THE PRESENT AND FUTURE of ANTICOAGULATION

THURSDAY, SEPTEMBER 29, 2022
7:30 - 8:30 pm ET

Welcome and Introductions

BETH L. ABRAMSON
MD, MSc, FRCP, FACC

Faculty

BETH L. ABRAMSON, MD, MSc, FRCP, FACC
Paul Albrechtsen Professor in Cardiac Prevention and Women's Health
Associate Professor of Medicine, University of Toronto
Division of Cardiology, St. Michael's Hospital

ATUL VERMA, MD, FRCPC, FHRS
Head of Division of Cardiology, McGill University Health Centre
Chair in Cardiology, Isadore Rosenfeld
Associate Professor, McGill University

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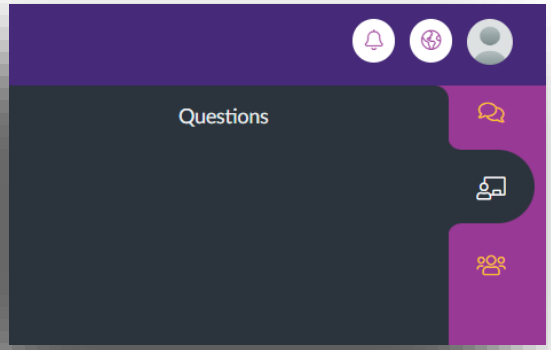
Send us your questions !

- Please send your questions to the faculty by selecting the questions tab on the right side of your screen



- Your questions will be answered during the live panel discussion and Q&A after the presentations

Agenda

TIME	TOPIC	SPEAKER
7:30-7:35 pm	**Welcome and Introductions**	Dr. Abramson
7:35-7:50 pm	**History of Anticoagulation in AF**	Dr. Abramson
7:50-8:05 pm	**Anticoagulation in High-Risk Populations**	Dr. Verma
8:05-8:15 pm	**Wearable Technologies for the Detection of AF**	Dr. Verma
8:15-8:30 pm	**Discussion / Q & A**	Dr. Abramson; Dr. Verma
8:30 pm	**Closing remarks**	Dr. Abramson

Learning Objectives

- Describe the evolving science of anticoagulation for stroke prevention in AF, from warfarin to Factor Xa inhibitors to currently investigated Factor XI inhibitors
- Examine RWE data around anticoagulation for high-risk patient populations with AF, including geriatric and renally impaired
- Evaluate the accuracy of wearable technologies for the detection of AF and how the clinicians can approach their use with their patients

Potential Conflicts of Interest

Beth L. Abramson, MD, MSc, FRCP, FACC

Relationships with financial sponsors:

- **Grants/Research Support:** Amgen, Bayer, Boehringer Ingelheim, Janssen, HLS Therapeutics, Novartis, Novo Nordisk
- **Speakers Bureau/Honoraria:** Amgen, Bayer, Biosyent, Boehringer Ingelheim, CHRC, HLS Therapeutics, Novartis, Novo Nordisk, BMS- Pfizer, Servier, Sanofi
- **Consulting Fees:** Amgen, Bayer, HLS Therapeutics, Novartis, Novo Nordisk, Sanofi
- **Patents:** N/A
- **Other:** Author: Heart Health for Canadians

Potential Conflicts of Interest

Atul Verma, MD, FRCPC, FHRS

Relationships with financial sponsors:

- **Research Grants:** Bayer, Biotronik, Biosense Webster, Medtronic
- **Advisory Board:** Galaxy Medical, Adagio Medical, Bayer, Biosense Webster, Kardium, Medtronic, Medlumics, Thermedical
- **Clinical trials:** Biosense Webster, Adagio Medical, Galaxy Medical, Medtronic, Thermedical

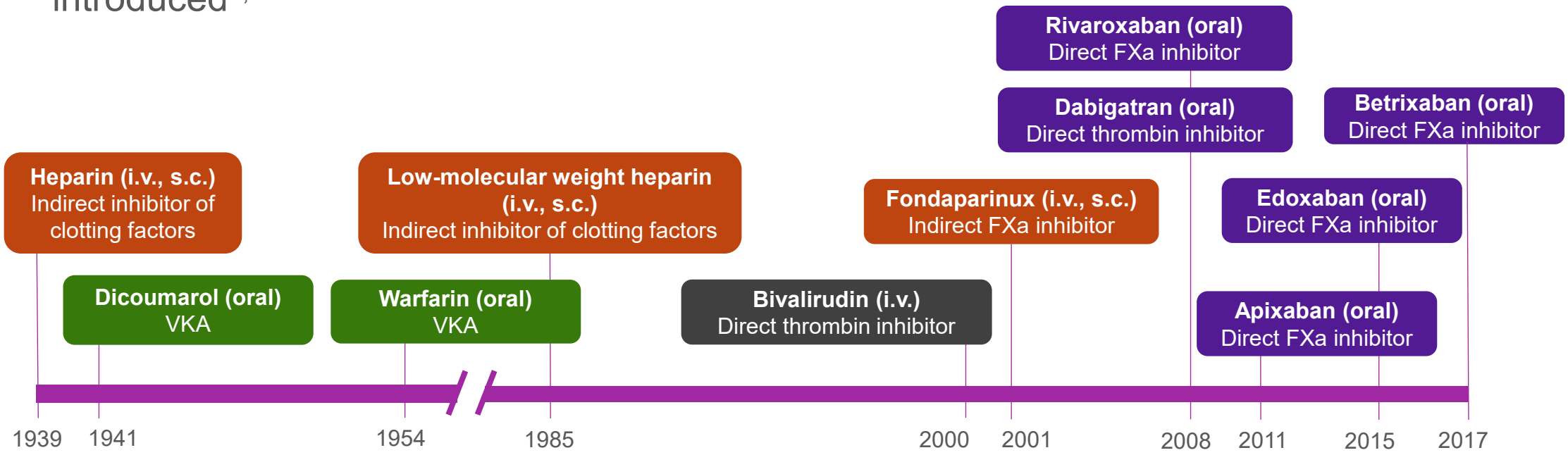
History of Anticoagulation in AF

Beth L. Abramson, **MD, MSc, FRCP, FACC**
Paul Albrechtsen, Professor in Cardiac Prevention & Women's Health
Associate Professor of Medicine, U. of Toronto
Director: Cardiac Prevention Centre & Women 's CV Health,
Division of Cardiology, St. Michael 's Hospital

Brief Review of Anticoagulation in AF

The evolution of anticoagulants

- The use of anticoagulants for the prevention and treatment of thrombosis was first established in the early 20th century[1]
- In the last two decades, a new class of anticoagulants, known as NOACs, has been introduced[1,2]

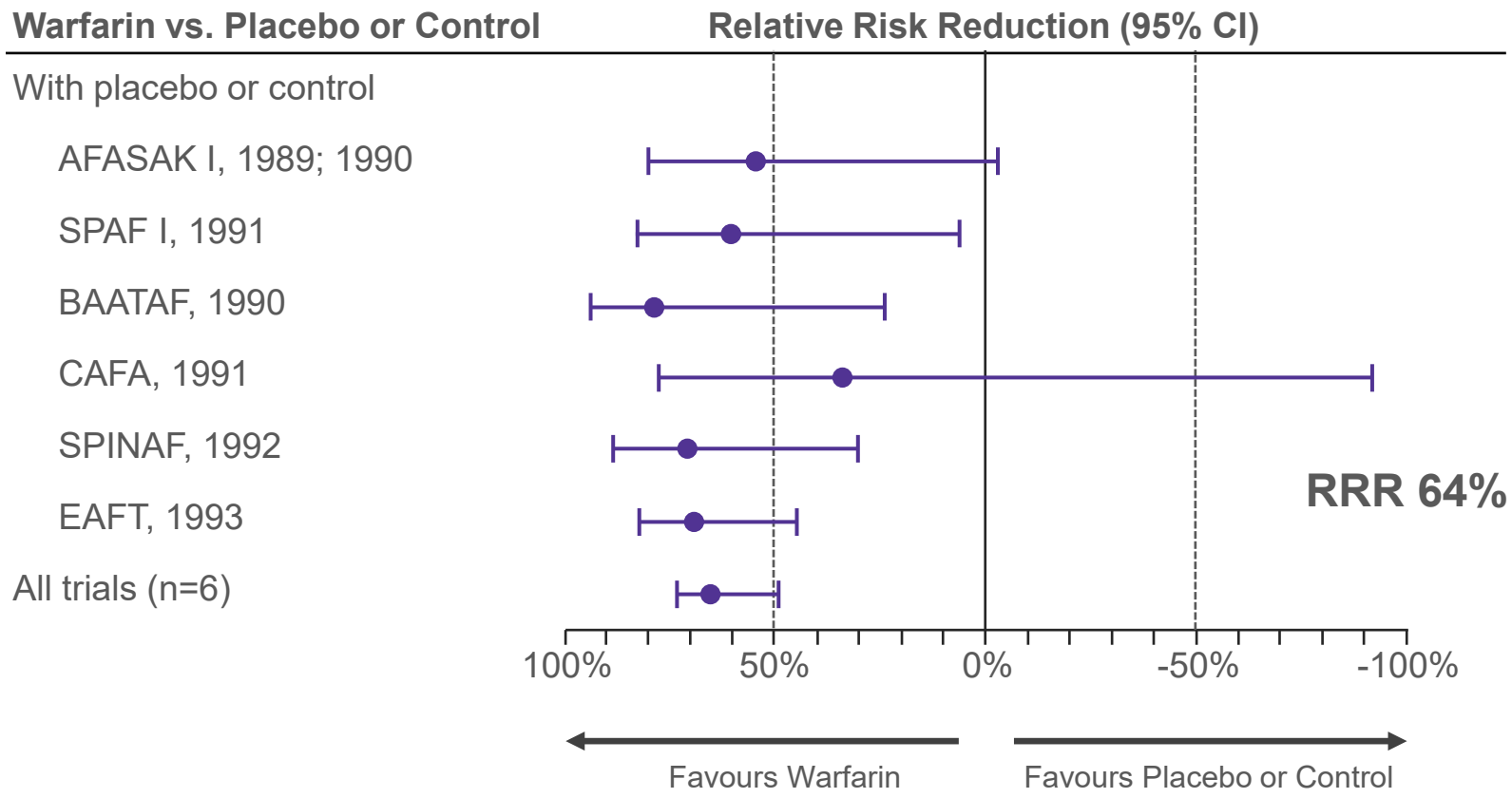


Pink boxes indicate heparins (and derivatives), green indicates VKAs, purple indicates bivalirudin and blue indicates NOACs

FXa, activated factor X; i.v., intravenous; NOAC, non-vitamin K antagonist oral anticoagulant; s.c., subcutaneous; VKA, vitamin K antagonist.

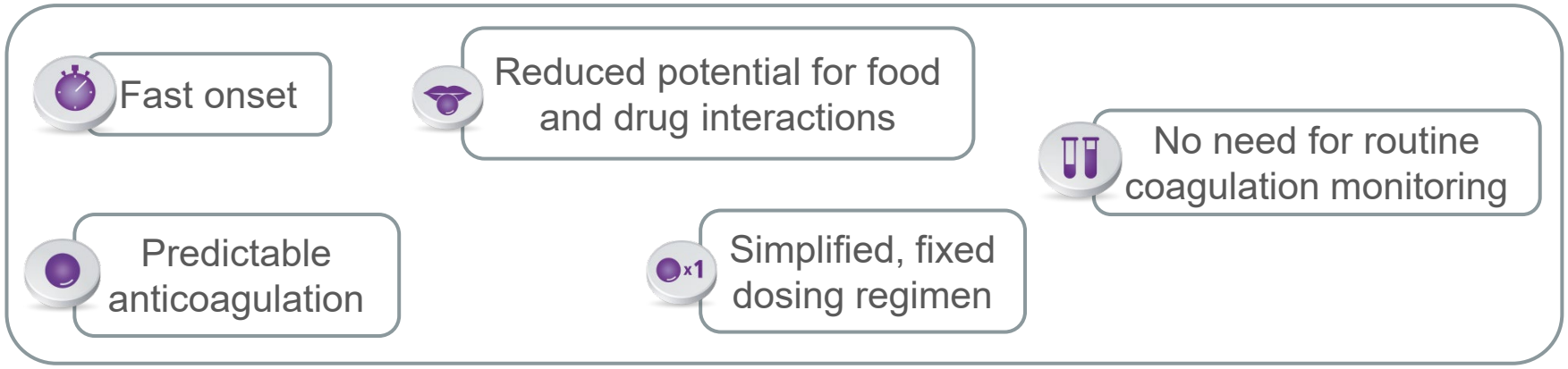
1. Weitz JI, Fredenburgh JC. Arterioscler Thromb Vasc Biol 2018;38:304–10; 2. Hirsh J et al. Eur J Intern Med 2019;70:1–7

OAC Therapy for Stroke Prevention in NVAF: Warfarin vs. Placebo or Control



1. Hart RG, Pearce LA, and Aguilar MI. Meta-analysis: Antithrombotic Therapy to Prevent Stroke in Patients Who Have Nonvalvular Atrial Fibrillation. Ann Intern Med. 2007;1461:857-67.

Important Benefits of NOACs Over VKAs[1–6]



Less labour-intensive → Reduced administrative costs

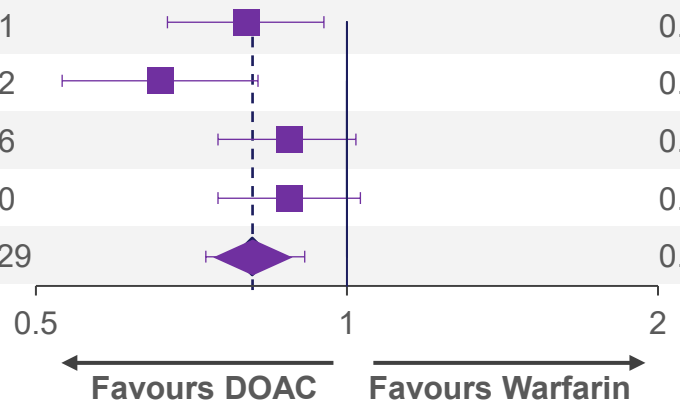
Less impact on patients' daily life → Improved QoL

Improved compliance → Improved benefit-risk profile

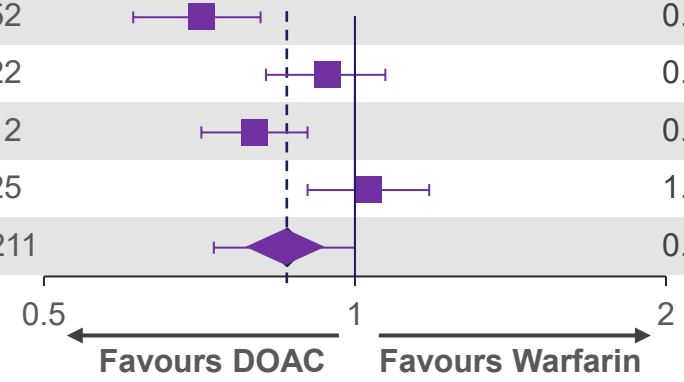
1. Ansell J et al. Chest. 2004;126(3):204S–233S; 2. Mueck W et al. Int J Clin Pharmacol Ther. 2007;45(6):335–344; 3. Mueck W et al. Clin Pharmacokinet. 2008;47(3):203–216;
4. Mueck W et al. Thromb Haemost. 2008;100(3):453–461; 5. Raghavan N et al. Drug Metab Dispos. 2009;37(1):74–81; 6. Shantsila E, Lip GY. Curr Opin Investig Drugs. 2008;9(9):1020–1033.

DOACs Have a Favourable Risk/Benefit Profile in Comparison to Warfarin

Stroke/Systemic Embolism	DOAC Events (n/N)	Warfarin Events (n/N)	RR (95% CI)	p value
ARISTOTLE (apixaban 5 mg BID)	212/9120	265/9081	0.80 (0.67-0.95)	0.012
RE-LY (dabigatran 150 mg BID)	134/6076	199/6022	0.66 (0.53-0.82)	0.0001
ENGAGE AF (edoxaban 60 mg once daily)	296/7035	337/7036	0.88 (0.75-1.02)	0.10
ROCKET AF (rivaroxaban 20 mg once daily)	269/7081	306/7090	0.88 (0.75-1.03)	0.12
Combined (random)	911/29312	1107/29229	0.81 (0.73-0.91)	<0.0001
Heterogeneity: I^2=47%, p=0.13				



Major Bleeding	DOAC Events (n/N)	Warfarin Events (n/N)	RR (95% CI)	p value
ARISTOTLE (apixaban 5 mg BID)	327/9088	462/9052	0.71 (0.61-0.81)	<0.0001
RE-LY (dabigatran 150 mg BID)	375/6076	397/6022	0.94 (0.82-1.07)	0.34
ENGAGE AF (edoxaban 60 mg once daily)	444/7012	557/7012	0.80 (0.71-0.90)	0.0002
ROCKET AF (rivaroxaban 20 mg once daily)	395/7111	386/7125	1.03 (0.90-1.18)	0.72
Combined (random)	1541/29287	1802/29211	0.86 (0.73-1.00)	0.06
Heterogeneity: I^2=83%, p=0.001				



CI: confidence interval; RR: risk ratio; SSE: stroke and systemic embolism.

