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Patient Assessments in Heart Failure: New Opportunities for Pharmacists

Disclosure

The program chair and presenters for this continuing education activity have reported no relevant financial relationships, except:

- **Benjamin Van Tassell** - Novartis: Grant/Research Support

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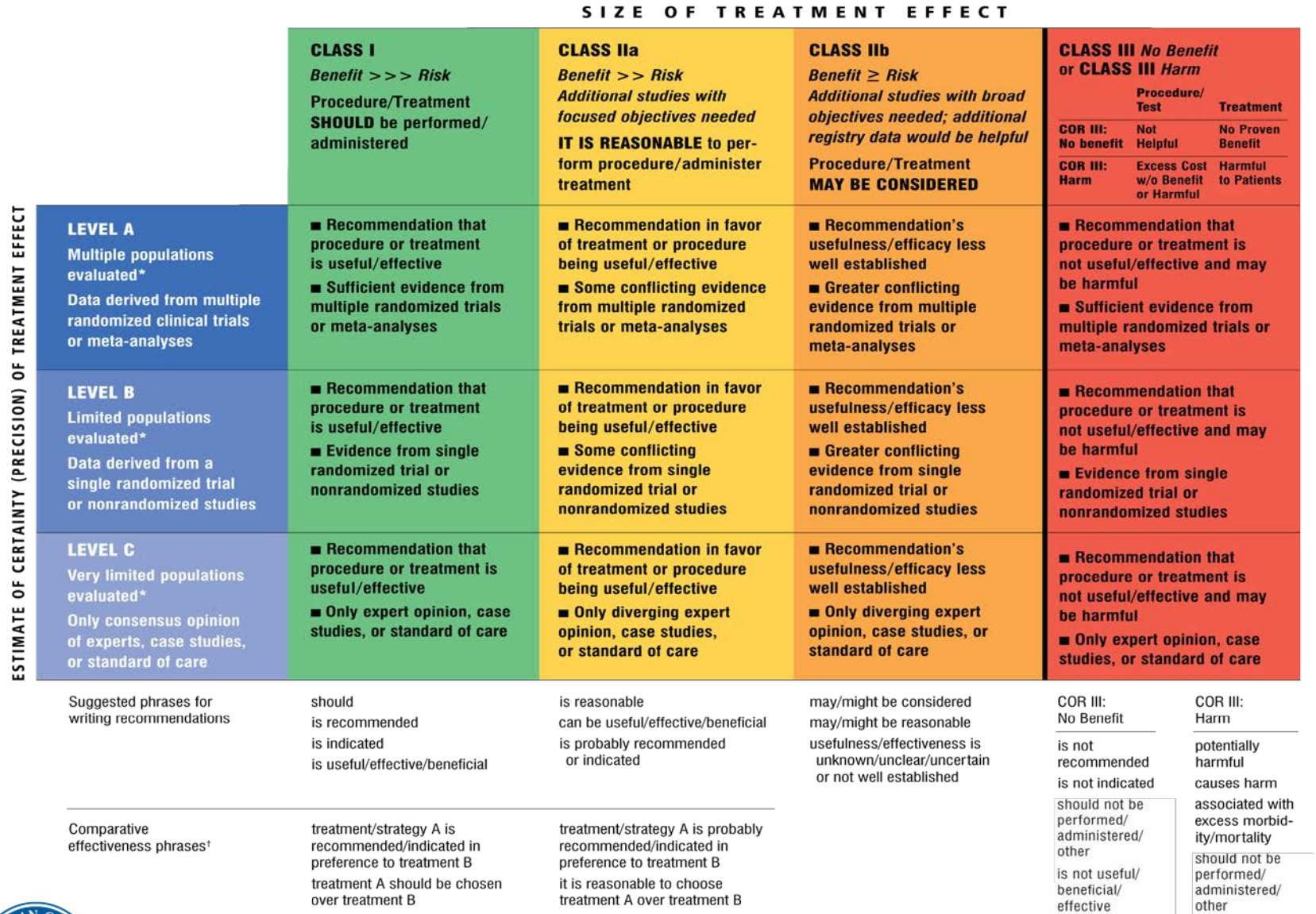
Expanding the Heart Failure Toolbox: Patient Assessments

Barry E. Bleske, Pharm. D, FCCP, Department Chair and Professor, Pharmacy Practice and Administrative Sciences, University of New Mexico, College or Pharmacy

Initial and Serial Evaluation of the HF Patient - HF Guidelines

Classification of Recommendations and Levels of Evidence



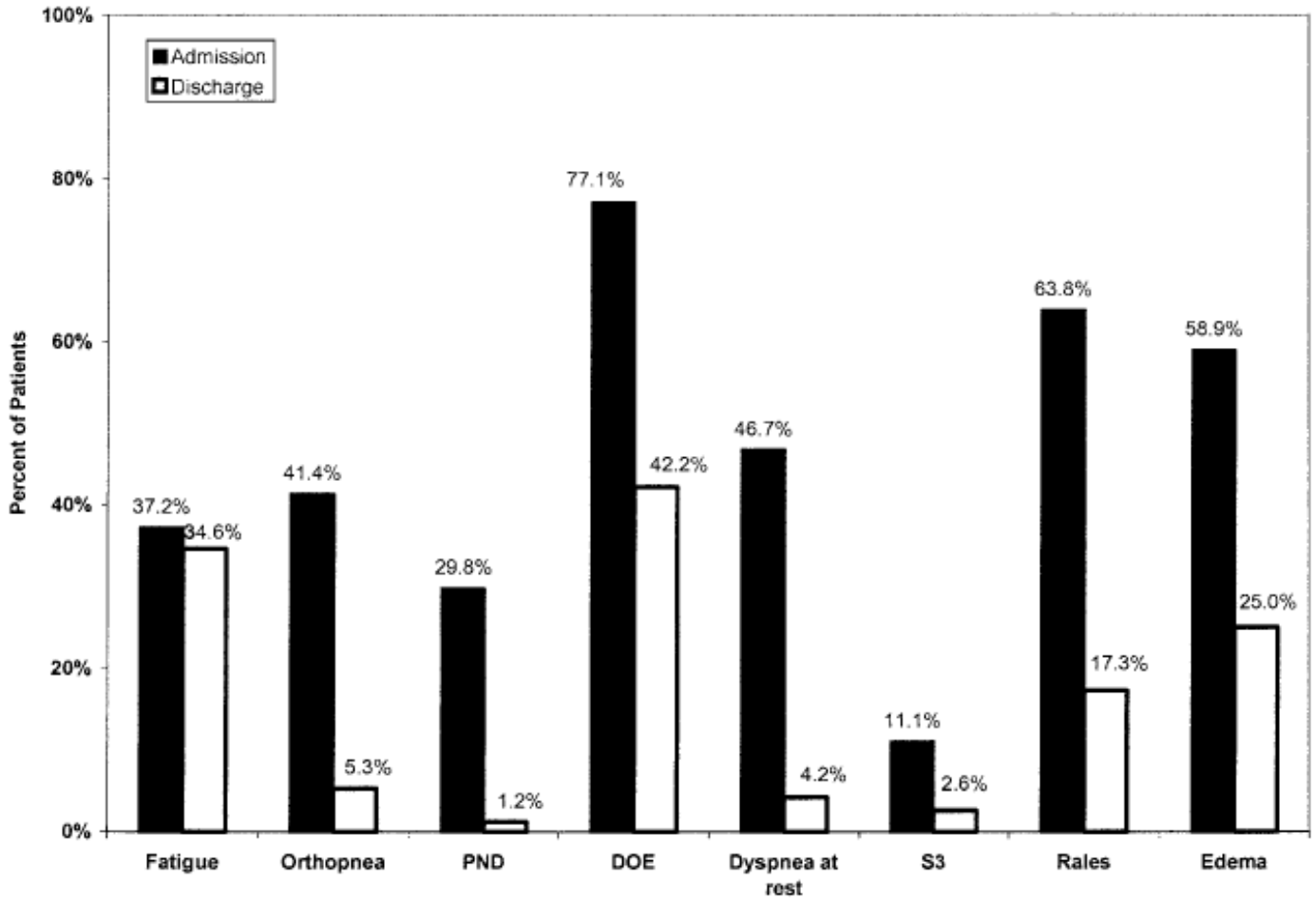
History and Physical Examination

A thorough history and physical examination should be obtained/performed in patients presenting with HF to identify cardiac and noncardiac disorders or behaviors that might cause or accelerate the development or progression of HF.

Volume status and vital signs should be assessed at each patient encounter. This includes serial assessment of weight, as well as estimates of jugular venous pressure and the presence of peripheral edema or orthopnea.

Physical Assessment - What to Assess?

- Impact HF Registry (JACC 2005;11:200-205)



Physical Assessment - What to Assess?

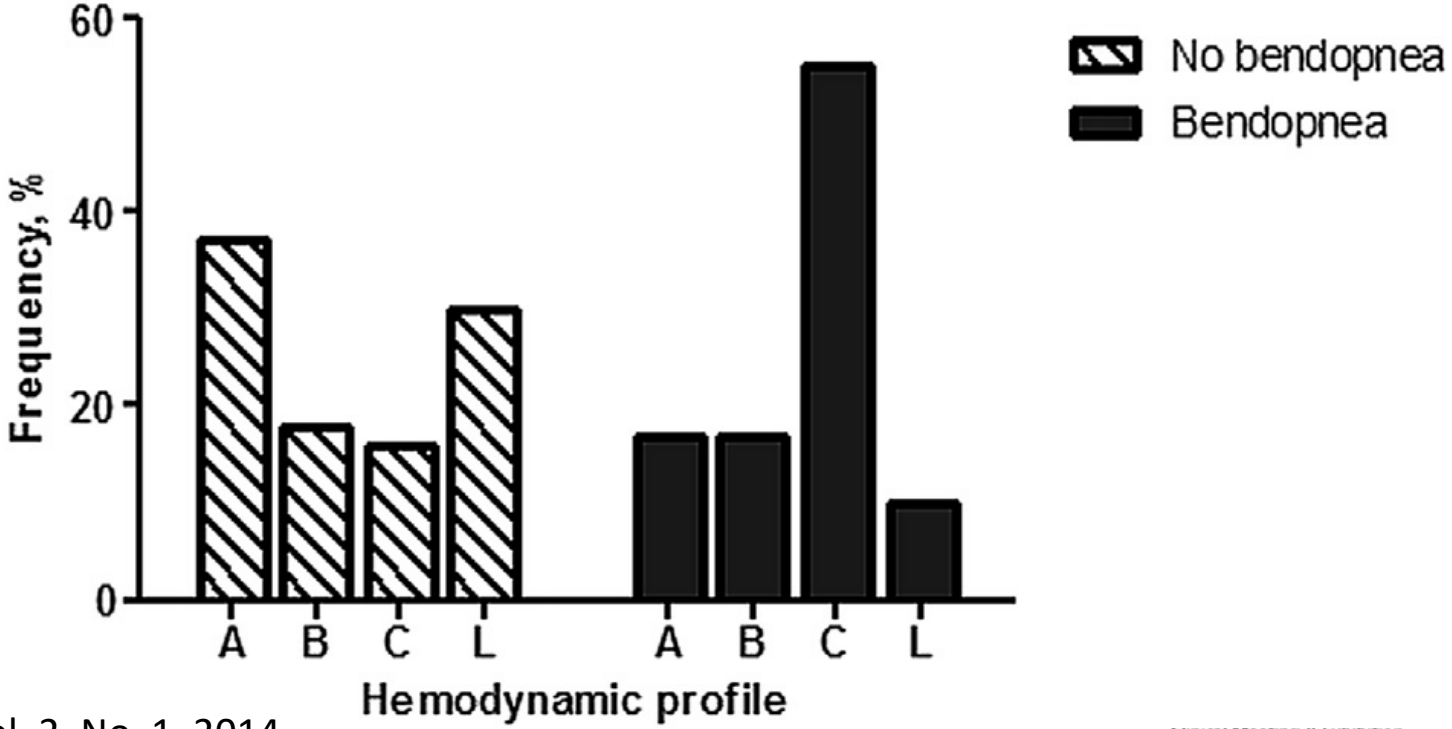
- ADHERE Registry (>100,000 patients)
  - Edema – 69%
  - Rales – 69%
  - Dyspnea at rest – 34%
- OPTIMIZE-HF (~48,000 patients)
  - Edema – 62%
  - Rales – 63%
  - Dyspnea at rest – 44%
  - Dyspnea on exertion – 63%

JACC Vol. 50, No. 8, 2007

Arch Intern Med. 2008;168(8):847-854

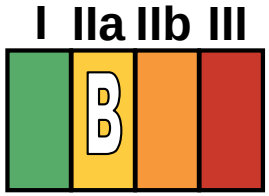
Bendopnea-New HF Symptom? (Add to Tool Box?)

- Dyspnea when bending forward with symptom onset within 30 seconds of bending.
- Appears to be related to elevated filling pressure (PCWP, RAP, PAP) (C profile = Cold and Wet – Subset IV)



JACC: Heart Failure Vol. 2, No. 1, 2014

Risk Scoring



Validated multivariable risk scores can be useful to estimate subsequent risk of mortality in ambulatory or hospitalized patients with HF.

Risk Scores to Predict Outcomes in HF (Add to Toolbox?)

Risk Score	Reference (from full-text guideline)/Link
Seattle Heart Failure Model (Mobile App)	http://SeattleHeartFailureModel.org
Heart Failure Survival Score	http://handheld.softpedia.com/get/Health/Calculator/HFSS-Calc-37354.shtml
Readmission Risk Score for Heart Failure (Mobile App)	http://www.readmissionscore.org/heart_failure.php
Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC)	http://www.heartfailurerisk.org/

Many other "predictors" available – all have limitations and provides estimates only

Diagnostic Tests

Initial laboratory evaluation of patients presenting with HF should include complete blood count, urinalysis, serum electrolytes (including calcium and magnesium), blood urea nitrogen, serum creatinine, glucose, fasting lipid profile, liver function tests, and thyroid-stimulating hormone.

Serial monitoring, when indicated, should include serum electrolytes and renal function.

Possible Markers for Congestion (Follow over time)

- ↓ Sodium levels
- ↓ Hemoglobin (also evaluate anemia!)
- ↓ Hematocrit
  - Hemoconcentration a sign of decongestion?
  - Limited – anemia, volume shifts, nutritional status
- ↓ Albumin
- ↑ LFT's
- ↑ Serum creatinine
- ↑ Brain Natriuretic Peptide (or pro-B-type naturetic peptide)

Circulation. 2010;122:265-272.
J Cardiac Fail 2016;22:680-688

Drug Assessment: Diuretics, RAAS blockers, MRA, Beta-Blockers, Digoxin, H&I

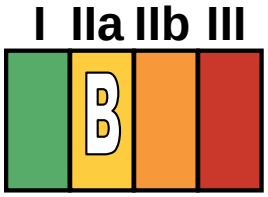
- Diuretic response (ask the patient)
- Weight (Diet)
- K+, Mg+, Na+
- Serum Creatinine, blood urea nitrogen
- Digoxin levels (≤ 0.8 ng/mL)
- ECG (heart rate, AV conduction, QTc-interval)
- Blood pressure
- Headache, dizziness
- PHYSICAL ACTIVITY

Ambulatory/Outpatient

In ambulatory patients with dyspnea, measurement of BNP or N-terminal pro-B-type natriuretic peptide (NT-proBNP) is useful to support clinical decision making regarding the diagnosis of HF, especially in the setting of clinical uncertainty.

