patients taking rivaroxaban or apixaban in combination with diltiazem or amiodarone but largely driven by CRNMB or minor bleeding
    - Major bleeding was similar between DDI and non-DDI groups

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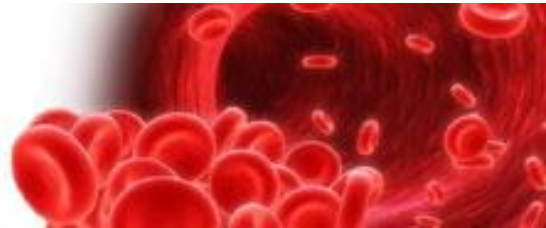
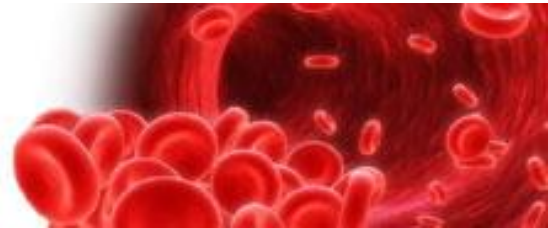


Questions for Discussion

- How should clinics “manage” or “monitor” for DOAC DDIs?
  - How/when/how often to screen for DDIs
  - Should we use drug levels/anti-Xa levels to assess DDIs?
- What role do other factors play in the clinical significance of a potential DDI?
  - Advanced age, renal/hepatic impairment, concomitant antiplatelet therapy, multiple moderate inhibitors
- What other drugs should we consider, perhaps in a non-AF population? Are there indication-specific interaction concerns?
- Are single-modality inducers/inhibitor interactions clinically relevant?
  - Riva/apixa + p-gp only
  - Riva/apixa + CYP3A4 only
- What is the best methodology to study these questions?



March Webinar Lunch & Learn

Don't Miss Our *next* Upcoming Live Webinar!

Thursday | March 19, 2020 | 12:00 PM EST

Antithrombotic Therapy for Atrial Fibrillation with Stable Coronary Disease

Published in the *The New England Journal of* Medicine in December 2019

Presenter:

Geoffrey Barnes, MD, MSc, FACC, FAHA, FSVM

Panel:

Renato Lopes, MD, PhD, MHS

Dominick Angiolillo, MD, PhD, FACC

Moderators:

Sara Vazquez, PharmD, BCPS, CACP

Diane Wirth, RN, MSN, ANP-BC, CACP

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