Stroke Prevention in AF with Kidney Disease: Challenges and Opportunities

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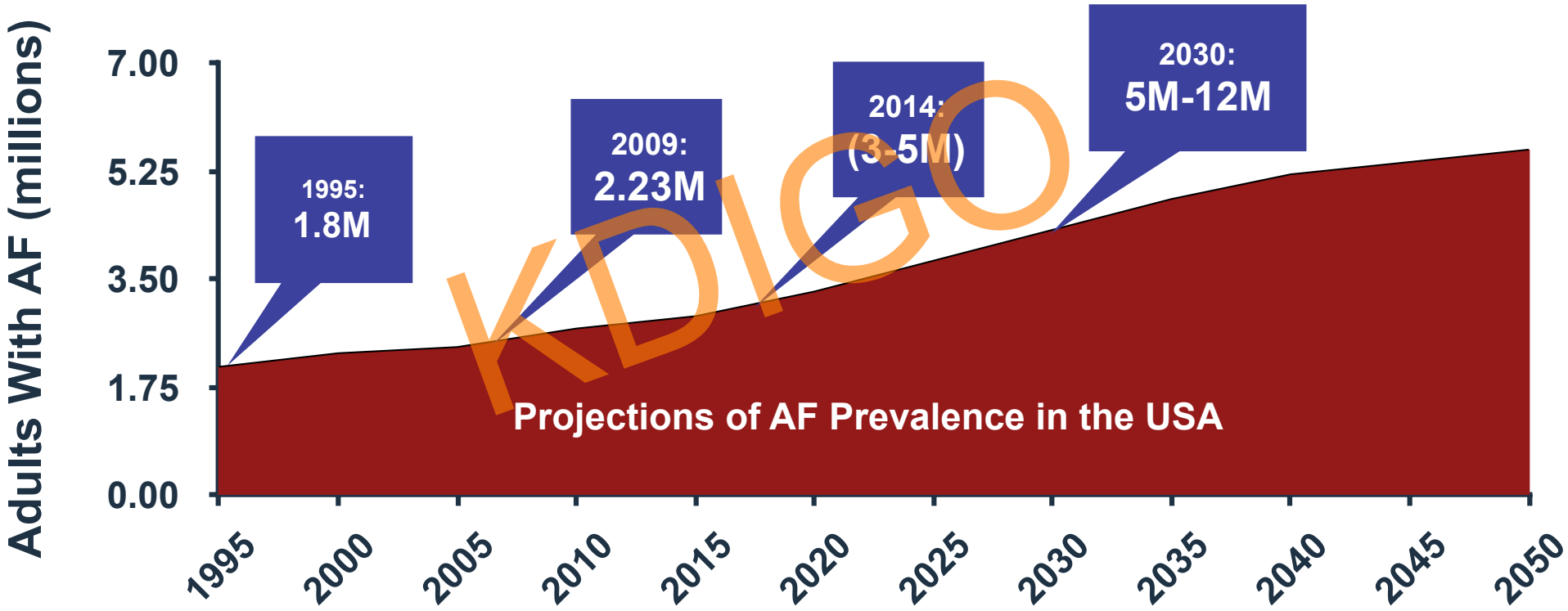
Stanford MEDICINE

Disclosures

- Research support
  - VA, NIH
  - Janssen, Medtronic, iRhythm, Boehringer Ingelheim, AstraZeneca
- Advisor/Consultant
  - St Jude Medical, Medtronic, Daiichi Sankyo, Zipline Medical, Precision Health Economics, Cyberheart, thryva, AliveCor, Armetheon, Abbott, Myokardia, Nokia
- Lecture honoraria
  - Medtronic, St Jude Medical

Prevalence of AF

- Most common sustained arrhythmia in clinical practice
- 4% of the population over age 60; 10% over age 80

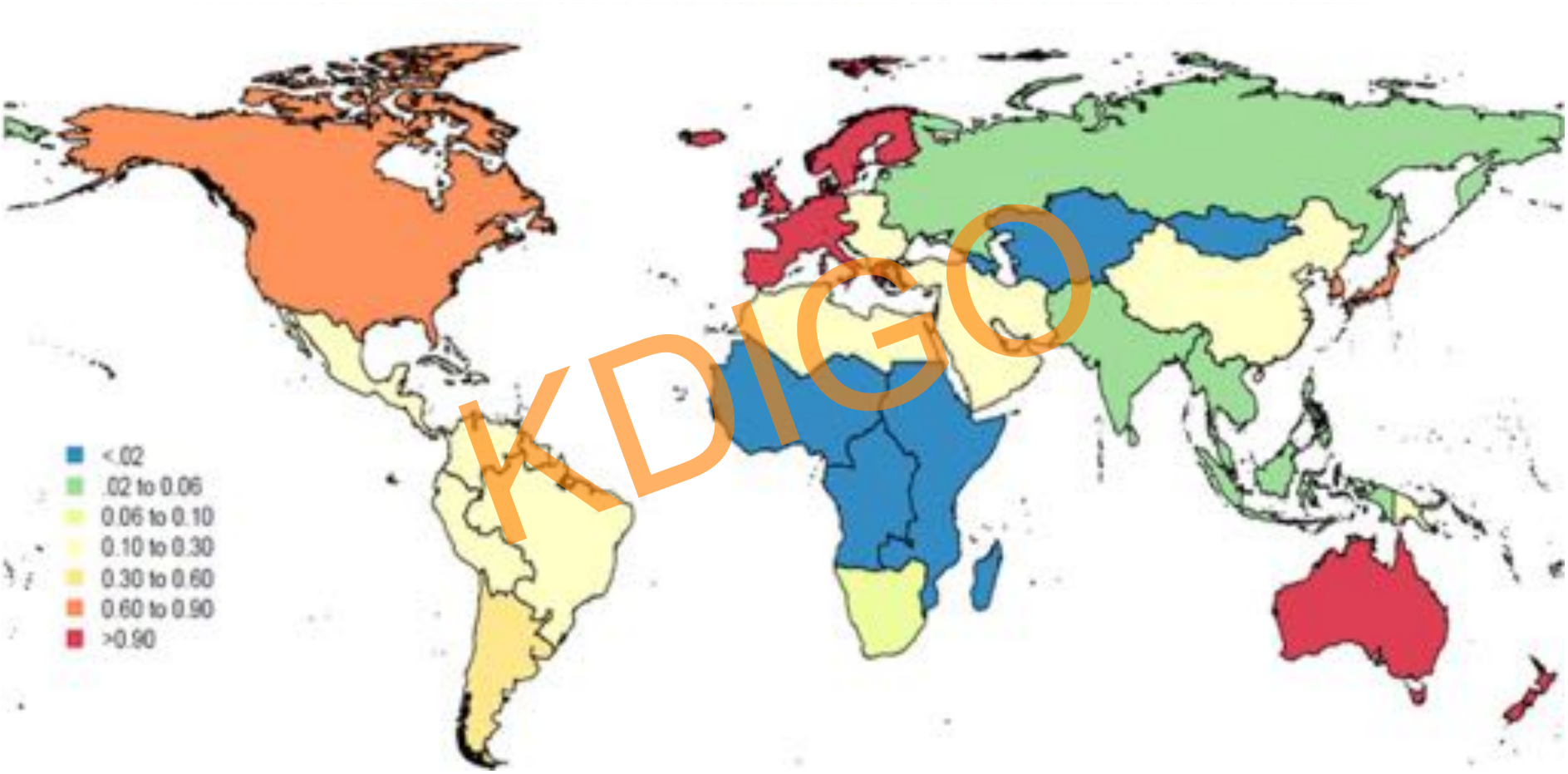


Go AS. JAMA. 2001;285:2370.
Miyasaka Y. Circulation 2006;114:119-125
Naccarelli GV. Am J Cardiol. 2009.

Prevalence of AF (per 100,000)