Measurement of BNP or NT-proBNP is useful for establishing prognosis or disease severity in chronic HF.

Ambulatory/Outpatient (cont.)



BNP- or NT-proBNP guided HF therapy can be useful to achieve optimal dosing of GDMT in select clinically euvolemic patients followed in a well-structured HF disease management program. (Guide – HF?)

The usefulness of serial measurement of BNP or NT-proBNP to reduce hospitalization or mortality in patients with HF is not well established. (What is your patient baseline BNP, may be helpful?)

Measurement of other clinically available tests such as biomarkers of myocardial injury or fibrosis may be considered for additive risk stratification in patients with chronic HF.

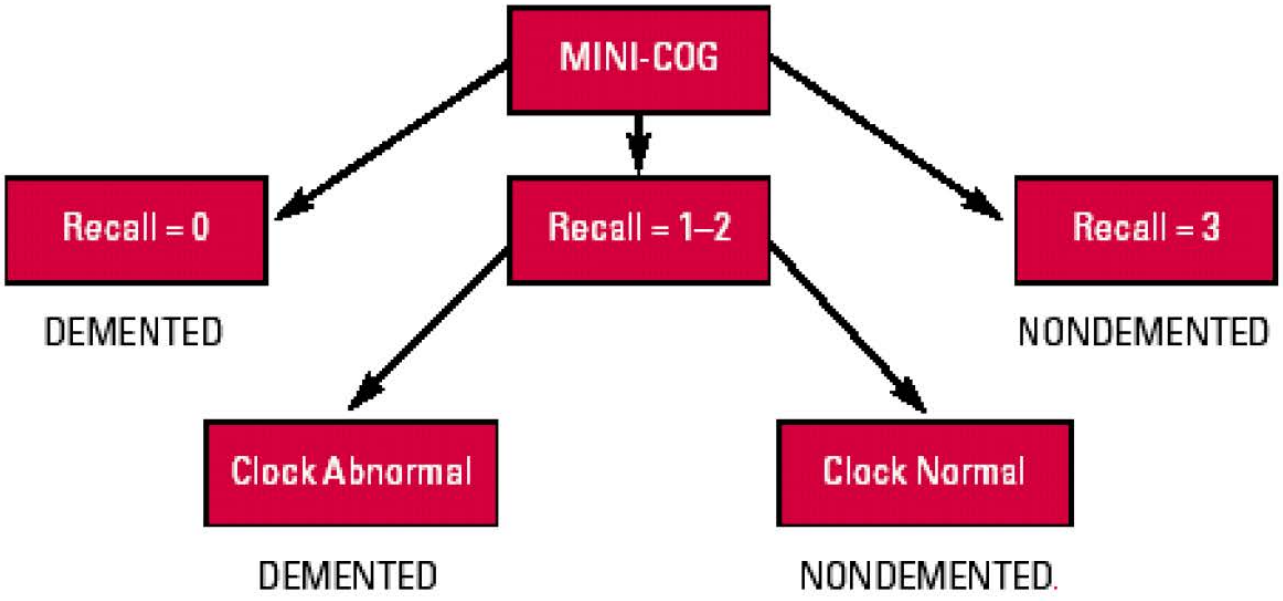
Other Clinical Assessments

Clinical Assessment – Cognitive Function

- Increase mortality, morbidity and hospitalizations
- Increase health care costs
- Affects self-care
  - Self Care of Heart Failure Index (http://www.self-careofheartfailureindex.com/)
- Incidence 25% to 75% (90% in hyponatremic patients)
- Young and old HF patients
- HFrEF and HFpEF
- MMSE, Montreal Cognitive Assessment, Mini-Cog
- Every patient should be assessed?

Clinical Assessment Tool – Mini-Cog™

Figure 1. The Mini-Cog scoring algorithm. The Mini-Cog uses a three-item recall test for memory and the intuitive clock-drawing test. The latter serves as an "informative distractor," helping to clarify scores when the memory recall score is intermediate.



http://mini-cog.com/mini-cog-instrument/standardized-mini-cog-instrument/

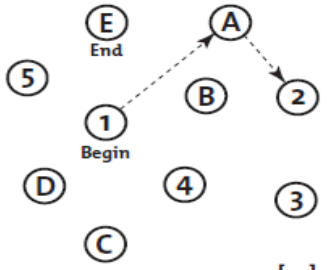
Int J Geriatr Psychiatry 2000;15(11):1021

Clinical Assessment Tool – Montreal Cognitive Assessment

MONTREAL COGNITIVE ASSESSMENT (MOCA)

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE — POINTS



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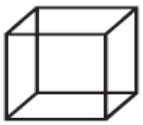


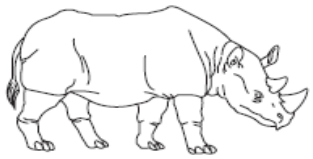
[ ] [ ]

Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands ___/5

NAMING

[ ]



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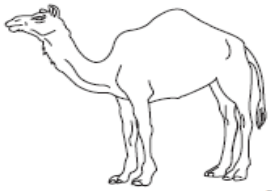


[ ] ___/3

MEMORY — Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION — Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4
Subject has to repeat them in the backward order [ ] 7 4 2 ___/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B ___/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt** ___/3

LANGUAGE — Repeat : I only know that John is the one to help today. [ ]
The cat always hid under the couch when dogs were in the room. [ ] ___/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] ____ (N ≥ 11 words) ___/1

ABSTRACTION — Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler ___/2

DELAYED RECALL ___/5

	Has to recall words WITH NO CUE	FACE	VELVET	CHURCH	DAISY	RED	Points for UNCUED recall only
		[ ]	[ ]	[ ]	[ ]	[ ]	
Optional	Category cue						
	Multiple choice cue						

ORIENTATION — [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City ___/6

www.mocatest.org

Normal ≥ 26 / 30

TOTAL ___/30
Add 1 point if ≤ 12 yr edu

Clinical Assessment Tool – Depression

- Approximatley 21% (9% to 60%) of patients may have depression?
- Poor quality of life, limited functional status, increase morbidity and mortality.
- HF Guidelines – no guidance
- There are a number of screening tools – simple assessment that may be quickly done in clinic includes:
  - PHQ2 and PHQ9 [AHA recommends for CAD pts for routine screening (Circulation. 2008;118:1768-1775)]
  - Data available in HF patients (mostly inpatient)

Circ Heart Fail. 2015;8:464-472

Clinical Assessment Tool – PHQ-2

Over the past 2 weeks, how often have you been bothered by any of the following problems	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3

http://www.phqscreeners.com/

Implications of Non-adherence in HF

- Rates vary widely, with most rates between 40-60%
- Contributes to hospital admission in approximately one-third of HF patients
- Associated with increase in cardiac-related events, increase in health care costs, and reduction in QOL

Adherence to HF medications associated with a 35% reduction in mortality (HR 0.65, CI 0.57-0.75, p< 0.0001).

Heart Lung 2009; 38:427-34; *Am Heart J* 2009; 158:644-52; *Nurs Clin North Am* 2008; 43:133-53; *J Manag Care Pharm* 2014; 20:741-55; *Lancet* 2005; 366:2005-11. Permission to use slide - Z. Deyo, Pharm.D. - UNC

Clinical Assessment Tool – Medication Adherence

- Many approaches
  - Pill count
  - Drug levels
  - Refill rates
  - Self-report
- Medication Adherence Tools
  - Morisky-4 (MMAS-4)
  - Adherence Estimator (3 questions - http://www.adherenceestimator.com/
  - Others

Inov Pharm. 2014;5(3):Article 165.

Clinical Assessment Tool For Worsening HF– The One Minute Clinic for Heart Failure (TOM-C HF)

- Simple assessment tool for worsening HF.
- Easily and quickly administered by anyone
  - Techs, students
- Clinic or community setting or long term care or phone assessment.
- Assessed in community pharmacy setting.
- Can be driven by pharmacy curriculum (i.e. students) in any setting.

J Am Pharm Assoc. 2014;54:634-641

The One Minute Clinic for Heart Failure (TOM-C HF) Community Intervention Program for Heart Failure

Since your last refill or visit to your doctor			
Triggers to Contact Physician/Nurse Today (one YES checked)			*No*
Have you had a change in weight? _____lbs	☐	YES > 5lbs weight gain	☐
Are you carrying more water? *Edema: Shoes fit – same or newly tight - or* *Ankle edema - > 1+ - or* *Patient observation - ankle or any edema or sense of increase water:*	☐	YES - MORE edema ☐ Tight shoes, and/or > 1+ edema ☐ Ankle edema ☐ Patient observation	☐
Do you have shortness of breath: (If yes, more or same or less)	☐	YES - MORE shortness of breath	☐
Do you wake up short of breath at night: (if yes – more or same or less)	☐	YES - MORE shortness of breath at night	☐
How many pillows do you sleep on _____? (more or same or less)	☐	YES - MORE pillows at night	☐
Have you been at all dizzy or have felt like you will faint: (If yes, upon standing?)	☐	YES - Symptoms of dizziness/fainting ☐ Dizzy or faint upon standing	☐
Heart Rate _____ (optional) Blood Pressure _____ (optional)	☐ ☐	Heart rate < 50 if symptoms of tiredness or dizziness or fainting Heart rate < 40 regardless of symptoms	☐
Triggers to Counsel Patient to Contact their Physician/Nurse Soon (one YES checked)			*No*
Have you felt more tired? *Examples* *1. Housework (more or same or less)* *2. Grocery shopping (more or same or less)* *3. Exercise/walking (more or same or less)* *4. Other*	☐	YES - Increased Tiredness ☐ Less housework ☐ Less Grocery shopping ☐ Less exercise/walking ☐ Other	☐
Are you having any problems sleeping?	☐	YES - Recent Sleep Problems	☐
Has your appetite changed recently?	☐	YES - Recent Loss of Appetite	☐

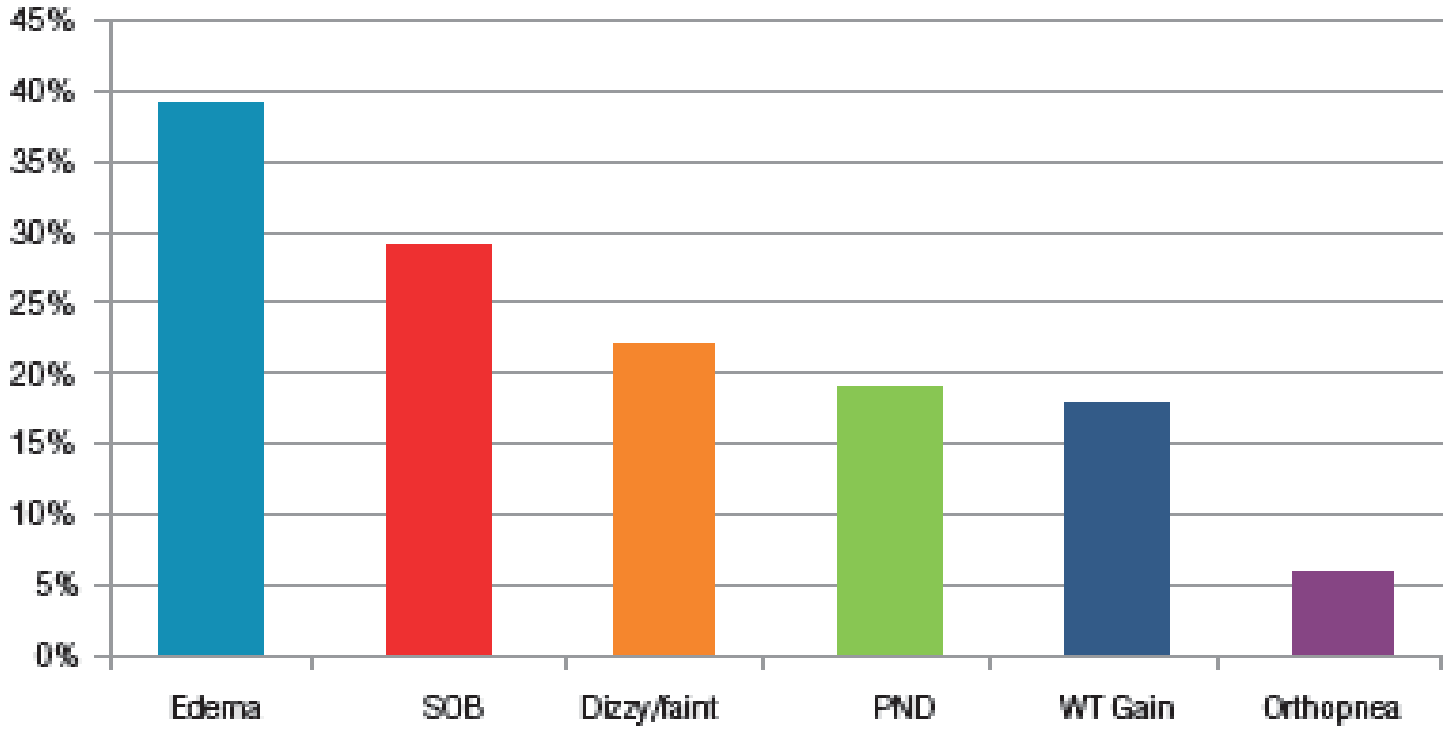
Optional Question (may be helpful in assessment of patients with YES answers)

1 Last time you took your water pill (drug name) do you think it is working the same as usual or not as well? (This may be key information to relay to physician/nurse)

2. May want to consider asking questions addressing adherence (especially diuretic and diet)
How many times in the past week have you not taken a dose of your medications?
(0 1-2 3-4 5+ times)

- 121 self identified HF patients assessed in 10 community pharmacy settings

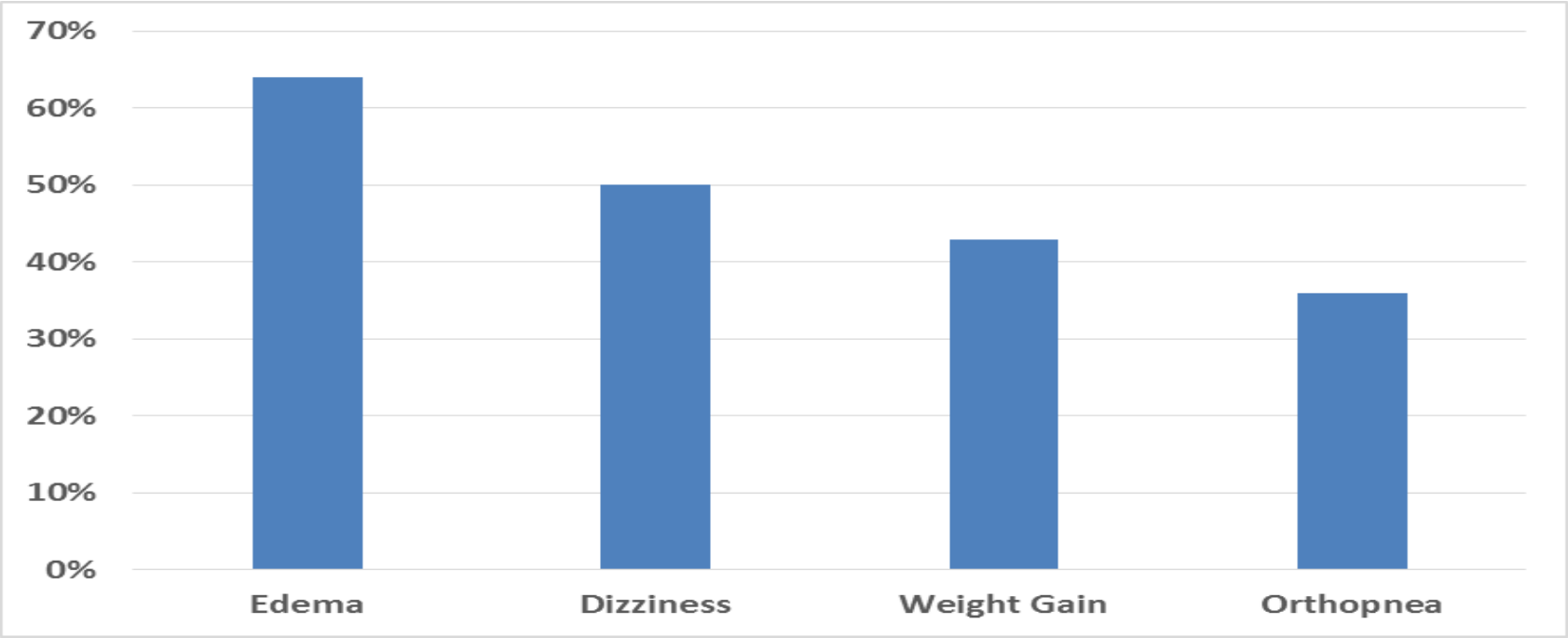
Figure 2. Percentage of patients reporting specific signs and symptoms of heart failure (n = 75)



Abbreviations used: SOB, shortness of breath; PND, paroxysmal nocturnal dyspnea; WT gain, weight gain >5 pounds (2.3 kg).

