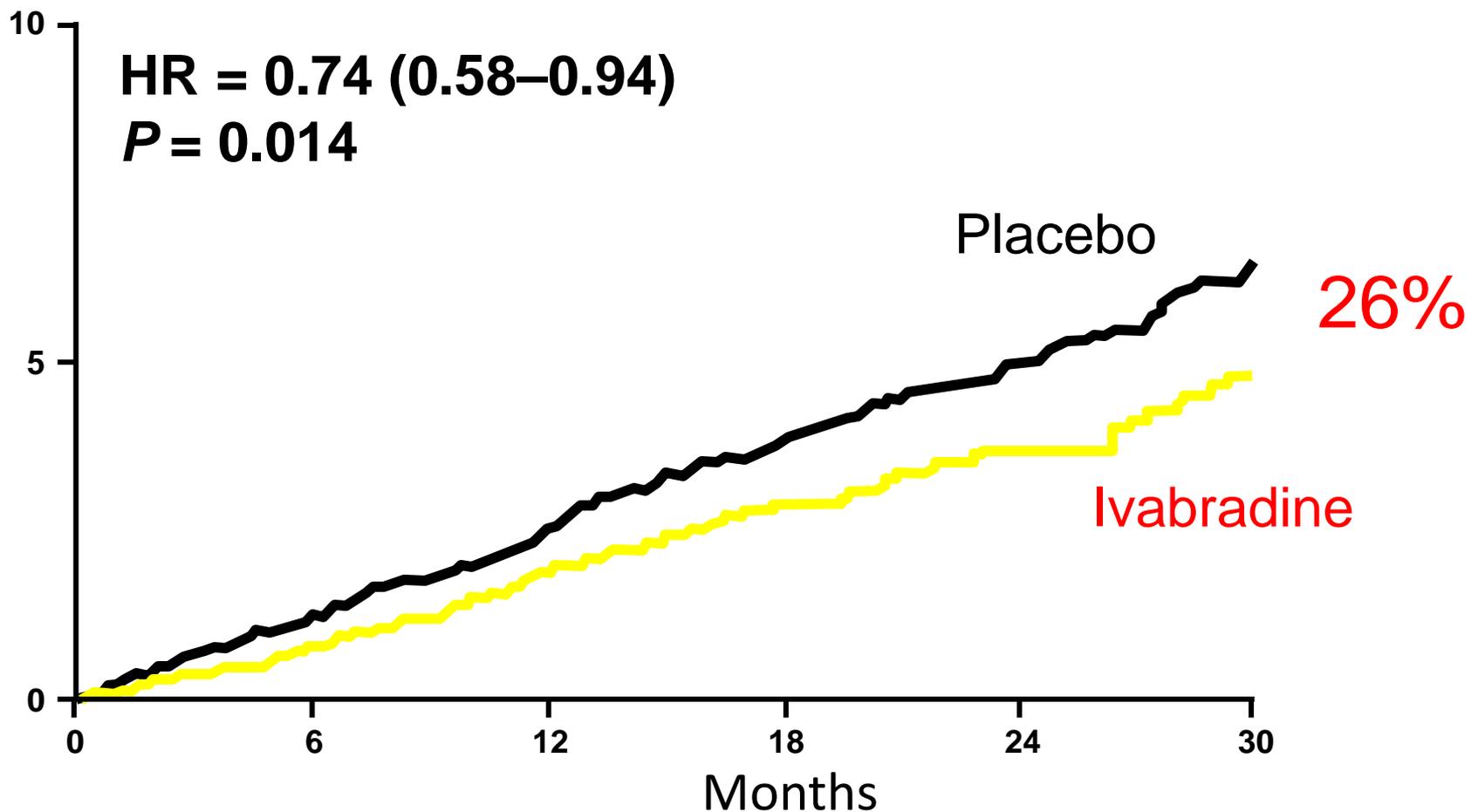


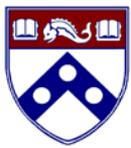


Death from heart failure

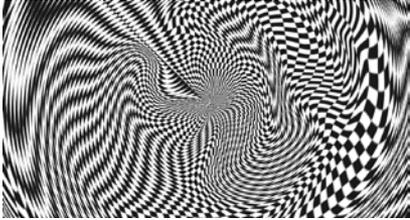


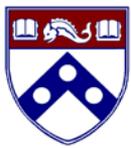
Cumulative frequency (%)





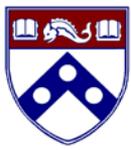
Considerations With Ivabradine

- Improvement in NYHA class
- Improvement in outcomes
- Limited side effect profile
 - Visual changes – phosphenes 
 - Increased risk of atrial fibrillation
- Effect may be largely contingent on basal heart rate
- Is not a beta-blocker and is “add-on” therapy
- “Personalized” medicine based on HR?



