

# What does protection mean for NVAF Patients with Diabetes and Renal Impairment ?

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# Disclosures

- I have the Relationships with commercial interests from Bayer pharmaceutical company
- This learning activity has received in-kind support from Bayer pharmaceutical pharma in the form of logistical & financial support.

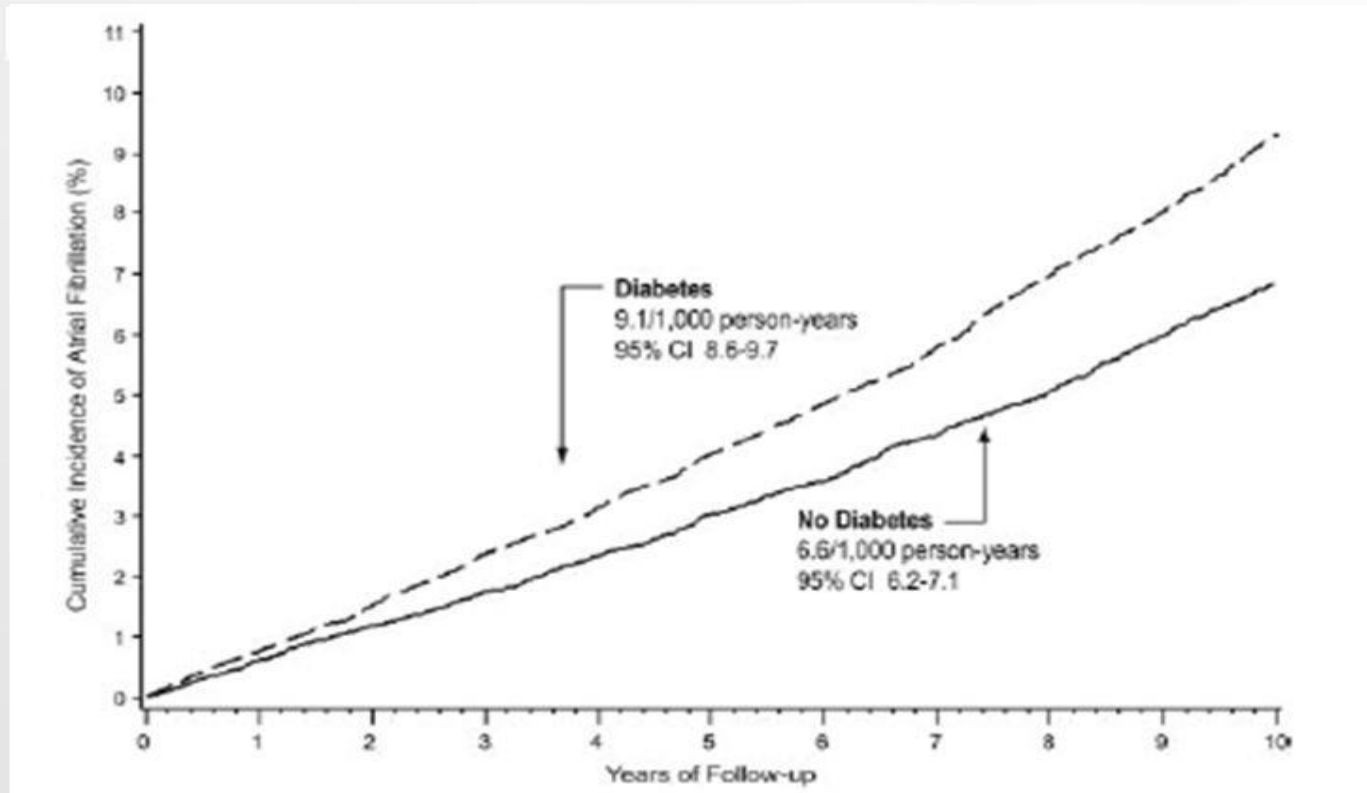
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The association of comorbidities in AF patients with increased adverse outcomes is expected.

**Quantifying** the incremental risk is an important contribution to our clinical knowledge of the effects of multimorbidity

