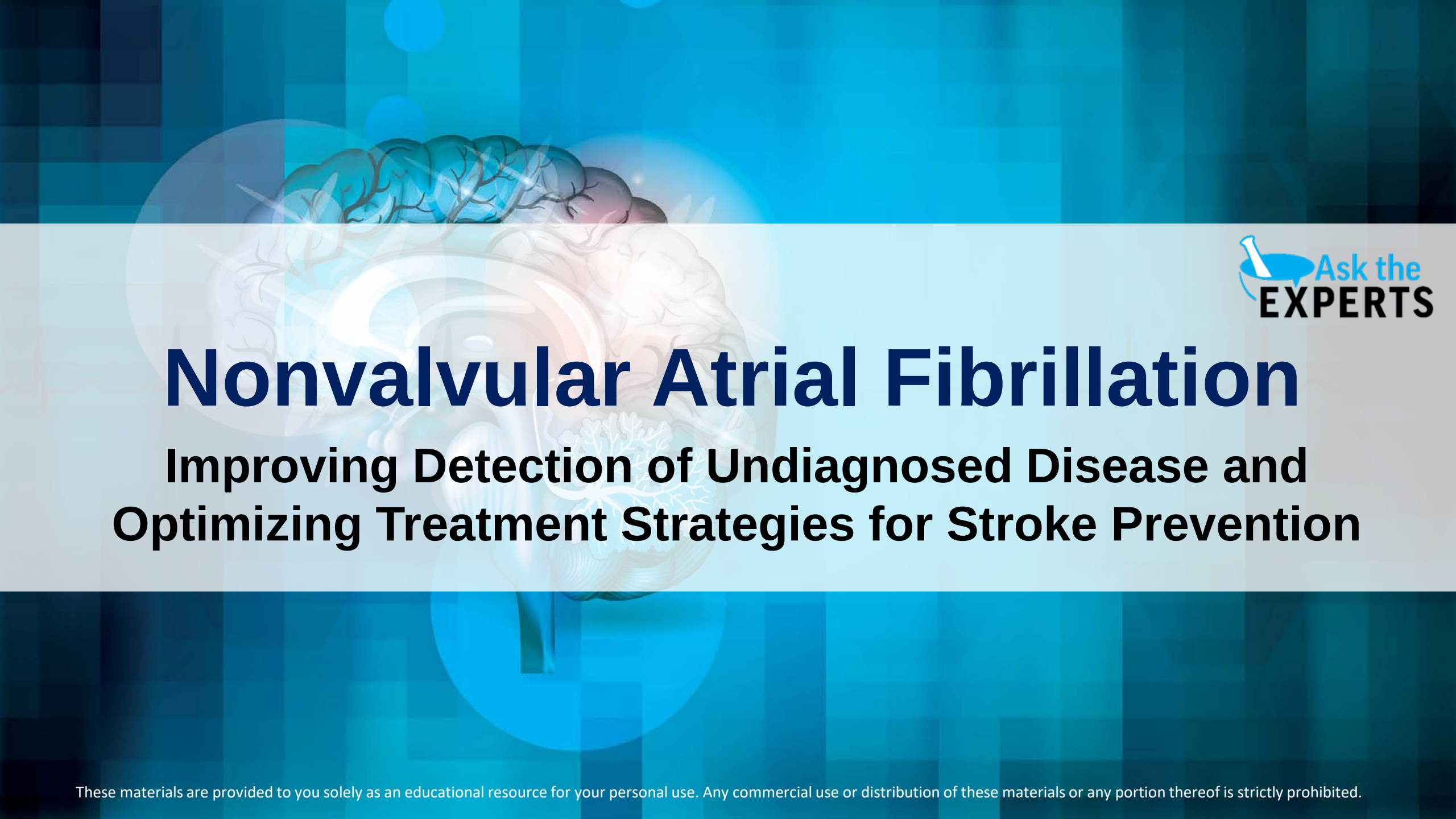

Nonvalvular Atrial Fibrillation

Improving Detection of Undiagnosed Disease and Optimizing Treatment Strategies for Stroke Prevention

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Disclosures

Drs. Cryder and **Lusk** have disclosed that they have no actual or potential conflicts of interest in relation to this program.

The clinical reviewer, **Tracy Macaulay, PharmD**, has disclosed that she has no actual or potential conflicts of interest related to this program.

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UAN: 0430-0000-22-123-H01-P
Credits: 1.5 hours (0.15 CEUs)
Type of Activity: Application

Learning Objectives

- **Discuss** the consequences of nonvalvular atrial fibrillation (NVAF) in patients who are undiagnosed or untreated
- **Summarize** different atrial fibrillation (AF) screening methods and opportunities to improve AF detection
- **Differentiate** between direct acting oral anticoagulants (DOACs) used for NVAF and the rationale for their use in stroke prevention
- **Formulate** strategies to optimize individualized anticoagulant selection and patient management to enhance treatment outcomes for NVAF

Nonvalvular Atrial Fibrillation and Stroke Risk

Atrial Fibrillation: Incidence/Prevalence

- Lifetime risk of AF: 1 in 4 when age ≥40 years
- Women > Men

2010

Total: 5.2 million

New: 1.2 million

2030

Total: 12.1 million

New: 2.6 million

AF, atrial fibrillation.

Circulation. 2022;145(8):e153. *Circulation.* 2004;110(9):1042.

Incidence/Prevalence of AF

- 1% to 2% of general population
- Lifetime risk

Ethnicity/Race	Gender	Lifetime Risk
White	Male	36%
	Female	30%
Black	Male	21%
	Female	22%

Circulation. 2022;145(8):e153. *Circ Arrhythm Electrophysiol.* 2020;13(1):e007698.
Am J Cardiol. 2013;112(8):1142. *Circ Arrhythm Electrophysiol.* 2018;11(7):e006350.

Incidence/Prevalence of AF

Ethnicity/Race	Prevalence (clinically detected AF)	Prevalence (monitor-detected AF)
White	11.3	7.1
Hispanic	7.8	6.9
Black	6.6	6.4
Chinese	9.9	5.2

Circulation. 2022;145(8):e153. *Circ Arrhythm Electrophysiol.* 2020;13(1):e007698.
Am J Cardiol. 2013;112(8):1142. *Circ Arrhythm Electrophysiol.* 2018;11(7):e006350.