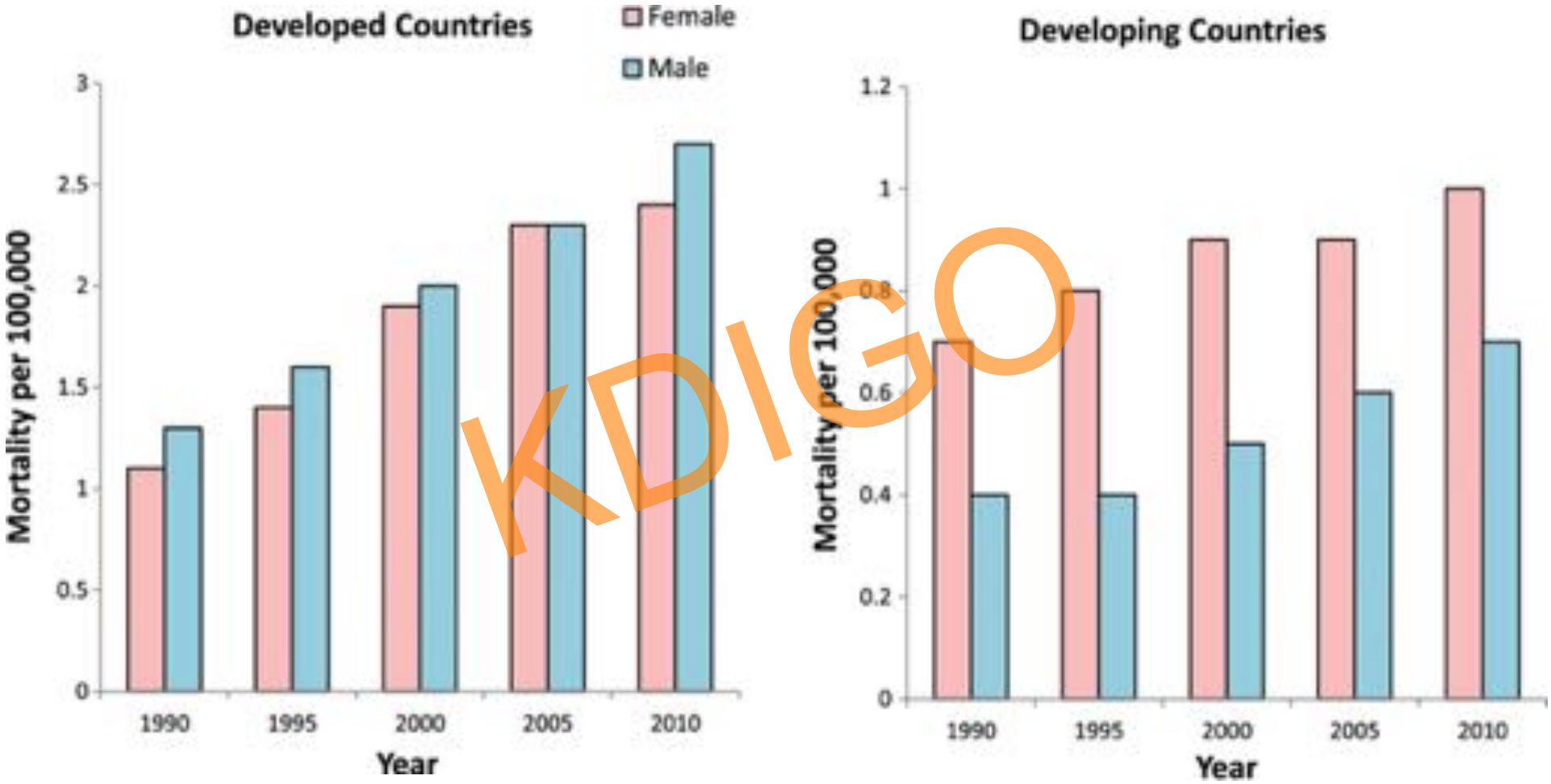
Chugh SS et al, *Circulation*, 2014

Deaths attributable to AF



Chugh SS et al, *Circulation*, 2014

AF-associated mortality, stratified

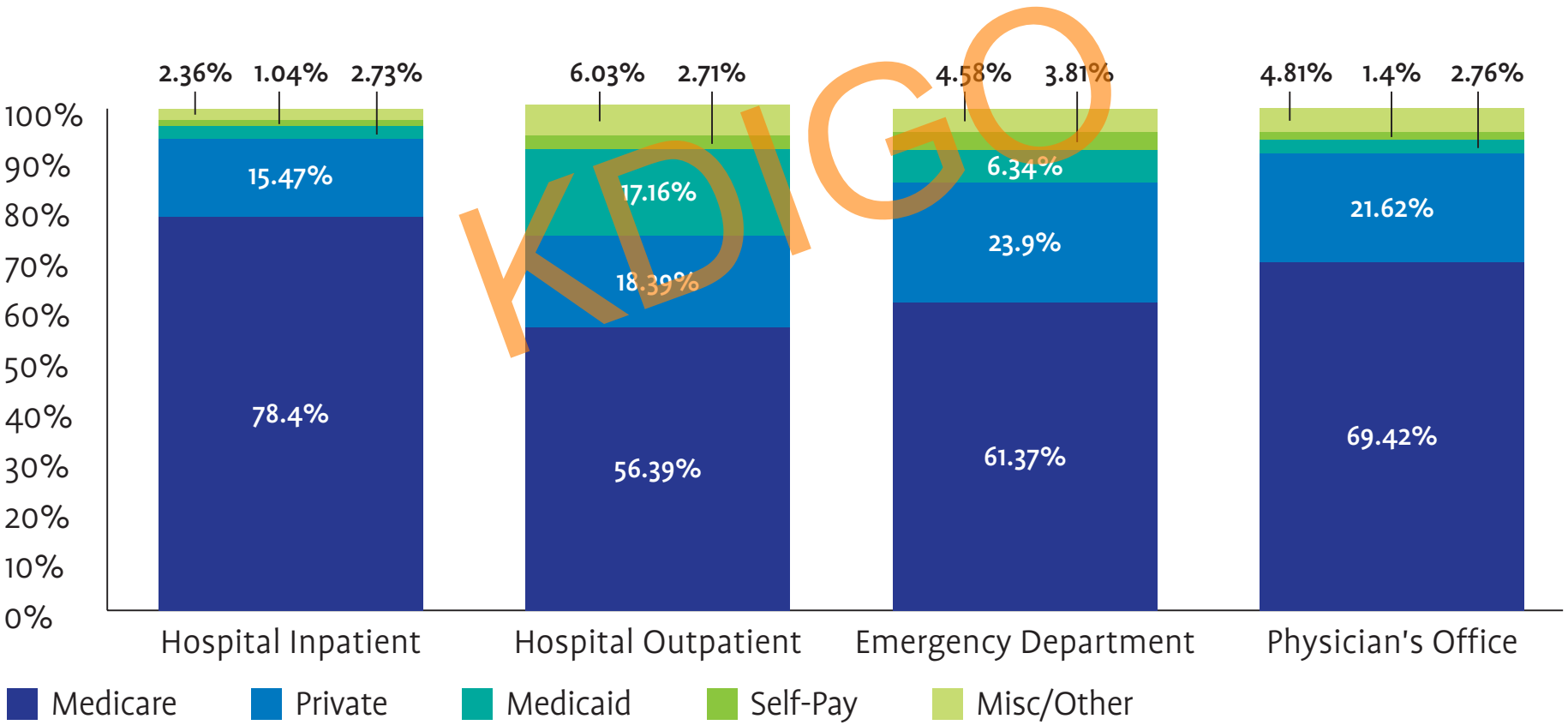


Chugh S S et al. Circulation. 2014;129:837-847

AF is the most expensive cardiac dx

- Direct annual cost age < 65: **$6.65 billion**
- Medicare spending for new AF: **$15.7 billion**
  - Mainly due to **complications** (stroke, CHF, MI, tachycardia)
- Direct and indirect cost of **stroke**: **$58 billion**

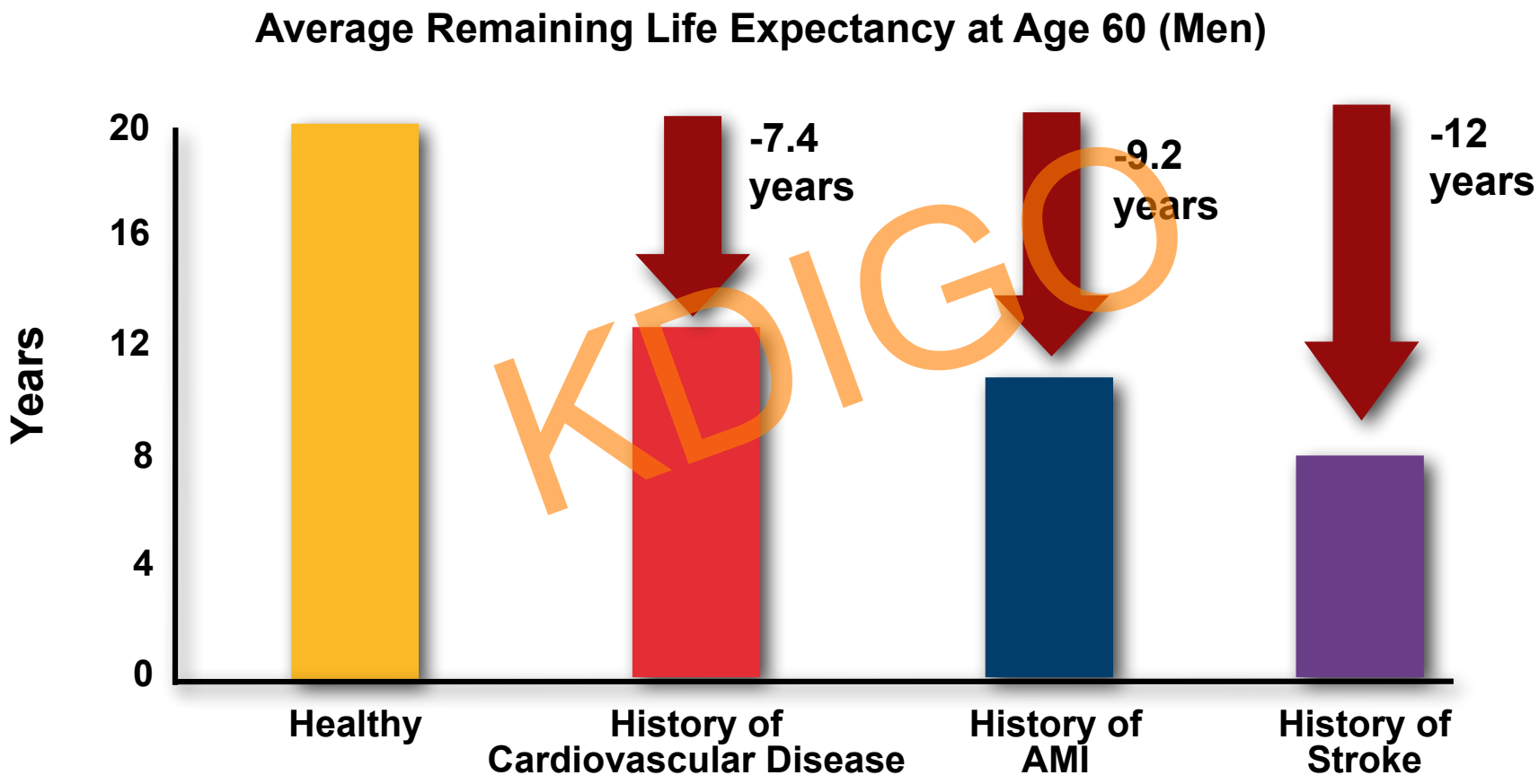
FIGURE 3: MEDICARE IS THE PRIMARY PAYER FOR AFIB ACROSS ALL SETTINGS OF CARE



Avalere report, 2009

Stroke shortens lifespan the most

Framingham Heart Study



(Peeters A, et al. Eur Heart J. 2002)

AF and stroke: the classical model

Physiology

- Loss of coordinated atrial activity
- Impaired emptying, stasis, hyper-coagulability, clot formation

Implications for stroke risk

- 15% of 700,000 strokes/ year in U.S.
- Risk if untreated: 3-12%/yr
- Stroke from AF has higher severity, disability and mortality (larger territory)

Therapies can prevent stroke in AF

First, there was $CHADS_2$

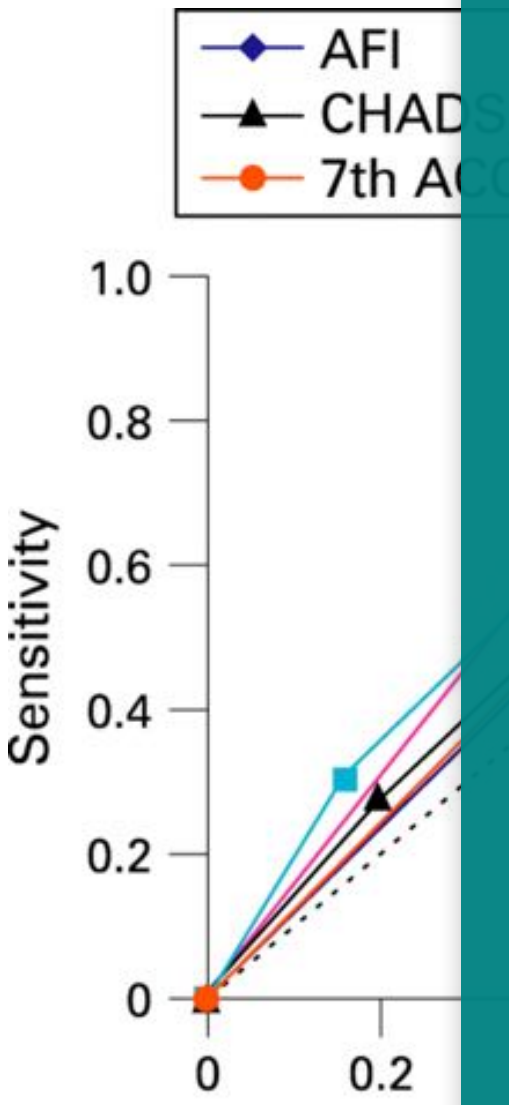
- 1 point for each of the following:
  - **C**ongestive heart failure
  - **H**ypertension
  - **A**ge ≥ 75
  - **D**iabetes
- 2 points for prior **S**troke/TIA

(Gage BF, JAMA 2001; AHA 2006 guidelines; ACCP 2012 guidelines)

National Registry of AF (NRAF)

- Source of $CHADS_2$ data
- Quality improvement Medicare registry
- 1733 *inpatients*, age 65-95, discharged from a hospital with AF
- 7 hospitals from stroke belt states
- ICD9 codes, not chart review
- Max follow-up: 2.7 years
- CKD not assessed
- **Non-generalizable**

Validation: how good is CHADS2?



c-statistic = 0.56-0.62

(0.50 = pure chance)

- Substantial misclassification
- Untreated "low risk" patients who get strokes
- Treated "high risk" patients who bleed

(Fang M, JACC 2006)

Why did $CHADS_2$ survive this long?