1. Ruff et al. Lancet. 2014;383:955-62.

There still is a Medical Need for Alternative Treatment Options for Stroke Prevention in AF[1]

- **23%** of patients **did not receive** the **correct label-recommended dose** of NOAC according to a study of AF in the United Kingdom[2]
- Underdosing of NOACs is **common** due to concerns about bleeding[3]

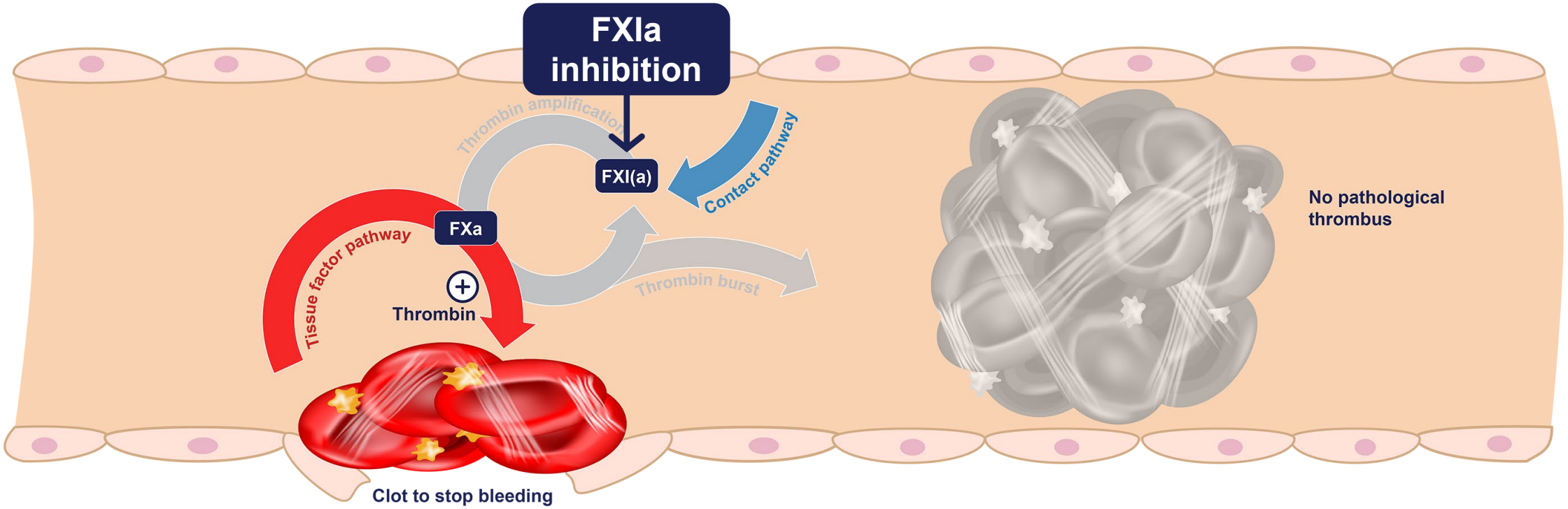
- **~40%** of patients with AF in the GLORIA-AF antithrombotic treatment registry did not receive NOACs[4]

There remains a **medical need** for **alternative treatment options for stroke prevention in AF** with an **improved safety profile** and **equivalent or superior efficacy** to current treatment options[1]

•AF, atrial fibrillation; NOAC, non-vitamin K antagonist oral anticoagulant.

1. Weitz JL, Fredenburgh. *Front Med (Lausanne)* 2017;4:19; 2. García Rodríguez LA *et al. BMJ Open* 2019;9:e031341; 3. Suarez Fernandez C *et al. J Comp Eff Res* 2020;9:509–523;
4. Bayer V *et al. J Am Heart Assoc* 2022;11:e023907.

FXIa Inhibition
(Hypothesis: Uncoupling Haemostasis from Thrombosis)[1–3]



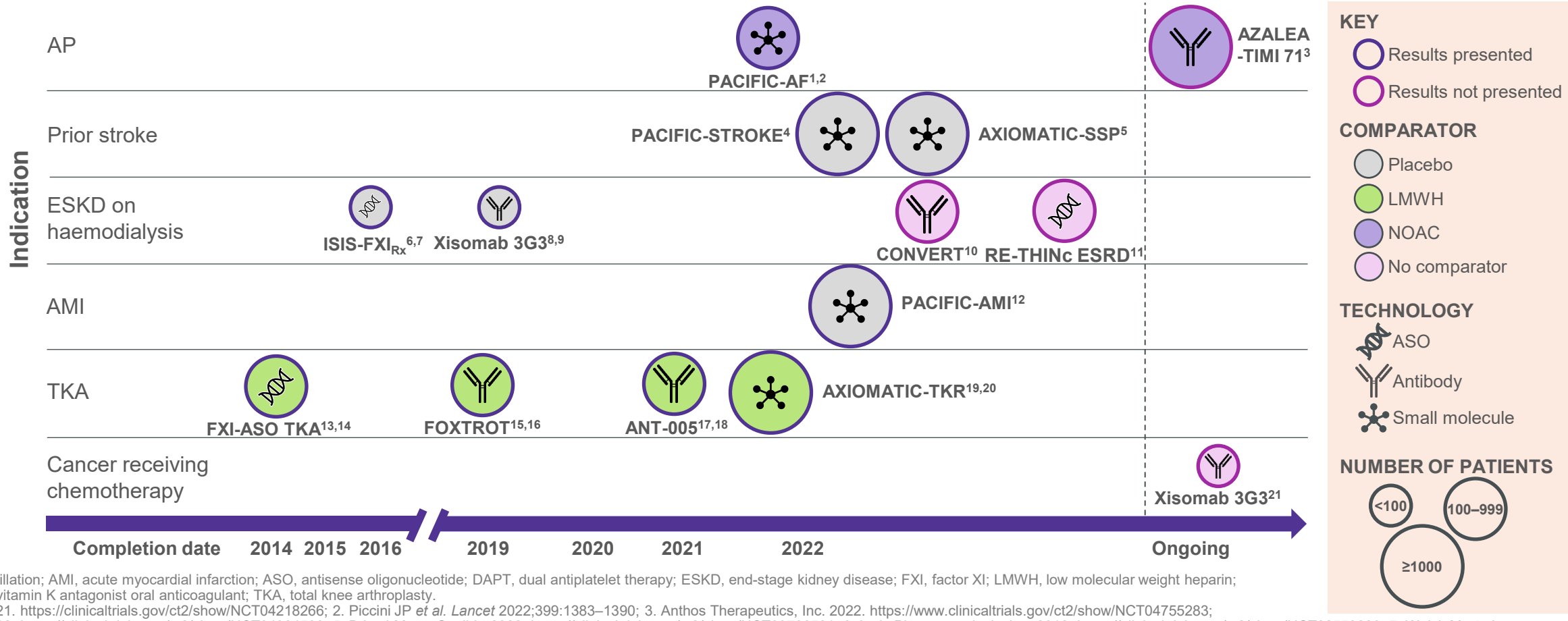
AND the tissue factor pathway still produces thrombin, which allows beneficial blood clots to form

When FXIa inhibition occurs, the proposed hypothesis is that thrombin amplification is inhibited, which prevents the formation of pathological thrombi

Figure provided courtesy of Manesh Patel.
FXa, activated factor X; FXI, factor XI; FXIa, activated factor XI.
1. Piccini JP *et al*. *Lancet* 2022;399:1383–1390; 2. Fredenburgh JC, Weitz JI. *Hamostaseologie* 2021;41:104–110; 3. Gailani D *et al*. *J Thromb Haemost* 2015;13:1383–1395.

Clinical Trials Investigating FXI Inhibition

The products shown are currently investigational and are not licensed for use in any country

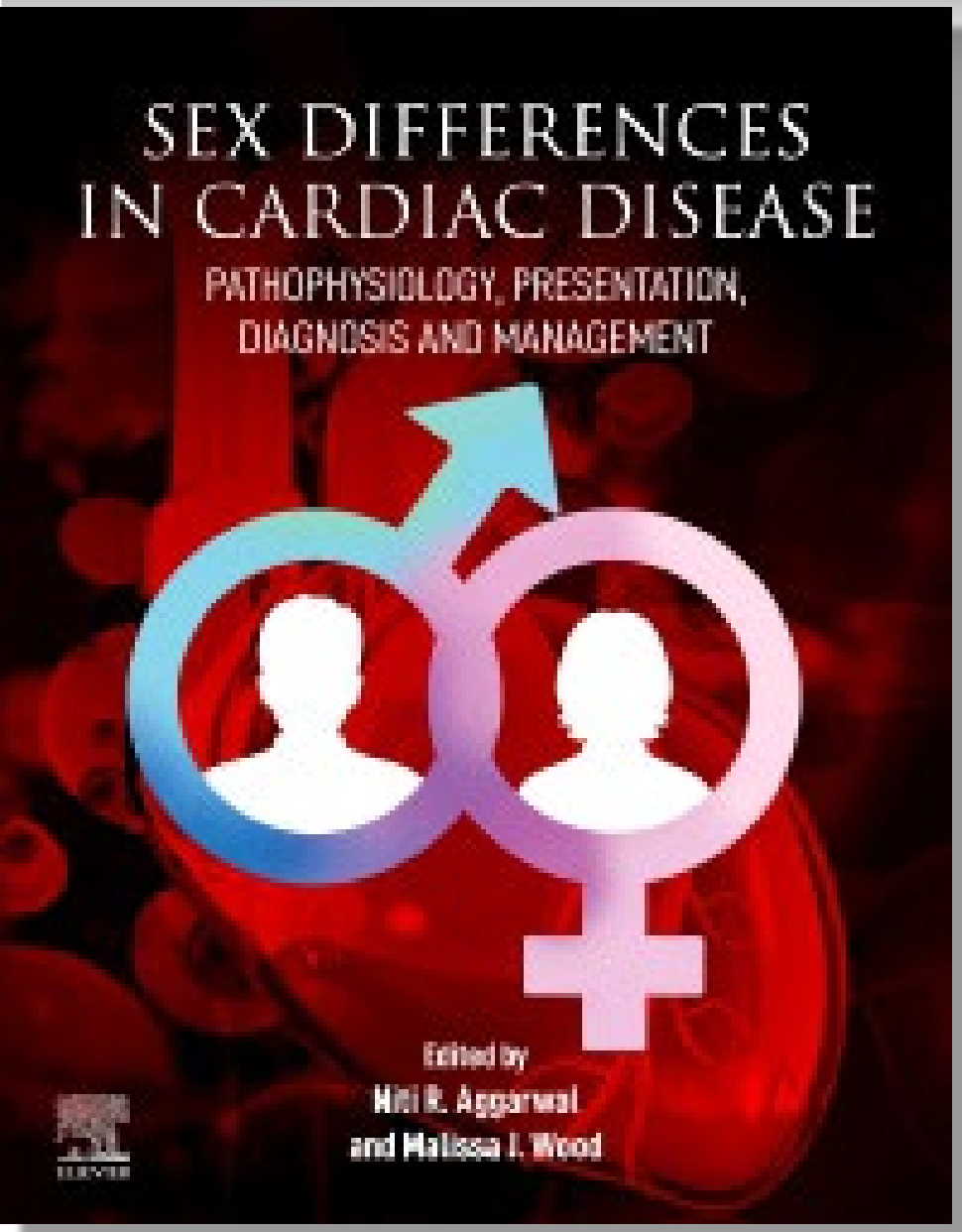


AF, atrial fibrillation; AMI, acute myocardial infarction; ASO, antisense oligonucleotide; DAPT, dual antiplatelet therapy; ESKD, end-stage kidney disease; FXI, factor XI; LMWH, low molecular weight heparin; NOAC, non-vitamin K antagonist oral anticoagulant; TKA, total knee arthroplasty.

1. Bayer. 2021. https://clinicaltrials.gov/ct2/show/NCT04218266; 2. Piccini JP *et al. Lancet* 2022;399:1383–1390; 3. Anthos Therapeutics, Inc. 2022. https://www.clinicaltrials.gov/ct2/show/NCT04755283; 4. Bayer. 2022. https://clinicaltrials.gov/ct2/show/NCT04304508; 5. Bristol-Myers Squibb. 2022. https://clinicaltrials.gov/ct2/show/NCT03766581; 6. Ionis Pharmaceuticals, Inc. 2016. https://clinicaltrials.gov/ct2/show/NCT02553889; 7. Walsh M *et al. Kidney Int Rep* 2021;7:200–209; 8. Aronora, Inc. 2022. https://clinicaltrials.gov/ct2/show/NCT03612856 ; 9. Lorentz CU *et al. Blood* 2021;138:2173–2184; 10. Bayer. 2022. https://clinicaltrials.gov/ct2/show/NCT04523220; 11. Bayer. 2022. https://clinicaltrials.gov/ct2/show/NCT04534114; 12. Bayer. 2022. https://clinicaltrials.gov/ct2/show/NCT04304534; 13. Ionis Pharmaceuticals, Inc. 2014. https://clinicaltrials.gov/ct2/show/NCT01713361; 14. Büller HR *et al. N Engl J Med* 2015;372:232–240; 15. Bayer. 2020. https://clinicaltrials.gov/ct2/show/NCT03276143; 16. Weitz JI *et al. JAMA* 2020;323:130–139; 17. Anthos Therapeutics, Inc. 2022. https://www.clinicaltrialsregister.eu/ctr-search/trial/2019-003756-37/LT; 18. Verhamme JI *et al. N Engl J Med* 2021;385:609–617; 19. Janssen Research & Development, LLC. 2021. https://clinicaltrials.gov/ct2/show/NCT03891524; 20. Weitz JI *et al. N Engl J Med* 2021;385:2161–2172; 21. OHSU Knight Cancer Institute. 2022. https://clinicaltrials.gov/ct2/show/NCT04465760 [all links accessed June 2022].

Women and Atrial Fibrillation: Exploring Sex Differences

Beth Abramson, MD, MSc, FRCP, FACC
Paul Albrechtsen, Professor in Cardiac Prevention & Women's Health
Associate Professor of Medicine, U of Toronto,
Division of Cardiology, St. Michael's Hospital

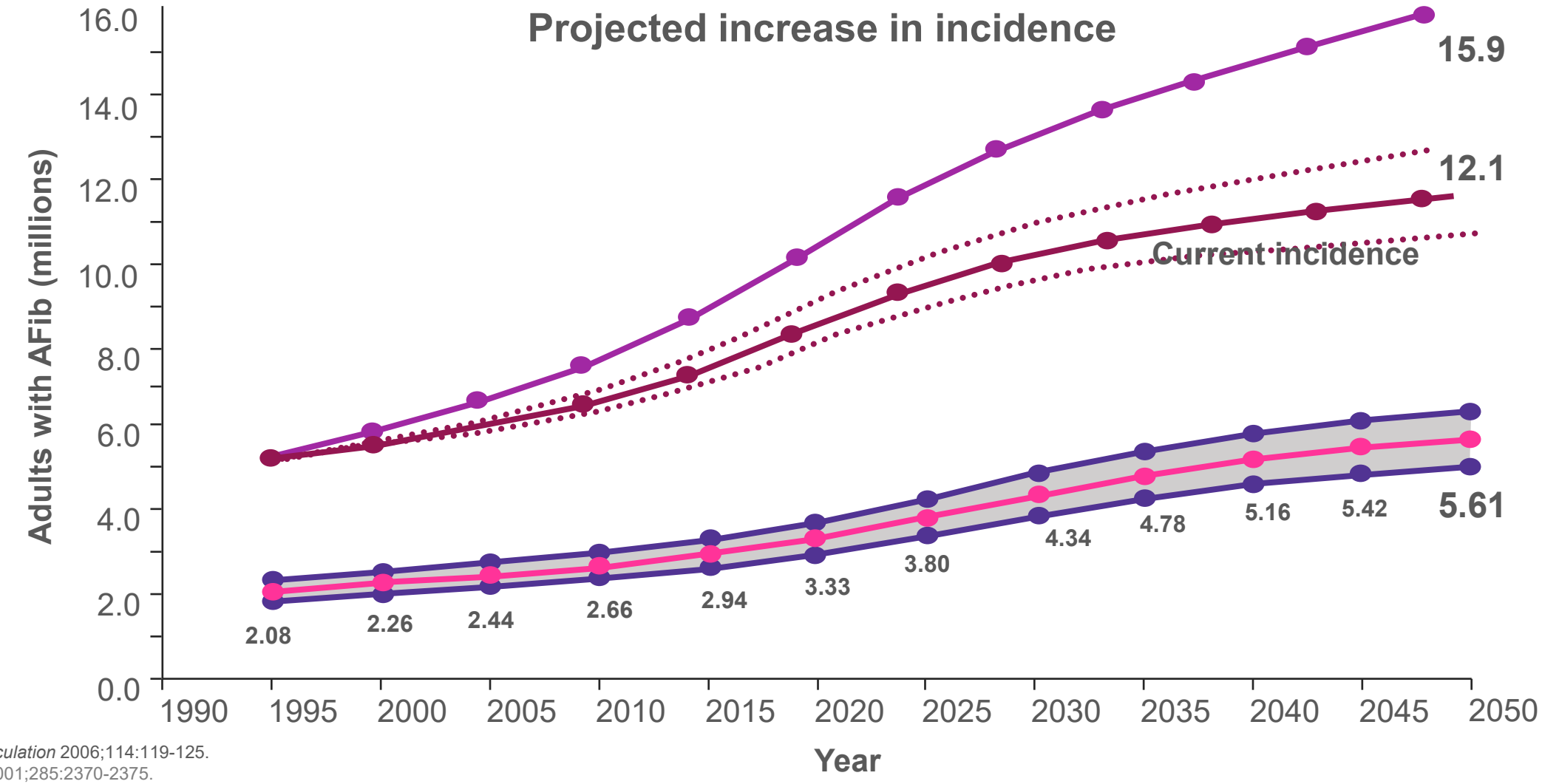

SEX DIFFERENCES
IN CARDIAC DISEASE
PATHOPHYSIOLOGY, PRESENTATION,
DIAGNOSIS AND MANAGEMENT
Edited by
Nitti R. Aggarwal
and Melissa J. Wood


Art & Science

Atrial Fibrillation in women and men: is it the same disease?