# Diabetes and Atrial Fibrillation

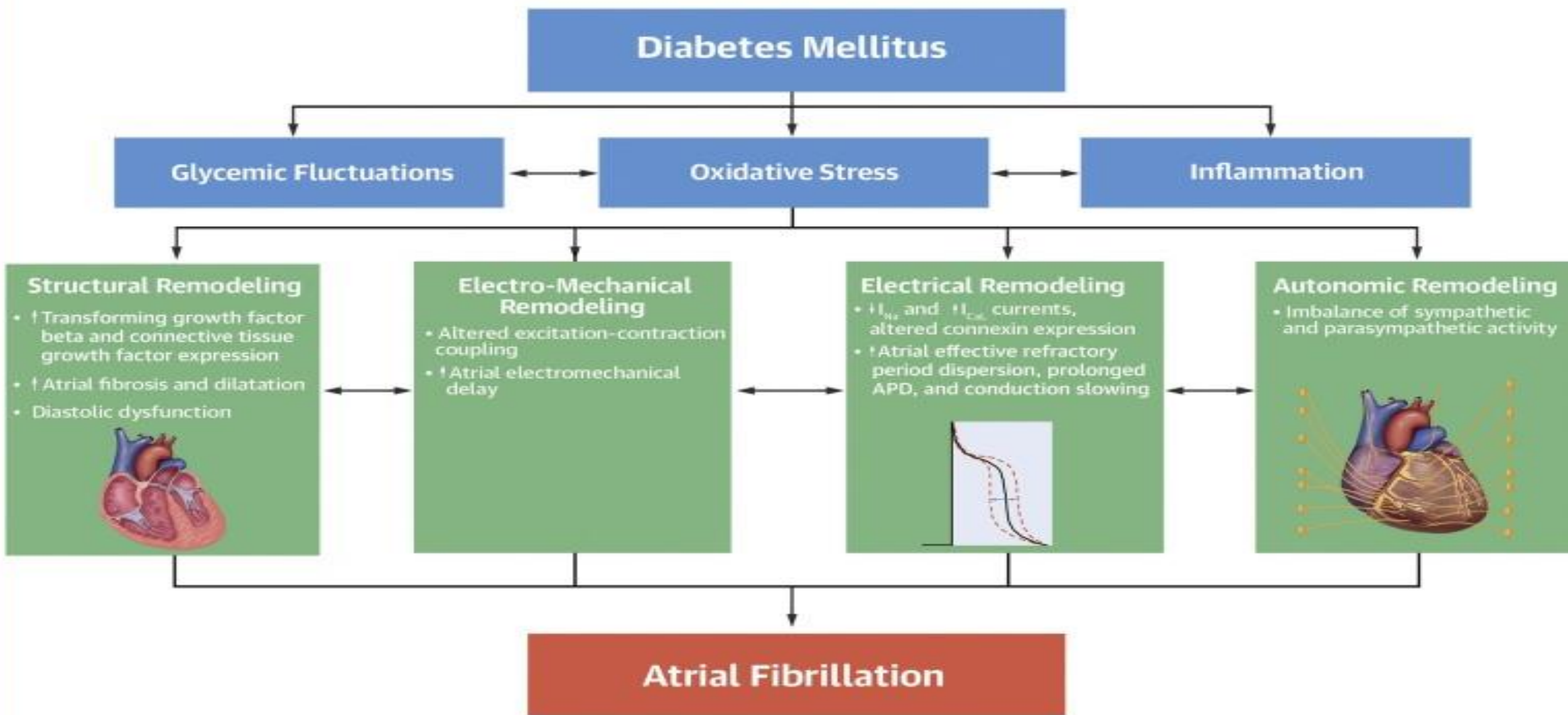
## Incidence of new onset AF

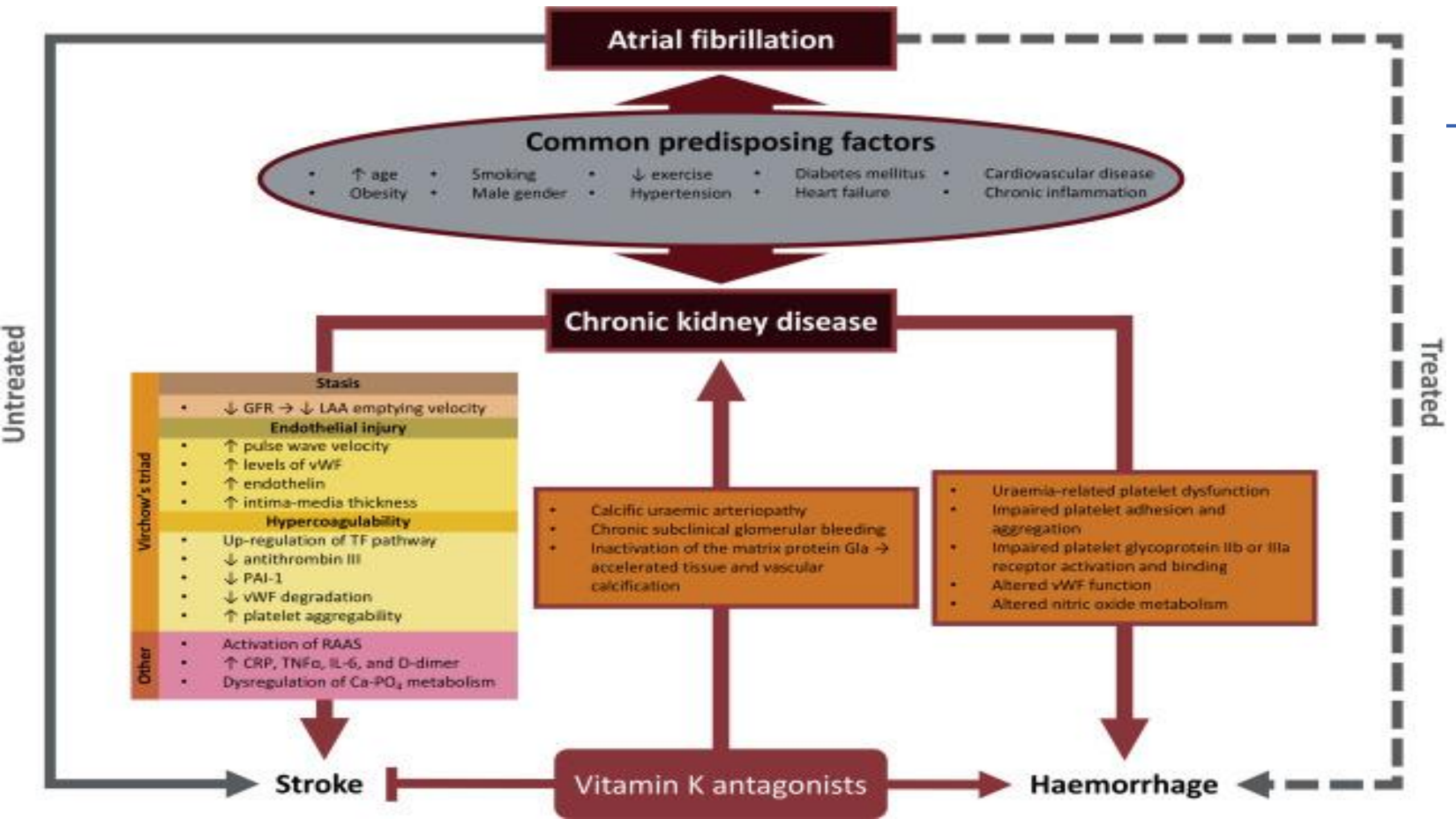


- AF is 44% more prevalent in DM
- AF is 38% more likely to develop in DM
- DM is a highly significant independent predictor of AF in women

AF = Atrial fibrillation  
DM = Diabetes mellitus

# CENTRAL ILLUSTRATION: Pathophysiology of Diabetes and Atrial Fibrillation







# How can Mr. A. be protected?

## Mr. A.

76 years old

- ◆ Non-valvular atrial fibrillation
- ◆ Diabetes
- ◆ Moderate renal impairment (46 ml/min)



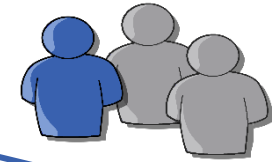
“

*My friend had a stroke and he needs a caretaker each day. He ended up on dialysis and I'm really scared that could happen to me too.*

*I want to do everything I can so that my future doesn't end up the same way.*

”

Kidney disease occurs in around **1 in 3 patients** with type 2 diabetes<sup>1</sup>



Diabetes is a major cause of kidney failure requiring dialysis<sup>2</sup>

Patients with chronic kidney disease and diabetes are **more likely** to die from CV causes than those without diabetes<sup>3</sup>

Risk of stroke due to atrial fibrillation **increases with age**<sup>4</sup>

50–59 years:	1.5%
70–79 years:	9.9%
80–89 years:	23.5%

# The CHA<sub>2</sub>DS<sub>2</sub>-VASc score of this patient

## CHA<sub>2</sub>DS<sub>2</sub>-VASc<sup>1</sup>

	Risk Factors <sup>2</sup>	Points
C	Congestive heart failure/LV dysfunction	1
H	<b>Hypertension</b>	1
A <sub>2</sub>	Age ≥75 years	2
D	Diabetes mellitus	1
S <sub>2</sub>	Stroke/TIA/thromboembolism	2
V	Vascular disease <sup>a</sup>	1
A	<b>Age 65 to 74 years</b>	1
Sc	<b>Sex category (female)</b>	1
<b>Maximum score</b>		<b>9</b>

**CHA<sub>2</sub>DS<sub>2</sub>-VASc = 3**

LV: left ventricular; TIA: transient ischemic attack; INR: international normalized ratio

<sup>a</sup> Vascular disease includes myocardial infarction, complex aortic plaque, and peripheral artery disease

1. Camm et al. *Europace*. 2012;14:1385–1413.

2. Lip et al. *CHEST*. 2010;137:263–272.



# CHA<sub>2</sub>DS<sub>2</sub>-VASc-Score and Stroke Risk in Patients With AF

Risk factor	Points		CHA <sub>2</sub> DS <sub>2</sub> -VASc	Stroke rate %/year
Prior stroke/TIA or systemic embolism	2	Add points together →	9	23.64
Age ≥75 years	2		8	22.38
Congestive heart failure*	1		7	21.50
Hypertension	1		6	19.74
Diabetes mellitus	1		5	15.26
Age 65–74 years	1		4	9.27
Female gender	1		3	5.92
Vascular disease	1		2	3.71
			1	2.01
			0	0.78

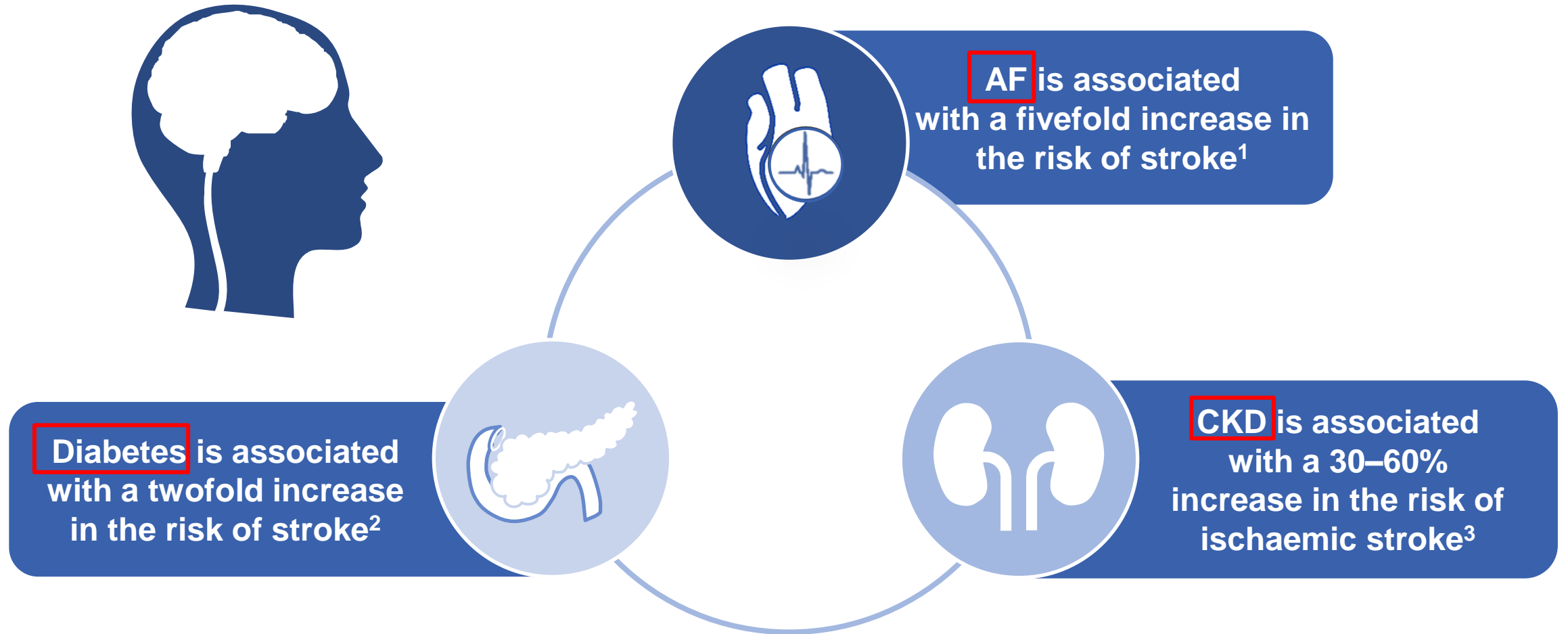
\*Or moderate-to-severe left ventricular systolic dysfunction (left ventricular ejection fraction ≤40%).

