

The background of the slide features a photograph of Northwestern University buildings. On the left is the historic Old Chapel building with its Gothic architecture and a prominent tower. To the right is a modern glass skyscraper with the Northwestern 'M' logo on its upper facade. The sky is blue with light clouds. A large, dark blue diagonal shape is overlaid on the left side of the image, containing the text.

M Northwestern Medicine[®]
Feinberg School of Medicine

Challenges in Oral Anticoagulation Therapy: Age, BMI, Renal Function, Cost

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Feinberg School of Medicine, Northwestern University

ACC/India 2023 Cardiovascular Symposium

Sunday, January 23, 2023

Overview

- Case
- Age
- BMI
- Renal Function
- Cost



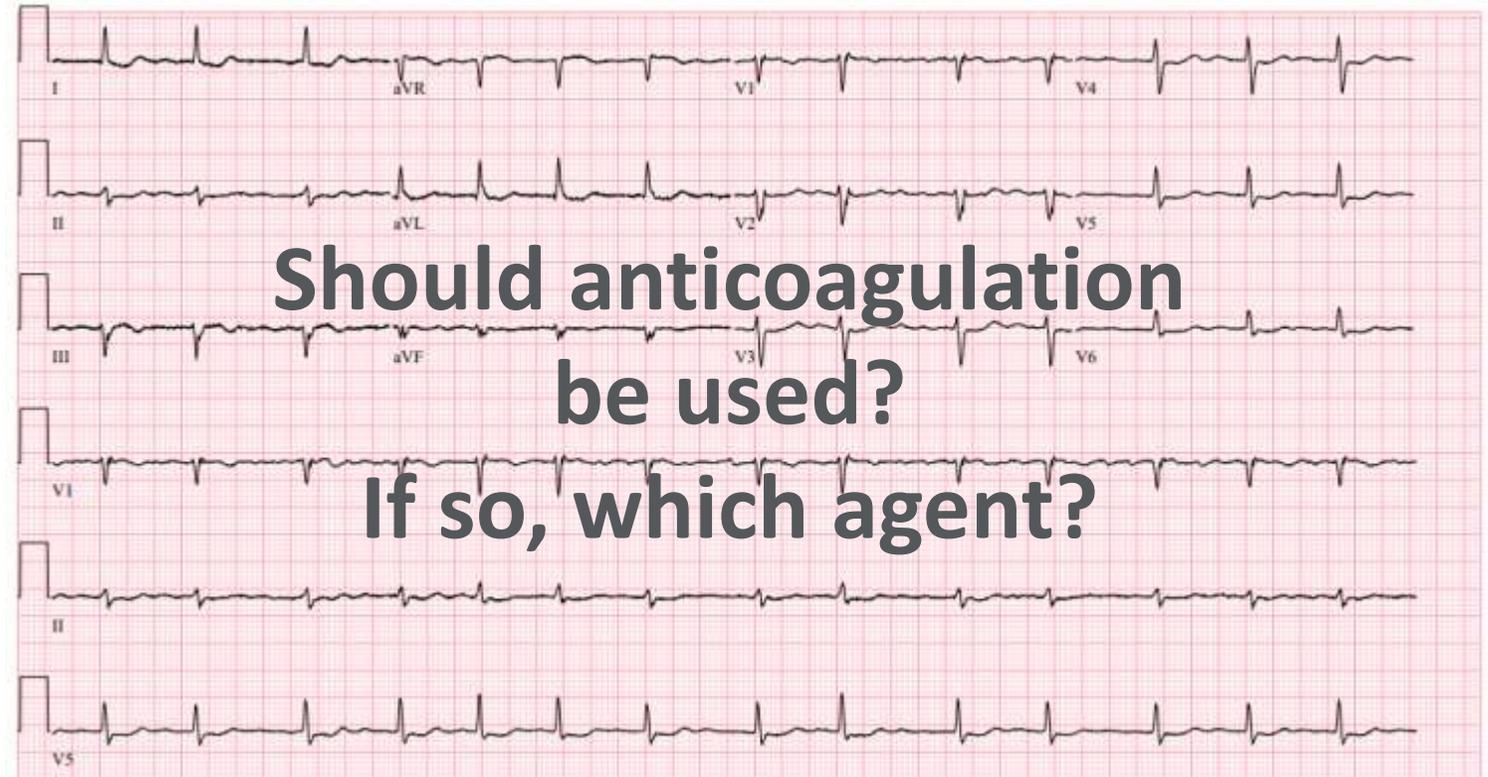
Overview

- Case
- Age
- BMI
- Renal Function
- Cost



Case

- **77** male smoker with hypertension, diabetes mellitus, **obesity (BMI 35)**, and **chronic kidney disease (CrCl 39)**, presents with paroxysmal atrial fibrillation.
 - No valvular heart disease
- **CHA₂DS₂-VASc = 4** (age, HTN, DM)
 - Annual Stroke Risk 4.8%
- **HAS-BLED = 2** (age, HTN)
 - Annual Bleeding Risk 1.88/100 pt years



Overview

- Case
- **Age**
- BMI
- Renal Function
- Cost



Warfarin in Elderly Patients with AF

BAFTA Study 2007

	Warfarin (n=488)		Aspirin (n=485)		Warfarin vs aspirin	
	n	Risk per year	n	Risk per year	RR (95% CI)	p
Stroke	21	1.6%	44	3.4%	0.46 (0.26-0.79)	0.003
By severity						
Fatal	13	1.0%	21	1.6%	0.59 (0.27-1.24)	0.14
Disabling non-fatal	8	0.6%	23	1.8%	0.33 (0.13-0.77)	0.005
Type of stroke*						
Ischaemic	10	0.8%	32	2.5%	0.30 (0.13-0.63)	0.0004
Haemorrhagic	6	0.5%	5	0.4%	1.15 (0.29-4.77)	0.83
Unknown	5	0.4%	7	0.5%	0.69 (0.17-2.51)	0.53
Other intracranial haemorrhage†	2	0.2%	1	0.1%	1.92 (0.10-113.3)	0.65
Systemic embolism‡	1	0.1%	3	0.2%	0.32 (0.01-3.99)	0.36
Total number of events	24	1.8%	48	3.8%	0.48 (0.28-0.80)	0.0027

RR=relative risk. *Type of stroke was determined by the endpoint committee on the basis of brain imaging or post-mortem findings. If neither of these was available, the stroke was classified as unknown. †The three other intracranial haemorrhages were subdural; two of these were fatal (one in each treatment group). ‡Two of the systemic emboli were fatal (one in each treatment group).

Table 3: Nature of primary events

	INR 2-3	
	Warfarin	Aspirin 75 mg
Number of patients	488	485
Age (years)	81.5 (4.3)	81.5 (4.2)
Age group		
75-79	197 (40%)	200 (41%)
80-84	196 (40%)	190 (39%)
≥85	95 (19%)	95 (20%)
Male	267 (55%)	264 (54%)
Method of identification		
Practice register	342 (70%)	341 (70%)
Screening	146 (30%)	144 (30%)
CHADS2 score*		
1-2	349 (72%)	349 (72%)
3-6	139 (28%)	136 (28%)
On warfarin	194 (40%)	187 (39%)
On aspirin	203 (42%)	204 (42%)
History of stroke or TIA	64 (13%)	60 (12%)
History of hypertension	259 (53%)	269 (55%)
Systolic BP (mm Hg)	139.9 (19.2)	141.3 (19.9)
Diastolic BP (mm Hg)	78.1 (11.1)	78.9 (12.5)
Systolic BP (mm Hg)		
≤160	426 (87%)	408 (84%)
>160	62 (13%)	77 (16%)
Diabetes mellitus	68 (14%)	61 (13%)
Heart failure	96 (20%)	94 (19%)
Myocardial infarction	47 (10%)	56 (12%)
Angina	80 (16%)	75 (15%)

Data are number (%) or mean (SD). TIA=transient ischaemic attack. BP=blood pressure. *A risk stratification scheme for atrial fibrillation. A score of 0-6 is derived based on the following factors: congestive heart failure (1 point); hypertension (1 point); age ≥75 years (1 point); diabetes mellitus (1 point); and previous stroke or TIA (2 points).