- AF is more common in men but women “catch up” as they age
- QoL is worse in women than men
- CVA risk is higher in women
- Anticoagulant treatment at least as beneficial in women vs. men
- The relationship between elevated blood pressure and AF in women is strong and occurs at BP below the “hypertensive range” (< 140/90 mm Hg)

The AF epidemic-USA

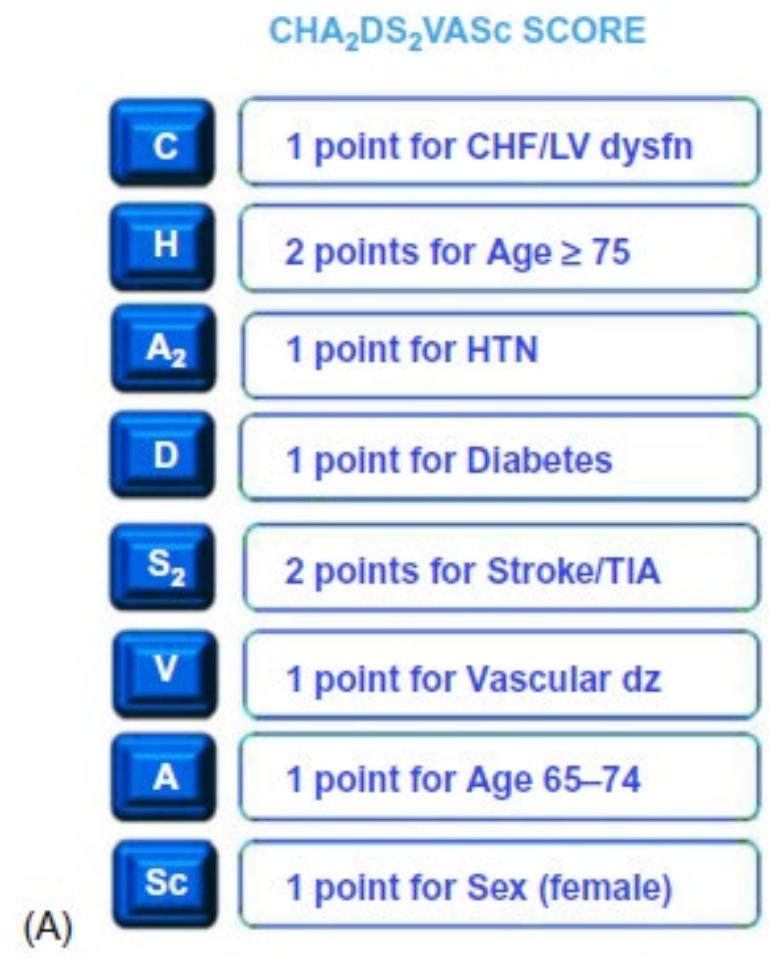


Miyasaka Y *et al*. *Circulation* 2006;114:119-125.
Go AS *et al*. *JAMA* 2001;285:2370-2375.

Sex Differences in Risk Factors for Atrial Fibrillation.

BMI, Body mass index; BP, blood pressure, HTN, hypertension; MI, myocardial infarction

Sex is part of the CHADSVASC SCORE… treat all women over 65!



Utilization of Rate vs. Rhythm Control

Women tend to be more symptomatic than men, yet are more likely to receive rate control over rhythm control treatment than men [5].

Reviews of treatment disparities of AF patients found that compared with white men, women and blacks: (1) experienced longer-lasting and more frequent symptomatic AF episodes with worse quality of life [3, 5, 36, 37, 35, 52]; (2) had less stroke prevention treatment [53]; (3) had more drug-related adverse events [4]; (4) were treated less aggressively to maintain sinus rhythm [4, 42, 51, 54, 55]; and (5) had a higher adjusted mortality risk [42].

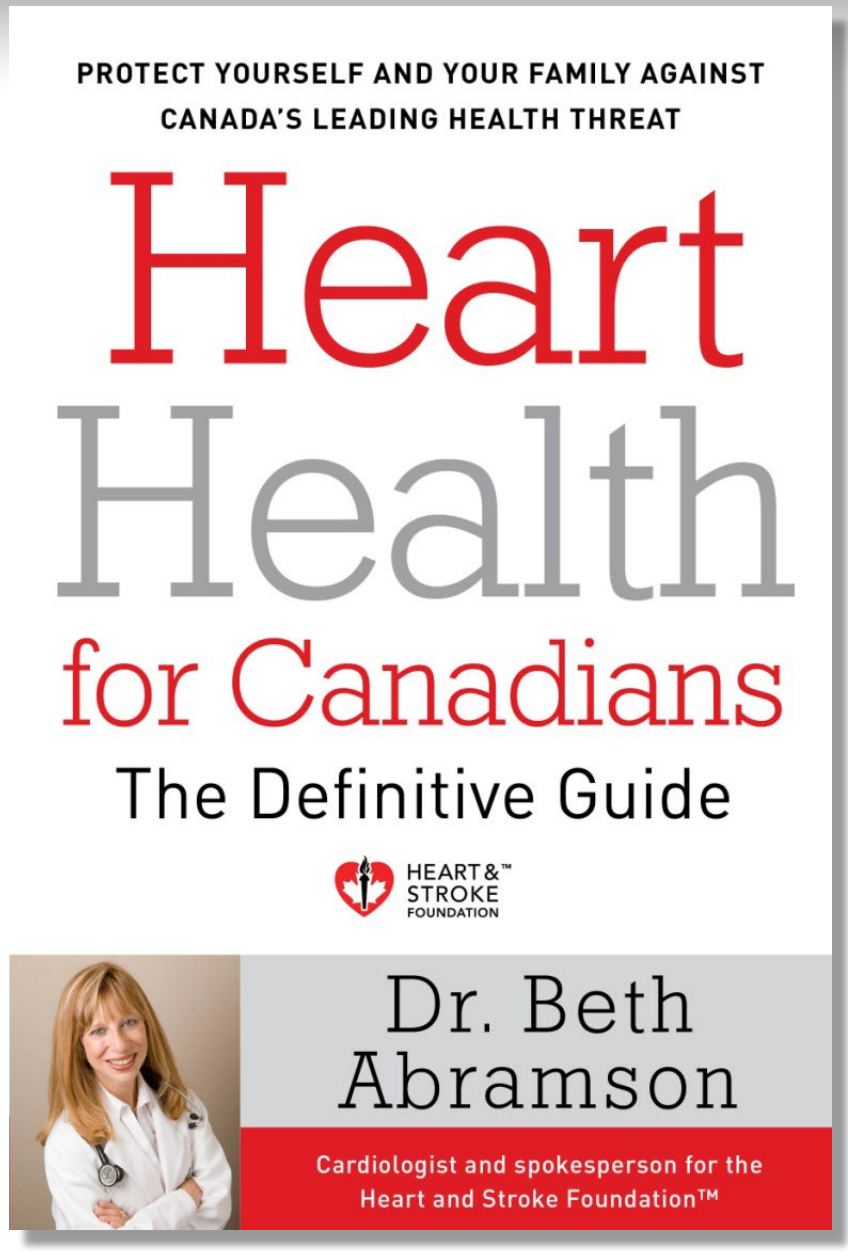
Differences in Prevention and Risk of Stroke

	Statistical Significance	Author (Year)
Stroke Prevention		
Women less likely to receive anticoagulation (United States)	56.7% vs. 61.3%; $P<0.001$	Thompson (2017) [53]
No difference in receiving oral anticoagulation (global)	73.4% vs. 73.45; $P=0.4456$	Lip (2015) [100]
Women spent more time outside the therapeutic range	40% vs. 37%; $P=0.0001$	Sullivan (2012) [99]
Women spent more time below the therapeutic range	29% vs. 26%; $P=0.0002$	Sullivan (2012) [99]
Strokes		
Women have higher risk of stroke than male atrial fibrillation patients	1.31 (1.18–1.46)	Wagstaff (2014) [81]
	1.24 (1.14–1.36)	Marzona (2018) [82]
Women with more debilitating strokes than men	1.99 (1.07–3.72)	Martin (2017) [91]

Take Home Messages – Women and Atrial Fibrillation

Risk of Thromboembolism

- Female sex is associated with higher risk of stroke in AF
- Women suffer more from disabling stroke
- Women with AF are older than men & have more comorbidities which may explain increased stroke risk
- Women have more strokes on warfarin than men
- DOACs are equally safe and effective in men and woman
- Therapeutic anticoagulation may be used less often in women despite a higher risk of thromboembolic events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Cardiologist and spokesperson for the
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Anticoagulation in High-Risk Populations

Present and Future of OAC

Atul Verma, MD, FRCPC, FHRS
Head of Division of Cardiology, McGill University Health Centre
Chair in Cardiology, Isadore Rosenfeld
Associate Professor, McGill University

Information Disclaimer

- This presentation may contain information regarding indications and/or instructions which differ from the approved use of products available in Canada
- Statements of fact and opinions expressed are those of the speaker and do not necessarily reflect the opinions or position of the manufacturers of any of the direct oral anticoagulants

Indications

- **Rivaroxaban:** XARELTO (rivaroxaban) film-coated tablet (10 mg, 15 mg, 20 mg) is indicated for the prevention of stroke and systemic embolism in patients with atrial fibrillation, in whom anticoagulation is appropriate
- **Apixaban:** ELIQUIS (apixaban) is indicated for the prevention of stroke and systemic embolism in patients with atrial fibrillation
- **Edoxaban:** LIXIANA (edoxaban) is indicated for prevention of stroke and systemic embolic events in patients with atrial fibrillation, in whom anticoagulation is appropriate
- **Dabigatran:** PRADAXA (dabigatran etexilate) is indicated for the prevention of stroke and systemic embolism in patients with atrial fibrillation, in whom anticoagulation is appropriate

Diabetes predicts AF

- Framingham Heart Study reported that DM and HTN were independent risk factors for developing AF, conferring a 1.4-1.6 fold risk (Kannel et al)
- Large retrospective study: AF occurred in 14.9% of DM group, but only 10.3% of non-DM group (p=0.0001) (Movahed et al)
- Meta-analysis of seven prospective cohort studies and four population-based case-control studies showed that DM had 40% increased risk of AF (Huxley et al)

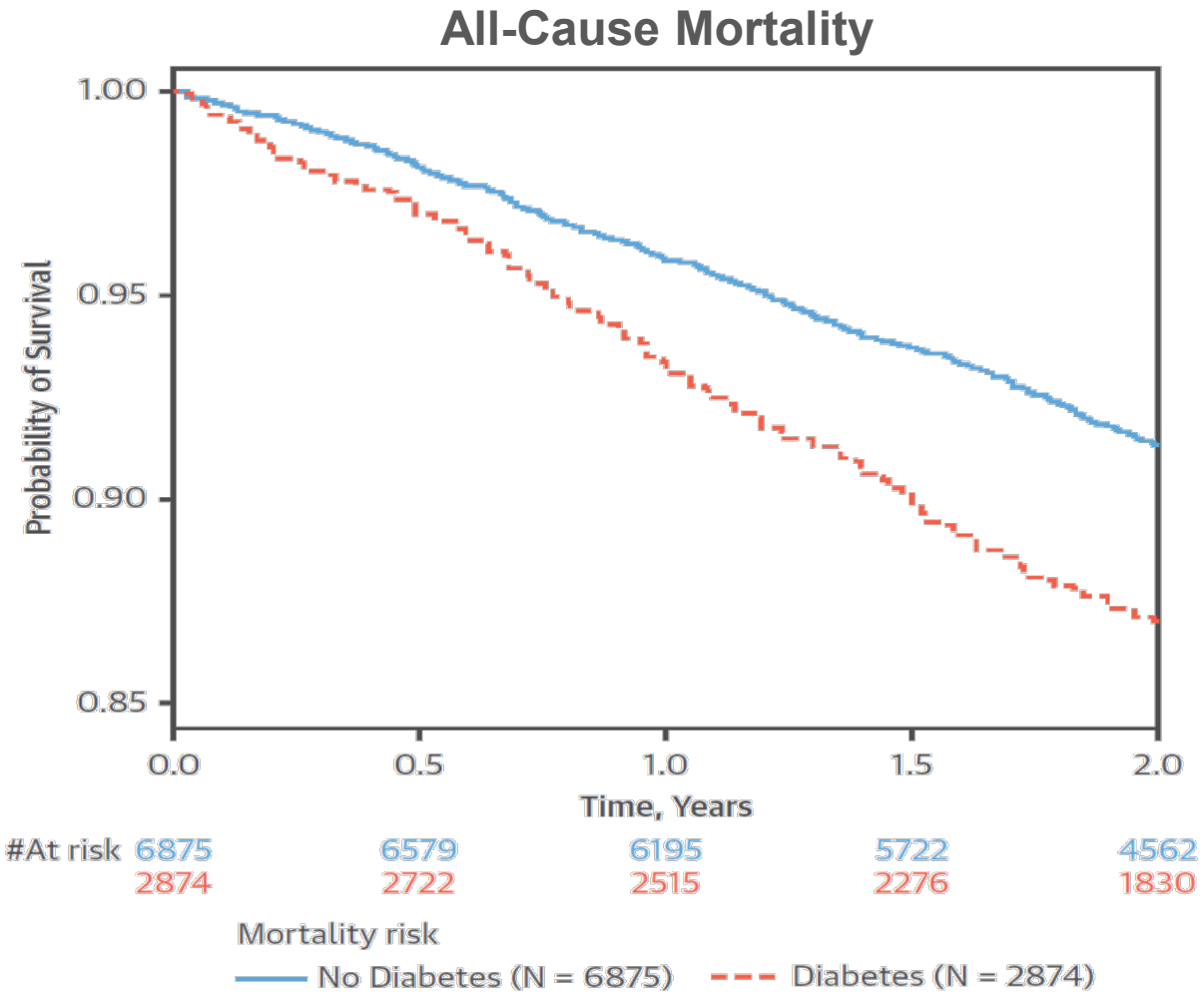
Moss, A. S., G. Dimitropoulos, et al. (2017). Expert Opin Pharmacother **18**(11): 1101-1114
Kannel WB, Wolf PA, et al. (1998) Am J Cardiol 82:2N–9N
Movahed MR, Hashemzadeh M, et al. (2005) Int J Cardiol 105:315–318
Huxley RR, Filion KB, et al. (2011) Am J Cardiol 108:56–62.