Incorporating Ivabradine

- In addition to maximally tolerated beta blocker
- Concern about limiting cardiac output in patients with advanced disease who have fixed stroke volumes
- May have largest impact in those with mild to moderate disease but who cannot tolerate much beta blocker due to hypotension or pulmonary side-effects
- Not for use in patients with atrial fibrillation



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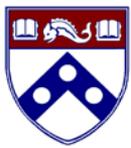
ESTABLISHED IN 1812

SEPTEMBER 11, 2014

VOL. 371 NO. 11

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

John J.V. McMurray, M.D., Milton Packer, M.D., Akshay S. Desai, M.D., M.P.H., Jianjian Gong, Ph.D.,
Martin P. Lefkowitz, M.D., Adel R. Rizkala, Pharm.D., Jean L. Rouleau, M.D., Victor C. Shi, M.D.,
Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., and Michael R. Zile, M.D.,
for the PARADIGM-HF Investigators and Committees*

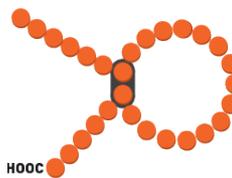


NEP is a zinc dependent membrane endopeptidase

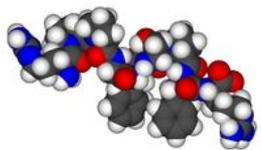
cleaves peptides containing up to 40–50 amino acids



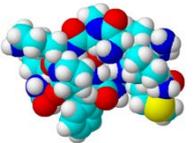
Natriuretic peptides (ANP, BNP, CNP)



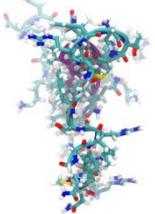
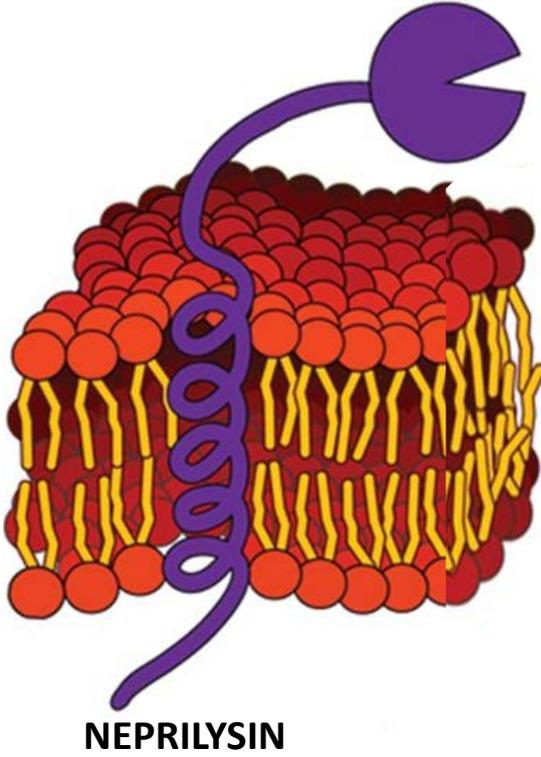
Bradykinin



