Interpreting the Quality of Evidence Supporting New Drug Approvals for the Geriatric Population

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Disclosure

- Faculty have nothing to disclose.

Objectives

- Discuss age-related physiological changes that can affect drug efficacy and safety, and explain the implications for use of the drug in a geriatric patient.
- Evaluate the medical literature to determine whether data may be extrapolated to the geriatric patient population.
- Recommend appropriate use of recently introduced drugs and discuss their place in geriatric patient care.

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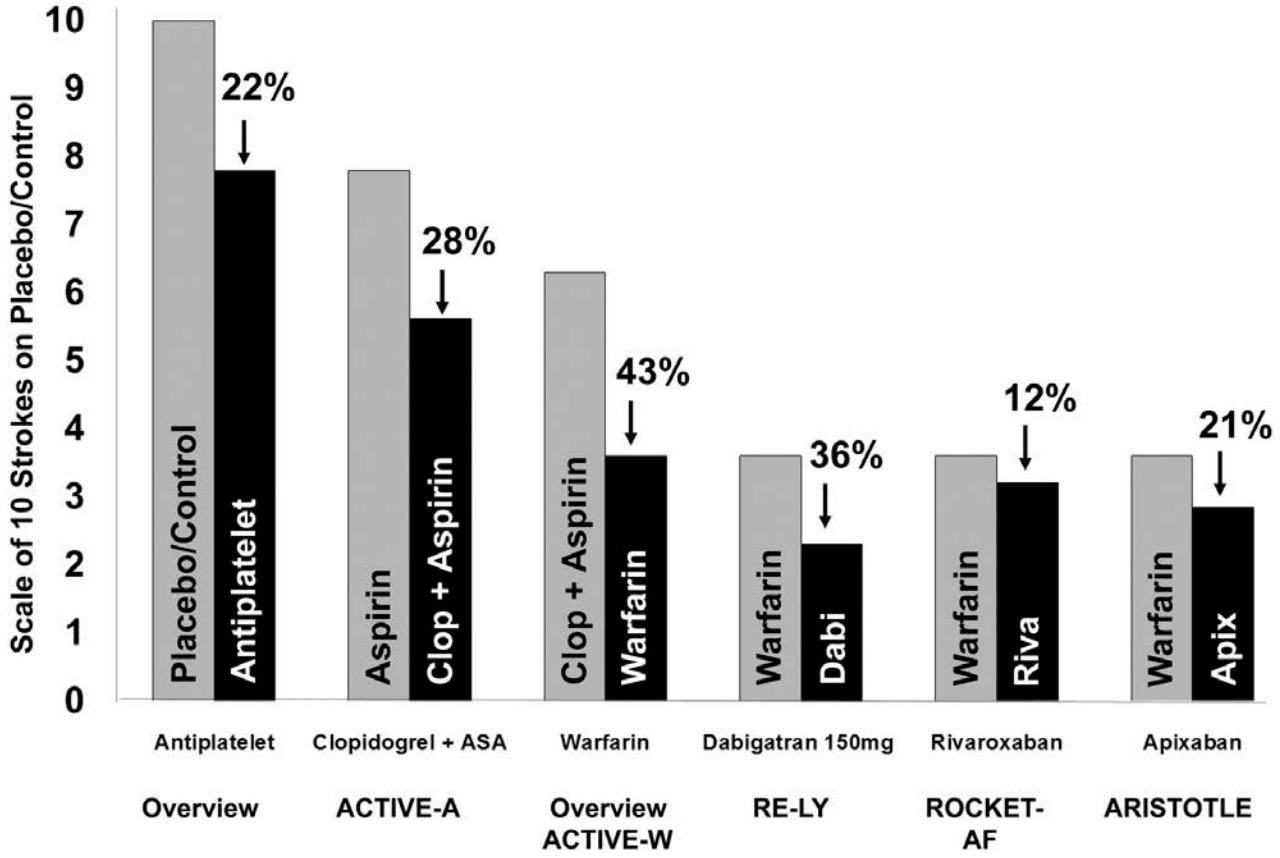
Anticoagulation in Elderly Patients

- Average age of atrial fibrillation (AF) onset is 75 to 85 years
- 82% of AF patients in the U.S. are ≥ 65 years old
- Risk factors for bleeding in elderly patients
  - Comorbidities
  - Drug interactions
- Patients > 70 years of age have up to a 75% increased risk of bleeding compared with those younger than 70 years of age

Kim D, et al. *Am J Cardiovasc Drug*. 2014; 14(1):15-29.

Goldhaber SZ. *J Am Coll Cardiol*. 2010;56(2):1-7.

Stroke Risk Reductions --- Randomized Atrial Fibrillation Trials



Granger CB, et al. *Circulation*. 2012;125:159-64.

Time for a Poll

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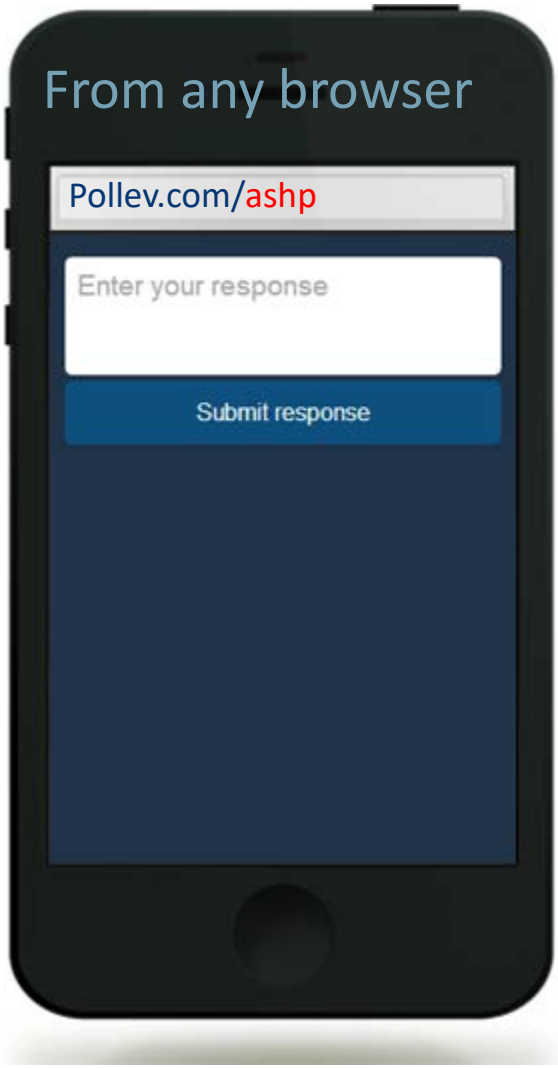