- **Specific**, not sensitive
- Warfarin was too risky to be broadly used
  - High INR+uncontrolled BP+ASA = ICH
- As warfarin management improved (and ICH decreased), goal was to find a **high sensitivity** risk tool

Turakhia M, *Circ Qual Care Outcomes*, 2013

Then came CHA_2DS_2-VASc…

Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥75	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease[a]	1
Age 65–74	1
Sex category (i.e. female sex)	1
Maximum score	**9**

Lip GY, *et al. Chest.* 2010

Weaknesses of CHA_2DS_2-VASc

- CHADS2 score gets reclassified upward
  - Age, CAD, female
- Few stroke events in derivation
- European Heart Survey
  - 1,577 of 5,333 untreated AF patients from cardiology practices in 35 countries
  - 2003-2004
  - 1-year follow up

CHA_2DS_2-VASc score	Patients (n = 7329)	Adjusted stroke rate (%/year)[b]
0	1	0%
1	422	1.3%
2	1230	2.2%
3	1730	3.2%
4	1718	4.0%
5	1159	6.7%
6	679	9.8%
7	294	9.6%
8	82	6.7%
9	14	15.2%

Lip GY, *et al. Chest.* 2010

R_2CHADS_2: Yet another score

- Derivation: ROCKET-AF (rivaroxaban vs. warfarin)
- Validation: Kaiser
- Adding GFR<60 improves discrimination and reclassification
  - **c-statistic 0.74**
- AHA/ACC/HRS 2014 guidelines did not endorse

(Piccini J, Circulation 2012)

Q: What is this patient's annual risk of stroke?

- Risk factors
  - Age 67
  - Female
  - Carotid disease
  - GFR < 60
- $CHADS_2$: 0 (low)
- CHA_2DS_2-VASc: 3 (med)
- R_2CHADS_2: 2 (med)

Answer choices:

1. Very low (< .5%)
2. Low (~1-2%)
3. Medium (~3-6%)
4. High (~8-18%)

So why did new guidelines go with CHA_2DS_2-VASc?

- Calibrated for for high sensitivity
- Contemporary therapy has tilted in favor of having a low treatment threshold
  - Low bleeding risk with DOACs
  - Warfarin: less ICH, major bleeding now

The biggest limitation of the CHADS-based scores is the diagnosis of AF itself

- AF defined by treatment, not disease
  - Reimbursement codes, mostly hospitalized patients
- Transient or lone AF not well represented
- Diagnosis creep
  - Device-detected AF
  - Ambulatory ECG
  - Episodic detection with wearables

How much AF should be treated?

- 30 seconds?
- 1 minute?
- 6 minutes?
- 6 hours?
- Depends on vascular risk?

- Is this a condemnation to lifelong therapy?

ASSERT Study

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Subclinical Atrial Fibrillation and the Risk of Stroke

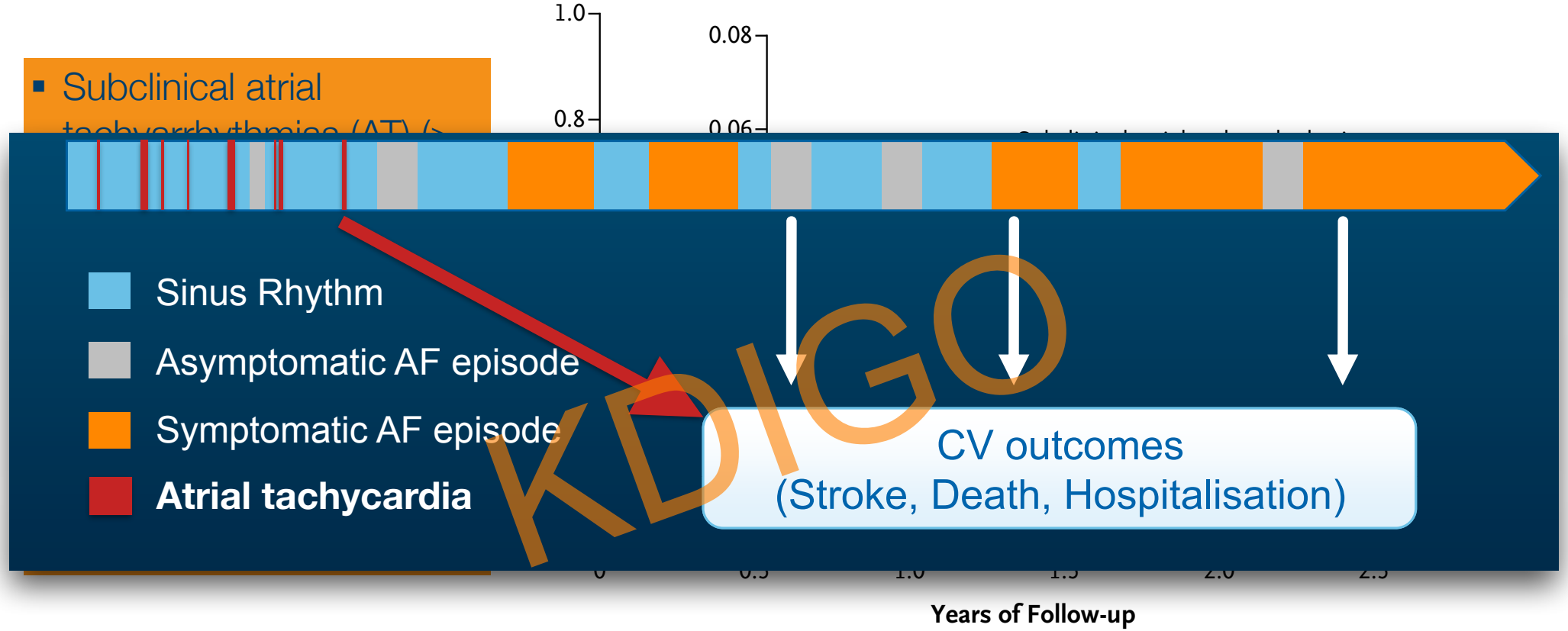
Jeff S. Healey, M.D., Stuart J. Connolly, M.D., Michael R. Gold, M.D., Carsten W. Israel, M.D., Isabelle C. Van Gelder, M.D., Alessandro Capucci, M.D., C.P. Lau, M.D., Eric Fain, M.D., Sean Yang, M.Sc., Christophe Bailleul, M.D., Carlos A. Morillo, M.D., Mark Carlson, M.D., Ellison Themeles, M.Sc., Elizabeth S. Kaufman, M.D., and Stefan H. Hohnloser, M.D., for the ASSERT Investigators*

METHODS

We enrolled 2580 patients, 65 years of age or older, with hypertension and no history of atrial fibrillation, in whom a pacemaker or defibrillator had recently been implanted. We monitored the patients for 3 months to detect subclinical atrial tachyarrhythmias (episodes of atrial rate >190 beats per minute for more than 6 minutes) and followed them for a mean of 2.5 years for the primary outcome of ischemic stroke or systemic embolism. Patients with pacemakers were randomly assigned to receive or not to receive continuous atrial overdrive pacing.

Healey JS, *et al,* NEJM 2012.

B **Risk of Ischemic Stroke or Systemic Embolism**



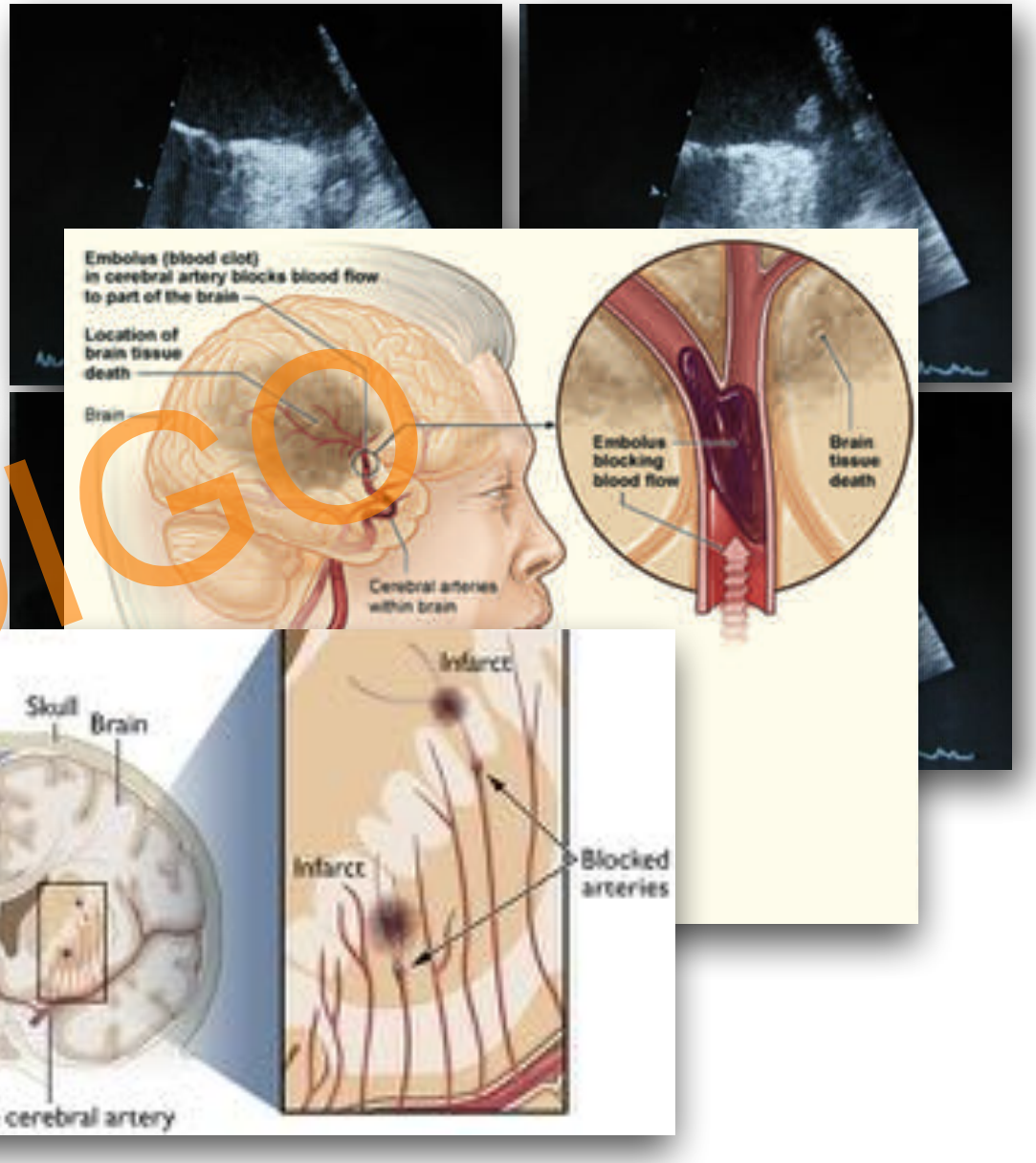
No. at Risk

Subclinical atrial tachyarrhythmias present	261	249	238	218	178	122
Subclinical atrial tachyarrhythmias absent	2319	2145	2070	1922	1556	1197