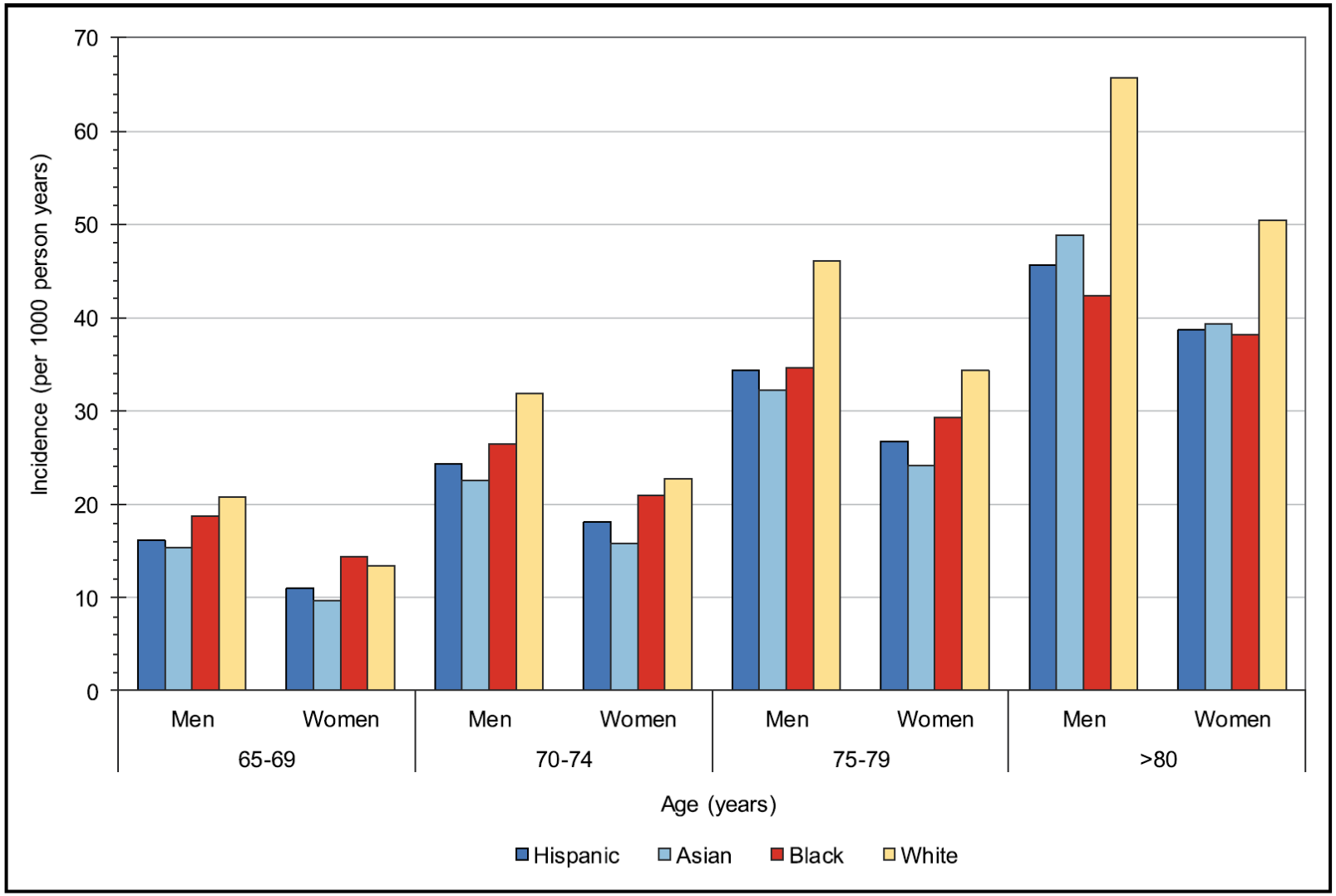


Chart 17-4. Atrial fibrillation incidence by race, 2005 to 2009.
Incidence increased with advancing age among different races and sexes in California.
Source: Data derived from Dewland et al.[68]

Circulation. 2022;145(8):e153.

Risk Factors for AF

- Hypertension
  - ~22% of AF cases
- Obesity
  - RR 1.51 (95% CI, 1.35-1.68)
- Smoking
  - RR 1.32 (95% CI, 1.12-1.56)
- Cardiovascular disease
  - MI: HR 1.64 (95% CI, 1.38-1.96)
  - HF: HR 2.02 (95% CI, 1.64-2.48)
- Diabetes
  - RR 1.11 (95% CI, 1.06-1.16)
- Physical inactivity
- Hypothyroidism
- CKD
- Moderate-high alcohol consumption
- Sleep apnea
- Psychosocial factors
  - Depression, PTSD, stress, exhaustion

CI, confidence interval; HF, heart failure; HR, hazard ration; MI, myocardial infarction; PTSD, post-traumatic stress disorder; RR, relative risk.

Circulation. 2022;145(8):e153. *Circulation.* 2011;123(14):1501. *J Cardiovasc Electrophysiol.* 2018;29(5):725. *Eur Prev Cardiol.* 2018;25(13):1437. *PLoS One.* 2017;12(3):e0170955. *J Am Heart Assoc.* 2013;2(2):e000102.

Complications/Consequences

- Stroke
  - 15% of strokes annually
  - AF-associated strokes → greater disability and morbidity
- Systemic embolism
- Cardiomyopathy/heart failure
- Cognitive decline
- Falls
- Mortality: age-adjusted mortality rate 6.5 per 100,000 people (2019)
  - Males: OR 1.5 (95% CI, 1.2-1.8); Females: OR 1.9 (95% CI, 1.5-2.2)

Arch Intern Med. 1994;154(13):1449. *Circulation.* 2022;145(8):e153. *Stroke.* 2001;32(12):2735. *Circulation.* 1998;98(10):946.
CDC WONDER online database. Accessed September 15, 2022. https://wonder.cdc.gov/mcd-icd10.html

Economic Burden

- Management costs rising
  - Hospitalizations
  - Complications (eg, heart failure, stroke/systemic embolism)
  - Medications (eg, antiarrhythmic drugs)
  - Procedures (eg, cardioversion, ablation)
- Annual costs for AF treatment: $28.4 billion in 2016
  - AF hospitalizations: $2.93 billion
  - Hospitalizations with AF comorbidity: $1.95 billion
  - Outpatient management: $1.53 billion
  - Medications: $235 million

Value Health. 2006;9(5):348. *JAMA.* 2020;323(9):863.

Economic Burden

- Mean per capita medical spending (AF vs no AF)
  - 18-64 years old: $38,861 vs $28,506
  - ≥65 years old: $25,322 vs $21,706
- Incremental annual AF medical cost: $6 to $26 billion
- Estimated US incremental cost burden of undiagnosed NVAF: $3.1 billion

True cost burden of AF underestimated

Am J Cardiol. 2015;116(5):733.

Screening

Audience Response #1: Patient Case

- 72-year-old male patient that you have been working with on hypertension management
- “Check out my new smart watch, I hear it can tell me if I have a dangerous arrhythmia”
- **How would you respond?**

A. “That sounds great, but I don’t think the technology is there yet”
B. “Absolutely, the new smartwatches are just as good as the ECG at the medical center”
C. “Yes, the new smartwatches are very good at sensing irregular heart rates, but cannot identify specific arrhythmias at this time”

Traditional Methods of NVAF Screening

- Primary method = 12-lead ECG
- “Clinical Atrial Fibrillation”
  - Screening with ECG triggered by irregular pulse palpation AND/OR symptoms of palpitations, chest pain, exercise intolerance, dizziness, syncope, or sleep disorders
- “Subclinical Atrial Fibrillation”
  - No classic symptoms observed
  - Incidentally found on continuous monitoring device (eg, pacemaker) or when monitored for other reasons

J Intern Med. 2021;289(4):474.

Methods of NVAF Screening

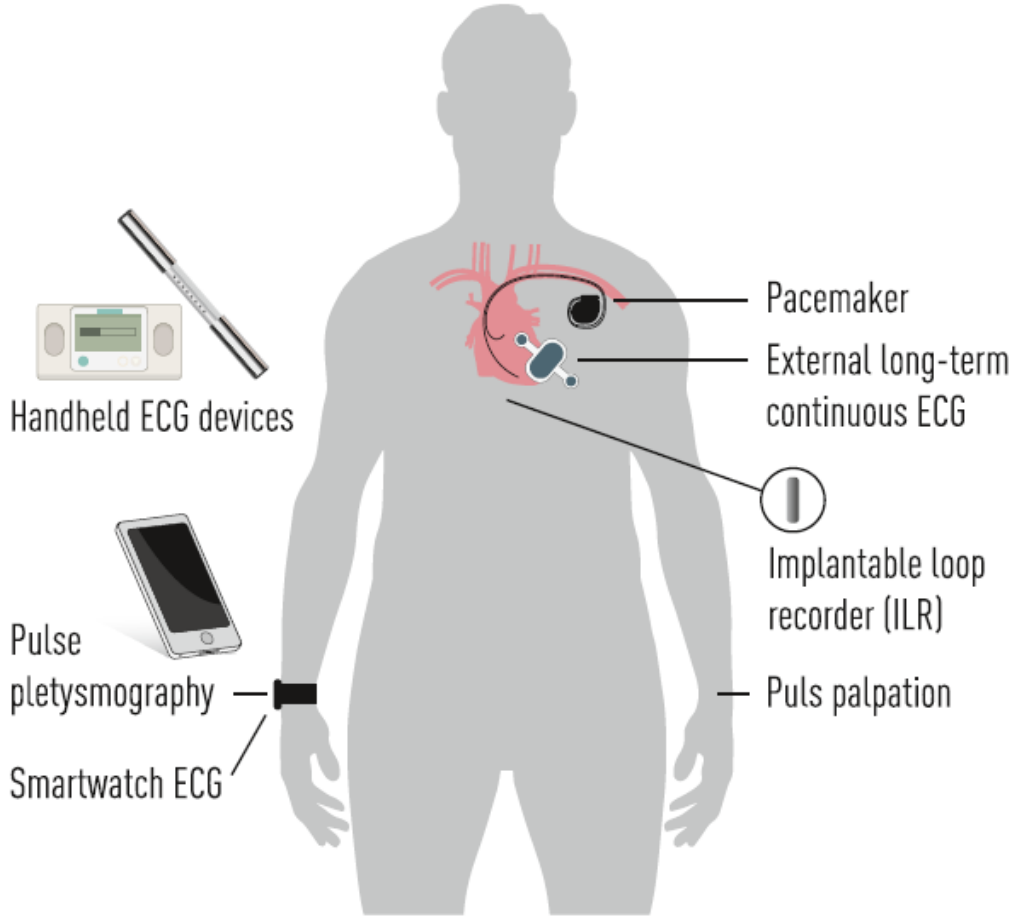


Fig. 2 *Examples of methods and devices used for atrial fibrillation screening.*

J Intern Med. 2021;289(4):474.