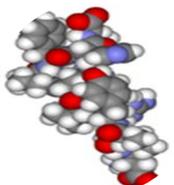
Substance P



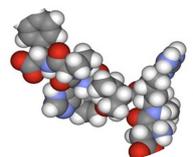
Adrenomedullin

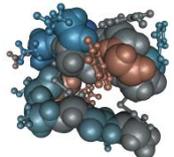
Angiotensin I



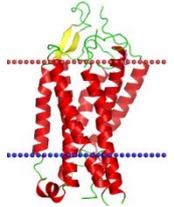
Angiotensin II



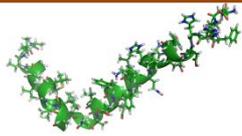
Endothelin I



Neurotensin



Amyloid β Peptide



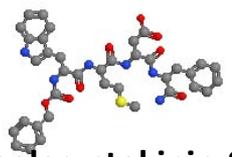
Enkephalins, Endomorphins



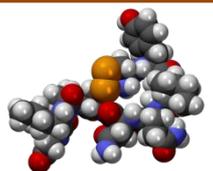
Corticotropin Neuropeptide γ



Gastrin, Cholecystokinin-8, Somatostatin, Glucagon, VIP

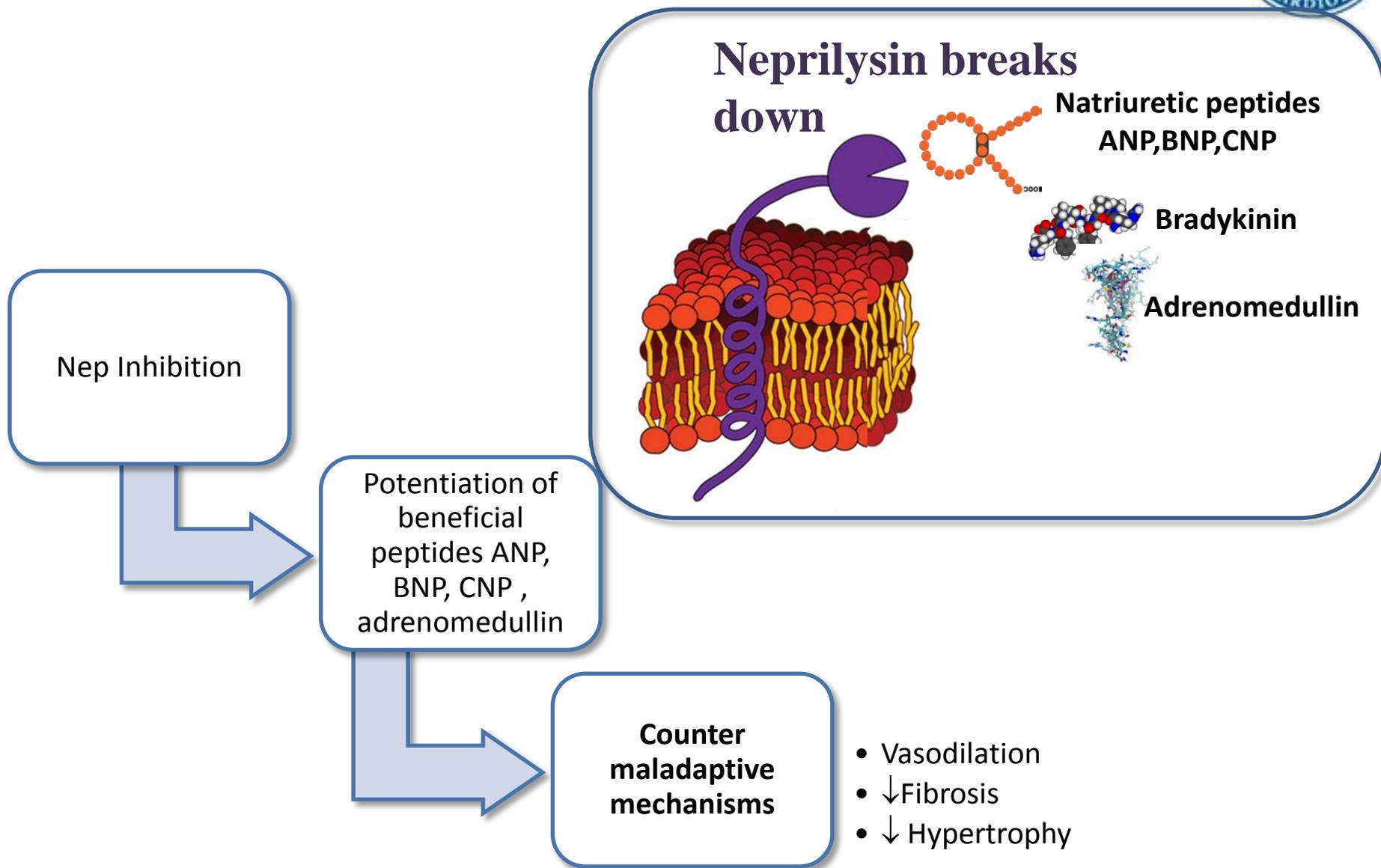


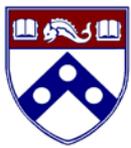
Oxytocin





NEP Inhibition in CVD





Balance of NEP Inhibition

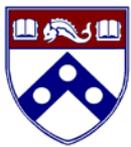


**Increased levels of ANP, BNP, CNP,
Potentiation of endogenous peptides
that counter maladaptive mechanisms
Vasodilation , ↓ Fibrosis, ↓ Hypertrophy**



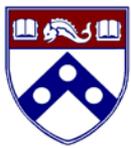
**Reduced breakdown of angiotensin II,
(endothelin I) increased activity of the
RAAS sympathetic nervous system
Vasoconstriction, ↑ Fibrosis, ↑ Hypertrophy**

The antihypertensive effects may be offset by an increased activity of the RAAS and sympathetic nervous system and/or by downregulation of ANP receptors.



