ashp® MIDYEAR 2016
Clinical Meeting & Exhibition

Check or Hold?
Three Clinical Controversies in Cardiovascular Pharmacotherapy

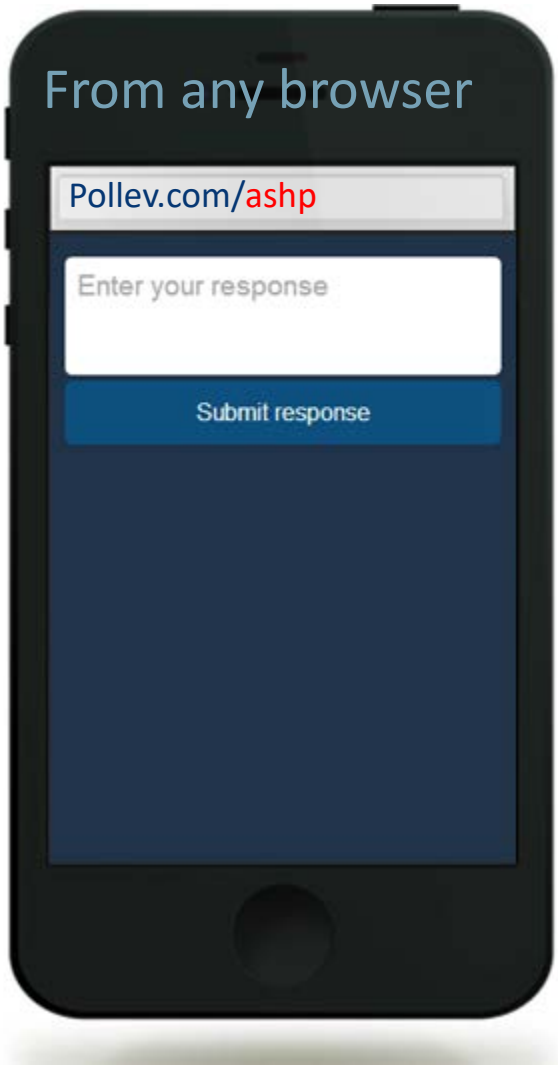
Christopher Betz, Pharm.D., BCPS, FKSHP, FASHP
Professor
Sullivan University College of Pharmacy
Snehal H. Bhatt, Pharm.D, BCPS
Associate Professor
MCPHS University

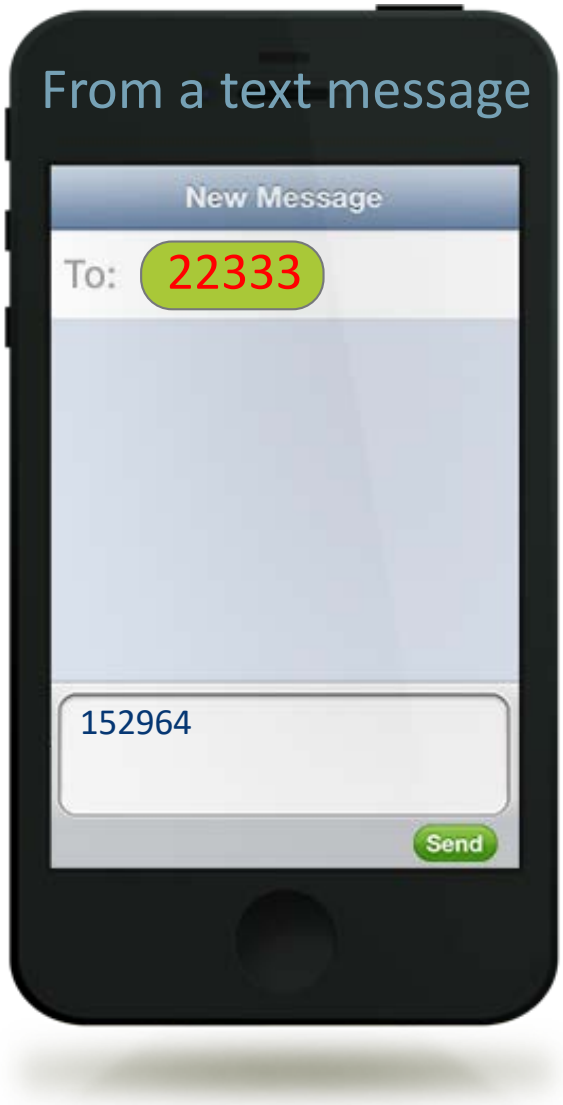
Disclosures

- The program chair and presenters for this continuing education activity have reported no relevant financial relationships.

Time for a Poll

How to vote via the web or text messaging





How to vote via text message

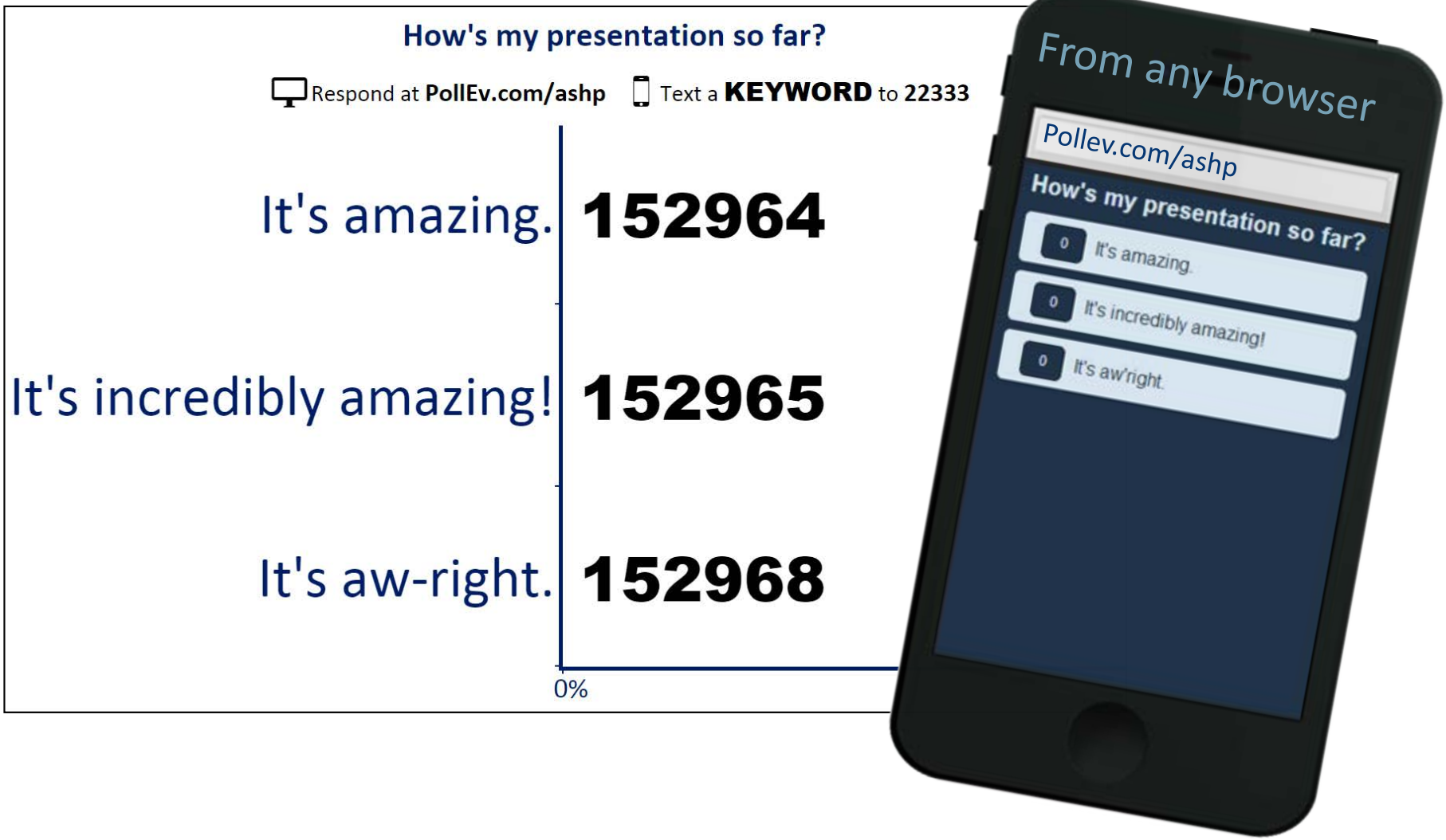
How's my presentation so far?

Respond at **PollEv.com/ashp** Text a **KEYWORD** to **22333**

It's amazing.	**152964**
It's incredibly amazing!	**152965**
It's aw-right.	**152968**

0%

How to vote via the web



Learning Objectives

- Compare and contrast the data supporting unfractionated heparin versus bivalirudin in acute coronary syndromes and design a regimen for patients in the cath lab.

- Evaluate the morbidity and mortality data of digoxin use in heart failure and atrial fibrillation patients, and determine if the use of digoxin should be continued

- Recommend appropriate NSAID therapy in patients with underlying cardiovascular disease

Case

- AD is a 57 year-old man who presents to the emergency department complaining of 10/10 sharp, crushing chest pain that started 20 minutes ago. An ECG performed reveals ST-segment elevations in Leads II, III and aVF, and he is urgently taken to the cardiac catheterization laboratory for suspected STEMI.
- Past Medical History:
  - Dyslipidemia
  - Impaired Glucose Tolerance

- Serum electrolytes and creatinine are all within normal limits
  - Cardiac enzymes: CK: 310, Troponin T: 2.51

Your poll will show here

1

Install the app from
pollev.com/app

2

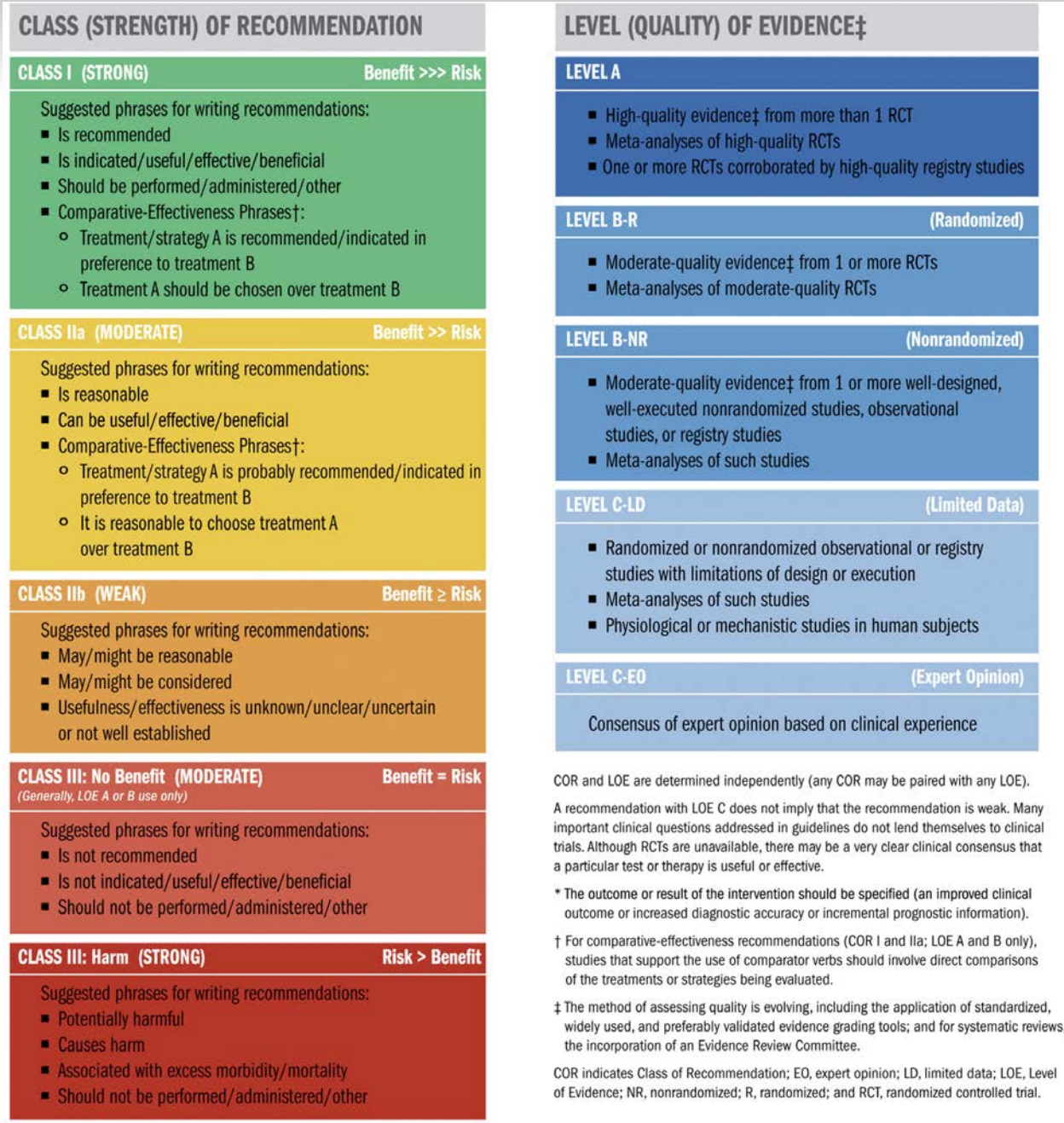
Make sure you are in
Slide Show mode

Still not working? Get help at pollev.com/app/help

or

Open poll in your web browser

ACC/AHA Clinical Practice Guideline Recommendation Classification System



CLASS (STRENGTH) OF RECOMMENDATION

CLASS I (STRONG) — Benefit >>> Risk

Suggested phrases for writing recommendations:
- Is recommended
- Is indicated/useful/effective/beneficial
- Should be performed/administered/other
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is recommended/indicated in preference to treatment B
  - Treatment A should be chosen over treatment B

CLASS IIa (MODERATE) — Benefit >> Risk

Suggested phrases for writing recommendations:
- Is reasonable
- Can be useful/effective/beneficial
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is probably recommended/indicated in preference to treatment B
  - It is reasonable to choose treatment A over treatment B

CLASS IIb (WEAK) — Benefit ≥ Risk

Suggested phrases for writing recommendations:
- May/might be reasonable
- May/might be considered
- Usefulness/effectiveness is unknown/unclear/uncertain or not well established

CLASS III: No Benefit (MODERATE) — Benefit = Risk
(Generally, LOE A or B use only)

Suggested phrases for writing recommendations:
- Is not recommended
- Is not indicated/useful/effective/beneficial
- Should not be performed/administered/other

CLASS III: Harm (STRONG) — Risk > Benefit

Suggested phrases for writing recommendations:
- Potentially harmful
- Causes harm
- Associated with excess morbidity/mortality
- Should not be performed/administered/other

LEVEL (QUALITY) OF EVIDENCE‡

LEVEL A
- High-quality evidence‡ from more than 1 RCT
- Meta-analyses of high-quality RCTs
- One or more RCTs corroborated by high-quality registry studies

LEVEL B-R (Randomized)
- Moderate-quality evidence‡ from 1 or more RCTs
- Meta-analyses of moderate-quality RCTs

LEVEL B-NR (Nonrandomized)
- Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies
- Meta-analyses of such studies

LEVEL C-LD (Limited Data)
- Randomized or nonrandomized observational or registry studies with limitations of design or execution
- Meta-analyses of such studies
- Physiological or mechanistic studies in human subjects

LEVEL C-EO (Expert Opinion)

Consensus of expert opinion based on clinical experience

COR and LOE are determined independently (any COR may be paired with any LOE).