Methods of NVAF Screening

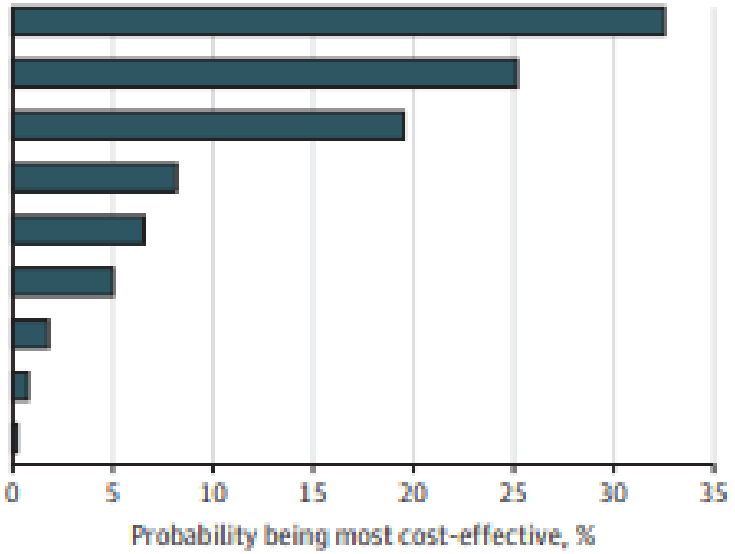
	Implanted	Wearable Technology	Mobile Device Apps	Patch
Mechanism	Direct measurement of electrical activity via leads - Like an internal ECG	**Photoplethysmography (PPG)** - Also used in pulse oximetry - Detects changes in blood flow - 100s of light flashes per second helps detect interval changes in pulse	Measurement of electrical activity via finger/thumb placed on stainless steel "leads" on device	Patch worn for 7-14 days, stores record of cardiac electrical activity
Examples	Pacemaker, implanted cardioverter-defibrillator (ICD)	Smartwatches	Apps on smartphones and smart watches	Zio XT
Evidence	MOST[1]: 100% sensitivity 97.6% specificity	Positive predictive value of AF with irregular rhythm alerts Apple Heart Study[2]: 84% FitBit Heart Study[3]: 98%	N/A	mSTOPS[4]: Higher rate of AF detections compared to usual monitoring

1. *Circulation*. 2003;107(12):1614. 2. *N Engl J Med*. 2019;381(20):1909. 3. Lubitz AS. AHA Scientific Sessions 2021. 4. *JAMA*. 2018;320(2):146.

Cost-Effectiveness of NVAF Screening

Figure 3. Probabilistic Sensitivity Analysis

Pulse palpation	12-Lead ECG	Watch PPG	Watch ECG	Patch monitor	Frequency
		×	×	×	Life
×	×	×		×	Life
	×		×	×	Life
×	×	×	×	×	Life
×	×			×	Once
		×		×	Life
	×	×	×	×	Life
No screening					
	×				Once



Each bar indicates the probability that a given strategy is cost-effective, when accounting for parameter uncertainty. Strategies are displayed in order of decreasing probability of cost-effectiveness, with the strategy most likely to be cost-effective at the top. Every row in the table to the left represents a given strategy. For each row, an X indicates that a given modality was included in the screening strategy. Absence of an X indicates that a given modality was not included. ECG indicates electrocardiography; PPG, photoplethysmography.

JAMA Health Forum. 2022;3(8):e222419.

Consensus Recommendations for NVAF Screening

“The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for atrial fibrillation.”

Table. Summary of USPSTF Rationale

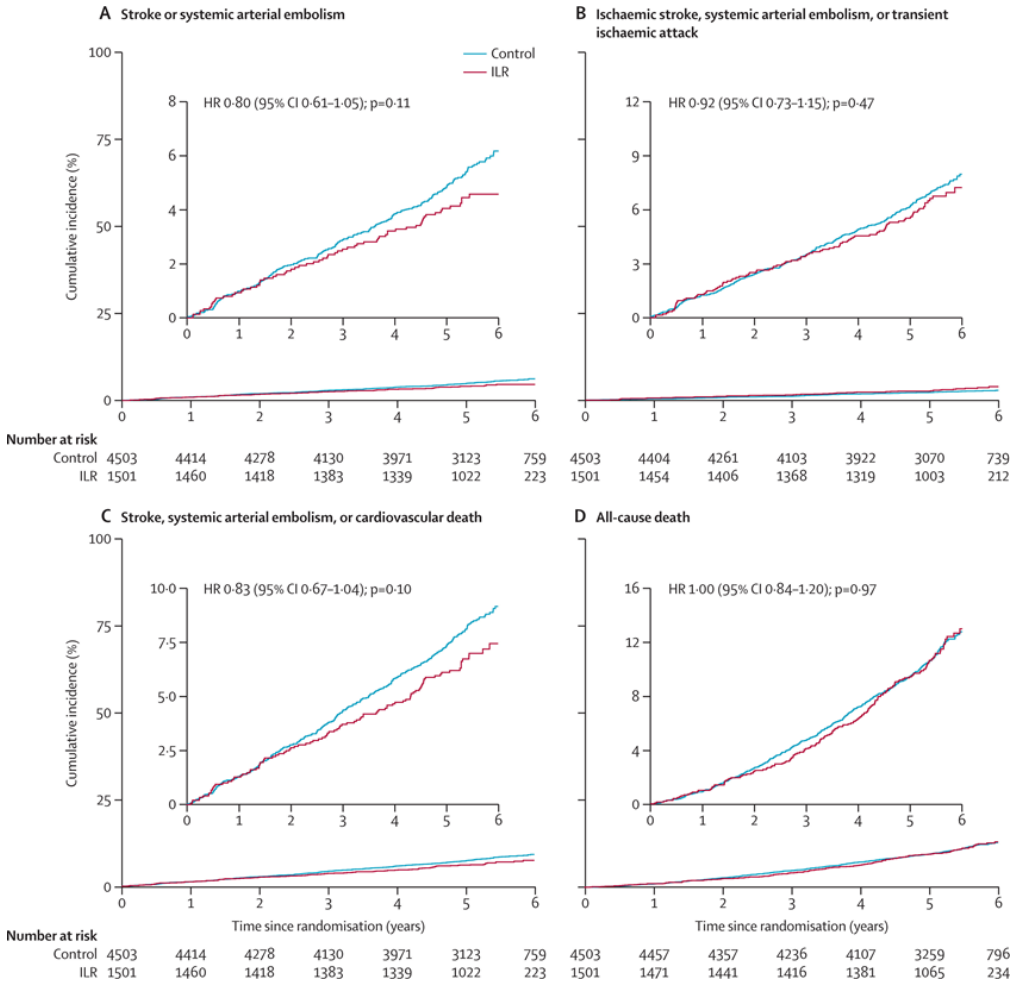
Rationale	Assessment
Detection	• Inadequate evidence to assess whether 1-time screening strategies identify adults 50 years or older with previously undiagnosed AF more effectively than usual care. • Adequate evidence that intermittent and continuous screening strategies identify adults 50 years or older with previously undiagnosed AF more effectively than usual care.
Benefits of early detection and intervention and treatment	• Inadequate direct evidence on the benefits of screening for AF. • Inadequate evidence on the benefits of treatment of screen-detected AF, particularly paroxysmal AF of short duration.
Harms of early detection and intervention and treatment	• Inadequate direct evidence on the harms of screening for AF. • Adequate evidence that treatment of AF with anticoagulant therapy is associated with small to moderate harm, particularly an increased risk of major bleeding.
USPSTF assessment	Evidence is lacking, and the balance of benefits and harms of screening for AF in asymptomatic adults cannot be determined.

Abbreviations: AF, atrial fibrillation; USPSTF, US Preventive Services Task Force.

USPSTF. *JAMA*. 2022;327(4):360.

LOOP Study

- **RCT in Denmark (4 centers)**
- Patient characteristics
  - Age 70-90 years
  - No history of AF
  - At least 1 other CVA risk factor (HF, HTN, DM, prior CVA)
- Implanted loop recorder (n = 1501) vs usual care (n = 4503)
- 5-year follow-up
- Take home results
  - ILR = ↑ AF detection (3-fold)
  - OAC started in ~90% of cases
  - No difference in outcomes



CVA, cerebrovascular accident (stroke); DM, diabetes mellitus; HF, heart failure; HTN, hypertension; ILR, implantable loop recorder; OAC, oral anticoagulant; RCT, randomized controlled trial.

Lancet. 2021;398(10310):1507.