Addressing Increased RAAS Activity

- In order to address the concern about increased RAAS activity, neprilysin inhibitor combined with RAAS blocker
- Early trials with ACE inhibitor lead to increased incidence of angioedema
- For this reason, ARB chosen as does not increase bradykinin levels
- Neprilysin inhibitor contraindicated with ACE inhibitor



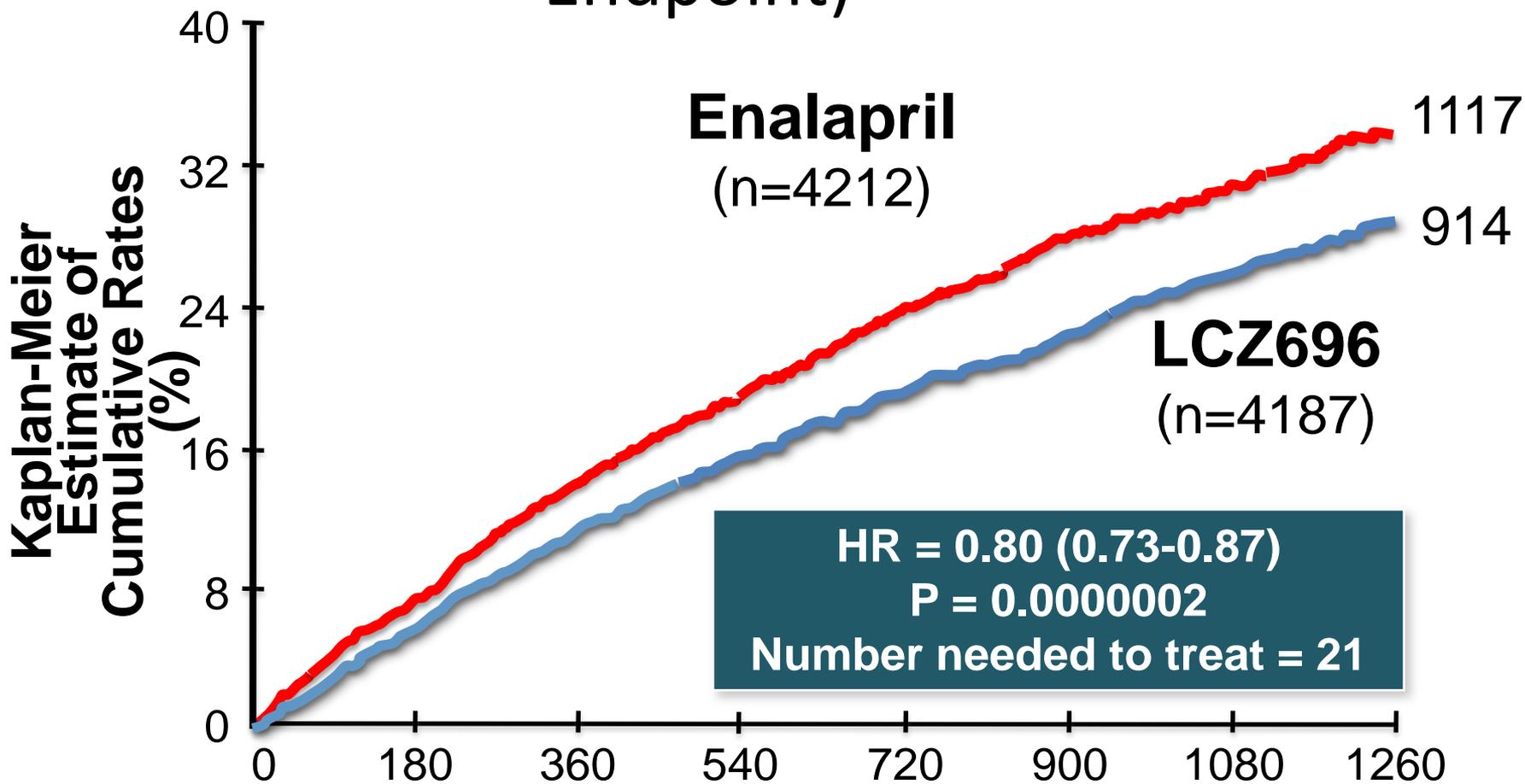
ARNI Treatment for HFrEF: The PARADIGM-HF Study