Outcomes for AF in Diabetes

- Most studies suggest that AF outcomes are worse in diabetics compared to non-diabetics
- Mechanisms are not entirely clear:
  - Multiplicative effect of diabetes, vascular disease, renal disease, and AF-related stroke risk
  - Increased thrombotic activation in diabetes
  - Dysautonomia in diabetic persons

Moss, A. S., G. Dimitropoulos, et al. (2017). Expert Opin Pharmacother **18**(11): 1101-1114

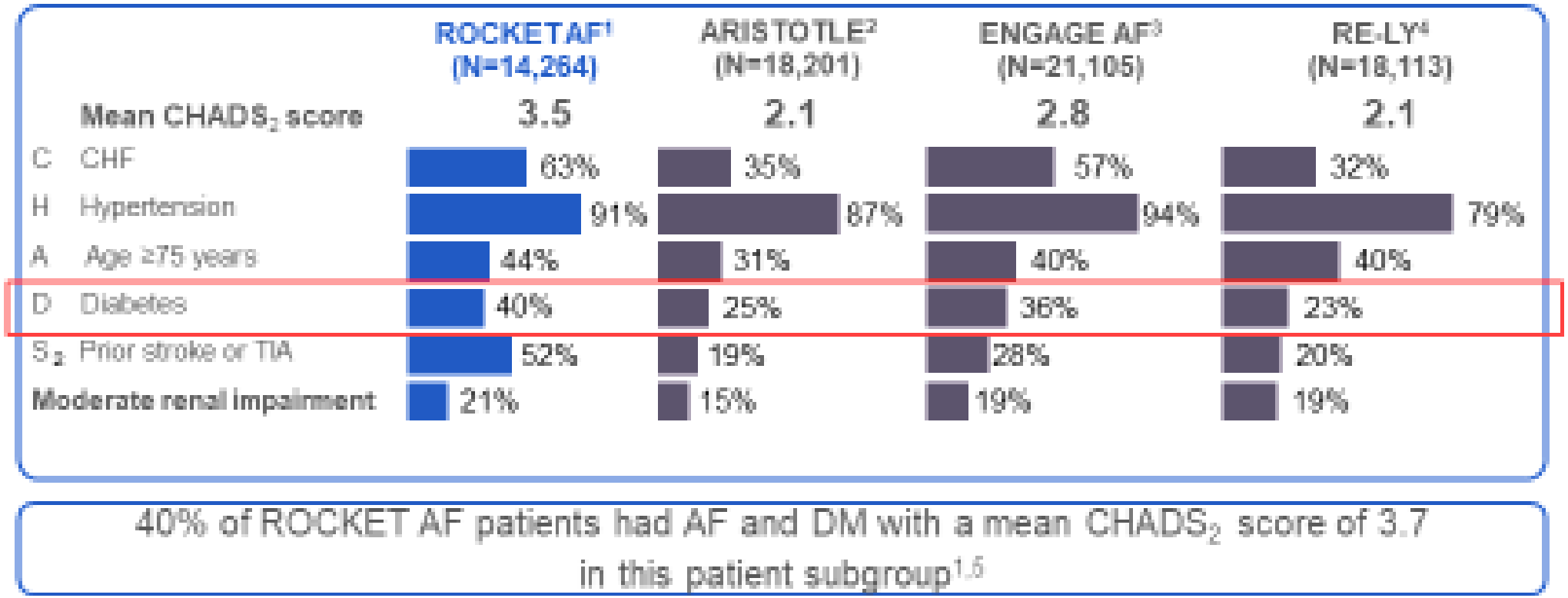
ORBIT AF Registry



Echouffo-Tcheugui, J. B., P. Shrader, et al. (2017). J Am Coll Cardiol **70**(11): 1325-35

ROCKET AF Had the Highest Proportion of DM Patients and highest Patient $CHADS_2$ Score Among Similar NOAC RCTs

Baseline characteristics of the study participants enrolled into each NOAC RCT

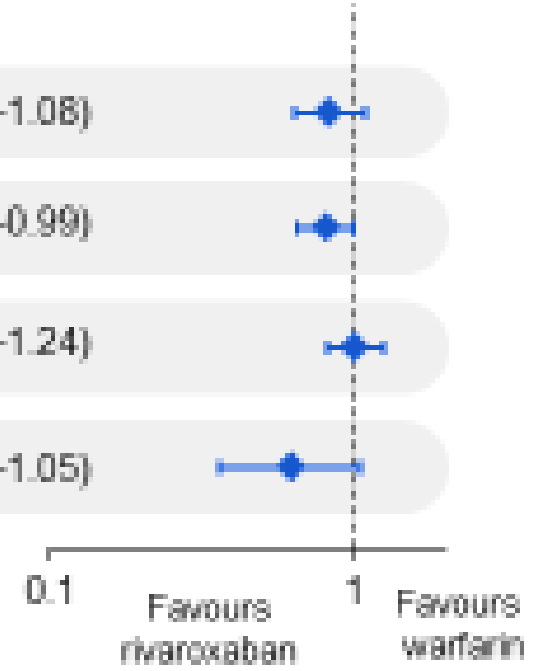


40% of ROCKET AF patients had AF and DM with a mean $CHADS_2$ score of 3.7 in this patient subgroup[1,5]

1. Petel MR et al. *N Engl J Med* 2011;365:883-891; 2. Granger CB et al. *N Engl J Med* 2011;365;981-992; 3. Giugliano RP et al. *N Engl J Med* 2013;369:2093-2104; 4. Connolly SJ et al. *N Engl J Med* 2009;361:1139-1151; 5. Bensilal B et al. *Am Heart J* 2015;170:675-692

Rivaroxaban Demonstrated Consistent Efficacy and Safety in Patients with DM in the ROCKET-AF Trial

AF patients with diabetes	Events/100 PY		HR (95% CI
	Rivaroxaban	Warfarin	
Stroke/SE	1.74	2.14	0.82 (0.63–1.08)
Cardiovascular death	2.83	3.65	0.80 (0.64–0.99)
Major bleeding	3.79	3.90	1.00 (0.81–1.24)
Intracranial hemorrhage	0.50	0.82	0.62 (0.36–1.05)



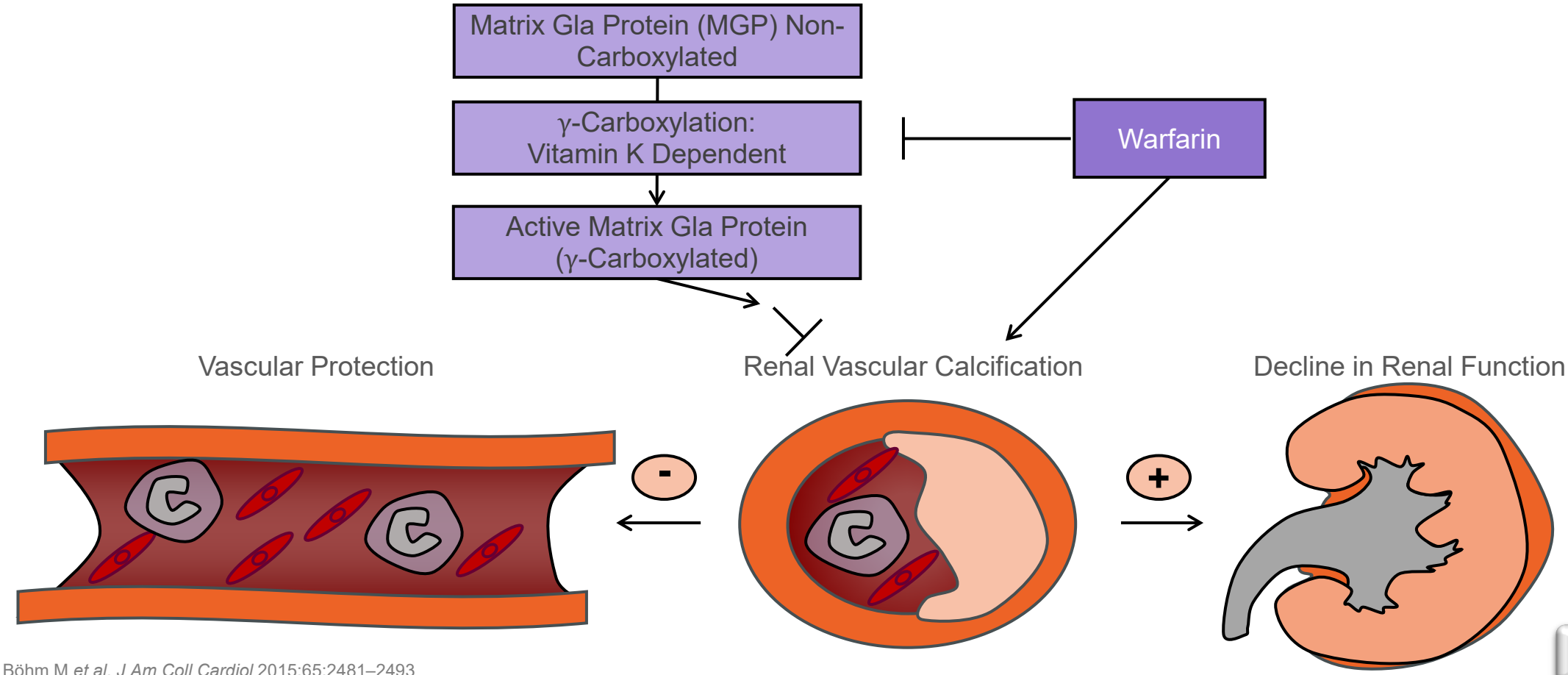
Bensilal B et al. *Am Heart J* 2015;170:675-682e8

Diabetes and Renal Failure

- Diabetes is associated with diabetic nephropathy
- Diabetes is one of the leading causes of end-stage renal disease in the Americas, EU
- Can we trust effectiveness of NOACs in patients with diabetic renal failure?

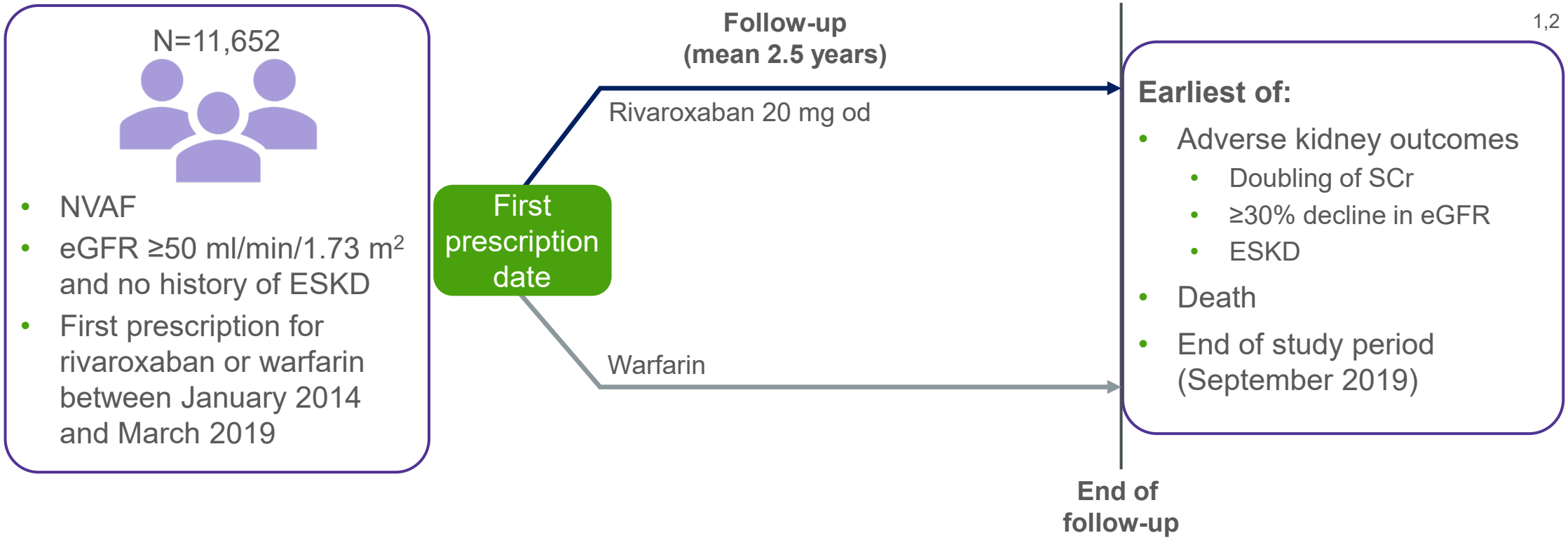
Warfarin may adversely affect renal function over time

- Vitamin K-dependent factors protect against calcification in the renal arteries



Adapted from: Böhm M *et al*, *J Am Coll Cardiol* 2015;65:2481–2493

ANTENNA Evaluated Adverse Kidney Outcomes in Patients with NVAF and eGFR ≥50 ml/min/1.73 m^2 and No History of ESKD[1]

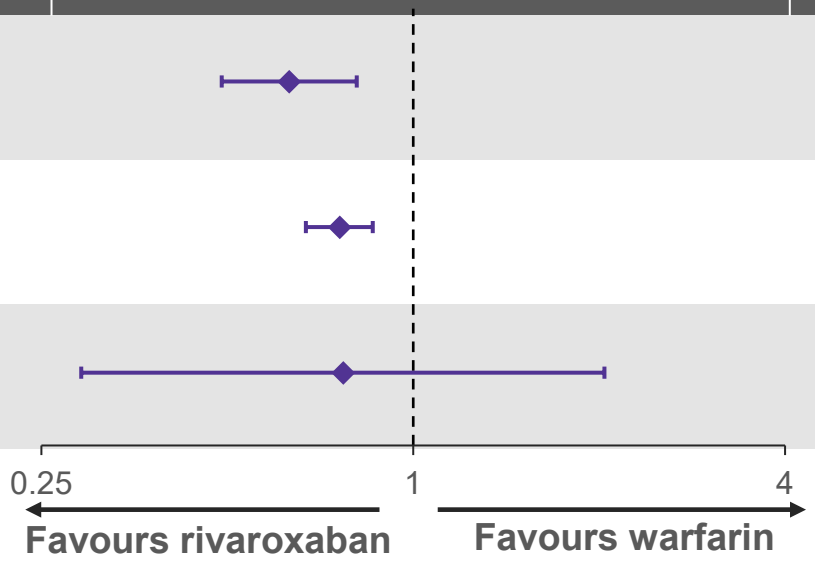


- Population-based cohort study using IMRD-UK database primary electronic health records[1]
  - Database covers 6% of the UK population[3]
  - Patient health and treatment information are recorded, including measurements of kidney function[1,3]

1. Yanina Lenz *et al*. ESC. Virtual, 27–31 August 2021. Poster. CPC choice. https://esc2021-abstract.medicalcongress.online/mediatheque/media.aspx?channel=103467&mediaId=104597 [accessed 23 August 2021]. 2. González Pérez *et al*. ICPE. Virtual, 23–25 August 2021. Presentation. Lightning Session. https://icpemeeting.secure-platform.com/a/solicitations/1/sessiongallery/161/application/245 [accessed 23 August 2021]. 3. The Health Improvement Network. 2021. https://www.the-health-improvement-network.com/patient?hsLang=en [accessed 23 August 2021].

Patients with NVAF Receiving Rivaroxaban Had a Reduced Risk of Adverse Renal Outcomes Compared to Those Receiving Warfarin

Adverse renal outcomes	Incidence rate per 10,000 patients-years		Adjusted HR* (95% CI)	Adjusted HR*‡ (95% CI)
	Rivaroxaban (n=5338)	Warfarin (n=6314)		
100% increase in SCr	77.8	128.9		**0.63 (0.49–0.81)**
≥30% decline in eGFR#	359.8	469.1		**0.76 (0.67–0.86)**
ESKD‡	5.1	8.8		0.77 (0.29–2.04)



*Adjusted for age, sex, baseline eGFR, number of previous measurements at baseline, Townsend index, polymedication, smoking, body mass index, health service use (PCP visits, referrals and hospitalisations) in the year before the start date, ischaemic heart disease, cancer, diabetes, heart failure, previous acute kidney injury, frailty and CHA_2DS_2-VASc score. #Confirmed by second measurement. ‡Coded entry for ESKD, CKD stage 5, chronic dialysis, or eGFR <15 ml/min/1.73 m^2 (confirmed by second measurement). ‡Significant values are highlighted in blue.

Yanina Lenz *et al*. ESC. Virtual, 27–31 August 2021. Poster. CPC choice. https://esc2021-abstract.medicalcongress.online/mediatheque/media.aspx?channel=103467&mediaId=104597 [accessed 23 August 2021].