Audience Response #2: Patient Case

- *The same* 72-year-old male patient that you have been working with on hypertension management
- “Check out my new smart watch, I hear it can tell me if I have a dangerous arrhythmia”
- **How would you respond?**

A. “That sounds great, but I don’t think the technology is there yet”
B. “Absolutely, the new smartwatches are just as good as the ECG at the medical center”
C. “Yes, the new smartwatches are very good at sensing irregular heart rates, but cannot identify specific arrhythmias at this time”

Questions & Answers

Standards of Care

CHA_2DS_2-VASc Score

Letter	Description	Points
C	Congestive heart failure	1
H	Hypertension	1
A_2	Age ≥75	2
D	Diabetes	1
S_2	Stroke/TIA/SE	2
V	Vascular disease (MI, PAD)	1
A	Age 65-74 years	1
Sc	Sex category: female	1

Score	Stroke risk	Stroke/TIA/ SE risk
0	0.2%	0.3%
1	0.6%	0.9%
2	2.2%	2.9%
3	3.2%	4.6%
4	4.8%	6.7%
5	7.2%	10.0%
6	9.7%	13.6%
7	11.2%	15.7%
8	10.8%	15.2%
9	12.2%	17.4%

MI, myocardial infarction; PAD, peripheral arterial disease; SE, systemic embolism; TIA, transient ischemic attack.

Chest. 2019;137(2):263. *Eur Heart J.* 2012;33(12):1500.

HAS-BLED Score

Letter	Description	Points
H	Hypertension (SBP >160 mmHg)	1
A	**Abnormal renal or liver function** • Renal disease (dialysis, transplant, SCr >2.26) • Liver disease (cirrhosis, bilirubin >2x ULN with AST/ALT/ALP >3x ULN)	1/1
S	Stroke	1
B	Prior major bleeding or predisposition to bleeding	1
L	Labile INR (unstable/high INRs, TTR <60%)	1
E	Elderly (age >65 years)	1
D	**Drugs/Alcohol** • Medications predisposing bleeding (aspirin, $P2Y_{12}$ inhibitor, NSAIDs) • Alcohol (≥8 drinks/week)	1/1

AST/ALT/ALP, alanine transaminase/aspartate transaminase/alkaline phosphatase; INR, international normalized ratio; NSAIDs, nonsteroidal anti-inflammatory drugs; SBP, systolic blood pressure; TTR, time in therapeutic range; ULN, upper limit of normal.

Chest. 2010;138(5):1093. *J Am Coll Cardio.* 2011;57(2):173.

HAS-BLED Score

Letter	Description	Points
H	Hypertension **(SBP >160 mmHg)**	1
A	**Abnormal renal or liver function** • Renal disease **(dialysis, transplant, SCr >2.26)** • Liver disease **(cirrhosis, bilirubin >2x ULN with AST/ALT/ALP >3x ULN)**	1/1
S	Stroke	1
B	Prior major bleeding or predisposition to bleeding	1
L	Labile INR (unstable/high INRs, TTR <60%)	1
E	Elderly **(age >65 years)**	1
D	**Drugs/Alcohol** • Medications predisposing bleeding **(aspirin, P2Y$_{12}$ inhibitor, NSAIDs)** • Alcohol **(≥8 drinks/week)**	1/1

AST/ALT/ALP, alanine transaminase/aspartate transaminase/alkaline phosphatase; INR, international normalized ratio; NSAIDs, nonsteroidal anti-inflammatory drugs; SBP, systolic blood pressure; TTR, time in therapeutic range; ULN, upper limit of normal.

Chest. 2010;138(5):1093. *J Am Coll Cardio.* 2011;57(2):173.

HAS-BLED Score

Letter	Description	
H	Hypertension (SBP >160 mmHg)	1/1
A	**Abnormal renal or liver function** • Renal disease (dialysis, transplant, SCr >2 • Liver disease (cirrhosis, bilirubin >2x ULN	1/2
S	Stroke	1/1
B	Prior major bleeding or predisposition to b	1/1
L	Labile INR (unstable/high INRs, TTR <60%)	1/1
E	Elderly (age >65 years)	1/1
D	**Drugs/Alcohol** • Medications predisposing bleeding (aspirin, $P2Y_{12}$ inhibitor, NSAIDs) • Alcohol (≥8 drinks/week)	1/1

Score	Risk Group	Major Bleeding Risk
0	Relatively low	0.9%
1		3.4%
2	Moderate	4.1%
3	High	5.8%
4		8.9%
5		9.1%
≥6	Very high	—

AST/ALT/ALP, alanine transaminase/aspartate transaminase/alkaline phosphatase; INR, international normalized ratio; NSAIDs, nonsteroidal anti-inflammatory drugs; SBP, systolic blood pressure; TTR, time in therapeutic range; ULN, upper limit of normal.

Chest. 2010;138(5):1093. *J Am Coll Cardio.* 2011;57(2):173.

2019 AHA/ACC/HRS Focused Update

CHA_2DS_2-VASc Score	Recommendation
Men	
≥2	Anticoagulation
1	Consider anticoagulation
0	Omit anticoagulation
Women	
≥3	Anticoagulation
2	Consider anticoagulation
1	Omit anticoagulation

ACC, American College of Cardiology; AHA, American Heart Association; HRS, Heart Rhythm Society.

Circulation. 2019;140(2):e125.

2019 AHA/ACC/HRS Focused Update

Population	Anticoagulant of Choice
NVAF	DOAC
Valvular atrial fibrillation (moderate-severe MS or mechanical valve)	Warfarin
CrCl <15 mL/min or ESRD	Apixaban or warfarin

Role of aspirin for stroke prevention for AF alone

Shared decision-making

- Risk vs benefit
- Patient values and preferences

DOAC, direct oral anticoagulant; ESRD, end-stage renal disease; MS, mitral stenosis.

Int J Stroke. 2017;12(6):589. *N Engl J Med*. 2018;378(23):2191. *Eur Heart J*. 2021;42(5):373. *Int J Stroke*. 2017;12(9):985. *Circulation*. 2019;140(2):e125. *Neurology*. 2016;87(18):1856.

Secondary Prevention of Cardioembolic Stroke

- Timing of OAC reinitiation after an ischemic stroke → expert opinion
  - Earlier initiation may reduce recurrent stroke without increasing risk of ICH
- Cryptogenic/embolic stroke with undetermined source
  - DOAC vs aspirin: no improved efficacy, increased bleeding
  - DOAC therapy may be beneficial in certain patients
    - Age >75 years, impaired renal function, enlarged left atrium

DOAC, direct oral anticoagulant; ICH, intracerebral brain hemorrhage; OAC, oral anticoagulant.

Int J Stroke. 2017;12(6):589. *N Engl J Med*. 2018;378(23):2191.
Eur Heart J. 2021;42(5):373. *Int J Stroke*. 2017;12(9):985. *Neurology*. 2016;87(18):1856.

Direct Oral Anticoagulants

DOAC[a]	Stroke/ SE	Major Bleeding	GI Bleeding	Mortality	Other ADRs
Apixaban	↓	↓	=	↓	—
Dabigatran	↓	=	↑	=	Dyspepsia
Edoxaban	=	↓	↓	↓	—
Rivaroxaban	=	=	↑	=	—

[a] Compared to warfarin.

ADRs, adverse drug reactions; GI, gastrointestinal; SE, systemic embolism.

N Engl J Med. 2011;36(11)5:981. *N Engl J Med.* 2009;361(12):1139. *N Engl J Med.* 2013;369(22):2093. *N Engl J Med.* 2011;365(10):883.

Direct Oral Anticoagulants

DOAC[a]	Stroke/ SE	Major Bleeding	GI Bleeding	Mortality	Other ADRs
Apixaban	↓	↓	=	↓	—
Dabigatran	↓	=	↑	=	Dyspepsia
Edoxaban	=	↓	↓	↓	—
Rivaroxaban	=	=	↑	=	—

[a] Compared to warfarin.

ADRs, adverse drug reactions; GI, gastrointestinal; SE, systemic embolism.

N Engl J Med. 2011;36(11)5:981. *N Engl J Med.* 2009;361(12):1139. *N Engl J Med.* 2013;369(22):2093. *N Engl J Med.* 2011;365(10):883.

DOAC Dosing and Costs

DOAC	Dosing	Dose Adjustments	Cost/Month
Apixaban	5 mg BID	**2.5 mg BID if ≥2**: Age ≥80 years Weight ≤60 kg SCr ≥1.5 mg/dL	$525-550
Dabigatran	150 mg BID	CrCl 15-30: 75 mg BID CrCl <15: not recommended	$484-511
Edoxaban	60 mg daily	**CrCl >95: contraindicated** CrCl 15-50: 30 mg daily CrCl <15: not recommended	$390-420
Rivaroxaban	20 mg daily	CrCl 15-50: 15 mg daily CrCl <15: not recommended	$515-540

N Engl J Med. 2011;36(11)5:981. *N Engl J Med.* 2009;361(12):1139. *N Engl J Med.* 2013;369(22):2093. *N Engl J Med.* 2011;365(10):883.