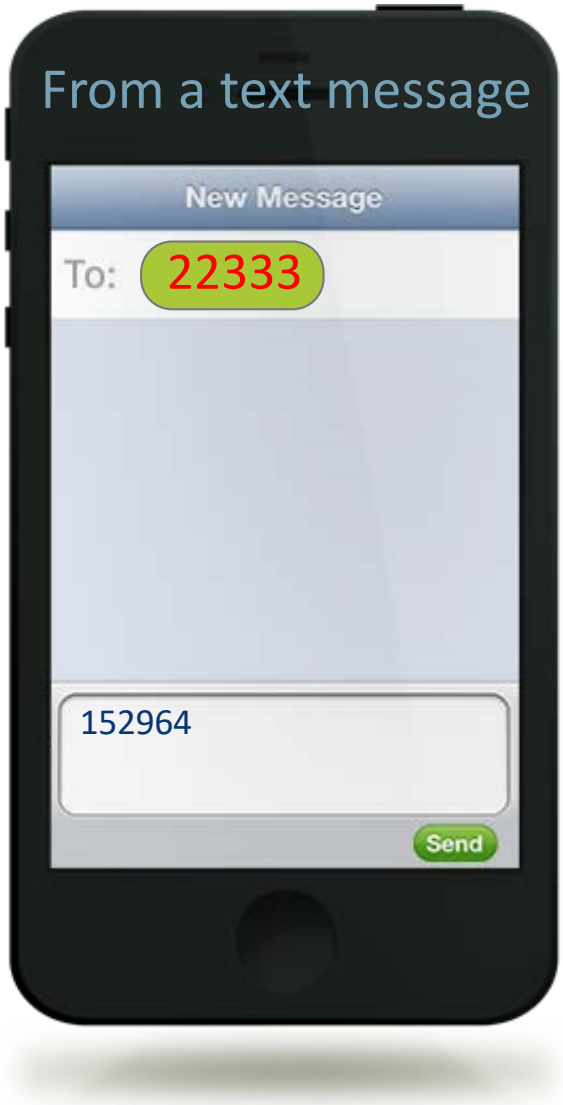

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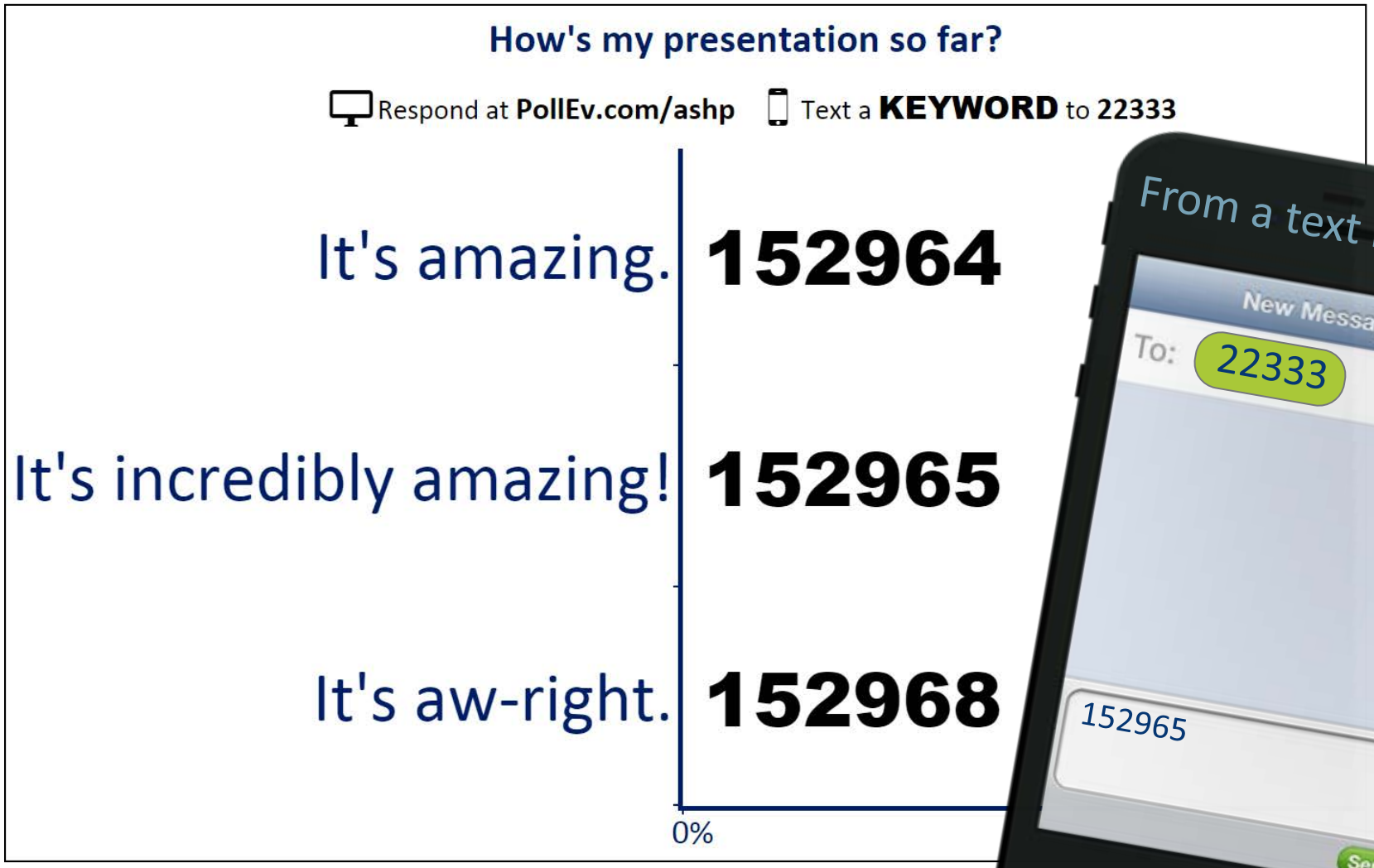
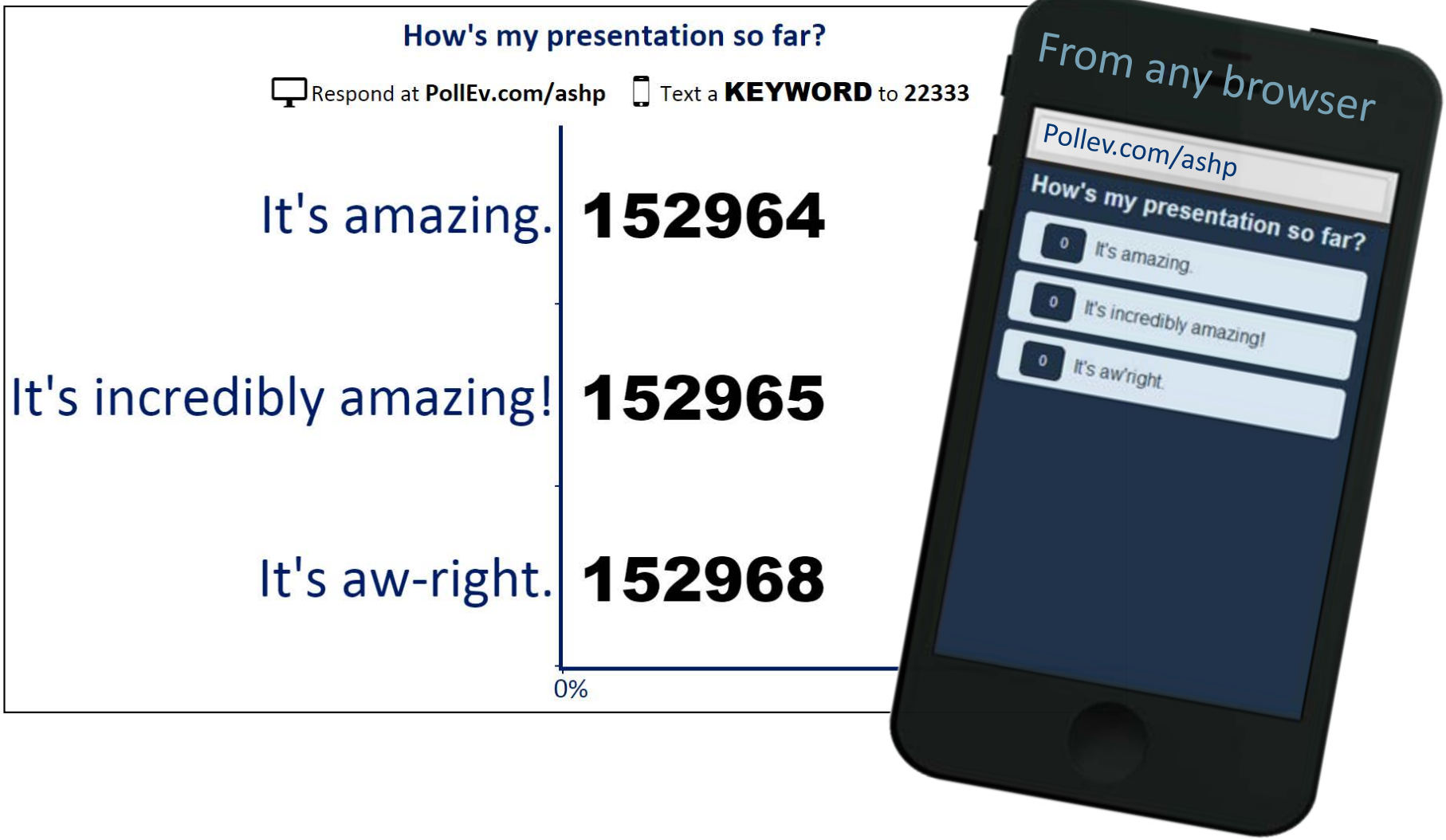


How to vote via the web



Question 1
Adult Patient Case 1

SS is a 76-year-old male with a past medical history significant for hypertension and type 2 diabetes mellitus. He has been diagnosed with nonvalvular atrial fibrillation and the decision has been made to start an oral anticoagulant.

- What agent should we choose?

A Warfarin 5 mg daily
B Aspirin 325 mg daily
C Dabigatran 75 mg twice daily
D Edoxaban 60 mg daily

Question 1

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American Heart Association/American College of Cardiology/Heart Rhythm Society Guidelines

- For patients with nonvalvular AF with prior stroke, transient ischemic attack (TIA), or a CHA_2DS_2-VASc score of 2 or greater, oral anticoagulants are recommended
  - Warfarin (INR 2.0 to 3.0)
  - Dabigatran
  - Rivaroxaban
  - Apixaban

January CT, et al. *J Am Coll Cardiol*. 2014;64(21):2246-80.

Edoxaban

- Once daily direct oral Xa inhibitor approved by the Food and Drug Administration (FDA) for
  - Prevention of stroke in nonvalvular AF
  - Treatment of venous thromboembolism
- For patients with AF, do not use if creatinine clearance (CrCl) > 95 mL/min
- Dosage reduction in all patients with CrCl 15 – 50 mL/min

Giugliano RP, et al. *N Engl J Med*. 2013; 369:2093-104.

Edoxaban. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: http://online.lexi.com. Accessed October 26, 2016

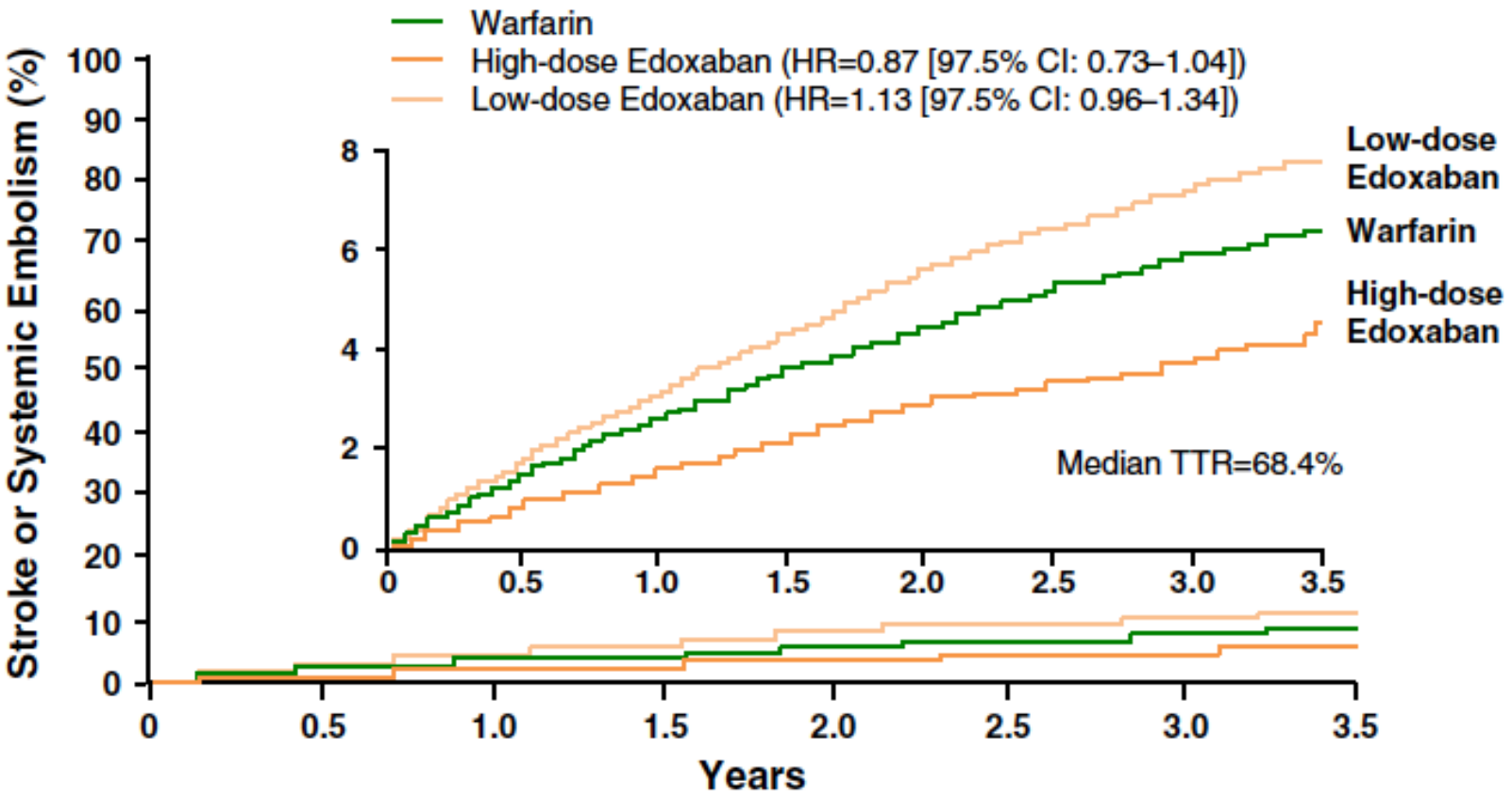
ENGAGE AF TIMI 48 Patient Characteristics

Characteristic	Value
Median Age [IQR]	72 [64,78]
Female gender	38%
$CHADS_2$ score (mean ± SD) CHADS2 ≤ 3 CHADS2 4 - 5	2.8 ± 1.0 77% 23%
Prior warfarin treatment	59%
Aspirin at randomization	29%
Amiodarone at randomization	12%
Median Follow-Up (years)	2.8
Median time in therapeutic range (TTR)	68%

Warfarin
Low dose edoxaban (30 mg daily)
High dose edoxaban (60 mg daily)

Giugliano RP, et al. *N Engl J Med*. 2013; 369:2093-104.

ENGAGE AF TIMI 48 Results



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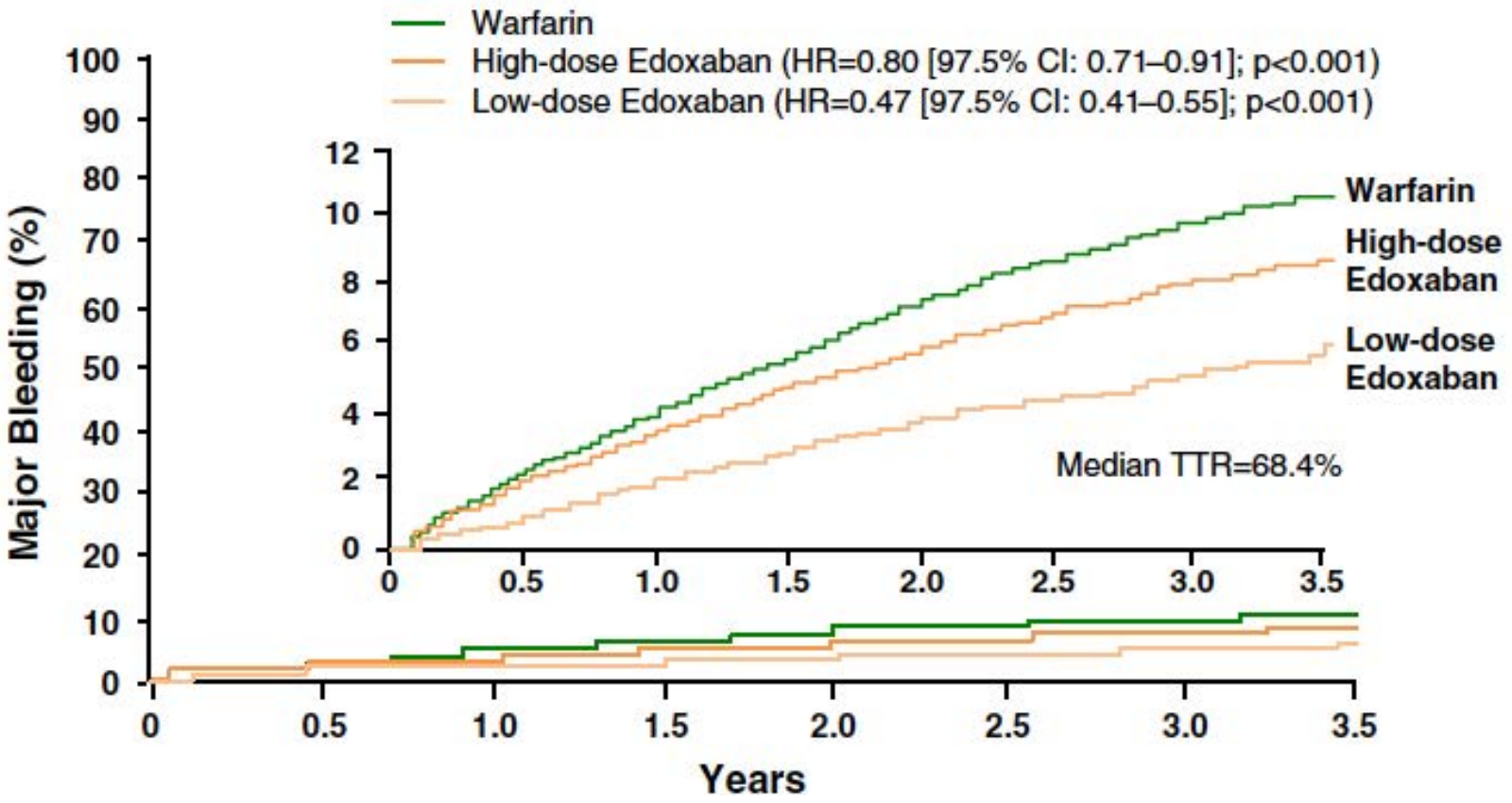
ENGAGE AF TIMI 48 Results



Giugliano RP, et al. *N Engl J Med*. 2013; 369:2093-104.