Factor XA – Inhibition in RENal patients with non-valvular AF Observational registry

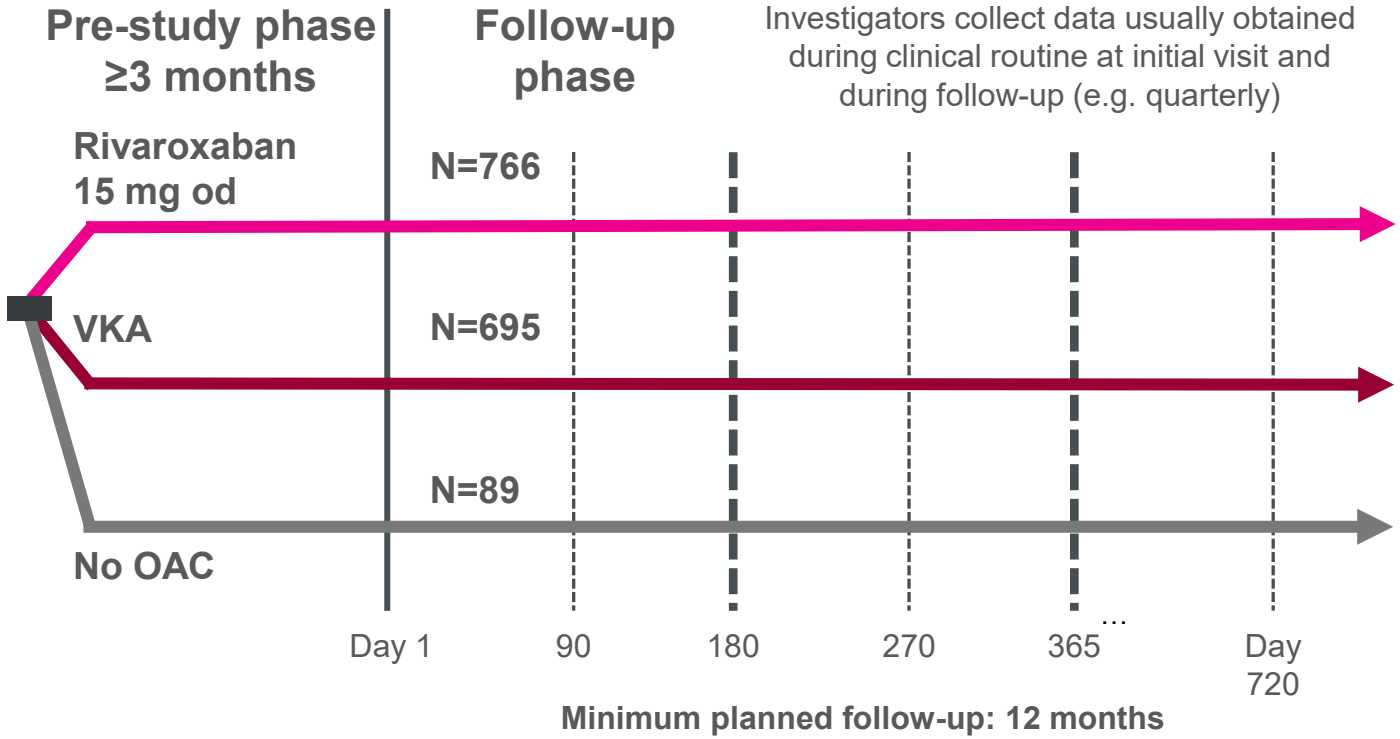
XARENO is a prospective, observational, real-world study of patients with AF and CKD prescribed rivaroxaban, VKA, or no anticoagulation

Study population

Patients with AF (N=1550) and CKD (eGFR 15–49 ml/min per 1.73m^2)

Patient selection and choice of type, dose and duration of drug used at discretion of attending physician

Outcome events were adjudicated by a blinded committee



Patients in the no anticoagulant arm can receive antiplatelet therapy.

AF, atrial fibrillation; CKD, chronic kidney disease; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; LPLV, last patient, last visit; OAC, oral anticoagulant; od, once daily; VKA, vitamin K antagonist.

XARENO study NCT02663076. https://clinicaltrials.gov/ct2/show/NCT02663076; Kreutz R *et al*. *Circulation* 2020;142: Abstract 13927; Kreutz R *et al*. Presented at ACC 2022.

XARENO – Baseline Characteristics

Characteristic	Total (n=1550)	Rivaroxaban (n=766)	VKA (n=695)	No OAC (n=89)
Age (mean +/- SD)	78.2 +/- 7.6	77.7 +/- 7.3	78.4 +/- 7.5	80.6 +/- 9.2
Male, n (%)	865 (55.8)	416 (54.3)	399 (57.4)	50 (56.2)
>75 years, n (%)	1002 (67.5)	465 (63.6)	475 (71.3)	62 (70.5)
CHA_2DS_2-VASc score (mean +/- SD)	4.0 (1.4)	3.9 (1.4)	4.0 (1.4)	4.0 (1.6)
eGFR ml/min per 1.73m^2 (mean +/- SD)	36.2 +/- 10.1	39.1 +/- 8.6	33.3 +/- 10.6	33.6 +/- 10.1
Hypertension	1242 (80.1)	611 (79.8)	559 (80.4)	72 (80.9)
Diabetes	614 (39.6)	297 (38.8)	287 (41.3)	30 (33.7)
Stroke/TIA	182 (11.7)	87 (11.4)	82 (11.8)	13 (14.6)
Heart failure	333 (21.5)	163 (21.3)	155 (22.3)	15 (16.9)
Myocardial infarction	202 (13.0)	90 (11.7)	99 (14.2)	13 (14.6)

- 1550 patients were enrolled in 6 countries in Europe; Patients had at least 12 months of follow-up
- Patients had a mean age of 78.2 +/- 7.6 years
- ~30% of patients enrolled had an eGFR <30ml/min at baseline
  - Of these, ~60% were on VKA, ~30% on rivaroxaban, and ~10% on no OAC

Kreutz R *et al*. *Circulation* 2020;142: Abstract 1392; Kreutz R *et al*. Presented at ACC 2022.

XARENO – Key Differences Between Patients Prescribed Rivaroxaban and VKA

- Due to real-world prescribing decisions, there were important differences in the characteristics of patients receiving rivaroxaban, VKA, or no OAC
  - Older patients were more likely to receive VKA or no anticoagulation
  - Patients with lower eGFR were more likely to receive VKA or no anticoagulation
- To compare outcomes between patients receiving rivaroxaban and VKA, a propensity score matching analysis was completed

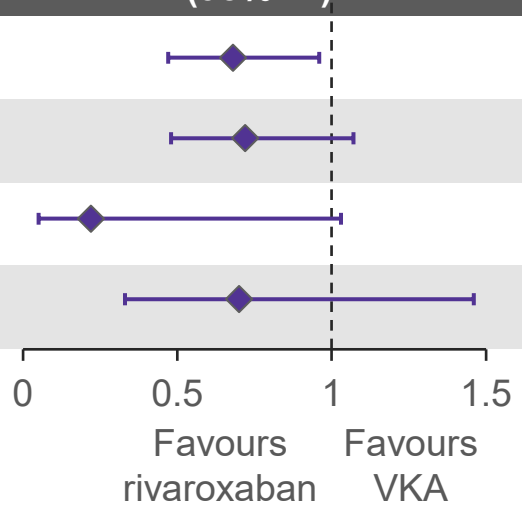
Propensity Scored Matched Cohort	Rivaroxaban (n=397)	VKA (n=410)
Age (mean +/- SD)	78.2 +/- 7.1	78.0 +/- 7.5
Male, n (%)	209 (52.6)	224 (54.6)
CHA_2DS_2-VASc score (mean +/- SD)	4.0 (1.4)	4.0 (1.4)
eGFR ml/min per 1.73m^2 (mean +/- SD)	37.0 +/- 8.3	36.6 +/- 9.0
Hypertension	319 (80.4)	327 (79.8)
Diabetes	156 (39.3)	174 (42.4)
Stroke/TIA	43 (10.8)	46 (11.2)
Heart failure	100 (25.2)	90 (22.0)
Myocardial infarction	39 (9.8)	64 (15.6)

Kreutz R *et al*. Presented at ACC 2022

XARENO – Primary Outcomes

- In the propensity score matched cohort analysis, rivaroxaban reduced the net clinical benefit outcome (stroke, other thromboembolic events, major bleeding, all-cause mortality) compared to VKA
  - The components of the net clinical benefit were numerically reduced with rivaroxaban compared to VKA

Outcome	Propensity-score weighted IRR (95% CI)	PS weighted IRR (95% CI)
Net clinical benefit		0.68 (0.47-0.96)
All-cause death		0.72 (0.48-1.07)
Stroke/TIA/SE		0.22 (0.05-1.03)
Major bleeding		0.70 (0.33-1.46)

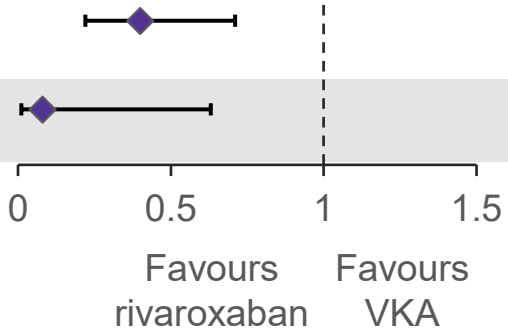


IRR = incidence risk ratio; Kreutz R *et al*. Presented at ACC 2022.

XARENO – Renal Outcomes

- Through its mechanism of action, warfarin inhibits vitamin K-dependent processes – this can lead to vascular calcification and damage of end organs
- In the propensity score matched cohort analysis, rivaroxaban reduced the progression to stage 5 chronic kidney disease or initiation of renal replacement therapy compared to VKA

Outcome	Propensity-score weighted IRR (95% CI)	PS weighted IRR (95% CI)
CKD Stage 5		0.40 (0.22-0.71)
Initiation of chronic RRT		0.08 (0.01-0.63)



CKD = chronic kidney disease; RRT = renal replacement therapy; IRR = incidence risk ratio; Kreutz R *et al*. Presented at ACC 2022.

Protecting Patients with NVAF and Co-morbid Diabetes or Moderate to Severe CKD Requires Consideration of MACE / Vascular Risk[1]

	n (%)	Risk of MACE HR (95% CI)*
Diabetes	37,114 (47.7)	1.11 (1.05–1.18)
Diabetic nephropathy	2167 (2.8)	1.08 (0.94–1.23)
CKD stage 3 or worse	NR	1.23 (1.15–1.31)
Polyvascular disease	6874 (8.8)	1.87 (1.53–2.28)
Hypertension#	76,610 (98.5)	1.18 (0.95–1.46)
Hypercholesterolaemia#	62,413 (80.3)	0.94 (0.83–1.06)

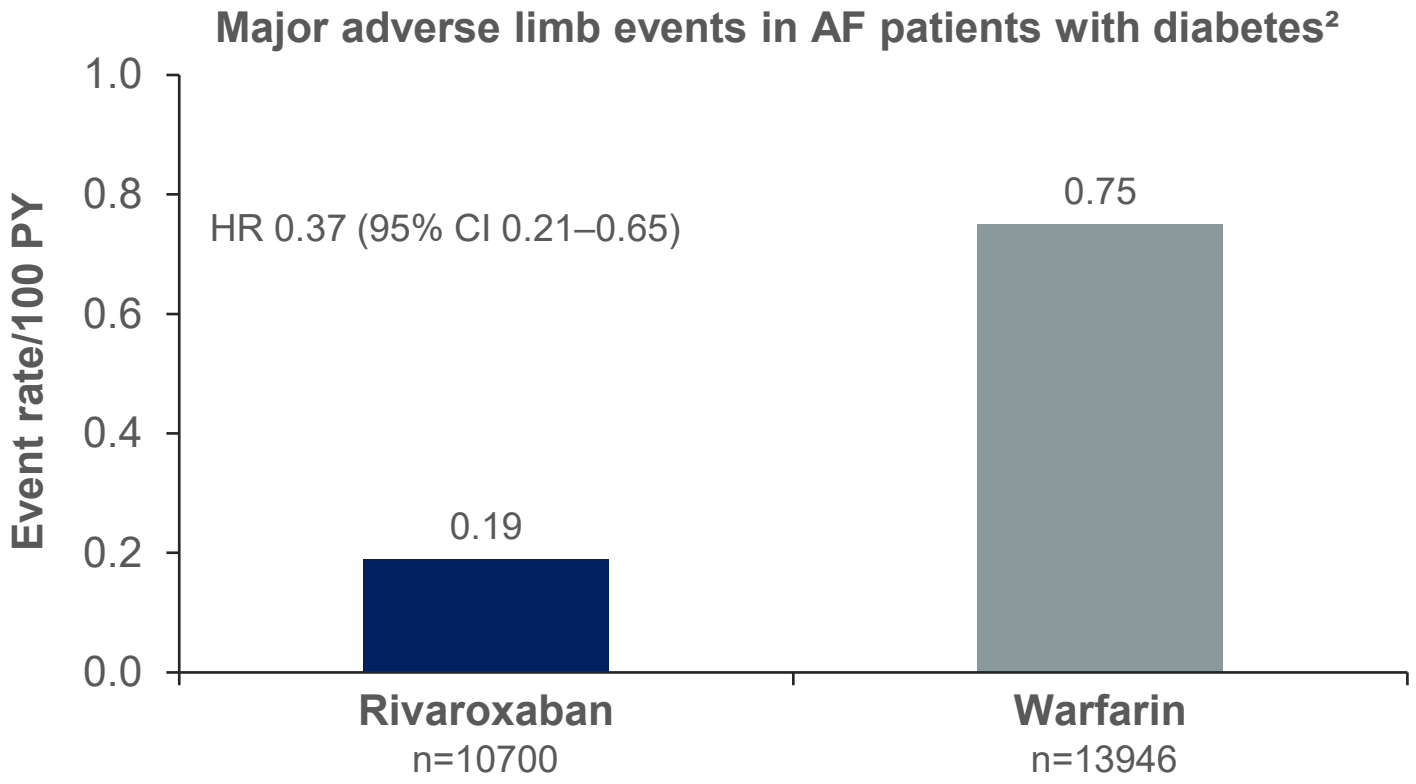
- Approximately 7 in 10 deaths of patients with NVAF receiving anticoagulation are cardiovascular related[2]

*Cox regression model of MACE at 4-year follow-up. #With treatment.

1. Miao B *et al. Clin Cardiol* 2020;43:524–531. 2. Pokorney SD *et al. J Am Heart Assoc* 2016;5:e002197.

RWE Indicates That Rivaroxaban Reduces MALE Events in AF Patients With DM Compared to Warfarin

- Patients with diabetes fear amputation almost as much as blindness or death[1]



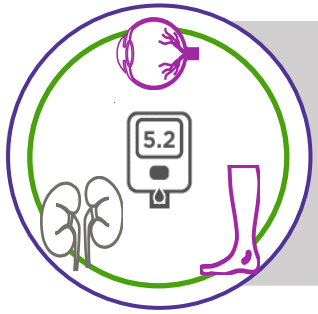
MarketScan claims data in patients with atrial fibrillation and diabetes; 24% of patients in the rivaroxaban arm were on a reduced dose of 15 mg OD.

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

Protecting Patients with NVAF and T2D in the Real World: The RIVA-DM Electronic Health Record Analysis Builds Confidence from Previous Studies

RIVA-DM analysed EHR data, which are more comprehensive and more accurately represent the general population compared with previous claims database studies[1,2]

RIVA-DM included a very large patient population (N=116,049)[1]



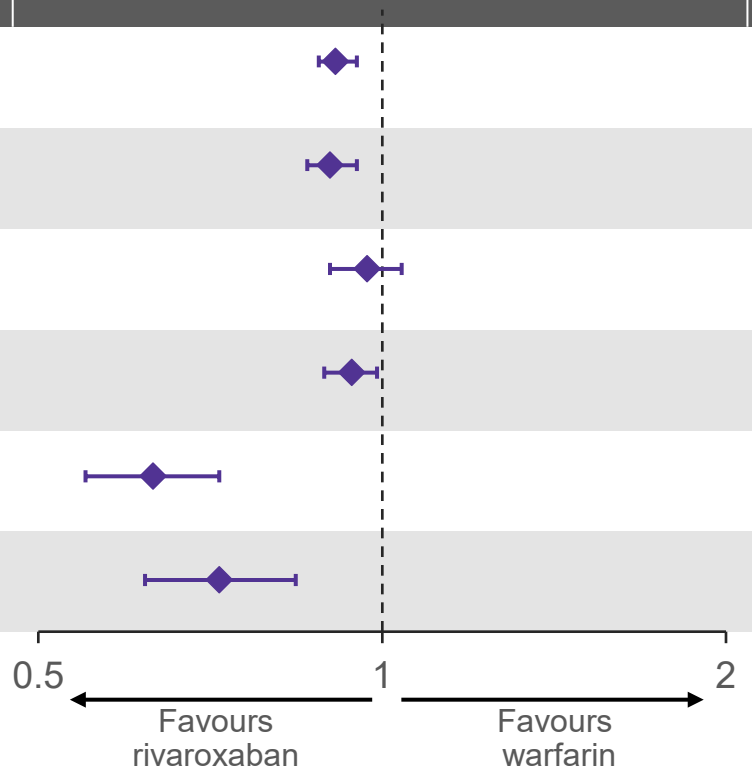
RIVA-DM analysed a breadth of outcomes that are clinically relevant to patients with T2D, such as kidney, limb and ophthalmic events

1. Coleman CI *et al*. *Cardiovasc Diabetol* 2021;20:52. 2. DeVoe JE *et al*. *Ann Fam Med* 2011;9:351–358.

How Can Patients with NVAF and T2D Be Protected from Vascular Death and Clinically Relevant Bleeding?