P4 Advanced Community APPE

- A total of 33/83 (40%) students completed 63 patient assessments at 16 sites, including 8 independent (N=33) and 8 chain (N=30) pharmacies.
- Thirty-five percent of patients (22/63) were candidates for an intervention.
- Patient Perception - “I’ve never sat down and talked to a pharmacist like that before. It’s nice to know someone cares”



Patient Tool

BEAVER DAM COMMUNITY HOSPITALS, INC.

HEART FAILURE ZONES

Which Heart Failure Zone are you in today? Green, Yellow or Red

EVERY DAY	Weigh yourself on your scale when you return home from the hospital. Your weight:_____ pounds. **EVERY DAY:** • Weigh yourself in the morning before breakfast, write it down & compare it to yesterday's weight • Take your medicine as prescribed • Check for swelling in your feet, ankles, legs and stomach • Eat low-salt food • Balance activity and rest periods
GREEN ZONE	**ALL CLEAR – This zone is your goal** Your symptoms are under control when: • No shortness of breath • No weight gain of more than 2 pounds in one day (it may change 1 or 2 pounds some days) • No swelling of your feet, ankles, legs or stomach • No chest pain
YELLOW ZONE **STOP & CALL**	**CAUTION – This zone is a warning** If you have one or more of the following: STOP Call Nurse:_____ Call Doctor:_____ • Weight gain of more than 3 pounds in 2 days or 5 pounds or more in 1 week • More shortness of breath than usual • More swelling of your feet, ankles, legs, or stomach than usual • Feeling more tired than usual (no energy)
RED ZONE	**EMERGENCY** Go to the emergency room or call 911 if you have any of the following: **DO NOT DRIVE YOURSELF** • Struggling to breathe: unrelieved shortness of breath while sitting still • Chest pain • Confusion of unable to think clearly

Key Takeaways

- Key Takeaway 1
  - Multiple assessments and tools can be utilized to assess HF status and risk (Get with the Guidelines - AHA http://www.heart.org/HEARTORG/), ACC HF Solutions - https://www.acc.org/tools-and-practice-support/clinical-toolkits/heart-failure-practice-solutions
- Key Takeaway 2
  - Need to assess beyond worsening HF symptoms to include cognitive function, depression, medication adherence. Simple tools are available to assist.
- Key Takeaway 3
  - Simple HF assessment can be performed in any setting and by any trained personnel.

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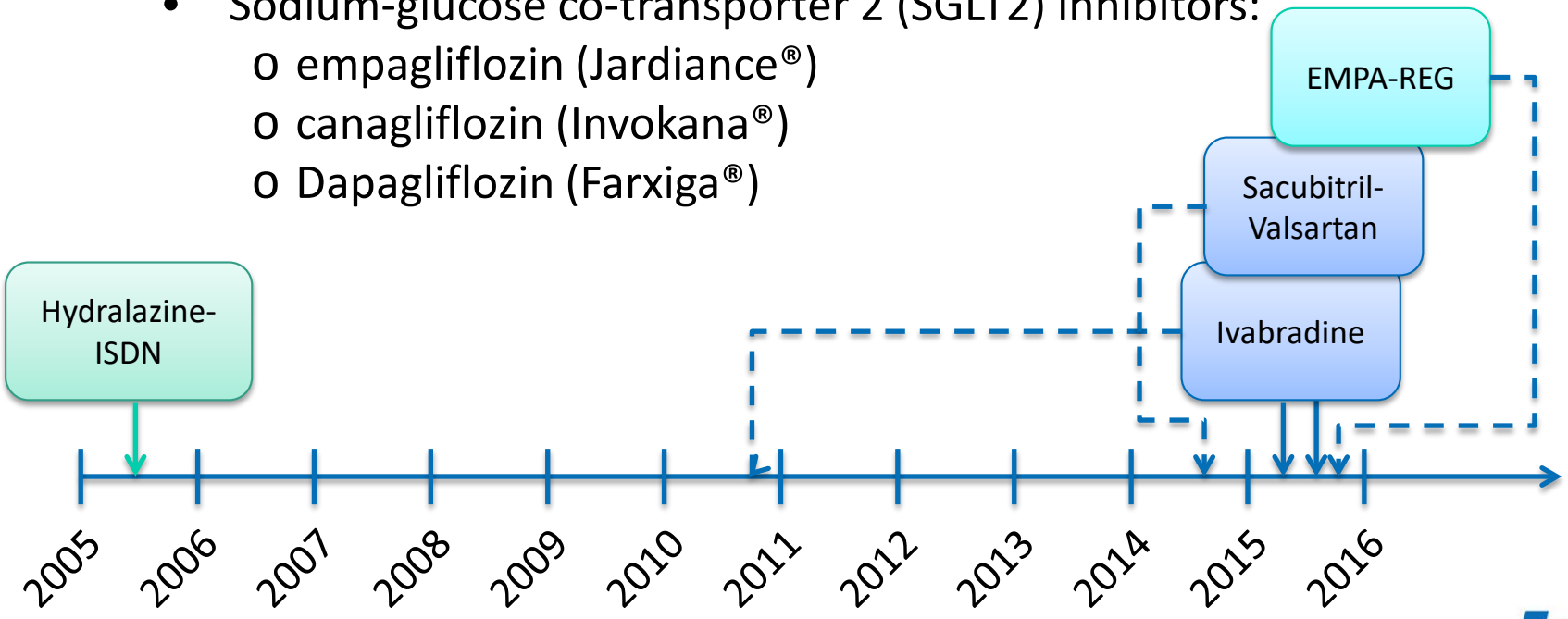
Opening the Heart Failure Toolbox Aligning Assessment and Treatment Options

Benjamin Van Tassell, PharmD, BCPS, FCCP, FAHA, ASH-CHC
Vice Chair for Research & Associate Professor
Pharmacotherapy and Outcomes Science
Virginia Commonwealth University

What's New in Chronic Heart Failure?

- 2 new classes of FDA-approved medications
  - Neprilysin inhibitor: sacubitril/valsartan (Entresto®)
  - Funny potassium channel blocker: ivabradine (Corlanor®)
- 1 new class that *might* be useful
  - Sodium-glucose co-transporter 2 (SGLT2) inhibitors:
    - empagliflozin (Jardiance®)
    - canagliflozin (Invokana®)
    - Dapagliflozin (Farxiga®)



Natriuretic Peptides

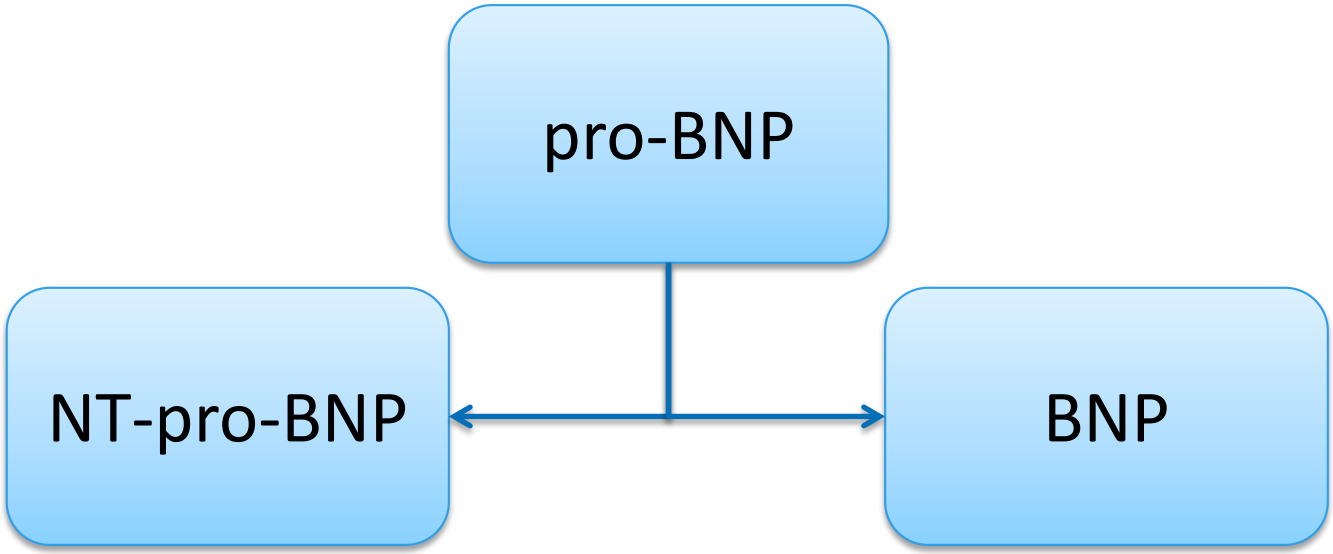
- Different types
  - Atrial natriuretic peptide – ANP
  - Brain natriuretic peptide – BNP
  - Secreted in response to atrial/ventricular "stretch"

Bind to the same receptor
- NPR-A

- Physiologic effects
  - Natriuresis
  - Vasodilation
  - Reduced aldosterone synthesis
  - Reduced vascular remodeling
  - Reduced sympathetic tone
  - Suppression of thirst

Circulation. 2002;105(20):2328-31. *Int J Cardiol*. 2016;221:1031-8.

Natriuretic Peptides



NT-pro-BNP

- Byproduct of BNP synthesis
- Physiologically inactive
- $t_{1/2}$ = 2 hours

BNP

- Physiologically active
- Metabolized by neprilysin
- $t_{1/2}$ = 20 minutes

Heart 2006;92:843–849

Neprilysin

- Neprilysin catalyzes degradation of multiple vasoactive peptides
  - Natriuretic peptides
  - Bradykinin
  - Adrenomedullin

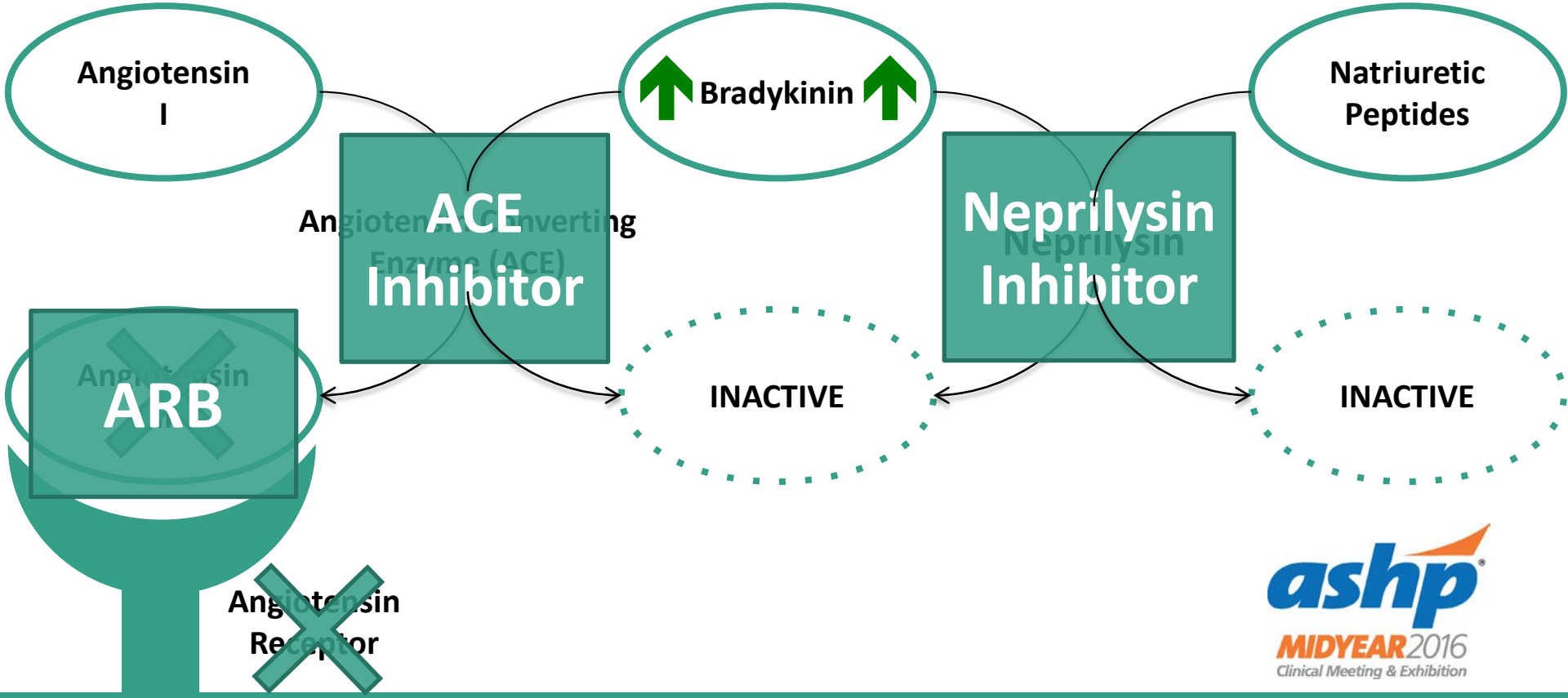
- 1st neprilysin inhibitor: Omipatrilat
  - Dual ACEI and neprilysin inhibitor
  - Initial efficacy as anti-hypertensive … and some promise in reducing death and HF hospitalization (OVERTURE, 2002)
  - Increased risk of angioedema compared to enalapril (OCTAVE, 2002) in patients with hypertension
    - Omipatrilat: 2.17%
    - Enalapril: 0.68%
    - **RR = 3.17 (95% CI 2.52 – 4.12)**

"It's tough being first."

Circulation. 2002;106:920-926. *Am J Hypertens*. 2004 Feb;17(2):103-11.