A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).

† For comparative-effectiveness recommendations (COR I and IIa; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

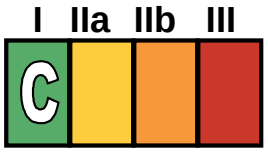
‡ The method of assessing quality is evolving, including the application of standardized, widely used, and preferably validated evidence grading tools; and for systematic reviews the incorporation of an Evidence Review Committee.

COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

Halperin JL, et al. *J Am Coll Cardiol*. 2016;67(13):1572-1574.

Anticoagulant Therapy to Support Primary PCI

For patients with STEMI undergoing primary PCI, the following supportive anticoagulant regimens are recommended:

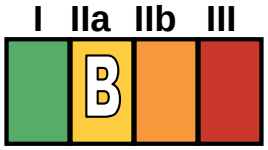


- UFH, with additional boluses administered as needed to maintain therapeutic activated clotting time levels, taking into account whether a GP IIb/IIIa receptor antagonist has been administered; or

- Bivalirudin with or without prior treatment with UFH.

O'Gara PT et al. Circulation. 2013; 127:529–55.

Anticoagulant Therapy to Support Primary PCI



In patients with STEMI undergoing PCI who are at high risk of bleeding, it is reasonable to use bivalirudin monotherapy in preference to the combination of UFH and a GP IIb/IIIa receptor antagonist.

Harm

Fondaparinux should not be used as the sole anticoagulant to support primary PCI because of the risk of catheter thrombosis.

O'Gara PT et al. Circulation. 2013; 127:529–55.

Initial Parenteral Anticoagulant Therapy in Patients With Definite NSTE-ACS

Anticoagulation, in addition to antiplatelet therapy, is recommended for all patients irrespective of initial treatment strategy. Treatment options include:

- UFH, with additional boluses administered as needed to maintain therapeutic activated clotting time levels, taking into account whether a glycoprotein (GP) IIb/IIIa inhibitor has been administered; or

- Bivalirudin: 0.10 mg/kg loading dose followed by 0.25 mg/kg per hour (only in patients managed with an early invasive strategy), continued until diagnostic angiography or PCI, with only provisional use of GP IIb/IIIa inhibitor (GPI), provided the patient is also treated with dual antiplatelet therapy (DAPT).

Amsterdam EA et al. J Am Coll Cardiol. 2014; 64:2645-2687.

Initial Parenteral Anticoagulant Therapy in Patients With Definite NSTE-ACS

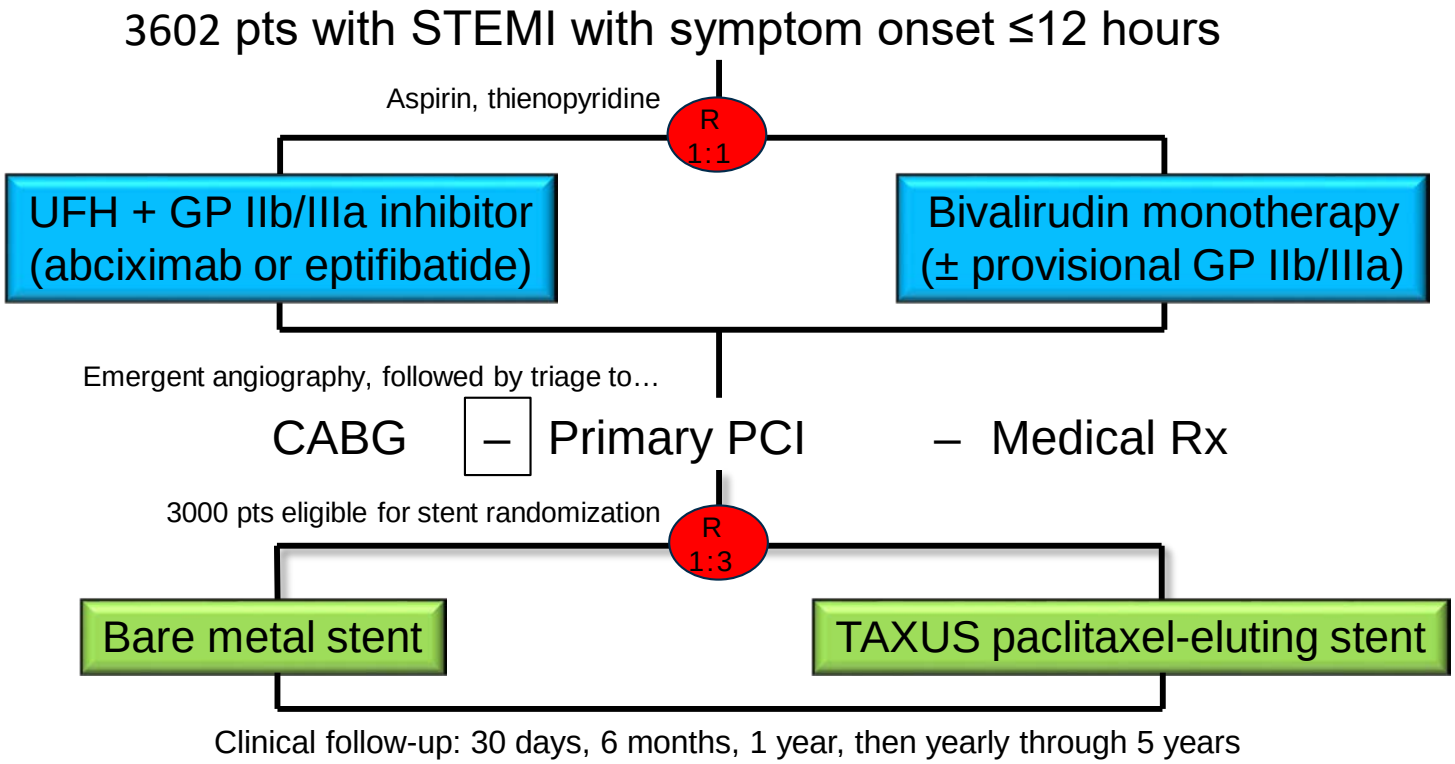
Recommendations	COR	LOE
• Enoxaparin: 1 mg/kg subcutaneously (SC) every 12 hours (reduce dose to 1 mg/kg SC once daily in patients with creatinine clearance [CrCl] <30 mL/min), continued for the duration of hospitalization or until PCI is performed. An initial intravenous loading dose is 30 mg. • Fondaparinux: 2.5 mg SC daily, continued for the duration of hospitalization or until PCI is performed.	I	A B

Amsterdam EA et al. J Am Coll Cardiol. 2014; 64:2645-2687.

Bivalirudin vs. Unfractionated Heparin

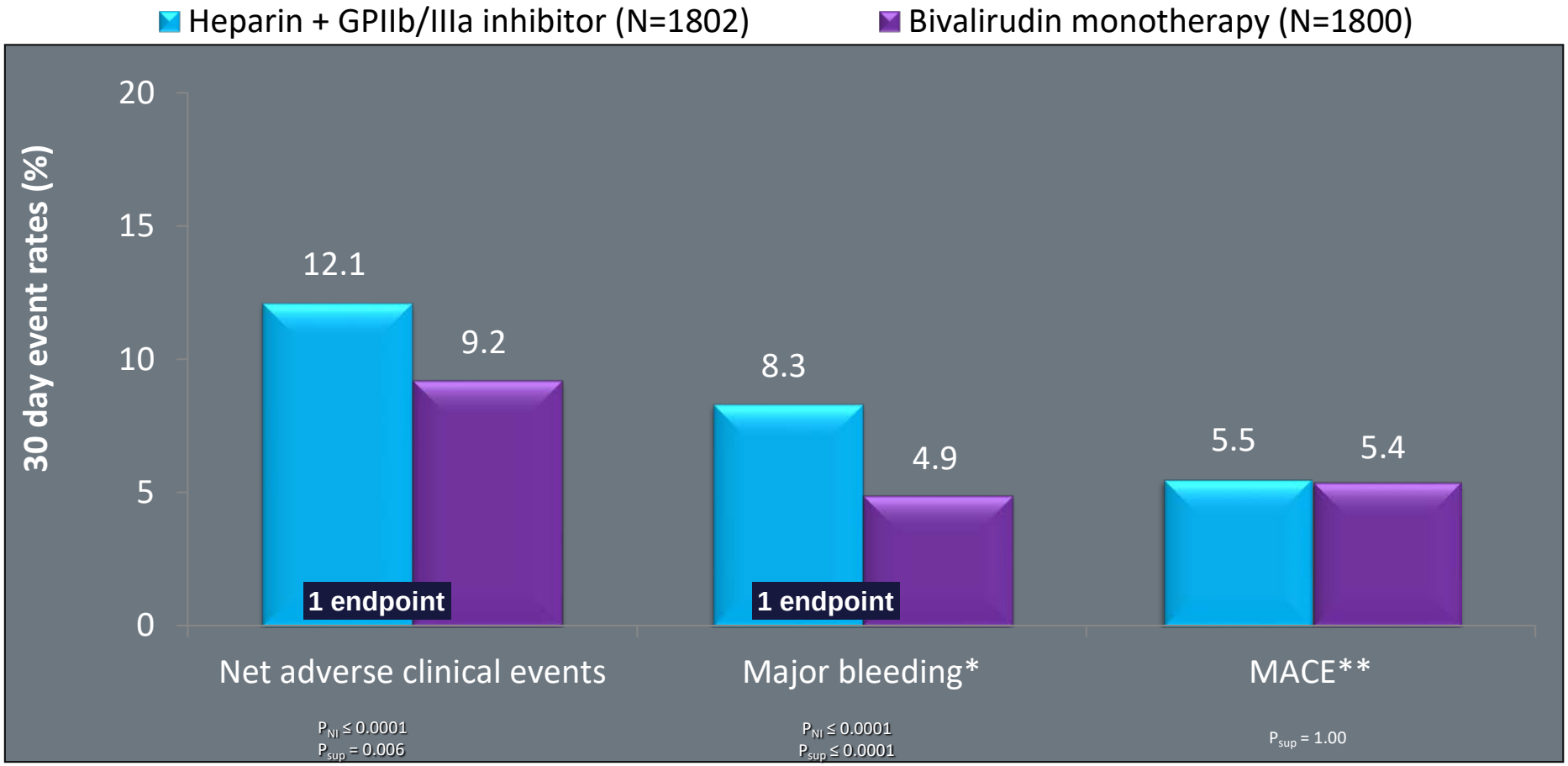
	Unfractionated Heparin	Bivalirudin
Clotting factor target	IIa and Xa	IIa
Clotting factor inhibition	Indirect (Antithrombin)	Direct
Anticoagulant activity	33%	100%
Onset of action	1 hour	Immediate
T ½	30 – 60 minutes	25 minutes
Monitoring in cath lab	ACT	None needed (ACT)
Elimination	Reticulo-endothelial system	Enzymatic/Renal
Inhibits clot-bound thrombin	No	Yes
Platelet binding	Yes	No

Horizons-AMI Trial



Stone GW et al. *N Engl J Med.* 2008; 358:2218-30.

Primary Outcomes



Net adverse clinical effects = MACE + Major Bleeding
MACE = All cause death, reinfarction, ischemic TVR or stroke

Stone GW et al. *N Engl J Med.* 2008; 358:2218-30.

30 Day MACE Components

	UFH + GP IIb/IIIa (N=1802)	Bivalirudin (N=1800)	P Value
Death	3.1%	2.1%	0.058
- Cardiac	2.9%	1.8%	0.035
- Non cardiac	0.2%	0.3%	0.75
Reinfarction	1.8%	1.8%	0.90
- Q-wave	1.2%	1.4%	0.66
- Non Q-wave	0.7%	0.4%	0.50
Ischemic TVR*	1.9%	2.6%	0.18
- Ischemic TLR**	1.8%	2.5%	0.14
- Ischemic remote TVR	0.3%	0.3%	1.0
Stroke	0.6%	0.7%	0.69

* = Target Vessel Revascularization
** = Target Lesion Revascularization

Stone GW et al. *N Engl J Med.* 2008; 358:2218-30.

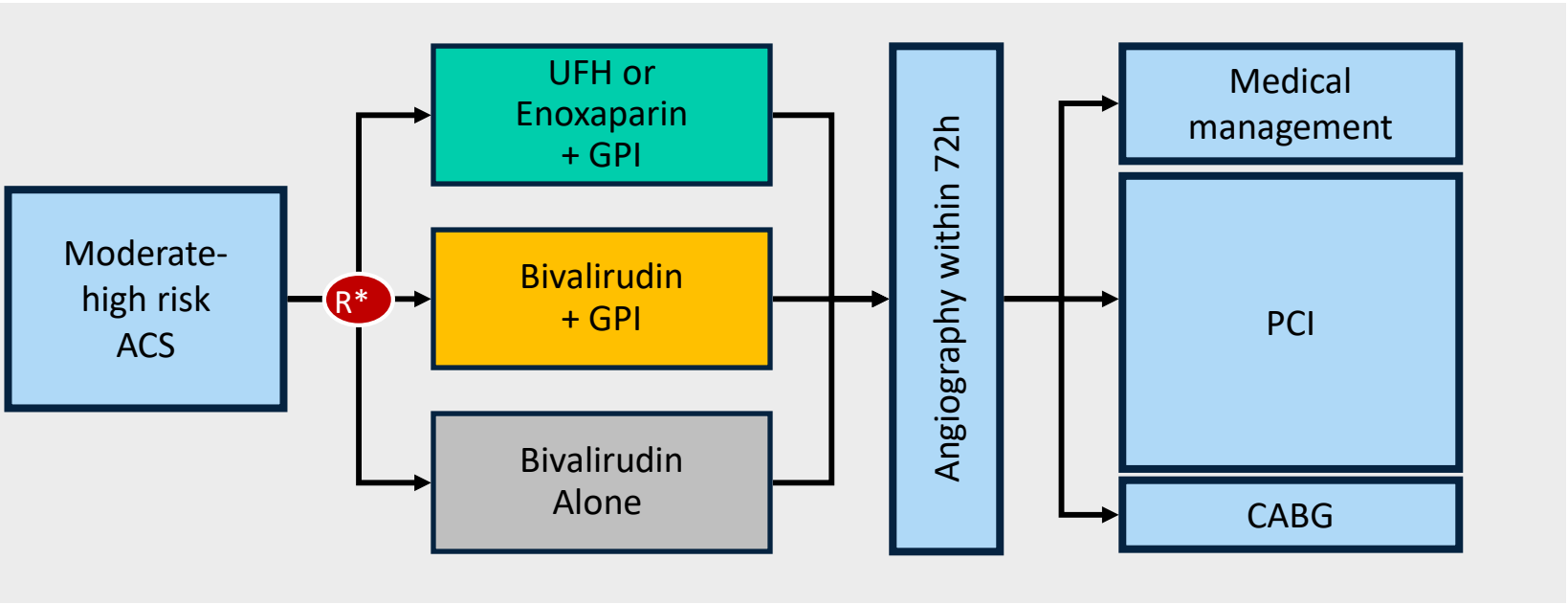
30 Day Bleeding Endpoints

	UFH + GP IIb/IIIa (N=1802)	Bivalirudin (N=1800)	P Value
Protocol Major, non CABG*	8.3%	4.9%	<0.0001
Protocol Major, All	10.8%	6.8%	<0.0001
Protocol Minor	15.4%	8.6%	<0.0001
Blood transfusion	3.5%	2.1%	0.01
TIMI Major	5.0%	3.1%	0.003
TIMI Minor	4.6%	2.8%	0.008
TIMI Major or Minor	9.6%	5.9%	<0.0001
GUSTO Life threatening (LT) /Severe	0.6%	0.4%	0.65
GUSTO Moderate	5.0%	3.1%	0.003
GUSTO LT or Severe or Moderate	5.6%	3.5%	0.003