DOAC Considerations

Advantages

- No routine monitoring
- Improved safety profile
- Rapid onset
- Short half-life
- Fixed dosing
- Greater convenience/patient satisfaction
- Fewer drug-disease interactions
- Fewer drug-diet interactions

Disadvantages

- Lack of readily available monitoring/ standardized references
- Dose adjustments/avoidance in renal impairment
- Avoidance in moderate-severe hepatic impairment
- Short half-life
- Higher drug acquisition cost to patient

J Thromb Thrombolysis. 2016;41(1):206.

DOAC Dosing: Room for Error

Overdosing

- ↑ All-cause mortality
- ↑ Major bleeding
- ↑ Stroke/SE

- ↑ Stroke/SE
- ↑ CV hospitalization
- ↑ All-cause mortality

Does **NOT** minimize bleeding

Underdosing

CV, cardiovascular; SE, systemic embolism.

Am J Med. 2021;134(6):788. *J Am Coll Cardiol*. 2016;68(24):2597. *Front Cariovasc Med.* 2021;8:724301.

Audience Response #3: Anticoagulant Selection

- KB is an 81-year-old male patient
- PMH of hypertension, dyslipidemia, CAD s/p MI, HFrEF, CKD 4 (SCr 1.8, CrCl 28 mL/min), and GERD
- Medications: metoprolol succinate, losartan, spironolactone, dapagliflozin, furosemide, rosuvastatin, aspirin, and pantoprazole
- He developed palpitations and fatigue, for which he was admitted to the hospital. Upon admission, he was diagnosed with NVAF
- **Which of the following anticoagulation regimens is most appropriate for stroke prevention?**

A. Warfarin 5 mg daily
B. Apixaban 5 mg BID
C. Dabigatran 150 mg BID
D. Rivaroxaban 15 mg daily

CAD s/p MI, coronary artery disease in stable post-myocardial infarction; GERD, gastroesophageal reflux disease; HFrEF, heart failure with reduced ejection fraction; PMH, past medical history.

295

Fall Risk and Bleeding

How many times must a person fall per year for DOAC risk of bleeding to outweigh ischemic benefit?

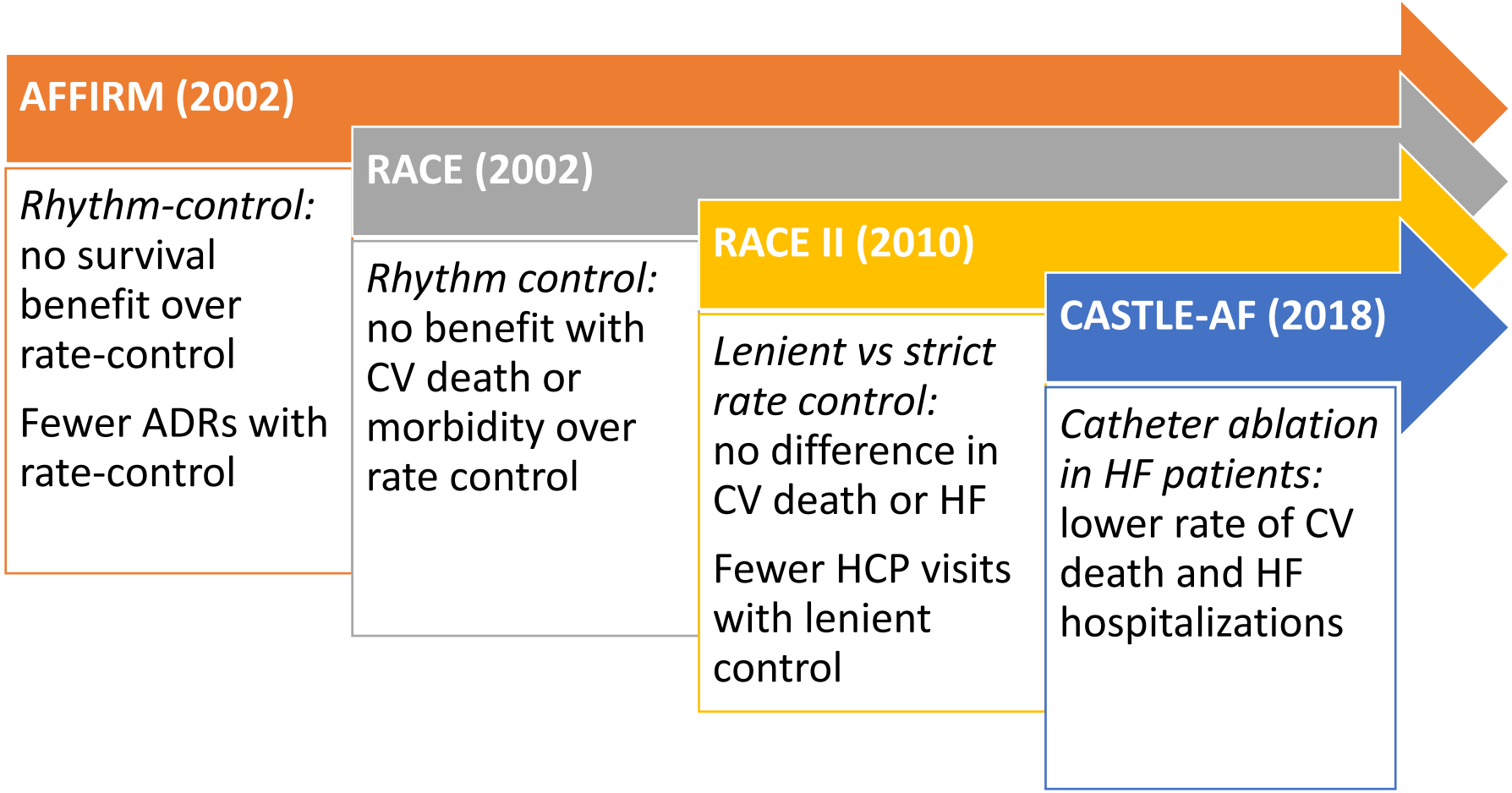
Arch Intern Med. 1999;159(7):677. *Eur Heart J*. 2021;42(5):373.

Reducing Bleeding Risk

- Select appropriate DOAC dose
- Address modifiable risk factors
  - Uncontrolled hypertension
  - Nonadherence
  - Concomitant medications
  - Alcohol intake
- Higher HAS-BLED score: more frequent monitoring

Arch Intern Med. 1999;159(7):677. *Eur Heart J*. 2021;42(5):373.

Rate vs Rhythm Control?



HCP, health care professional.

N Engl J Med. 2002;347(23):1825. *N Engl J Med.* 2002;347(23):1834.
N Engl J Med. 2010;362(15):1363. *N Engl J Med.* 2018;378(5):417.

Rate vs Rhythm Control: What Do the Guidelines Tell Us?

2014

- Repeated cardioversions for persistent AF, if sinus rhythm can be maintained, should be considered
- Severity of symptoms and patient preference should be considered

2019

- Catheter ablation may be reasonable in symptomatic AF and HFrEF to potentially lower mortality rate and reduce HF hospitalization

Circulation. 2014;130(23):e199.

Efficacy of Rhythm Control Strategies

AAD

- 1 year: 44-77% recurrence
- 1 year: 54% hospitalization
- ↑ withdrawal (ADRs)
- Proarrhythmic

DCCV

- 6 mo: 63% recurrence
- 1 year: 76% recurrence

Catheter Ablation

- 1 year: 11-13% recurrence
- 1 year: 9% hospitalization
- 52% asymptomatic w/o drugs + 23.9% w/AAD
- Improved QOL

AAD, antiarrhythmic drug; ADRs, adverse drug events; DCCV, direct current cardioversion; QOL, quality of life.

Arch Intern Med. 2006;166(7):719. *Circulation.* 2005;111(9):1100. *Circulation.* 2008;118(24):2498. *JAMA.* 2005;293(21):2634. *Heart.* 2019;105(suppl 6):A34.

Management of Comorbidities

- Heart failure
- Hypertension
- Coronary artery disease
- Obesity
- Sleep apnea
- Alcohol
- Thyroid disease

Nat Rev Cardio. 2016;13(3):131. *Ther Adv Cardiovasc Dis.* 2013;7(2):53.
N Eng J Med. 2020;382(1):20. *Mater Sociomed.* 2017;29(4):231.