Neprilysin Inhibition: Sacubitril

- "LCZ696" --> Sacubitril/valsartan®
  - Neprilysin inhibitor: Sacubitril
  - Angiotensin receptor blocker: Valsartan



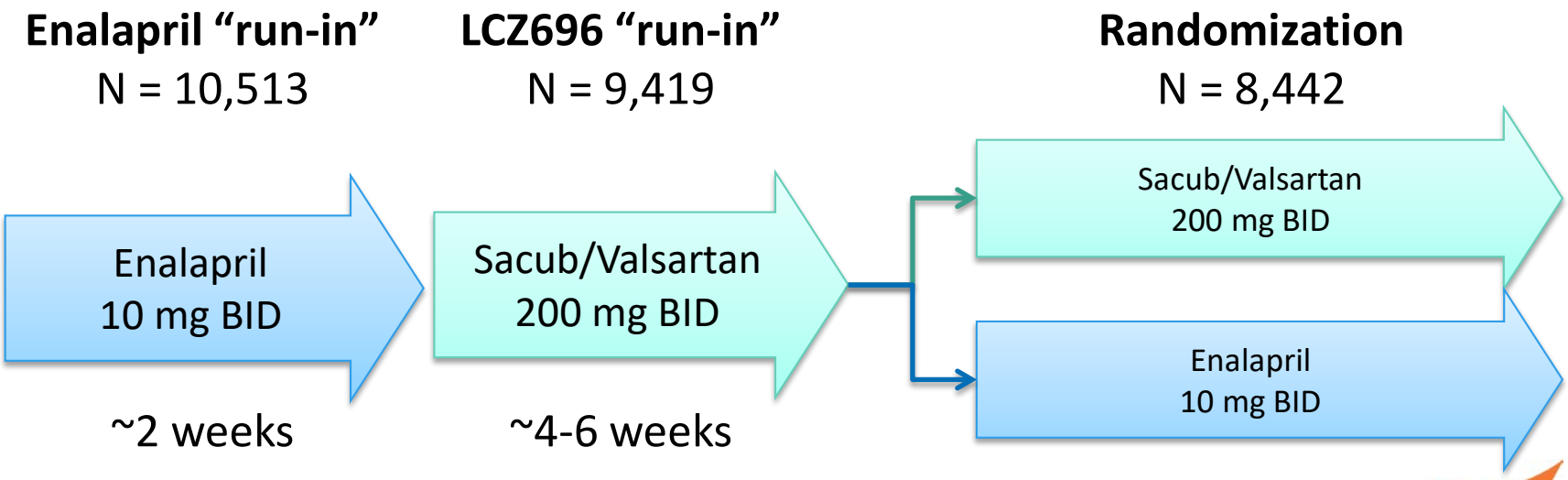
PARADIGM-HF

Multicenter, randomized, parallel-group, double-blind, active control

Primary Outcome: Death from CV cause + HF hospitalization

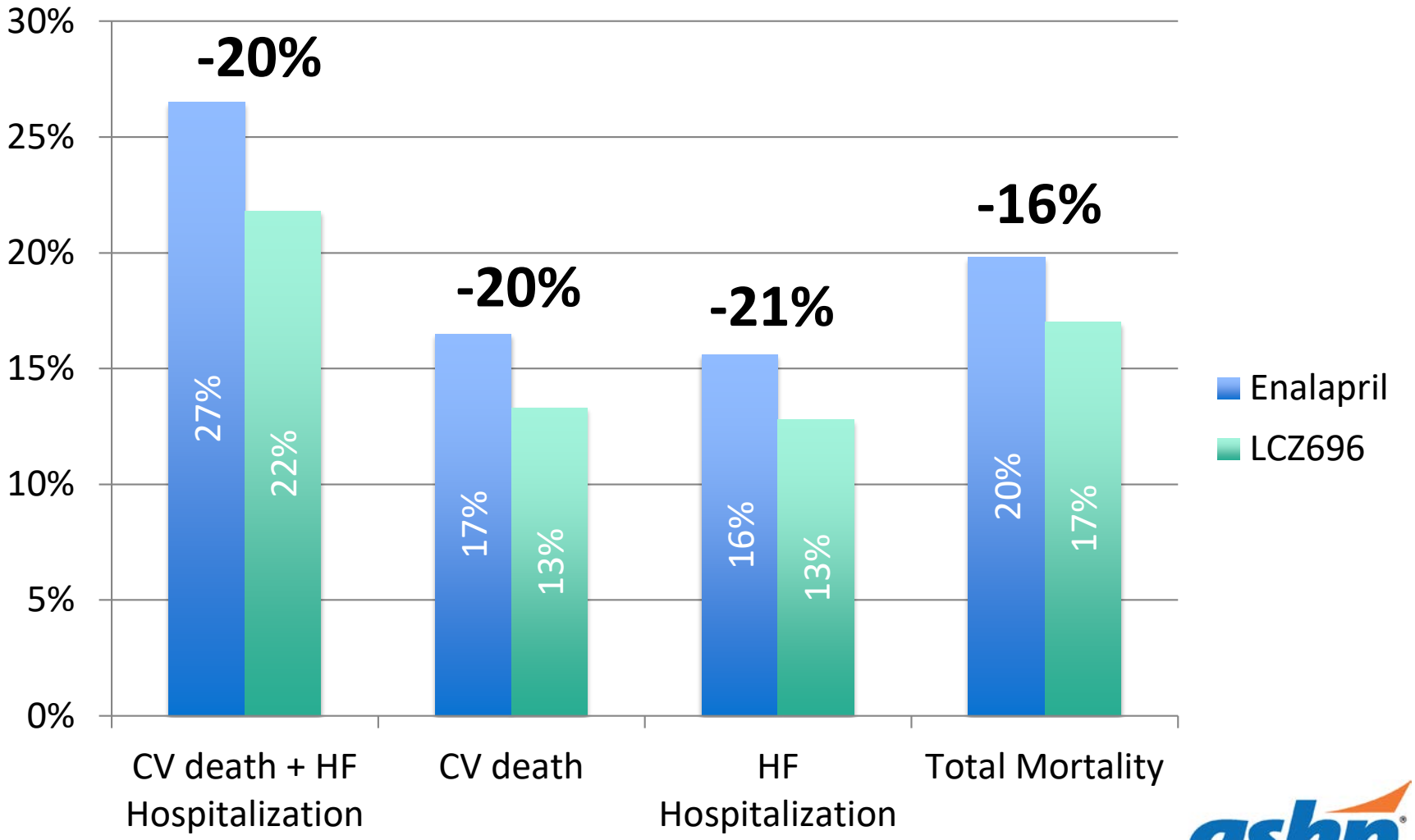
- Age > 18 years
- NYHA function class II – IV
- LV ejection fraction < 40%
- BNP > 150 pg/mL
- NTproBNP > 600 pg/mL

- SBP < 100 mmHg
- eGFR < 30 mL/min/1.73m^2
- K+ > 5.2 mmol/L
- Prior history of angioedema with ACEI



N Engl J Med 2014;371:993-1004.

PARADIGM-HF



N Engl J Med 2014;371:993-1004.

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PARADIGM-HF

Outcome	Enalapril	LCZ696	P value
Hypotension			
• Symptomatic	**9.2%**	**14.0%**	<0.001
• Symptomatic + SBP <90 mmHg	**1.4%**	**2.7%**	<0.001
Serum creatinine • ≥2.5 mg/dL	**4.5%**	**3.3%**	0.007
Serum potassium • ≥5.5 mmol/L	17.3%	16.1%	0.15
Cough	**14.3%**	**11.3%**	<0.001
Angioedema	0.1%	0.2%	0.31

N Engl J Med 2014;371:993-1004.

So … who benefits?

Demographics	
Age	63.8 yrs
Male	22%
Race	
• White	66%
• Black	5%
• Asian	18%
Blood pressure	122/73 mmHg
Heart rate	73 bpm
LVEF	30%
NYHA	
• I	5%
• II	70%
• III	24%
• IV	1%

Medications	
ACEI	78%
ARB	23%
Beta-blocker	93%
Diuretic	80%
Digoxin	30%
Aldosterone antagonist	56%
ICD	15%
CRT	7%

Only 43% with prior MI

N Engl J Med 2014;371:993-1004.

PARADIGM-HF

Multicenter, randomized, parallel-group, double-blind, active control

Primary Outcome: Death from CV cause + HF hospitalization

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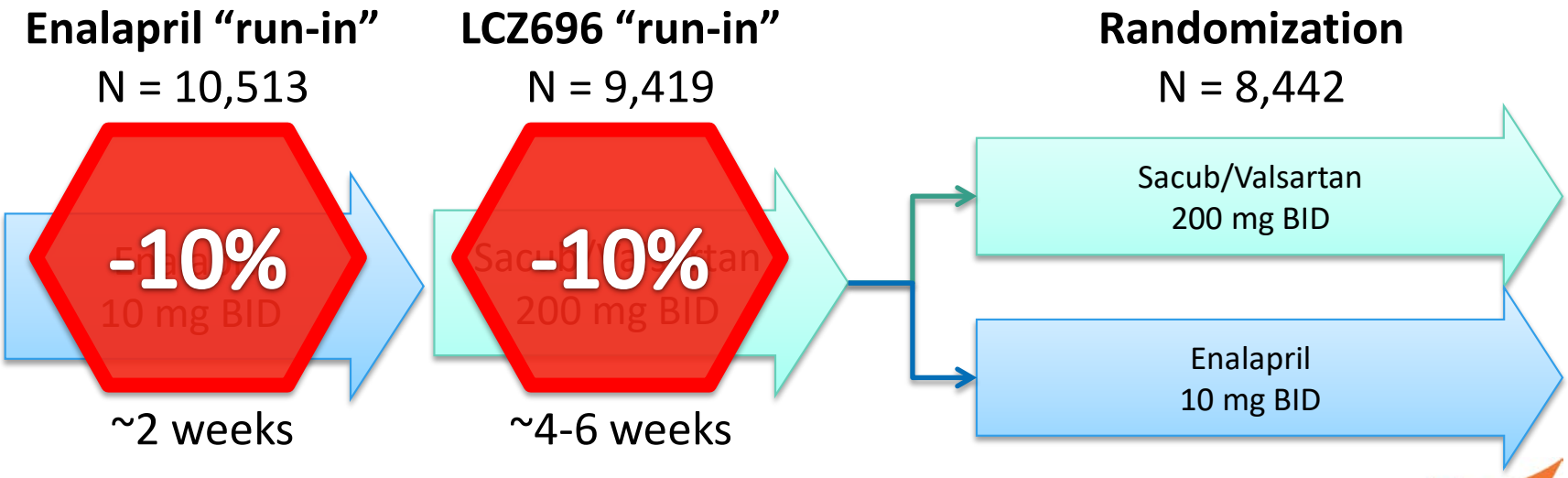


N Engl J Med 2014;371:993-1004.

Sacubitril/Valsartan

- Benefits
  - Reduced **CV death**, **HF hospitalizations**, and **death from any cause**
  - Improvement in **HF symptoms**
  - Less **cough**, less **SCr increases**, less **hyperkalemia**
  - No observed effects on angioedema
- Risks
  - Increased **hypotension**
  - Unclear whether run-in phase may have “sanitized” tolerability

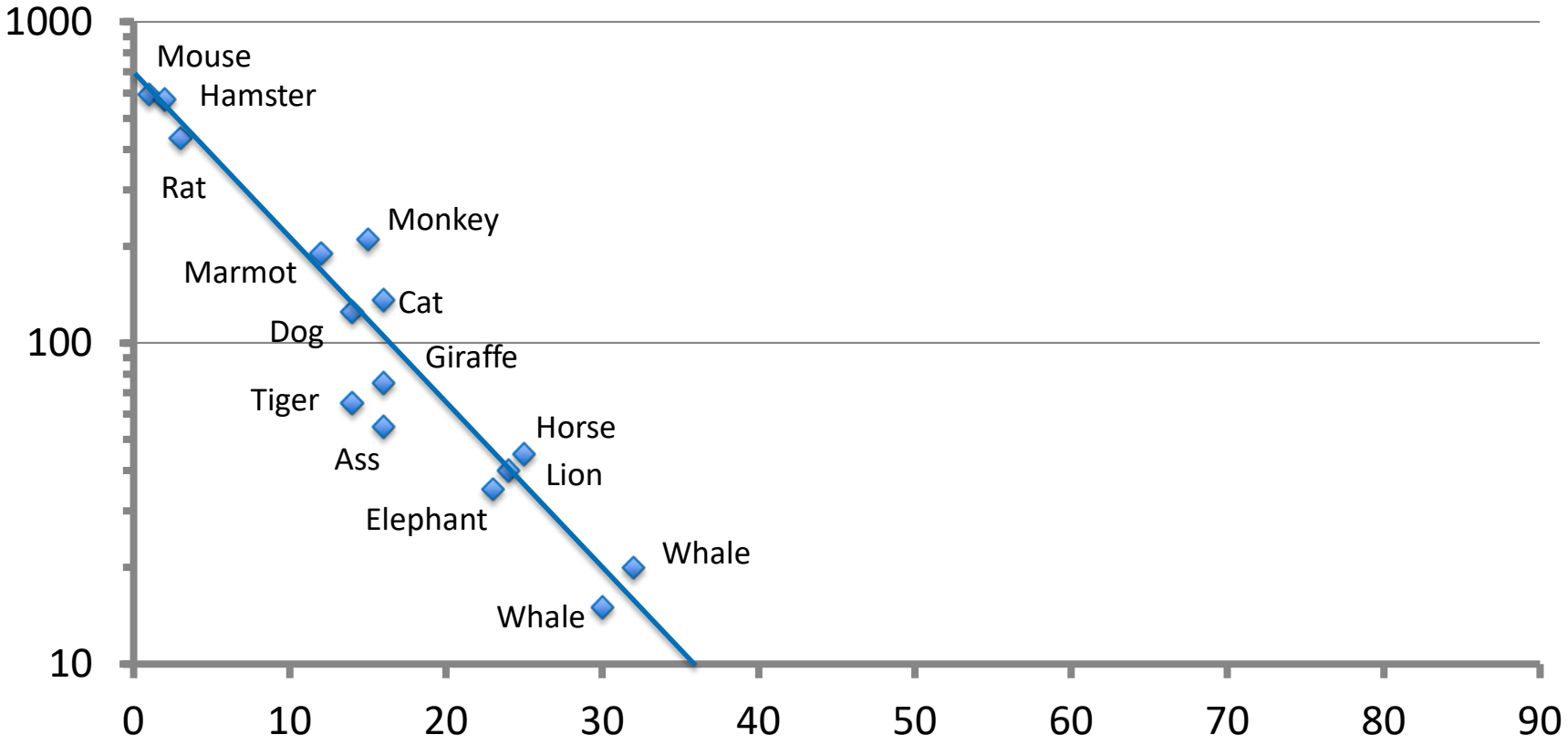
Neprilysin Inhibition

- Place in therapy:

Recommendations for Renin-Angiotensin System Inhibition With ACE Inhibitor or ARB or ARNI		
COR	**LOE**	**Recommendations**
I	**ACE: A**	**The clinical strategy of inhibition of the renin-angiotensin system with ACE inhibitors *(Level of Evidence: A)* (9-14), OR ARBs *(Level of Evidence: A)* (15-18), OR ARNI *(Level of Evidence: B-R)* (19) in conjunction with evidence-based beta blockers (20-22), and aldosterone antagonists in selected patients (23, 24), is recommended for patients with chronic HF*r*EF to reduce morbidity and mortality.**
	ARB: A	
	ARNI: B-R	
I	**ARNI: B-R**	**In patients with chronic symptomatic HF*r*EF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality (19).**

Circulation. 2016;134:000–000.