# HAS-BLED Bleeding Risk Score

Clinical characteristic	Points
Hypertension (systolic BP >160 mm Hg)	1
Abnormal renal or liver function	1 + 1
Stroke	1
Bleeding	1
Labile INRs	1
Elderly (age >65 years)	1
Drugs or alcohol	1 + 1
<b>Cumulative score</b>	<b>Range 0–9</b>

**HASBLED = 2**

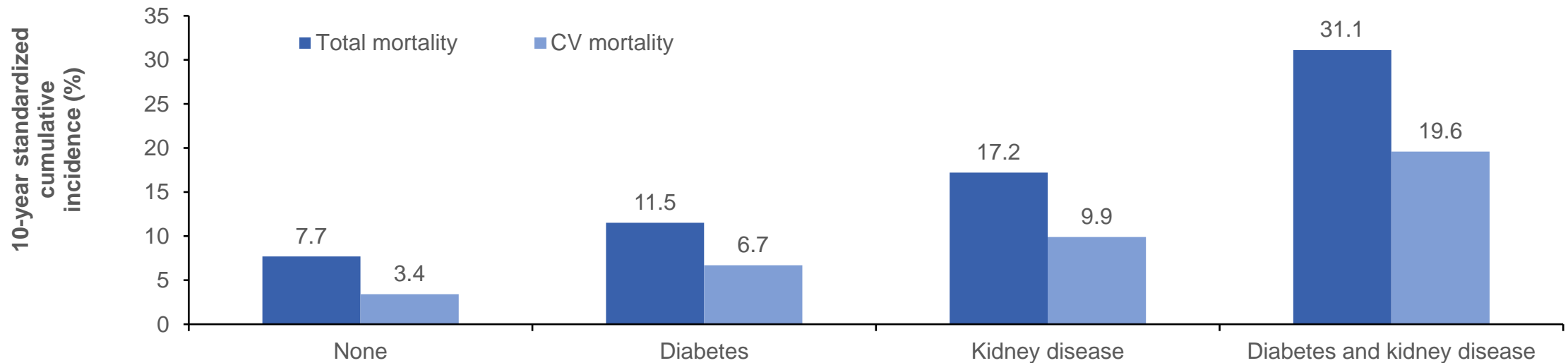
# Diabetes, AF and Kidney Disease Are All Risk Factors for Stroke



# Diabetes, Cardiovascular Risk and Renal Function are Closely Interlinked

- ◆ Diabetes is one of the leading causes of CKD, which in itself increases the risk of stroke and bleeding in patients with AF<sup>1-3</sup>
- ◆ Patients with type II diabetes and kidney disease have increased risk of mortality and CV death<sup>4</sup>

Cohort of 15,762 individuals with  $\geq 20$  years in the Third National Health and Nutrition Examination Survey



1. Jha V *et al*, *Lancet* 2013;382:20–26; 2. Tonelli M *et al*, *Am Soc Nephrol* 2006;17:2034–2047; 3. Olesen JB *et al*, *N Engl J Med* 2012;36:625–635; 4. Afkarian M *et al*, *J Am Soc Nephrol* 2013;24:302–308

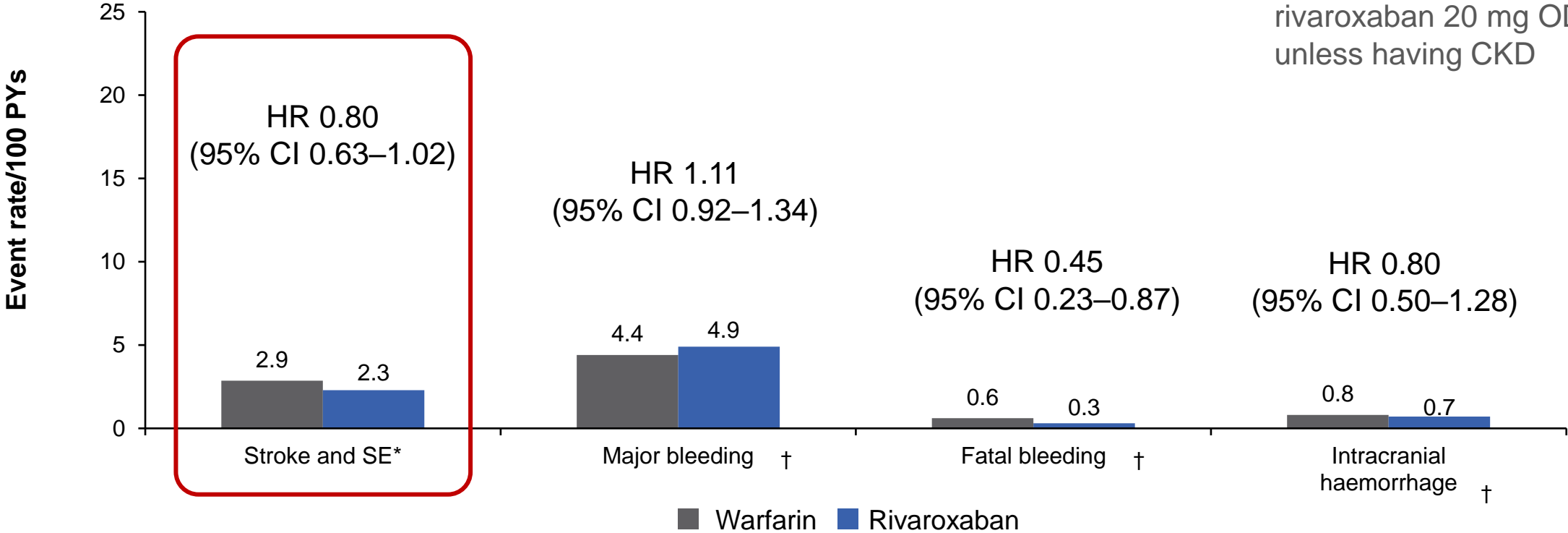
# Age-related risk of stroke

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# Protection for Amin means effective prevention of stroke

## ROCKET AF: Patients $\geq 75$ years

Patients were on rivaroxaban 20 mg OD unless having CKD

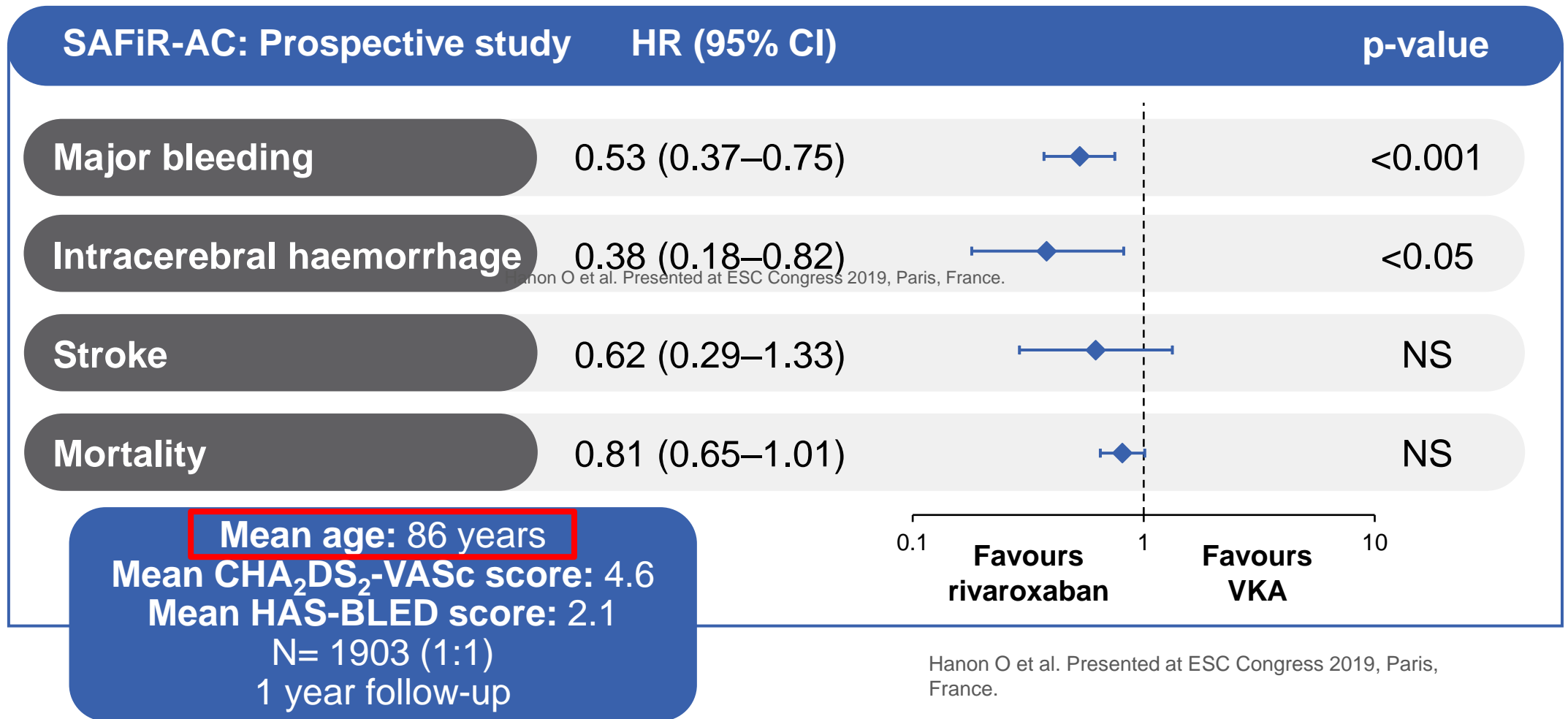


Primary safety endpoint: Major bleeding and clinically relevant non-major bleeding.

