Kamol Sindhvanandha Honorary Lecture

Updates to the Heart Failure Guidelines 2017

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Kamol Sindhvanandha, MD

- Studied in the United States
  - Barnes – St. Louis
  - Harvard Beth Israel – Boston (Dr. Louis Wolff)
  - University of Pennsylvania – Philadelphia
- Involved in Public Health with the World Health Organization
  - Rheumatic Heart Disease 1984
- Pioneer in Cardiology

WHO Rheumatic Heart Disease

WORLD HEALTH ORGANIZATION

ORGANISATION MONDIALE DE LA SANTE

12493

WHO/CVD/84.3

ENGLISH ONLY

E + F

WHO/CVD INTENSIFIED PROGRAMME

ACTION TO PREVENT RHEUMATIC FEVER/RHEUMATIC HEART DISEASE (RF/RHD)

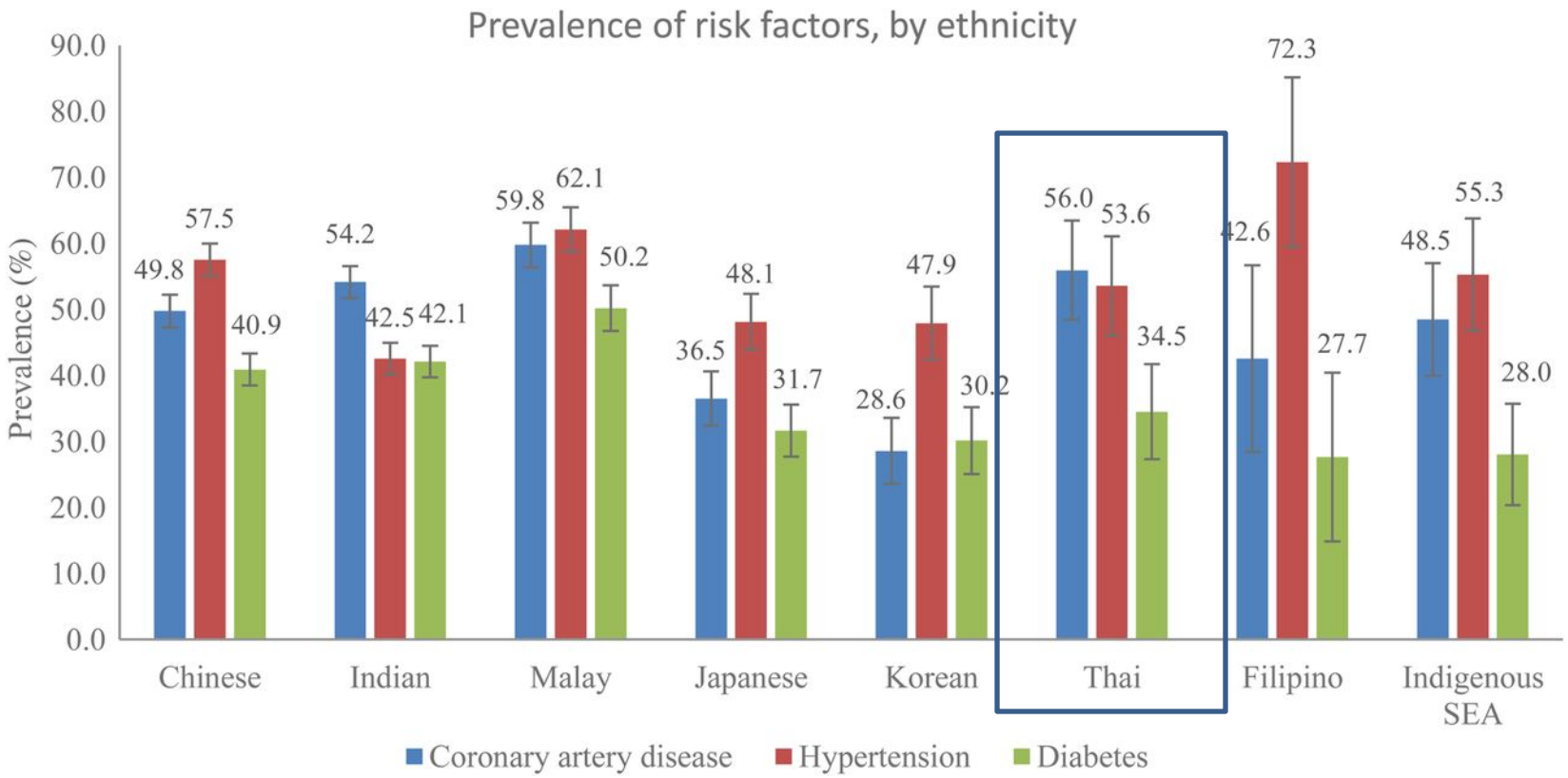
Report on Planning Meeting
Geneva, 4-5 April 1984

Dr Lu urged the meeting to concentrate on strategies for establishing and maintaining the services required for the prevention of RF/RHD, within the context of primary health care and the existing national health care delivery system.