Heart Rate and Mortality



JACC 1997; 30:1104-1106

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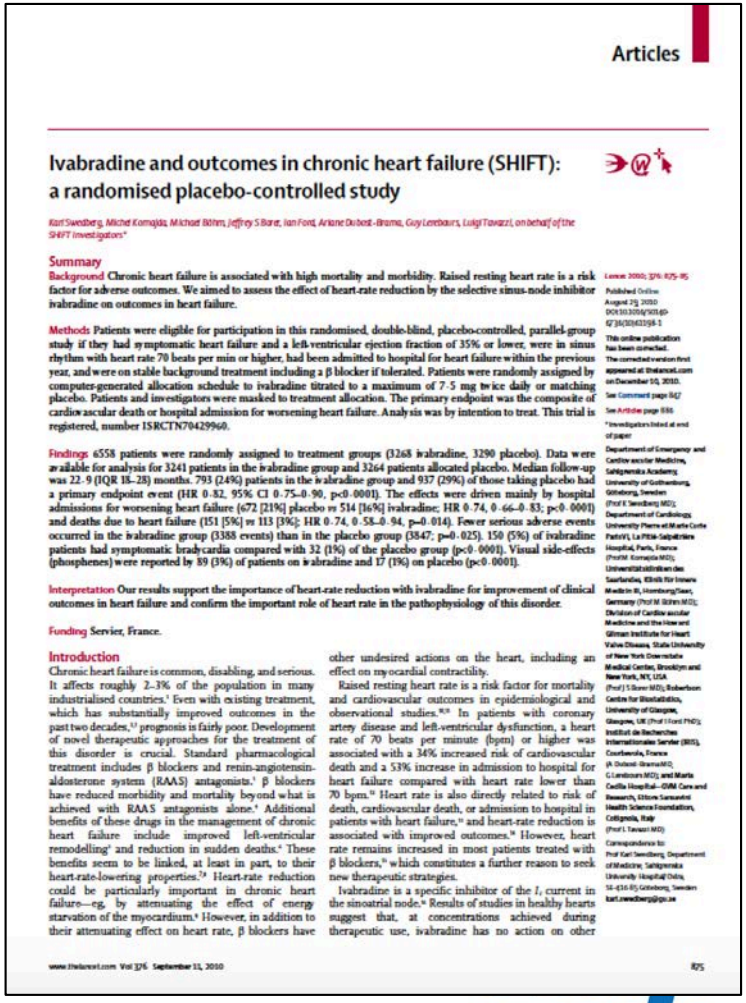
Ivabradine

- I_f blocker
  - "funny" current (K^+)
- Primary site of action
  - SA node
  - Phase IV of action potential
  - Lowers HR w/out affecting BP
- Dosing
  - 5 mg BID (initial)
  - 7.5 mg BID (target)
- FDA approved
  - HFrEF with HR >70 bpm



Articles

Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study

Karl Swedberg, Michel Komajda, Michael Böhm, Jeffrey S Borer, Ian Ford, Ariane Dubost-Brama, Guy Lerebours, Luigi Tavazzi, on behalf of the SHIFT Investigators*

Summary

Background Chronic heart failure is associated with high mortality and morbidity. Raised resting heart rate is a risk factor for adverse outcomes. We aimed to assess the effect of heart-rate reduction by the selective sinus-node inhibitor ivabradine on outcomes in heart failure.

Methods Patients were eligible for participation in this randomised, double-blind, placebo-controlled, parallel-group study if they had symptomatic heart failure and a left-ventricular ejection fraction of 35% or lower, were in sinus rhythm with heart rate 70 beats per min or higher, had been admitted to hospital for heart failure within the previous year, and were on stable background treatment including a β blocker if tolerated. Patients were randomly assigned by computer-generated allocation schedule to ivabradine titrated to a maximum of 7·5 mg twice daily or matching placebo. Patients and investigators were masked to treatment allocation. The primary endpoint was the composite of cardiovascular death or hospital admission for worsening heart failure. Analysis was by intention to treat. This trial is registered, number ISRCTN70429960.

Findings 6558 patients were randomly assigned to treatment groups (3268 ivabradine, 3290 placebo). Data were available for analysis for 3241 patients in the ivabradine group and 3264 patients allocated placebo. Median follow-up was 22·9 (IQR 18–28) months. 793 (24%) patients in the ivabradine group and 937 (29%) of those taking placebo had a primary endpoint event (HR 0·82, 95% CI 0·75–0·90, p<0·0001). The effects were driven mainly by hospital admissions for worsening heart failure (672 [21%] placebo vs 514 [16%] ivabradine; HR 0·74, 0·66–0·83; p<0·0001) and deaths due to heart failure (153 [5%] vs 113 [3%]; HR 0·74, 0·58–0·94, p=0·014). Fewer serious adverse events occurred in the ivabradine group (3388 events) than in the placebo group (3847; p=0·025). 150 (5%) of ivabradine patients had symptomatic bradycardia compared with 32 (1%) of the placebo group (p<0·0001). Visual side-effects (phosphenes) were reported by 89 (3%) of patients on ivabradine and 17 (1%) on placebo (p<0·0001).

Interpretation Our results support the importance of heart-rate reduction with ivabradine for improvement of clinical outcomes in heart failure and confirm the important role of heart rate in the pathophysiology of this disorder.

Funding Servier, France.

Introduction

Chronic heart failure is common, disabling, and serious. It affects roughly 2–3% of the population in many industrialised countries.[1] Even with existing treatment, which has substantially improved outcomes in the past two decades,[1,2] prognosis is fairly poor. Development of novel therapeutic approaches for the treatment of this disorder is crucial. Standard pharmacological treatment includes β blockers and renin-angiotensin-aldosterone system (RAAS) antagonists.[3] β blockers have reduced morbidity and mortality beyond what is achieved with RAAS antagonists alone.[4] Additional benefits of these drugs in the management of chronic heart failure include improved left-ventricular remodelling[5] and reduction in sudden deaths.[6] These benefits seem to be linked, at least in part, to their heart-rate-lowering properties.[7,8] Heart-rate reduction could be particularly important in chronic heart failure—eg, by attenuating the effect of energy starvation of the myocardium.[9] However, in addition to their attenuating effect on heart rate, β blockers have other undesired actions on the heart, including an effect on myocardial contractility.

Raised resting heart rate is a risk factor for mortality and cardiovascular outcomes in epidemiological and observational studies.[10,11] In patients with coronary artery disease and left-ventricular dysfunction, a heart rate of 70 beats per minute (bpm) or higher was associated with a 34% increased risk of cardiovascular death and a 53% increase in admission to hospital for heart failure compared with heart rate lower than 70 bpm.[12] Heart rate is also directly related to risk of death, cardiovascular death, or admission to hospital in patients with heart failure,[13] and heart-rate reduction is associated with improved outcomes.[14] However, heart rate remains increased in most patients treated with β blockers,[15] which constitutes a further reason to seek new therapeutic strategies.

Ivabradine is a specific inhibitor of the I_f current in the sinoatrial node.[16] Results of studies in healthy hearts suggest that, at concentrations achieved during therapeutic use, ivabradine has no action on other

www.thelancet.com Vol 376 September 11, 2010 875

Lancet 2010; 376: 875–85
Published Online August 25, 2010 DOI:10.1016/S0140-6736(10)61198-1
This online publication has been corrected. The corrected version first appeared at thelancet.com on December 10, 2010.

See Comment page 847
See Articles page 886

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Lancet 2010; 376: 875–85.

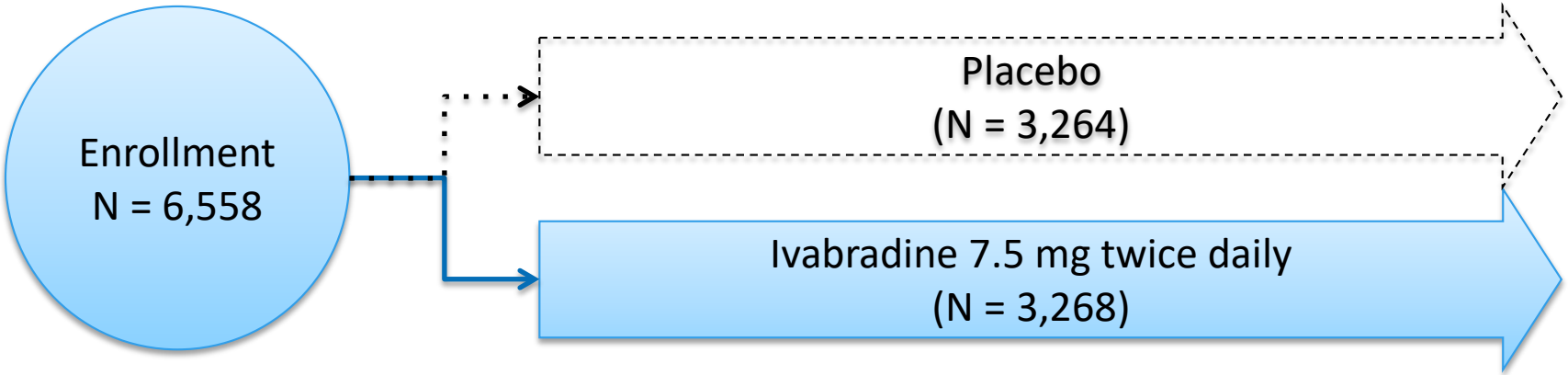
SHIFT

Multicenter, randomized, parallel-group, double-blind, placebo control

Primary Outcome: Death from CV cause + HF hospitalization

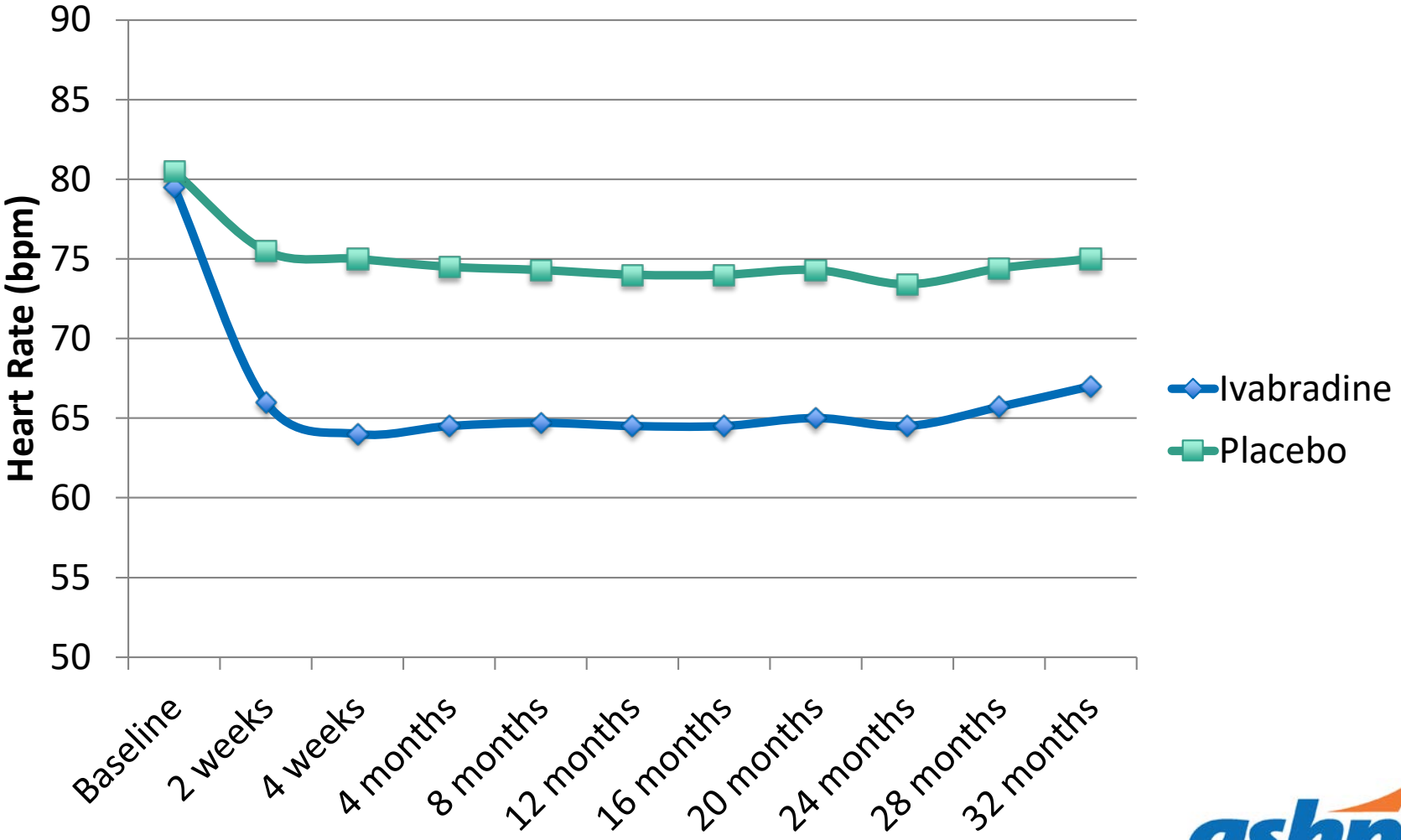
- Age > 18 years
- Moderate-to-severe HF for at least 4 months duration
- LV ejection fraction ≤ 35%
- Recent HF admission (1 year)

- **HR < 70 bpm**
- Recent MI (< 2 months)
- Symptomatic hypotension
- AV pacing for > 40% day
- AFib/flutter



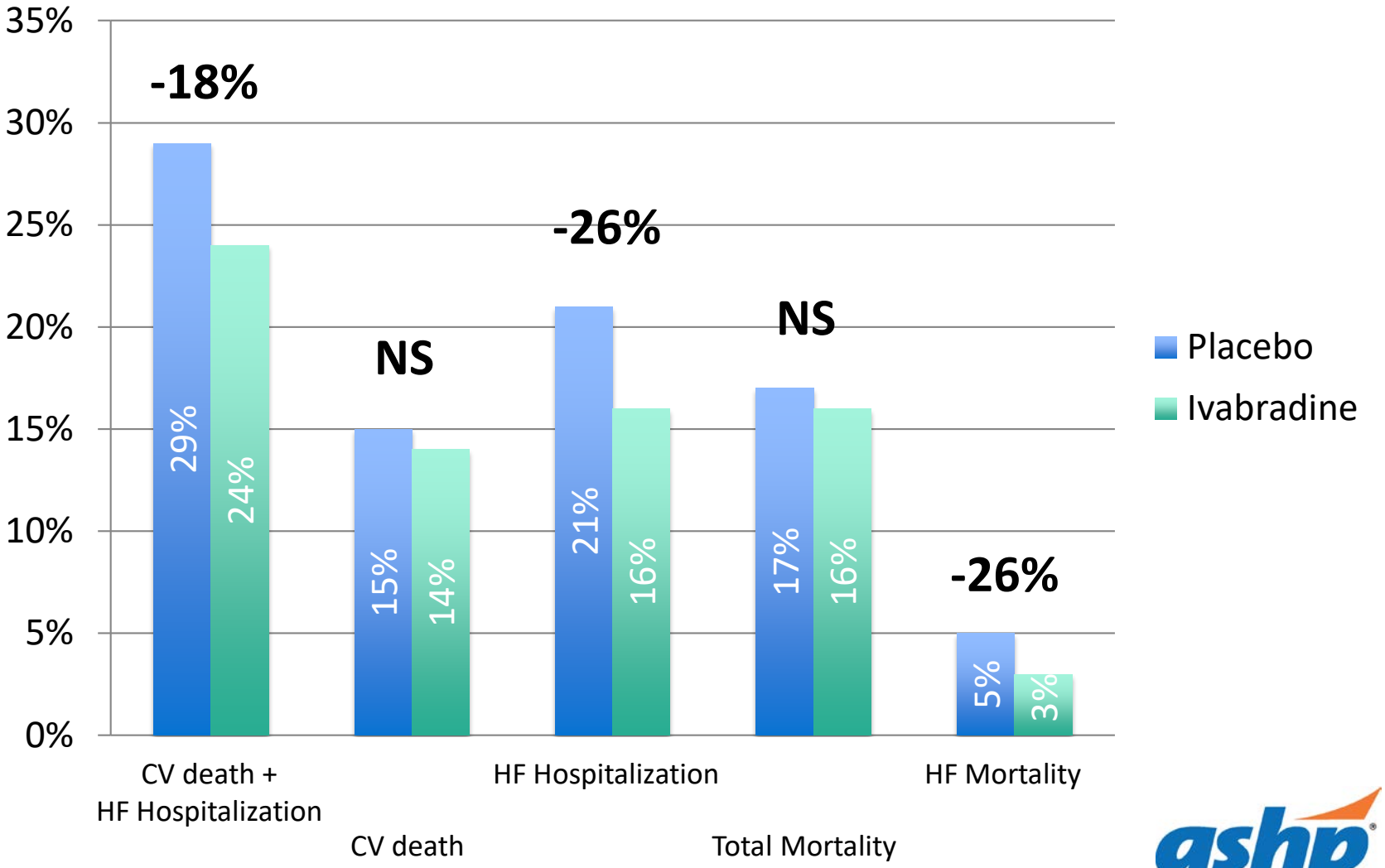
Lancet 2010; 376: 875–85.