Questions & Answers

Shared Decision-Making

Shared Decision-Making

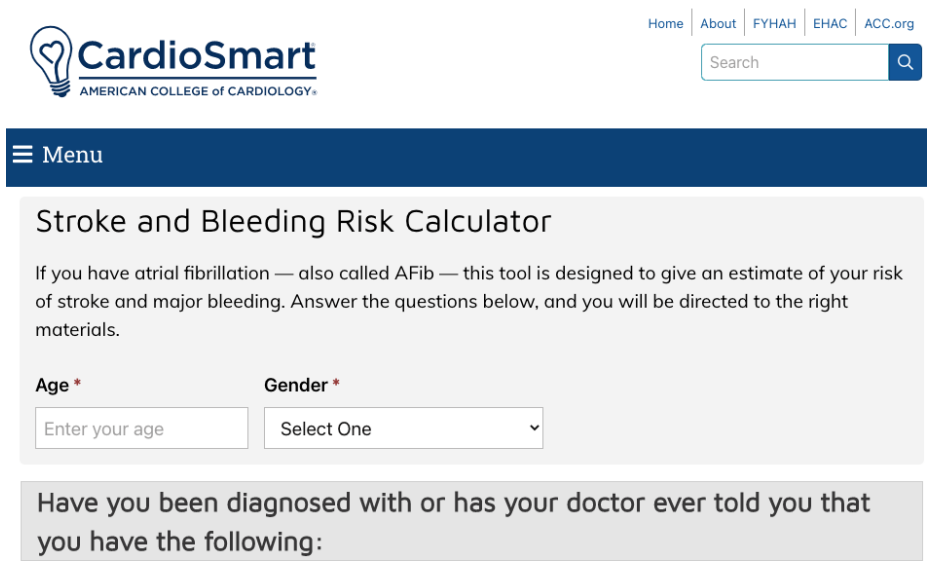
- A male patient returns for another hypertension focused visit, but all he wants to talk about is his new onset AF
- His primary care physician is recommending that he start using an anticoagulant medication, but he has heard so many negative stories about “blood thinners” that he wants to know how important these drugs really are

Age 72; PMH = hypertension, osteoarthritis, type 2 diabetes

Shared Decision-Making Tools

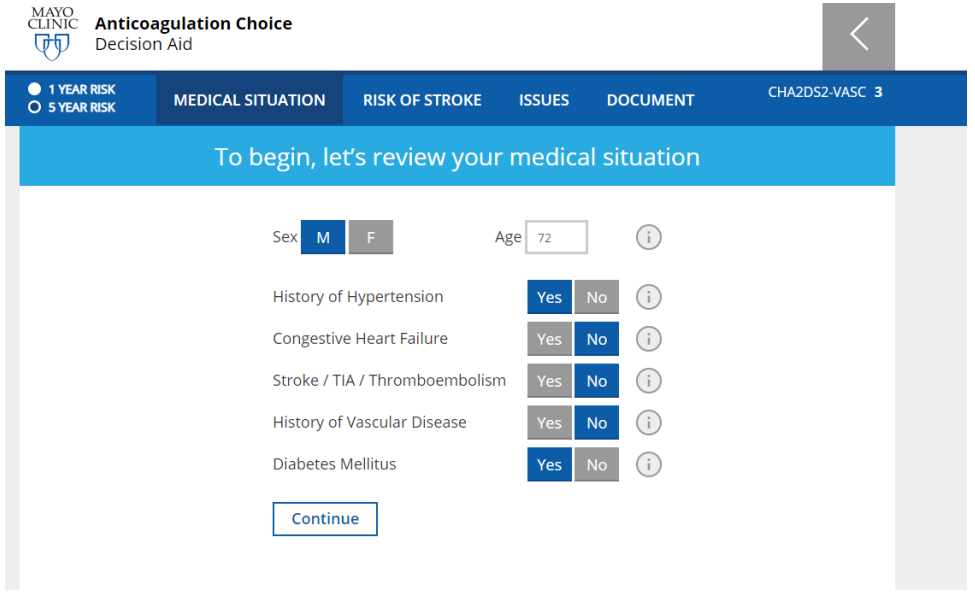
CardioSmart

- From the American College of Cardiology
- https://www.cardiosmart.org/stroke-and-bleeding-risk-calculator



Anticoagulation Choice Decision Aid

- From the Mayo Clinic
- https://anticoagulationdecisionaid.mayoclinic.org



Shared Decision-Making Tools

MAYO CLINIC **Anticoagulation Choice**
Decision Aid

1 YEAR RISK
5 YEAR RISK

MEDICAL SITUATION | RISK OF STROKE | ISSUES | DOCUMENT | CHA2DS2-VASC 3

Over the next 5 years

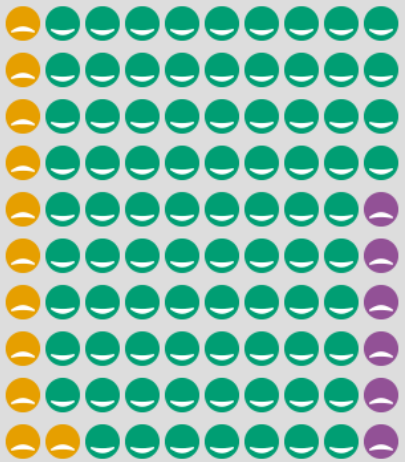
83 people will have no stroke

6 people will have a fatal or disabling stroke

11 people will have a non-disabling stroke

Current Risk of Stroke Without Anticoagulation

In 100 people like you who **are not** taking an anticoagulant, **at 5 years...**



Future Risk of Stroke With Anticoagulation

In 100 people like you who **are** taking an anticoagulant, **at 5 years...**

Over the next 5 years

95 people will have no stroke

1 person will have a fatal or disabling stroke

4 people will have a non-disabling stroke

12 people will avoid a stroke by taking anticoagulation

Balancing Risks:
Thrombosis vs Hemorrhagic Complications

CHA_2DS_2-VASc

- ✓ Important to confirm potential benefit of OAC

HAS-BLED

- ✓ Important to identify bleeding risk factors
- ✓ Does NOT disqualify OAC use

Chest. 2019;137(2):263. *Chest.* 2010;138(5):1093.

Factors Influencing Anticoagulant Choice

MAYO CLINIC **Anticoagulation Choice**
Decision Aid

1 YEAR RISK
5 YEAR RISK

MEDICAL SITUATION | RISK OF STROKE | ISSUES | DOCUMENT | CHA2DS2-VASC 3

Anticoagulation Choices

There are choices for anticoagulation medicines

Warfarin or **Direct Anticoagulant**

Apixaban	*Eliquis*
Dabigatran	*Pradaxa*
Edoxaban	*Savaysa*
Rivaroxaban	*Xarelto*

To choose between anticoagulaton approaches, **let's think about how the options would fit in your life**

Continue

Anticoagulant Choice: Important Considerations

- Dose frequency
- Monitoring requirements
- Anticoagulant reversal
- Cost of medication/monitoring

Anticoagulant Choice: Important Considerations

Table 4
Influential factors by choice of class of anticoagulant.

Factors that greatly influenced decisions[a]	Chose Warfarin (n = 33)	Chose DOACs (n = 45)
Comparison of benefit vs harm numbers	4 (12)	14 (31)
Know someone with AF taking same medication	0 (0)	1 (2)
Afraid of having stroke	6 (18)	6 (13)
Afraid of having a bleed	5 (15)	6 (13)
Afraid of having a heart attack	4 (12)	8 (18)
Prefer taking pill once/day rather than twice/day	6 (18)	9 (20)
Do not want regular blood tests	1 (3)	16 (36)
Prefer taking an older, more known drug	12 (36)	0 (0)
Prefer taking a newer drug	0 (0)	3 (7)
Do not want drug whose name is similar to rat poison	0 (0)	2 (4)
Cost of drug	4 (12)	5 (11)

Results are provided as n (%).

[a] Patients could pick more than one greatly influential factor.

Thromb Res. 2016;145:143-8.

Anticoagulant Interactions

- Food interactions
  - Warfarin—vitamin K
  - Rivaroxaban (15 and 20 mg) taken with food
- Medication interactions
  - DOACs
    - P-glycoprotein (P-gp)
    - CYP3A4

J Am Coll Cardiol. 2020; 75: 1341-1350.

DOACs: Impact of Drug Interactions

Drug	Amiodarone	Dronedarone	Verapamil	Diltiazem	CYP3A4 Inducers
Apixaban	Safe	Acceptable	Safe	Safe	Avoid
Dabigatran	Avoid CrCl <30 (AF)	CrCl 30-50: 75 mg BID CrCl <30: Avoid	Avoid if CrCl <30 (AF)	Safe	Avoid
Edoxaban	Safe	↓dose 50%	Safe	Safe	Avoid
Rivaroxaban	Avoid if CrCl <80	Avoid if CrCl <80	Avoid if CrCl <80	Avoid if CrCl <80	Avoid

J Am Coll Cardiol. 2020;75(11):1341.