1.1.1 Election of officers

Dr Kamol Sindhvananda was elected Chairman and Dr Edward Kaplan was elected Rapporteur.

Risk Factors for Heart Failure Across Asia



Regional and ethnic differences among patients with heart failure in Asia: the Asian sudden cardiac death in heart failure registry
Carolyn S.P. Lam, Tiew-Hwa Katherine Teng, Wan Ting Tay, Inder Anand, Shu Zhang, Wataru Shimizu, Calambur Narasimhan, Sang Weon Park, Cheuk-Man Yu, Tachapong Ngarmukos, Razali Omar, Eugene B. Reyes, Bambang B. Siswanto, Chung-Lieh Hung, Lieng H.Ling, Jonathan Yap, Michael MacDonald, A. Mark Richards **Eur Heart J 2016;eurheartj.ehw331**

Heart Failure May Not Be the Same in Asia

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STATE-OF-THE-ART PAPER

Heart Failure Clinical Trials in East and Southeast Asia

Understanding the Importance and Defining the Next Steps

Robert J. Mentz, MD,[a] Lothar Roessig, MD,[b] Barry H. Greenberg, MD,[c] Naoki Sato, MD, PhD,[d] Kaori Shinagawa, MD, PhD,[e] Daniel Yeo, MBBS,[f] Bernard W.K. Kwok, MBBS,[g] Eugenio B. Reyes, MD,[h] Henry Krum, MBBS, PhD,[i,†] Burkert Pieske, MD,[j] Stephen J. Greene, MD,[a] Andrew P. Ambrosy, MD,[a] Jacob P. Kelly, MD,[a] Faiez Zannad, MD,[k,l,m,n,o] Bertram Pitt, MD,[p] Carolyn S.P. Lam, MBBS[q]

May need specific trials in Asia to understand impact of therapies

CENTRAL ILLUSTRATION **HF Phenotype and Treatment in Asia Compared With Other Regions**

Mentz, R.J. et al. J Am Coll Cardiol HF. 2016;4(6):419-27.

ACE/ARB = angiotensin-converting enzyme/angiotensin receptor blocker; AHF = acute heart failure; CRT = cardiac resynchronization therapy; ICD = implantable cardioverter-defibrillator; MRA = mineralocorticoid receptor antagonist; RHD = rheumatic heart disease.

ACC/AHA Heart Failure Guidelines

- Two recent updates
  - 2013
  - 2016
- Major update expected to be released later in 2017

What's New in 2013 ACC/AHA Guideline Update

- Harmonization with other guidelines
- Emphasis on transitions and heart failure education as well as performance measures
- Team based care
- Risks and benefits of ICD's including ability to deactivate
- Sodium restriction is "reasonable" in heart failure with volume overload

What's New in 2013 Update Drugs and Devices

- Aldosterone antagonists – broadened to include NYHA Class II
- BiV pacing expanded to include NYHA Class 2 patients with left bundle branch block and QRS >= 150 ms (but not indicated in NYHA II, non LBBB and QRS <150 ms)

What's New in 2013 Update Advanced Therapies

- Expansion of mechanical circulatory support (VADs) now Class 2 as bridge to decision, bridge to recovery and destination therapy

What's New 2016 Update: Use of Newer Drugs for Heart Failure

- 2016 **ACC/AHA/HFSA** focused update
- Released simultaneously with **ESC HF** guideline update and endorsed by **HFSA** – more unified worldwide guideline

Sacubitril-Valsartan (ARNI)	Ivabradine
• In patients with NYHA class II-III chronic symptomatic HFrEF who tolerate ACE inhibitor or ARB, replacement by ARNI is recommended to further reduce morbidity and mortality • Use with β-blocker	Can reduce HF hospitalization in patients with NYHA class II-III stable chronic HFrEF (LVEF ≤35%) who are receiving GDMT, including maximally tolerated β-blocker, and who are in sinus rhythm with heart rate ≥70 bpm

ESC = European Society of Heart Failure; HFSA = Heart Failure Society of America.

Yancy CW, et al. *Circulation.* 2016 May 20. [Epub ahead of print]; Ponikowski P, et al. *Eur Heart J.* 2016;37:2129-2200.