SHIFT



Lancet 2010; 376: 875–85.

SHIFT



Lancet 2010; 376: 875–85.

SHIFT

Outcome	Placebo	Ivabradine	P value
Any adverse event	74%	75%	0.303
Serious adverse events	48%	45%	0.025
Heart failure	29%	25%	0.0005
Symptomatic bradycardia	1%	5%	<0.0001
Asymptomatic bradycardia	1%	6%	<0.0001
Atrial fibrillation	8%	9%	0.012
Phosphenes	1%	3%	<0.0001
Blurred vision	<1%	1%	0.042

Lancet 2010; 376: 875–85.

Ivabradine

- Benefits
  - Reduced **HF hospitalizations** and **death from HF**
  - Fewer **serious adverse events**
- Risks
  - Increased **bradycardia**
  - Increased **atrial fibrillation**
  - Increased **phosphenes**
  - Use with strong CYP3A4 inhibitors

I_f Inhibition

- Place in therapy:

Recommendation for Ivabradine		
COR	**LOE**	**Recommendation**
IIa	**B-R**	**Ivabradine can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II-III) stable chronic HF*r*EF (LVEF ≤35%) who are receiving GDEM, including a beta blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of 70 bpm or greater at rest (37-40).**

Circulation. 2016;134:000–000.

SGLT2 inhibition

- Sodium-glucose cotransporter-2
  - Reabsorbs glucose (w/sodium) in proximal tubule
  - Can become overwhelmed at BG >200 mg/dL
- SGLT2 inhibition
  - Increased urinary glucose secretion and mild reduction in hemoglobin A1c (0.7%)
  - Mild diuretic and BP lowering effect (4-6/1-2 mmHg)

What's the big deal?

Circulation. 2016;134:752-772

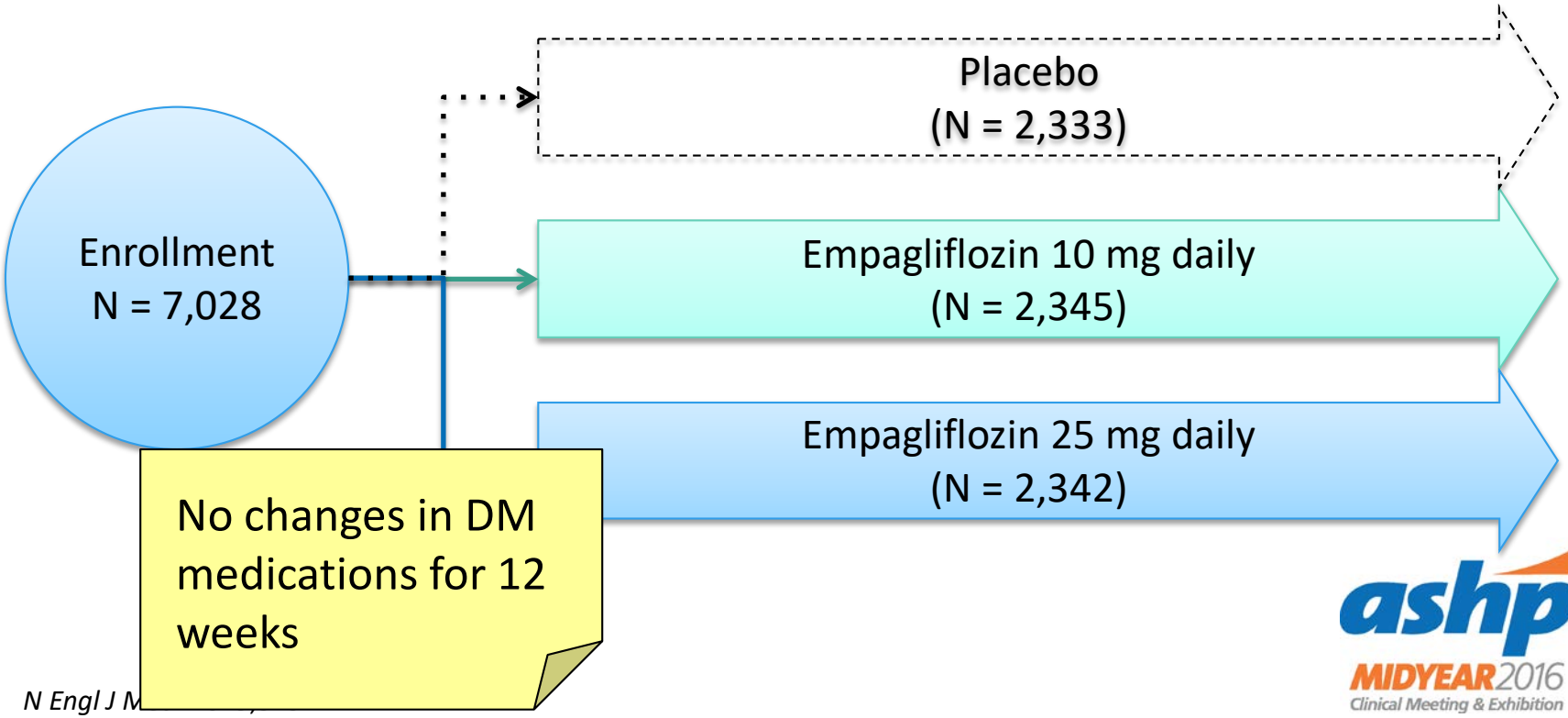
EMPA-REG OUTCOME

Multicenter, randomized, parallel-group, double-blind, placebo control

Primary Outcome: CV death + non-fatal MI + non-fatal stroke

- Age > 18 years
- Type 2 diabetes
- Established CV disease
- HgbA1c 7.0-9.0%

- BMI > 45 kg/m^2
- eGFR < 30 mL/min/1.73m^2
- No recent changes in DM medications



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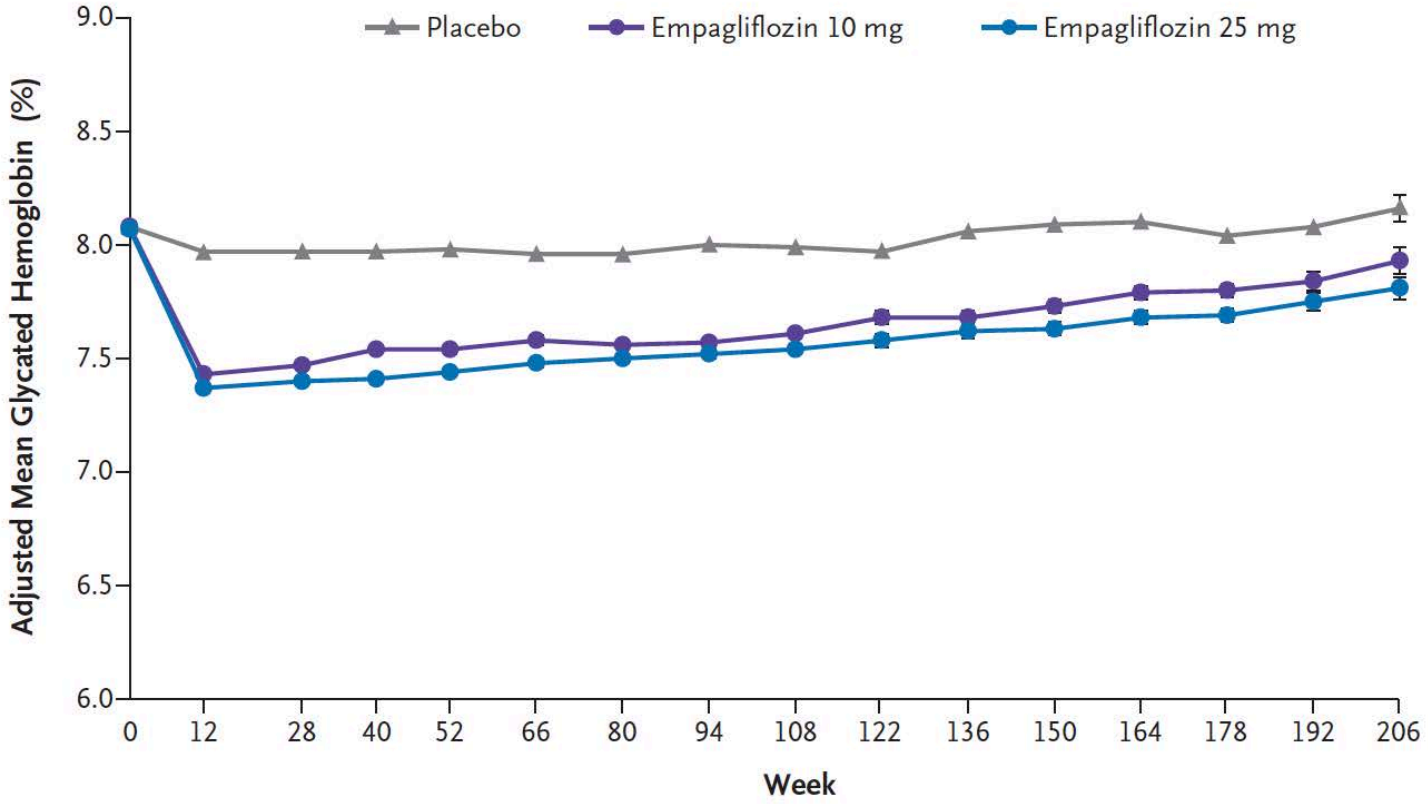


No. at Risk

Placebo	2294	2272	2188	2133	2113	2063	2008	1967	1741	1456	1241	1109	962	705	420	151
Empagliflozin 10 mg	2296	2272	2218	2150	2155	2108	2072	2058	1805	1520	1297	1164	1006	749	488	170
Empagliflozin 25 mg	2296	2280	2212	2152	2150	2115	2080	2044	1842	1540	1327	1190	1043	795	498	195

Figure 3. Glycated Hemoglobin Levels.

Shown are mean (±SE) glycated hemoglobin levels in the three study groups, as calculated with the use of a repeated-measures analysis as a mixed model of all data for patients who received at least one dose of a study drug and had a baseline measurement. The model included baseline glycated hemoglobin as a linear covariate, with baseline estimated glomerular filtration rate, geographic region, body-mass index, the last week a patient could have had a glycated hemoglobin measurement, study group, visit, visit according to treatment interaction, and baseline glycated hemoglobin according to visit interaction as fixed effects.

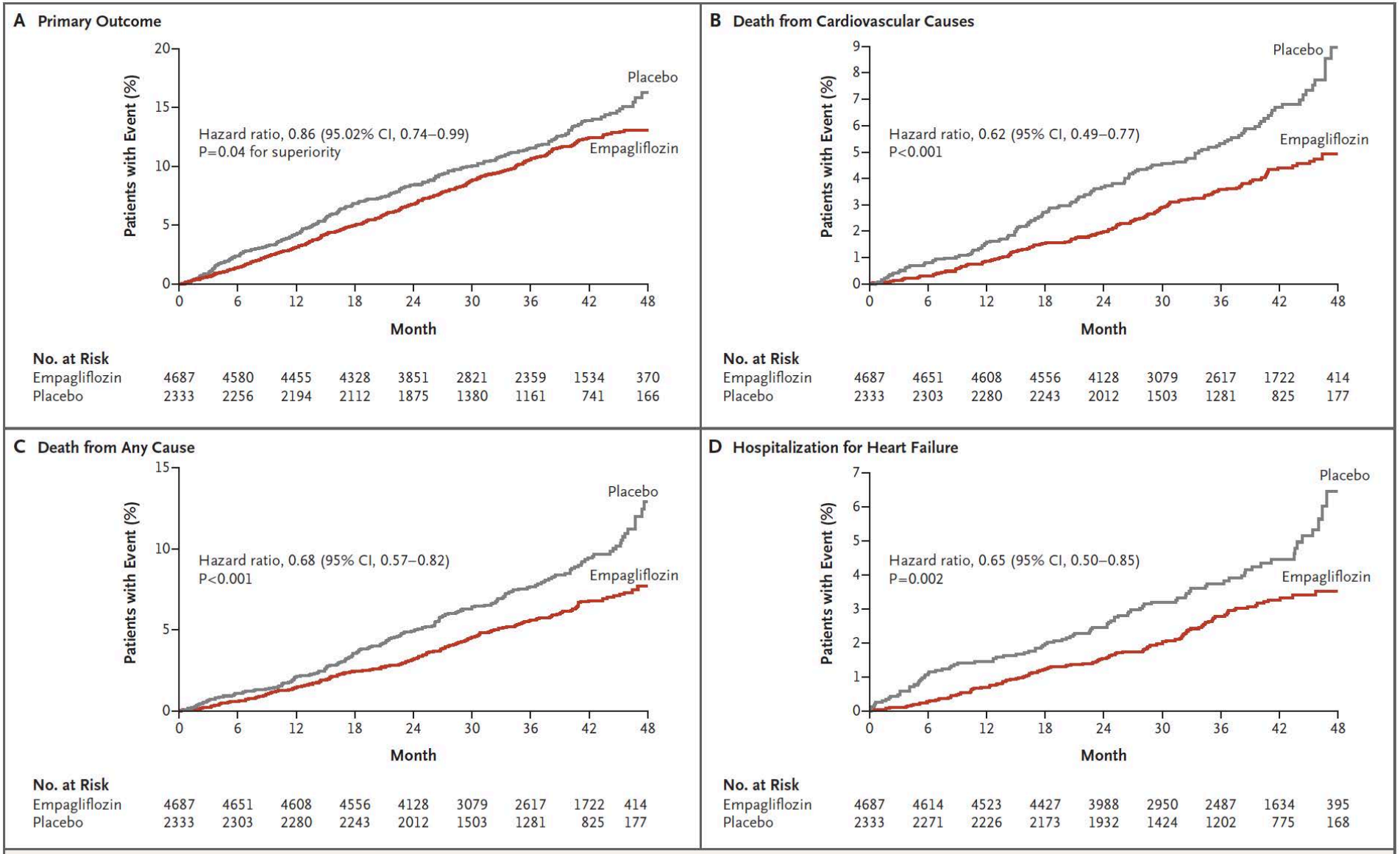
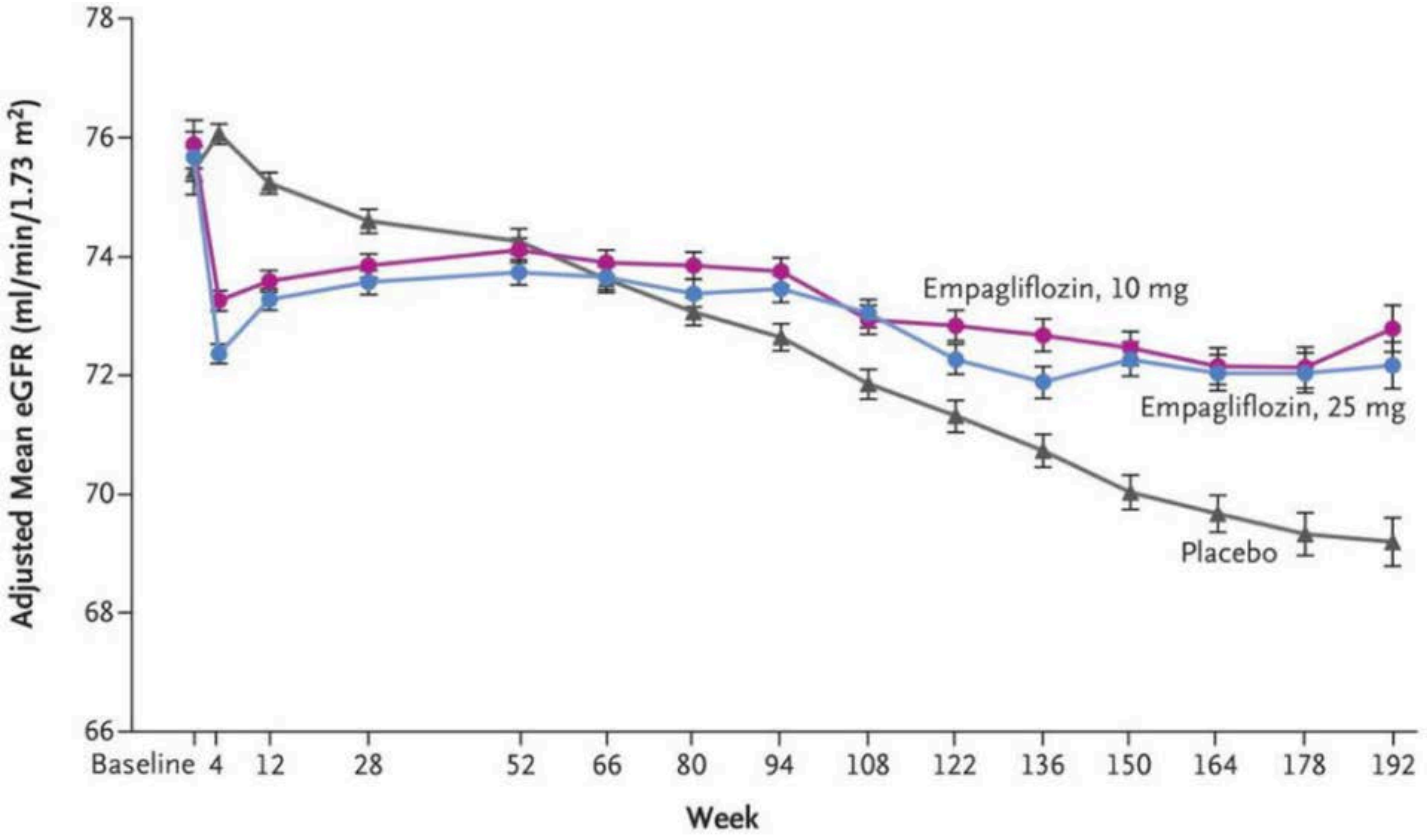