- Study description
 - Randomized, double-blind phase 3 trial
 - Evaluation of the efficacy and safety profile of angiotensin receptor-neprilysin inhibitor (ARNI) versus the ACE inhibitor, enalapril
 - 8442 patients with HFrEF (NYHA class II-IV)
 - Open-label run-in phase removed patients who were intolerant prior to randomization



PARADIGM-HF: Cardiovascular Death or Heart Failure Hospitalization (Primary Endpoint)

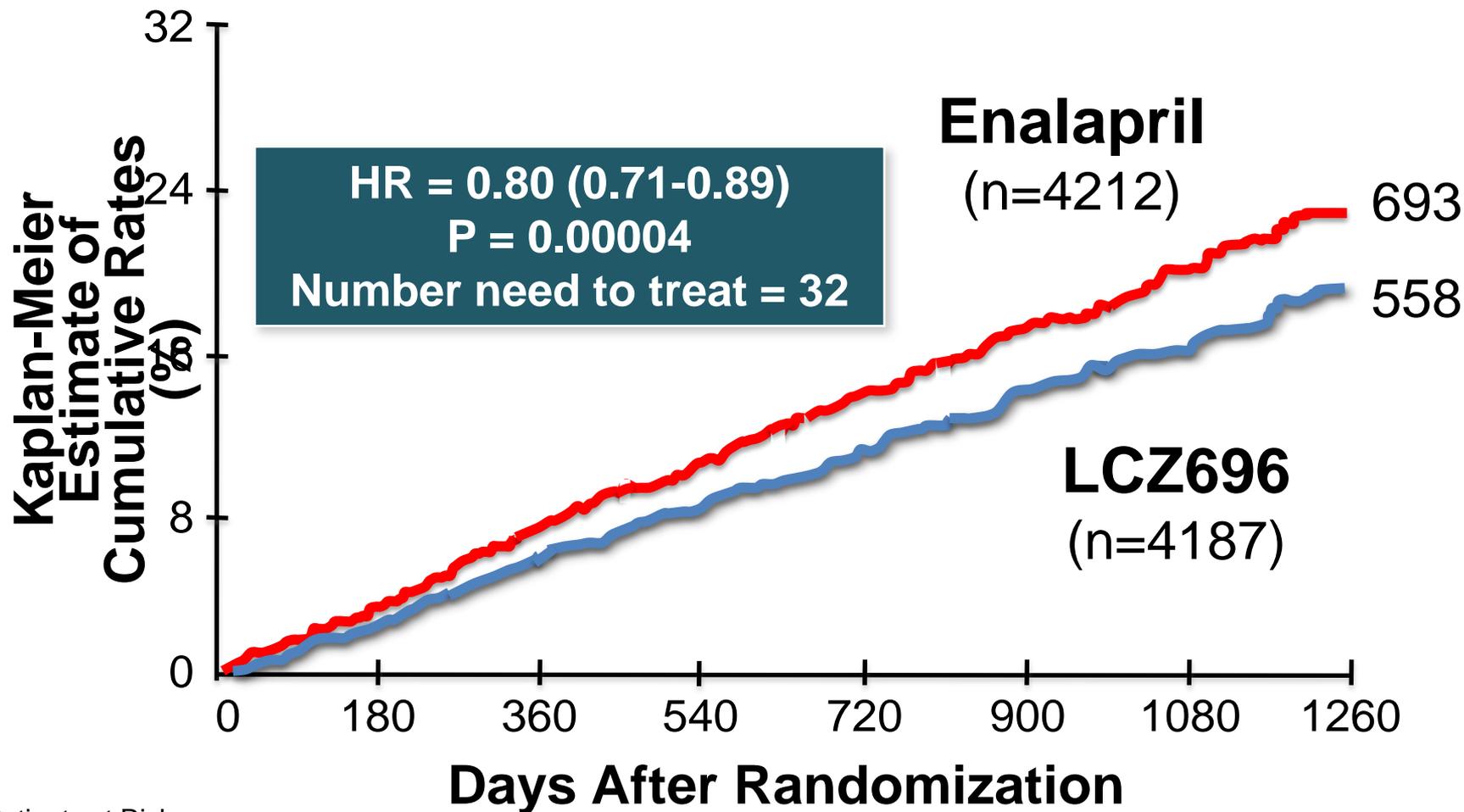


Patients at Risk

	0	180	360	540	720	900	1080	1260
LCZ696	4187	3922	3663	3018	2257	1544	896	249
Enalapril	4212	3883	3579	2922	2123	1488	853	236