Table 2: Baseline characteristics of patients subsequently treated with warfarin or aspirin

Antiplatelet vs Warfarin vs DOAC Therapy

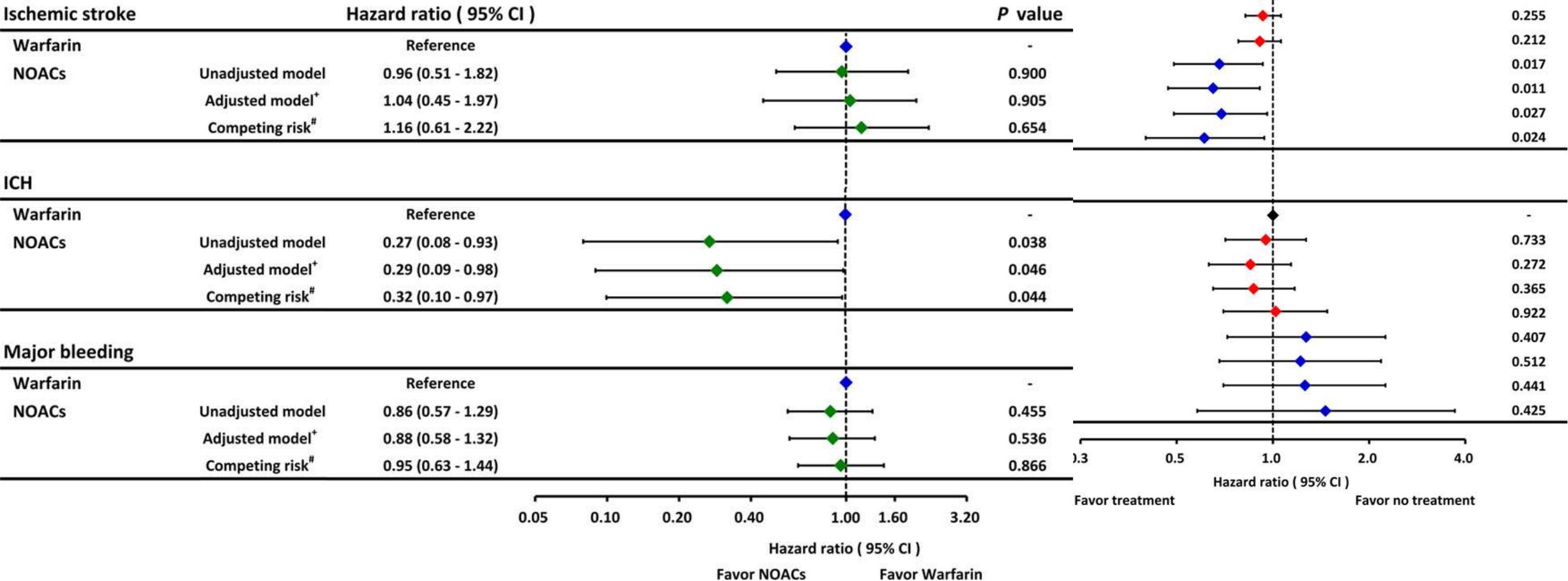
Circulation

Volume 138, Issue 1, 3 July 2018; Pages 37-47
<https://doi.org/10.1161/CIRCULATIONAHA.117.031658>

Era without NOACs (Year 1996 – 2011)

Ischemic stroke	Hazard ratio (95% CI)	P value
No antithrombotic therapy	Reference	-

Era with NOACs (Year 2012 - 2015)

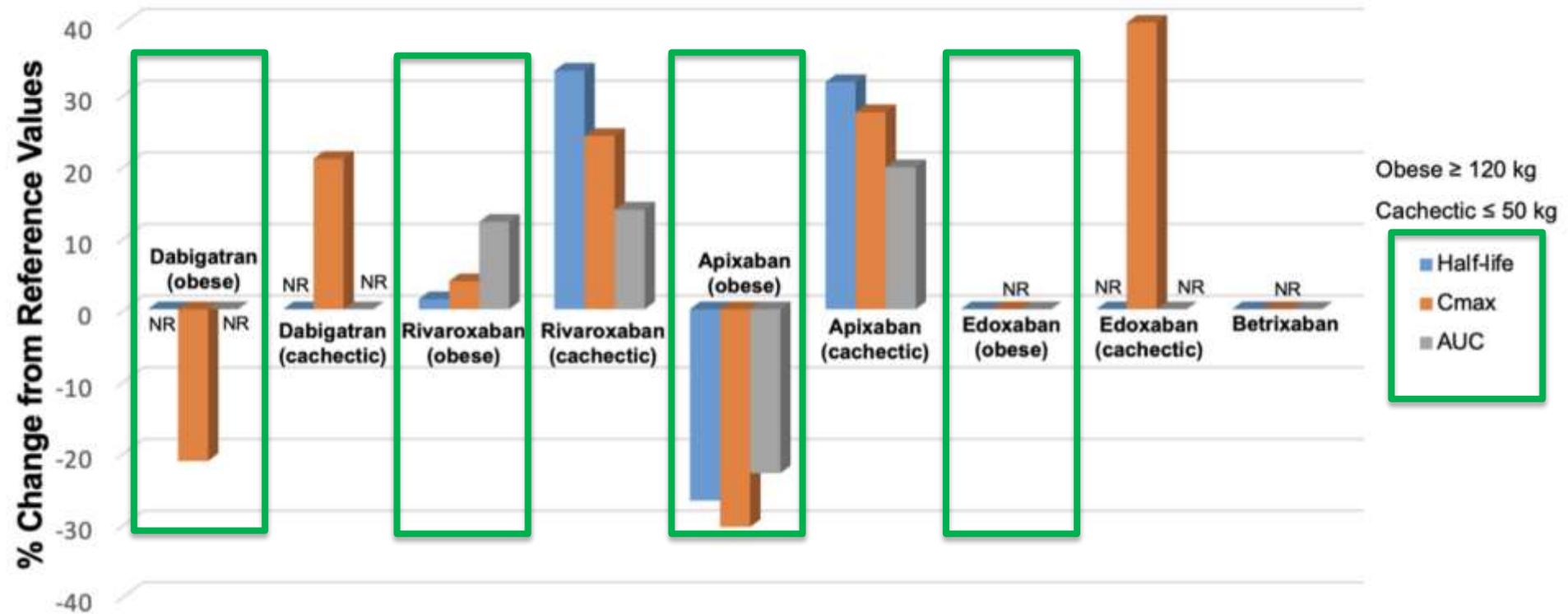


Overview

- Case
- Age
- **BMI**
- Renal Function
- Cost



Pharmacokinetics/-dynamics



DOAC Use in Overweight/Obese AF Patients

Journal of the American Heart Association

Table 1. Baseline Characteristics of the Study Population by BMI Categories

	Overall N=7642	Normal Weight (18.5 ≤ BMI <25.0) N=1720	Overweight (25.0 ≤ BMI <30.0) N=2804	Class 1 Obesity (30.0 ≤ BMI <35.0) N=1697	Class 2+3 Obesity (35.0 ≤ BMI) N=1421
Age, y	69 (12)	72 (13)	69 (12)	67 (12)	64 (11)
Male, n (%)	4546 (59.5)	782 (45.5)	1870 (66.7)	1088 (64.1)	806 (56.7)
White, n (%)*	6678 (87.4)	1494 (86.9)	2464 (87.9)	1483 (87.4)	1237 (87.1)
Hispanic, n (%)	193 (2.5)	23 (1.3)	76 (2.7)	54 (3.2)	40 (2.8)
Non-Hispanic Black, n (%)	356 (4.7)	58 (3.4)	97 (3.5)	95 (5.6)	106 (7.6)
BMI, kg/m ²	28.7 (25.3–33.2)	23.0 (21.5–24.1)	27.5 (26.3–28.7)	32.1 (31.0–33.4)	39.0 (36.6–43.0)
Weight, kg	87.1 (73.5–102.5)	65.8 (58.4–74.8)	83.9 (74.8–91.8)	97.5 (87.3–106.8)	118.7 (105.1–132.4)
Weight >120 kg, n (%)	756 (9.9)	3 (0.2)	6 (0.2)	74 (4.4)	673 (47.4)
Systolic BP	128 (19)	126 (20)	127 (19)	129 (19)	131 (19)
CHA ₂ DS ₂ -VASc Score	2.7 (2.0)	3.1 (2.0)	2.7 (2.0)	2.6 (2.0)	2.6 (1.9)
Heart failure, n (%)	959 (12.5)	213 (12.4)	304 (10.8)	205 (12.1)	237 (16.7)
Hypertension, n (%)	3826 (50.1)	770 (44.8)	1363 (48.6)	882 (52.0)	811 (57.1)
Diabetes mellitus, n (%)	1128 (14.8)	143 (8.3)	334 (11.9)	290 (17.1)	361 (25.4)
Stroke, n (%)	1289 (16.9)	391 (22.7)	473 (16.9)	253 (14.9)	172 (12.1)
TIA, n (%)	1185 (15.5)	357 (20.8)	436 (15.5)	239 (14.1)	153 (10.8)
VD, n (%)	603 (7.9)	170 (9.9)	228 (8.1)	124 (7.3)	81 (5.7)
DOAC, n (%)					
Apixaban, n (%)	3356 (43.9)	810 (47.1)	1271 (45.3)	708 (41.7)	567 (39.9)
Rivaroxaban, n (%)	2785 (36.4)	563 (32.7)	1002 (35.7)	650 (38.3)	570 (40.1)
Edoxaban, n (%)	10 (0.1)	1 (0.1)	5 (0.2)	3 (0.2)	1 (0.1)
Dabigatran, n (%)	1491 (19.5)	346 (20.1)	526 (18.8)	336 (19.8)	283 (19.9)

ORIGINAL RESEARCH

Efficacy and Safety of Direct Oral Anticoagulants for Atrial Fibrillation by Body Mass Index Category

Rachel M. Kaplan, MD, MS; Yoshihiro Tanaka , MD, PhD; Laura J. Rasmussen-Torvik, PhD; Suma Vupputuri ,

DOAC Use in Overweight/Obese AF Patients

Table 2. HRs of Stroke/Systemic Embolism Events in Excess BMI Categories Compared With Normal BMI

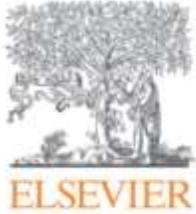
Stroke/Systemic Embolism Events		
BMI Subgroup	HR	95% CI
18.5 ≤ BMI <25.0	Section References	Section Reference
25.0 ≤ BMI <30.0	1.252	0.581–2.70
30.0 ≤ BMI <35.0	1.217	0.516–2.87
35.0 ≤ BMI	0.684	0.233–2.00

Table 3. HRs of Intracranial Hemorrhage Events by Each Excess BMI Category Compared With Normal BMI

Intracranial Hemorrhage Events			
BMI Subgroup	HR	95% CI	P Value
18.5 ≤ BMI <25.0	Section References	Section References	Section References
25.0 ≤ BMI <30.0	0.692	0.418–1.145	0.152
30.0 ≤ BMI <35.0	0.640	0.352–1.161	0.142
35.0 ≤ BMI	0.656	0.347–1.239	0.194

HRs with 95% CIs were adjusted for CHA₂DS₂-VASc score. BMI indicates body mass index; DOAC, direct oral anticoagulants; and HR, hazard ratio.