\*Primary efficacy endpoint. ITT population; †Safety population.



# Safety means always viewing Mr. A's bleeding risk alongside the importance of stroke prevention



Hanon O et al. Presented at ESC Congress 2019, Paris, France.

Hanon O et al. Presented at ESC Congress 2019, Paris, France.

Data shown are model 1: adjusted for age, sex, eGFR and Charlson index (n=22 variables).

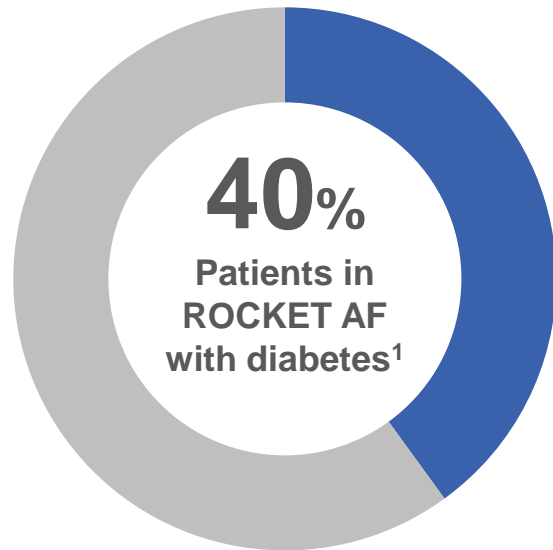
Hanon O et al. Presented at ESC Congress 2019, Paris, France.

Actual fears of Mr. A.

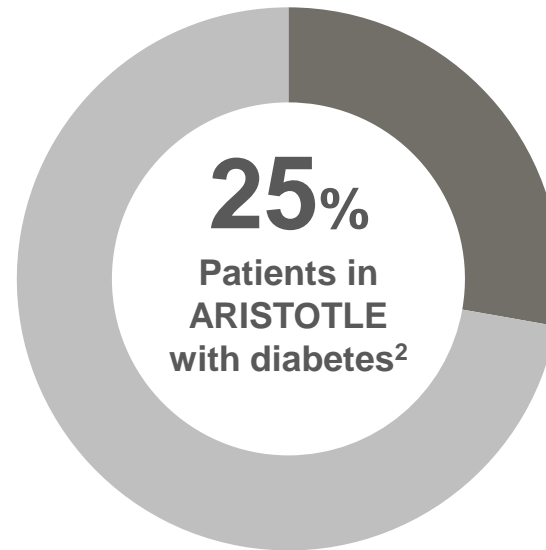


Can Mr. A.'s life be protected in addition to stroke prevention?

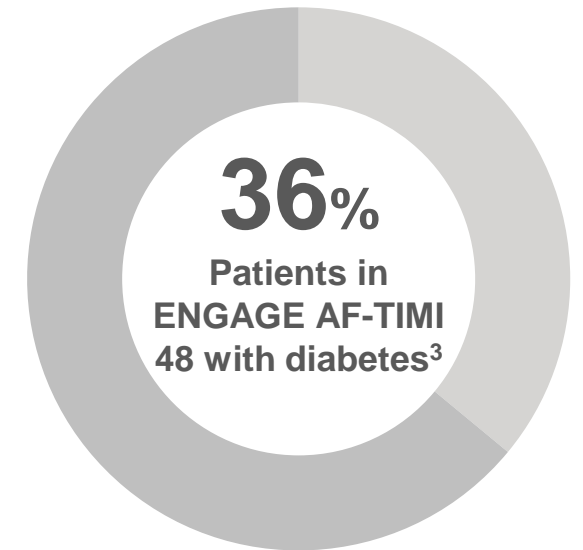
# ROCKET AF Included a Larger Proportion of Patients with Co-morbid Diabetes, Who Are at Increased Risk of Stroke, than Other Phase III NOAC Trials<sup>1-4</sup>



**N=14,264**



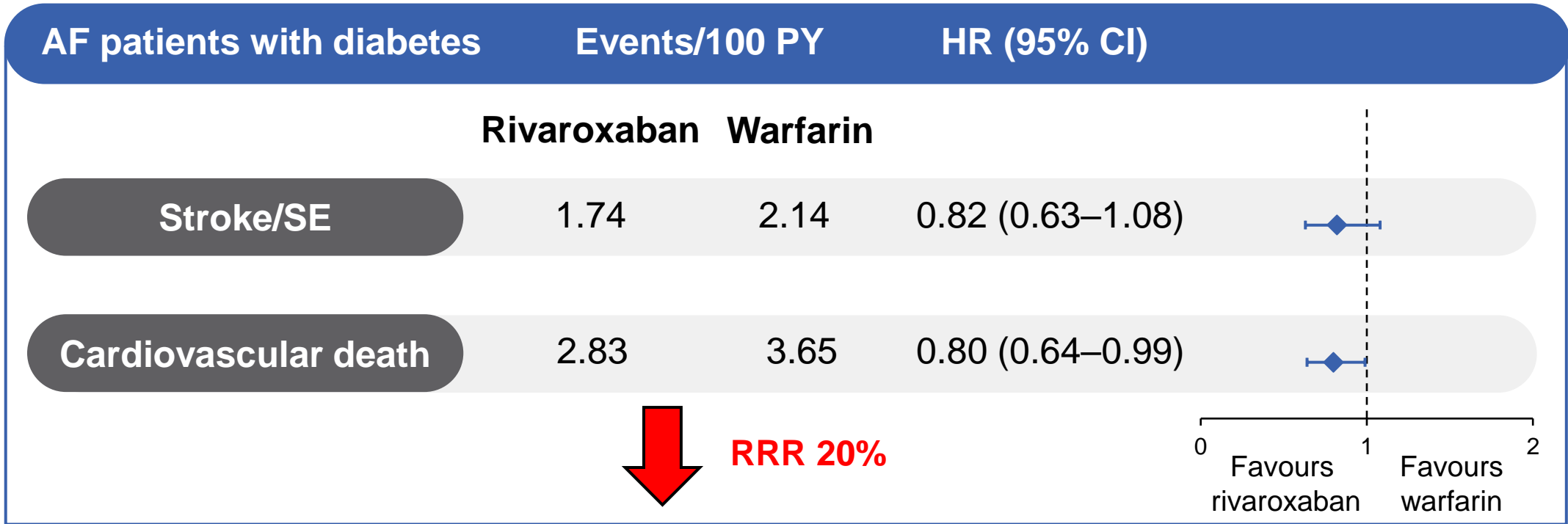
**N=18,201**



**N=21,105**

# Protecting Mr. A. requires consideration of CV death as well as stroke

## ROCKET AF



ROCKET AF subanalysis; 40% of patients in ROCKET AF had diabetes.

Bansilal et al. *Am Heart J* 2015;170:675–682.e8.

# C: Comorbidities/ Cardiovascular Risk Factor Management

Management of risk factors and CV disease complements stroke prevention and reduces AF burden and symptom severity