PARADIGM-HF: Cardiovascular Death

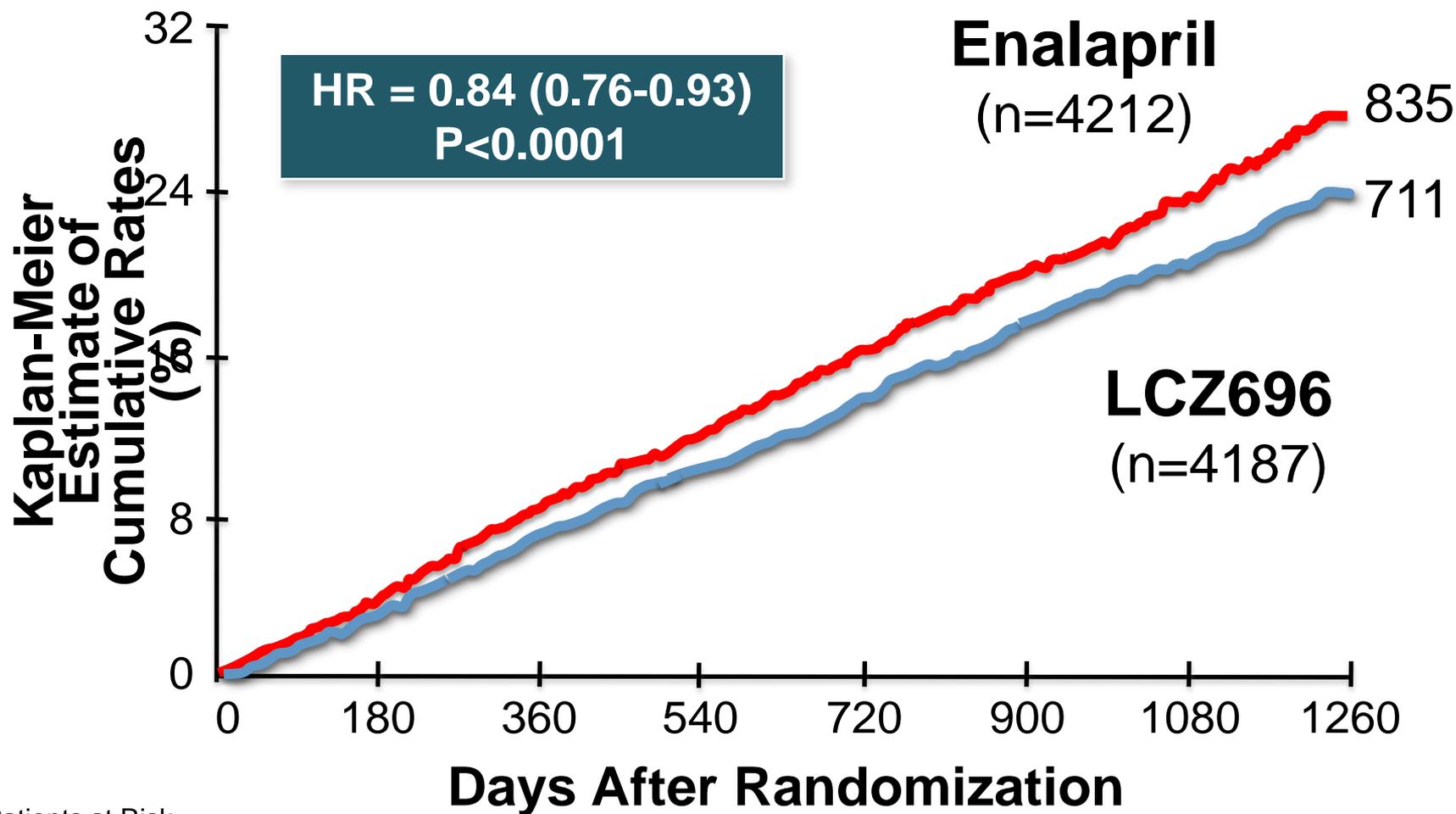


Patients at Risk

	0	180	360	540	720	900	1080	1260
LCZ696	4187	4056	3891	3282	2478	1716	1005	280
Enalapril	4212	4051	3860	3231	2410	1726	994	279