DOAC Outcomes



JACC: Clinical
Volume 7, Issue 5,

Focus on Atrial Fibrillation

New Research Paper: Atrial Fibrillation - Clinical Management

Outcomes of Direct Oral Anticoagulant in Patients Across Body Mass Index Categories

Amr F. Barakat MD, MSc^a, Sandeep Jain MD^a, Ahmad F. Alkhatib MD^a, Ahmet Sezer PhD^a, Yisi Wang MPH^a, Floyd Thoma BS^a, Suresh Mulukutla MD^a

CENTRAL ILLUSTRATION: Safety and Effectiveness of Direct Oral Anticoagulants in Patients With Nonvalvular Atrial Fibrillation Across Different Body Mass Index Categories

QUESTION Dose extreme body mass index affect the outcomes of direct oral anticoagulant in non-valvular atrial fibrillation patients?

METHODS

36,094 PATIENTS

- Non-valvular atrial fibrillation
- CHA₂DS₂ - VASc ≥1
- Treated with oral anticoagulation

FOUR Body Mass Index GROUPS	% on Direct Oral Anticoagulant vs. Warfarin	
Group 1 Underweight body mass index <18.5	56%	44%
Group 2 Normal / Overweight body mass index 18.5 - <30	49%	51%
Group 3 Grade 1, 2 obesity body mass index 30 - <40	53%	47%
Group 4 Grade 3 obesity body mass index ≥40	55%	45%

PRIMARY OUTCOMES:

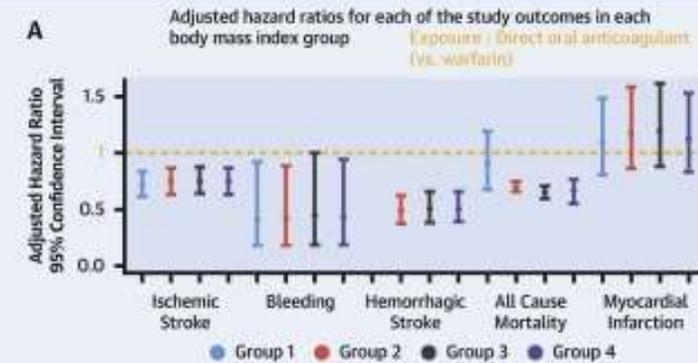
Ischemic stroke, significant bleeding events

Secondary Outcomes:

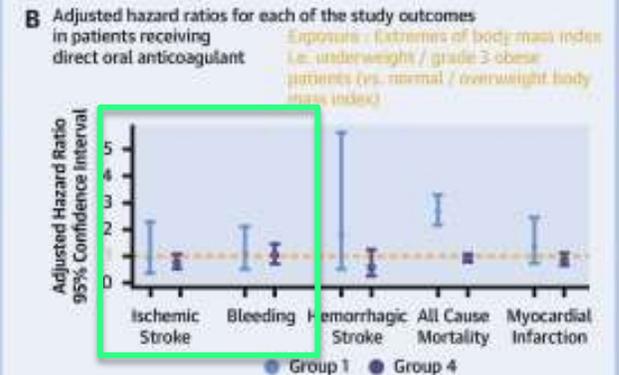
Hemorrhagic stroke, all-cause mortality, myocardial infarction

RESULTS

Direct oral anticoagulant, compared to warfarin, were associated with better safety and effectiveness **across all body mass index strata**, including underweight and grade 3 obese patients.



In the **18,454** patients who received **direct oral anticoagulant**, extreme body mass index was not associated with a higher risk of stroke or bleeding.



Overview

- Case
- Age
- BMI
- **Renal Function**
- Cost



Warfarin Use in Chronic Kidney Disease

- Data on safety and efficacy lacking
- Risk of warfarin-induced vascular calcifications and worsening nephropathy
- 15 Studies
- 45,000 patients
- 22% on warfarin therapy

Original Investigation | Cardiology



April 6, 2020

Association Between Use of Warfarin for Atrial Fibrillation and Outcomes Among Patients With End-Stage Renal Disease

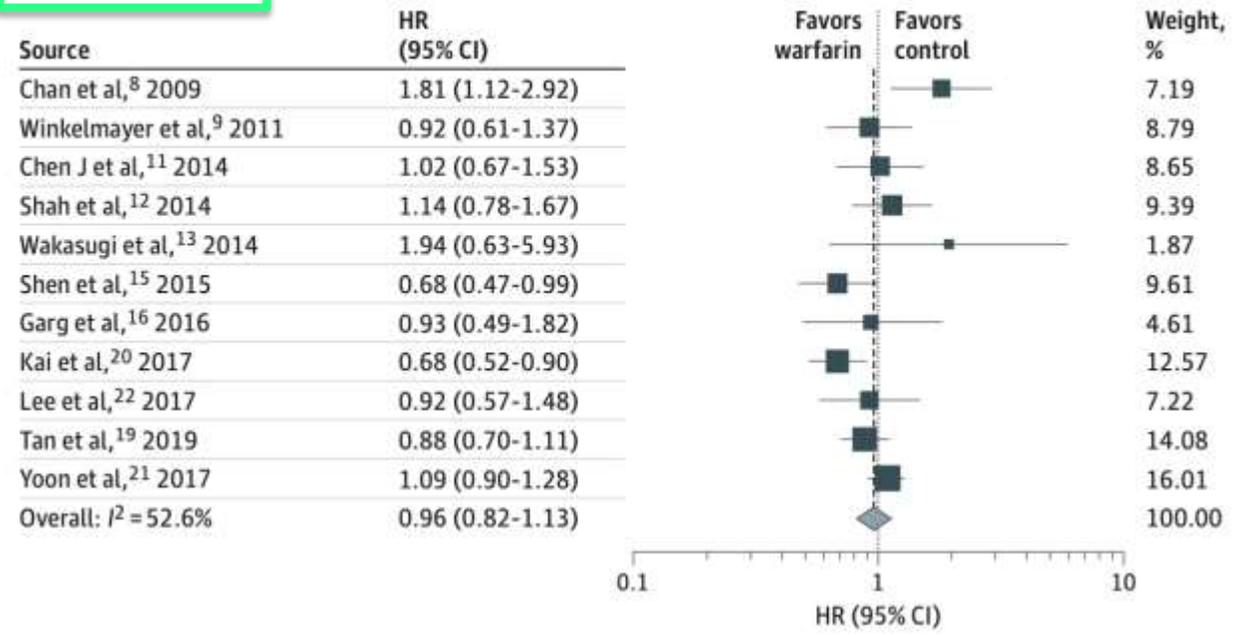
A Systematic Review and Meta-analysis

Mandeep S. Randhawa, MD^{1,2}; Rohanlal Vishwanath, BSc³; Manoj P. Rai, MD⁴; [et al](#)

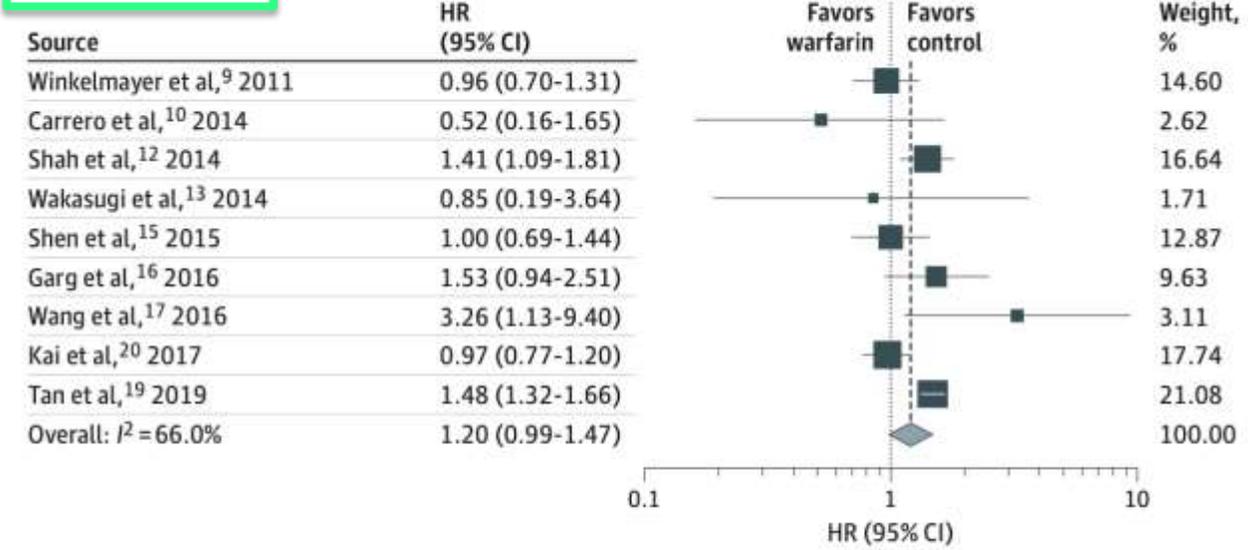
[» Author Affiliations](#) | [Article Information](#)