Classification of Heart Failure

Stage "Course of Disease" **Class** "Symptoms at that moment"

ACCF/AHA Stages		NYHA Functional Classification	
A	At high risk for HF but without structural heart disease or symptoms of HF	None	
B	Structural heart disease but without signs or symptoms of HF	I	No limitation of physical activity. Ordinary physical activity does not cause HF symptoms
C	Structural heart disease with prior or current symptoms of HF	I	No limitation of physical activity. Ordinary physical activity does not cause HF symptoms
		II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in HF symptoms
		III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes HF symptoms
		IV	Unable to carry on any physical activity without HF symptoms, or symptoms at rest
D	Refractory HF requiring specialized interventions	IV	Unable to carry on any physical activity without HF symptoms, or symptoms at rest

The minimal required therapies to prevent progression and reduce morbidity and mortality

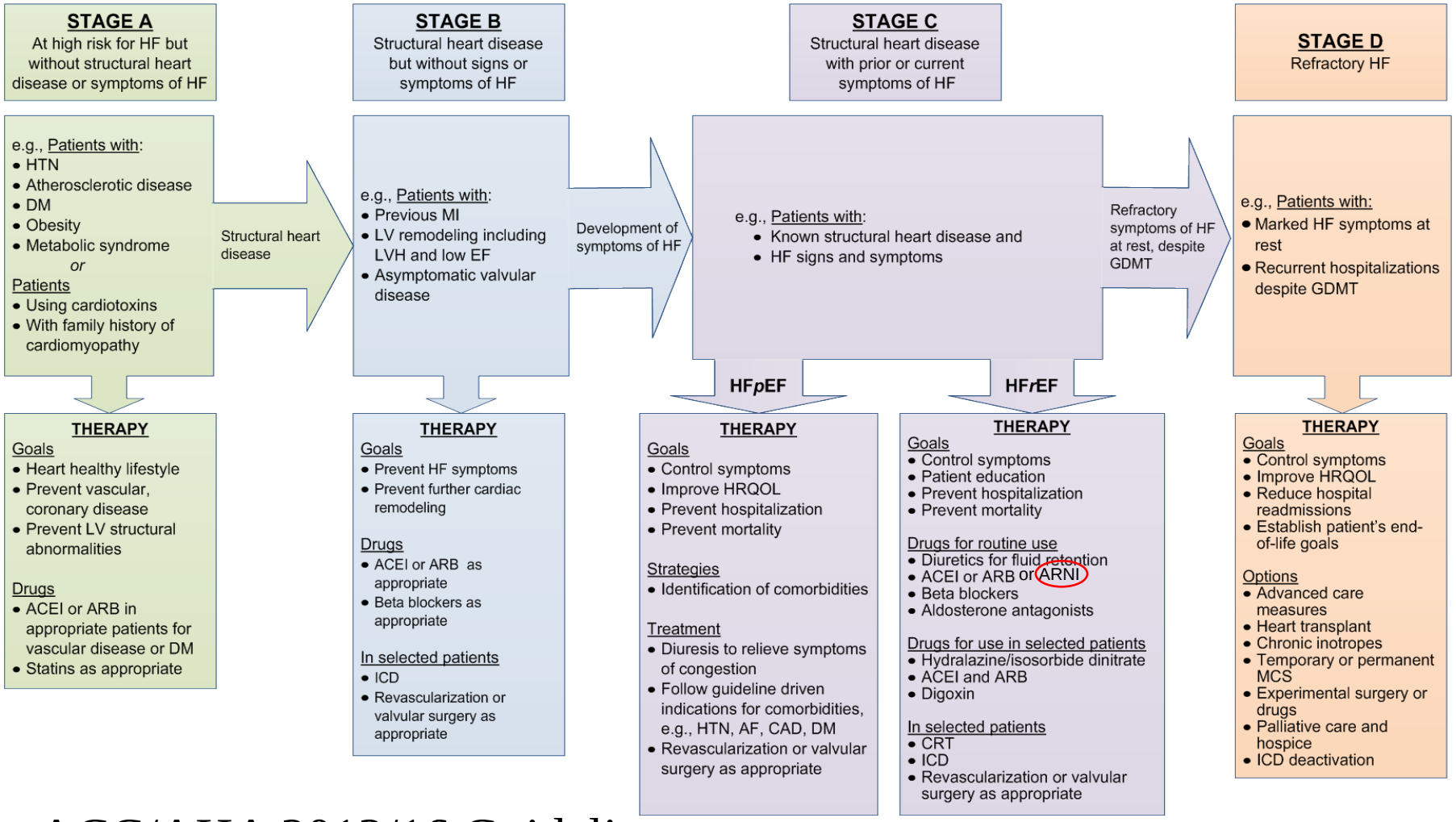
Therapies to reduce symptoms or trigger referral to advanced therapies or hospice

Yancy CW, et al. *Circulation*. 2013;128:1810-1852.