Application to Geriatrics

- Question of utility in geriatric patients
  - Not a question of “Yes” or “No”
  - A question of “Which subgroup?”
- Despite a median age of 72 and 40% of the study population being over age 75, data ceiling for age still appears to be around age 78
  - Study represents a subgroup sometimes referred to as “young old”, data not representative of subgroups older than this age ceiling

Giugliano RP, et al. *N Engl J Med*. 2013; 369:2093-104.

Other Direct Oral Anticoagulants (DOAC)

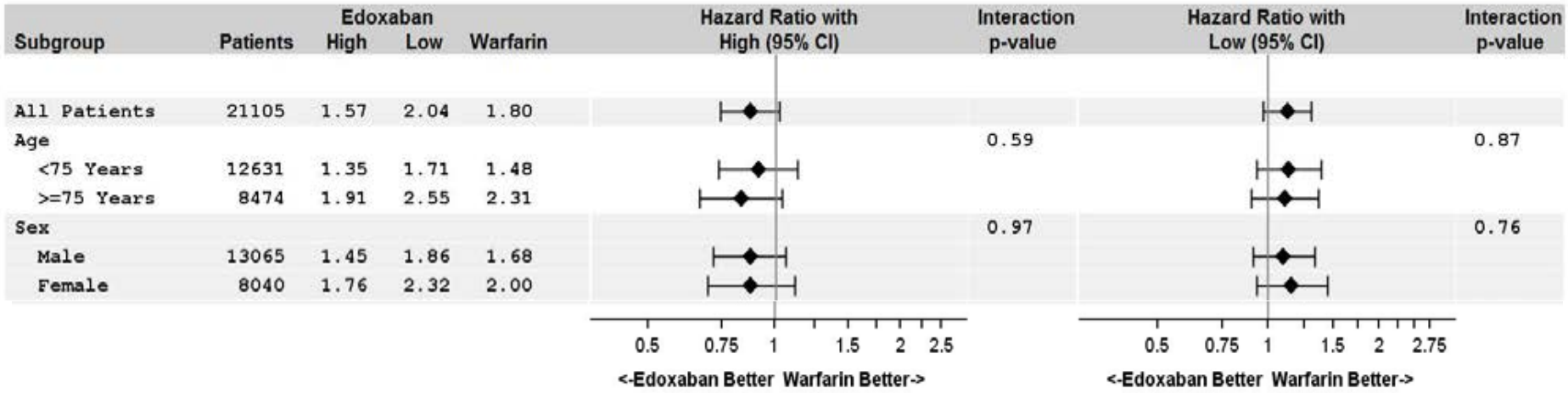
- Dabigatran
  - Mean age 71.4 ± 8.6 years
    - —40% of subjects >75, less than 1/3 (exact n?) >80
- Rivaroxaban
  - Median age 73 years
    - —43% of subjects >75, interquartile range 65-78
- Apixaban (ARISTOTLE)
  - Median age 70 years
    - —31% of subjects >75, 13% >80

Connolly, et al. *N Engl J Med*. 2009

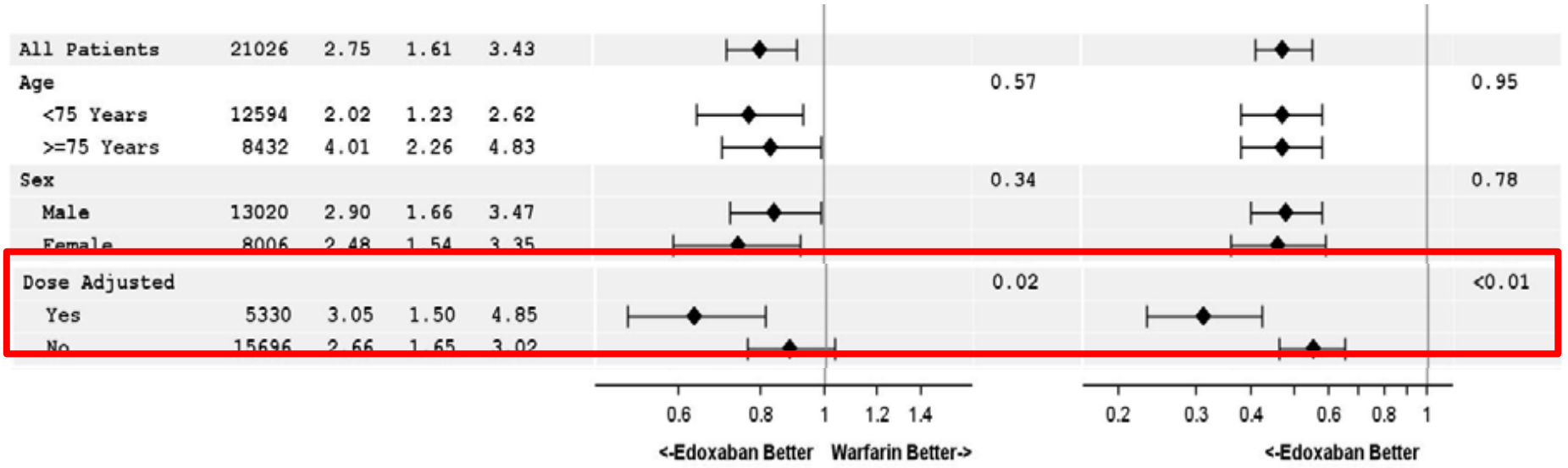
ROCKET AF investigators. *Am Heart J*. 2010

Halvorsen S, et al. *Eur Heart J*. 2014

Hazard Ratio (HR) for primary efficacy outcome
(stroke or systemic embolism edoxaban vs warfarin for intention to treat group)



HR for Principle safety outcome (major bleeding Edoxaban vs warfarin for on-treatment safety group)



Giugliano RP, et al. *N Engl J Med*. 2013; 369:2093-104.

Establishing Risk/Benefit Ratio

- Among 773 patients over age 75 (average age 85), with clear anticoagulation indication, 50% did not receive it regardless of $CHADS_2$ or bleeding assessment scores
- Why?
  - Maximum age for risk calculators
  - Lack of specificity for sex or age strata in some risk assessment tools

Maes F, et al. *Clin Interv Aging*. 2014;9:1091-9.

Comparison of Risk Scores

CHA_2DS_2-VASc

• Congestive heart failure (CHF)	1
• Hypertension (HTN)	1
• Age	
– <65	0
– 65-74	1
– ≥75	2
• Diabetes Mellitus (DM)	1
• Previous stroke/transient ischemic attack (TIA)/embolism	2
• Vascular disease history	1
• Sex	
– Male	0
– Female	1

HAS-BLED

• HTN (>160mmHg systolic)	1
• Renal disease (SCr >2.6)	1
• Stroke history	1
• Prior major bleeding or predisposition to bleeding	1
• Labile International Normalized Ratio (unstable/high INR, time in range <60%)	1
• Age >65	1
• Medication usage predisposing to bleeding (antiplatelet/non-steroidal anti-inflammatory drug [NSAID])	1
• Alcohol usage history	1

MD-CALC+. http://www.mdcalc.com/cha2ds2-vasc-score-for-atrial-fibrillation-stroke-risk/

MD-CALC+. http://www.mdcalc.com/has-bled-score-for-major-bleeding-risk

Event Risk vs. Bleed Risk

- Age > 75 is an independent risk factor for both bleeding episodes and CV events
  - For bleeding: HR 1.74; 95% CI, 1.05-2.87; *P*=0.030
  - For CV events: HR 2.20; 95% CI, 1.40-3.46; *P*=0.001
- Crude bleeding rates only exceeded thrombotic events at a HAS-BLED score > 3
  - Yet HAS-BLED only employs a single age threshold of 65 years

Gallego P, et al. *Circ Arrhythm Electrophysiol*. 2012;5(2):312-8.

Relationship of Age to Bleed Risk

Age	Relationship
>65	HR 1.3, 95% CI 1.0-1.7
>75	Rate of major hemorrhage >75 years was 4.2% per year, higher than the whole population (3.6% per year) and almost twice that seen in patients aged <75 years (2.5% per year).
≥80	Compared with patients <50 years of age, relative risk (RR) of life-threatening or fatal bleed on warfarin was 4.5 (95% confidence interval [CI] 1.3-15.6)
≥85	Compared with patients 70-74, odds ratio (OR) for intracranial hemorrhage was 2.5, (95% CI 1.3-4.7)

- Elderly patients who experience a severe hemorrhage while on anticoagulation have a higher mortality rate
  - Mortality rate 52% among warfarin users vs 25.8% among non users at 3 months post intracranial hemorrhage

Bushnell, et al. *Stroke*. 2014; 45(5):1545-88;
Gallego P, et al. *Circ Arrhythm Electrophysiol.* 2012; 5(2):312-8.

Tools and Variables

- HEMORR2HAGES or ATRIA
  - Does not add points for age > 65, age threshold for +1 is 75 years
  - Only variable for which sex is a distinguishing point is the threshold at which +1 is awarded for anemia
- Studied in context of atrial fibrillation
  - All tools had only modest predictive value for predicting any bleed; HAS-BLED performed the best, and was only tool to predict intracranial hemorrhage events

Apostolakis. *J Am Coll Cardiol*. 2012;60(9):861-7.

Influence of Gender on Risk

- Overall number of men and women with AF is comparable; about 60% of patients with AF over age 75 are women
  - < 65 years women have a lower stroke risk than men
  - > 75 years, women have a higher risk of stroke than men
    - —Regardless of warfarin use, although some data suggest a greater benefit of warfarin among women
- 1/3 of stroke admissions are among patients over age 80 (15.6% men, 20.4% women)
  - Women are slightly less likely to receive anticoagulant therapy (OR 0.93; 95% CI 0.88-0.98)

Bushnell, et al. *Stroke*. 2014; 45(5):1545-88.

What about falls?

- Patients with high fall risk have greater rate of intracranial hemorrhage (ICH): 2.8/100 patient years (95% CI 1.9–4.1) vs those with low fall risk: 1.1/100 patient years (95% CI 1.0 -1.3)
- Ischemic stroke rates/100 patient-years in those at high risk for falls: 13.7 vs. 6.9 in other patients.
- Warfarin use was associated with ICH mortality but not with ICH occurrence
- Anticoagulated patients who fall do have an elevated mortality rate
- At a rate of >295 falls/year, ICH bleed risk of warfarin outweighs the stroke prevention benefit

Gage, et al. *Am J Med*. 2005; Jacob et al. Am *J Geriatr Pharm*. 2009;
Man Son Hing, et al. *Ann Intern Med*. 1997.