*Primary endpoint

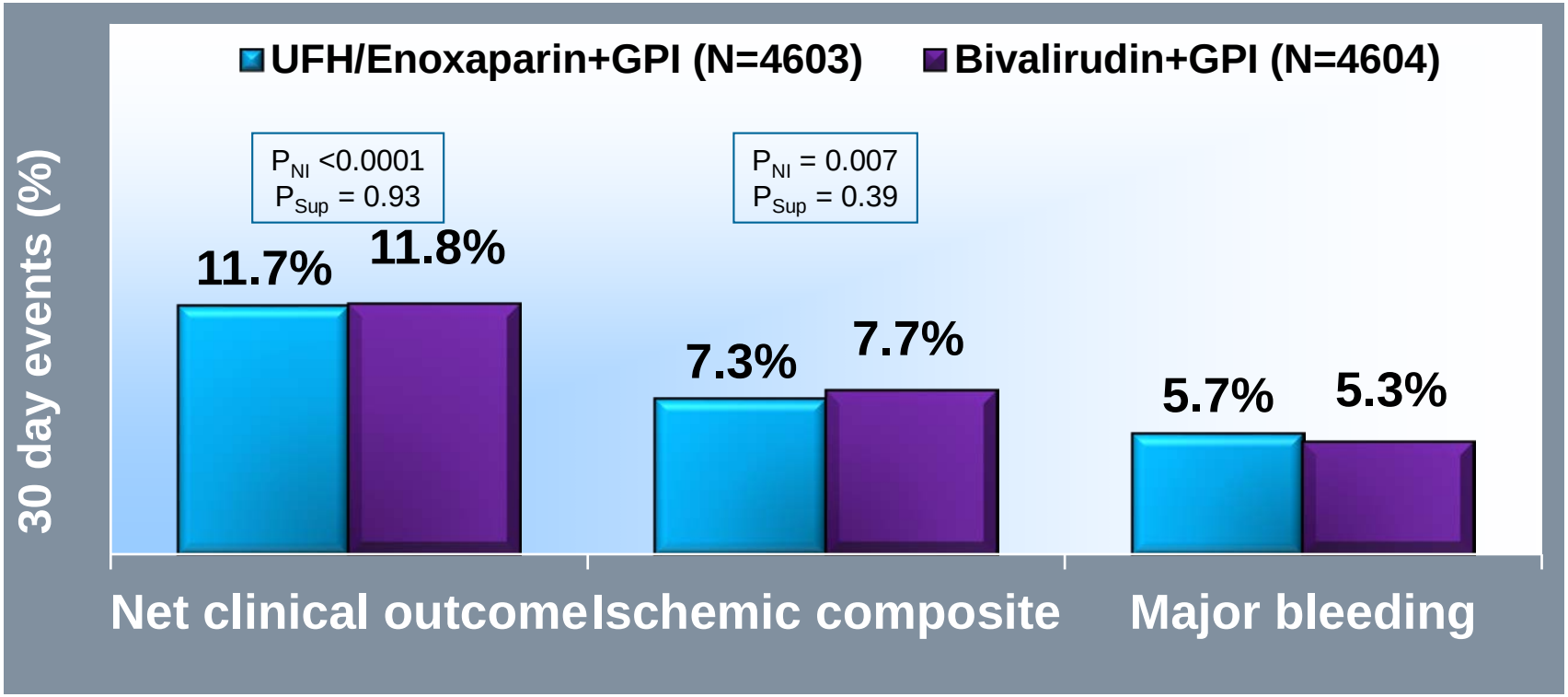
Stone GW et al. *N Engl J Med.* 2008; 358:2218-30.

ACUITY: Study Design



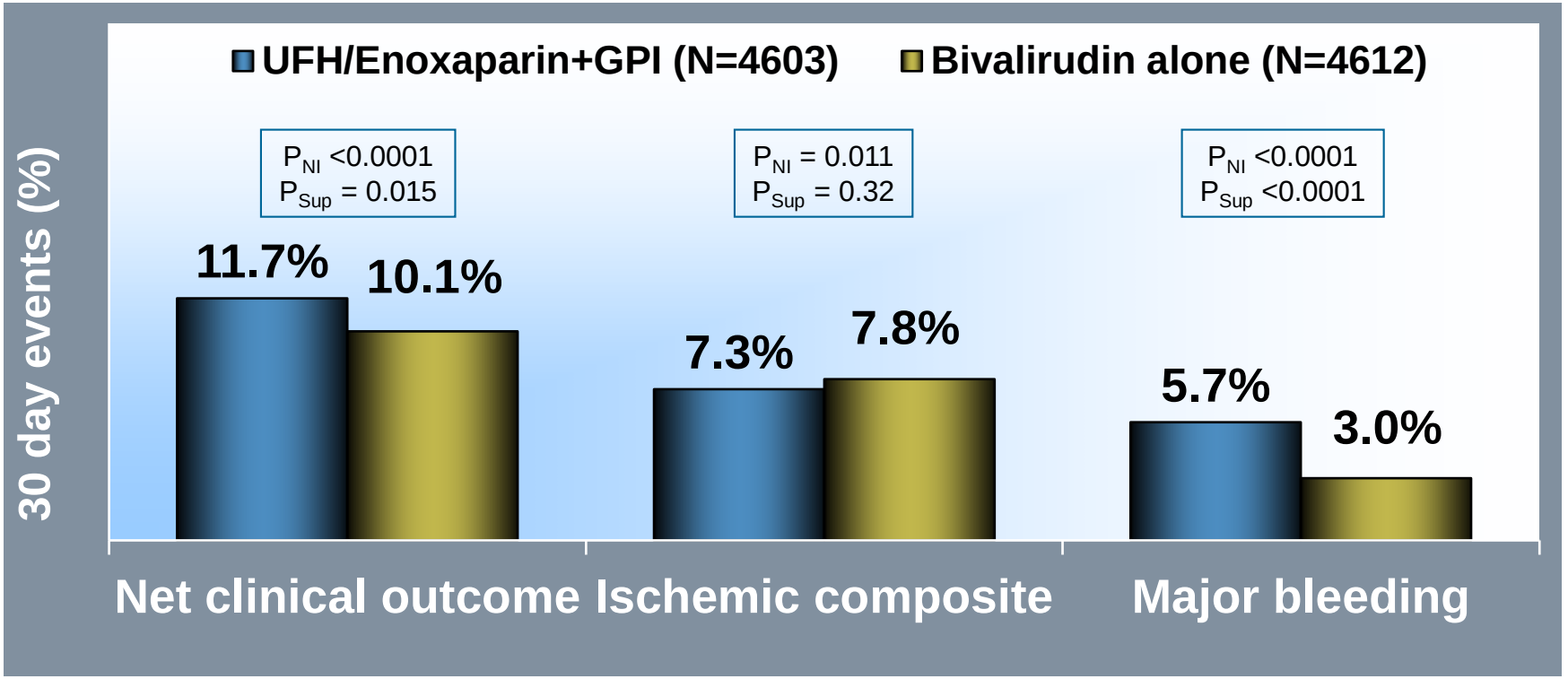
Stone GW et al. N Engl J Med 2006;355:2203-16.

Results: UFH/enox + GPI vs. Bival + GPI



Stone GW et al. N Engl J Med 2006;355:2203-16.

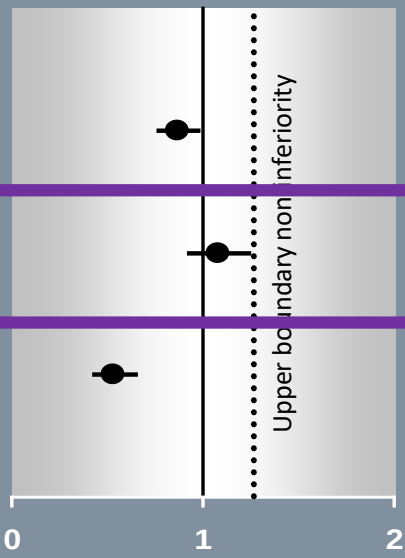
Results: UFH/enox + GPI vs. Bival Alone



Stone GW et al. N Engl J Med 2006;355:2203-16.

Results: UFH/enox + GPI vs. Bival Alone

Primary endpoint	Risk ratio ±95% CI	Bival alone	UFH/Enox + GPI	RR (95% CI)	p value (non inferior) (superior)
Net clinical outcome		10.1%	11.7%	0.86 (0.77-0.97)	<0.001 0.015
Ischemic composite		7.8%	7.3%	1.08 (0.93-1.24)	0.02 0.32
Major bleeding		3.0%	5.7%	0.53 (0.43-0.65)	<0.001 <0.001



Stone GW et al. N Engl J Med 2006;355:2203-16.

Bivalirudin: Conflicting data!

Study	UFH Dose	Ischemic Endpoints	Major Bleeding	Stent Thrombosis
HEAT – PPCI	70 units/kg	UFH: 5.7% Bival: 8.7%	UFH: 3.1% Bival: 3.5% (no significant difference)	UFH: 0.9% Bival: 3.4%
BRIGHT	100 units/kg	UFH: 13.2% Bival: 8.8%	UFH: 7.5% Bival: 4.1%	UFH: 0.9% Bival: 0.6% (no significant difference)

Shazad A et al. Lancet 2014;384:1849-58.
Han Y et al. JAMA 2015;313:1336-46.

Incidence of major Bleeding

Study	Bivalirudin	Heparin (UFH)
HORIZONS-AMI	89/1800 (5%)	149/1802 (8%)
EUROMAX	28/1089 (3%)	67/1109 (6%)
BRIGHT	4/729 (1%)	14/724 (2%)
HEAT PPCI	32/905 (4%)	28/907 (3%)
OVERALL	308/10 600 (3%)	593/10 900 (5%)

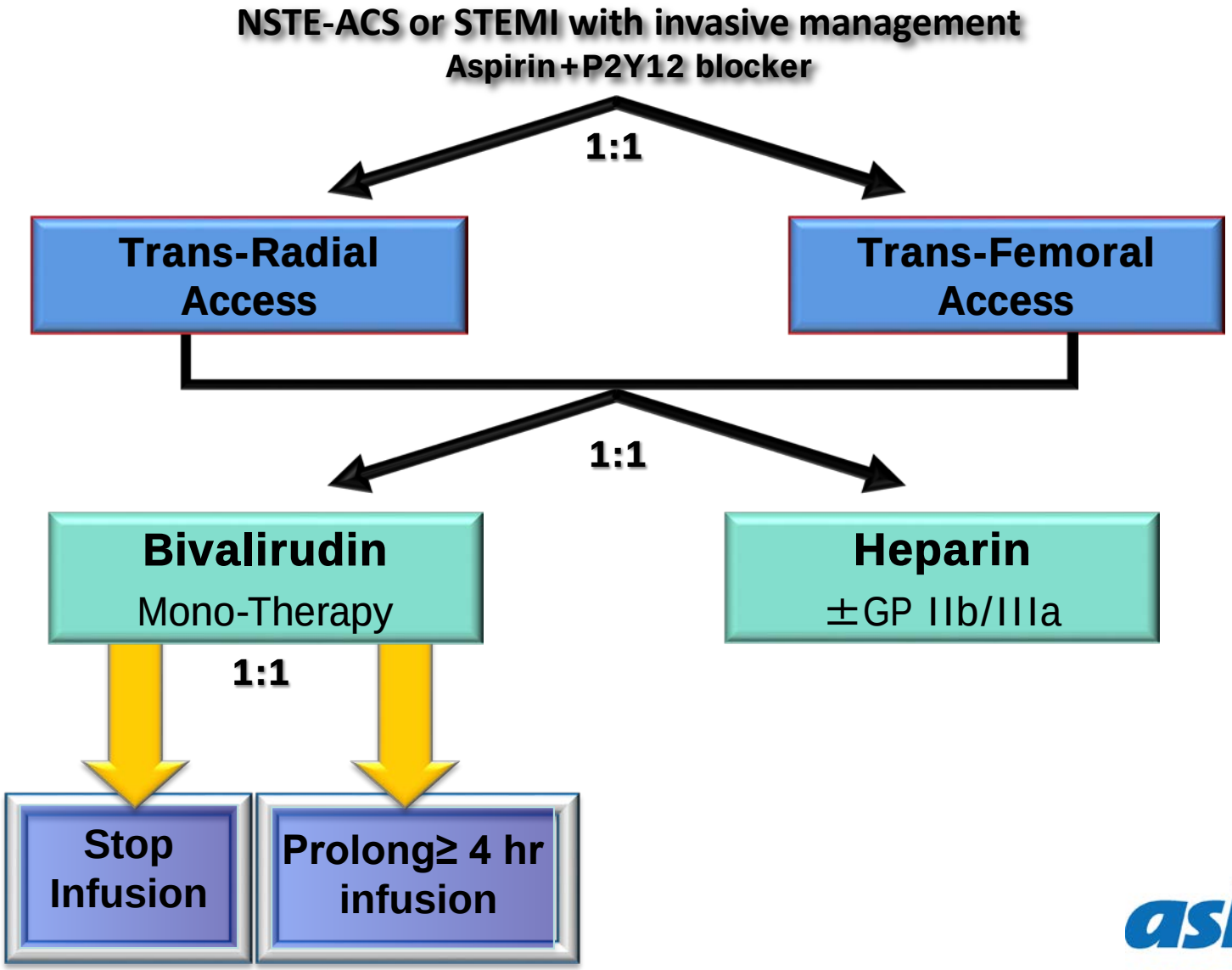
Cavendar MA. Lancet 2014;384:599-606.