Stages, Phenotypes and Treatment of HF

At Risk for Heart Failure

Heart Failure



ACC/AHA 2013/16 Guidelines

Review of Pharmacologic Management of Heart Failure

- Combining neurohormonal blockade with at least an angiotensin-renin (+/- neprilysin) and adrenergic (sympathetic) blocker is the cornerstone of therapy
- Additional pharmacologic and device therapies are added based on the stage and then symptoms

Current Pharmacologic Approach to Heart Failure

Recommended for routine use

ACE inhibitors

- Effect
  - Interferes with RAS; enhances actions of kinins, prostaglandin synthesis, delays remodeling
  - Alleviate symptoms, reduce death, hospitalizations
- Clinical use: systolic and diastolic heart failure
  - Given to all patients with systolic dysfunction
- Adverse effects
  - Hypotension, azotemia, hyperkalemia, cough, angioedema

ACEI dose effect

- ATLAS *Eur Heart J* 1998; 19:481
  - 3164 patients: 2.5-5.0 or 32.5-35 mg lisinopril
  - No significant difference in mortality
  - Hospitalizations lower in high dose group

- NETWORK Packer et al. *Circulation* 1999;100;2312
  - 1532 patients: 5, 10, or 20 mg enalapril
  - CHF, hospitalizations, death: NS

Current Pharmacologic Approach to Heart Failure

Recommended for routine use

Beta blockers

- Effect
  - Inhibit the adverse effects of sympathetic system
  - Delays and reverses remodeling
- Clinical use: systolic and diastolic heart failure
  - Given to all patients with systolic HF in *absence of fluid overload*
- Adverse effects
  - Hypotension, bradycardia, worsening HF

Effects of β-Blockade on Mortality

US carvedilol program[1]		**All-cause mortality**
1094 patients (Class II–IV)	**Carvedilol**	↓ 65% (*P*<0.001)
BEST[2]		
2708 patients (Class III–IV)	~~Bucindolol~~	↓ 10% (*P*=0.109, NS)
CIBIS-II Trial HF[3]		
2647 patients (Class III–IV)	**Bisoprolol**	↓ 34% (*P*<0.0001)
MERIT-HF[4]		
3991 patients (Class II–IV)	**Metoprolol Succinate**	↓ 34% (*P*=0.0062)
COPERNICUS[5]		
2000 patients (Class IV)	**Carvedilol**	↓ 35% (*P*=0.00014)

1 Packer M et al. *N Engl J Med* 1996;334:1349; 2 *Clin Cardiol* 2000;23:56;

3 CIBIS-II Investigators and Committees. *Lancet* 1999;353:9; 4 MERIT-HF Study Group. *Lancet* 1999;353:2001; 5 SCRIP *World Pharmaceutical News* 2000;2572:20

Should Physicians Increase the Dose of ACE Inhibitor or Add β-Blockade?

Dose of ACEI :	**"Low" vs. "High" ***	**"Average" + β-blockade†**
Symptoms	Unchanged	Improved
Morbidity/ mortality	↓ 12%	↓ 35%-40%
Mortality	↓ 8%	↓ 30%-35%

*Adapted from Packer et al. Eur Heart J. 1998;19(suppl):142.
†Adapted from Lechat et al. Circulation. 1998;98:1184-1191.

Current Pharmacologic Approach to Heart Failure

ARB's

- Effect
  - Blocks effect of AG-II at receptor site; delays remodeling
  - Alleviate symptoms, reduce death, hospitalizations
- Clinical use
  - Given to patients if they cannot tolerate ACEI specifically angioedema, cough
  - Val-HeFT and CHARM: some improvement when used with ACEI
- Adverse effects
  - Hypotension, azotemia, hyperkalemia, rarely cough

Aldosterone Antagonists: Spironolactone/Eplerenone

- Improved mortality for class IIIB or class IV patients – RALES Trial
- Creatinine < 2.5 in men < 2.0 in women and Potassium < 5.0
- More recent studies with eplerenone showed benefits in NYHA **Class II to IV** (Expanded indication 2013)
- Contraindicated if on both ACE and ARB due to risk of hyperkalemia
- ? Role in HF with preserved ejection fraction