Geriatric Patient Case 1

- GG is an 88-year-old female patient with a history of hypertension (current BP 152/88 mmHg) and prior stroke for which she receives antiplatelet therapy with aspirin. She has now been diagnosed with paroxysmal atrial fibrillation and the team is debating the initiation of anticoagulant therapy.
  - CHA_2DS_2-VASc score = 6
  - HAS-BLED score = 4

Question 2

Which of the following best describes the difficulty associated with the interpretation of her CHA_2DS_2-VASc and HAS-BLED scores?

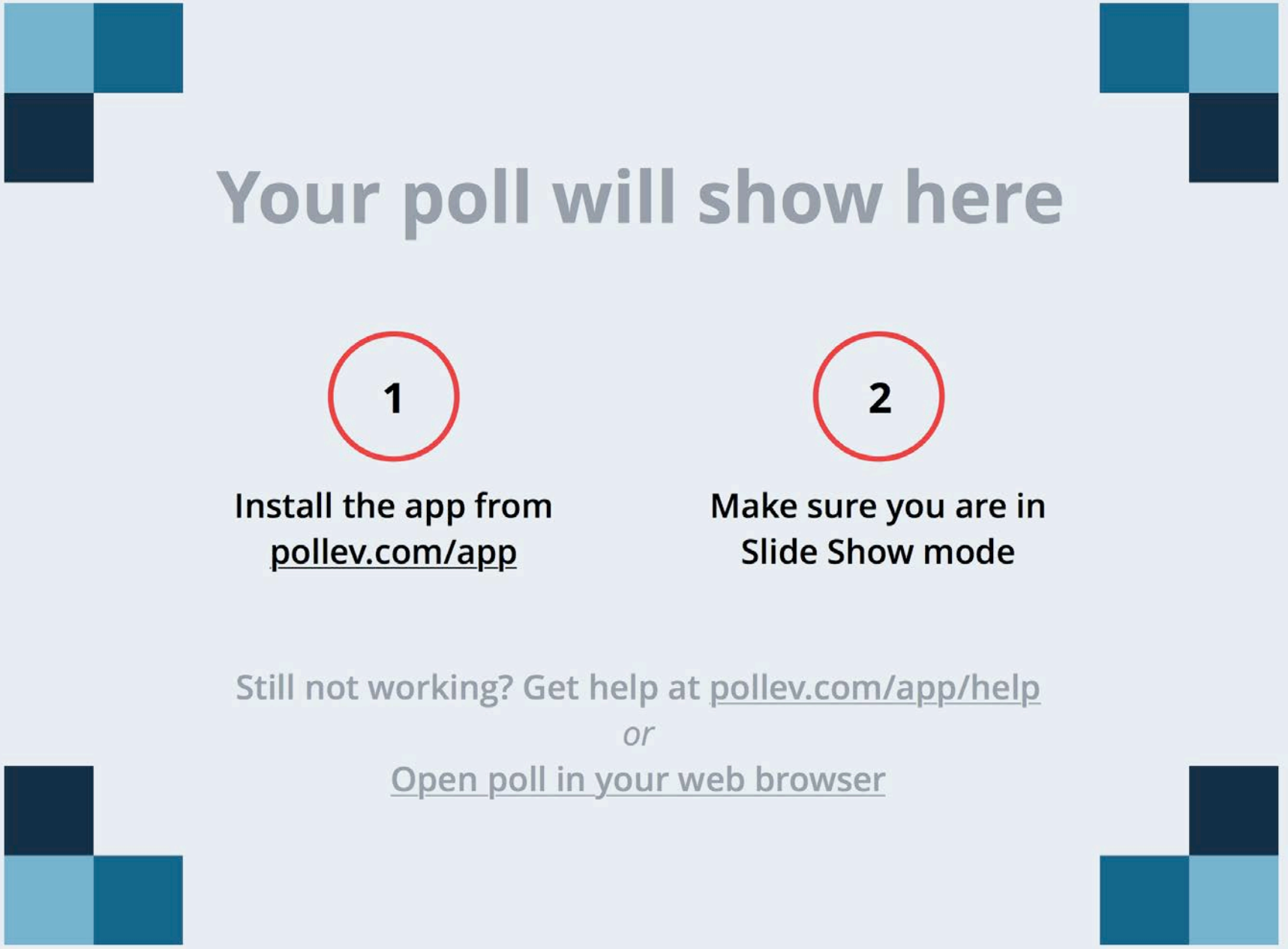
A. The CHA_2DS_2-VASc score likely underestimates her event risk because she is female

B. The CHA_2DS_2-VASc score likely overestimates her event risk due to age

C. The HAS-BLED score likely underestimates her bleeding risk due to age

D. The HAS-BLED score likely overestimates her bleeding risk because she is female

Question 2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C. **The HAS-BLED score likely underestimates her bleeding risk due to age**

D. The HAS-BLED score likely overestimates her bleeding risk because she is female

Adult Patient Case 2

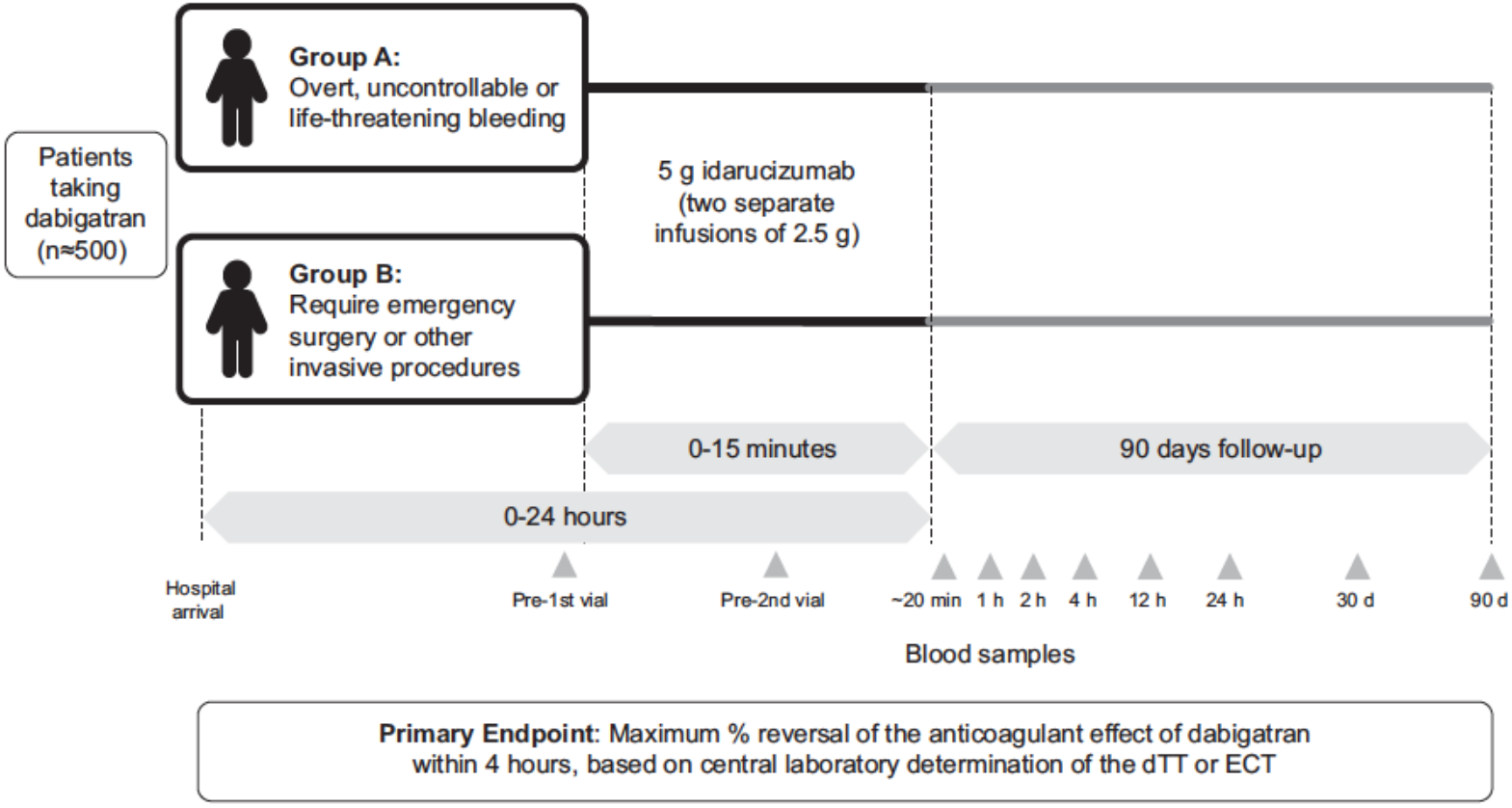
- The decision was made to start dabigatran. However, the patient presented to the Emergency Department 2 weeks after therapy initiation with dyspnea, pale appearance, and complaints of bright red blood per rectum. His last dabigatran dose was 5 hours ago. Laboratories are significant for a hemoglobin of 4.9 mg/dL and SCr = 2.4 mg/dL.

Idarucuzimab

- Humanized monoclonal antibody fragment with > 350 times the affinity for dabigatran vs. thrombin
- Approved by the FDA in February 2015
- Reversal of dabigatran for emergency surgery/urgent procedures or life-threatening or uncontrolled bleeding
- Data to support idarucuzimab largely based on small multicenter, prospective, cohort study
  - REVERSE-AD

Glund S, et al. *Thromb Haemost*. 2015; 113:943-51.

REVERSE-AD Study Design



Pollack CV Jr., et al. *N Engl J Med*. 2015; 373:511-20.
Eikelboom JW, et al. *Circulation*. 2015; 132:2412-22.

Limitations in REVERSE AD

- Last dose of dabigatran
  - 64% of subjects more than 12 hours prior
  - 30% of subjects more than 24 hours prior
- However, 68 and 81 out of 90 subjects had elevated dilute thrombin time and ecarin clotting time, respectively
- Lack of a control group (ethical concerns)
- Rebound

Patients in REVERSE AD

- 90 subjects
  - 50 subjects, 56% were male
    - —(32/51 in group A (63%) and 18/39 in group B (46%)
  - Median age 76.5 (range 48-93)
    - —77 years in group A, 76 years in group B
    - —No data provided regarding any further breakdown/distribution of age
  - 86% white (7% Asian, 7% Hawaiian or Pacific Islander)

Pollack CV Jr., et al. *N Engl J Med*. 2015;373:511-20.

Treatment Deaths

Study group	Age	Sex	# days to death	Type of event	Study group	Age	Sex	# Days to death	Type of event
A	60	M	1	Respiratory failure	B	82	F	<1	Cardiac Arrest
A	77	M	1	New Intracranial Hemorrhage	B	93	M	<1	Circulatory collapse
A	69	M	2	Progression of Intracranial Hemorrhage	B	88	F	<1	Hemodynamic collapse
A	69	M	4	Progression of Intracranial Hemorrhage	B	87	F	1	Septic shock
A	83	F	11	Pulmonary edema	B	60	M	1	GI bleed, sepsis/shock
A	73	M	30	Congestive Heart Failure	B	87	M	2	Multi-organ Failure
A	83	M	42	General health deterioration	B	78	F	21	Cardiac Arrest
A	80	M	43	Parkinson's Disease	B	72	F	26	Ischemic Stroke
A	86	F	94	Pneumonia	B	80	M	101	Progression of Cancer

Pollack CV Jr., et al. *N Engl J Med*. 2015;373:511-20.

If dabigatran is to be used…

- What additional considerations are important if dabigatran is to be employed for this patient?
  - Need to know her renal function
  - Some evidence suggests monitoring of serum drug concentration may still be needed
    - Range of 40-200ng/ml associated with more favorable safety profile, especially among patients with reduced renal function
      - Dose adjustment based on plasma concentration may reduce major bleeds by 30-40% compared with well controlled warfarin

Cohen D. *BMJ.* 2014 ;349:g4670.

Geriatric Patient Case 2

- Consider the same patient, GG, presented previously.
- GG is an 88-year-old female patient with a history of hypertension and prior stroke for which she receives antiplatelet therapy with aspirin. She has now been diagnosed with paroxysmal atrial fibrillation and the team is debating the initiation of anticoagulant therapy.
- The provider now wants to know how the availability of a reversal agent influences the choice to use an anticoagulant.

Question 3

Which of the following best describes how the availability of idarucuzimab affects the treatment decision for GG?