- Vascular death and clinically relevant bleeding were significantly lower with rivaroxaban versus warfarin in patients with NVAF and T2D

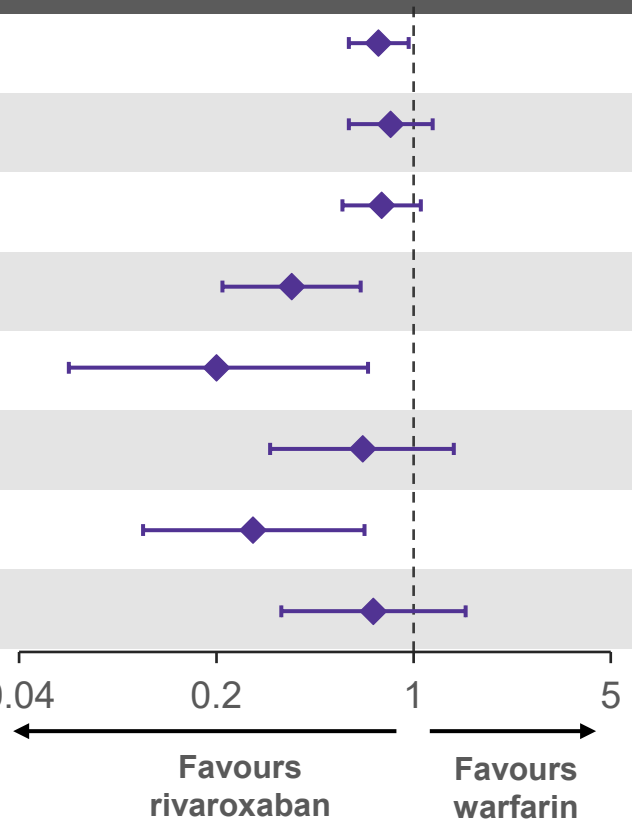
	Rivaroxaban (n=32,078)*	Warfarin (n=83,971)#	HR (95% CI)	HR (95% CI) ‡
Stroke/SE or vascular death	3.79	4.19		0.91 (0.88–0.95)
Vascular death	**2.81**	**3.18**		0.90 (0.86–0.95)
Stroke/SE	1.31	1.34		**0.97 (0.90–1.04)**
Hospitalization for major/CRNM bleeding	2.17	2.31		0.94 (0.89–0.99)
Critical organ bleeding	0.35	0.54		0.63 (0.55–0.72)
Intercranial haemorrhage	0.29	0.40		0.72 (0.62–0.84)



*31% of patients initiated reduced 15 mg od dose.
#Time in therapeutic range 47±28%. ‡Significant values are highlighted in blue.
Coleman CI *et al*. *Cardiovasc Diabetol* 2021;20:52.

Accumulating Real-World Evidence Supports Better Protection of Patients from MACE and MALE with Rivaroxaban Versus Warfarin

	Event rate (per 1000 PY)		HR (95% CI)	HR (95% CI)*
	Rivaroxaban (n=10,700)	Warfarin (n=13,946)		
MACE	1.26	2.07		**0.75 (0.59–0.96)**
Ischaemic stroke	0.66	1.01		0.83 (0.59–1.17)
MI	0.77	1.20		0.77 (0.56–1.06)
MALE	0.19	0.75		**0.37 (0.21–0.65)**
Major limb amputation	0.03	0.18		**0.20 (0.06–0.69)**
Surgical revascularization	0.12	0.27		0.66 (0.31–1.39)
Endovascular revascularization	0.07	0.39		**0.27 (0.11–0.67)**
Minor limb amputation	0.14	0.27		0.72 (00.34–1.53)

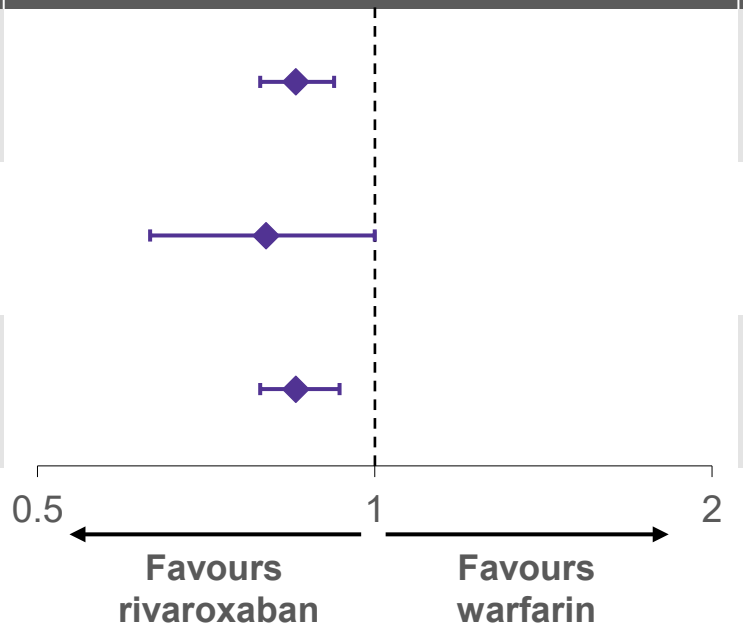


*Significant values are highlighted in blue.

Baker WL *et al*. *Diabetes Obes Metab* 2019;25:2107–2114.

RIVA-DM Demonstrates Ophthalmic Protection in Patients with NVAF and T2D Receiving Rivaroxaban Versus Warfarin

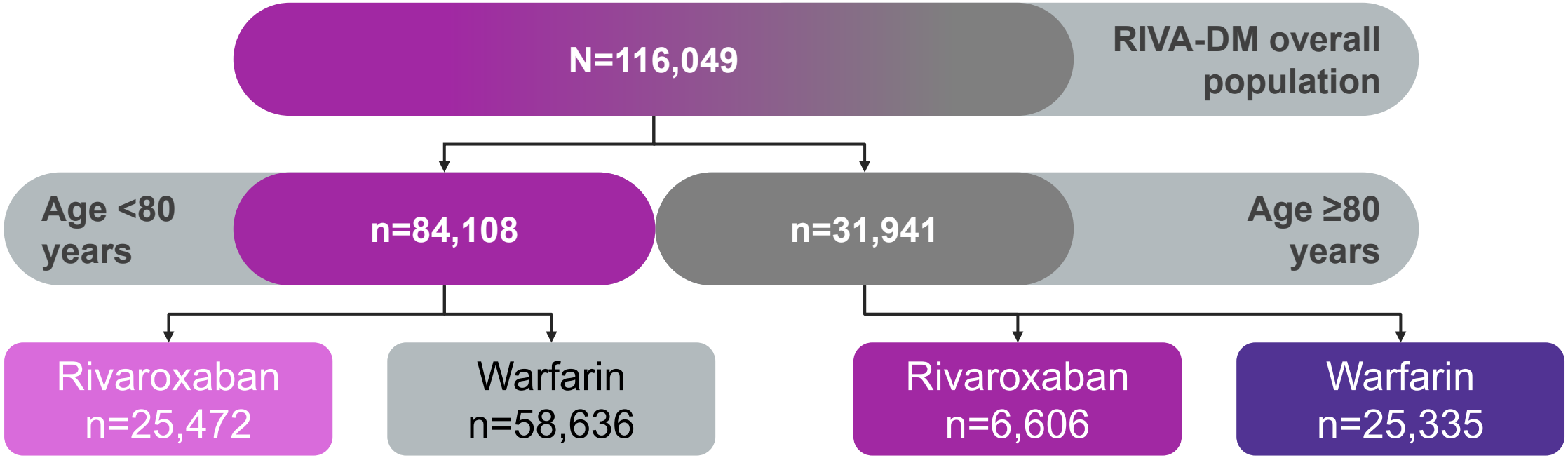
	Rivaroxaban (% per year) (n=32,078)	Warfarin (% per year) (n=83,971)	HR (95% CI)	PS OLW HR (95% CI)*
Any ophthalmic complication	1.25	1.79		**0.85 (0.79–0.92)**
Any ophthalmic bleeding event	0.15	0.19		0.80 (0.63–1.00)
Any type of diabetic retinopathy	1.15	1.34		**0.85 (0.79–0.93)**



*Significant values are highlighted in blue.
Costa OS *et al*. EHRA. Virtual, 23–25 April 2021. Oral presentation.

Diabetes, Renal Dysfunction, Elderly – the frail patient

A Subanalysis of RIVA-DM Compared Outcomes between Patients Aged <80 Years and ≥80 Years



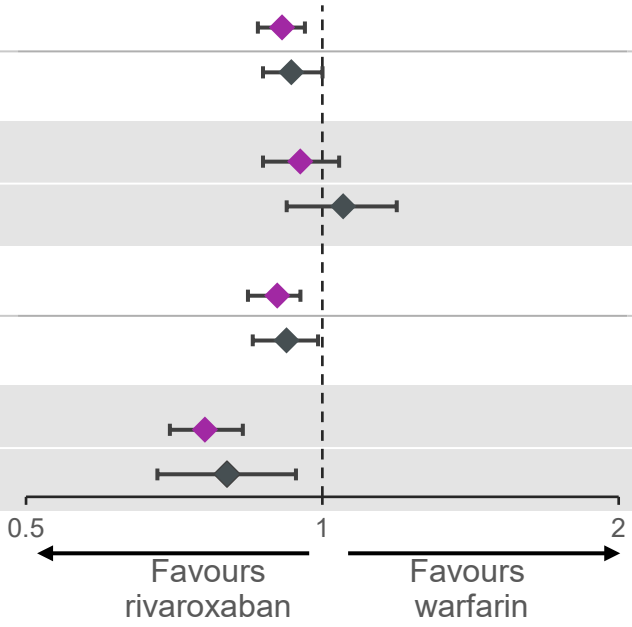
The objective of this subanalysis was to evaluate the impact of advanced age on the comparative effectiveness and safety of rivaroxaban compared with warfarin in a large cohort of patients with NVAF and comorbid diabetes in routine practice

Coleman C *et al*. ASH. Georgia, USA, 13 December 2021, Poster 3234.

Older and Younger Patients with NVAF Experience a Consistent Benefit from Anticoagulation with Rivaroxaban Rather than Warfarin Regardless of Age

- Comparison of effectiveness outcomes for rivaroxaban versus warfarin for patients with diabetes aged <80 years and ≥80 years with NVAF found no statistically significant difference due to age

	Age group	Incidence rate (%/year) Rivaroxaban (n=32,078)	Incidence rate (%/year) Warfarin (n=83,971)	HR (95% CI)	HR (95% CI)	*p*-int
Stroke/SE or vascular death	Age <80 years	3.24	3.62		0.91 (0.86–0.96)*	>0.99
	Age ≥80 years	6.31	6.86		0.93 (0.87–1.00)	
Stroke/SE	Age <80 years	1.15	1.21		0.95 (0.87–1.04)	>0.99
	Age ≥80 years	2.08	1.98		1.05 (0.92–1.19)	
Vascular death	Age <80 years	2.26	2.58		0.90 (0.84–0.95)*	>0.99
	Age ≥80 years	4.81	5.34		0.92 (0.85–0.99)*	
MALE	Age <80 years	1.10	1.44		0.76 (0.70–0.83)*	>0.99
	Age ≥80 years	1.09	1.37		0.80 (0.68–0.94)*	



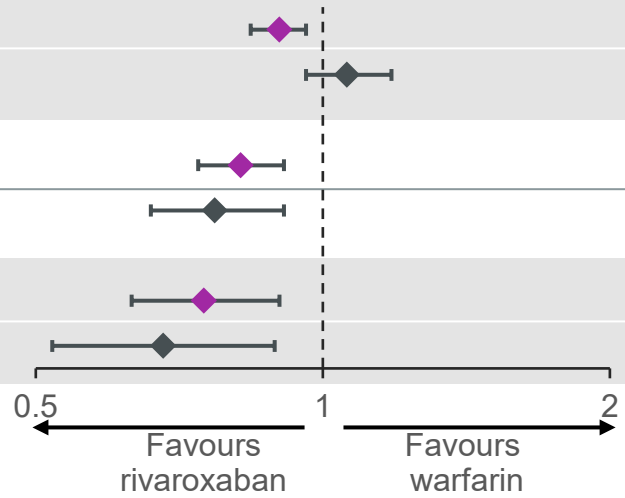
*Statistically significant benefit observed for treatment with rivaroxaban compared with warfarin.

Coleman C *et al*. ASH. Georgia, USA, 13 December 2021, Poster 3234.

Older Patients with NVAF Experience a Similar Safety Benefit to Younger Patients from Anticoagulation with Rivaroxaban Rather Than Warfarin

- Comparison of safety outcomes for rivaroxaban versus warfarin for patients with diabetes aged <80 years and ≥80 years with NVAF found no statistically significant difference due to age

	Age group	Incidence rate (%/year) Rivaroxaban (n=32,078)	Incidence rate (%/year) Warfarin (n=83,971)	HR (95% CI)	HR (95% CI)	*p*-int
Major bleeding or CRNM hospitalisation	Age <80 years	2.00	2.22		0.90 (0.84–0.96)*	0.2265
	Age ≥80 years	3.29	3.09		1.06 (0.96–1.18)	
Major bleeding	Age <80 years	0.86	1.05		0.82 (0.74–0.91)*	>0.99
	Age ≥80 years	1.11	1.43		0.77 (0.66–0.91)*	
Intracranial haemorrhage	Age <80 years	0.26	0.34		0.75 (0.63–0.90)*	>0.99
	Age ≥80 years	0.26	0.63		0.68 (0.52–0.89)*	

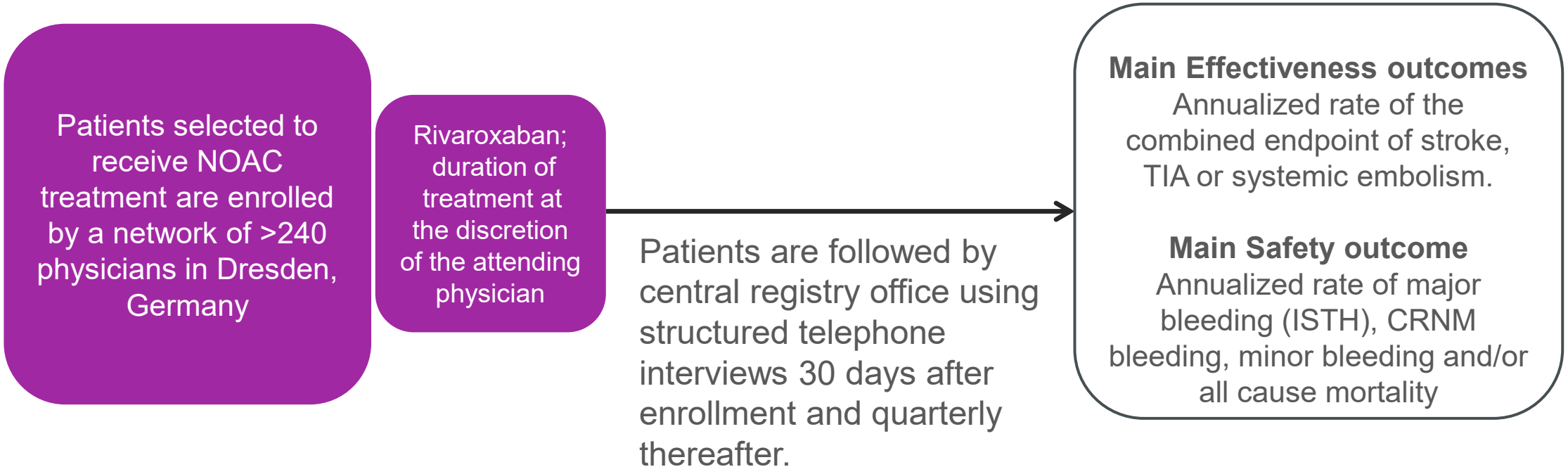


*Statistically significant benefit observed for treatment with rivaroxaban compared with warfarin.

Coleman C *et al*. ASH. Georgia, USA, 13 December 2021, Poster 3234.

The Dresden NOAC Registry: Prospective, non-interventional registry

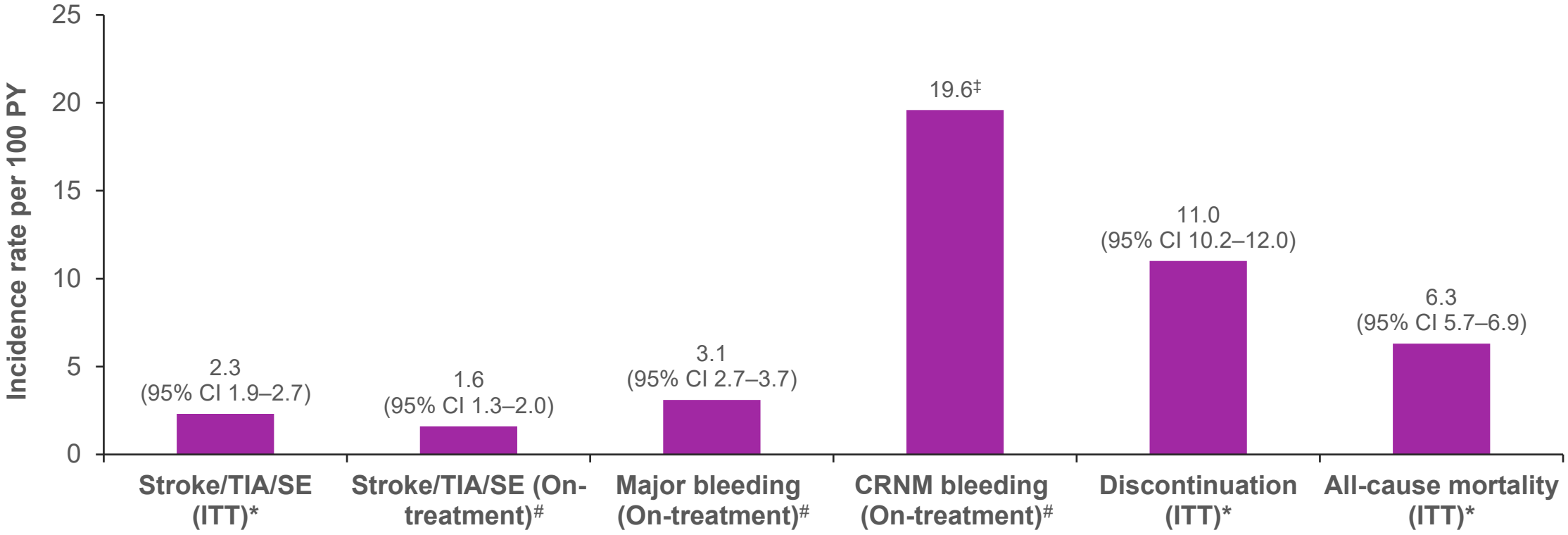
- **Objective:** To collect real-life data on effectiveness and safety of rivaroxaban therapy



Tittl L *et al. Thromb Res* 2021;202:24–30.