(Healey JS, NEJM 2012)

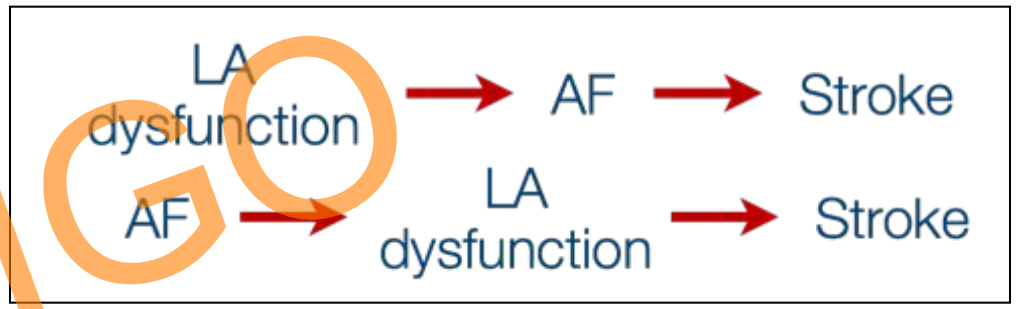
Mechanisms of stroke in AF are diverse

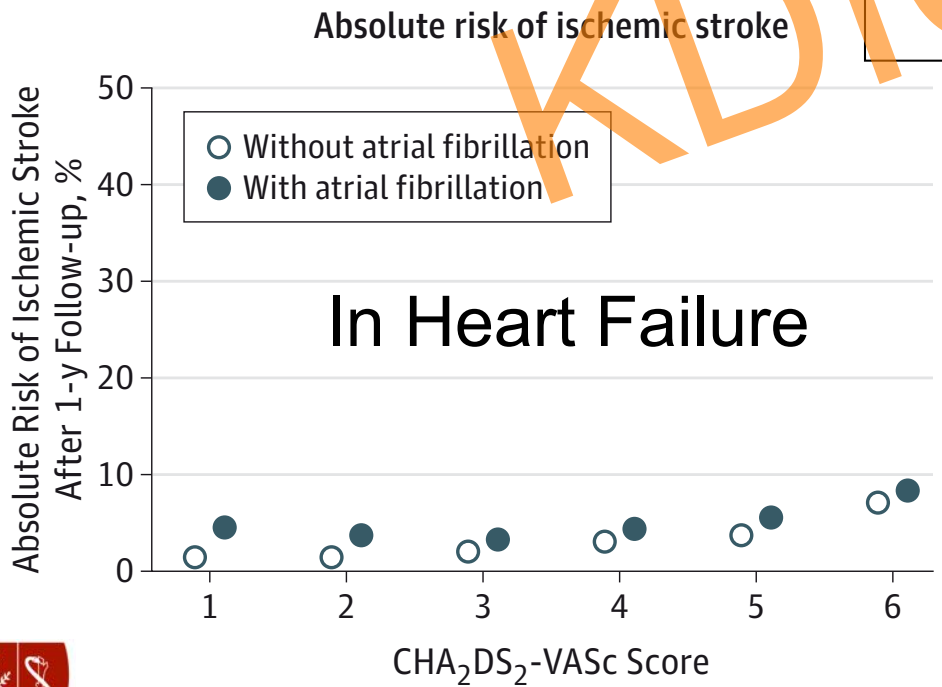
- Cardioembolic
- Atheroembolic
- Small vessel



Vascular risk factors also predict AF, stroke

- In patients with CHD/CHF but without AF, CHADS2 and other scores predict…
  - Left atrial dysfunction, LA appendage clot
  - Ischemic stroke
  - Incident AF





Azarbal F / Whooley MA / Turakhia M, Am J Cardiol 2014
Welles C / Whooley MA / Turakhia M, JACC 2011
Welles C / Whooley MA / Turakhia M, Am Heart J 2013
Wong J / Whooley MA / Turakhia M, Am Heart J 2014
Melgaard L, JAMA 2015

AF correlates with brain disease

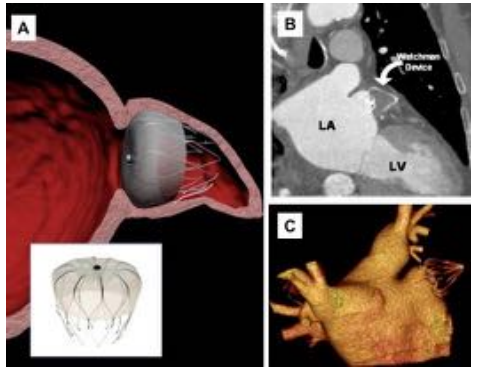
- Manhattan Cohort Study subset (CABL)
- n = 455 without stroke history; all received MRI
- LA volume and LA function also associated with brain ischemic lesions

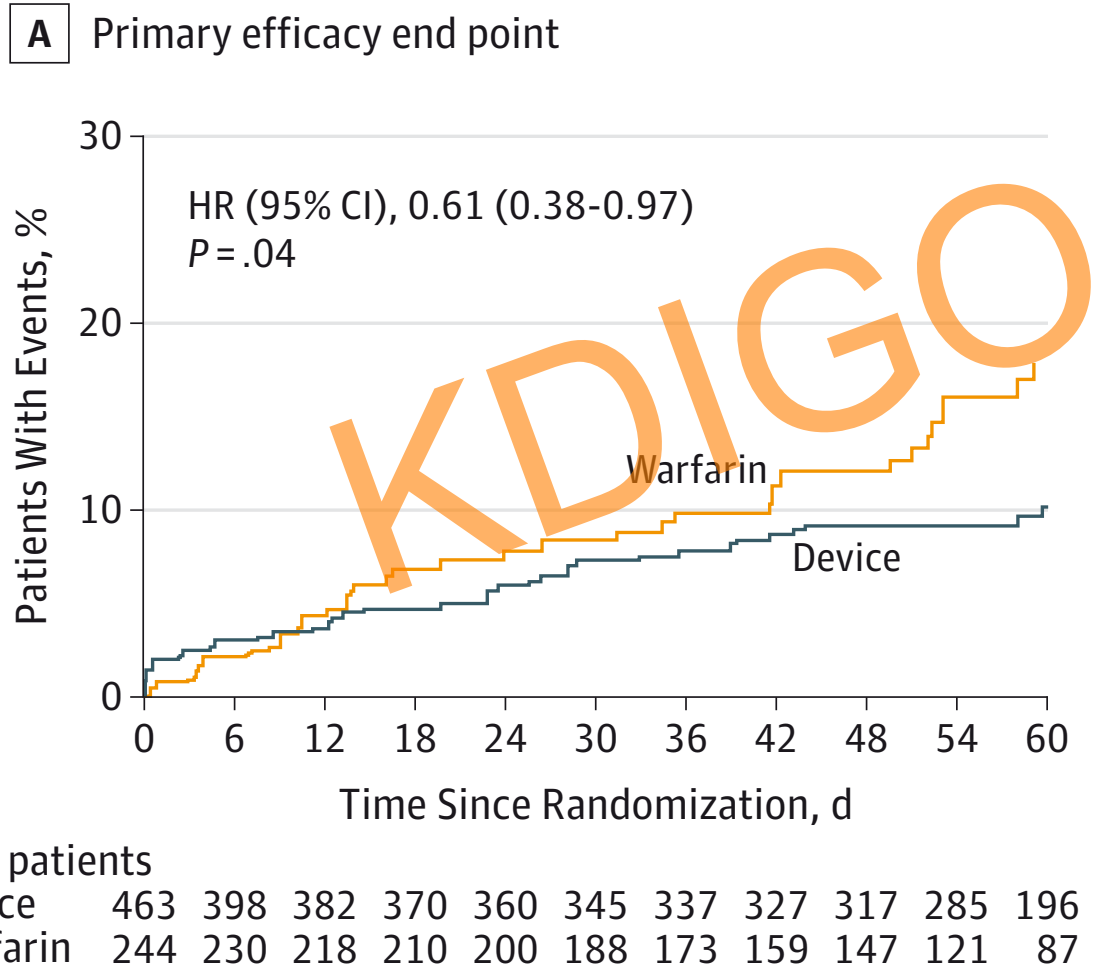
Univariate correlates of subclinical cerebrovascular disease

	SBI		Log-WMHV	
	B (SE)	**P value**	**B (SE)**	**P value**
Age	0.06 (0.01)	<0.01	4.7 (0.4)	<0.01
Male sex	–0.2 (0.3)	0.46	0.9 (9.3)	0.92
BMI	–0.02 (0.03)	0.47	–3.4 (1.0)	<0.01
Hypertension	0.9 (0.4)	<0.05	43.0 (10.4)	<0.01
Diabetes	0.5 (0.3)	0.05	–3.3 (10.1)	0.75
Hypercholesterolemia	–0.03 (0.27)	0.90	–9.9 (9.4)	0.29
Atrial fibrillation	1.6 (0.4)	<0.01	64.6 (20.0)	<0.01
CAD	0.7 (0.5)	0.15	38.7 (18.7)	<0.05
Cigarette smoking	0.1 (0.3)	0.70	10.3 (9.1)	0.26
LV mass	0.02 (0.004)	<0.01	0.8 (0.2)	<0.01
Relative wall thickness	2.4 (1.4)	0.07	248.1 (48.9)	<0.01
LV ejection fraction	–0.03 (0.01)	0.07	–0.9 (0.6)	0.12
LV diastolic dysfunction	0.5 (0.3)	0.07	43.6 (8.9)	<0.01
MV regurgitation (> mild)	0.9 (0.4)	<0.05	11.3 (16.2)	0.48
Heart rate	0.01 (0.01)	0.22	0.2 (0.4)	0.56