A. Idarucuzimab makes dabigatran the clear anticoagulant of choice
B. Idarucuzimab does not guarantee that the bleeding risk of dabigatran is negated
C. Idarucuzimab availability doesn't matter. Dabigatran would be the preferred choice anyway
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Percutaneous Coronary Interventions (PCI) in Geriatric Patients

- Age is a significant cardiovascular (CV) risk factor
- 66% of all CV deaths occur in individuals > 75 years of age
- A British analysis found octogenarians as the fastest growing group undergoing PCI
  - 46% had calcified lesions
  - Bleeding is more common

Shanmugam VB, et al. *J Geriatric Cardiol*. 2015;12:174-84.

Rajani R, et al. *Br J Cardiol*. 2011;18:73-6.

Cangrelor

- Rapid-acting (within 2 minutes) and reversible intravenous platelet P2Y12 inhibitor
- 30 mcg/kg bolus prior to PCI followed by a 4 mcg/kg/min infusion for at least 2 hours
- Pivotal trial
  - CHAMPION-PHOENIX

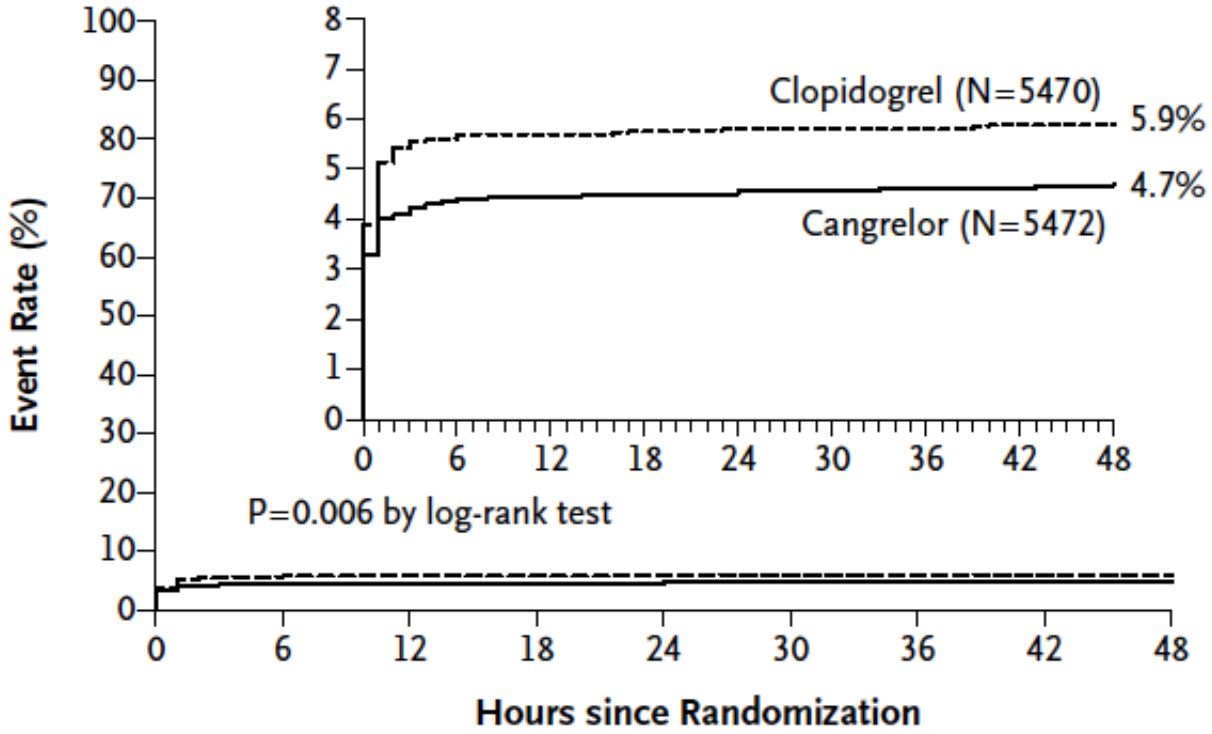
Bhatt DL, et al. *N Engl J Med* 2013;368;1303-13.

CHAMPION-PHOENIX Patient Characteristics

	Femoral		Radial	
	Cangrelor (n=4053)	Clopidogrel (n=4011)	Cangrelor (n=1410)	Clopidogrel (n=1445)
Median Age (years)	64	64	64.5	64
Female (%)	28.2	27.6	29.3	26.4
Weight (median, kg)	84	84	84	85
Comorbidities (%)				
Diabetes	27.3	27.3	29.1	30.3
Hypertension	80.2	78.9	79.9	80.7
Prior stroke/TIA	5.2	4.5	4.3	4.2
Prior MI	20.9	23.0	17.5	18.0
Prior PTCA/PCI	22.6	23.7	25.1	26.5
CABG	12.2	10.9	5.7	4.4
Heart failure	10.2	11.1	9.7	9.7

Bhatt DL ,et al. *N Engl J Med* 2013;368;1303-13.

CHAMPION-PHOENIX Outcomes



No. at Risk

Cangrelor	5472	5233	5229	5225	5223	5221	5220	5217	5213
Clopidogrel	5470	5162	5159	5155	5152	5151	5151	5147	5147

Event rate = death from any cause, myocardial infarction, ischemia-driven revascularization, or stent thrombosis at 48 hours after randomization.

Bhatt DL, et al. *N Engl J Med* 2013;368;1303-13.

Subgroup Analysis

Subgroup	Total No. of Patients	Cangrelor	Clopidogrel	Odds Ratio (95% CI)
		no. of events/total no. (%)		
Overall	10,939	257/5470 (4.7)	322/5469 (5.9)	0.79 (0.67–0.93)
Age				
≥75 yr	2,008	55/1021 (5.4)	73/987 (7.4)	0.71 (0.50–1.02)
<75 yr	8,931	202/4449 (4.5)	249/4482 (5.6)	0.81 (0.67–0.98)
Sex				
Male	7,889	183/3913 (4.7)	219/3976 (5.5)	0.84 (0.69–1.03)
Female	3,050	74/1557 (4.8)	103/1493 (6.9)	0.67 (0.50–0.92)
Weight				
≥60 kg	10,356	239/5155 (4.6)	302/5201 (5.8)	0.79 (0.66–0.94)
<60 kg	583	18/315 (5.7)	20/268 (7.5)	0.75 (0.39–1.45)

Bhatt DL, et al. *N Engl J Med* 2013;368;1303-13.

Epidemiology among older cohorts

- The average age at which individuals experience a first myocardial infarction is (for men) 66 years and (for women) 70 years
- Acute coronary syndromes (ACS) account for roughly 35% of all deaths among individuals ≥ 65 years of age
  - 83% of ischemic heart disease deaths are among individuals > 65 years
    - For every 10-year increase in age, risk of hospital mortality from ACS increases by 70%
  - 60% of deaths due to myocardial infarction (MI) are among individuals over age 75 years
  - More than 50% of patients ≥ 75 years of age develop heart failure following MI

Alexander KP, et al. *Circulation* 2007;115:2549-69. Granger CB, et al. *Arch Intern Med* 2003;163:2345.

CHAMPION-PHOENIX

- Median age: 64
- Interquartile range: 56-72
  - Proportion of patients ≥ age 75 was very small
  - Non-significant result in this subgroup, possibly due to lack of power
- Do we know what the best approach should be in patients of advanced age?

Bhatt DL, et al. *N Engl J Med* 2013;368;1303-13.

Best Approaches Controversial

- Is PCI better than medical management?
  - TRIANA study 2009 - Age >75 (average age 81 years)
    - Similar outcomes for PCI and thrombolysis with respect to death, reinfarction or stroke at 30 days
    - Actually NO increased risk of intracranial bleeding in thrombolytic group
    - Lower need for revascularization in the percutaneous coronary intervention (PCI) group
  - Page et al 2010 – subset of TRIANA , age ≥80 years
    - Use of PCI or coronary artery bypass graft (CABG) associated with improved 1-year mortality
- Consider
  - Atypical presentation often associated with delayed presentation to emergency department by older patients
    - Dyspnea, diaphoresis, nausea, vomiting, syncope
    - Lower proportion of elderly patients present with chest pain, some may be asymptomatic
    - Older patients are more likely to have non-diagnostic electrocardiogram
- Data suggests that PCI is particularly preferred when patients present > 6-12 following symptom onset

Bueno H, et al. TRIANA. *Eur Heart J*. 2011; 32(1):51-60; Alexander KP, et al. *Circulation*. 2007;115:2570-89.

Medication Management

- Low molecular weight heparin
  - Patients ≥ 75 years experience *higher rates of intracranial hemorrhage with enoxaparin* compared to unfractionated heparin when used as adjunctive therapy with tenecteplase; when properly adjusted for renal function, some data suggest enoxaparin is more effective than unfractionated heparin
- Intravenous beta blockers
  - Data among patients between 65-75 suggest elderly ST-segment elevated myocardial infarction (STEMI) patients may benefit more from intravenous β-blockers than younger patients
  - Other data suggest that patients >70 years with STEMI are more vulnerable to hypotension and bradycardia with intravenous β-blockers, with subsequent higher risk of cardiogenic shock
- Oral beta blockers
  - Some data suggest elderly patients may derive more benefit from aspirin and beta-blockers

O'Gara PT, et al. *J Am Coll Cardiol*. 2013;61(4):e78-140.

Alexander KP, et al. *Circulation*. 2007;115:2570-89.

Medication Management

- TRIANA reported medication therapy associated with improved 1-year survival (p<0.0001).
  - ACE inhibitors or ARBs(HR 0.85; 95% CI 0.770.93)
  - Statins (HR 0.78; 95% CI 0.69-0.88)
  - Beta-blockers (HR 0.86; 95%CI 0.79-0.95)
  - Aspirin (HR 0.90; 95%CI 0.82-0.99)
- Outcomes data describing magnitude of benefit with glycoprotein IIb/IIIa receptor inhibitors in the elderly is mixed
  - Some studies suggest similar benefits among elderly and younger groups
  - One study suggested worse outcomes with eptifibatide for patients >80 years
  - Increasing age is associated with greater risk of bleeding, especially with declining renal function
  - Data evaluating glycoprotein IIb/IIIa receptor inhibitors in patients with NSTEMI non-invasive therapy (no PCI) is lacking

Bueno H, et al. *Eur Heart J.* 2011;32(1):51-60.
Wright FS, et al. *J Am Coll Cardiol*. 2011;57(19):1920-59.

Bleeding Risk Reported in the CURE trial

- Bleeding complications with aspirin in advancing age
  - 2.1% (< 65 years)
  - 3.1% (65-74 years)
  - 3.6% (> 75 years)
- Bleeding incidence with combination aspirin & clopidogrel in advancing age
  - 2.5% (< 65 years)
  - 4.1% (65-74 years)
  - 5.9% (> 75 years)

Mehta S, et al. *Lancet.* 2001;358:527-33.

Geriatric Patient Case 3

- AL is an 85-year-old female patient who is admitted to the emergency department with syncope. Her recent history also includes nausea and diaphoresis before passing out. The initial workup in not conclusive, but after 10 hours a non-ST segment elevated myocardial infraction (NSTEMI) is confirmed.

Question 4
Adult Patient Case

JS is a 63-year-old female with a longstanding history of heart failure (HF). She is on target doses of carvedilol and lisinopril. In addition, JS is prescribed spironolactone, furosemide, and is counseled on avoiding NSAIDs.

- What therapy should be considered?

A. None, patient therapy is optimized
B. Add ivabradine
C. Replace lisinopril with an angiotensin-receptor/neprilysin inhibitor (ARNI)
D. Add an ARNI

Question 4

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Question 4
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- What therapy should be considered?

A None, patient therapy is optimized
B Add ivabradine
C **Replace lisinopril with an angiotensin-receptor/neprilysin inhibitor (ARNI)**
D Add an ARNI

Heart Failure Epidemiology

- Approximately 5.7 million people in the U.S. have heart failure
- Heart failure costs the U.S. $30.7 billion annually
- Mortality within 5 years of diagnosis is high
  - 50% of people diagnosed

Mozzafarian D, et al. *Circulation*. 2016; 133:e38-e360.
Heidenreich PA, et al. *Circulation*. 2011; 123(8):933-44.