Incidence of acute stent thrombosis

Study	Bivalirudin	Heparin (UFH)
HORIZONS-AMI	21/1571 (1.3%)	4/1553 (0.2%)
EUROMAX	12/1089 (1.1%)	2/1109 (0.2%)
HEAT PPCI	20/697 (2.8%)	6/682 (0.8%)
OVERALL	53/3357 (1.5%)	12/3344 (0.3%)

Cavendar MA. Lancet 2014;384:599-606.

MATRIX Trial



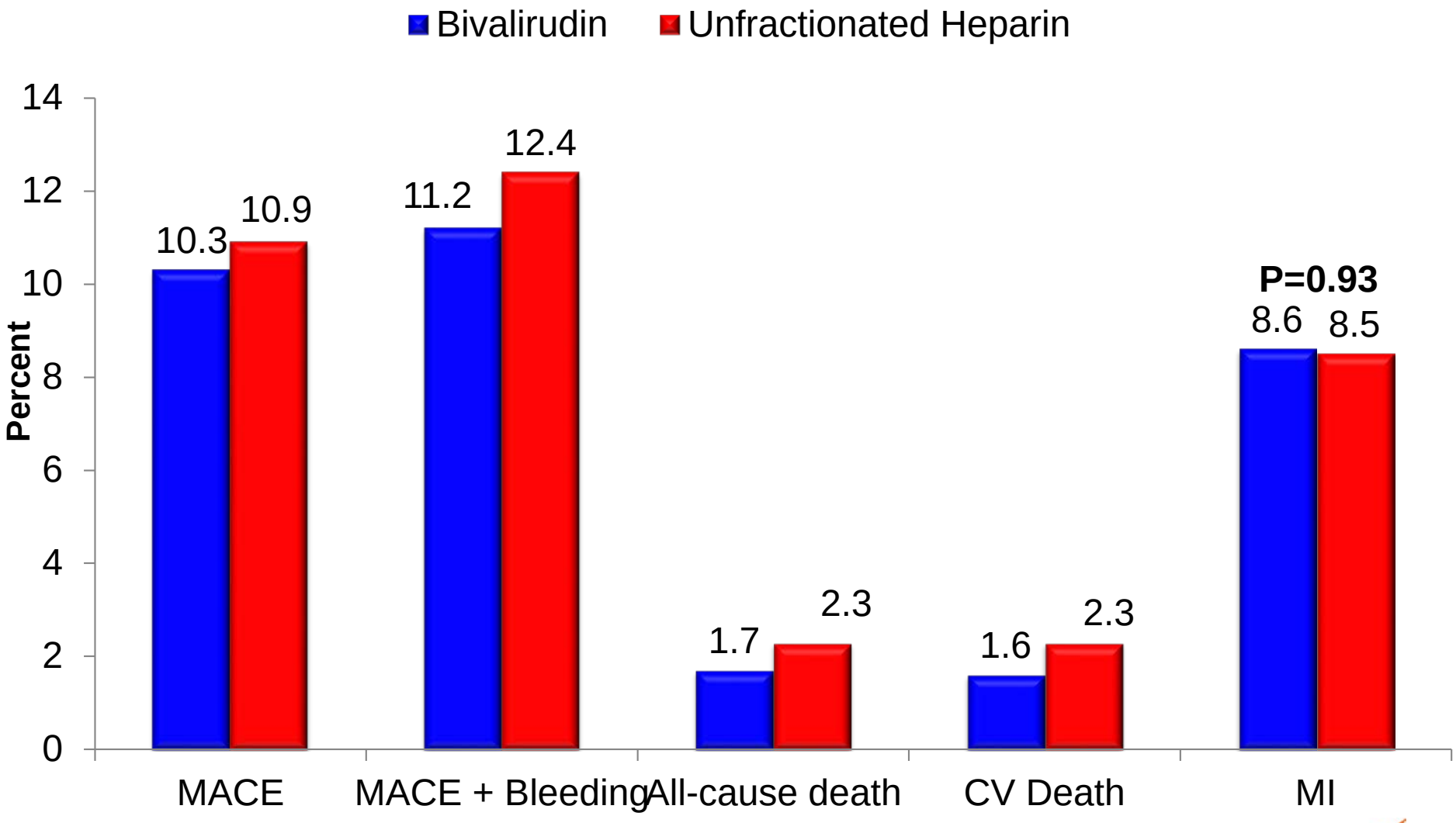
Valgimigli M et al. N Engl J Med 2015;373:997-1009.

Matrix Trial: Co-primary Endpoints

- **Major adverse cardiovascular events (MACE)**
  - **Death from any cause**
  - **Myocardial Infarction (MI)**
  - **Stroke**
- **Net adverse clinical events (NACE)**
  - **Bleeding Academic Research Consortium (BARC) type 3 or 5 bleeding**
  - **MACE**

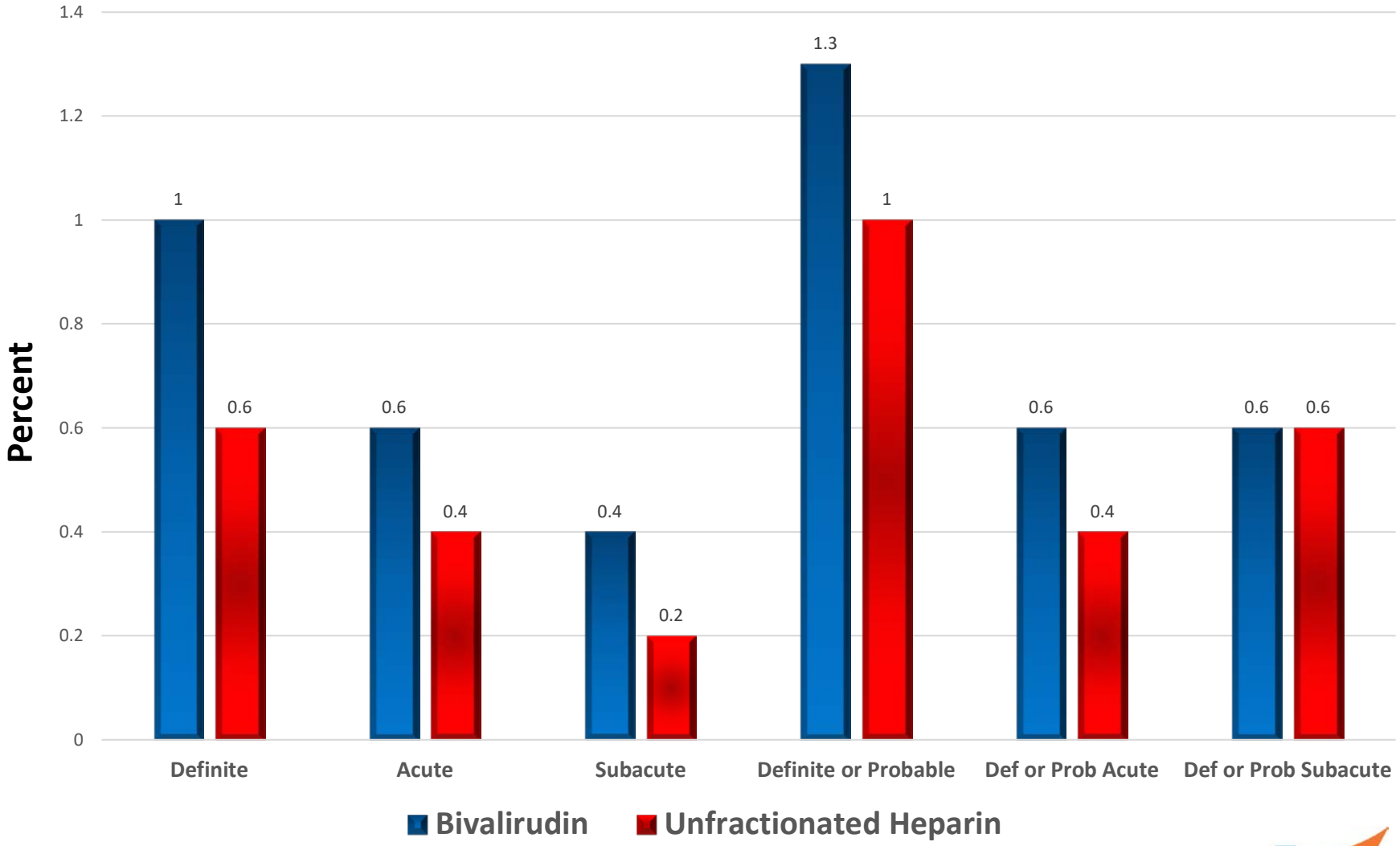
Valgimigli M et al. N Engl J Med 2015;373:997-1009.

Matrix Trial: Primary Endpoint



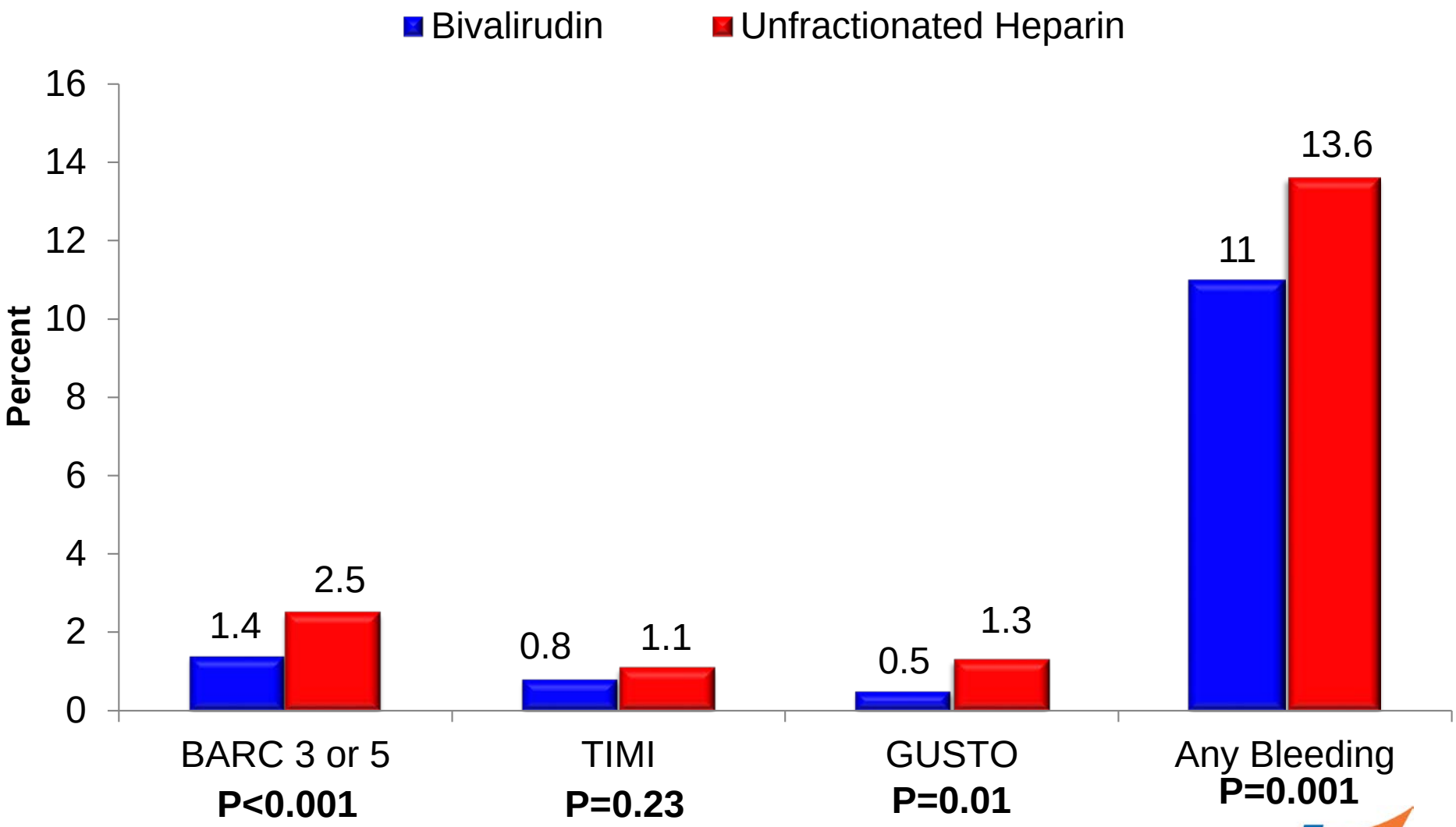
Valgimigli M et al. N Engl J Med 2015;373:997-1009.

Matrix Trial: Stent Thrombosis



Valgimigli M et al. N Engl J Med 2015;373:997-1009.

Matrix Trial: Major Bleeding



Valgimigli M et al. N Engl J Med 2015;373:997-1009.

Case

- AD is a 57 year-old man who presents to the emergency department complaining of 10/10 sharp, crushing chest pain that started 20 minutes ago. An ECG performed reveals ST-segment elevations in Leads II, III and aVF, and he is urgently taken to the cardiac catheterization laboratory for suspected STEMI.
- Past Medical History:
  - Dyslipidemia
  - Impaired Glucose Tolerance

- Serum electrolytes and creatinine are all within normal limits
  - Cardiac enzymes: CK: 310, Troponin T: 2.51

Your poll will show here

1

Install the app from
pollev.com/app

2

Make sure you are in
Slide Show mode

Still not working? Get help at pollev.com/app/help

or

Open poll in your web browser

Key Takeaways

- Compared with Unfractionated Heparin, use of Bivalirudin in STEMI
  - Benefit of ischemic endpoints and mortality benefit
- NSTE-ACS
  - Risks of stent thrombosis probably outweigh any ischemic endpoint benefit
- Overall in ACS and PCI:
  - Probable increase in stent thrombosis
  - Prolonged infusion may help reduce risk of stent thrombosis
  - Reduced major bleeding could result in mortality benefit
  - Further studies are needed

Your poll will show here

1

Install the app from
pollev.com/app

2

Make sure you are in
Slide Show mode

Still not working? Get help at pollev.com/app/help

or

Open poll in your web browser

History of Digoxin

- William Withering was an English botanist, chemist, and physician:
  - First discussed the use if foxglove, digitalis purpurea, for the treatment of dropsy (edema) in 1785
  - Withering has been inappropriately given credit for the development of this treatment

- Mother Hutton was an English botanist, pharmacist, and general practitioner of medicine:
  - Discovered through experimentation that foxglove was useful in treating heart disease, kidney troubles, and dropsy

Ziff OJ, Kotecha D. *Trends Cardiovas Med*. 2016;16:S1050-1738
Silverthrone E, Fulghan, G. *Women Pioneers in Texas Medicine*. Temple, TX: Texas A&M, 1997

Digoxin Pharmacology

- Neurohormonal
  - Augments parasympathetic tone
    - Possibly reducing plasma norepinephrine

- Parasympathetic actions lead to electrophysiological effects
  - Slows conduction and increases the refractory period of the AV node

- Cellular actions leading to hemodynamic effects
  - Inhibits sodium-potassium ATPase, which increases intracellular calcium
    - Calcium is prevented from leaving the cell via the sodium-calcium pump while more calcium is released from the sarcoplasmic reticulum
    - = Positive inotrope (stronger contraction)

Ziff OJ, Kotecha D. *Trends Cardiovas Med*. 2016;16:S1050-1738

Digoxin Serum Concentrations

- Safest serum concentration range: of 0.5 to 0.9 ng/mL
- Wait at least 7 days following initiation or dose adjustment to ensure acurate serum concentrations
- Draw levels 8 – 12 hours following the dose
  - Ensures proper distribution and avoids falsely elevated concentrations
- At risk patient populations
  - Low muscle mass
  - Renal impairment

Yancy CW, et al. *J Am Coll Cardiol.* 2013;62(16):e147-e239.
January CT, et al. J Am Coll Cardiol 2014;64:e1-e76.
Ziff OJ, Kotecha D. *Trends Cardiovas Med*. 2016;16:S1050-1738.