JAMA Netw Open. 2020;3(4):e202175. doi:10.1001/jamanetworkopen.2020.2175

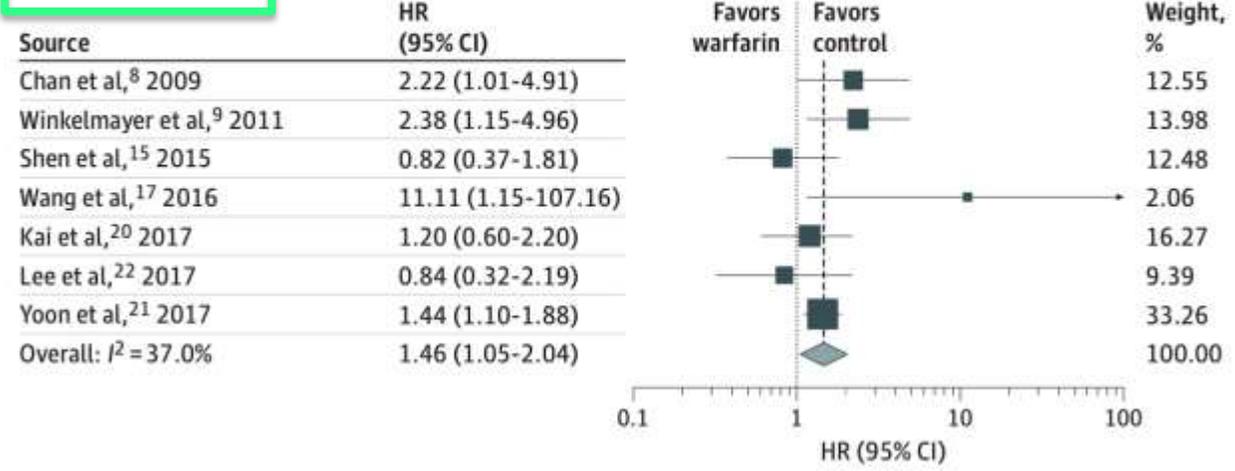
A Ischemic stroke



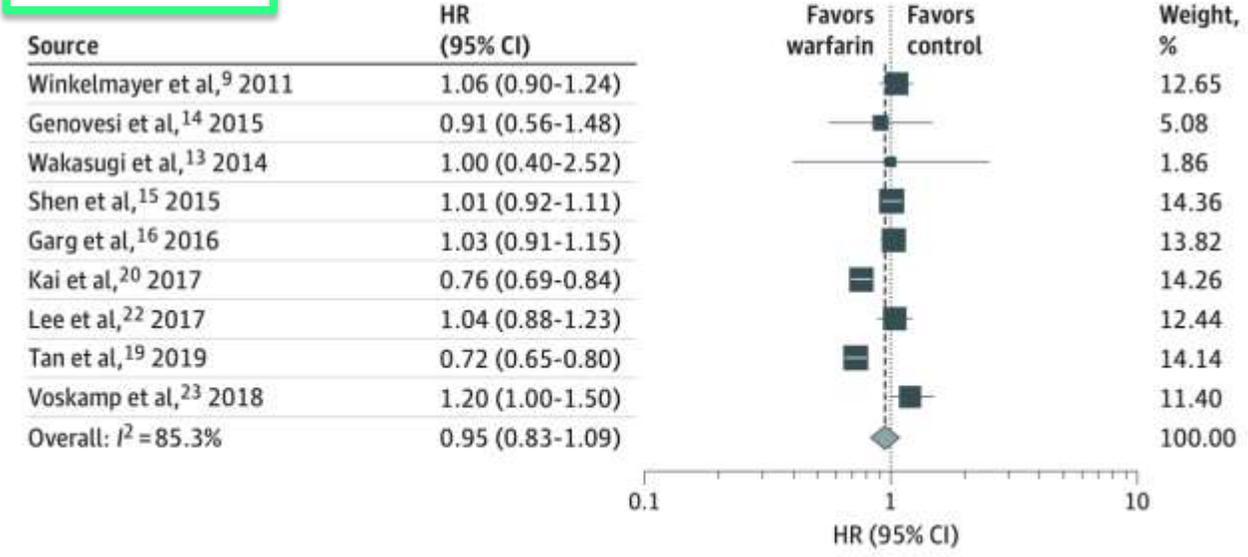
A Major bleeding



B Hemorrhagic stroke



B Mortality



DOAC Dosing in Chronic Kidney Disease

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 17, 2009 VOL. 361 NO. 12

Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Stuart J. Conn
John Eikelboom, M.D.
Ellison Thrombosis, B.J.
Jun Zhu, M.D., Rafae

ESTABLISHED IN 1812 SEPTEMBER 8, 2011 VOL. 365 NO. 10

Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

Guohua Pan, Ph.D., Daniel E. Singer, M.D.,
Halperin, M.D., Graeme J. Hankey, M.D.,
Nessel, M.D., John F. Paolini, M.D., Ph.D.,
B., Robert M. Califf, M.D.,
OCKET AF Investigators*

Edoxaban versus Warfarin in Patients with Atrial Fibrillation

Robert P. Giugliano, M.D., Christian T. Ruff, M.D., M.P.H., Eugene Braunwald, M.D.,
Sabina A. Murphy, M.P.H., Stephen D. Wiviott, M.D., Jonathan L. Halperin, M.D.,
Albert L. Waldo, M.D., Michael D. Ezekowitz, M.D., D.Phil., Jeffrey I. Weitz, M.D.,
Jindřich Špinar, M.D., Witold Ruzyllo, M.D., Mikhail Ruda, M.D.,
Yukihiro Koretsune, M.D., Joshua Betcher, Ph.D., Minggao Shi, Ph.D.,
Laura T. Grip, A.B., Shirali P. Patel, B.S., Indravadan Patel, M.D.,
James J. Hanyok, Pharm.D., Michele Mercuri, M.D., and Elliott M. Antman, M.D.,
for the ENGAGE AF-TIMI 48 Investigators*

CrCl ≥ 30

ESTABLISHED IN 1812 SEPTEMBER 15, 2011 VOL. 365 NO. 11

Apixaban versus Warfarin in Patients with Atrial Fibrillation

Christopher B. Granger, M.D., John H. Alexander, M.D., M.H.S., John J.V. McMurray, M.D., Renato D. Lopes, M.D., Ph.D.,
Elaine M. Hylek, M.D., M.P.H., Michael Hanna, M.D., Hussein R. Al-Khalidi, Ph.D., Jack Ansell, M.D., Dan Atar, M.D.,
Alvaro Avezum, M.D., Ph.D., M. Cecilia Bahit, M.D., Rafael Diaz, M.D., J. Donald Easton, M.D.,
Justin A. Ezekowitz, M.B., B.Ch., Greg Flaker, M.D., David Garcia, M.D., Margarida Geraldes, Ph.D.,
Bernard J. Gersh, M.D., Sergey Golitsyn, M.D., Ph.D., Shinya Goto, M.D., Antonio G. Hermosillo, M.D.,
Stefan H. Hohnloser, M.D., John Horowitz, M.D., Puneet Mohan, M.D., Ph.D., Petr Jansky, M.D., Basil S. Lewis, M.D.,
Jose Luis Lopez-Sendon, M.D., Prem Pais, M.D., Alexander Parkhomenko, M.D., Freek W.A. Verheugt, M.D., Ph.D.,
Jun Zhu, M.D., and Lars Wallentin, M.D., Ph.D., for the ARISTOTLE Committees and Investigators*

Cr < 2.5, CrCl ≥ 25

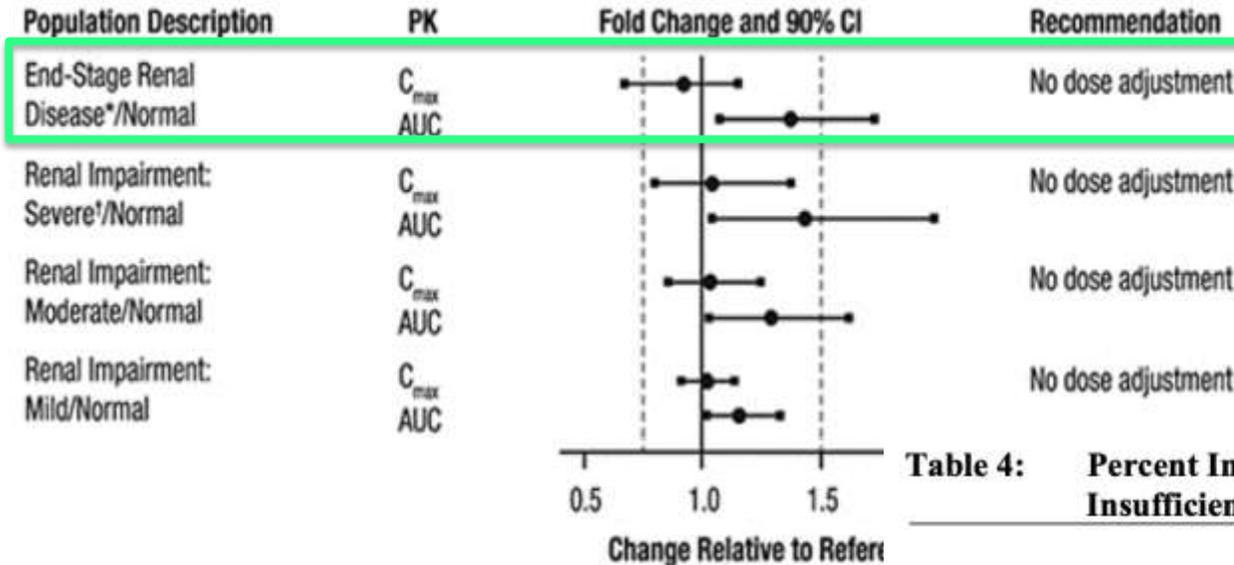
Stage of CKD	eGFR result	What it means
Stage 1	90 or higher	- Mild kidney damage - Kidneys work as well as normal
Stage 2	60-89	- Mild kidney damage - Kidneys still work well
Stage 3a	45-59	- Mild to moderate kidney damage - Kidneys don't work as well as they should
Stage 3b	30-44	- Moderate to severe damage - Kidneys don't work as well as they should
Stage 4	15-29	- Severe kidney damage - Kidneys are close to not working at all
Stage 5	less than 15	- Most severe kidney damage - Kidneys are very close to not working or have stopped working (failed)