Ivabradine

- Has been approved in Europe since 2005 and recently approved by the FDA (2015)
- Selective and specific inhibition of hyperpolarization activated cyclic nucleotide (HCN) channels within sinoatrial node (SA) node of cardiac tissue
  - Human ether-a-go-go related gene (hERG) potassium channel blockade
- Pivotal trial
  - Systolic heart failure treatment with the If inhibitor ivabradine trial (SHIFT)

Nawarskas JJ. *Cardiol Rev*. 2015; 23(4):201-11.

Swedberg K, et al. *Lancet*. 2010; 376(9744):875-5.

SHIFT Patient Characteristics

Characteristic	Ivabradine	Placebo
Mean age (years)	60.7	60.1
Female (%)	24	23
Ischemic etiology (%)	68	67
NYHA III or IV	51	51
Previous MI	56	56
Diabetes	30	31
Hypertension	67	66
eGFR (mL/min/1.73 m2)	75	75
Beta blocker	89	90
ACE inhibtors	91	91
Aldosterone antagonists	61	59

Reprinted from *Lancet*, 376(9744, Swedberg K, et al., Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study, 875-85, 2010, with permission from Elsevier.

SHIFT Outcomes

	Ivabradine (n=3241)	Placebo (n=3264)	HR (95% CI)	P value
Primary Endpoint[a]	793 (24%)	937 (29%)	0.82 (0.75 – 0.90)	<0.0001
All-cause mortality	503 (16%)	552 (17%)	0.90 (0.80 – 1.02)	0.092
Death from heart failure	113 (3%)	151 (5%)	0.74 (0.58 – 0.94)	0.014
Hospital admission[b]	514 (16%)	672 (21%)	0.74 (0.66 – 0.83)	<0.0001

[a]Cardiovascular death or hospital admission for worsening heart failure
[b]Worsening heart failure

What do the guidelines say?

- Ivabradine can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II-III) stable chronic heart failure with reduced ejection fraction (HFrEF; left ventricular ejection fraction [LVEF] ≤35%) who are receiving guideline-directed evaluation and management (GDEM), including a beta-blocker at maximum tolerated dose and in sinus rhythm with a heart rate of 70 bpm or greater at rest (IIa; B-R)

Yancy CW, et al. *Circulation*. 2016; Epub ahead of print May 20.

What do the guidelines say?

- In patients with chronic symptomatic HFrEF New York Heart Association (NYHA) class II or III who tolerate an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), replacement by an ARNI is recommended to further reduce morbidity and mortality (I; B-R)

Yancy CW, et al. *Circulation*. 2016; Epub ahead of print May 20.

Epidemiology in older patients

- Incidence of heart failure increases with age.
  - 9.3% in men and 4.8% in women between the ages of 60-79 years
  - 13.8% in men and 12.2% in women greater than age 80
- Incidence of mortality associated with HF also higher in the geriatric population.
- Presentation is atypical
  - Subjective symptom complaints: anorexia, confusion, generalized weakness, fatigue
  - Cough/non-specific respiratory symptoms can be primary and often, ONLY presenting complaint
    - May be confused with respiratory conditions such as COPD, asthma, or infection such as bronchitis or pneumonia
  - B-type natriuretic peptide (BNP) difficult to accurately interpret
    - BNP concentrations tend to be higher in the elderly, unclear if different "normative" values should be established for frail populations

Redfield MM, et al. *J Am Coll Cardiol.*2002;40:976-82

Assessment Considerations

- Leg Edema
  - While still common, not universal and more non-specific
- Fatigue
  - Exacerbated by depression, beta blocker use, over diuresis. In addition, relatively higher incidence of concomitant anemia >age80
- Weight gain/loss
  - Non-specific (depression, dementia, frailty), not always good indicator of fluid status
- Syncope and orthostatic hypotension
  - Common, in particular postprandial hypotension (need HR to differentiate)
- Mental status
  - Includes somnolence and confusion, common if very old/frail, often accompanied by dyspnea or fatigue. More common with vascular dementia and less common if euvolemic without dyspnea or fatigue
- Left ejection fraction
  - More common in patients over age 80 (LVEF > 45%: 39% among > age 80 vs. 28% among < age 80, $p<0.001$

EHFS II. *Eur Heart J*. 2009; 30:478-86.

Patient Characteristics in SHIFT

Characteristic	Ivabradine	Placebo
Mean age (years)	60.7	60.1
Female (%)	24	23
Ischemic etiology (%)	68	67
NYHA III or IV	51	51
Previous MI	56	56
Diabetes	30	31
Hypertension	67	66
eGFR (mL/min/1.73 m2)	75	75
Beta blocker	89	90
ACE inhibtors	91	91
Aldosterone antagonists	61	59

Issues in Heart Failure Literature

Drug class	Trial	Mean age (yrs)	Level of evidence support			
			LVEF ≤40%		LVEF >40-50%	
			Age <75	Age >75	Age <75	Age >75
Beta Blockers	COPERNICUS US Carvedilol CIBIS II MERIT-HF BEST SENIORS	63 58 61 64 60 76	Excellent	Good[1,2]	Fair[1]	Limited
ACE Inhibitors	SOLVED ATLAS	61 64	Excellent	Fair[1,2]	Fair[4]	Limited
ARBs	CHARM-Added Val-HEFT	64 63	Excellent	Fair[1]	Fair[4]	Limited
ARAs	RALES	65	Good	Fair[1]	None	None
Digoxin	DIG	63	Good[3]	Mixed[1]	None	None

[1] Subgroup analysis [2] Retrospective analysis [3] Outcome limited to HF re-hospitalization [4] Small body of evidence or limited benefit

Geriatric Patient Case 4

- JJ is an 82-year-old female patient who is seen in the HF clinic. She complains of fatigue and poor exercise tolerance. Her vitals average BP 142/80mmHg, HR 90; LVEF is > 40%. Her medications include: metoprolol tartrate 12.5 mg twice daily, enalapril 20 mg once daily, furosemide 40 mg once daily, KCl 10 mEq once daily.

Question 5

Which of the following is the best action to take first in addressing JJ's complaints of fatigue and poor exercise tolerance?

A Initiate ivabradine

B Increase furosemide

C Assess her hemoglobin and hematocrit

D Reassess her LVEF

Question 5

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Question 5

Which of the following is the best action to take first in addressing JJ's complaints of fatigue and poor exercise tolerance?

A Initiate ivabradine

B Increase furosemide

C **Assess her hemoglobin and hematocrit**

D Reassess her LVEF

Dyslipidemia Epidemiology

- 73.5 million adults (31.7%) in the U.S. have high LDL-C
  - Less than half are on treatment
  - Key risk factor for heart disease
- Heart disease is the leading cause of death
  - 1 in every 4 deaths is related to heart disease

Mozzafarian D, et al. *Circulation*. 2016; 133:e38-e360.

AHA/ACC versus National Lipid Association (NLA) Guidelines

	AHA/ACC Guideline	National Lipid Association
Low-density lipoprotein cholesterol (LDL-C)	Primary goal of therapy	Non-high density lipoprotein cholesterol (HDL-C) considered more predictive of ASCVD. LDL-C and non-HDL-C goals provided
Non-Statin Therapy	May be beneficial in certain subgroups; niacin is not an option	Consider non-statin therapy when HDL-C and LDL-C not at goals
PCSK-9 (proprotein convertase subtilisin/kexin type 9) inhibitor	Patients on max tolerated statin therapy with ASCVD with LDL-C ≥ 190 mg/dL Further, ezetimibe should be considered before the use of a PCSK9 inhibitor	Patients on max tolerated statin therapy with ASCVD not at goal

ASCVD = atherosclerotic cardiovascular disease

Jacobson TA, et al. *J Clin Lipidol*. 2014; 8(5):473-88.; Stone NJ, et al. *Circulation*. 2014;129(25 Suppl 2):S1-45.; Lloyd-Jones DM, et al. *J Am Coll Cardiol*. 2016. pii: S0735-1097(16)32398-1. [Epub ahead of print].

Question 6
Adult Patient Case

JC is a 56-year-old male with a history significant for hypertension, type 2 diabetes mellitus (T2DM), obesity, and chronic pulmonary pulmonary disease (COPD). He had an NSTEMI in 2013. His recent cholesterol panel found an LDL-C of 152 mg/dL. He is currently taking atorvastatin 80 mg/day.

- What is the most appropriate therapy at this time?

A Change to rosuvastatin
B Add ezetimibe
C Add evolucumab
D Add fenofibrate

Question 6

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Question 6
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- What is the most appropriate therapy at this time?

A Change to rosuvastatin

B **Add ezetimibe**

C Add evolucumab

D Add fenofibrate

Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK-9) Inhibition

- Current agents
  - Alirocumab (75-150 mg SubQ once every 2 weeks)
  - Evolocumab (140 mg SubQ once every 2 weeks)
- FDA approved for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic disease requiring additional LDL-C lowering
- Evolocumab also approved for adjunct in homozygous familial hypercholesterolemia (HoFH)

Patient Characteristics in Selected Clinical Studies

Study Name	Study duration	Age	Male (%)	LDL-C baseline
ALIROCUMAB				
OPTIONS I[a]	32 weeks	62.2 64.2	57.9 66.0	104 ± 35 mg/dL 116 ± 37 mg/dL
OPTIONS II[a]	32 weeks	57.9 62.2	51.9 63.3	107 ± 26 mg/dL 118 ± 32 mg/dL
EVOLOCUMAB				
DESCARTES	52 weeks	55.9	48.4	104 ± 22 mg/dL
LAPLACE	12 weeks	59.6	56.0	110 ± 42 mg/dL
GAUSS-2[a]	12 weeks	61 63	55 55	192 ± 57 mg/dL 192 ± 62 mg/dL
[a]Multiple study groups				

Robinson JG, et al. *JAMA*. 2014;311(18):1870-82; Blom D, et al. *N Engl J Med*. 2014; 370:1809-19; Robinson JG ,et al. *Clin Cardiol*. 2014;10:597-604; Stroes E, et al. *JACC*. 2014; 63:2541-8; Robinson JG, et al. *N Engl J Med*. 2015; 372(16):1489-95.

Reduction in Cardiovascular Morbidity and Mortality

High-dose PCSK9 inhibitors vs placebo in primary hypercholesterolemia*

Outcomes	Number of trials (n)	Weighted event rates		At 12 to 78 wk	
		PCSK9 inhibitors	Placebo	RRR (95% CI)	NNT (CI)
All-cause mortality	13 (11 430)	0.2%	0.5%	57% (18 to 78)	345 (252 to 1094)
Cardiovascular mortality	12 (11 340)	0.2%	0.3%	50% (−13 to 78)	Not significant
MACE	12 (11 340)	1.2%	1.7%	33% (−4 to 57)	Not significant
				RRI (CI)	NNH (CI)
Neurocognitive adverse events	6 (9581)	0.7%	0.3%	133% (11 to 388)	269 (93 to 3257)

Lipinski NJ, et al. *Eur Heart J*. 2016; 37:536-45

Santos RD. *Ann Intern Med*. 2016; 164(6): JC31. doi: 10.7326/ACPJC-2016-164-6-031

LDL-C Reduction in Geriatrics

- Systematic review of 19 cohort studies with a total of 69, 094 elderly patients
- Findings:
  - High LDL-C is inversely associated with mortality
- The 2013 ACC/AHA Guideline for treatment of cholesterol has specific recommendations for patients over the age of 75 years
  - Secondary prevention – moderate intensity statin
  - Primary prevention – no recommendation

Ravnskov U, et al. *BMJ Open*. 2016;6:e010401.

Stone NJ, et al. *Circulation*. 2014;129(25 Suppl 2):S1-45

Primary Prevention > age 75

- Few data were available to indicate an ASCVD event reduction benefit in primary prevention among individuals >75 years of age who do not have clinical ASCVD.
- Initiation of statins for primary prevention of ASCVD in individuals ≥ 75 years of age requires consideration of additional factors, including increasing comorbidities, safety considerations, and priorities of care.
- The Pooled Cohort Equations can also provide information on expected 10-year ASCVD risk for those 76 to 79 years of aged that may inform the treatment decision.

Stone NJ, et al. *Circulation*. 2014;129(25 Suppl 2):S1-45.