Eplerenone in Patients with Systolic Heart Failure and **Mild Symptoms** (EMPHASIS-HF)

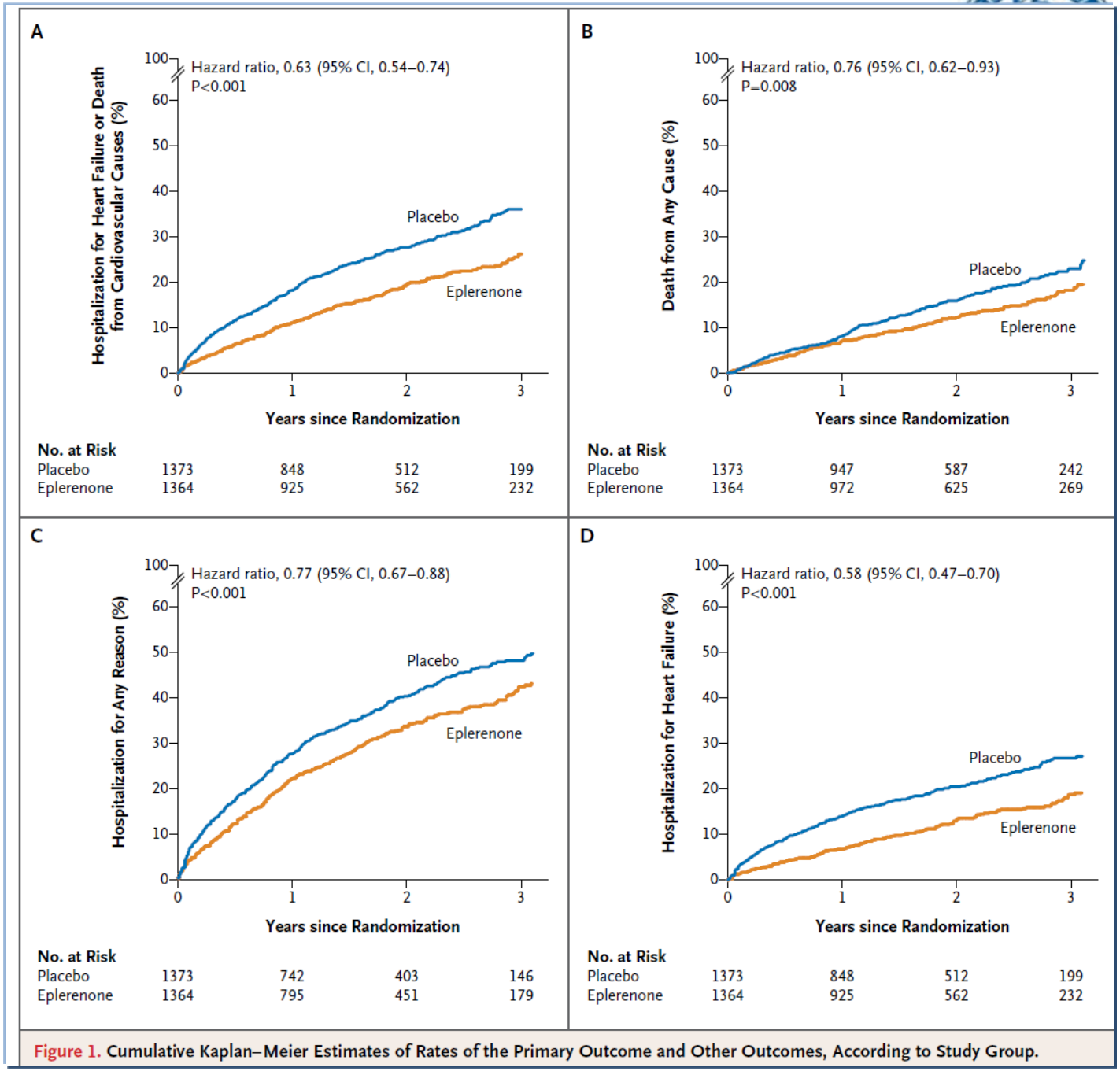


Figure 1. Cumulative Kaplan–Meier Estimates of Rates of the Primary Outcome and Other Outcomes, According to Study Group.

N Engl J Med 2011;364:11-21.