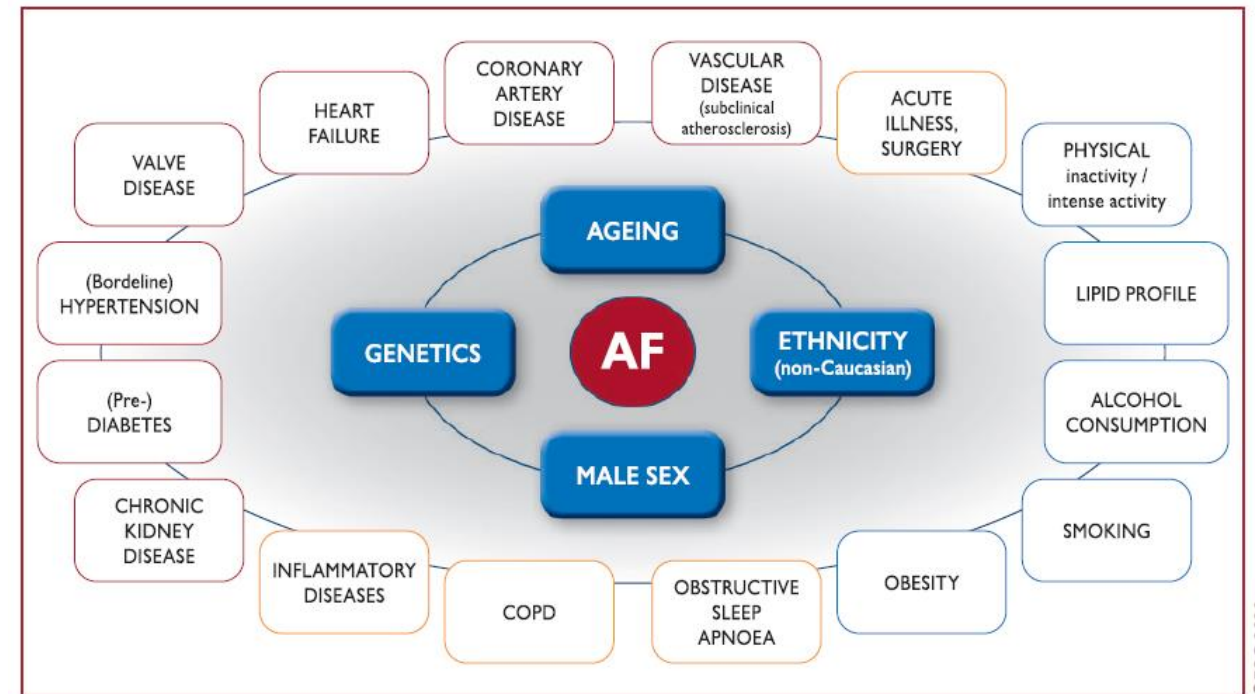
- ◆ *Bleeding risk reduction with NOACs was similar in diabetic and non-diabetic patients except for apixaban, where a lower reduction in haemorrhagic complications was reported in the AF patients with diabetes compared with AF patients without diabetes.*

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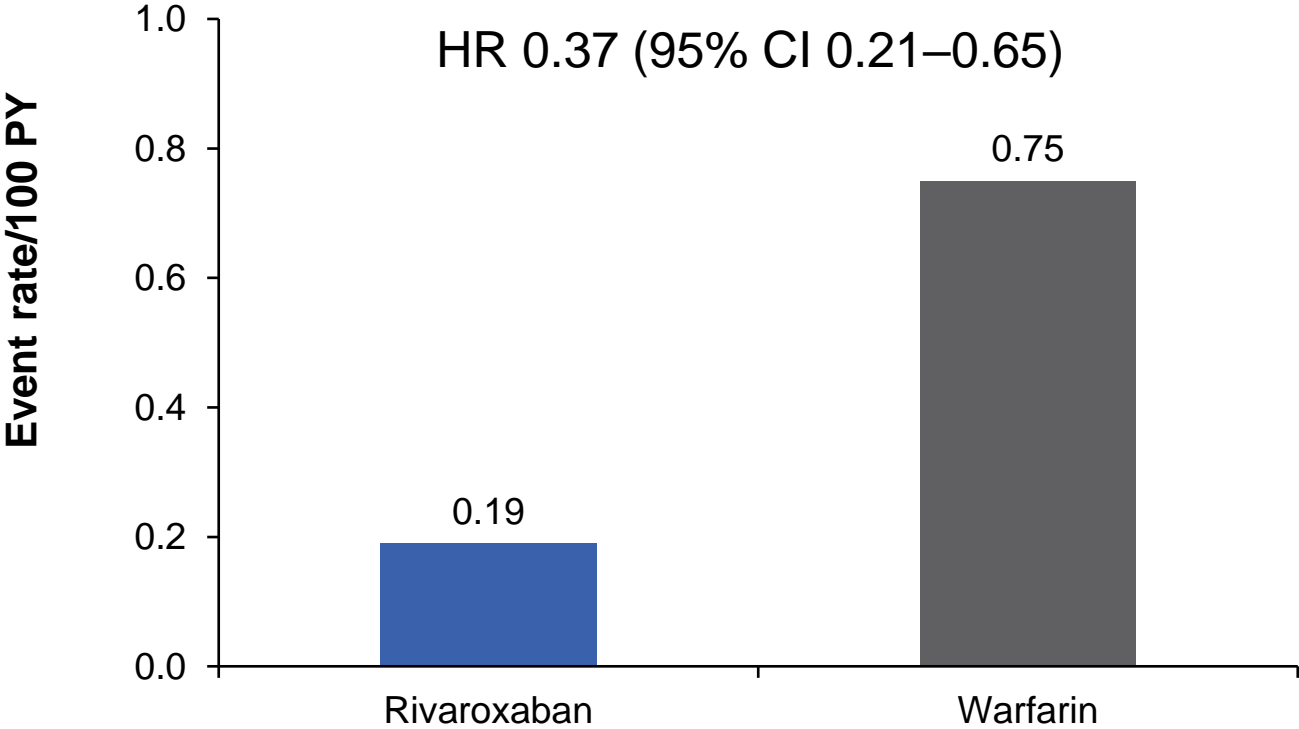


Can we protect Mr. A's limbs from being amputated?

# Mr. A's fears becoming one of the many people whose diabetes leads to limb amputation

Patients with diabetes fear amputation almost as much as blindness or death<sup>1</sup>

## Major adverse limb events in AF patients with diabetes<sup>2</sup>



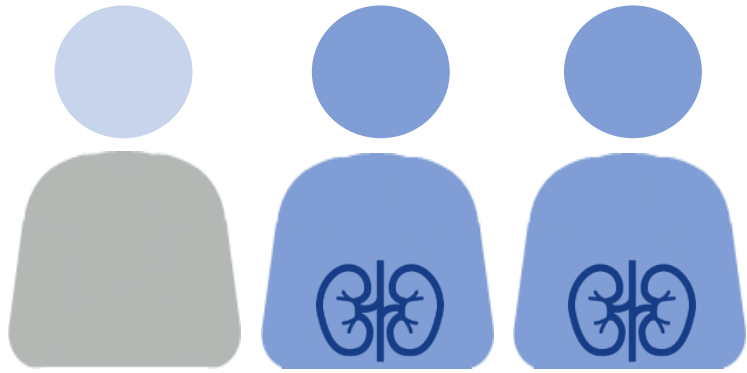
MarketScan claims data in patients with atrial fibrillation and diabetes; 24% of patients in the rivaroxaban arm were on a reduced dose of 15 mg OD.

1. Wukich DK et al. *Foot Ankle Spec* 2018;11:17-21; 2. Baker WL et al. *Diabetes Obes Metab* 2019;21:2107-2114.

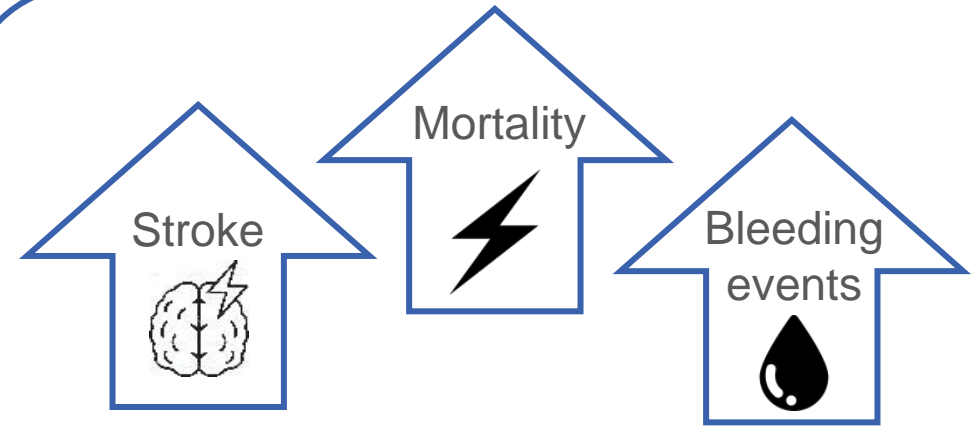
What are the biggest challenges in managing AF renally impaired patients?