Secondary Prevention > age 75

- In individuals with *clinical* ASCVD >75 years of age, it is reasonable to evaluate the potential for ASCVD risk-reduction benefits and for adverse effects, drug-drug interactions and to consider patient preferences, when initiating a moderate- or high-intensity statin. It is reasonable to continue statin therapy in those who are tolerating it.

  —Evidence level: E (Expert Opinion)

- *Clinical* ASCVD is defined by the inclusion criteria for the secondary prevention statin randomized controlled trials (acute coronary syndromes, or a history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, or peripheral arterial disease presumed to be of atherosclerotic origin).

Stone NJ, et al. *Circulation*. 2014;129(25 Suppl 2):S1-45.

Age as a Surrogate for Treatment

- Relatively few individuals >75 years of age were included in RCTs of high-versus moderate-intensity statin therapy; there was not clear evidence of an additional reduction in ASCVD events from high-intensity statin therapy.
- Individuals >75 years of age did experience a reduction in ASCVD events in the trials of mostly moderate-intensity statin therapy, compared with control. Moderate-intensity statin therapy should be considered for individuals >75 years of age with *clinical* ASCVD.
- Older participants in RCTs were likely to be healthier than many older individuals in the general population, the use of statin therapy should be individualized in persons >75 years of age with *clinical* ASCVD, based on the potential for ASCVD risk reduction benefits, the potential for adverse effects and drug-drug interactions, and patient preferences.

Stone NJ, et al. *Circulation*. 2014;129(25 Suppl 2):S1-45.

Considerations for Treatment

- Primary prevention:
- "Young old" = > 65 years to ≤ 75 years
  - Young old cohorts appear appropriately included in general adult recommendations for age 40-75 in both primary and secondary prevention contexts
- "Middle old" = > 75 years to ≤ 80-82 years
  - Data unclear
    - Consider prognosis/estimate of life expectancy
    - Patient values and goals
    - Apply Pooled Estimate Calculator (if <79 years), assess cardiovascular risk (using testing methods patients can tolerate)
    - Consider cognition, function/venue of care, and risk for statin related ADRs
- "Old old" = over 80-82 years
  - No evidence of benefit

Considerations for treatment

- Secondary prevention
- "Young old" = > 65 years, ≤ 75 years
  - Young old cohorts appear appropriately included in general adult recommendations for age 40-75 in both Primary and Secondary prevention contexts
- "Middle old" = > 75 years, ≤ 80-82 years
  - Benefit in evidence base limited to moderate intensity statins, data strongest for male patients with low HDL
    - Consider prognosis/estimate of life expectancy
    - Patient values and goals
    - Apply Pooled Estimate Calculator (if < 79 years), assess cardiovascular risk (using testing methods patients can tolerate)
    - Consider cognition, function/venue of care, and risk for statin related adverse drug reactions (ADR)
- "Old old" = over 80-82 years
  - No evidence of benefit

Geriatric Patient Case 5

- TR is a 90-year-old male patient with a history of hypertension, familial hyperlipidemia, a history of TIA, and mild cognitive impairment who resides in an assisted living environment. His current medications include hydrochlorothiazide 25 mg daily and aspirin 81 mg daily. At his appointment today, his son asks about initiating medication therapy to treat his cholesterol.

Diabetes Therapeutics

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Medications Leading to Emergency Department Admissions

- Surveillance data for hospitalization after emergency department visits
- Approximately 99,628 hospitalizations/year for ADR in adults ≥ 65 years
  - 48% of adults were ≥ 80 years
- Four medications/classes were implicated in 67.0%
  - Warfarin (33.3%)
  - **Insulin (13.9%)**
  - Oral antiplatelet agents (13.3%)
  - **Oral hypoglycemic agents (10.7%)**

Budnitz DS., et al. *N Engl J Med*. 2011; 365:2002-12.

Insulin Hypoglycemic Events

Table 1. Number of Cases and Estimates of ED Visits for IHEs by Patient Characteristics (United States, 2007-2011)[a]

Patient Characteristic	ED Visits for IHEs		Annual National Estimate	
	Cases, No.	Annual National Estimate, No. (%)	Persons With DM Receiving Insulin Treatment With or Without Oral Antidiabetic Agents, No. (%)	ED Visits per 1000 Persons With DM Receiving Insulin Treatment With or Without Oral Antidiabetic Agents, Rate (95% CI)
Age, y				
<18[b]	265	2088 (2.1)	152 555 (2.8)	13.7 (4.9-22.5)
18-44	1675	21 189 (21.7)	871 150 (15.9)	24.3 (15.0-33.6)
45-64	2817	34 173 (35.0)	2 492 704 (45.5)	13.7 (9.1-18.3)
65-79	2190	24 720 (25.3)	1 515 077 (27.7)	16.3 (10.7-21.9)
≥80	1153	15 479 (15.9)	443 497 (8.1)	34.9 (20.5-49.3)
Sex[c]				
Female	4080	48 458 (49.6)	2 740 352 (50.1)	17.7 (11.9-23.5)
Male	4019	49 186 (50.4)	2 734 631 (49.9)	18.0 (11.4-24.5)
Total	8100	97 648 (100.0)	5 474 983 (100.0)	17.8 (11.8-23.8)

Insulin glargine and degludec

- Insulin glargine 300 units/mL vs. 100 units/mL
- EDITION 2 study
  - RCT in T2DM previously on basal-bolus insulin on oral agents, 1 year duration
  - Similar efficacy and adverse effects
  - Less nocturnal hypoglycemia
  - Mean age 58

- Insulin degludec 200 units/mL vs. glargine 100 units/mL
- BEGIN Once Long trial
  - RCT in T2DM inadequately controlled on oral agents, 1 year duration
  - Similar efficacy and adverse effects
  - Similar adverse effects
  - Less nocturnal hypoglycemia
  - Mean age 59

Yki-Jarvinen H, et al. *Diabetes Obes Metab*. 2015; 17:1142-9; Zinman B, et al. *Diabetes Care*. 2012;35:2464-71; Gough SCL, et al. *Diabetes Care*. 2013;36(9):2536-42.

Long-acting Effect---Convenience or Complication?

- Determining variables
  - Frailty
  - Diet
  - Factors affecting ease of monitoring

Geriatric Patient Cases

- 70-year-old patient with Alzheimer's Disease and type 2 diabetes mellitus (T2DM) residing in a long-term care facility
- Good appetite, consistent intake
- Fingerstick values tend to run 150-320, but gets agitated with frequent testing. One nurse requested psychoactive medication due to almost being struck when attempting to perform monitoring

- 89-year-old patient with type 2 diabetes mellitus (T2DM) and functional dependence/swallow impairment following stroke
- Poor appetite, inconsistent intake of mechanically altered food
- Fingerstick values are variable without predictable pattern

Sodium-glucose Cotransporter-2 (SGLT2) Inhibitors

- Blocks the SGLT2 protein involved in 90% of glucose reabsorption in the proximal renal tubule
  - —Reduces reabsorption of filtered glucose from the tubular lumen
  - —Lowers the renal threshold for glucose

Nair S, et al. *Pract Diabetes Int*. 2010;27:311-6.

SGLT2 Inhibitors

- Advantages
  - Lower both fasting and post-prandial glucose
  - Weight loss (~3 kg)
  - Blood pressure (3 – 5 mmHg reduction)
  - Low risk of hypoglycemia
- Disadvantages
  - Vulvovaginal candidiasis and mycotic infections (10%)
  - Urinary tract infections
  - Hyperkalemia and renal insufficiency
  - Require renal dosing

Jardiance® [package insert]. Ridgefield, CT: Boehringer Engelheim; 2016.
Invokana®[package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc; 2013.
Farxiga® [package insert]. Princeton, NJ: Bristol-Myers Squibb; 2014.

Cardiovascular Outcomes with SGLT2

- In T2DM patients with high CVD risk treated with empagliflozin
  - Primary major adverse cardiac event end point (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke) significantly reduced
  - HR 0.86; 95 % CI, 0.74 to 0.99; p=0.04
- Mechanisms?
  - Diuretic effect
  - Blood pressure lowering
  - Arterial elasticity
  - Sympathetic tone
- Class effect?

Zinman B, et al. *N Engl J Med* 2015;373:2117-28.

Abdul-Ghani M, et al. *Diabetes Care*. 2016;39:717-25.

Comparison of SGLT2 Inhibitors

	Canagliflozin	Dapagliflozin	Empagliflozin
A1c lowering (%) monotherapy combination	 1 0.9	 0.9 0.8	 0.8 0.8
Dose	100-300 mg daily	5-10 mg daily	10-25 mg daily
CrCL < 45 mL/min	Avoid	Avoid	Avoid
CrCL < 60 mL/min	100 mg daily	Avoid	No dose adjustment

Stenlöf K, et al. *Diabetes Obes Metab*. 2013; 15(4):372-382; Ferrannini E, et al. *Diabetes Care*. 2010; 33(10):2217-24; Roden M, et al. *Lancet Diabetes Endocrinol*. 2013; 3:208-19.

Demographics in Phase III Trials

	Canagliflozin (N=584)	Dapagliflozin (n=559)	Empagliflozin (n=899)
Mean age, years	55.4	47.9-54.5	55.0
Female, %	55.8	50.5	39
White, %	67.6	NR	34
HbA1c, %	8.0	7.8-10.8	7.9
Duration of T2DM, years	4.4	0.20-1.4	22% T2DM > 5 years

NR=not reported

Stenlöf K, et al. *Diabetes Obes Metab*. 2013; 15(4):372-82; Ferrannini E, et al. *Diabetes Care*. 2010; 33(10):2217-24; Roden M, et al. *Lancet Diabetes Endocrinol*. 2013;3:208-19.

Guidelines on SGLT2 Inhibitors

- American Diabetes Association (ADA)
  - Option for add on to metformin if inadequate response at three months
- American Academy of Clinical Endocrinologists (AACE)
  - SGLT2 inhibitors are an option for monotherapy or add on therapy
- ADA/American Geriatric Society (AGS)
  - Consider patient comorbidities/life expectancy

Garber AJ, et al. *Endocrine Prac.* 2016;22(1):84-113.

Kirkman MS, et al. *Diabetes Care*. 2012;35(12):2650-64.

American Diabetes Association. *Diabetes Care*. 2016;39(suppl 1):S1-S106.

Cautions in Older Patients

- Side effects include urinary tract infection and acute kidney injury
- Ketoacidosis is rare, yet a possibility
- Patient > 65 years more likely to experience hypotension, dizziness and dehydration
- Drug efficacy is reduced among patients with poor kidney function
- Kidney failure is higher among older patients
- Significance of side effects increases > 75 years

Stenlöf K, et al. *Diabetes Obes Metab*. 2013; 15(4):372-82; Ferrannini E, et al. *Diabetes Care*. 2010; 33(10):2217-24; Roden M, et al. *Lancet Diabetes Endocrinol*. 2013; 3:208-19.

Geriatric Patient Case 6

- AK is 79-year-old male patient with poorly controlled T2DM, MI, and a persistent wound of the left foot. A1c is 11.2% and calculated GFR is 30 mL/min. He has mild cognitive impairment but lives at home. Because of the diagnosis of the wound, he is receiving home health visits.

Neuropsychiatric Therapeutics

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Antiepileptics in the Elderly

- Approximately 10% of nursing home patients receive an antiepileptic
- Concerns in the elderly population include
  - Age related drug clearance changes
  - Polypharmacy (CYP450)
  - Altered protein binding

Perucca E, et al. *Epilepsy Res*. 2005;46(s4):31-7.

Brivaracetam

- High-affinity synaptic vesicle protein 2A (SV2A) ligand
  - Greater than a 30-fold higher affinity for SV2A than levetiracetam
- Low protein binding (20%)
- High bioavailability
- CYP2C19 substrate (major)
- No dose adjustment needed in mild to severe renal impairment

Gillard M, et al. *Eur J Pharmacol*. 2011; 664:36-44.

Pack AM. *Epilepsy Curr*. 2014; 14(4):196-8.

Monotherapy vs. Adjunct Therapy

- Brivaracetam and levetiracetam are approved as adjunct therapy
  - Investigational AED cannot be evaluated against placebo in studies of seizure disorders
  - Temptation to use agents with fewer interactions or no serum monitoring
  - Experience with monotherapy emerges with use
    - Levetiracetam has a history of off-label use---strategically and indiscriminately
    - Includes use for manic symptoms
      - Data limited (e.g., small open label study of Bipolar I patients with acute mania already on haloperidol)
  - Assuming either agent is an effective mood stabilizer is an extrapolation

Grunze H, et al. *J Clin Psychiatry*. 2003; 64:781-4. .