Lack of robust evidence for benefit of DOAC

FDA Approval Based on Pharmacokinetics/Dynamics

Apixaban and Rivaroxaban

Apixaban: 2.5 bid if 2 of 3





Age
≥80 years



Body weight
≤60 kg



Creatinine ≥1.5 mg/dl
(133 μmol/l)

• OR have **severe renal impairment** (CrCl 15–29 mL/min) **alone**

Table 4: Percent Increase of Rivaroxaban PK and PD Parameters from Normal in Subjects with Renal Insufficiency from a Dedicated Renal Impairment Study

Parameter		Renal Impairment Class [CrCl (mL/min)]		
		Mild [50 to 79] N=8	Moderate [30 to 49] N=8	Severe [15 to 29] N=8
Exposure	AUC	44	52	64
(% increase relative to normal)	C_{max}	28	12	26
FXa Inhibition	AUC	50	86	100
(% increase relative to normal)	E_{max}	9	10	12
PT Prolongation	AUC	33	116	144
(% increase relative to normal)	E_{max}	4	17	20

PT = Prothrombin time; FXa = Coagulation factor Xa; AUC = Area under the concentration or effect curve; C_{max} = maximum concentration; E_{max} = maximum effect; and CrCl = creatinine clearance

Apixaban in End-Stage Renal Disease on Dialysis

- Data limited

Circulation

Volume 138, Issue 15, 9 October 2018; Pages 1519-1529

<https://doi-org.ezproxy.galter.northwestern.edu/10.1161/CIRCULATIONAHA.118.035418>

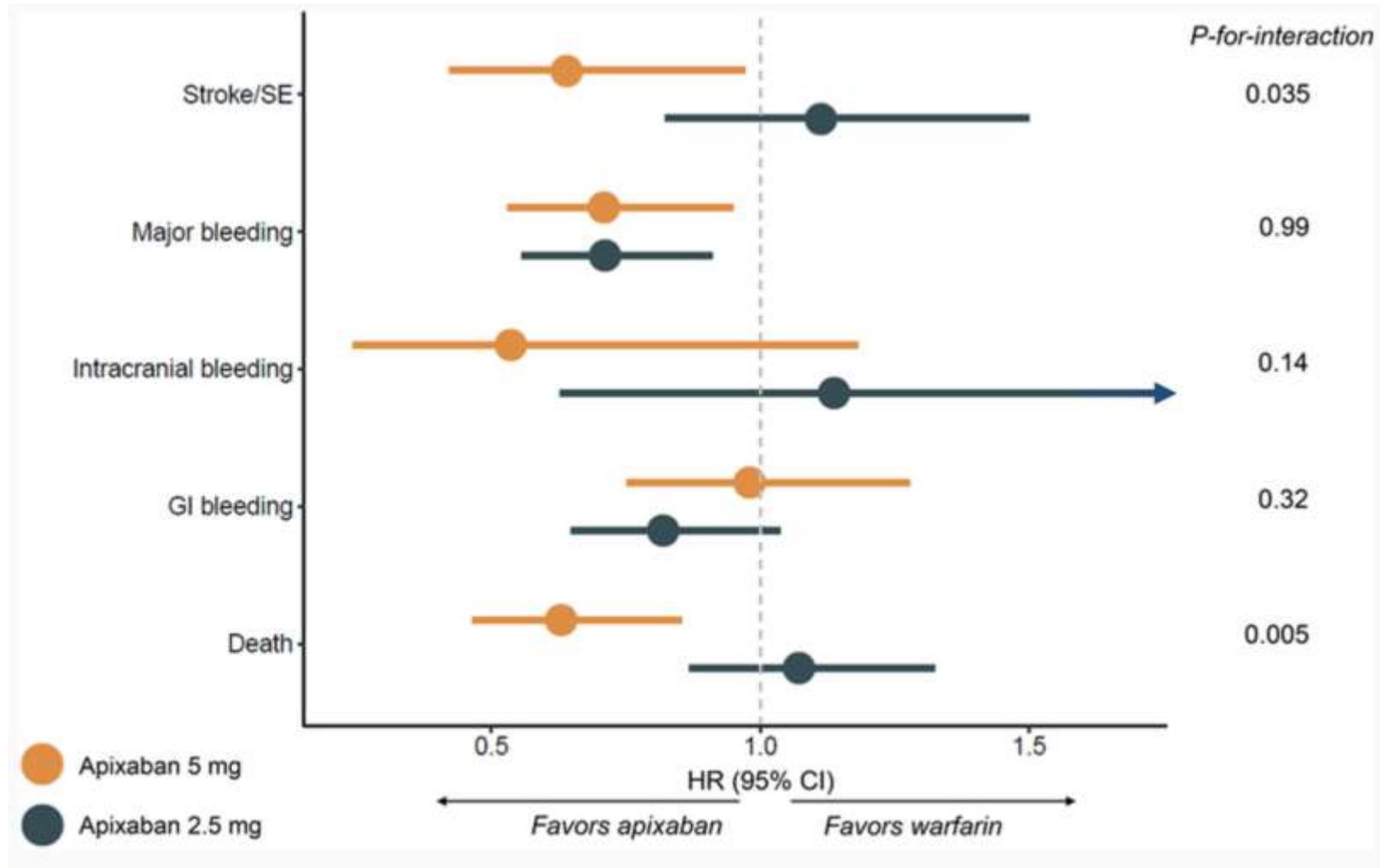


ORIGINAL RESEARCH ARTICLE

Outcomes Associated With Apixaban Use in Patients With End-Stage Kidney Disease and Atrial Fibrillation in the United States

- Retrospective Cohort Study
- Medicare Beneficiaries
- 25,000 patients
- 1:3 apixaban: warfarin use
 - Matched by propensity score
- Stroke or systemic embolism, major bleeding, gastrointestinal bleeding, intracranial bleeding, and death

Apixaban v Warfarin in ESRD



Apixaban v Warfarin

Prospective Randomized Controlled Trial

Circulation

Volume 146, Issue 23, 6 December 2022; Pages 1735-1745
<https://doi-org.ezproxy.galter.northwestern.edu/10.1161/CIRCULATIONAHA.121.054990>



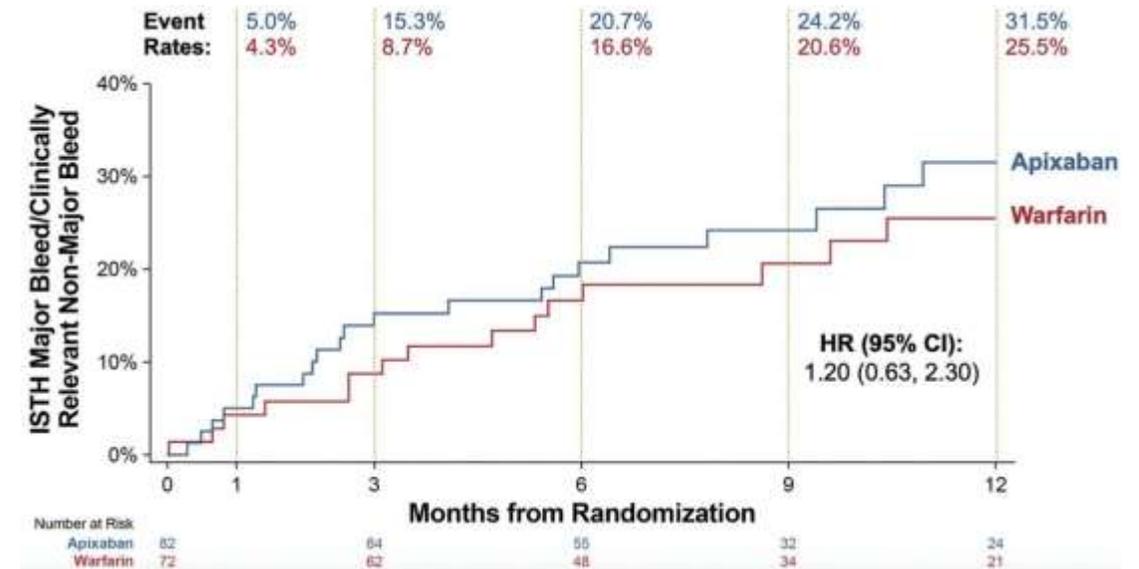
ORIGINAL RESEARCH ARTICLE

Apixaban for Patients With Atrial Fibrillation on Hemodialysis: A Multicenter Randomized Controlled Trial