Your poll will show here

1

Install the app from
pollev.com/app

2

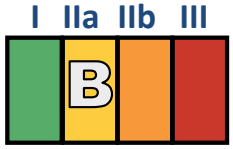
Make sure you are in
Slide Show mode

Still not working? Get help at pollev.com/app/help

or

Open poll in your web browser

Digoxin HF Recommendation



- Digoxin can be beneficial in patients with HFrEF, unless contraindicated, to decrease hospitalizations for HF

Yancy CW, et al. *J Am Coll Cardiol.* 2013;62(16):e147-e239.

Your poll will show here

1

Install the app from
pollev.com/app

2

Make sure you are in
Slide Show mode

Still not working? Get help at pollev.com/app/help

or

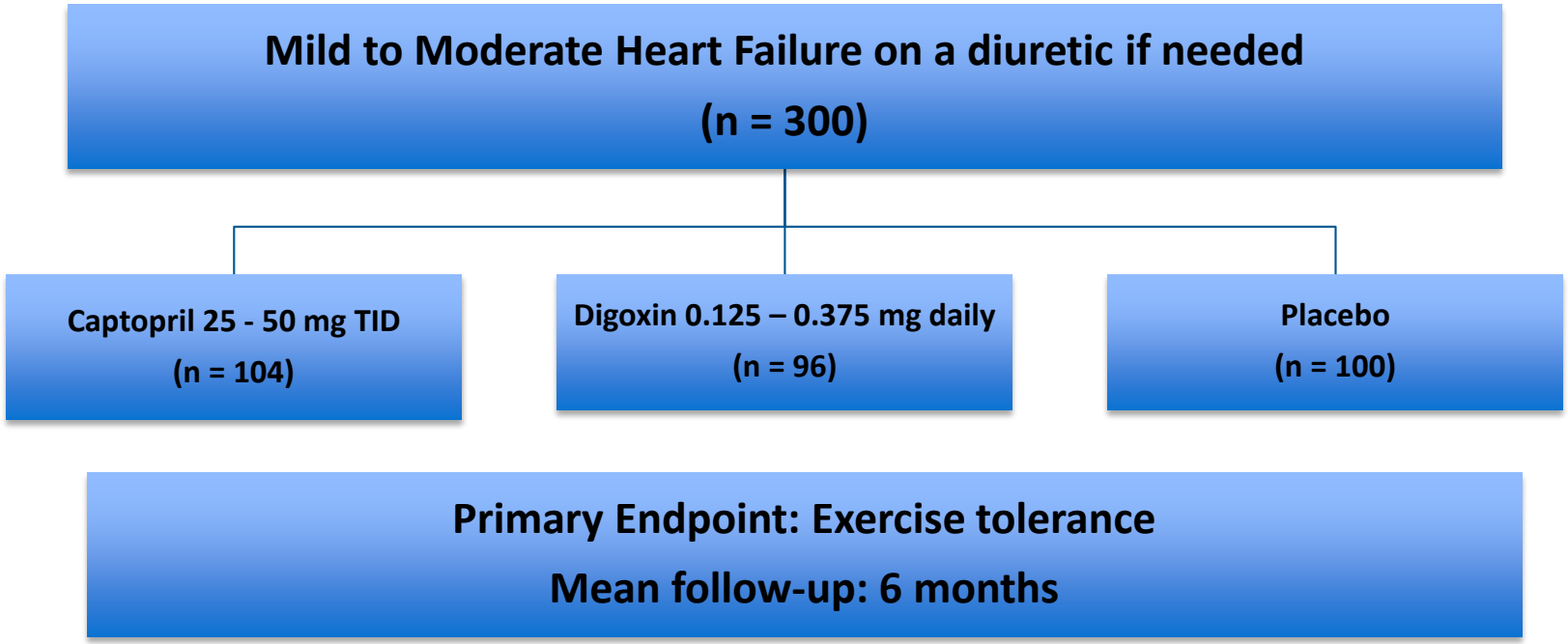
Open poll in your web browser

Specifics from the HF Recommendations

- "Several placebo-controlled trials have shown that treatment with digoxin for 1 to 3 months can improve symptoms, HRQOL, and exercise tolerance in patients with mild to moderate HF. These benefits have been seen regardless of the underlying rhythm (normal sinus rhythm or AF), cause of HF (ischemic or nonischemic cardiomyopathy), or concomitant therapy (with or without ACE inhibitors)."

Yancy CW, et al. *J Am Coll Cardiol.* 2013;62(16):e147-e239.

Captopril-Digoxin Multicenter Research Group



The Captopril-Digoxin Multicenter Research Group. *JAMA*. 1988;259:539-544.

Captopril-Digoxin Multicenter Research Group

- Exercise time compared with placebo:
  - Captopril significantly improved (82s vs 35s)
  - No improvement with digoxin (54s)

- Notable secondary outcomes
  - NYHA Classification compared with placebo
    - Captopril significantly improved (41% vs 22%)
    - No improvement with digoxin (31%)
  - Left ventricular ejection fraction compared to placebo
    - Digoxin significantly improved LVEF (4.4% vs 0.9%)
    - No improvement was seen with captopril (1.8%)

The Captopril-Digoxin Multicenter Research Group. *JAMA*. 1988;259:539-544.

Maintenance of digoxin after an episode of heart failure

- Clinically stable outpatients with HF in sinus rhythm or AF with no history of a heart rate > 120 bpm (n = 46)

- Patients who had been clinically stable for 3 months were given digoxin or placebo
  - After 6 weeks their treatment was crossed over
- Patients completed a questionnaire and were examined by a blinded physician at each visit
  - An unblinded clinician could restart active treatment when indicated
- A third clinician analyzed records
  - 16 patients who deteriorated on placebo were classified as group 1
  - 30 patients who did not were compared as group 2

Dobbs SM, et al. *Br Med J.* 1977;1:749-752.

Maintenance of digoxin after an episode of heart failure

- "Our findings showed the value of maintenance digoxin but cast some doubt on that of long-term diuretics"

Dobbs SM, et al. *Br Med J.* 1977;1:749-752.

Heart Failure in Outpatients: Digoxin vs Placebo

- Clinically stable outpatients with HF on diuretics, but without AF (n = 25)
- Randomized, double-blind, cross-over design of digoxin versus placebo
- Utilized a clinicoradiographic scoring system to determine severity of heart failure
  - 14 patients showed improvement
- Third heart sound was the strongest correlation to digoxin response
- "These data suggest that long-term digoxin therapy is clinically beneficial in patients with heart failure unaccompanied by atrial fibrillation whose heart failure persists despite diuretic therapy and who have a third heart sound"

Lee DC, et al. *N Engl J Med.* 1982;306:699-705.

Controlled Trial of Dig in CHF

- Heart failure patients in sinus rhythm (n = 20)
- Randomized, cross-over design of digoxin versus placebo
  - 7 weeks of digoxin titrated to a level of 1.54 – 2.56 ng/mL
  - 7 weeks matched placebo
- 7 placebo patients required premature termination due to worsening symptoms
- Significant improvements seen in dyspnea, walking, and LVEF
- "Oral digoxin improved quality of life and functional exercise capacity in some patients with CHF in sinus rhythm"

Guyatt GH, et al. *Am J Cardiol* 1988;61:371-375.

Oral Milrinone, Dig, & Their Combination in CHF

- Patients with moderated severe HF in sinus rhythm (n = 230)
- Randomized, double-blind, placebo controlled trial designed to compare the effects of oral milrinone, digoxin, and their combination on exercise capacity over 12 weeks

- "Milrinone significantly increased exercise tolerance and reduced the frequency of worsened heart failure"
- "Milrinone or the combination of milrinone and digoxin offered no advantage over digoxin alone"

DiBianco R, et al. *N Engl J Med.* 1989;320:677-683.

Digoxin Withdrawal Trials

- PROVED (without ACEI)
- Radiance (with ACEI)

PROVED Trial

NYHA Class II or III HF and normal sinus rhythm receiving digoxin and diuretics

(n = 88)

Placebo

(n = 46)

Digoxin titrated to a concentration of 0.9 – 2 ng/mL

(n = 42)

Primary endpoints: 1) treadmill time; 2) distance covered in 6 min; 3) treatment failure; 4) time to treatment failure

Duration: 20 weeks

8 week baseline phase (all on digoxin) followed by a 12 week withdrawal phase

Uretsky BF, et al. *J Am Coll Cardiol.* 1993;22:955-962.

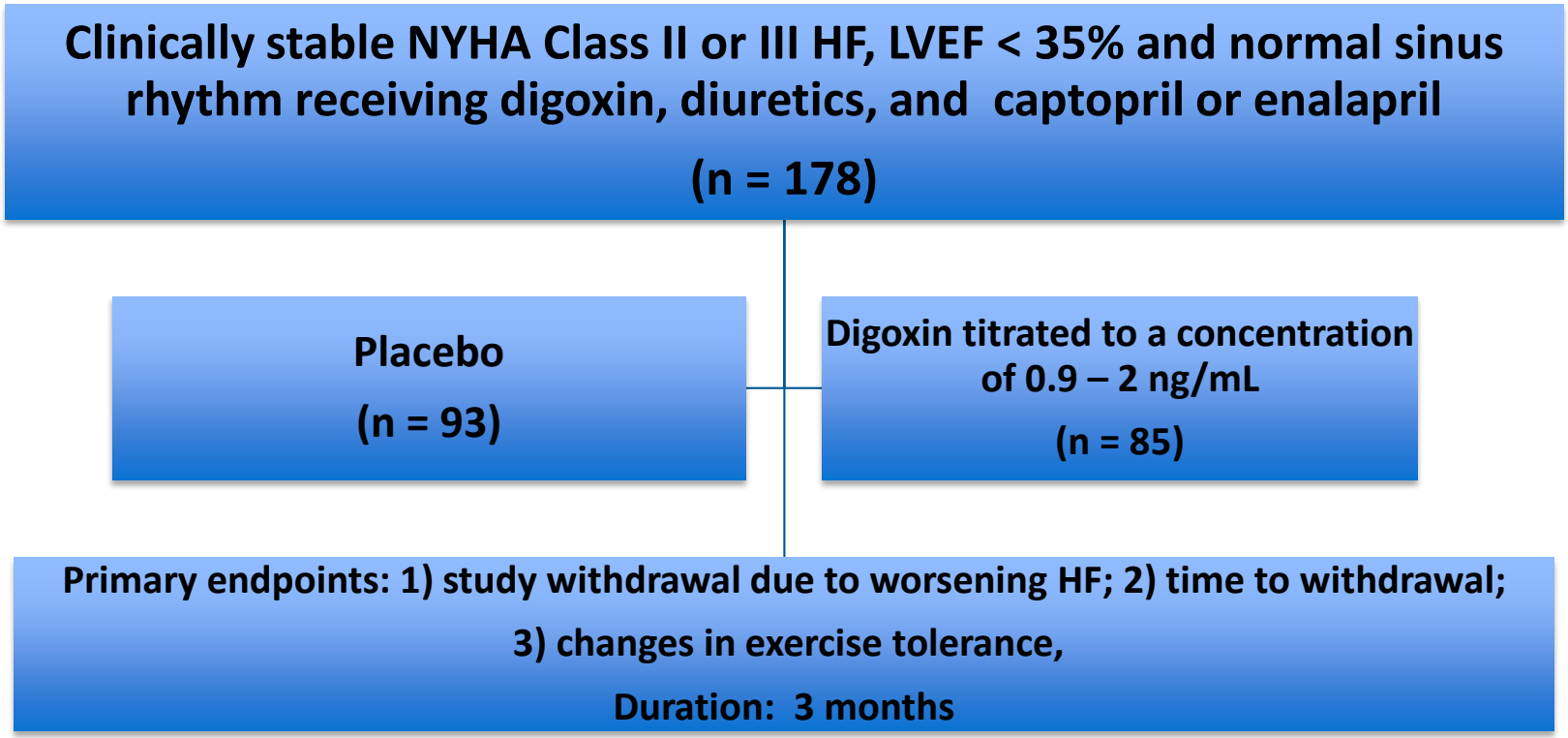
PROVED

Endpoint	Placebo	Digoxin	p value
Exercise duration decrease (seconds)	96	4.5	0.003
Treatment failures*	39%	19%	0.039
Distance covered in 6 mins	Data was not reported		NS
Secondary Endpoints Reported			
LVEF (%)	- 3	+ 2	0.016
Weight (kg)	+ 0.5	- 0.9	0.044
HR (bpm)	+ 11	- 0.2	0.003
BUN (mg/dL)	3	0.2	0.003
Cr (mg/dL)	+ 0.09	- 0.02	0.024

*Increased drug therapy, hospital admission for HF, ED treatment for HF, or death

Uretsky BF, et al. *J Am Coll Cardiol.* 1993;22:955-962.

RADIANCE Trial



Packer M, et al. *N Engl J Med.* 1993;329:1-7

RADIANCE

Endpoint	Placebo	Digoxin	p value
Number of patients with worsening HF leading to study withdrawal	23	4	< 0.001
Changes in exercise tolerance (duration)	46 second difference		0.033
Changes in exercise distance	41 m difference		0.01
Interesting Secondary Endpoints Reported			
LVEF (%)	- 4	- 1	0.001
Weight (kg)	+ 7	0	0.001
HR (bpm)	+ 1	- 1	< 0.001

"These findings indicate that the withdrawal of digoxin carries considerable risk for patients with chronic heart failure and impaired systolic function who have remained clinically stable while receiving digoxin and angiotensin converting enzyme inhibitors."