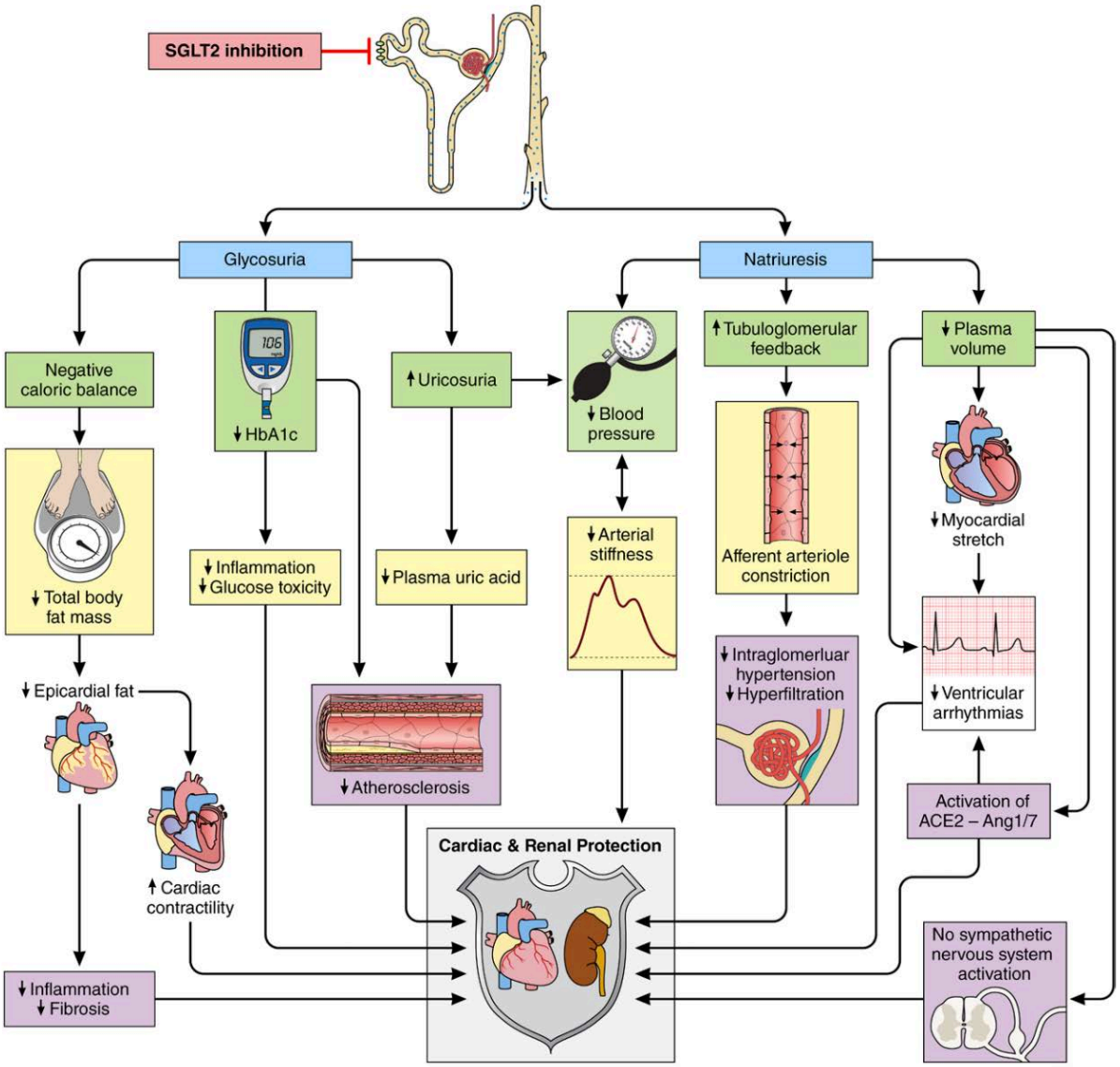
Figure 1. Cardiovascular Outcomes and Death from Any Cause.

Shown are the cumulative incidence of the primary outcome (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) (Panel A), cumulative incidence of death from cardiovascular causes (Panel B), the Kaplan–Meier estimate for death from any cause (Panel C), and the cumulative incidence of hospitalization for heart failure (Panel D) in the pooled empagliflozin group and the placebo group among patients who received at least one dose of a study drug. Hazard ratios are based on Cox regression analyses.

EMPA-REG OUTCOMES



Circulation. 2016;134:752-772



Circulation. 2016;134:752-772

SGLT2 use in Heart Failure?

	Empagliflozin		Placebo		HR (95% CI)
	n with event/*n*	%	*n* with event/*n*	%	
Heart failure hospitalization or cardiovascular death					
All patients	265/4687	5.7	198/2333	8.5	0.66 (0.55–0.79)
Heart failure at baseline					
No	190/4225	4.5	149/2089	7.1	0.63 (0.51–0.78)
Yes	75/462	16.2	49/244	20.1	0.72 (0.50–1.04)
Hospitalization for heart failure					
All patients	126/4687	2.7	95/2333	4.1	0.65 (0.50–0.85)
Heart failure at baseline					
No	78/4225	1.8	65/2089	3.1	0.59 (0.43–0.82)
Yes	48/462	10.4	30/244	12.3	0.75 (0.48–1.19)
Cardiovascular death					
All patients	172/4687	3.7	137/2333	5.9	0.62 (0.49–0.77)
Heart failure at baseline					
No	134/4225	3.2	110/2089	5.3	0.60 (0.47–0.77)
Yes	38/462	8.2	27/244	11.1	0.71 (0.43–1.16)
All-cause mortality					
All patients	269/4687	5.7	194/2333	8.3	0.68 (0.57–0.82)
Heart failure at baseline					
No	213/4225	5.0	159/2089	7.6	0.66 (0.51–0.81)
Yes	56/462	12.1	35/244	14.3	0.79 (0.52–1.20)

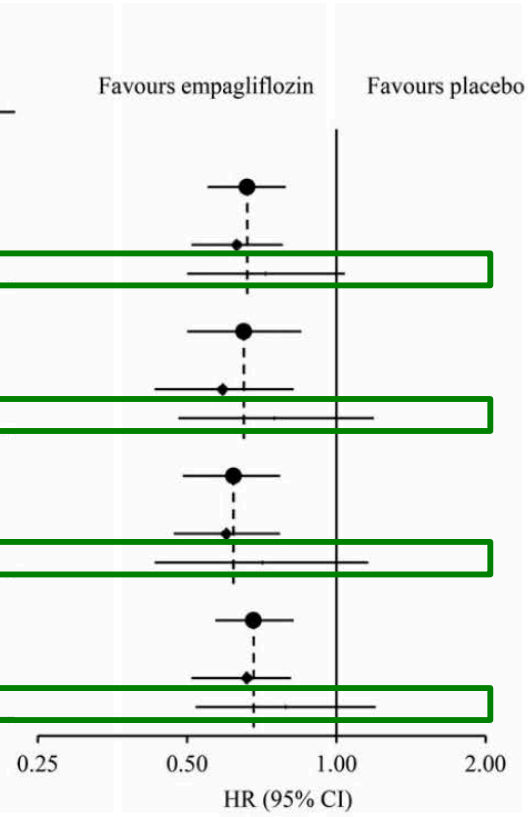


Figure 3 Outcomes in patients with and without heart failure at baseline. Cox regression analysis. Patients treated with at least one dose of study drug. CI, confidence interval; HR, hazard ratio.

Eur Heart J. 2016;37:1526-1534

SGLT2 inhibition

- Benefits **(in patients with T2DM)**
  - Reduced composite of **CV mortality, non-fatal MI, non-fatal stroke**
  - Reduced **total mortality**
  - Reduced **HF hospitalization**
  - Reduced **acute kidney injury** and **renal failure**
- Risks
  - Increased risk of **urinary tract infections (women)** and **genital infections (men/women)**
  - Potential risk of volume depletion
- Place in therapy?
  - No guideline recommendations

Data in patients with HF comes from underpowered sub-group analysis

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Opening the Heart Failure Toolbox Aligning Assessment and Treatment Options

Lynette Moser, Pharm.D.
Clinical Associate Professor
Eugene Applebaum College of Pharmacy and Health Sciences
Wayne State University

Case #1:

LC is a 52 year old white male with NYHA class II HFrEF who presents to clinic complaining of mild fatigue and shortness of breath with moderate physical activity. He was last hospitalized 4 months ago when he was also diagnosed with atrial fibrillation

PMH: HF (EF 30%), hyperlipidemia, Atrial fibrillation

Physical Exam: BP 98/66, ventricular rate 84, 82 kg (stable), 1+ pitting edema (baseline), JVD 8-9 cm (baseline), no crackles / rales

Labs: K+ 4.3 mEq/mL, BUN 25 mg/mL, sCr 1.9 mg/mL (stable), est. CrCl 50 ml/min, NT-proBNP (1 month ago when stable) – 800 pg/mL

Current medications: furosemide 40mg BID, lisinopril 20mg daily, metoprolol XL 200mg daily, apixaban 5 mg bid, and atorvastatin 40mg daily.

What further assessment should be done for this patient?

A. NT-ProBNP

B. Seattle Heart Failure Score

C. MoCA

D. Medication Adherence

How would NT-proBNP impact therapeutic decision making?

- If increased – 800 pg/ml → 1,500 pg/ml:

A Increase diuretic therapy

B Add spironolactone

C Switch to sacubitril/valsartan

D Hospitalize patient

How would NT-proBNP impact therapeutic decision making?

- If no significant change in NT-proBNP:

A. Confirms lack of fluid overload, no changes necessary
B. Increase diuretic therapy
C. Add spironolactone
D. Switch to sacubitril/valsartan

The real question: Would this decision be any different than if you did not have the NT-proBNP level?

Seattle Heart Failure Score

- Information not included in the case:
  - Na
  - Total Cholesterol
  - Hemoglobin
  - Lymphocytes
  - Uric Acid

- For this patient
  - 97.6% anticipated 1 year survival
  - 88.6% anticipated 5 year survival

The real question: Will this score change any of your clinical decision making at this clinic visit?

MoCA – Montreal Cognitive Assessment

- Takes approximately 10 minutes to administer (per mocatest.org)
- Score 28 points – considered to be “normal”

- Was it worth performing this test?

A YES

B NO

Medication Adherence

- Prescription refills: 90 day supply
  - 4 months ago (when discharged from hospital)
  - 1 month ago (after last physician visit)
- Prescription bottles at this visit have the appropriate number of pills
- Morisky score: 4
  - Does not forget to take medicine
  - Does not have problems remembering to take medicine
  - Does not stop taking medicine when feels better
  - Does not stop taking medicine when feels worse

Do these findings impact your decisions about the treatment plan for this patient?

A YES

B NO

Case #1:

LC is a 52 year old white male with NYHA class II HFrEF who presents to clinic complaining of mild fatigue and shortness of breath with moderate physical activity. He was last hospitalized 4 months ago when he was also diagnosed with atrial fibrillation

PMH: HF (EF 30%), hyperlipidemia, Atrial fibrillation

Physical Exam: BP 98/66, ventricular rate 84, 82 kg (stable), 1+ pitting edema (baseline), JVD 8-9 cm (baseline), no crackles / rales

Labs: K+ 4.3 mEq/mL, BUN 25 mg/mL, sCr 1.9 mg/mL (stable), est. CrCl 50 ml/min, NT-proBNP (1 month ago when stable) – 800 pg/mL

Current medications: furosemide 40mg BID, lisinopril 20mg daily, metoprolol XL 200mg daily, apixaban 5 mg bid, and atorvastatin 40mg daily.

What Recommendation would you make to optimize LC's therapy?

A. Keep therapy as is. No changes are needed at this time.

B. Discontinue lisinopril and start sacubitril/valsartan

C. Initiate ivabradine

D. Start Spironolactone

If you chose not to switch to Sacubitril/valsartan, why not?