Editorial, see p 1746

Sean D. Pokorney, MD, MBA , Glenn M. Chertow, MD, Husse Dianne Gallup, MS, Pat Dignacco, BA, Kurt Mussina, MBA, Nis Gadegbeku, MD, David A. Garcia, MD, Samira Garonzik, Pharm PhD , Kenneth W. Mahaffey, MD, Kelly Matsuda, PharmD, Jo Jennifer A. Rymer, MD, MBA , George H. Sands, MD, Ravi Thomas, MD , Jeffrey B. Washam, PharmD, Wolfgang C. Win Christopher B. Granger, MD , and on behalf of the RENAL-A

Stopped early, lack of enrollment



Secondary outcomes	Apixaban n=82	Warfarin n=72
Stroke, n (%)	2 (2)	2 (3)
Ischemic	1 (1)	2 (3)
Hemorrhagic	1 (1)	0 (0)
Systemic embolism, n (%)	0 (0)	0 (0)
Death, n (%)	21 (26)	13 (18)
Cardiovascular	9 (11)	4 (6)
Noncardiovascular	5 (6)	8 (11)
Undetermined	7 (9)	1 (1)
Major bleeding-related death*	1 (1)	2 (3)

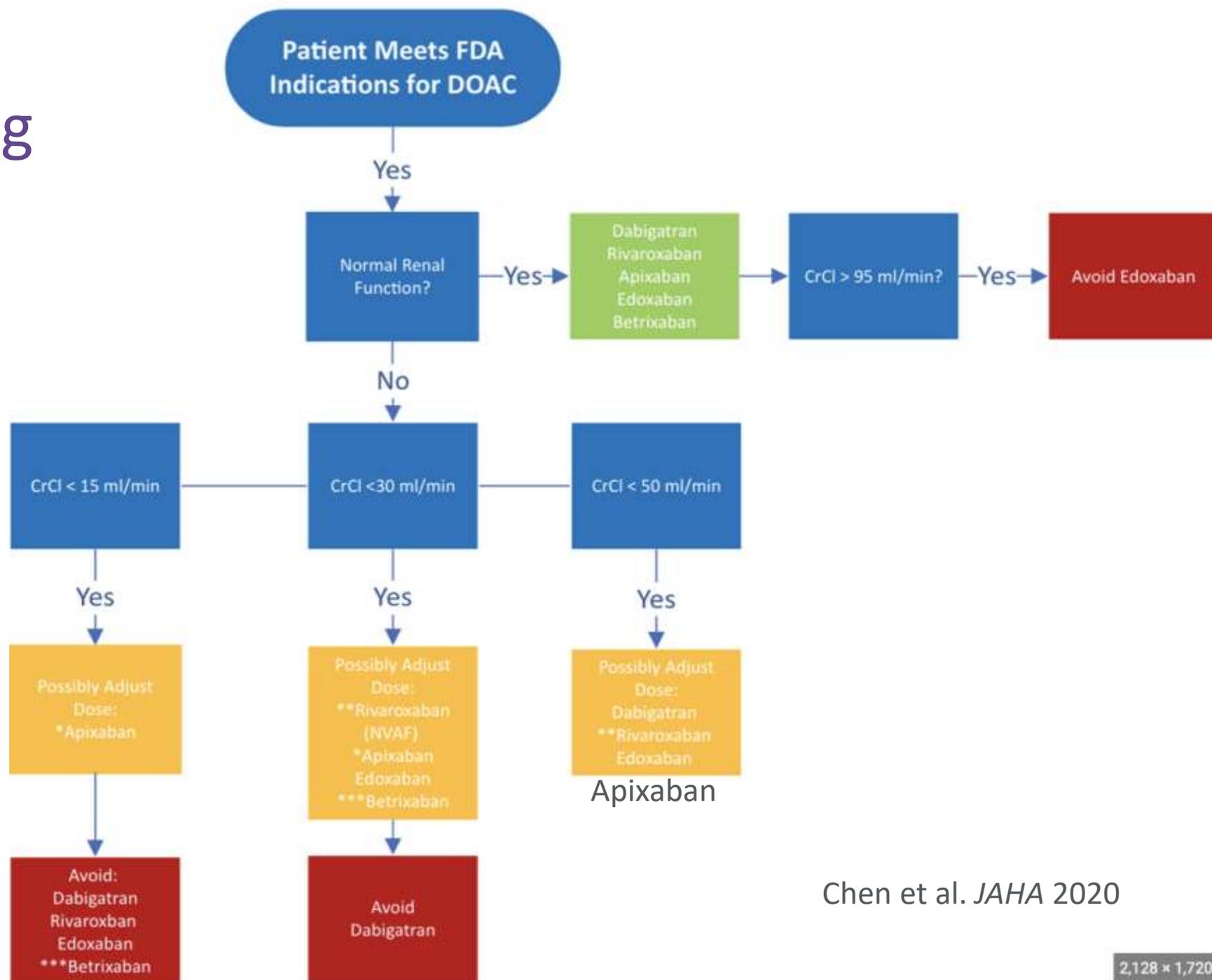
DOAC Dosing

Renal Dosing

% Renal Clearance

- Dabigatran 80%
- Edoxaban 50%
- Rivaroxaban 36%
- Apixaban 27%

ESRD: ?Apixaban 5 mg bid
?Warfarin



Chen et al. *JAHA* 2020

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VKA vs DOAC In Practice

Table 1

Baseline information on practice characteristics of respondents

Parameter	Variables	n (%)
Highest qualification	DM/MCh	29 (58)
	MD/MS	16 (32)
	Other post-MD fellowships	5 (10)
Type of practice	Private medical college	17 (34)
	Government medical college	10 (20)
	Private hospital >100 beds	16 (32)
	Private hospital <100 beds	3 (6)
	Private practice: Urban	3 (6)
	Private practice: Rural	1 (2)
Approximate patients in clinic per week	<30	6 (12)
	>30	44 (88)
Approximate patients on anticoagulation seen per week	2-5	33 (66)
	5 and above	17 (34)

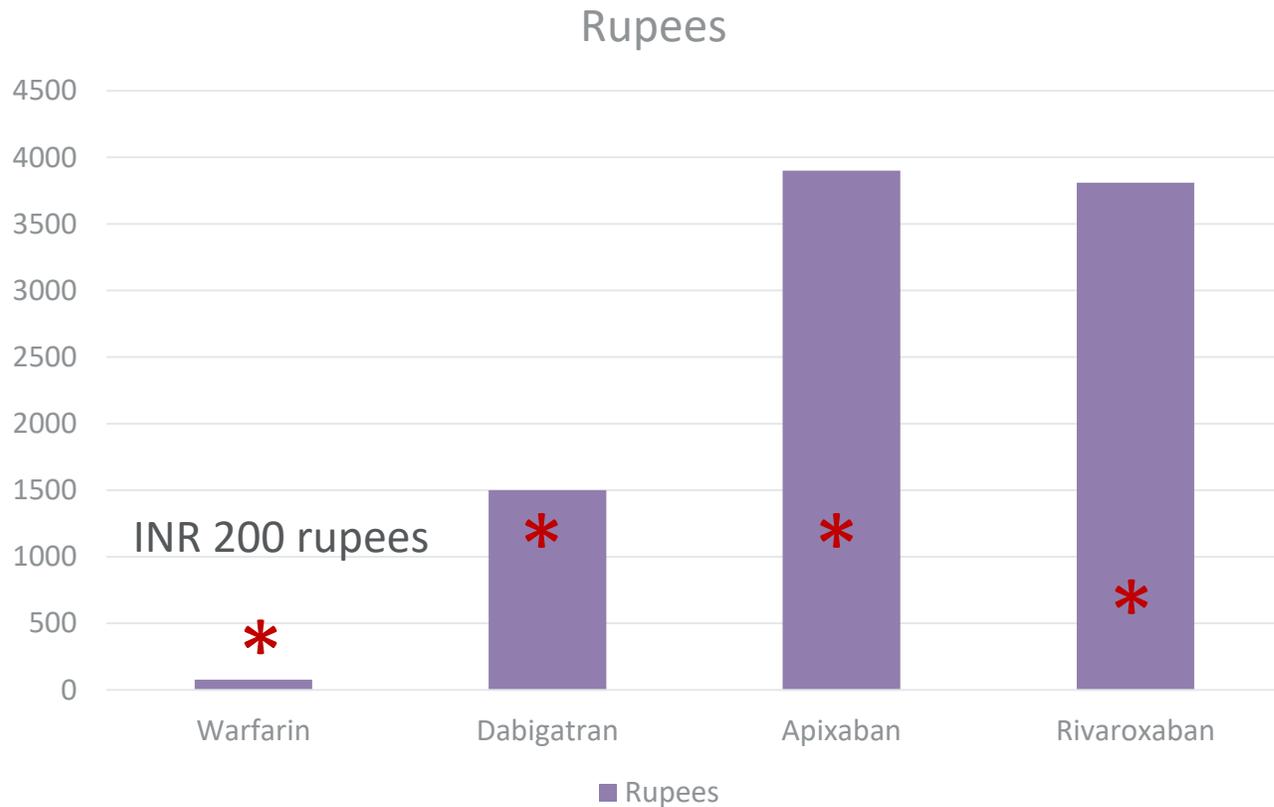
Table 2

Characteristics of clinical practice of anticoagulants

Parameter	Variables	n (%)
Newly started DOACs for any patient	Yes	42 (84)
	Dabigatran	24
	Rivaroxaban	11
	Apixaban	7
	No	8 (16)
If yes, indication	Post-DVT/PE	21 (50)
	Atrial fibrillation	16 (38)
	Primary DVT prophylaxis	6 (14)
Choice of agent for young patient with unprovoked DVT	VKA	23 (46)
	Dabigatran	11 (22)
	Rivaroxaban	9 (18)
	Apixaban	3 (6)
Regular PT/INR asked at each visit on VKAs	Yes	44 (88)
	No	6 (12)
	None	12 (24)
Patients missing INR tests when instructed	Up to 1/3 rd	23 (46)
	1/3 rd -2/3 rd	10 (20)
	>2/3 rd or most patients	4 (8)