Side Effect Profile

- Similar to other Antiepileptic drugs
  - Dizziness
  - Sedation/somnolence
  - Cerebellar ataxia/balance problems
- Labeling discloses increased risk of suicidal ideation/behavior (13%)
  - Other psychiatric symptoms reported include psychosis, hallucinations, paranoia, irritability, anger, aggression, affect lability/mood swings, anxiety, depressed mood or psychomotor hyperactivity
- Few drug-drug interactions
  - Rifampin most significant

Product Information: brivaracetam. UCB, Inc (per manufacturer), Smyrna, GA, 2016.

Geriatric case

- RT is an 89-year-old male patient with a history of stroke (ICH 7 years ago). Since that time, he has been receiving phenytoin with no documentation of seizure activity in the medical record. As his nutritional status has declined, his serum concentrations have fluctuated. He is becoming increasingly annoyed with the repeated laboratory testing required to monitor his drug therapy.

Question 7

Which of the following is the most appropriate intervention for RT at this time?

A Continue phenytoin therapy

B Add brivaracetam to phenytoin

C Switch phenytoin to brivaracetam

D Discontinue phenytoin therapy

Question 7

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Cariprazine and Brexpiprazole

- Cariprazine
  - Partial agonist of central dopamine D_2 and serotonin 5-HT_{1A}
  - Antagonist of serotonin 5-HT_{2A}
  - FDA approved for schizophrenia and acute treatment of manic or mixed episodes associated with bipolar I disorder
- Brexiprazole
  - Partial agonist of central dopamine D_2 and serotonin 5-HT_{1A}
  - Antagonist of serotonin 5-HT_{2A} and norepinephrine α_{1B} and α_{2C}
  - FDA approved as an adjunctive therapy to antidepressants in adults with major depressive disorder and schizophrenia

VRAYLAR™ [package insert] Actavis, Parsippany, NJ September 2015.

REXULTI [package insert] Lundbeck, Deerfield, IL August 2015.

Antipsychotic Labeling

- Although the mechanisms of the two drugs are similar, there are differences in FDA approved indications
  - They differ slightly with respect to the drug regimen review implications of the product labeling
- Products carry same mortality warnings as other antipsychotics for elderly dementia patients

VRAYLAR™ [package insert] Actavis, Parsippany, NJ September 2015.

REXULTI [package insert] Lundbeck, Deerfield, IL August 2015.

Antipsychotic or antidepressant?

- Extended spectrums of receptor activity has resulted in new compounds that influence a wider range of psychiatric symptoms
  - FDA approved for schizophrenia and adjunctive antidepressant therapy
    - —Consumer directed advertising focuses on the latter
  - Classified and regulated as antipsychotic
- Implications for LTCF: regulatory requirements for drug regimen review?

Brexpiprazole in the Elderly

- ***"Interventional, randomised, double-blind, parallel-group, placebo-controlled, fixed-dose study to evaluate the efficacy and safety of brexpiprazole (1 and 3 mg/day) as adjunctive treatment in elderly patients with major depressive disorder with an inadequate response to antidepressant treatment"***
  - Target outpatient men and women over age 65 with major depressive disorder
  - Study proposed in 2013, ClinicalTrials.gov ID 01837797, trial terminated on 2/4/2016 due poor recruitment

https://clinicaltrials.gov/ct2/show/NCT01837797.

Antipsychotic for Alzheimer's Disease?

- ***"A phase III, 12-week, multicenter, randomized, double-blind, placebo controlled trial to evaluate the efficacy, safety, and tolerability of 3 fixed doses of brexpiprazole (OPC-34712) in the treatment of subjects with agitation associated with dementia"***
  - Currently enrolling ClinicalTrials.gov ID NCT01862640, anticipated end date June 2017
  - Target 420 men and women age 55-90 with agitation due to Alzheimer's type dementia

https://www.nia.nih.gov/alzheimers/clinical-trials/brexpiprazole-agitation-alzheimers-dementia

Geriatric Case 7

- BB is an 83-year-old male resident of an Alzheimer's unit. His psychoactive history is poorly documented and medication history has included quetiapine 25mg daily at bedtime with associated diagnosis documentation that has ranged from "dementia" to "agitation" to "depression". Repeated drug therapy interventions have been submitted to consider a trial hold of this medication. At last visit, quetiapine was discontinued and brexpiprazole added. The diagnosis tagged to the order states "depression". A formal psychiatric assessment is not present in the chart.

Question 8

Which of the following best characterizes the intervention made for this patient?

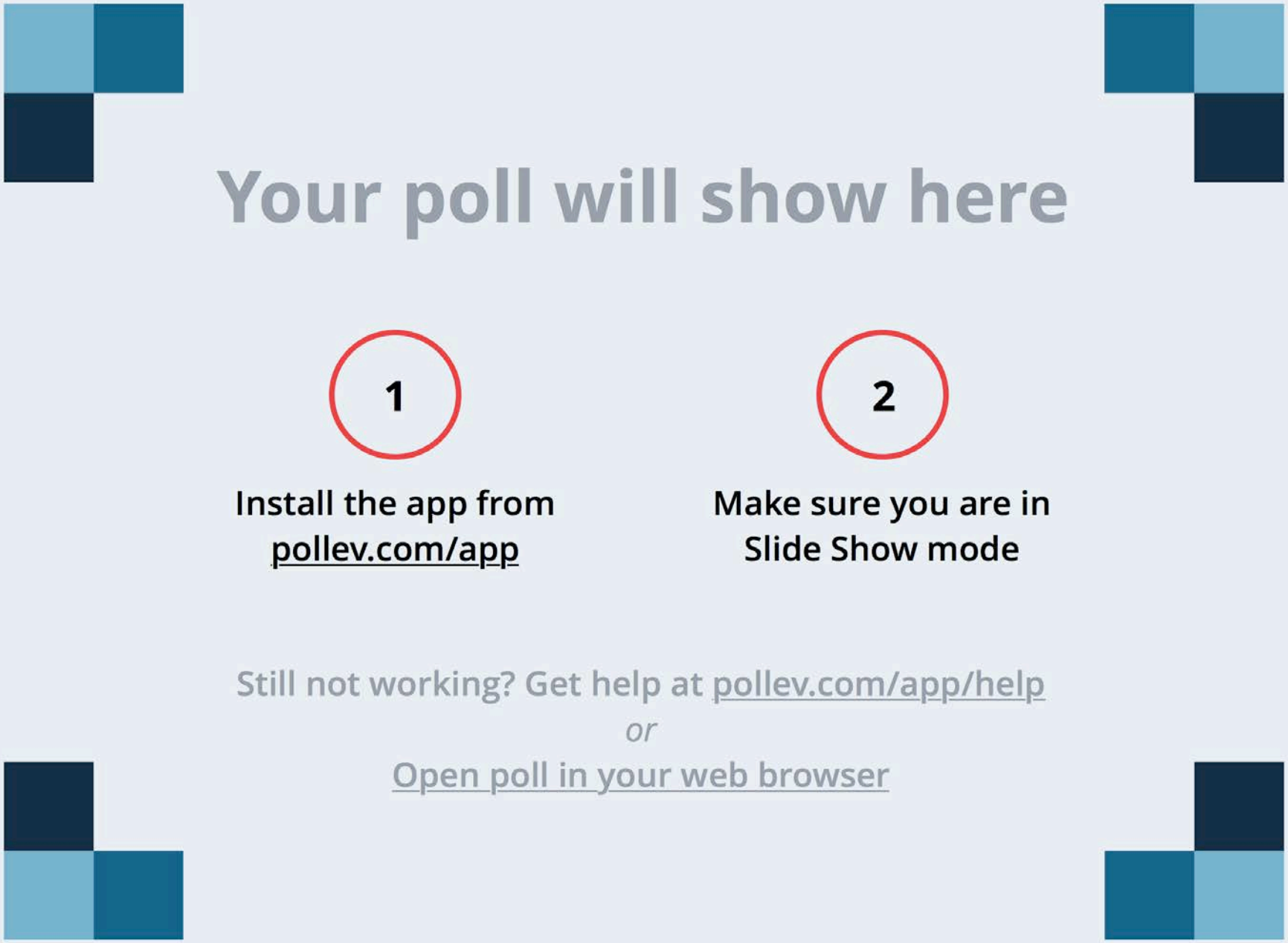
A. Brexpiprazole is not an appropriate option for this patient

B. Diagnosis of depression will substantiate the addition of brexpiprazole

C. Psychiatric history and diagnosis clarification is necessary to select appropriate therapy

D. Cariprazine should have been selected instead of brexpiprazole

Question 8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Gout

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Current Urate-Lowering Treatments

	Drug	Limitations
First Line	Allopurinol	Dosing recommendations in renal disease, hypersensitivity reactions, drug interactions
	Feboxistat	Post marketing cases of hepatic failure, limited data in CrCl < 30 mL/min, potential cardiovascular events
Second Line	Probenecid	Drug interactions, reduced urate lowering as CrCl declines

Stamp LK, et al. *Drugs Aging*. 2014;31:777-86.

Lesinuard (Zurampic®)

- FDA approved urate transporter 1 (URAT1) inhibitor indicated in combination with a xanthine oxidase inhibitor
  - Black box warning, acute renal failure more common when use without xanthine oxidase inhibitor
- Do not use if CrCl < 45 mL/min
- Several phase III studies have evaluated safety and efficacy

http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207988lbl.pdf

Summary of Phase III Clinical Trials

Trial	Design	Treatment	Primary Outcome
CLEAR 1 N=600	RCT, 12 months	Allopurinol Allopurinol + Lesinurad 200 mg Allopurinol + Lesinurad 400 mg	28% 54%* 59%*
CLEAR 2 N=600	RCT, 12 months	Allopurinol Allopurinol + Lesinurad 200 mg Allopurinol + Lesinurad 400 mg	23% 55%* 67%*

Allopurinol dose ranged between 200 to 900 mg/day (~80-90% on 300 mg/day)
Primary outcome = proportion of patients with a serum uric acid < 6 mg/dL
*p-value < 0.0001 vs. control group

Saag K, et al. *Ann Rheum Dis*. 2015 June; 74(Suppl2):540. Abstract FRI0320.
Bardin T, et al. *Ann Rheum Dis*. 2015 June; 74(Suppl2):545. Abstract FRI0333.

Data limits

- CLEAR 1 study population was:
  - Predominantly male (94%)
  - Mean age of 51.9 (+/-11.3) years
    - —Although inclusion criteria allowed subjects up to age 85, 518 of the 603 enrolled subjects were <65 years
  - BMI of 34.77 (+/-6.66)kg/m^2
- CLEAR 2 study population was:
  - Predominantly male (96%)
  - Mean age 51.2 (+/- 10.9) years
    - —Same inclusion criteria as above, but 544 of the 610 enrolled subjects were <65 years

Saag K, et al. *Ann Rheum Dis*. 2015 June; 74(Suppl2):540.

Bardin T, et al. *Ann Rheum Dis*. 2015 June; 74(Suppl2):545.

Geriatric Patient Case 8

- HG is a 68-year-old female patient complains of recurrent pain in the right elbow. She has presented three times over several months with the same complaint, yet has had no relief from multiple non-pharmacological strategies, acetaminophen, and non-steroidal anti-inflammatory therapy. She is in otherwise good health and has normal renal function. Her physician suggests a test for possible gout and she is surprised. “Why?? My toe doesn’t hurt!”

Question 9

Which of the following best describe the use of lesinuard in this patient's case?

A. Lesinuard should not be used because this is likely not gout
B. Allopurinol should be initiated first as this is likely gout
C. Lesinuard could be a reasonable choice if her CrCl is > 45mL/min
D. Lesinuard should not be used because of patient's age

Question 9

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Conclusions

- Geriatric patients are under-represented in clinical trials
  - Consider ***subgroups*** and ***baseline characteristics*** when determining if data can be extrapolated
    - Age strata, functional/cognitive status, living environment, comorbidities, weight/frailty status, prognosis
- Time to benefit and cost are important considerations
- Most importantly, the treatment goals may actually be very different
  - Different from the younger population
  - Different from the endpoints measured in trials

Questions?