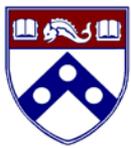


PARADIGM-HF: All-Cause Mortality



Patients at Risk

	0	180	360	540	720	900	1080	1260
LCZ696	4187	4056	3891	3282	2478	1716	1005	280
Enalapril	4212	4051	3860	3231	2410	1726	994	279



Considerations with Valsartan/Sacubitril

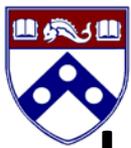
In heart failure with reduced ejection fraction:

Valsartan/Sacubitril as compared to enalapril

- Reduced the risk of CV death and HF hospitalization
- Reduced the risk of CV death by *incremental* 20%
- Reduced the risk of HF hospitalization by *incremental* 21%
- Reduced all-cause mortality by *incremental* 16%
- Improved symptoms and physical limitations

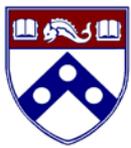
Valsartan/Sacubitril as compared to enalapril

- Less likely to cause cough, hyperkalemia or renal impairment
- Less likely to be discontinued due to an adverse event
- More hypotension, but no increase in discontinuations
- **Not more likely to cause serious angioedema**



Incorporating Valsartan/Sacubitril

- PARADIGM-HF Trial enrolled mostly NYHA Class II and some Class III patients
- May be limited by blood pressure in patients with more advanced disease
- Incorporated in lieu of an ACE or ARB for Stage C with NYHA Class 2 or 3 symptoms without significant renal insufficiency or hyperkalemia
- PARAGON-Trial evaluating Valsartan/Sacubitril versus valsartan in HFpEF



**HFrEF Stage C
NYHA Class I – IV
Treatment:**

Class I, LOE A
ACEI or ARB **AND**
Beta Blocker

Class 1 LOE B ARNI
Class 2A LOE B Ivabradine

For all volume overload,
NYHA class II-IV patients

For persistently symptomatic
African Americans,
NYHA class III-IV

For NYHA class II-IV patients.
Provided estimated creatinine
>30 mL/min and K+ <5.0 mEq/dL

Add

Add

Add

Class I, LOE C
Loop Diuretics

Class I, LOE A
Hydral-Nitrates

Class I, LOE A
Aldosterone
Antagonist

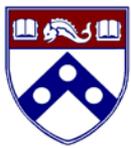


Updates to Device Therapy in Heart Failure



- 2013 Guidelines expanded the indications for biventricular pacing

Modality	Impact
BiV Pacing	Improved survival in patients with mild heart (NYHA Class 2) failure



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ORIGINAL ARTICLE

Survival with Cardiac-Resynchronization Therapy in Mild Heart Failure

Ilan Goldenberg, M.D., Valentina Kutiyfa, M.D., Ph.D., Helmut U. Klein, M.D., David S. Cannom, M.D., Mary W. Brown, M.S., Ariela Dan, Ph.D., James P. Daubert, M.D., N.A. Mark Estes III, M.D., Elyse Foster, M.D., Henry Greenberg, M.D., Josef Kautzner, M.D., Robert Klempfner, M.D., Malte Kuniss, M.D., Bela Merkely, M.D., Ph.D., Marc A. Pfeffer, M.D., Ph.D., Aurelio Quesada, M.D., Ph.D., Sami Viskin, M.D., Scott McNitt, M.S., Bronislava Polonsky, M.S., Ali Ghanem, M.D., Scott D. Solomon, M.D., David Wilber, M.D., Wojciech Zareba, M.D., Ph.D., and Arthur J. Moss, M.D.