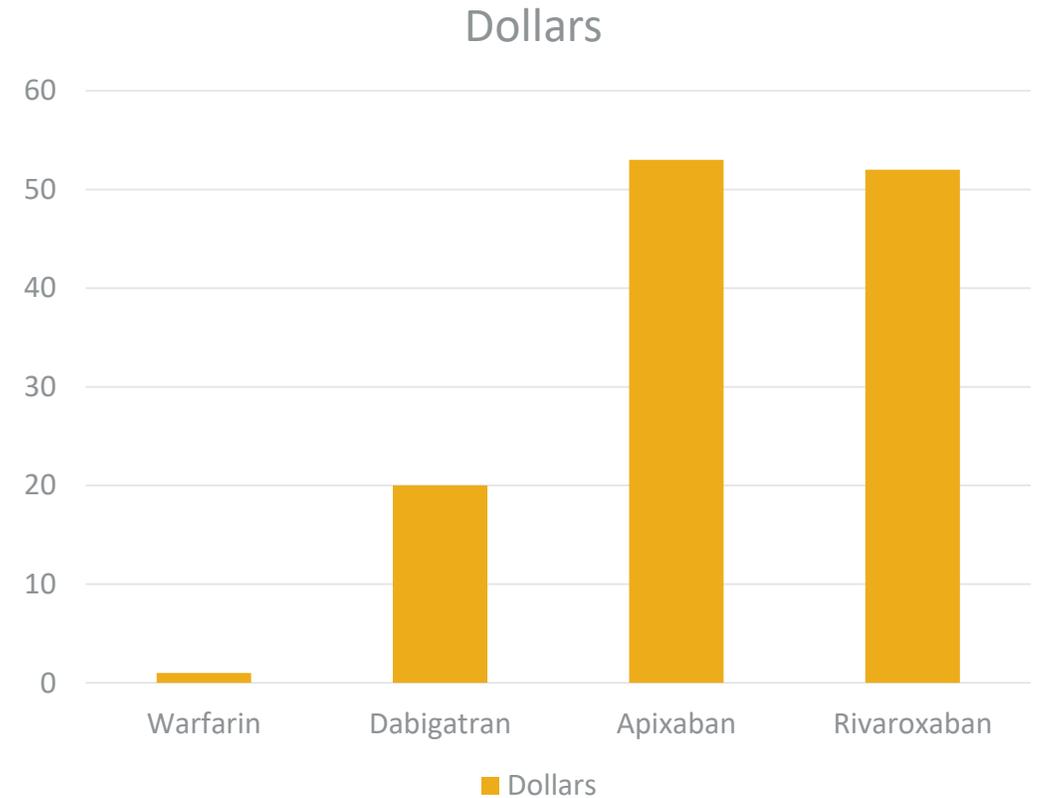
Cost

Monthly Cost of Anticoagulation in India as of January 2021



INR 200 rupees

Net National Income per Month 2021: 10,000 Rupees



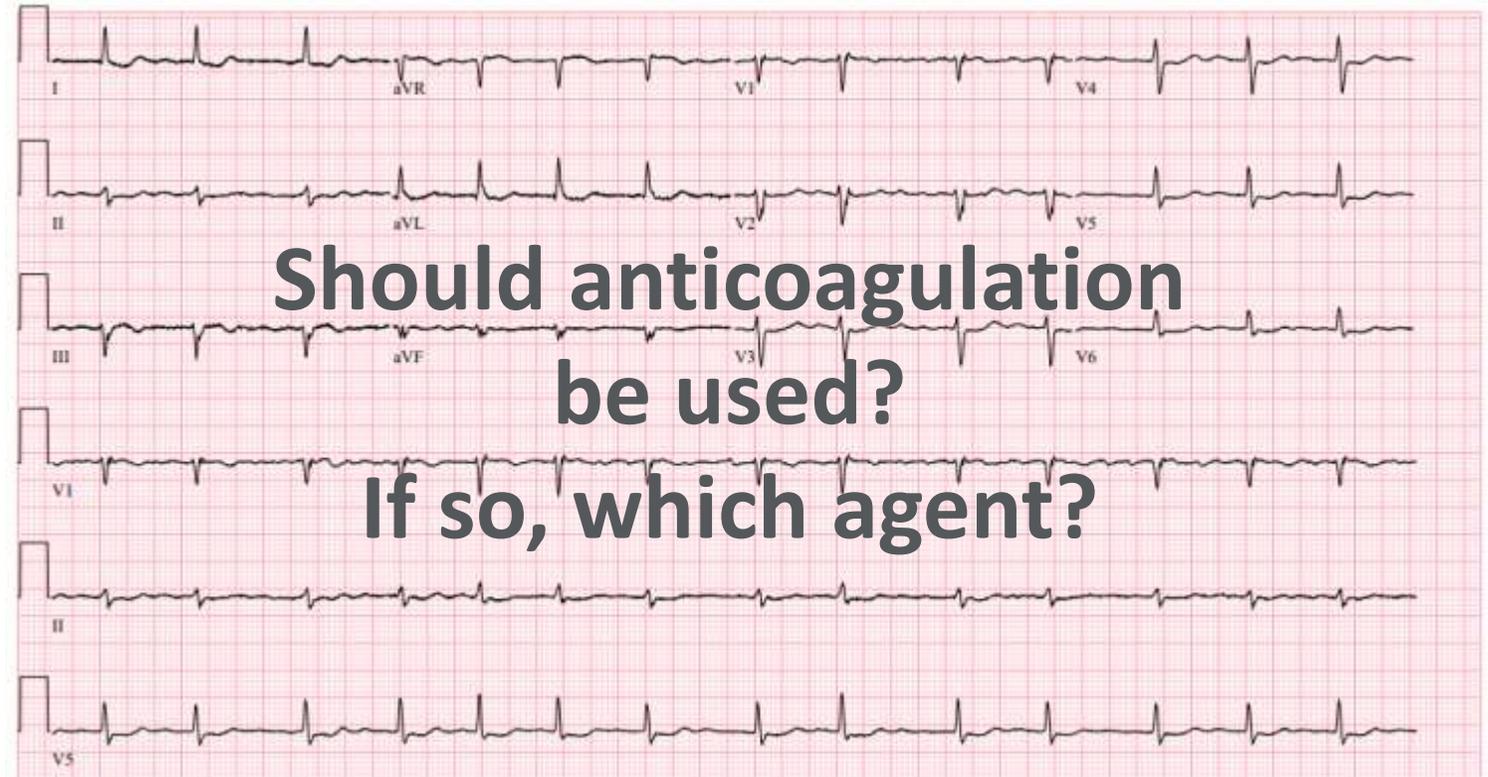
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Case

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 - No valvular heart disease
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 - Annual Stroke Risk 4.8%
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Case