- "The patient's blood pressure it so low."

- Paradigm HF exclusion criteria: SBP < 100 mmHg at screening or SBP < 95 mmHg at randomization.
- Paradigm HF Baseline Characteristics: Mean SBP 122

Paradigm HF Blood Pressure results	**Sac/Val**	**Enalapril**	
SAE – Hypotension defining trial endpoint	1.4%	1.61%	
Symptomatic Hypotension	14%	9.2%	P< 0.001
Hypotension requiring hospitalization	7.5%	12.3%	P< 0.001
BP difference at 8 months / Mean BP difference	3.2 mmHg / 2.7 mmHg		

NEJM 2014;271:11.
HFSA 2016 Abstract 088.

If you chose not to switch to Sacubitril/valsartan, why not?

- "Patient is currently stable."

"The purpose of switching patients to sacubitril/valsartan is not to improve symptoms (although this occurs) but instead to maintain clinical remission in patients who are destined to develop worsening heart failure or die suddenly."

Milton Packer. Angiotensin Neprilysin Inhibition for Patients With Heart Failure: What If Sacubitril/Valsartan Were a Treatment For Cancer? JAMACard Sept. 2016.

What does Paradigm HF say about the stable patient?

- Entry criteria: NYHA FC II, III, or IV; EF < 40%
  - NT-proBNP ≥ 600 pg/ml
  - ≥ 400 pg/ml if hospitalized in last 12 months
- Paradigm HF Demographics –
  - NYHA FC II – 71%
- Paradigm HF Primary Outcome
  - Death from cardiovascular causes or first hospitalization for worsening heart failure:
    - Sac/Val – 21.8%
    - Enalapril 26.5%
    - P < 0.001

NEJM 2014;271:11.

If you chose not to switch to Sacubitril/valsartan, why not?

- "It is too expensive."

- This offer negates all price concerns regarding Entresto.

A TRUE

B FALSE

Sacubitril/valsartan Coverage: What does it all mean?

- Example prior authorization coverage criteria
  - The patient has the diagnosis of chronic heart failure (NYHA Class II-IV) and reduced ejection fraction ≤ 40%.
  - The patient has no contraindications
  - The patient is being treated with a beta blocker or it is contraindicated
  - The patient has previously tried or has a contraindication to an ACE inhibitor
  - Cardiologist prescribes or is on consult

What is the cost of sacubitril/valsartan?

- 30 day supply: $480 (Costco.com)
- $10 Co-Pay Card: http://www.entresto.com/info/savings.jsp
- Novartis Patient Assistance Foundation
- https://www.pharma.us.novartis.com/our-products/patient-assistance/patient-assistance-foundation-enrollment

- What is your experience?

If you chose to add spironolactone instead of sacubitril/valsartan, why?

- "MRA's have proven mortality benefit in HF"

- Emphasis Trial Primary Outcome
  - Death from cardiovascular causes or first hospitalization for worsening heart failure:
    - Eplerenone 18.3%
    - Placebo 25.9%
    - P < 0.001

ARR = 7.6%

- Paradigm HF Primary Outcome
  - Death from cardiovascular causes or first hospitalization for worsening heart failure:
    - Sac/Val – 21.8%
    - Enalapril 26.5%
    - P < 0.001

ARR = 4.7%

NEJM 2011;364:11-21
NEJM 2014;271:11.

If you chose to add spironolactone instead of sacubitril/valsartan, why?

- "MRA's have a safer blood pressure profile."

- Emphasis HF exclusion criteria: symptomatic hypotension or SBP < 85 mmHg.
- Emphasis HF Baseline Characteristics: Mean SBP 124
- Means change in BP:
  - Eplerenone – 2.5 mmHg
  - Placebo – 0.3 mmHg
  - P = 0.001

NEJM 2011;364:11-21

Should MRA's and Sacubitril/Valsartan be used in combination?

Patients experiencing the primary endpoint according to background therapy in Paradigm HF Study

MRA	Enalapril	Sac/Val	HR (95% CI)	Interaction P value
No N= 3,728	27.2%	20.8%	0.74 (0.65-0.84)	0.104
Yes N=4,671	26.0%	22.7%	0.85 (0.76-0.96)	

Circ Heart Fail 2016;9(9);DOI: 10.1161/CIRCHEARTFAILURE.116.003212

If you chose not to add ivabradine, Why not?

- "The patient has atrial fibrillation."

- Atrial fibrillation in BEAUTIFUL and SHIFT trials
  - Atrial fibrillation patients excluded
  - Incidence of Atrial fibrillation
    - Ivabradine – 501/5,940 = 8%
    - Placebo – 400/5,957 = 7%
    - P < 0.001

Eur Heart J 2013;34:2263-2270.

If you chose to add ivabradine, why?

- "Because the beta blocker is maxed and the HR = 84"

- Ivabra
  - "F
  - Pr

Ba
VR
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What do the experts say?

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Case #2:

RA is a 63 year old black female with NYHA class III HFrEF who presents to clinic complaining of mild fatigue and shortness of breath when completing activities of daily living. She was last hospitalized 2 weeks ago because she was short of breath at rest.

PMH: HF (EF 25%), CAD with MI 5 years ago, Type 2 DM, hyperlipidemia

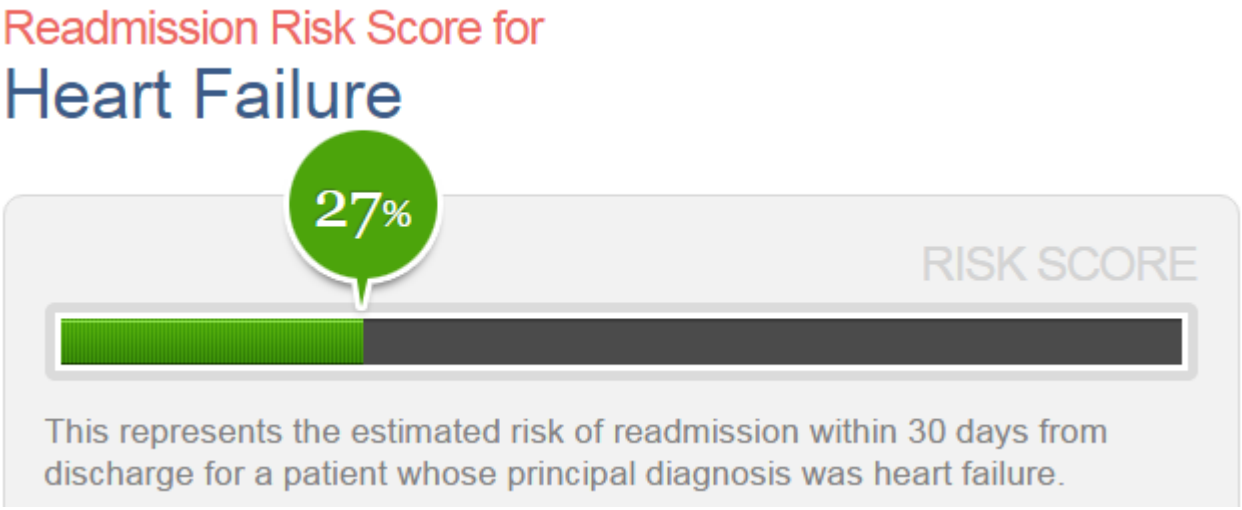
Physical Exam: BP 150/94, HR 92, 78 kg (2 kg increase since discharge),2+ pitting edema, crackles and rales in lower half of lungs

Labs: K+ 3.6mEq/mL, BUN 25 mg/mL, sCr 1.1 mg/mL, eGFR 50ml/min, fasting BG 140 mg/dl

Current medications: furosemide 40mg BID, lisinopril 20mg daily, carvedilol 12.5 mg bid, hydralazine 50mg TID, isosorbide dinitrate 20mg TID, glipizide XL 10mg daily, and atorvastatin 40mg daily.

Risk for Readmission

- Readmission Risk Score: http://www.readmissionscore.org/heart_failure.php



- Is this the whole story for this patient?

What is the best method to prevent readmission in this patient?

A. Optimize diuretic therapy

B. Discontinue lisinopril and start sacubitril/valsartan

C. Increase Carvedilol

D. Initiate empagliflozin to 10 mg daily

If you chose to “Optimize Diuretic Therapy”, what is the evidence?

Evidence-Based Diuretic Therapy

- Dosing of loop diuretics in chronic heart failure: it's time for evidence. Eur J Heart Fail 2016;Aug. 5. doi: 10.1002/ejhf.619.
- Age + BUN = Lasix dose: Samuel Shem, Laws of the House of God. The House of God 1979: ISBN 0-440-13368-8
- HFSA Guidelines
  - Diuretic therapy is recommended to restore and maintain normal volume status in patients with clinical evidence of fluid overload.
  - Loop diuretics rather than thiazide-type diuretics are typically necessary to restore normal volume status in patients with HF.

hfsa.org

Best Practice Diuretic Therapy

- Doing the best we can with what we have:
  - Use lowest dose to achieve optimal fluid status
  - May use loop diuretics in combination with metolazone
  - Patient self-monitoring and self-titration may be helpful

Curr Treat Opt in Card Med 2009;11:426.

If you chose to add Sacubitril/Valsartan, how can we extrapolate the evidence for this patient?

- From Paradigm HF Trial
  - 5% of patients were Black
  - 7% from North America
- From Package Insert:
  Percent of patients experiencing angioedema

	Sac/Val	Enalapril
Overall	0.5%	0.2%
Black	2.4%	0.5%

NEJM 2014;271:11.

If you chose to increase carvedilol, will it provide the desired outcome?

- Desired outcome: Decrease readmission in a patient with a 2 kg weight gain accompanied by crackles and rales.
- HFSA Guideline recommendations:
  - Beta blockers should not be initiated in patients with acute decompensated heart failure with persistent symptoms and congestion.
- Medicare Database: Beta-blocker neither increased or decreased 30 day readmission

- Is this the most important outcome? Will increasing the beta blocker dose decrease mortality, improve symptoms over time, improve blood pressure?

HFSA.org
Am J Med 2015;128:715-21

If you chose to initiate empagliflozin…

- Empagliflozin increases urine output by 107-450 mL/day
  - Is this a dose dependent effect?
- Empa-Reg Outcome Trial – Heart Failure patients (706/7020)

Outcome	Placebo (n=244)	Empagliflozin (n=462)	HR (95% CI)
Heart failure hospitalization or CV death	49 (20%)	75 (16.2%)	0.72 (0.50-1.04)
Hospitalization for heart failure	30 (12.3%)	48 (10.4%)	0.75 (0.48-1.19)

Eur Heart J 2016 1526–34.
Trends in Cardiovascular Medicine 2016
http://dx.doi.org/10.1016/j.tcm.2016.07.008

What do the experts say?

ashp
MIDYEAR 2016
Clinical Meeting & Exhibition

What other questions should we be asking? What topics should we prioritize for next year's MCM Symposium?

- A What should the blood pressure goal be for this patient and why?
- B How should the role of the hydralazine / isosorbide dinitrate combination evolve with the new therapies?
- C What impact do blood pressure and/or individual agents have on cognitive function in elderly patients?
- D What is the relationship between the role of digoxin and ivabradine

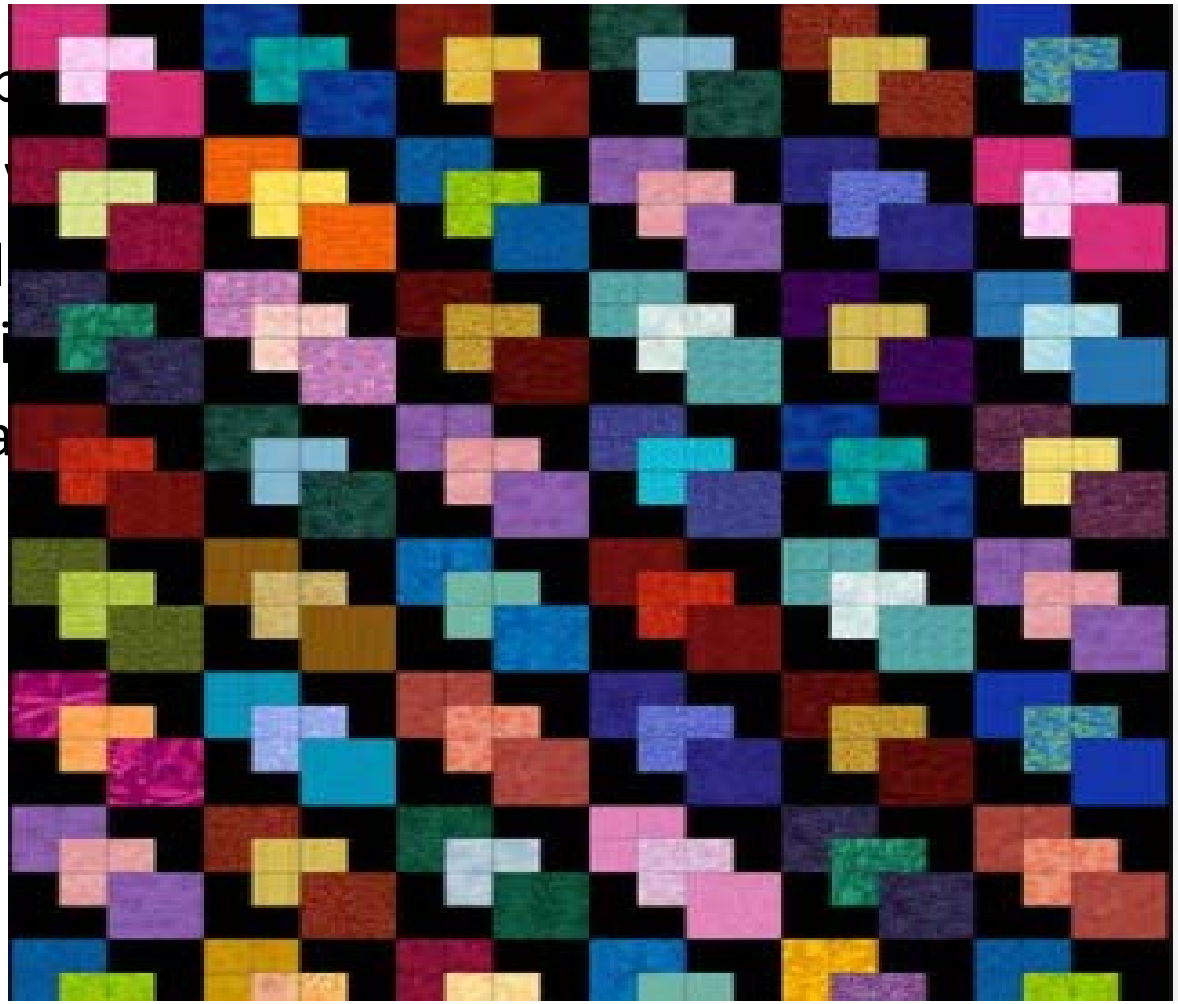
Which of the following assessments provide a role for student engagement in the care of a heart failure patient?

A Bendop

B Cogniti

C Clinical e– The One Mi

D Medica



Key Takeaways

- Key Takeaway #1
  - Patient assessments can be enhanced by pharmacist participation and adherence, cognitive function, and an understanding of patient symptoms should be included.
- Key Takeaway #2
  - Designing appropriate heart failure regimens for patients should include an understanding of their heart failure status and a thorough understanding of the benefits and risks of the medications involved.
- Key Takeaway #3
  - Pharmacy student participation in the process of patient assessment can enhance the pharmacists ability to participate in the care of heart failure patients.