N Engl J Med Volume 370(18):1694-1701 May 1, 2014

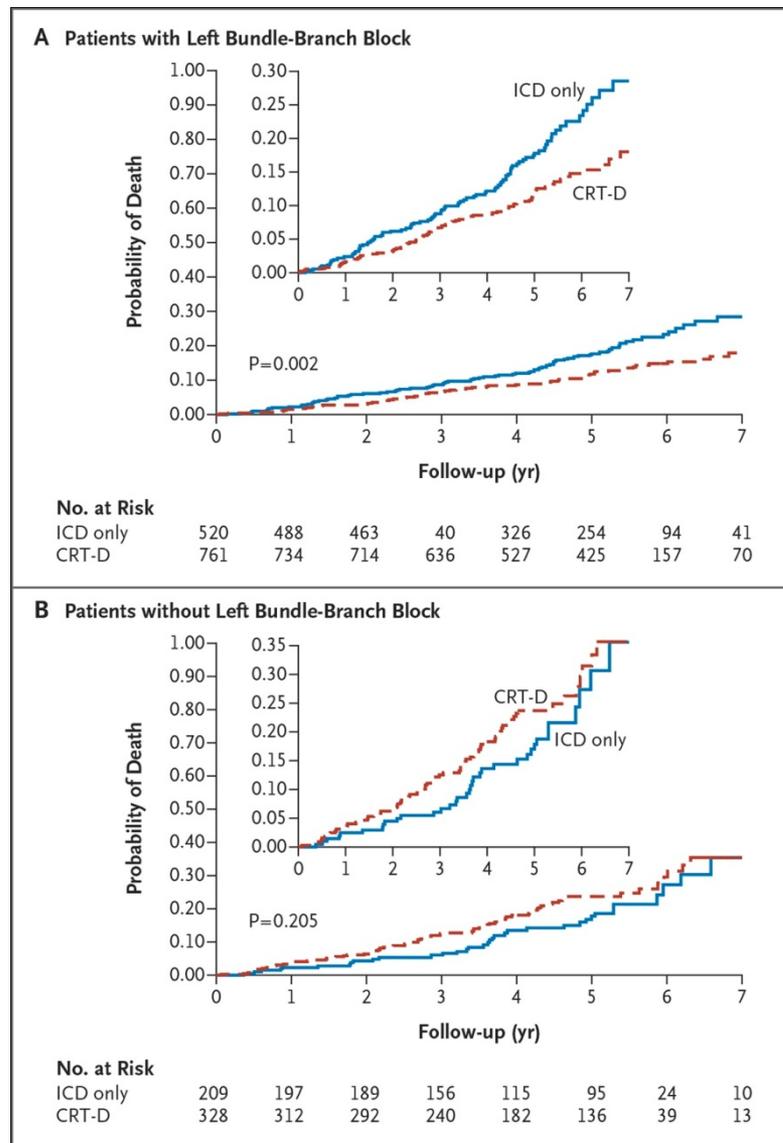


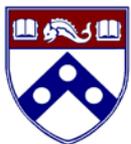
MADIT-CRT Long Term Follow-up

- The Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) showed that early intervention with cardiac-resynchronization therapy with a defibrillator (CRT-D) in patients with left bundle-branch block was associated with a significant reduction in heart-failure events over a median follow-up of 2.4 years, as compared with defibrillator therapy alone
- This study is the longer term follow-up to a median of 7 years



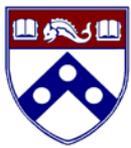
Kaplan–Meier Estimates of the Cumulative Probability of Death from Any Cause among Patients with and Those without Left Bundle-Branch Block





Conclusions- MADIT-CRT F/U

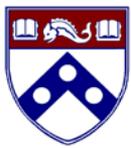
In patients with mild heart-failure symptoms, left ventricular dysfunction, and left bundle-branch block, early intervention with CRT-D was associated with a significant long-term survival benefit



Current State of Guidelines



- Incorporated Ivabradine into ACC/AHA/HFSA and European Guidelines
 - In addition to ACE or ARB, (?ARNI) and Beta blocker – stage C NYHA Class 2/3
 - Heart rate >75 beats/minute on maximally tolerated beta blocker
- Incorporated of ARB/neprilysin inhibitor (sacubitril/valsartan) into ACC/AHA/HFSA and European Guidelines
 - In lieu of ACE or ARB – Stage C – NYHA Class 2/3
- Continued expansion of BiV pacing indications



Anticipating 2017 Guideline Update



- Part II – 2017 – Focused Updated
 - Prevention
 - Heart Failure with preserved ejection fraction (HFpEF)
 - Heart Failure comorbidities
 - Anemia – role of IV iron (CONFIRM HF)
 - Sleep apnea – Serve HF
 - Hypertension
- New Heart Failure Guidelines tool kit
 - APP and web-based tools to aid implementation



Thank You

ขอบคุณ ครับ