Watchman 4-year data

Strokes still occur





- 579 of 707 (82%) of randomized pts

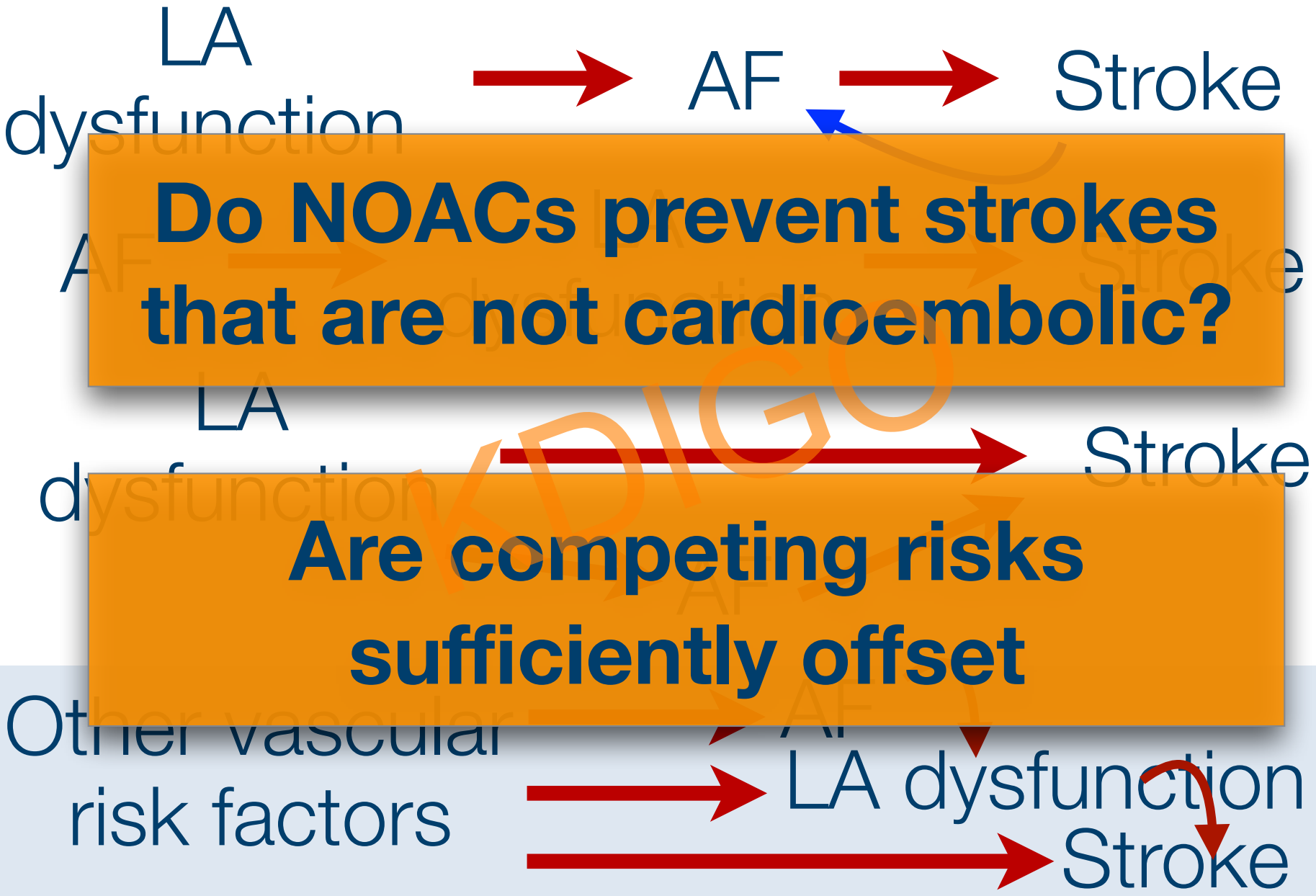
Reddy V, *JAMA* 2014

AF temporally discordant

- ASSERT
  - 1 of 51 stroke patients had AF at time of stroke
  - 25 (49%) had no AT/AF (including post-stroke)
  - Median time to AF was 339 days prior
- In larger device cohorts, AF does transiently increase risk but attributable risk is low
- AF also discordant with ICH on OAC

Brambatti M, *et al. Circulation,* 2014
Turakhia M, *et al. Circ EP*, 2015

What is the mechanism of ischemic stroke?



Trials in progress

Table 2 Summary of ongoing trials investigating the safety/efficacy of OAC treatment of occult AF

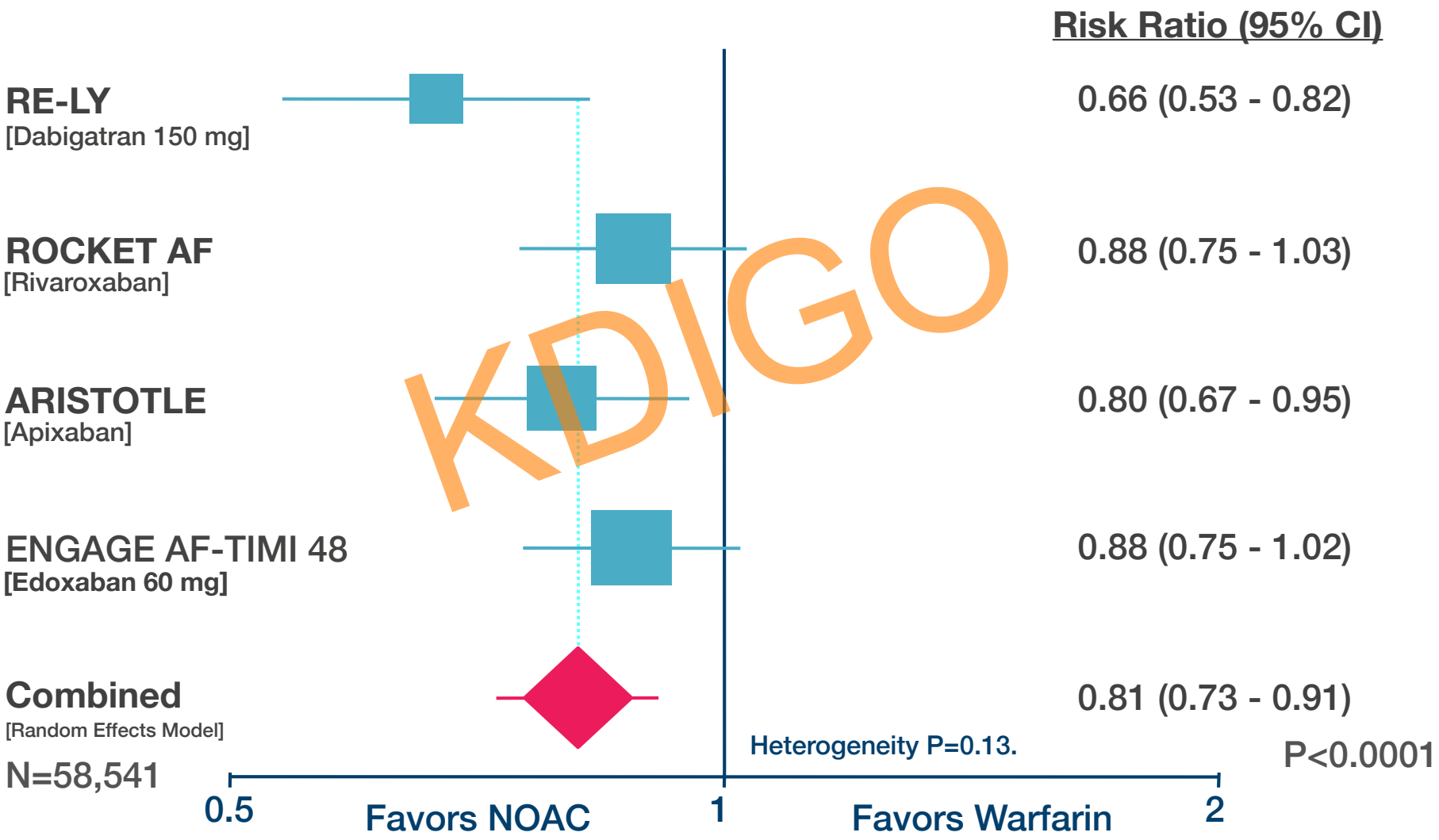
	Population	Intervention	Primary outcomes
ARTESiA	CHA2DS2-VASc ≥4 with at least a single AHRE ≥175 bpm lasting ≥6 min detected by ILR or intracardiac device *No history or ECG evidence of clinical AF*	Randomised to either aspirin 81 mg daily (control) or apixaban 5 mg twice daily (intervention)	Incidence of stroke and major bleeding events
STROKESTOP	All persons aged 75 years and 76 years in two Swedish provinces *No history of AF*	Twice-daily ECG screening+OAC treatment if AF detected (single episode duration >30 s, or 2 or more episodes >10 s)	Incidence of stroke and major bleeding events

Keach W, Turakhia M, *et al*. *Heart*, 2015

Treatment

Target specific oral anticoagulants vs. warfarin

Outcome of stroke or systemic embolism



Ruff CT, *et al.* Lancet. 2014

	RE-LY (Dabigatran)	ROCKET-AF (Rivaroxaban)	ARISTOTLE (Apixaban)	ENGAGE AF TIMI 48 (Edoxaban)
% Renal Excretion	80%	35%	27%	50%
Efficacy % Warfarin vs. OAC (CVA or SE)	1.69 vs. 1.11 p<.001 NNT = 167 *150 mg shown	2.42 vs. 2.12 p=.12 (2.2 vs 1.7 on treatment)	1.60 vs. 1.27 p < .001 NNT = 303	1.80 vs. 1.57 p=.08 (1.5 vs. 1.18 on treatment) *High-dose (60 mg)
Major Bleeding %	3.57 vs. 3.32 p=0.31	3.45 vs. 3.6 p=0.58	3.09 vs. 2.13 p<.001	3.43 vs. 2.75 p<.001
ICH%	0.74 vs. 0.30 p< .001	0.74 vs. 0.49 p=.019	0.47 vs. 0.24 p< .001	0.85 vs. 0.39 p< .001
All-cause mortality %/yr	4.13 vs. 3.64 p = 0.051 NNT = 204	4.91 vs. 4.52 p=NS	3.94 vs 3.52 p = 0.05 NNT = 238	4.35 vs. 3.99 p=0.08 NNT = 277
Conclusion vs. warfarin	Superior efficacy, similar bleeding, less ICH	Non-inferior on efficacy and safety measures	Superior efficacy, less major bleeding and ICH, lower mortality	Non-inferior on efficacy; less bleeding

Connolly SJ et al. *N Engl J Med*. 2009
Patel MR et al. *N Engl J Med*. 2011
Granger CB et al. *N Engl J Med*. 2011
Giugliano RP et al. *N Engl J Med*. 2013

Dosing in chronic kidney disease

Agent	Standard AF Dose (Prescribing info)	Renal Dosing	Trial and Other Experience
Dabigatran	**150mg Twice Daily** (CrCl > 30ml/min)	75mg Twice Daily (CrCl 15-30ml/min)	• **RE-LY trial: 150mg or 110mg BID if CrCl > 30ml/min** • **No trial experience in pts w/ CrCl < 30ml/min** • **75mg dose not studied in RCTs** • **European dosage:** **150mg BID if CrCl >50ml/min** **75mg BID if CrCl 30-50ml/min** **Contraindicated if CrCl < 30ml/min**
Rivaroxaban	**20mg Once Daily (CrCl > 50ml/min)**	**15mg Once Daily (CrCl 15-50ml/min)**	**> 50ml/min** **15mg Daily if CrCl 30-50ml/min** **No trial experience in pts w/ CrCl < 30ml/min**
Apixaban	**5mg Twice Daily**	**2.5mg Twice Daily if ≥ 2 of the following: ≥ 80 y/o, Weight ≤ 60kg, Serum Cr ≥ 1.5 mg/dL (133 µmol/L) (or ESRD on dialysis with or without hemodialysis)**	**dose studied as per prescribing information.** **No trial experience in pts w/ CrCl < 25ml/min** **No trial experience with ESRD patients**

Edoxaban	**60mg Once Daily (CrCl 50-95ml/min)**
	
	BLACK BOX WARNING: Avoid use if CrCl > 95ml/min
		30mg Once Daily (CrCl 15-50ml/min)	• **TIMI-ENGAGE: Randomized to 60mg or 30mg Daily**
			  • **Dose halved if**
			  • **CrCl 30-50ml/min, Weight ≤ 60kg, or**
			  • **Concomitant verapamil, quinidine, or dronedarone (strong P-gp inhibitors)**
			• **No trial experience in pts w/ CrCl < 30ml/min**
			• Worse outcomes in patients with CrCl > 95ml/min

Bottom Line:

None have been evaluated in randomized trials for CrCl < 25-30 or dialysis

ESRD trials in development

Issues

- Treatment benefit in CKD subgroups?
- Treatment harm?
- Stability of kidney function?
  - How often should CrCl be assessed?
  - Titration of ACE/ARB?
- Cockroft-Gault vs MDRD or CKD-EPI

Pivotal NOAC trials and CKD

Table 1 Selected patient characteristics of the included trials

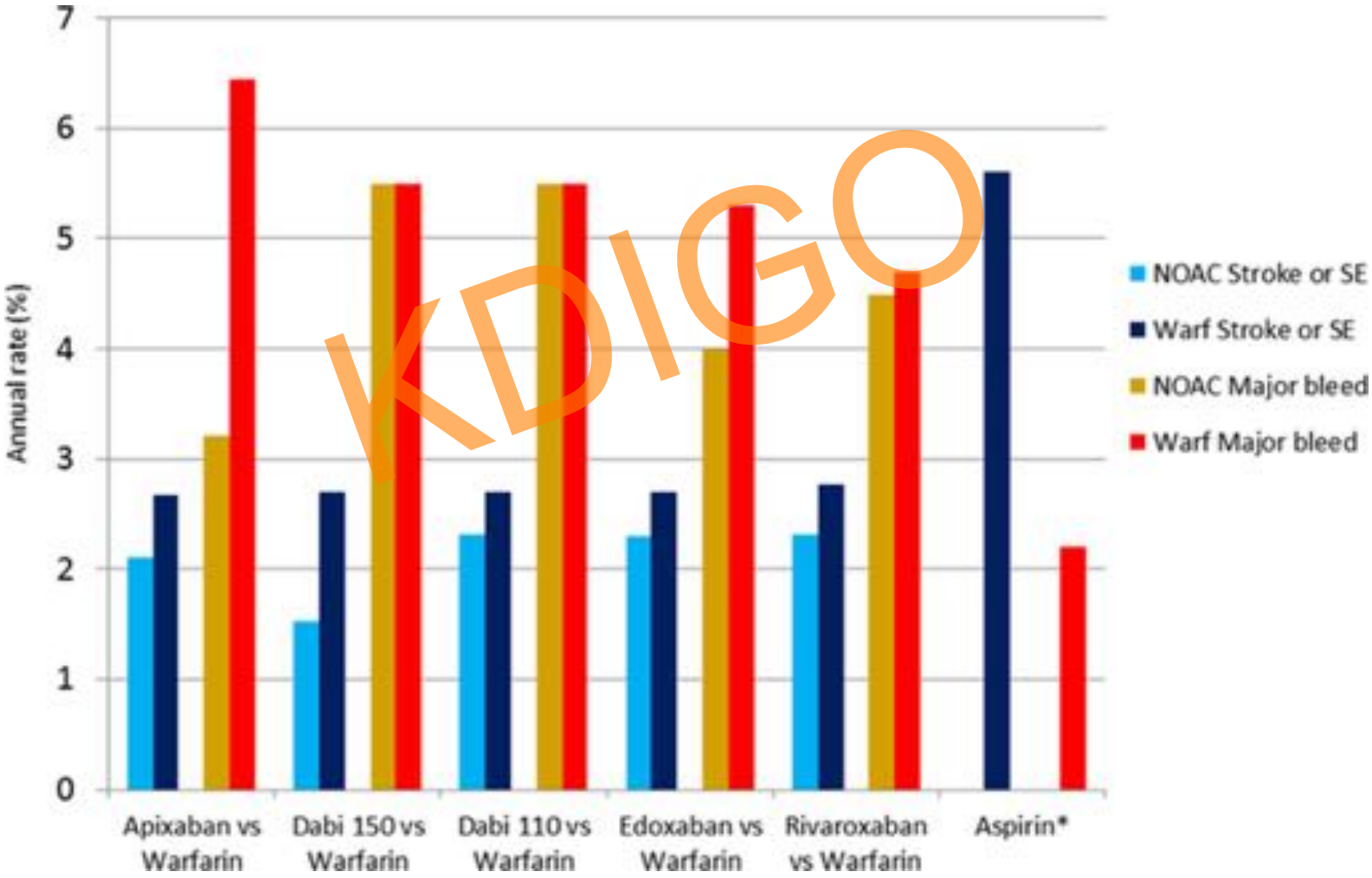
Characteristics	Trial											
	RE-LY (n = 18,113)			ARISTOTLE (n = 18,201)		ROCKET AF (n = 14,262)		J-ROCKET AF (n = 1,278)		ENGAGE AF-TIMI 48 (n = 21,105)		
	Dab 110 mg	Dab 150 mg	Warfarin	Apix	Warfarin	Riva	Warfarin	Riva	Warfarin	Edox 30 mg	Edox 60 mg	Warfarin
Creatinine clearance[c] %												
30–49 mL/min	19.4	19.2	19.4	16.5	16.6	21.0	20.6	22.1	22.4	19.3	19.6	19.0
50–79 mL/min	48.6	48.1	48.5	41.6	41.8	46.6	48.8	51.3	51.3	NR	NR	NR
>80 mL/min	32.3	32.0	32.2	41.2	41.4	32.3	31.3	26.6	26.3	NR	NR	NR

	Moderate renal impairment (95 % CI)	Mild renal impairment (95 % CI)	Non renal impairment (95 % CI)
Safety			
Dabigatran 110 [39]	0.99[b] (0.77–1.28)	0.76 (0.62–0.94)	0.61[c] (0.44–0.84)
Dabigatran 150 [39]	1.01[b] (0.79–1.30)	0.91 (0.75–1.11)	0.84[c] (0.62–1.13)
Rivaroxaban [40]	0.98[b] (0.84–1.14)	NR	1.04[d] (0.96–1.13)
J-ROCKET [41]	1.22[b] (0.78–1.91)	NR	1.07[d] (0.80–1.43)
Apixaban [30]	0.50[a] (0.38–0.66)	0.77 (0.65–0.94)	0.80[d] (0.61–1.04)
Edoxaban 30 [9]	0.31[b] (0.23–0.42)[e]	NR	0.55[d] (0.46–0.65)[e]
Edoxaban 60 [9]	0.63[b] (0.50–0.81)[e]	NR	0.88[d] (0.76–1.03)[e]
Efficacy			
Dabigatran 110 [39]	0.85[b] (0.59–1.24)	0.93 (0.70–1.23)	0.84[d] (0.54–1.32)
Dabigatran 150 [39]	0.56[b] (0.37–0.85)	0.68 (0.50–0.92)	0.67[d] (0.42–1.09)
Rivaroxaban [40]	0.84[b] (0.57—1.23)	NR	0.78[d] (0.63–0.98)
J-ROCKET [41]	0.82[b] (0.25–2.69)	NR	0.36[d] (0.14–0.93)
Apixaban [30]	0.79[a] (0.55–1.14)	0.74 (0.56–0.97)	0.88[c] (0.64–1.22)
Edoxaban 30 [9]	1.17[b] (0.92–1.45)[e]	NR	1.10[d] (0.92–1.32)[e]
Edoxaban 60 [9]	0.86[b] (0.68–1.15)[e]	NR	0.87[d] (0.82–1.05)[e]

Nielsen PB, *et al*. Clin Rsrch Cardiol, 2015

Subgroup analyses of NOAC trials

- For CrCl ≤ 50 mL/min



On-Treatment Outcomes in Patients With Worsening Renal Function With Rivaroxaban Compared With Warfarin

Insights From ROCKET AF

Table 2. Baseline Characteristics by Renal Function Over the Follow-Up

Variable	All Patients (n=12 612)	SRF Patients (n=9292)	WRF Patients (n=3320)	*P* Value
Randomized to rivaroxaban, % (n)	50 (6253)	49 (4565)	51 (1688)	0.090
Age, y	73 (65, 78)	72 (65, 78)	73 (66, 78)	<0.0001
Female, % (n)	39 (4959)	38 (3555)	42 (1404)	<0.0001

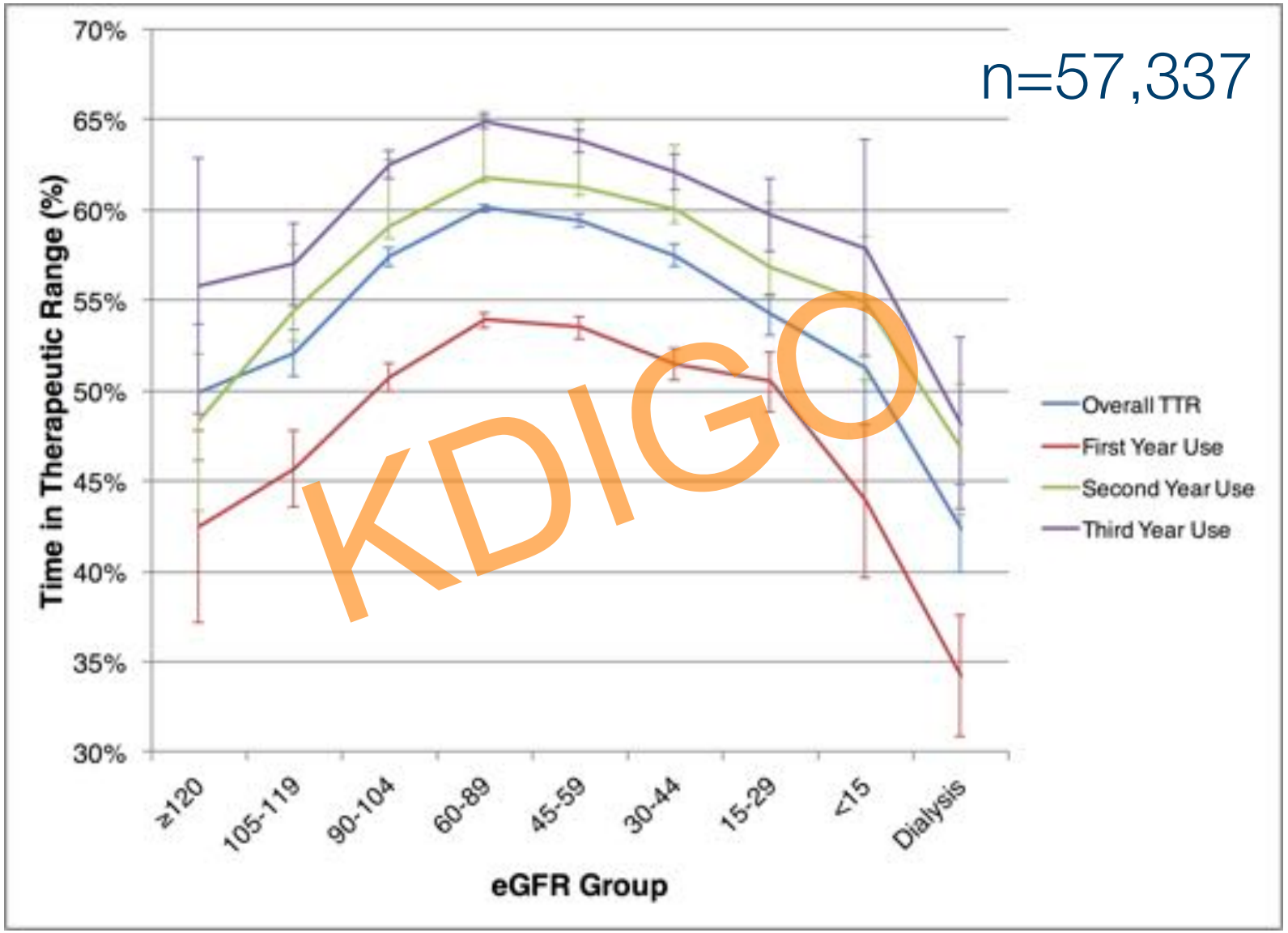
Fordyce CB, *Circulation*. 2016

Table 3. Outcomes by Renal Function Over the Course of the Study On-Treatment Period