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# Among Patients with NVAF, Renal Dysfunction Is Common and Increases Progressively with Age



64% of patients with NVAF have **renal impairment**<sup>1,2</sup>

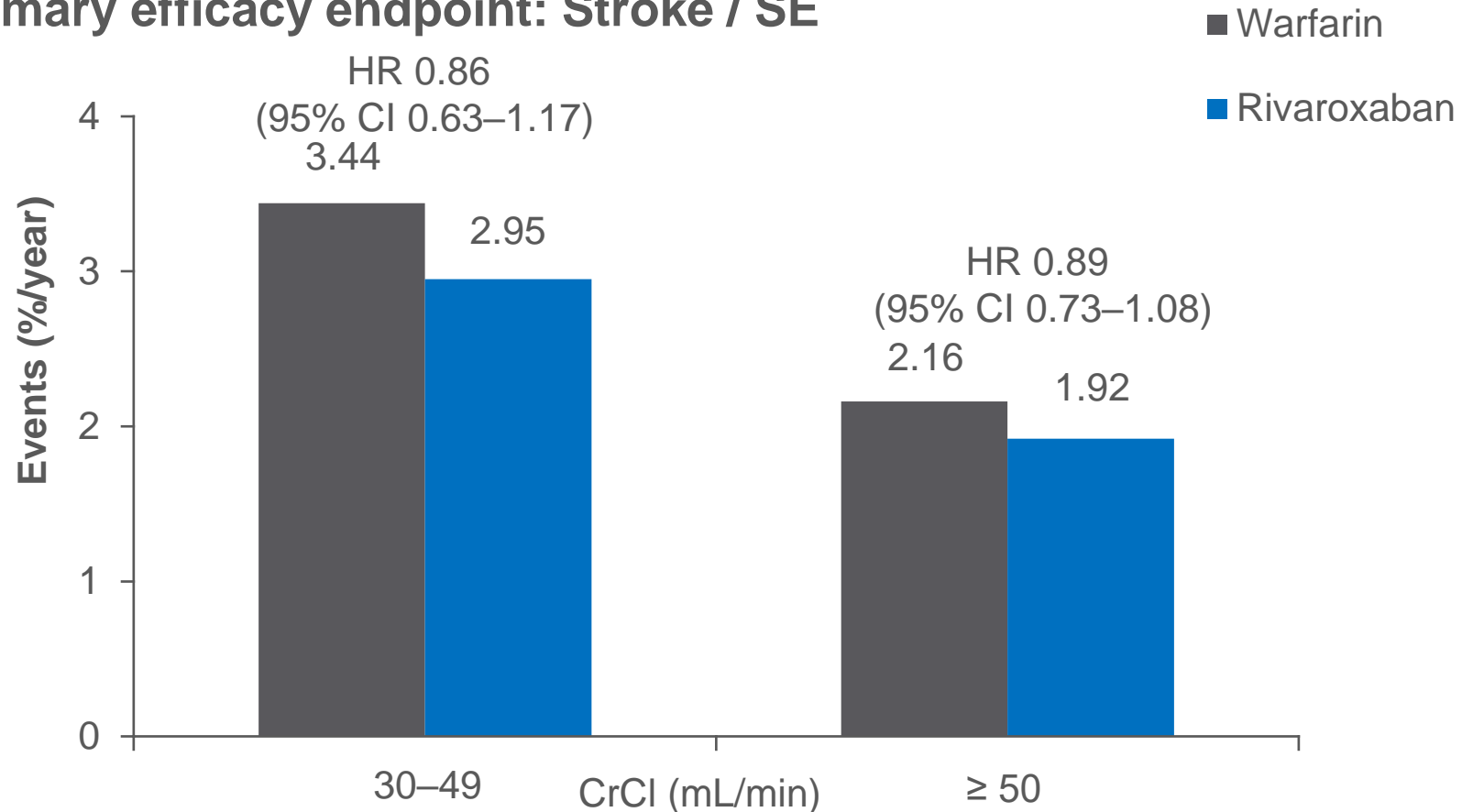


**Renal impairment** increases the risk of stroke, bleeding events and mortality in patients with NVAF<sup>2,3</sup>

Furthermore, in some warfarin-treated patients with AF, accelerated chronic kidney disease progression and acute kidney injury can occur in association with excessive anticoagulation<sup>4,5</sup>

# ROCKET AF: Primary Efficacy Endpoint in Patients with Moderate Renal Impairment

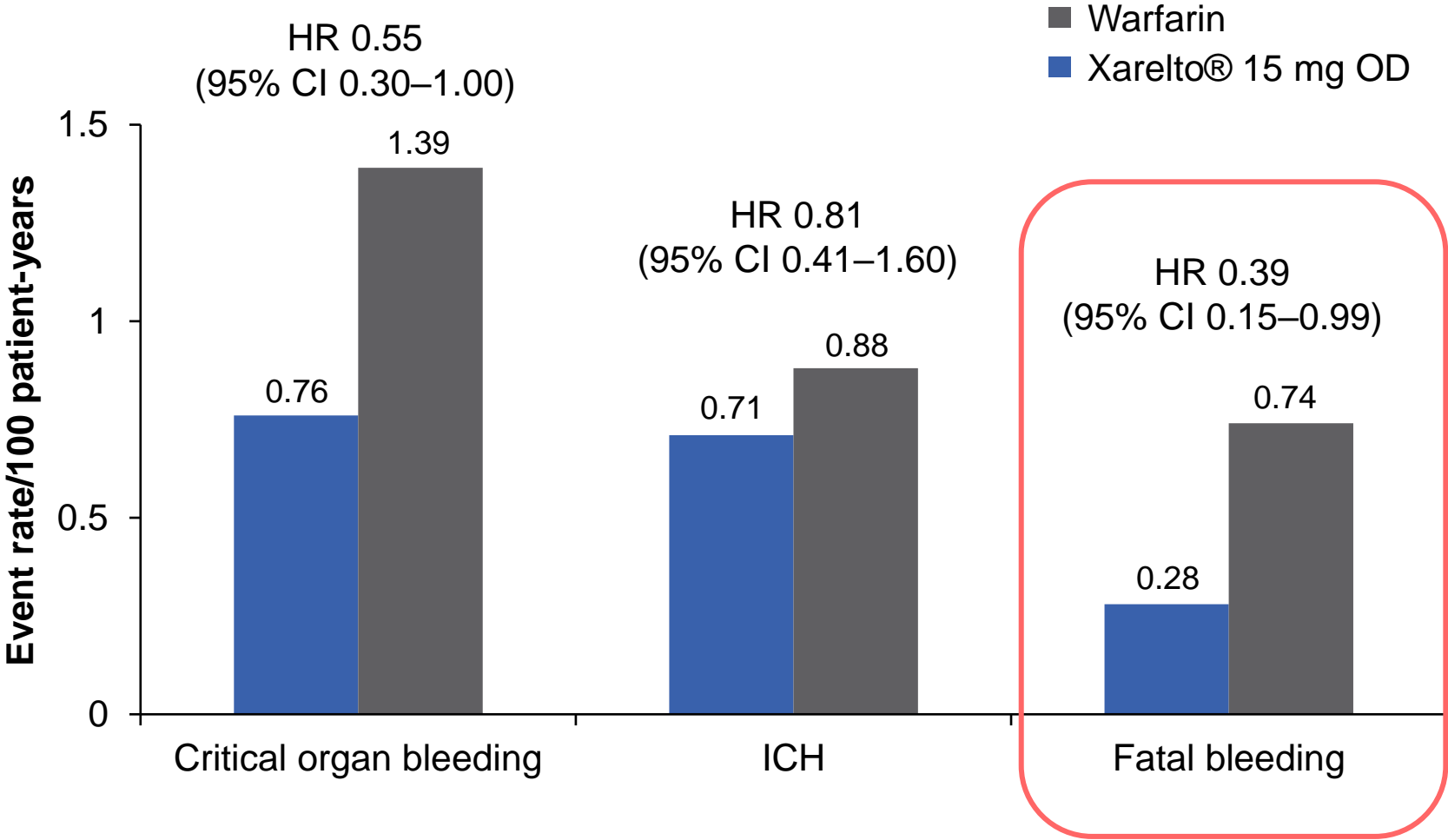
## Primary efficacy endpoint: Stroke / SE



Consistent efficacy of rivaroxaban vs. warfarin in NVAf patients with moderate renal impairment