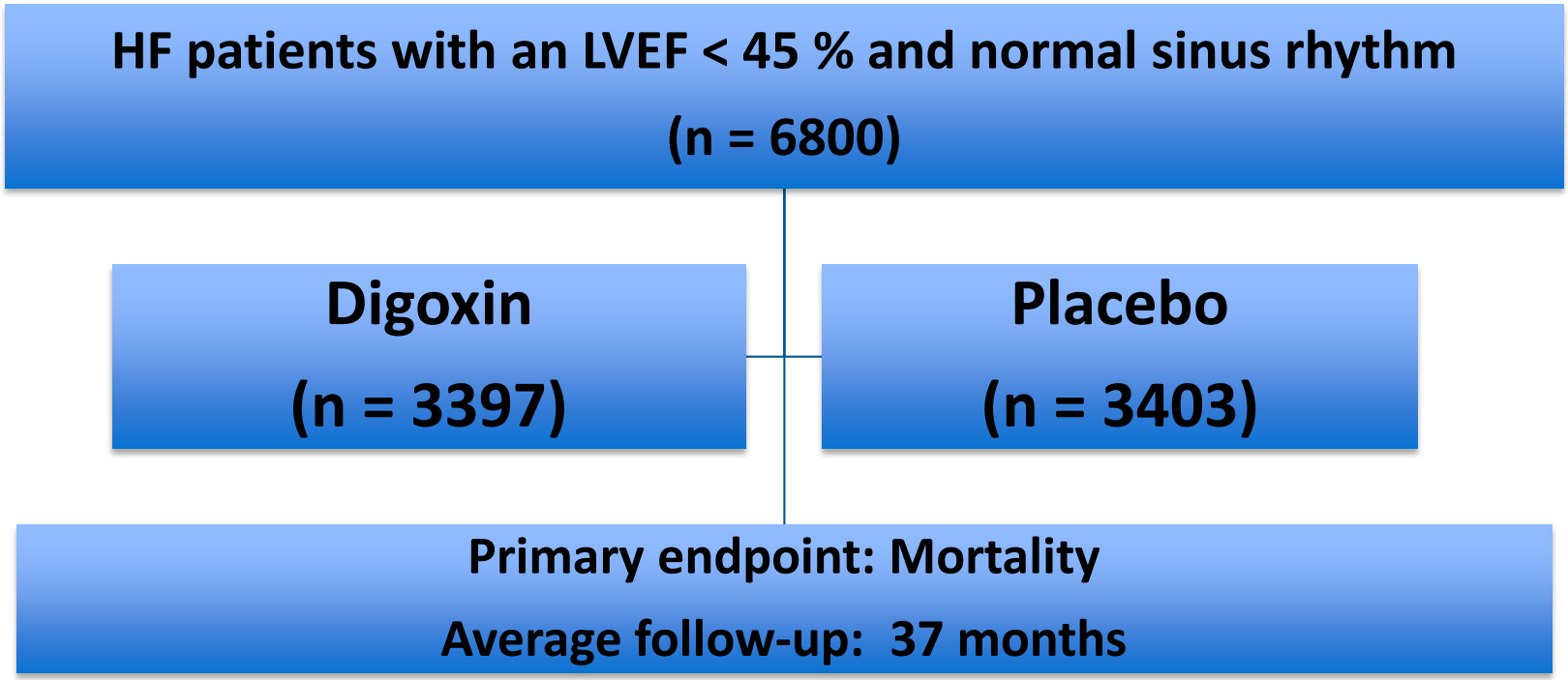
Packer M, et al. *N Engl J Med.* 1993;329:1-7

Specifics from the HF Recommendations

- "In a long-term trial that primarily enrolled patients with NYHA class II or III HF, treatment with digoxin for 2 to 5 years had no effect on mortality but modestly reduced the combined risk of death and hospitalization."

Yancy CW, et al. *J Am Coll Cardiol.* 2013;62(16):e147-e239.

DIG Trial



The Digitalis Investigation Group. *N Engl J Med.* 1997;336:525-533.

DIG Trial

Baseline characteristics	Digoxin	Placebo
Age	63.4	63.5
Ejection fraction	28.6	28.4
NYHA Class II	53.3	54.5
Previous digoxin use*	44.1	44.6
Ischemic cause of HF	70.8	70.4
Concomitant Diuretics	81.2	82.2
Concomitant ACEI	94.1	94.8
Concomitant Nitrates	42.1	43.1
Concomitant other vasodilators**	0.9	1.5
Most common daily dose of digoxin (0.25 mg)	70.6	70

*Patients on digoxin were randomly assigned to digoxin or placebo without a washout period
**clonidine, doxazosin, labetalol, minoxidil, prazosin, and terazosin

The Digitalis Investigation Group. *N Engl J Med.* 1997;336:525-533.

DIG Trial

Endpoint	Digoxin	Placebo	p value
Deaths	1181 (34.8%)	1194 (35.1%)	0.80
Secondary Endpoints			
Deaths from CV causes	1016 (29.9%)	1004 (29.5%)	0.78
Deaths from worsening HF	394 (11.6%)	449 (13.2%)	0.06
Hospitalizations	2184 (64.3%)	2282 (67.1%)	0.006
Hospitalizations for HF	910 (26.8%)	1180 (34.7%)	< 0.001
Hospitalizations for suspected digoxin toxicity	67 (2%)	31 (0.9%)	< 0.001
Combined Endpoints			
Death due to worsening HF or hospitalization for HF	1041 (30.7%)	1291 (37.9%)	< 0.001

The Digitalis Investigation Group. *N Engl J Med.* 1997;336:525-533.

Your poll will show here

1

Install the app from
pollev.com/app

2

Make sure you are in
Slide Show mode

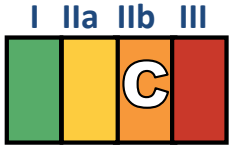
Still not working? Get help at pollev.com/app/help

or

Open poll in your web browser

Digoxin AF Recommendations: Special Populations

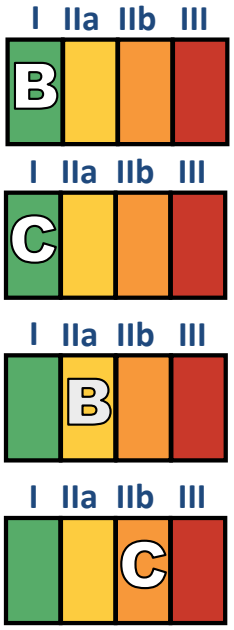
- Wolf Parkinson White and pre-excitation syndromes
  - IV amiodarone, adenosine, **digoxin**, or nondihydropyridine calcium channel antagonists should be avoided



- AF complicating ACS
  - Administration of amiodarone or digoxin may be considered to slow a rapid ventricular response in patients with ACS and AF associated with severe left ventricular dysfunction and HF or hemodynamic instability.

January CT, et al. J Am Coll Cardiol 2014;64:e1-e76.

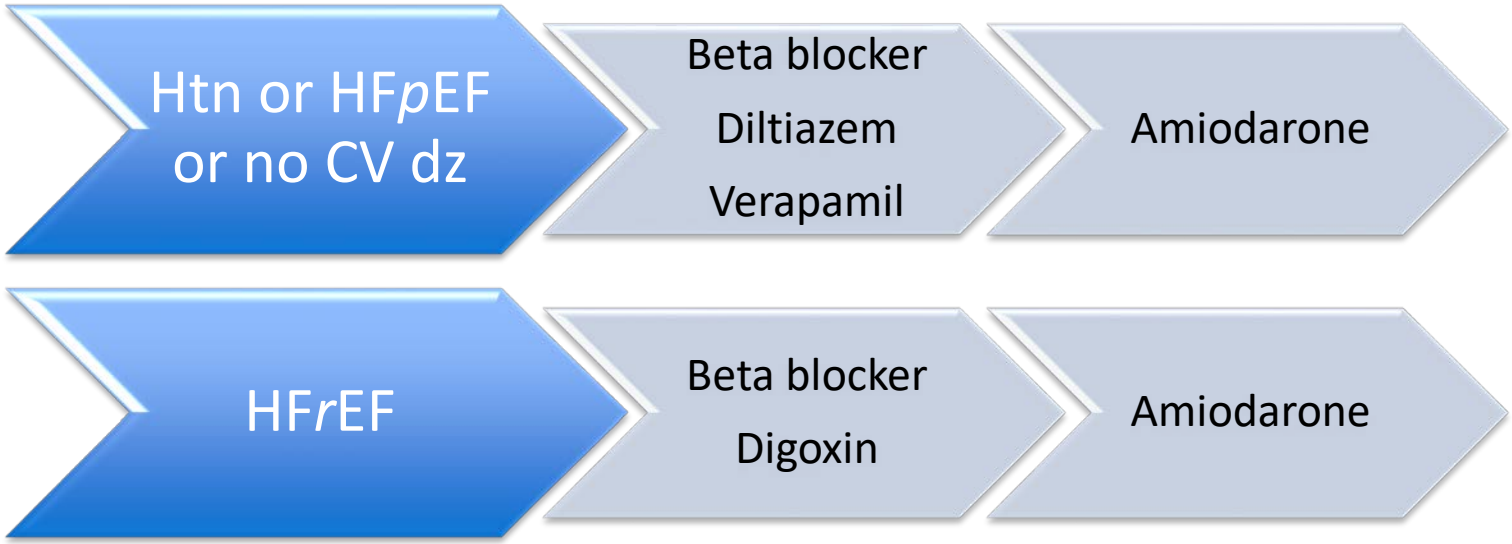
Digoxin AF Recommendations: Special Populations



- Heart Failure
  - In the absence of pre-excitation, IV **digoxin** or amiodarone is recommended to control heart rate acutely
  - Digoxin is effective to control resting heart rate with HFrEF
  - A combination of digoxin and beta blocker (or a nondihydropyridine calcium channel antagonist with HFpEF) is reasonable to control resting and exercise heart rate with AF
  - Amiodarone may be considered when resting and exercise heart rate cannot be controlled with a beta blocker (or a nondihydropyridine calcium channel antagonist with HFpEF) or digoxin, alone or in combination

January CT, et al. J Am Coll Cardiol 2014;64:e1-e76.

Controlling Ventricular Rate in AF



- Digoxin may be combined with a beta blocker or CCB when rate control is not sufficient
- Amiodarone should be reserved for patients who do not respond or are intolerant to beta blockers and CCBs due its side effect profile

January CT, et al. J Am Coll Cardiol 2014;64:e1-e76.

Your poll will show here

1

Install the app from
pollev.com/app

2

Make sure you are in
Slide Show mode

Still not working? Get help at pollev.com/app/help

or

Open poll in your web browser

Recent Systemic Reviews & Meta-Analyses

Digoxin Mortality Data

Increased All-Cause Mortality Associated With Digoxin Therapy in Patients With Atrial Fibrillation: An Updated Meta-Analysis

Population: AF	N = 408,660 from 17 studies
	Observational trials
	AF with HF = 14% increase in all-cause mortality (RR=1.14, 95% CI 1.04 – 1.24)
	AF alone = 36% increase in all-cause mortality (RR=1.36, 95% CI 1.18 – 1.56)
	Significantly higher all-cause mortality in AF patients without HF compared with those with HF (p = 0.04)
	"Given other available options, digoxin should be avoided as a first-line agent for heart rate control in AF patients."

Chen Y, et al. *Medicine.* 2015;94:1-7.

Meta-Analysis of Digoxin Use and Risk of Mortality in Patients With Atrial Fibrillation

Population: AF

N = 318,191 from 11 studies

Observational trials

21% increased risk for mortality (HR = 1.21, 95% CI 1.12 to 1.30)

Increased mortality was seen in patients with or without HF

"The results suggest that digoxin use was associated with a greater risk for mortality in patients with AF, regardless of concomitant heart failure. A well-powered randomized trial is necessary to reveal the true effect of digoxin."

Ouyang AJ, et al. *Am J Cardiol.*2015;115:901-906.

Digoxin Is Associated With Increased All-cause Mortality in Patients With Atrial Fibrillation Regardless of Concomitant Heart Failure: A Meta-analysis.

Population: AF	N = 302,738 from 8 studies
	Observational trials
	Increased all-cause mortality overall (HR = 1.375, 95% CI 1.201-1.574, p = 0.0001)
	AF with HF = increase in all-cause mortality (HR = 1.201, 95% CI 1.074 – 1.344, p = 0.001)
	AF alone = increase in all-cause mortality (HR = 1.172, 95% CI 1.148 – 1.198, p = 0.0001)
	"Digoxin use was associated with significantly increased all-cause mortality in patients with AF regardless of concomitant HF."

Wang ZQ, et al. *J Cardiovasc Pharmacol.* 2015;66:270-275.

Digoxin-associated mortality: a systemic review and meta-analysis of the literature

Population: AF or HF	N = 326,426 from 19 studies
	Observational and randomized controlled trials
	21% increase in all-cause mortality (HR=1.21, 95% CI 1.07 – 1.38, p < 0.01)
	AF alone = 29% increase in all-cause mortality (HR=1.29, 95% CI 1.21 – 1.39, p < 0.01)
	HF alone = 14% increase in all-cause mortality (HR=1.14, 95% CI 1.06-1.22, p < 0.01)
	"Until proper randomized controlled trials are completed, digoxin should be used with great caution, particularly when administered for rate control in AF."

Vamos M, et al. *Eur Heart J.*2015;36:1831-1838.

Safety and efficacy of digoxin: systemic review and meta-analysis of observational and controlled trial data

Population: N = 621,845 from 52 studies

All

Observational and randomized controlled trials analyzed separately

Unadjusted mortality rates from 33 observational trials showed higher mortality rates in the digoxin group (RR = 1.76; 95% CI 1.57 - 1.97; P<0.001)

Adjusted mortality data from 22 observational trials showed higher rates of death in the digoxin group (RR = 1.61, 95% CI 1.31 to 1.97, p <0.001; hazard ratio 1.17, 1.07 to 1.29, p =0.001)

In 7 HF RCTs there was no difference between digoxin mortality and placebo (RR 0.99, 95% CI 0.93 - 1.05; p = 0.75)

"Digoxin use has a neutral effect on mortality in randomized trials and reduces hospital admissions. Regardless of statistical analysis, prescription biases limit the value of observational data. "

Ziff OJ, et al. *Br Med J.*2015;351:h4451.

C.A.M. Cardiology: The Digoxin Story

Future studies: 2019?