Outcomes	SRF Patients, Event Rate per 100 patient-years (95% CI) (Total Events, n)	WRF Patients, Event Rate per 100 patient-years (95% CI) (Total Events, n)	HR (95% CI), WRF Versus SRF Patients	*P* Value
Efficacy outcomes				
Stroke or systemic embolism	1.82 (1.60–2.04) (262)	2.37 (1.68–3.07) (45)	1.25 (0.89–1.75)	0.19
Vascular death	1.41 (1.21–1.60) (203)	2.21 (1.54–2.88) (42)	1.47 (1.05–2.06)	0.026
MI	0.93 (0.77–1.09) (134)	1.22 (0.72–1.72) (23)	1.19 (0.75–1.90)	0.47
Stroke/embolism/vascular death/MI	3.87 (3.55–4.19) (557)	5.66 (4.59–6.74) (107)	1.40 (1.13–1.73)	0.0023
All-cause mortality	1.93 (1.70–2.15) (279)	3.10 (2.31–3.89) (59)	1.49 (1.12–1.98)	0.0067
Ischemic stroke	1.24 (1.06–1.42) (179)	1.63 (1.06–2.21) (31)	1.25 (0.83–1.87)	0.29
Safety outcomes				
Major or NMCR bleeding	11.44 (10.87–12.01) (1529)	11.97 (10.34–13.61) (206)	1.05 (0.90–1.21)	0.55
Major bleeding	3.16 (2.87–3.45) (451)	3.69 (2.82–4.56) (69)	1.08 (0.83–1.40)	0.59
Fatal bleeding	0.28 (0.19–0.36) (40)	0.26 (0.03–0.49) (5)	0.98 (0.37–2.56)	0.96
Critical organ bleeding	0.98 (0.82–1.14) (141)	0.74 (0.35–1.12) (14)	0.68 (0.38–1.21)	0.19
Transfusion ≥2 U	0.73 (0.59–0.87) (105)	1.11 (0.63–1.58) (21)	1.34 (0.81–2.22)	0.25
Hemoglobin decrease ≥2 g/dL	2.21 (1.96–2.45) (316)	2.72 (1.97–3.46) (51)	1.08 (0.78–1.48)	0.64
ICH	0.63 (0.50–0.76) (91)	0.68 (0.31–1.05) (13)	1.00 (0.54–1.83)	0.99
NMCR bleeding	8.56 (8.07–9.06) (1159)	8.53 (7.16–9.90) (149)	1.02 (0.86–1.21)	0.82

CI indicates confidence interval; HR, hazard ratio; ICH, intracranial hemorrhage; MI, myocardial infarction; NMCR, nonmajor clinically relevant; SRF, stable renal function; and WRF, worsening renal function.

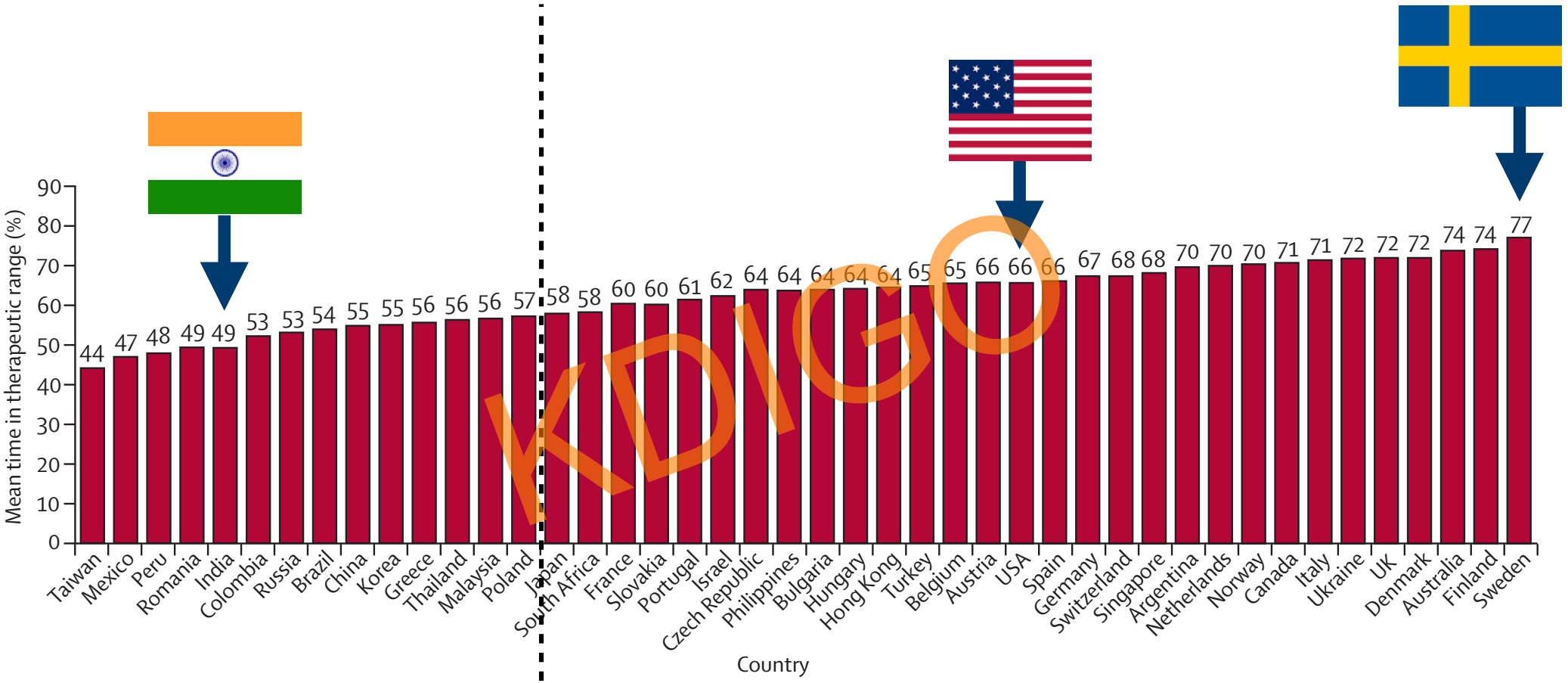
INR control (VA TREAT-AF cohort)



Yang F / Turakhia M, in press

INR control by country

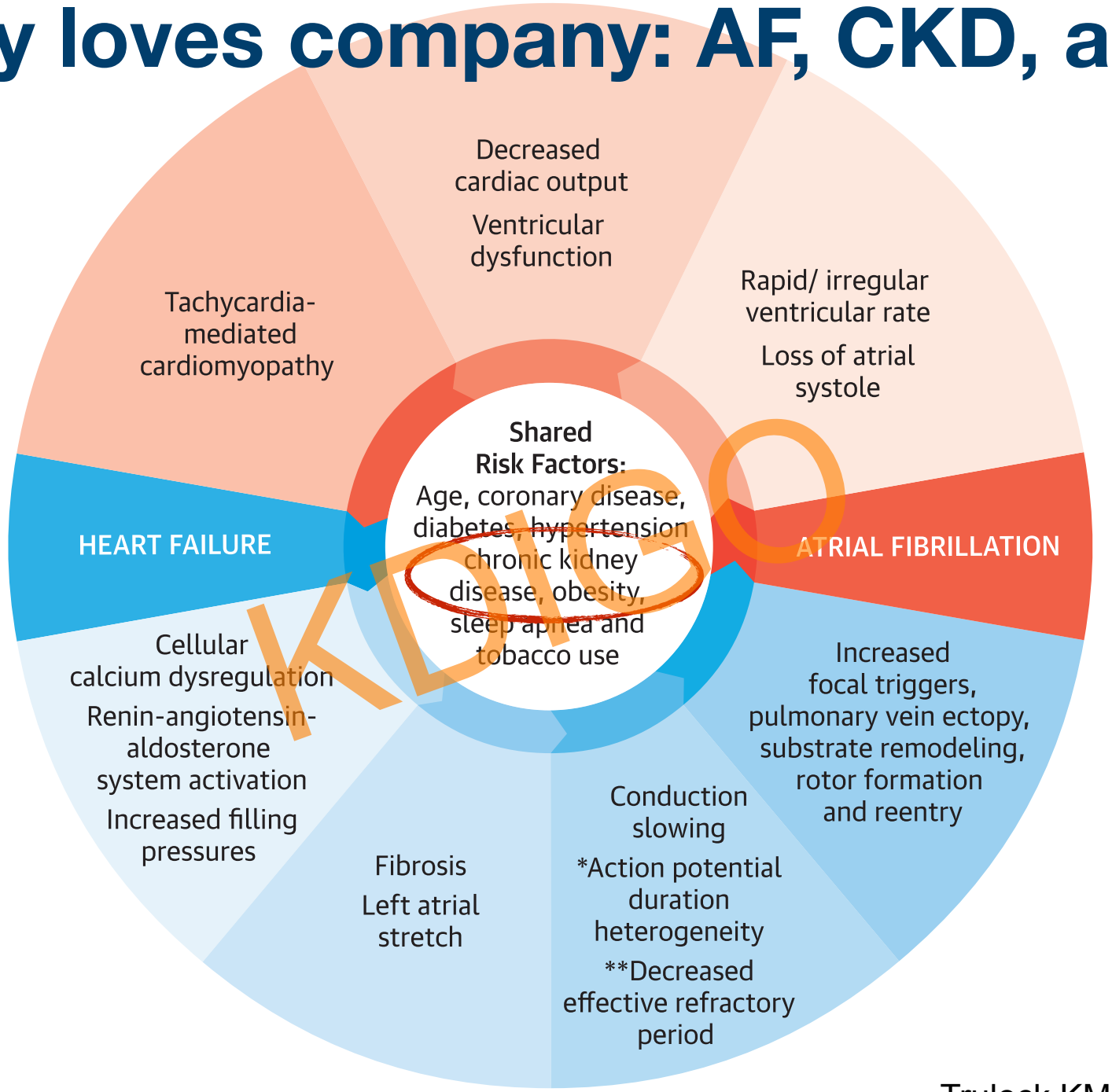
RE-LY trail (warfarin vs. dabigatran)