Other Considerations: Comorbidities

- Renal (kidney) disease
- Obesity
- Frailty

Comorbidities: Renal Disease

Drug	CrCl ≥50 mL/min	CrCl 30-49 mL/min	CrCl 15-29 mL/min	CrCl <15 mL/min or ESRD on RRT
VKA	If TTR ≥70%	If TTR ≥70%	If TTR ≥70%	If TTR ≥70%
Dabigatran	150 mg bid[a] (or 110 mg bid)	150 mg bid (or non-US, 110 mg bid)[a]	✖ (Outside US) 75 mg bid in US[a]	✖
Rivaroxaban	20 mg qd	15 mg qd	15 mg qd	✖
Apixaban	5 mg bid[b]	5 mg bid[b]	2.5 mg bid	✖ (Outside US) 5 mg bid in US only[b]
Edoxaban	60 mg qd	30 mg qd	30 mg qd	✖

a. 110-mg dose of dabigatran not available in US

b. Apixaban 2.5-mg dose only used in US when 2 of 3 adjustment factors present (SCr ≥1.5, age ≥80, weight ≤60 kg)

ESRD, end-stage renal disease; RRT, renal replacement therapy; TTR, time in therapeutic range; VKA; vitamin K antagonist.

Chest. 2018;154(5):1121.

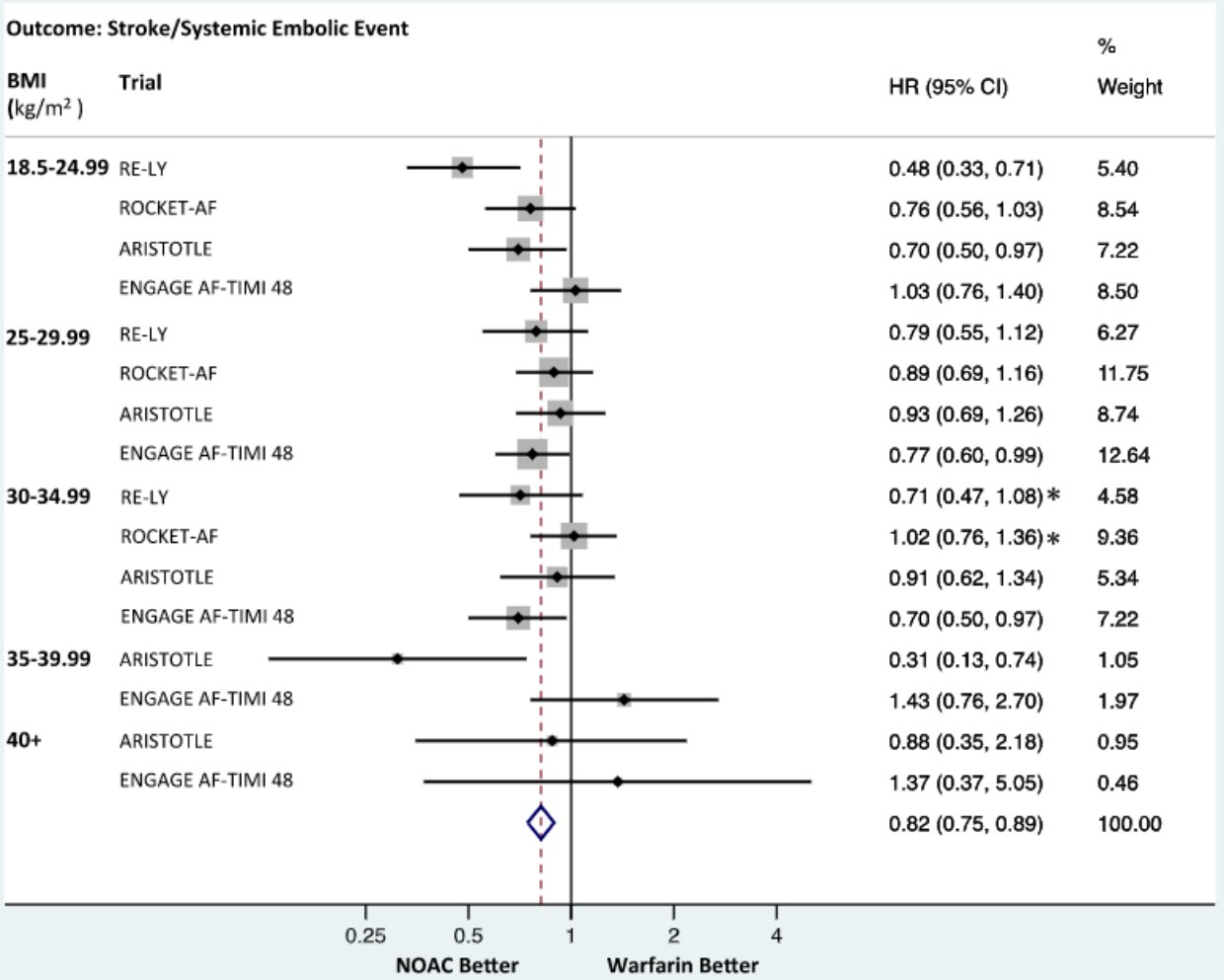
Comorbidities: Obesity

- International Society of Thrombosis and Haemostasis (ISTH)
  - 2016 Guidance did not support use of DOACs if:
    - Weight >120 kg
    - BMI >40 kg/m^2
    - Concerns about decreased drug exposure/underdosing
  - 2021 Update Guidance
    - For VTE: rivaroxaban and apixaban can be used at any BMI/weight; other DOACs still limited to <120 kg and <40 kg/m^2 due to lack of data
    - No AF-specific guidance from ISTH

BMI, body mass index; VTE, venous thromboembolism.

J Thromb Haemost. 2021;19(8):1874.

Comorbidities: Obesity



Am J Cardiol. 2020;127:176.

Comorbidities: Patient Frailty

- Fall risk/frailty
  - Many patients and prescribers avoid anticoagulants due to fear of bleed risk
  - Risk analysis
    - History of fall or high fall risk = 1.9 higher risk of ICH[1]
    - An older study estimated that patient “would have to fall 295 times in 1 year” for the hemorrhagic risk to outweigh the thrombotic risk[2]
  - Methods to decrease risk of falls are preferred over avoidance of anticoagulant medications

ICH, intercranial hemorrhage.

1. *Am J Med*. 2005;118(6):612.
2. *Arch Intern Med*. 1999;159(7):677.

Audience Response #4: Shared Decision-Making

- **Based on the information below, which DOAC regimens should our patient choose?**

Age 72; PMH = hypertension, osteoarthritis, type 2 diabetes

CrCl = 25 mL/min (SCr = 1.85); Wt = 102 kg (BMI ~32); no significant cost barriers

Medications: lisinopril 20 mg daily, amlodipine 10 mg daily, metoprolol ER 25 mg daily, insulin glargine 15 units daily

A. Apixaban 5 mg BID
B. Dabigatran 150 mg BID
C. Edoxaban 60 mg daily
D. Rivaroxaban 20 mg daily

Questions & Answers

Monitoring, Counseling, and Education

Education

- Patient education
  - CHEST Guideline (2018; e-Table 26)

- Recommended themes
  1. The condition—AF
  2. Treatment options
  3. Dosing
  4. Bleeding
  5. Lifestyle
  6. Before discharge

Chest. 2018;154(5):1121.

Adherence

Table 5. Survival Analysis, Ischemic Stroke, and Systemic Embolism as the Outcome

Time Not Taking OAC	Hazard Ratio (95% CI)
CHA_2DS_2-VASc score 0 or 1	
<1 wk	Ref
1 wk to 1 mo	0.87 (0.23–3.23)
1–3 mo	1.57 (0.55–4.44)
3–6 mo	1.76 (0.58–.37)
≥6 mo	1.53 (0.60–3.91)
CHA_2DS_2-VASc score 2 or 3	
<1 wk	Ref
1 wk to 1 mo	1.08 (0.64–1.82)
1–3 mo	1.21 (0.74–2.00)
3–6 mo	1.63 (0.96–2.78)
≥6 mo	2.73* (1.76–4.23)
CHA_2DS_2-VASc score ≥4	
<1 wk	Ref
1 wk to 1 mo	1.21 (0.91–1.60)
1–3 mo	1.96* (1.48–2.60)
3–6 mo	2.64* (1.93–3.61)
≥6 mo	3.66* (2.68–5.01)

- Importance of adherence
  - <50% of patients consistently adherent
  - DOACs have higher frequency of PDC >80%
    - 47.5% vs 38.7% ($P < .001$)
  - In CHA_2DS_2-VASc ≥4: higher stroke rate after 1 month of nonadherence

PDC, percentage of days covered.
Am Heart Assoc. 2016;5(2):e003074.