Dresden Registry: Patients with AF and a Median Age of 75 Years Treated with Rivaroxaban and Followed for 5 Years

- Event rates in the 5-year follow-up period in patients receiving rivaroxaban (n=1204)



*ITT analysis included all patients enrolled receiving rivaroxaban at baseline and incorporates all effectiveness outcome events that occurred throughout the follow-up period, regardless of interruption or discontinuation of rivaroxaban. #On-treatment analysis included all patients who were still enrolled at the respective timepoint and were still receiving treatment with rivaroxaban. The data for major bleeding were reported only in on-treatment analysis. ‡95% CI not reported for CRNM bleeding.

Tittl L *et al*. *Thromb Res* 2021;202:24–30.

Bleeding Rates in Patients Receiving Rivaroxaban Correlate With Patient Risk Across Prospective Studies

Results are not intended for direct comparison

*Major bleeding definition according to ISTH.

1. Patel MR *et al. N Engl J Med* 2011;365:883–891; 2. Tittl L *et al. Thromb Res* 2021;202:24–30; 3. Camm AJ et al. *Eur Heart J* 2016; 37:1145-53.

Wearable Technologies for the Detection of AF

Present and Future of OAC

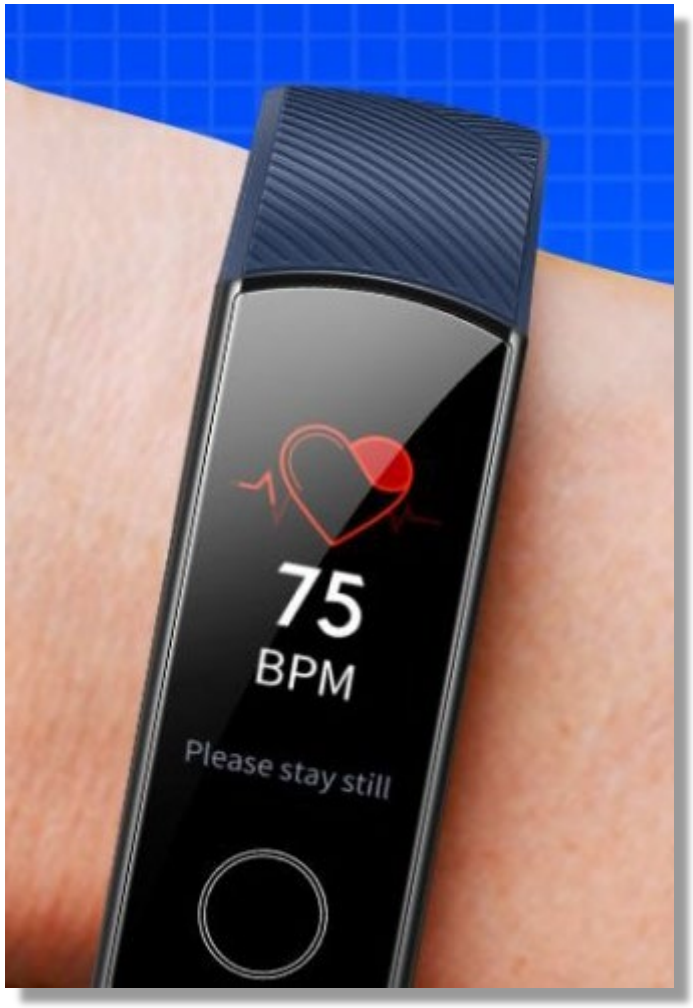
Atul Verma, MD, FRCPC, FHRS
Head of Division of Cardiology, McGill University Health Centre
Chair in Cardiology, Isadore Rosenfeld
Associate Professor, McGill University

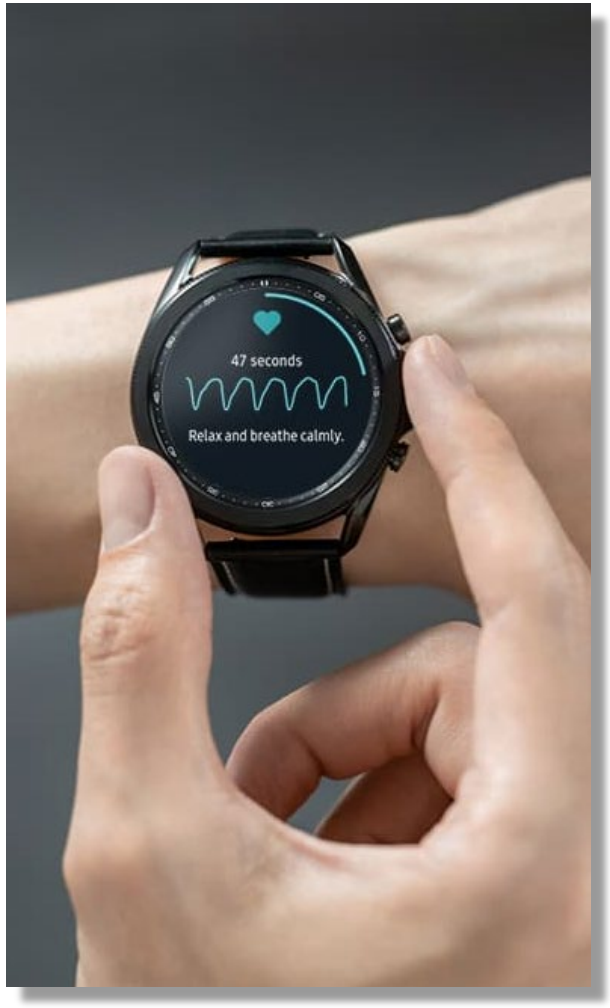
Methods of AF Wearable Detection

- Photoplethysmography (PPG) – light transmitted into skin and then reflected back to a sensor – signal changes as blood flows through the arteries
- Direct ECG recording – limited number of leads (1 to 6) that are incorporated into a device, usually requires user to place finger(s) on an electrode with another located on skin or another finger
- Some devices have more than one capability