Intention-to-treat population

# ROCKET AF: Consistent Safety Outcomes in NVAF Patients With Moderate Renal Impairment



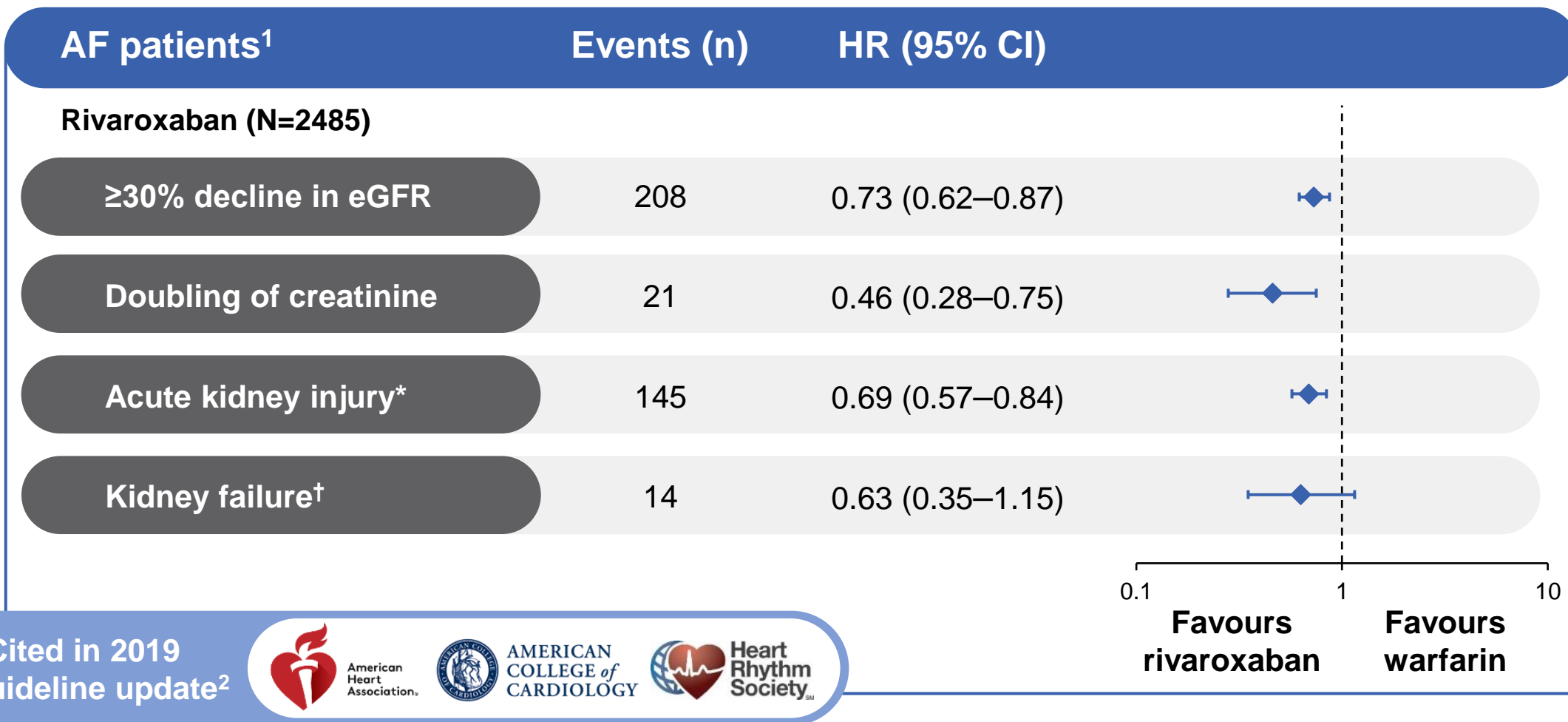
Safety on-treatment population.

Fox KA et al. *Eur Heart J* 2011;32:2387–2394.



# Kidney preservation

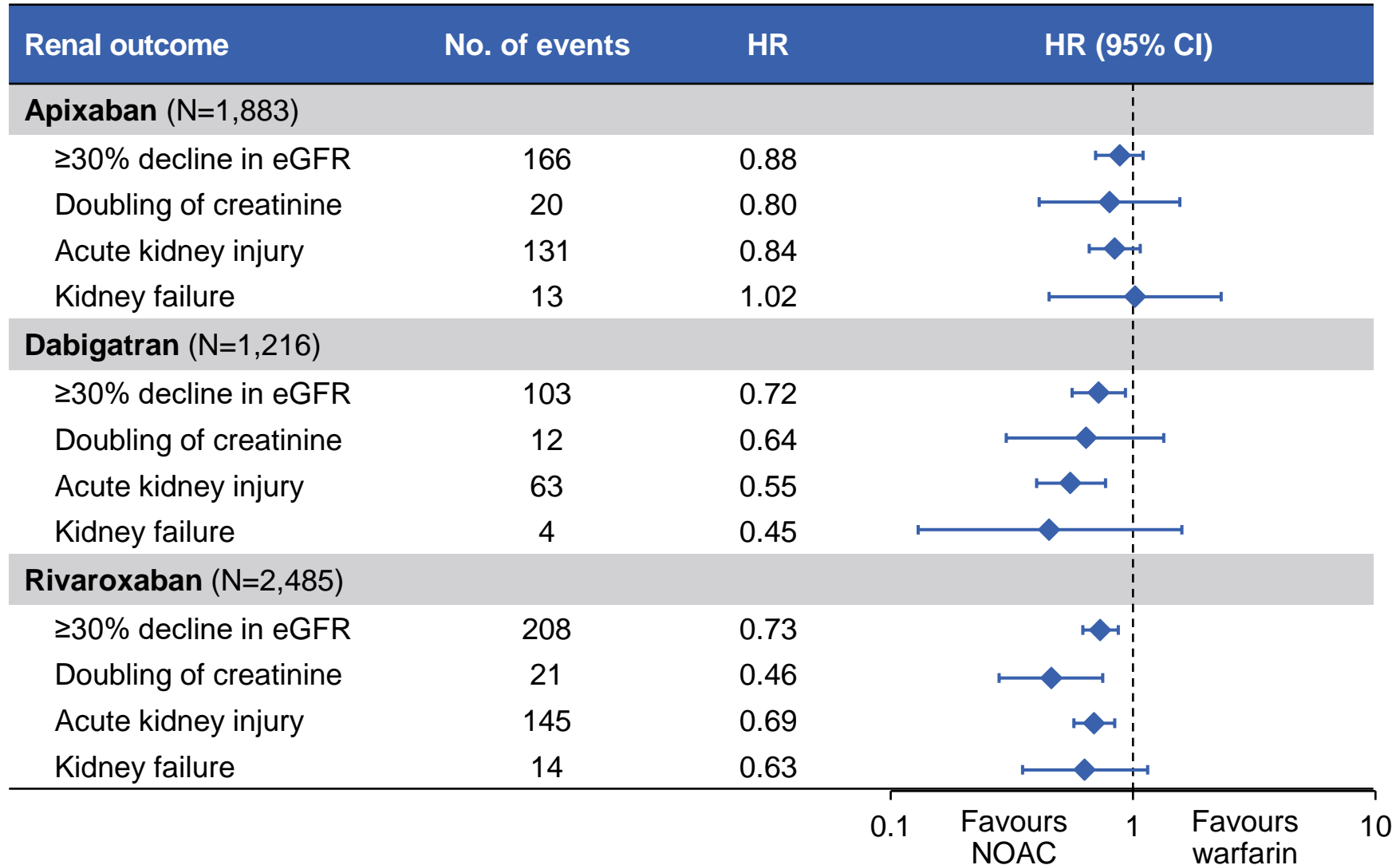
# Protection for Mr. A means safeguarding his aging kidneys against the effects of treatment



\*Defined as a hospitalisation or emergency department visit with a diagnosis code of AKI at the primary or secondary position; †Defined as eGFR <15 mL/min/1.73 m<sup>2</sup>, having kidney transplant, or undergoing long-term dialysis.

1. Yao X et al. *J Am Coll Cardiol* 2017;70:2621–2632; 2. January CT et al. *Circulation* 2019; doi.org/10.1016/j.jacc.2019.01.011.

# Real-world Evidence Confirms that Renal Function is Maintained in Patients Receiving Rivaroxaban



# Recent guidelines recommend NOACs in patients with AF to reduce risk of renal outcomes

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2019 focused update of  
AHA/ACC/HRS AF Guidelines



American  
Heart  
Association.



AMERICAN  
COLLEGE of  
CARDIOLOGY



Heart  
Rhythm  
Society<sup>SM</sup>

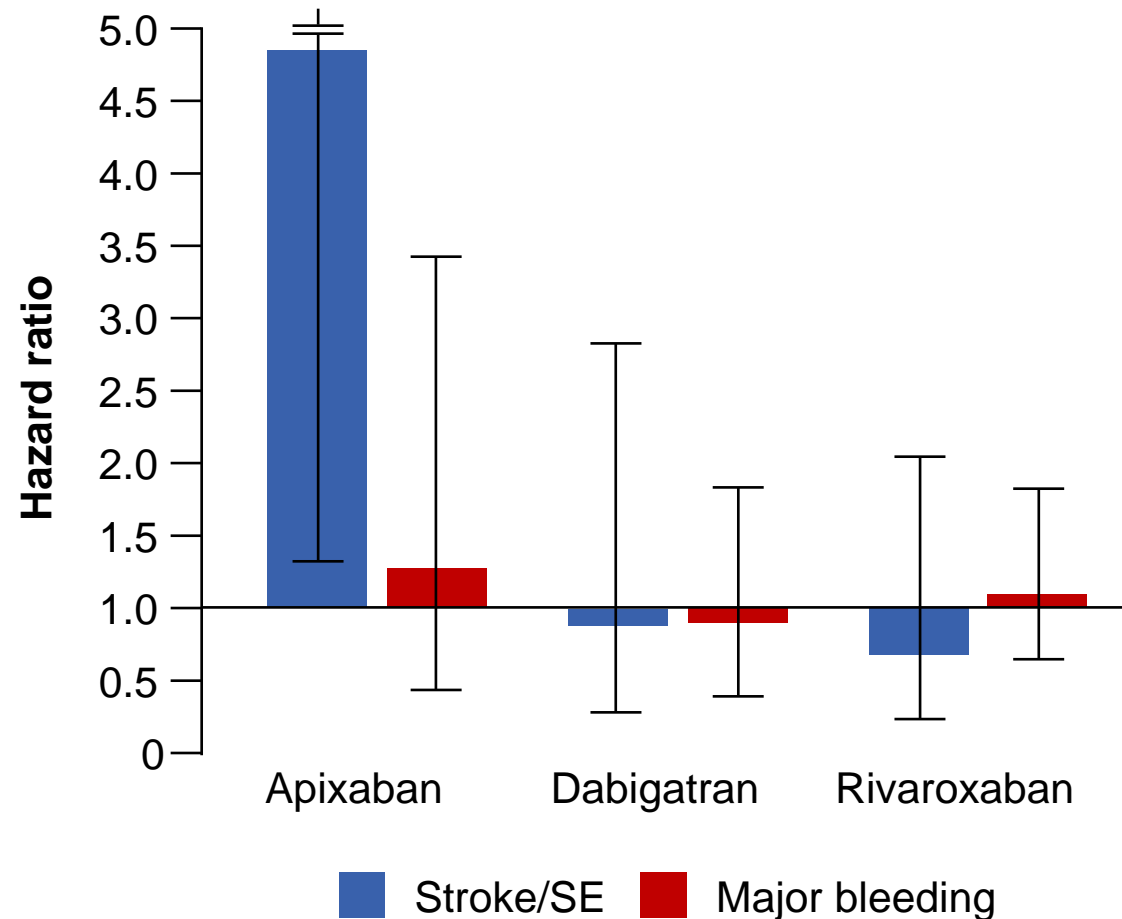
“Over time, NOACs (particularly dabigatran and rivaroxaban) may be associated with lower risks of adverse renal outcomes than warfarin in patients with AF”