Heart Failure Therapies Demonstrated to **Increase Risk of Mortality** and/or Hospitalization

Mortality and/or Hospitalizations

NSAIDS

Calcium Channel Blockers (Dihydropyridine)

Inotropic Agents

RV pacing (induced dys-synchrony) (Block HF trial)

New Therapies for the Treatment of HF With Novel Mechanisms of Action

Agent	Mechanism of Action
Ivabradine	Selectively inhibits the sinus node I_f channel, thereby decreasing heart rate
Angiotensin receptor-neprilysin inhibitor (ARNI)	Combines angiotensin receptor blockade with inhibition of neprilysin,* thereby inhibiting RAAS and augmenting natriuretic peptide activity

RAAS, renin-angiotensin-aldosterone system.
*The metallopeptidase neprilysin hydrolyzes natriuretic peptides.
von Lueder TG, et al. *Pharmacol Ther*. 2014;144(1):41-49.
DiFrancesco D *Circ Res*. 2010;106(3):434-446.
Rosa GM, et al. *Expert Opin Drug Metab Toxicol*. 2014;10(2):279-291.

Ivabradine

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

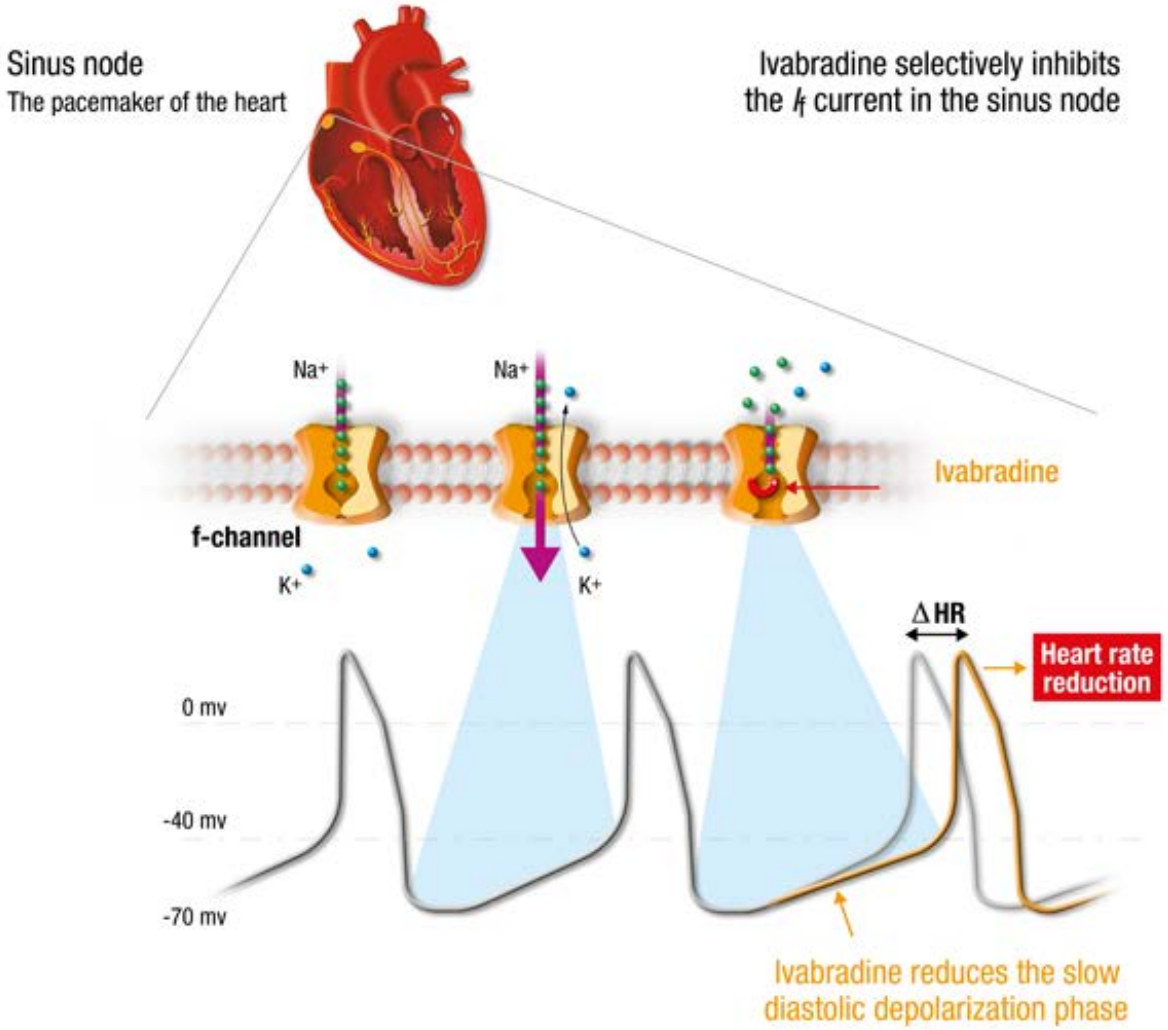
*Karl Swedberg, Michel Komajda, Michael Böhm, Jeffrey S Borer, Ian Ford, Ariane Dubost-Brama, Guy Lerebours, Luigi Tavazzi, on behalf of the SHIFT Investigators**