- Digitoxin to Improve Outcomes in Patients with Advanced Systolic Heart Failure (DIGIT-HF)
  - Digitoxin versus placebo in HF*r*EF with or without AF
    - NYHA III-IV HF, LVEF < 40%
    - NYHA II HF, LVEF < 30%
  - Primary outcome: composite of overall mortality and hospitalization for worsening HF

- Rate control Therapy Evaluation in Atrial Fibrillation (RATE-AF)
  - Digoxin versus beta-blockers for first line rate control in permanent AF patients NYHA Class I or II HF.
  - Primary outcome: patient-reported QOL

Ziff OJ, Kotecha D. *Trends Cardiovas Med*. 2016;16:S1050-1738

Your poll will show here

1

Install the app from
pollev.com/app

2

Make sure you are in
Slide Show mode

Still not working? Get help at pollev.com/app/help

or

Open poll in your web browser

Your poll will show here

1

Install the app from
pollev.com/app

2

Make sure you are in
Slide Show mode

Still not working? Get help at pollev.com/app/help

or

Open poll in your web browser

Key Takeaways

- Key Takeaway #1
  - The recommendations for the use of digoxin in HF*r*EF are largely based on the results of one RCT (DIG) and two digoxin withdrawal trials (PROVED & RADIANCE)
- Key Takeaway #2
  - There are no randomized control trials that support the use of digoxin in atrial fibrillation. However, there are several meta-analysis that raise mortality concerns when digoxin is used in this population
- Key Takeaway #3
  - More RCTs are needed to determine the safety of digoxin use in patients with HF and/or AF

NSAID Case

- GB is a 64 year-old male who recently presented to the hospital with NSTE-ACS. His hospital course was unremarkable until 1 day prior to discharge when he suddenly felt chest pain that was different from when he presented with NSTE-ACS. He is diagnosed with pericarditis and the team consults you for appropriate pharmacotherapy. The team would like to use an NSAID to treat GB.
- Past Medical History:
  - Hypertension
  - Hyperlipidemia
  - CAD, s/p MI
- Serum Creatinine: 0.9 mg/dL, all other laboratory values are within normal limits

Your poll will show here

1

Install the app from
pollev.com/app

2

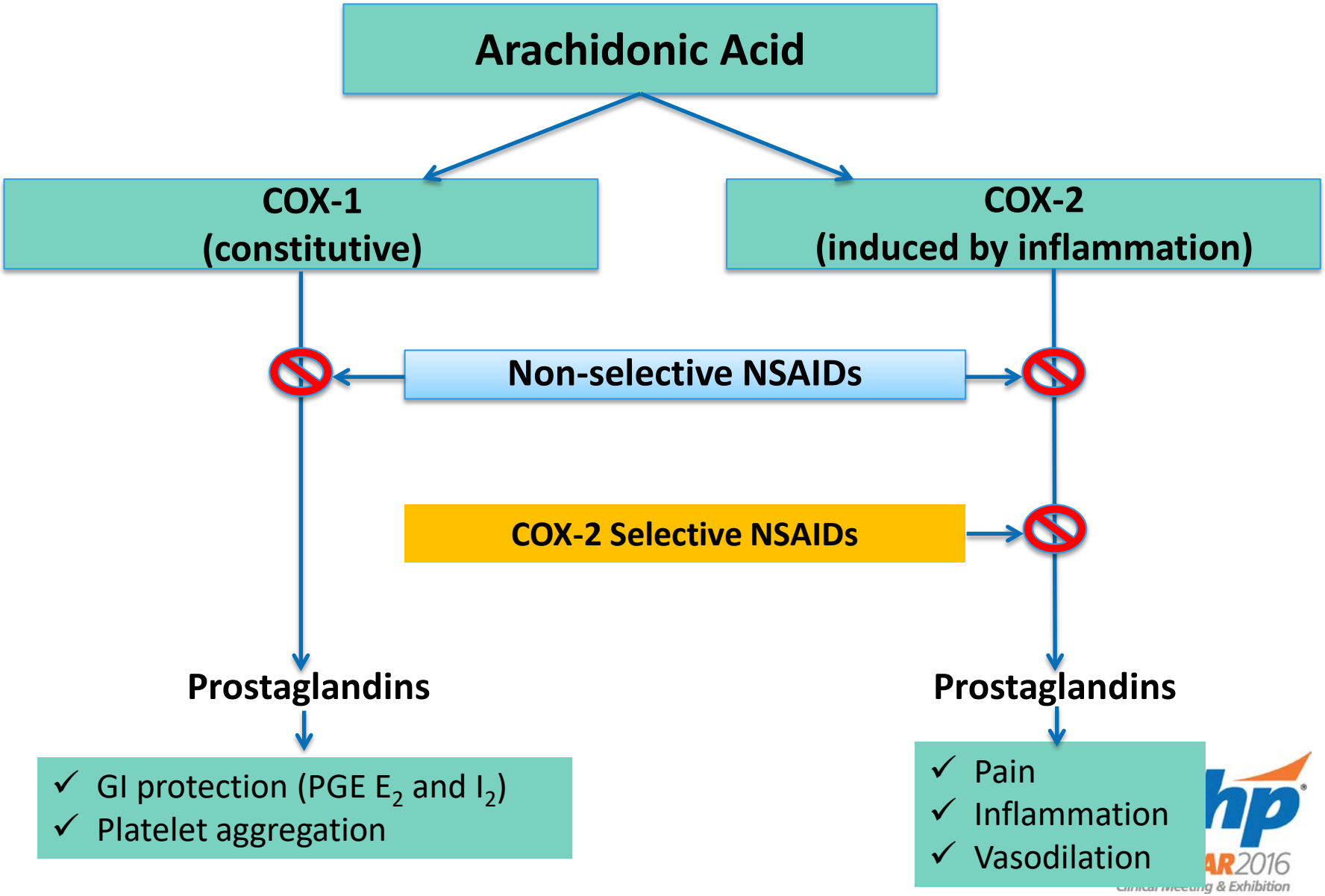
Make sure you are in
Slide Show mode

Still not working? Get help at pollev.com/app/help

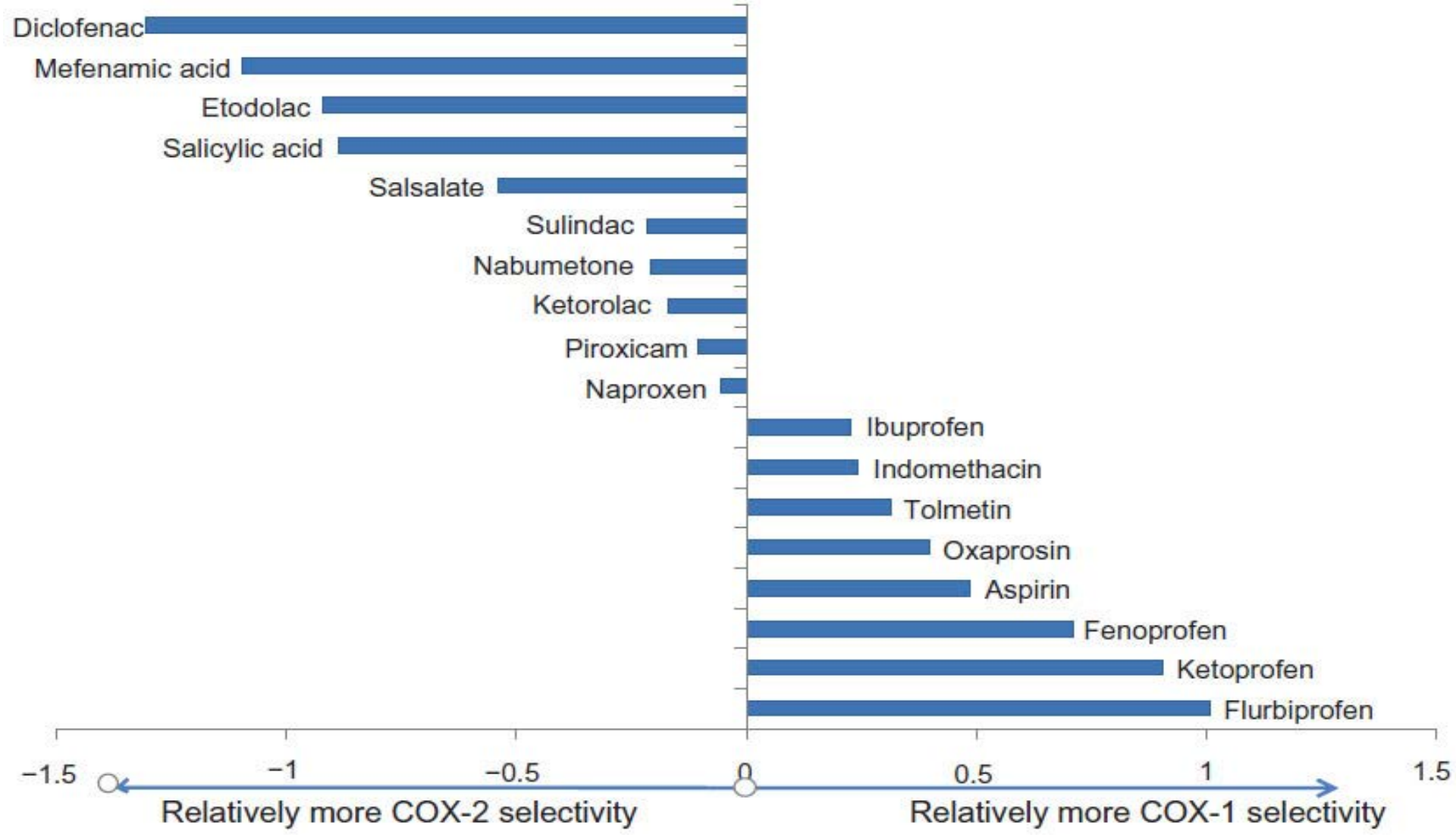
or

Open poll in your web browser

NSAIDs inhibit COX enzymes



NSAIDs inhibit COX enzymes



Park K et al. Vascular health and risk management 2014;10:25-32

2014 ACC/AHA Guidelines: NSAIDs

Recommendations	COR	LOE
Before hospital discharge, the patient's need for treatment of chronic musculoskeletal discomfort should be assessed, and a stepped-care approach should be used for selection of treatments. Pain treatment before consideration of NSAIDs should begin with acetaminophen, nonacetylated salicylates, tramadol, or small doses of narcotics if these medications are not adequate.	I	C
It is reasonable to use nonselective NSAIDs, **such as naproxen**, if initial therapy with acetaminophen, nonacetylated salicylates, tramadol, or small doses of narcotics is insufficient.	IIa	C
NSAIDs with increasing degrees of relative cyclooxygenase-2 selectivity should not be administered to patients with NSTE-ACS and chronic musculoskeletal discomfort when therapy with acetaminophen, nonacetylated salicylates, tramadol, small doses of narcotics, or nonselective NSAIDs provide acceptable pain relief.	III: Harm	B

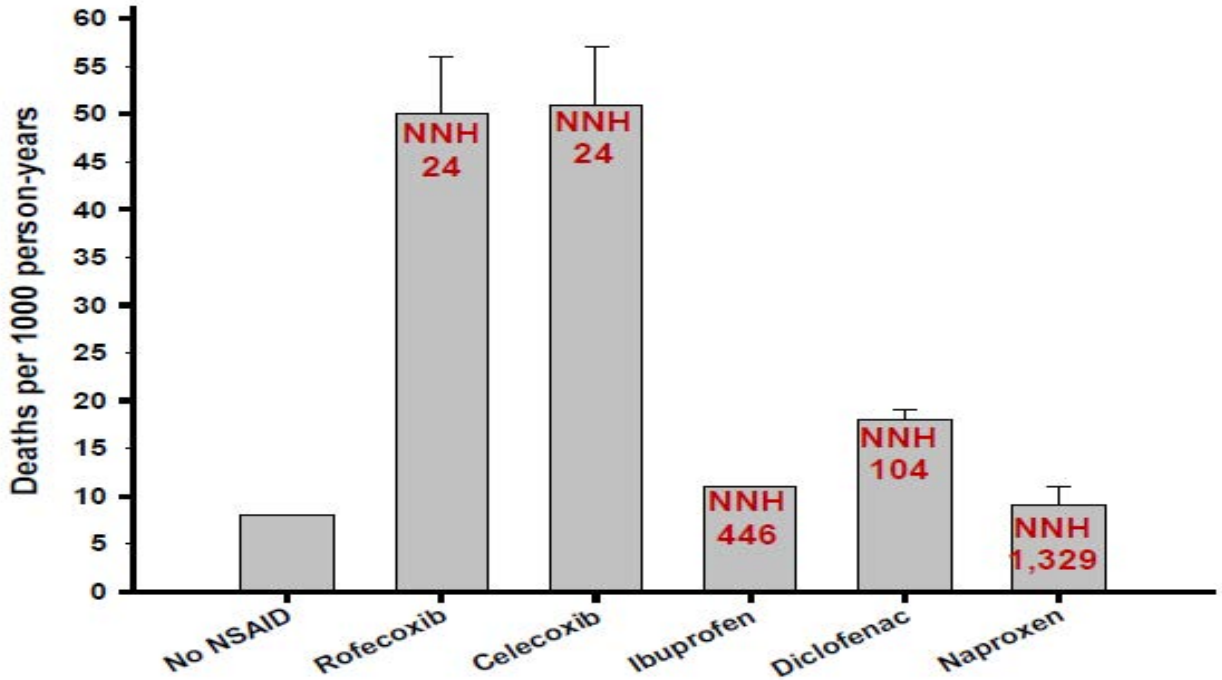
Amsterdam EA et al. J Am Coll Cardiol. 2014; 64:2645-2687.

NSAIDs and Cardiovascular Risk

- All NSAIDs appear to increase risk for:
  - MI
  - Heart Failure
  - Gastrointestinal Bleeding

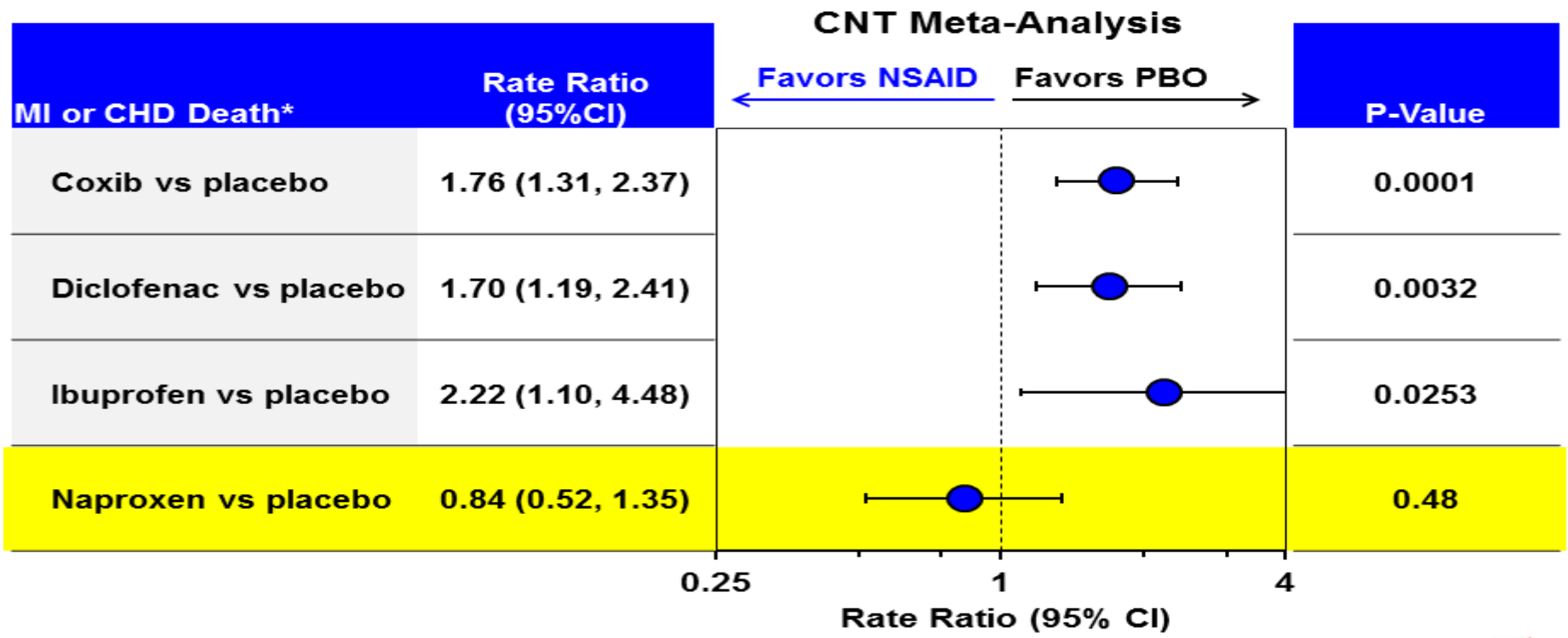
- Are all NSAIDs equal in terms of risk?