ARS #5: Barriers to Adherence

- **Which of the following do you believe is the most common reason patients do not remain adherent with their DOAC medication?**

  A. Complicated dose schedule
  B. No symptoms of AF to emphasize importance of medication
  C. Cost of the medications
  D. Distrust in effectiveness
  E. Fear of bleeding complications

Barriers to Adherence

- Reasons for nonadherence to apixaban (Tarn et al)
- 42 NVAF patients prescribed apixaban (8/2019-7/2020)
  - 35 patients “started but stopped, skipped, or decreased apixaban dosing”
- 30- to 45-minute semi-structured interviews
- 7 main themes identified:
  1. Cost (~67% of patients)
  2. Bleed risk—either fear of bleeding or actual experience with bleeding
  3. Lack of symptoms
  4. Belief that it is safe to skip doses
  5. Confusion about measurable effects (ie, no change in AF symptoms)
  6. Incomplete or discordant communication with prescriber
  7. “Natural” treatment used as alternative (eg, turmeric, omega-3 fatty acids)

J Am Geriatr Soc. 2021;69(12):3683.

Barriers to Adherence

- Common changes as therapy progresses
  - Changes in comorbidities
  - Insurance/formulary changes
    - In Medicare Part D population: Step therapy and prior authorization policies were associated with reduced DOAC use and higher stroke rates among patients with new AF (HR 1.098; 95% CI, 1.079-1.118)
  - Transitions of care
  - Interruptions in anticoagulation due to medical procedures

Am J Manag Care. 2022;28(10):521.

Transitions of Care: “ACDC” List

Anticoagulation **C**ommunication at **D**is**C**harge List

- 15-item list identified by expert panel as core elements (1-8):
  1. Anticoagulant currently used
  2. Indication for anticoagulant therapy
  3. Documentation that patient is new or experienced user of anticoagulants
  4. If new user of anticoagulants, document start date
  5. Duration of therapy—chronic vs acute
  6. Duration of therapy—if acute (short term), identify timeline of use
  7. Date, time, route, and dose of last 2 doses administered
  8. Date, time, and dose of next scheduled anticoagulant administration

Jt Comm J Qual Patient Safe. 2018;44(11):630.

Transitions of Care: “ACDC” List

- 15-item list (continued, 9-15):
  9. Most recent renal function assessment
  10. Documentation of patient education provided
  11. Assessment of patient/caregiver understanding of anticoagulant regimen
  12. If transition to noninstitutional setting, expectation for who is responsible for anticoagulant management
  13. If warfarin, INR target is documented
  14. If warfarin, minimum of 2-3 consecutive INR results are provided
  15. If warfarin, expected date for next INR assessment is communicated

Jt Comm J Qual Patient Safe. 2018;44(11):630.

Monitoring and Addressing Risk

- Role as pharmacist to address
  - DOAC version of anticoagulation monitoring service
    - Assess adherence/address barriers to medication access
  - Warfarin anticoagulation management service
  - Improve modifiable HAS-BLED risk factors
    - Hypertension
    - Alcohol intake
    - Decrease use of other medications with hemorrhagic risk (when possible)
    - Improve TTR when warfarin used
  - Improve modifiable AF risk factors
    - Alcohol intake
    - Physical activity

J Am Coll Cardiol. 2011;57:427-436.
Heart Lung Circ. 2018;27:1078-1085.

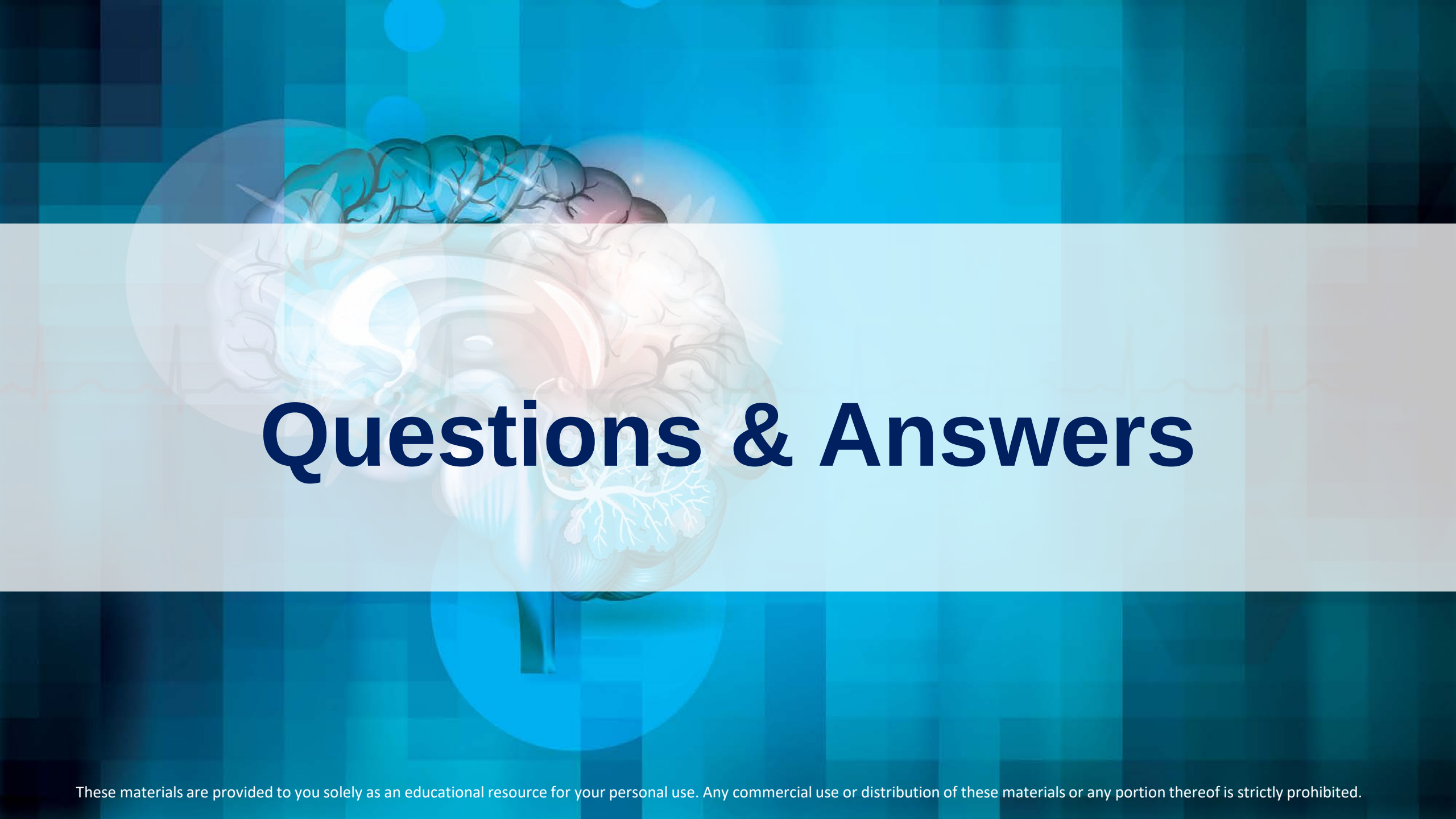
Periprocedural Anticoagulant Use

Direct Oral Anticoagulant	Procedure Bleeding Risk	Pre-Procedure DOAC Interruption						Surgery/Procedure (Day 0)	Post-Procedure Resumption*			
		Day -6	Day -5	Day -4	Day -3	Day -2	Day -1		Day +1	Day +2	Day +3	Day +4
Apixaban	High											
	Low/Mod											
Dabigatran (CrCl ≥ 50 ml/min)	High											
	Low/Mod											
Dabigatran (CrCl < 50 ml/min)	High											
	Low/Mod											
Edoxaban	High											
	Low/Mod											
Rivaroxaban	High											
	Low/Mod											

No DOAC administered that day

*DOAC can be resumed ~24 hours after low/moderate-bleed-risk procedures, and 48-72 hours after high-bleed-risk procedures. In selected patients at high risk for VTE, low-dose anticoagulants (i.e., enoxaparin, 40 mg daily or dalteparin, 5,000 IU daily) can be given for the first 48-72 hours post-procedure.

Chest. 2022 Aug 11;S0012-3692(22)01364-2.



Questions & Answers

Thank You!