Lancet 2010; 376: 875–85

Ivabradine Mechanism

- Inhibits the If “funny” (pacemaker) current in the sinoatrial node to decrease heart rate but does not impact contractility

Ivabradine Mechanism of Action



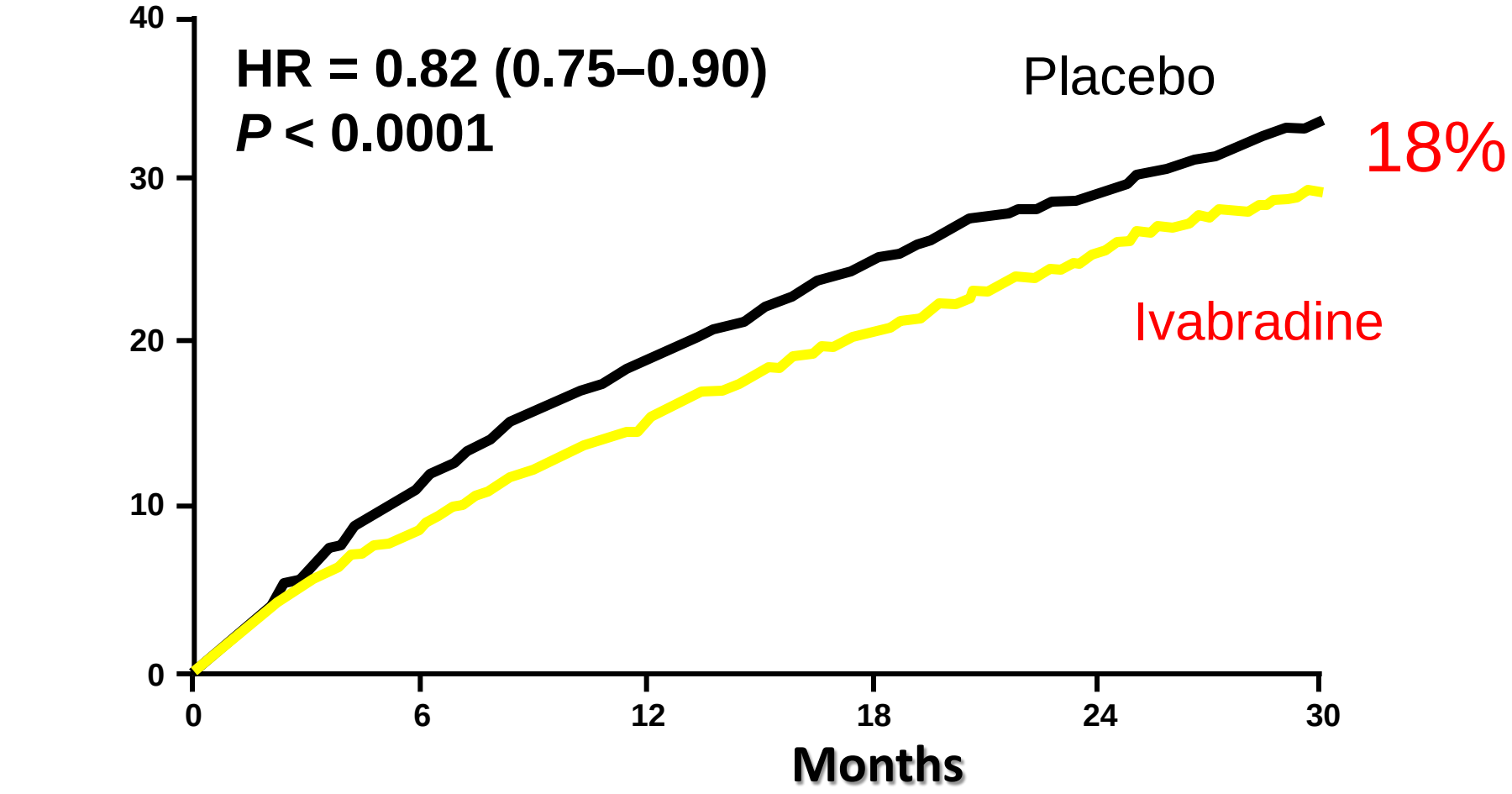
Ivabradine for Moderate-to-Severe HF and LV Systolic Dysfunction: The SHIFT Study

- Study description
  - Phase 3 multicenter, randomized, double-blind, placebo-controlled, outcomes trial
  - Comparison of ivabradine to placebo added on to standard-of-care therapies including beta-blockers
  - >6500 patients with symptomatic chronic HF in sinus rhythm with reduced LV function and heart rate ≥70 bpm

Borer JS, et al. *Eur Heart J*. 2012;33(22):2813-2820.