# Appropriate dose benefits

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# Mr. A. can be protected with the correct rivaroxaban dose

Inappropriate under-dosing does not offer an efficacy or bleeding benefit



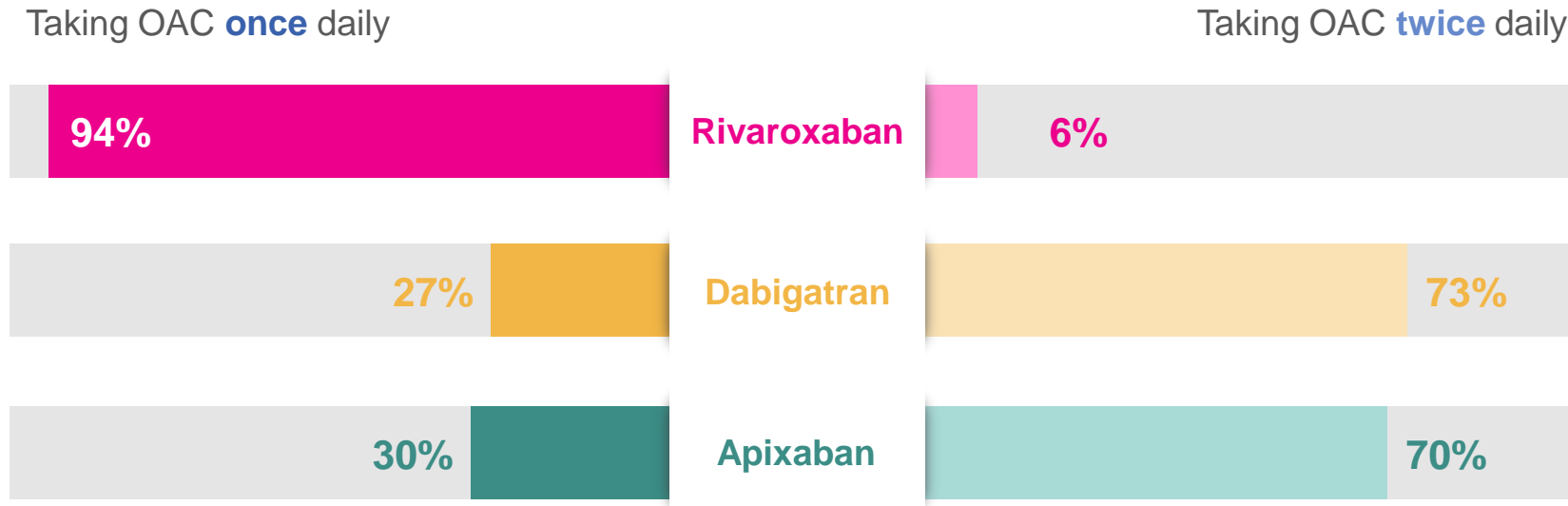
# Once vs twice daily: The compliance issue



# One-Third of Twice-Daily Prescribed Medications Were Being Taken Once Daily

## Therapy adherence

Self-reported patient survey (N=266)





# Rivaroxaban for Stroke Prevention in Non-Valvular AF

- ◆ Indication: prevention of stroke and systemic embolism (SE) in adult patients with non-valvular AF with  $\geq 2$  risk factors, such as CHF, hypertension, age  $\geq 75$  years, diabetes mellitus or prior stroke/TIA

Rivaroxaban 20 mg OD

To be taken with food



In patients with moderate/severe renal impairment 15 mg OD\* (15-49 ml/min)

To be taken with food

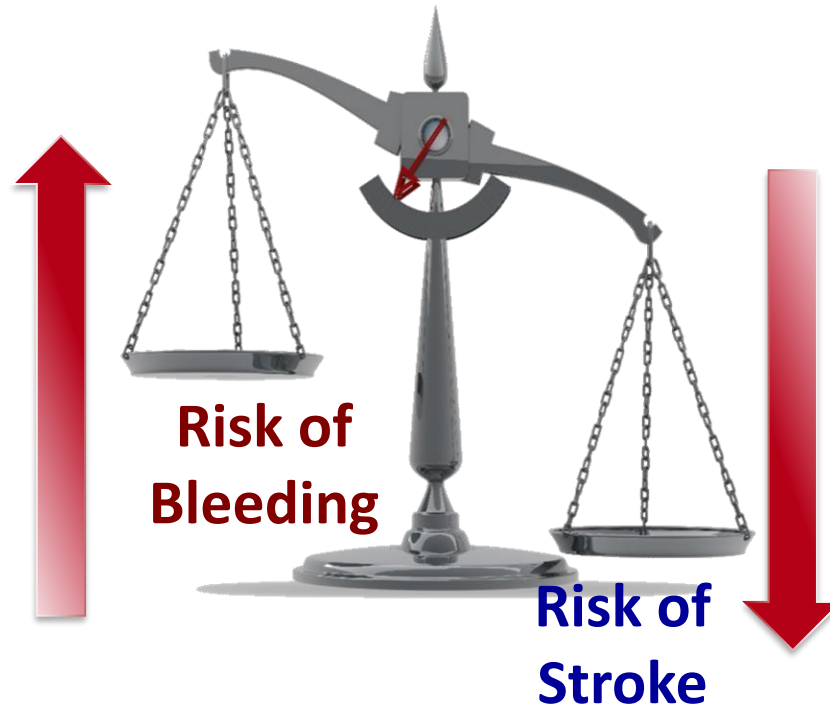


Continued long-term, benefit of prevention of stroke/SE outweighs bleeding risk

BAV reaches almost 80% - 100% with food

\*Moderate renal impairment (CrCl 30-49 mL/min) – specific dose (15 mg OD) tested in ROCKET AF; Severe renal impairment (CrCl 15-29 mL/min) – use with caution; limited clinical data indicate that rivaroxaban plasma concentrations are significantly increased in these patients CrCl <15 mL/min – use not recommended

# Physicians, Patients And Oral Anticoagulant Therapy: A Major Difference In Perspectives



- ◆ Physicians underuse and underdose OAC for stroke prevention in AF<sup>1</sup> given their concern with bleeding – a “first do no harm” focus
- ◆ Patients view severe strokes as being equal to or worse than death<sup>2,3</sup>

Patients place more weight on the risk of stroke

*Concern about bleeding (unless patient risk is extreme) should not lead to the underdosing, let alone withholding, of anticoagulant therapy*

OAC=oral anticoagulant

1. Devereaux PJ, et al. *BMJ* 2001;323:1218-1223; 2. Gage et al, *Arch Intern Med* 1996;56:1829-1836; 3. Solomon et al. *Stroke* 1994;25:1721-1725.

# What does protection mean for your patients with NVAf?



**Mr. A.**  
76 years old

- NVAf
- eGFR 46 mL/min
- Diabetes



Preventing stroke<sup>1</sup>



Preserving renal function<sup>2</sup>



Reducing limb events<sup>8</sup>



Mitigating bleeding risk<sup>3</sup>



Preventing CV death<sup>4</sup>



Protection following stent placement<sup>5</sup>



Optimising dose<sup>6</sup>



Supporting adherence<sup>7</sup>

1. Patel MR et al. *N Engl J Med* 2011;365:883–891; 2. Yao X et al. *J Am Coll Cardiol* 2017;70:2621–2632; 3. Hanon O et al. Presented at ESC Congress 2019, Paris, France; 4. Bansilal S et al. *Am Heart J* 2015;170:675–682.e8; 5. Gibson CM et al. *N Engl J Med* 2016;375:2423–2434; 6. Yao X et al. *J Am Coll Cardiol* 2017;69:2779–2790; 7. Mueller S et al. Poster presented at: ESC Congress 2019. 8. Baker WL et al. *Diabetes Obes Metab* 2019;21:2107–2114



THANK YOU