TTR < 58:
Warfarin no better than aspirin

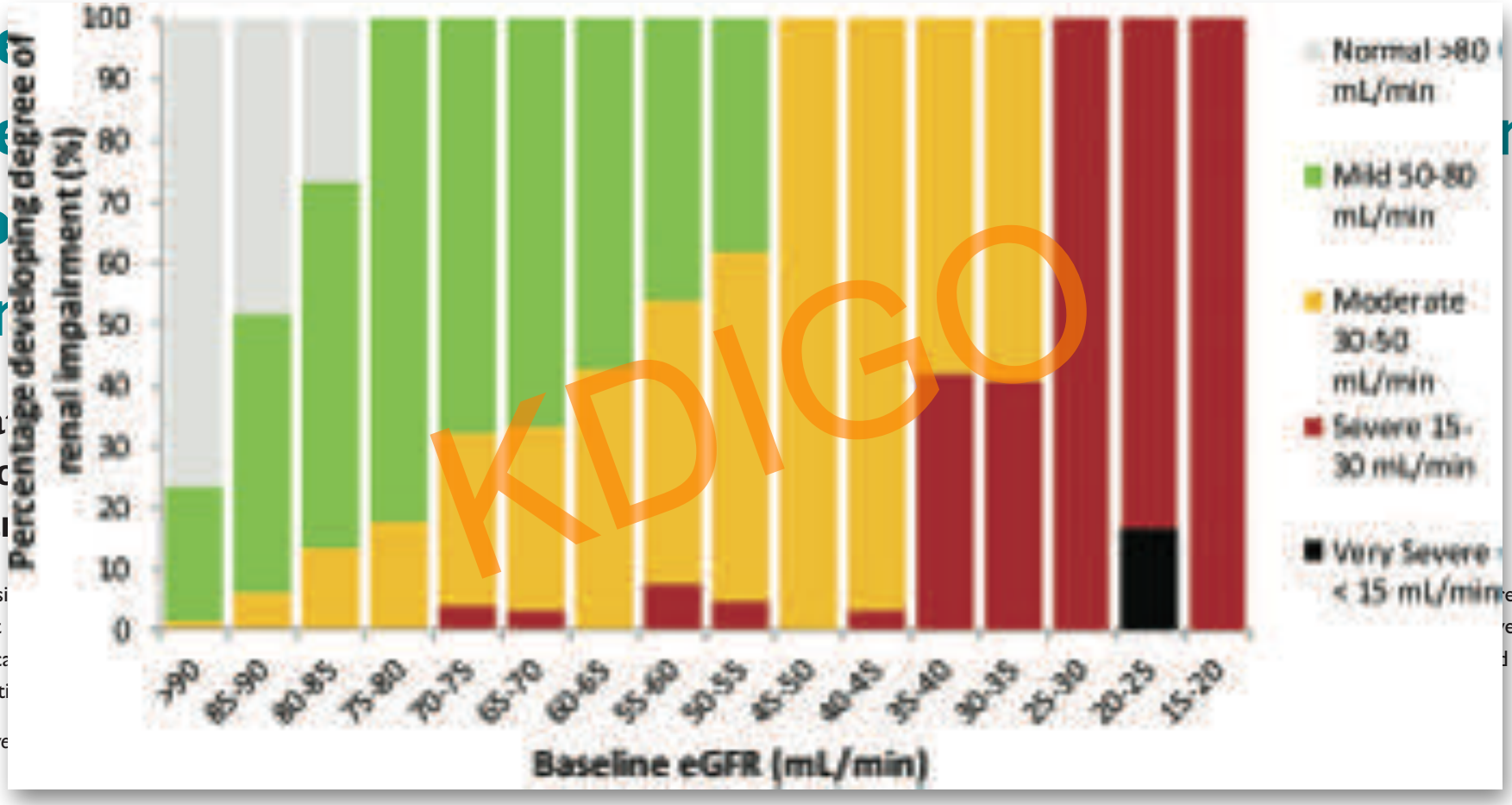
(Wallentin L, Lancet 2010)

Misery loves company: AF, CKD, and HF



Trulock KM, JACC 2014

CHARM trial: (candesartan in HF)



Hawkins NM, *Eur J Heart Fail*, 2016

What about bleeding risk?

Patient factors affecting bleeding risk

- Age
- Prior major bleeding
- Anemia
- Kidney disease
- Antiplatelet agents, NSAIDS
- Hypertension (SBP > 160)
- Prior stroke
- High alcohol use
- Moderate to severe liver disease
- Low TTR / unstable INRs

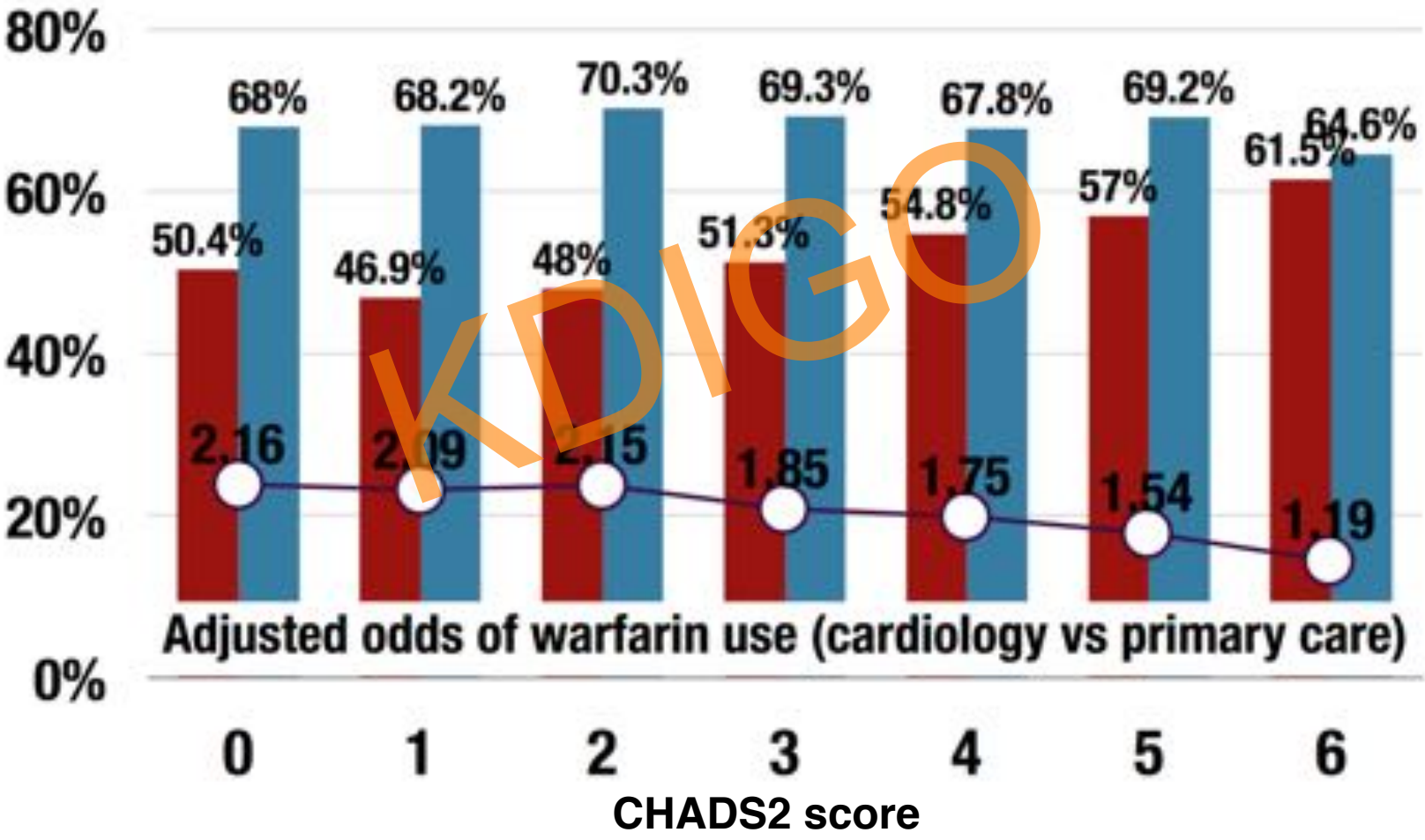
These factors also affect risk of stroke

Gage BF, *et al*. *Am Heart J*. 2006
Fang MC, *et al*. *J Am Coll Cardiol*. 2011
Pisters R, *et al*. *Chest*. 2010
Piccini JP, *et al*. *Circulation*. 2013

Quality and Coordination of Care

Anticoagulation prescription in new AF: Primary care vs. cardiology in VA system

n = 140,000



Turakhia M, *Am Heart J*, 2012

Nephrology and Cardiology care not coordinated

- In outpatient setting, most patients take on role of care coordinator
- In U.S., bundled payments are disease focused
- Problem of care structure
  - "I defer to the other"

We are learning, but need to learn more from you

Europace
doi:10.1093/europace/euv202

EHRA POSITION PAPER

Chronic kidney disease in patients with cardiac rhythm disturbances or implantable electrical devices: clinical significance and implications for decision making-a position paper of the European Heart Rhythm Association endorsed by the Heart Rhythm Society and the Asia Pacific Heart Rhythm Society

Giuseppe Boriani (Chair, Italy)*, Irina Savelieva (Co-chair, UK), Gheorghe-Andrei Dan (Romania), Jean Claude Deharo (France), Charles Ferro (UK), Carsten W. Israel (Germany), Deirdre A. Lane (UK), Gaetano La Manna (Italy), Joseph Morton (Australia), Angel Moya Mitjans (Spain), Marc A. Vos (The Netherlands), Mintu P. Turakhia (USA), and Gregory Y.H. Lip (UK)

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Boriani G, *et al.* Europace 2015

VIEWPOINT

Renal Function in Patients With Atrial Fibrillation Receiving Anticoagulants

The Canaries in the Coal Mine

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The past few years have witnessed unprecedented progress in the field of anticoagulation for atrial fibrillation (AF). Since 2010, 4 direct oral anticoagulants (DOACs) have been approved in nonvalvular AF based on pivotal trials. Patients with advanced chronic kidney disease (CKD) are arguably the highest-risk patients receiving anticoagulation from the standpoint of both stroke/systemic embolism and bleeding events. Although patients with estimated creatinine clearance (eCrCl) less than 30 mL/min/1.73m^2 (to convert to milliliters per second per meters squared, multiply by 0.0167) were excluded from trials, about 15% to 20% of enrollees had stage 3 CKD, providing clinicians representative data to derive meaningful conclusions to guide practice. Prespecified subgroup analysis and meta-analysis concur that the overall trial results (ie, noninferiority of the DOACs vs warfarin in the prevention of stroke/systemic embolism) are applicable to patients with stage 3 CKD, and several agents may actually have specific advantages.[1]

Not enough attention has been focused on systemic approaches to recognize and anticipate the fresh cluded that errors by prescribers related to incorrect dosing/indication were major contributors in the context of clinical characteristics that affect accurate dosing (ie, higher age, impaired renal function).

In these examples, the lack of recognition of the significance of underlying renal impairment was a unifying denominator. The CKD population is most vulnerable to needing dose adjustments because of the high renal clearance of the DOACs, ranging from 25% (apixaban) to 80% (dabigatran). A post hoc observation of the Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) trial highlighted the temporal deterioration in eCrCl among all 3 study arms receiving long-term anticoagulation (high- and low-dose dabigatran and warfarin), albeit statistically significant in the warfarin arm.[5] This observation may lend credence to the notion of warfarin-related nephropathy/glomerulopathy, but more importantly perhaps, indicates the need for temporal monitoring of renal function during anticoagulant therapy for AF, particularly in patients with CKD. Although most clinicians use estimated glomerular filtration rates to monitor renal function in practice, the doses

Summary

- Challenges
  - We have enough data to be worried, but not enough to know what to do
  - Trials of every permutation are unlikely
    - Reliance on observational data
    - More precision risk stratification?
- Opportunities
  - Defining areas of controversy, gaps in evidence, and a roadmap for research
  - Starting down a longer path of joint recommendations for clinical care and process measures
  - New friends, new collaborations!

Thank you !

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