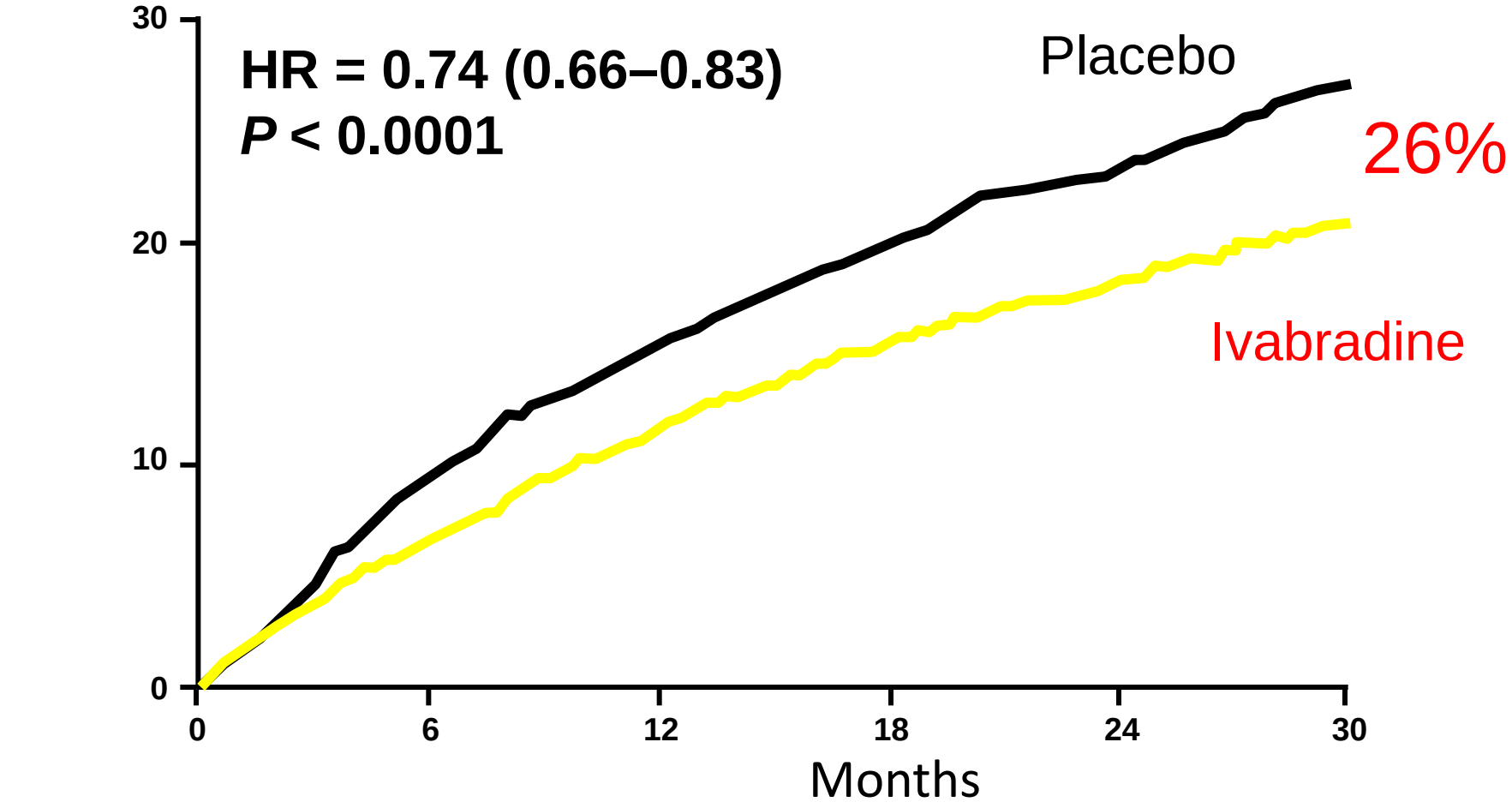
SHIFT Primary Composite Endpoint

(CV death or hospital admission for worsening HF)



Swedberg K, et al. *Lancet*. 2010;376(9744):875-885

Hospitalization for Heart Failure



Swedberg K, et al. *Lancet* 2010;376(9744):875-885