PPG Devices

FitBit

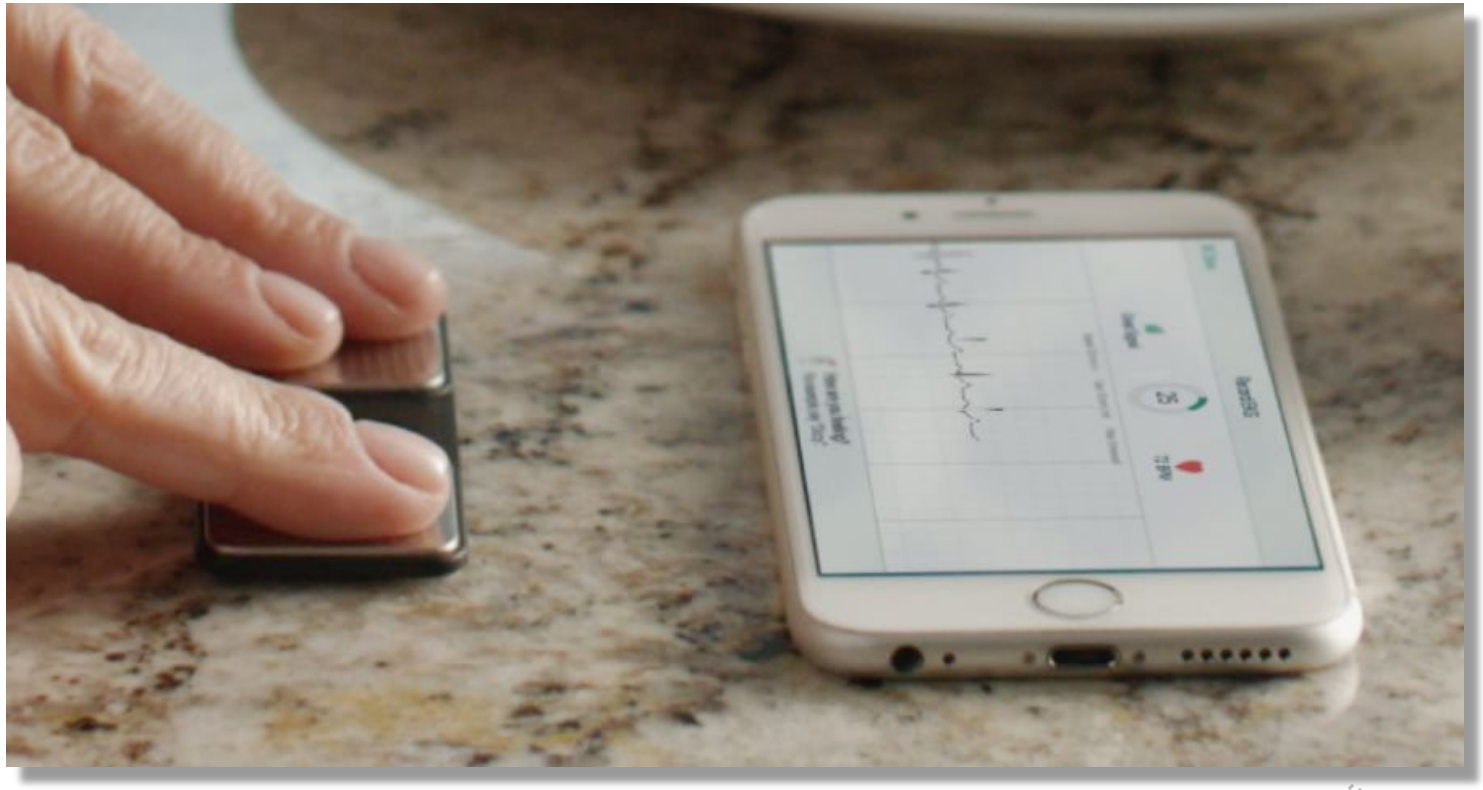




Samsung Watch

ECG Based Device

AliveCor



My Diagnostick

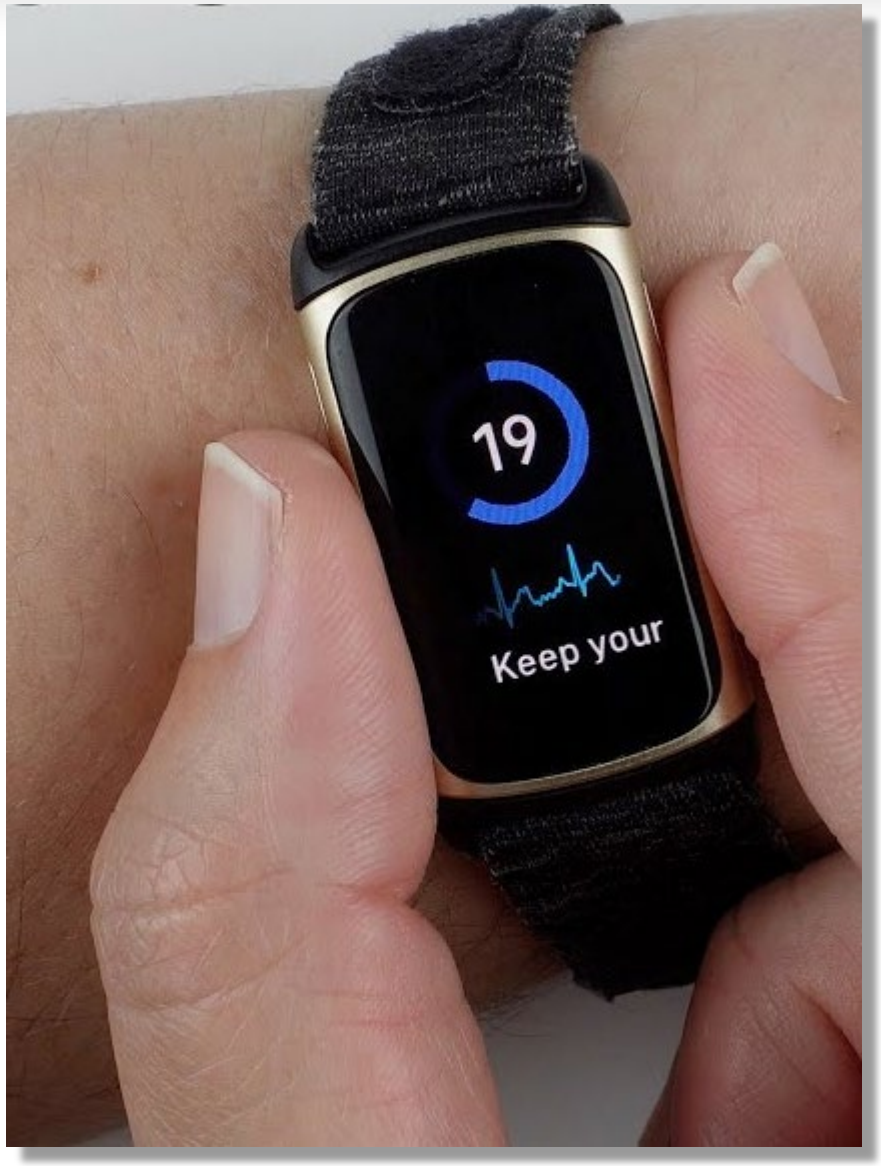
Combination Devices

AppleWatch Series 1-3

AppleWatch Series 4-6

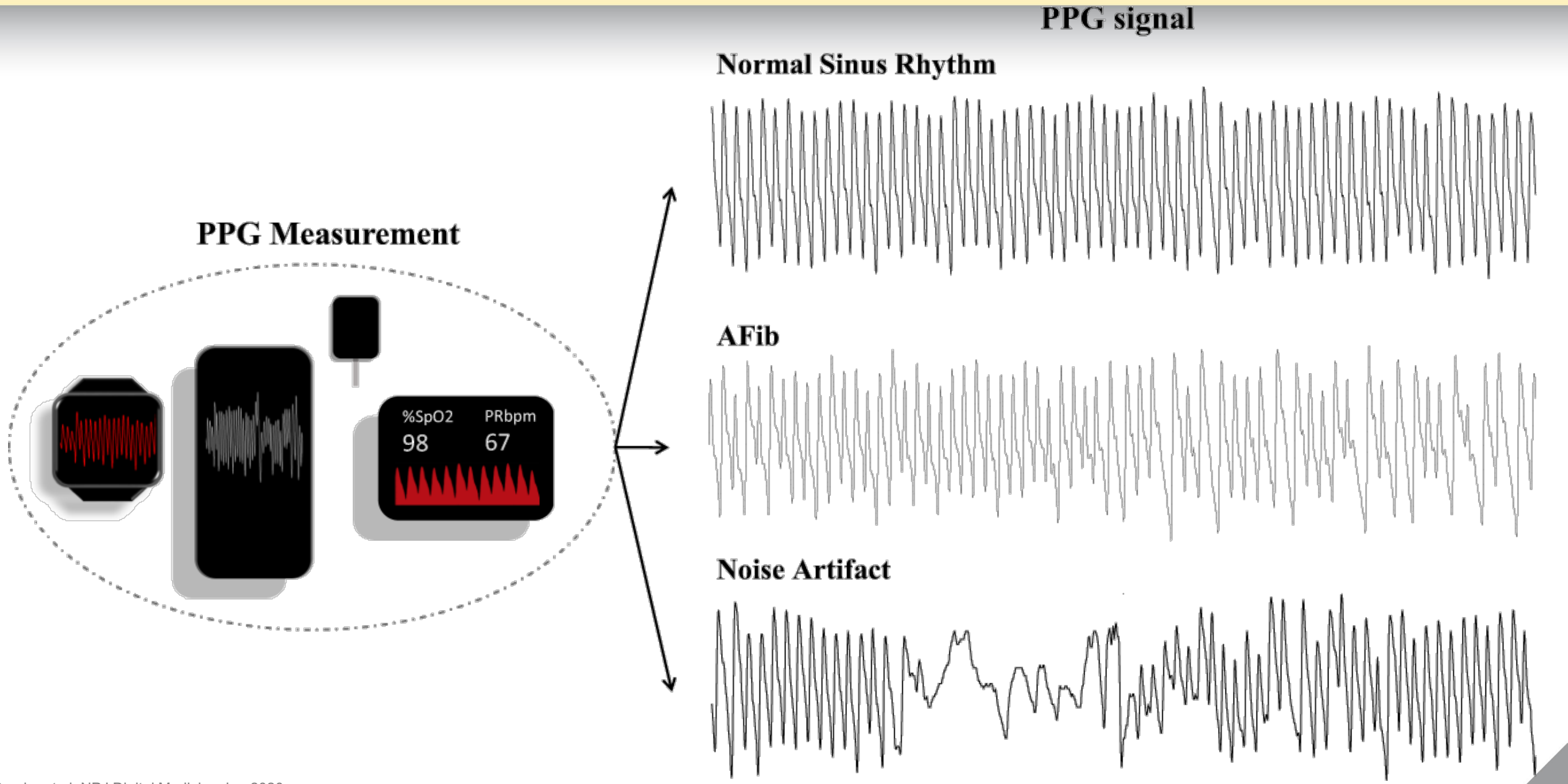
Combination Devices

FitBit ECG Device
Charge 5

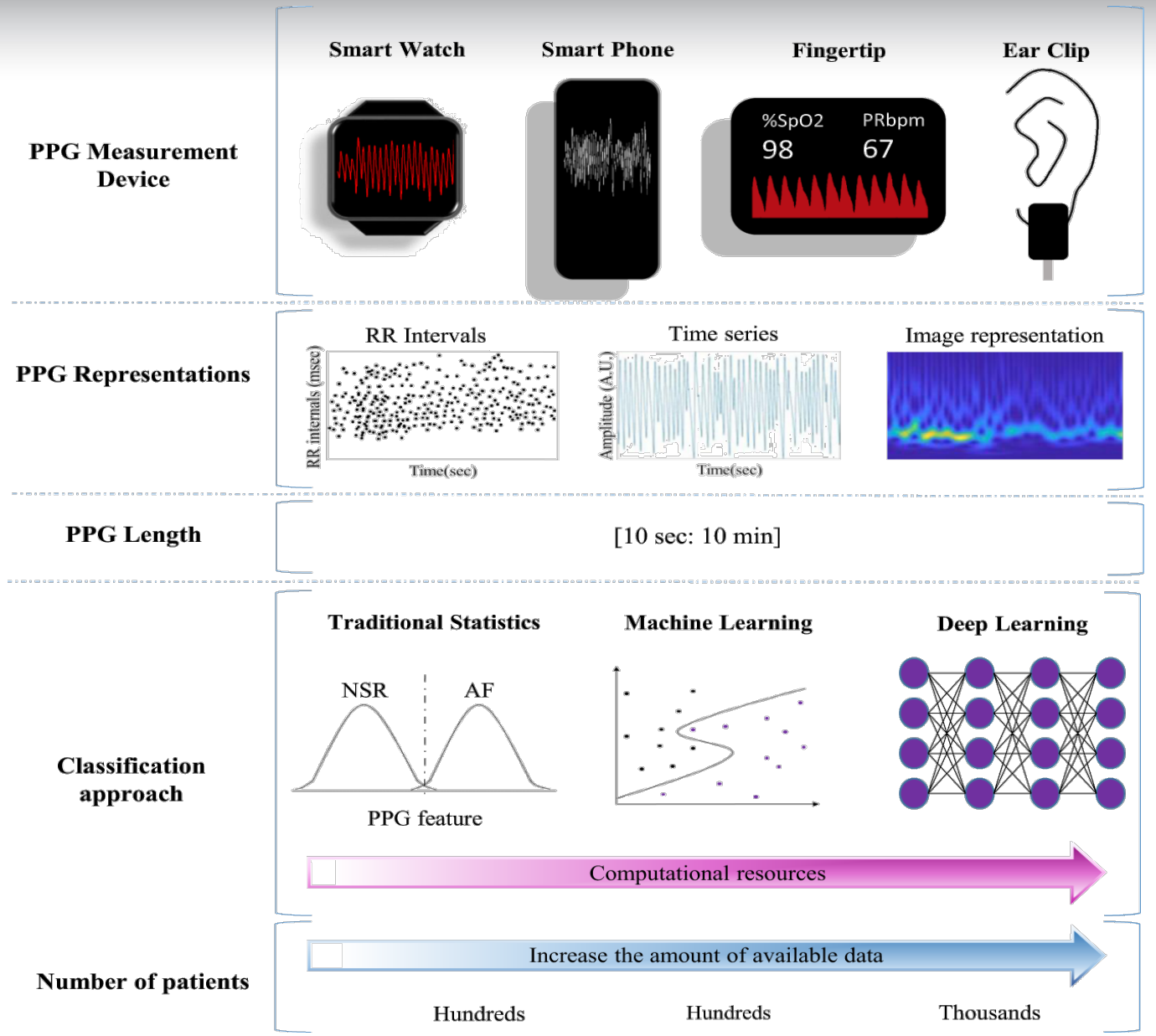


PPG Devices

- Usually require an additional algorithm to detect AF
- Algorithms are often some form of machine-based, or deep-learning-based algorithm
- Use both the regularity, amplitude, and area of the PPG tracings



Pereira et al, NPJ Digital Medicine Jan 2020



Pereira et al, NPJ Digital Medicine Jan 2020

Apple Watch – NEJM Nov 2019

Large-Scale Assessment of a Smartwatch to Identify Atrial Fibrillation

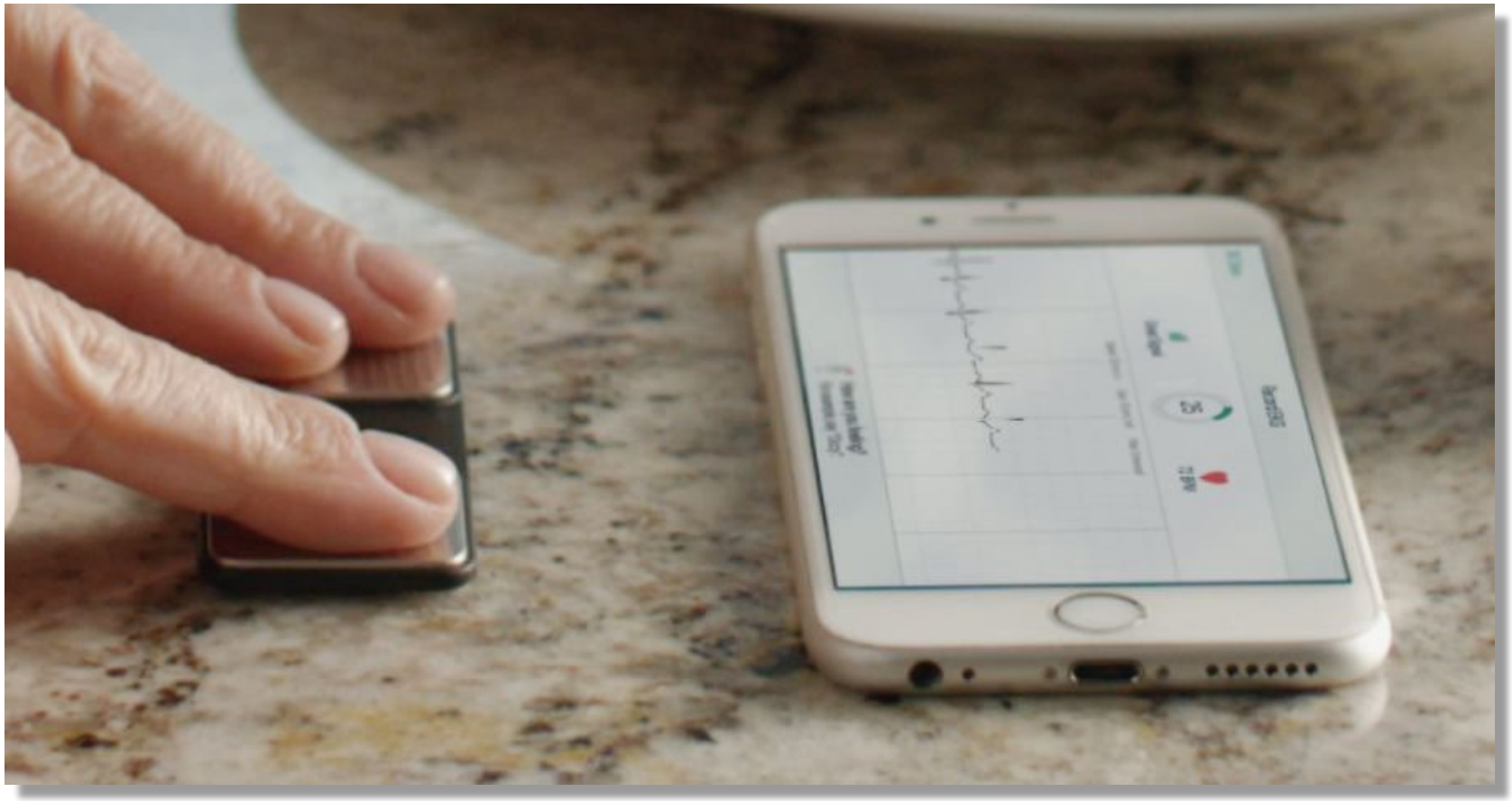
Marco V. Perez, M.D., Kenneth W. Mahaffey, M.D., Haley Hedlin, Ph.D., John S. Rumsfeld, M.D., Ph.D., Ariadna Garcia, M.S., Todd Ferris, M.D., Vidhya Balasubramanian, M.S., Andrea M. Russo, M.D., Amol Rajmane, M.D., Lauren Cheung, M.D., Grace Hung, M.S., Justin Lee, M.P.H., et al., for the Apple Heart Study Investigators*

overall and in 35% (97.5% CI, 27 to 43) of participants 65 years of age or older. Among participants who were notified of an irregular pulse, the positive predictive value was 0.84 (95% CI, 0.76 to 0.92) for observing atrial fibrillation on the ECG simultaneously with a subsequent irregular pulse notification and 0.71 (97.5% CI, 0.69 to 0.74) for observing atrial fibrillation on the ECG simultaneously with a subsequent irregular tachogram. Of 1376 notified participants who returned a 90-day survey, 57%

High sensitivity, but low specificity, PPG only feature

ECG Based Device

AliveCor®



Positive predictive value 77%, negative predictive value 99.6% - both sensitive and specific

J Am Heart Assoc 2017, DOI: 10.1161/JAHA.116.003428

Sensitivity and Specificity of Devices

Sensitivity, specificity, PPV, and NPV of Smart Watch, Wearables, and Handheld EKG devices in detecting AF

Smart Watch/Wearable/Handheld EKG	Studies	Sensitivity/specificity/PPV/NPV
Cardiio Rhythm app	Chan *et al.*, 2016	Sensitivity: 92.9%; specificity: 97.7%; PPV: 53.1%; NPV: 99.8%
Apple watch (FDA approved)	Turakhia *et al.*, 2019	PPV of tachogram: 71%; PPV of notification: 84%
Kardia Band (FDA approved)	Bumgarner *et al.*, 2018	Sensitivity: 93%; specificity: 84%
Alive Cor single lead EKG (FDA approved)	Chan *et al.*, 2016	Sensitivity: 71.4%; specificity: 99.4%; PPV: 76.9%; NPV: 99.2%
	Desteghe *et al.*, 2016	Cardiology ward: sensitivity: 54.5%; specificity: 97.5% Geriatrics ward: sensitivity: 78.9%; specificity: 97.9%
	Koshy *et al.*, 2018	Sensitivity: 77%; specificity: 76%
My Diagnostick	Desteghe *et al.*, 2016	Cardiology ward: sensitivity: 81.8%; specificity: 94.2% Geriatrics ward: sensitivity: 89.5%; specificity: 95.7%

PPV, positive predictive value; NPV, negative predictive value; EKG, electrocardiogram; FDA, Food and Drug Administration.

Ann Transl Med 2019;7(17):417 | http://dx.doi.org/10.21037/atm.2019.06.79

Circulation

ORIGINAL RESEARCH ARTICLE

Screening for Atrial Fibrillation in Older Adults at Primary Care Visits: VITAL-AF Randomized Controlled Trial

Steven A. Lubitz, MD, MPH; Steven J. Atlas, MD, MPH; Jeffrey M. Ashburner, PhD, MPH; Ana T. Trisini Lipsanopoulos, BS; Leila H. Borowsky, MPH; Wyliena Guan, MS; Shaan Khurshid, MD, MPH; Patrick T. Ellinor, MD, PhD; Yuchiao Chang, PhD; David D. McManus, MD, MSc; Daniel E. Singer, MD

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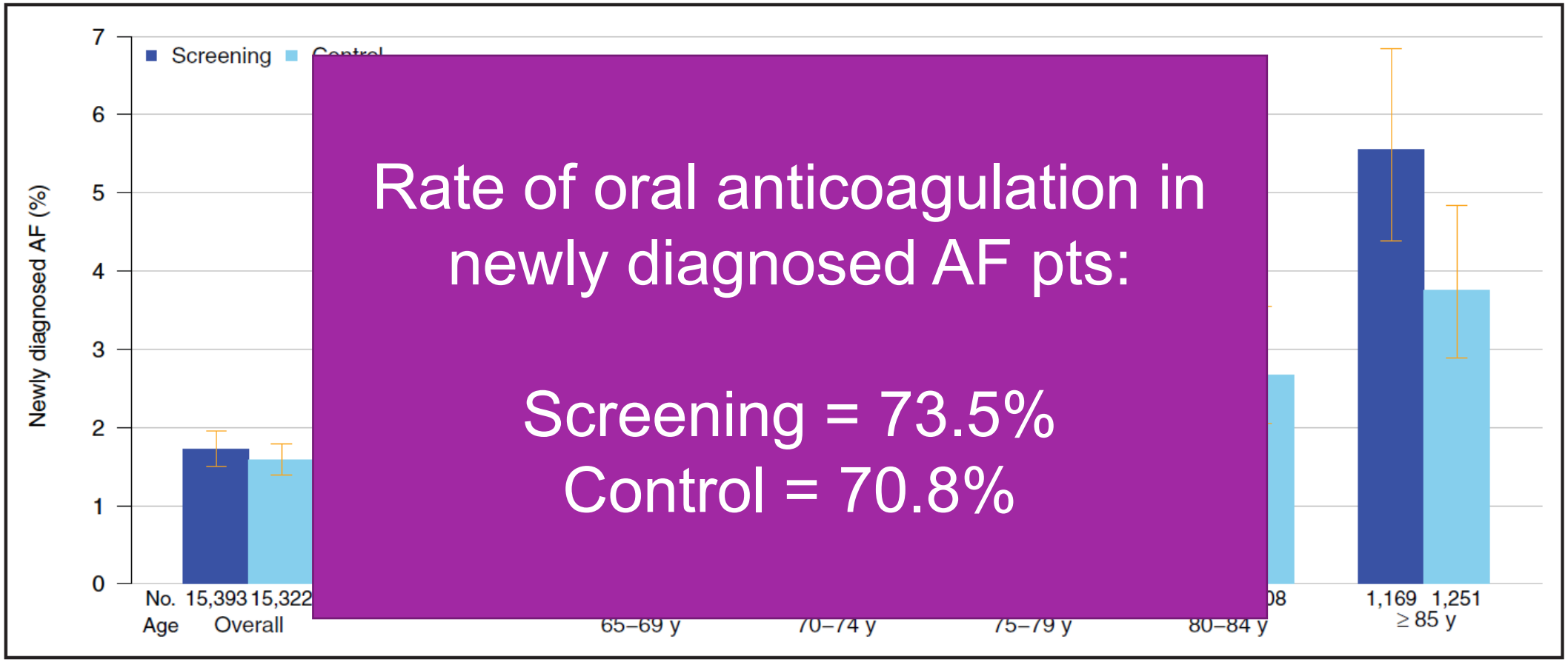
Methods

- 16 primary care clinics in US
- Patients enrolled to usual care or enhanced screening by a cluster randomization trial based on clinic (8 = screening, 8 = control)
- Enhanced screening performed with AliveCor single-lead device at the time vital signs were collected by the clinic nurse when the patient visited
- Patients had a median of 2 visits to their clinic in one year
- Only included patients >65 years old, no history of AF
- 15,393 enrolled in screening program
- 15,322 enrolled in control arm
- Outcome was newly diagnosed AF in one year follow-up

Results



Rate of oral anticoagulation in newly diagnosed AF pts:

Screening = 73.5%
Control = 70.8%

Figure 2. Proportion of individuals with newly diagnosed AF within 12 months in the screening and control groups overall and stratified by age.

Depicted are 95% CIs. AF indicates atrial fibrillation.

Conclusions

- Know your technology – PPG or ECG based
- ECG based are more “accurate”
- PPG dependent on background algorithm for analysis
- AliveCor ECG and AppleWatch ECG are best widely available devices
- Routine screening with these devices may or may not change population outcomes

Closing Remarks

ATUL VERMA
MD, FRCPC, FHRS

EVALUATION FORM

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Please complete the online evaluation form by one of the following options:

1. Scan the QR code with your mobile device

2. The link to the evaluation is in the chat box

3. We will email you the evaluation link shortly after the event

THANK YOU FOR JOINING US TODAY!