Cardiol Ther (2022) 11:49–79
<https://doi.org/10.1007/s40119-022-00254-w>

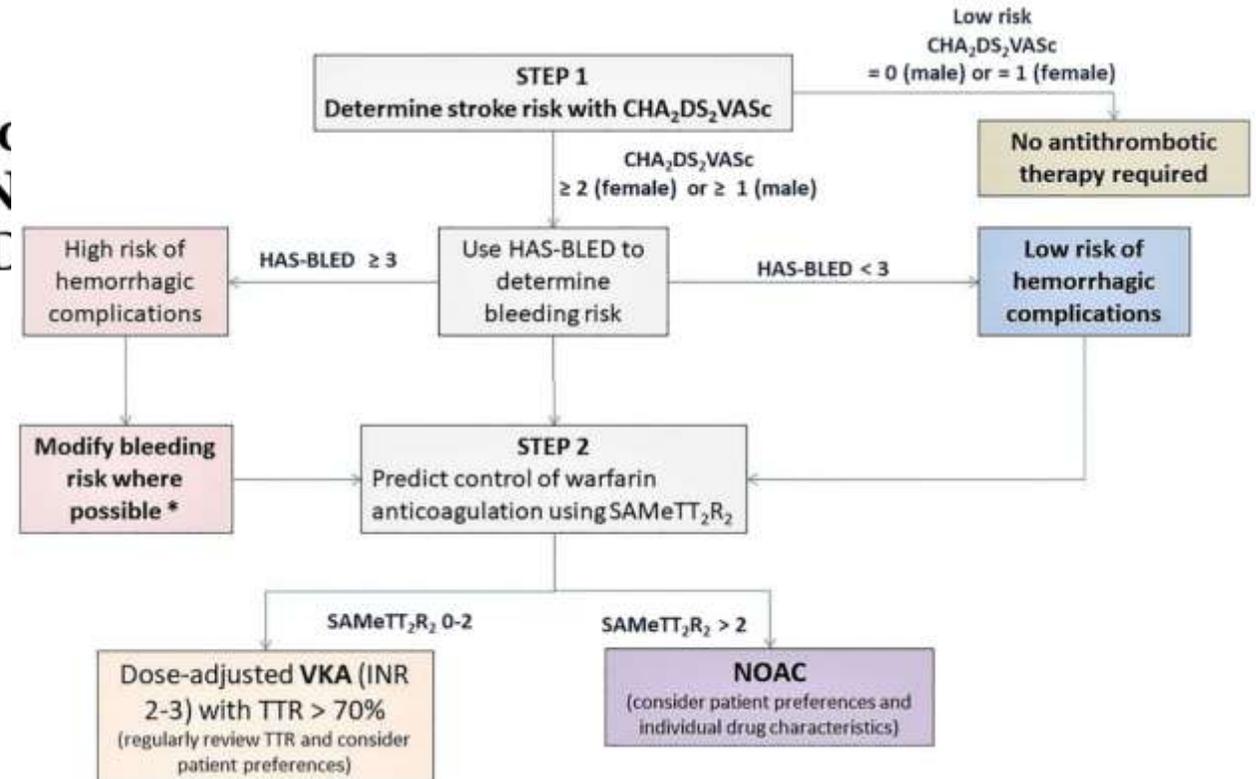


REVIEW

Expert Recommendations on the Usage of Non-vitamin K Antagonist Oral Anticoagulants (NOACs) from India: Current Perspective and Future I

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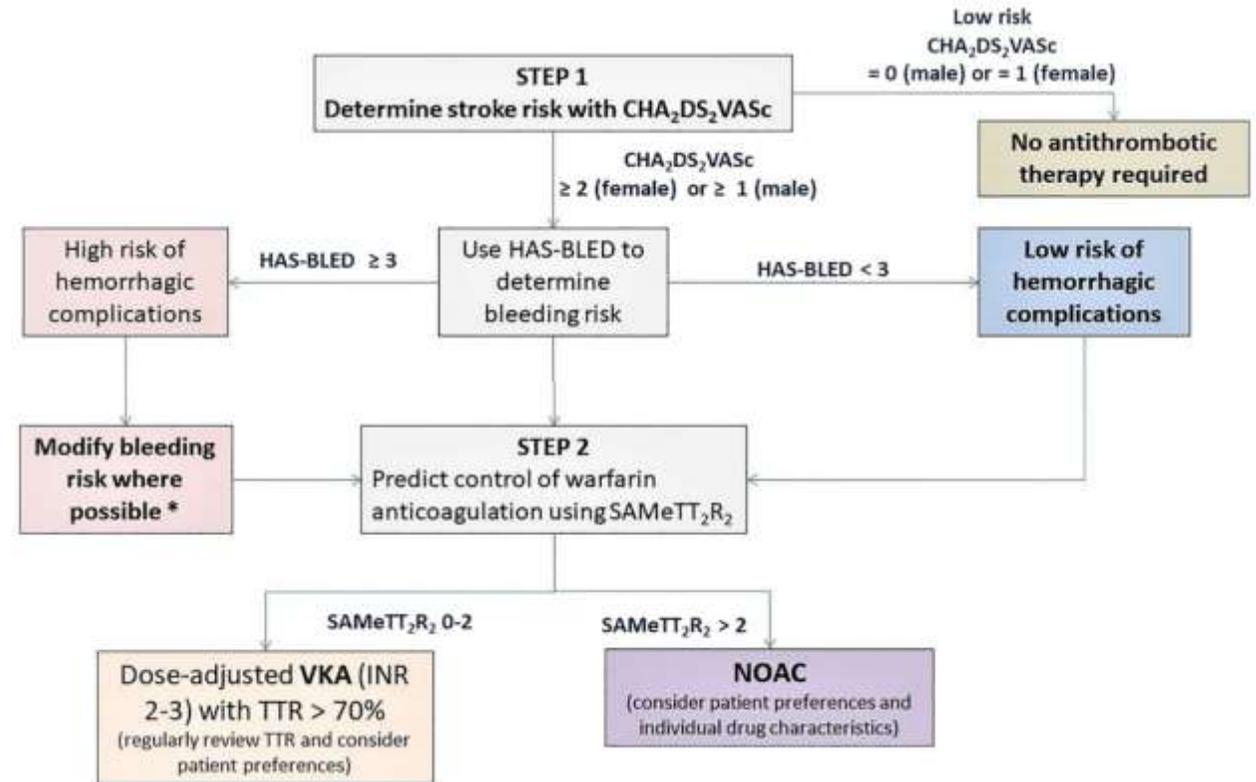


Case

- $CHA_2DS_2-VASc = 4$ (age, HTN, DM)
- $HAS-BLED = 2$ (age, HTN)
- $SAMeTT_2R_2 > 2$

Sex (female)	1
Age (less than 60)	1
Medical history (> 2 comorbidities)	1
Treatment strategy (rhythm control)	1
Tobacco use	2
Race (non-white)	2

- NOAC
 - Or VKA with close monitoring

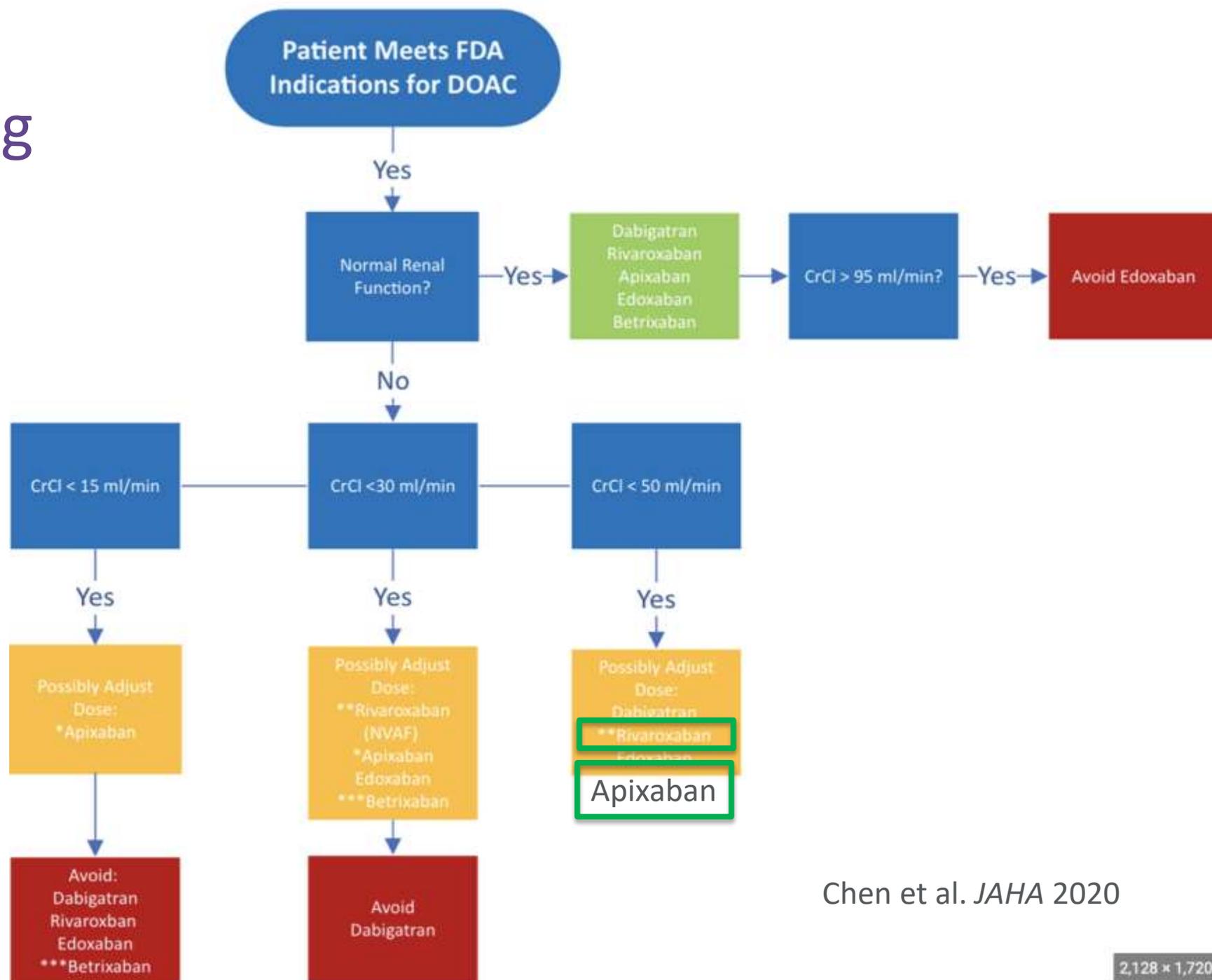


DOAC Dosing

Renal Dosing

% Renal Clearance

- Dabigatran 80%
- Edoxaban 50%
- Rivaroxaban 36%
- Apixaban 27%



Chen et al. *JAHA* 2020

Conclusions

- Age
 - Advanced age still benefit from anticoagulation
 - Lower ICH risk with DOAC
- Obesity
 - Despite lower C_{max}, AUC, clinical effect of DOAC similar to normal BMI
- Renal dysfunction
 - Do not avoid
 - Choose dose properly (avoid over- and under-dosing)
- Cost
 - As generics drop costs, consider DOACs

Thank you