NSAIDs and risk of MI/Death



Fosbol EL et al. Clin Pharmacol Ther 2009;85:190-7

Type of NSAID: Death/MI events



CNT Collaboration. Lancet 2013;382:769-79.

NSAIDs: Does Dose Matter - Death

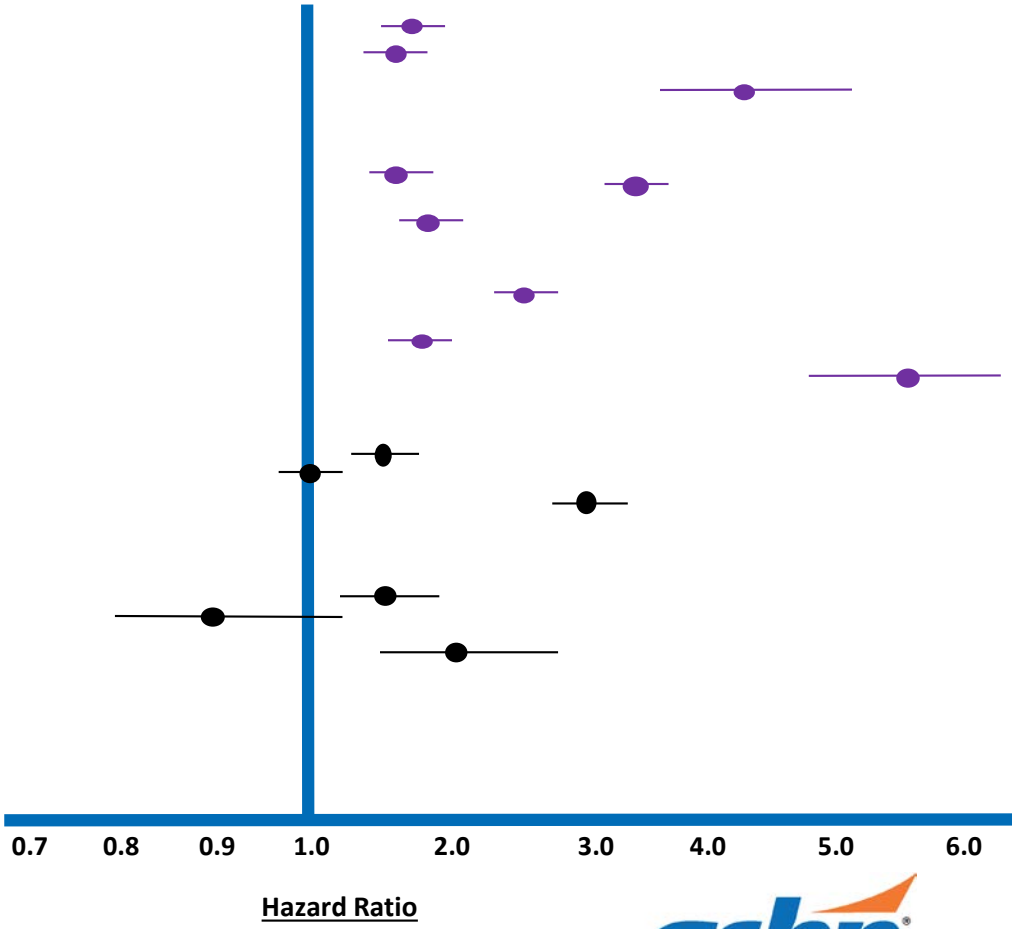
Rofecoxib any dose
≤ 25mg/day
≥ 25 mg/day

Celecoxib any dose
≤ 200 mg/day
≥ 200 mg/day

Diclofenac any dose
≤ 100 mg/day
≥ 100 mg/day

Ibuprofen any dose
≤ 1200 mg/day
≥ 1200 mg/day

Naproxen any dose
≤ 500 mg/day
≥ 500 mg/day



Gislason GH et al. Arch Intern Med 2009;169:141-9.

NSAIDs: Does Dose Matter - MI

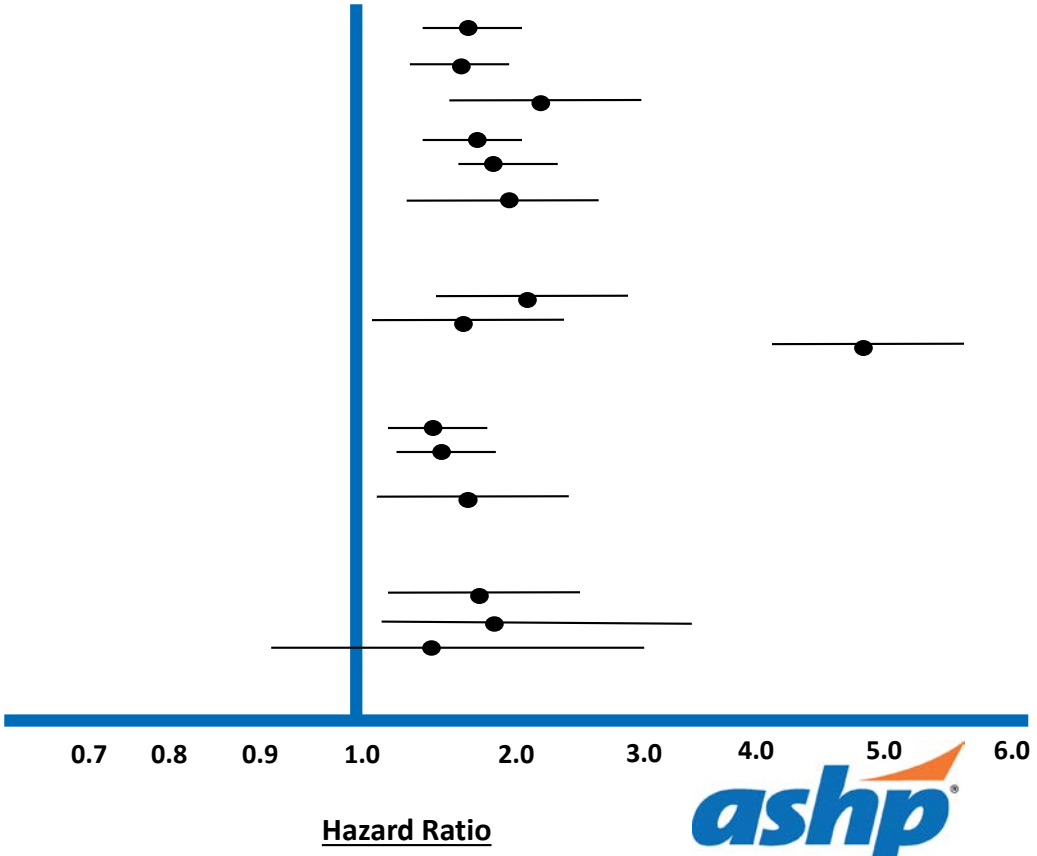
Rofecoxib any dose
≤ 25mg/day
≥ 25 mg/day

Celecoxib any dose
≤ 200 mg/day
≥ 200 mg/day

Diclofenac any dose
≤ 100 mg/day
≥ 100 mg/day

Ibuprofen any dose
≤ 1200 mg/day
≥ 1200 mg/day

Naproxen any dose
≤ 500 mg/day
≥ 500 mg/day



Gislason GH et al. Arch Intern Med 2009;169:141-9.

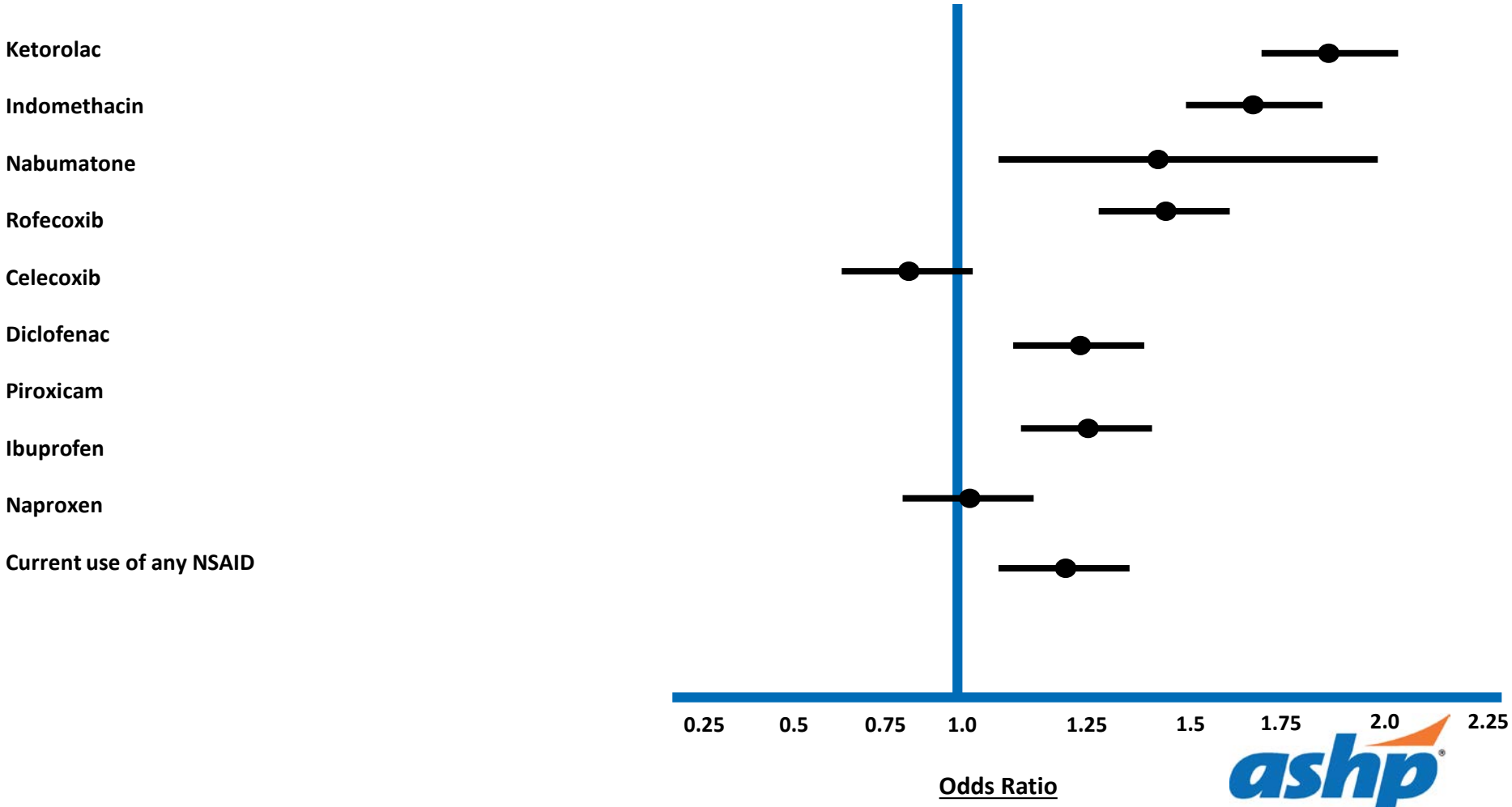
NSAIDs and Heart Failure

- Nested case control study of patients in 4 countries
  - Netherlands, Italy, Germany, United Kingdom
- Matched 92,163 patients admitted to the hospital for HF with 8,246,403 controls

- Main outcome measure:
  - Association between HF hospitalization and NSAID use

Arfe A et al. BMJ 2016;354:i4857 (published September 28, 2016)

NSAIDs and HF Risk: Current NSAID Users



Arfe A et al. BMJ 2016;354:i4857 (published September 28, 2016)

NSAIDs and HF Risk: Does NSAID Dose Matter?

NSAID and Dose Type	Odds Ratio (95% CI)
Celecoxib	
Low	1.1 (0.7 – 1.6)
Moderate	1.0 (0.9 – 1.1)
High	1.5 (0.7-3.1)
Ibuprofen	
Low	1.1 (0.9 – 1.3)
Moderate	1.1 (1.0 – 1.3)
High	0.8 (0.6 – 1.1)
Naproxen	
Low	1.1 (0.6 – 2.0)
Moderate	1.2 (0.9 – 1.5)
High	1.3 (1.0 – 1.8)
Indomethacin	
Low	1.4 (0.7 – 2.8)
Moderate	1.7 (1.2 – 2.5)
High	1.7 (1.1 – 2.7)

NSAID Case

- GB is a 64 year-old male who recently presented to the hospital with NSTE-ACS. His hospital course was unremarkable until 1 day prior to discharge when he suddenly felt chest pain that was different from when he presented with NSTE-ACS. He is diagnosed with pericarditis and the team consults you for appropriate pharmacotherapy. The team would like to use an NSAID to treat GB.
- Past Medical History:
  - Hypertension
  - Hyperlipidemia
  - CAD, s/p MI
- Serum Creatinine: 0.9 mg/dL, all other laboratory values are within normal limits

Your poll will show here

1

Install the app from
pollev.com/app

2

Make sure you are in
Slide Show mode

Still not working? Get help at pollev.com/app/help

or

Open poll in your web browser

Key Takeaways

- NSAID use in patients with cardiovascular disease
  - Increases risk for:
    - Myocardial Infarction
    - Heart Failure
    - Cardiovascular death
- Impact of NSAID doses is not consistent:
  - Naproxen, Ibuprofen = Maybe
  - Indomethacin = Yes
- Risk is different for each NSAID
  - Highest with: Rofecoxib, Indomethacin
  - Lowest with: Naproxen, Ibuprofen, Celecoxib
- While NSAID use is unavoidable
  - Try to limit duration
  - Limit doses to lowest effective