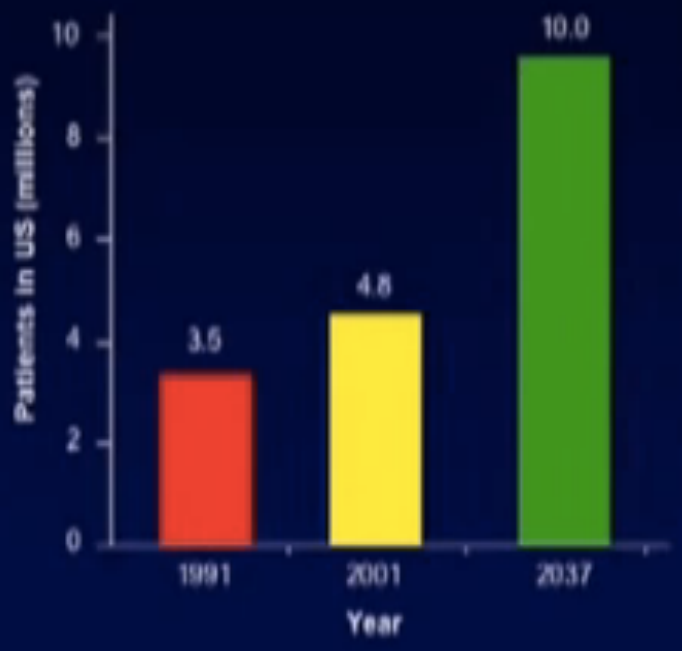
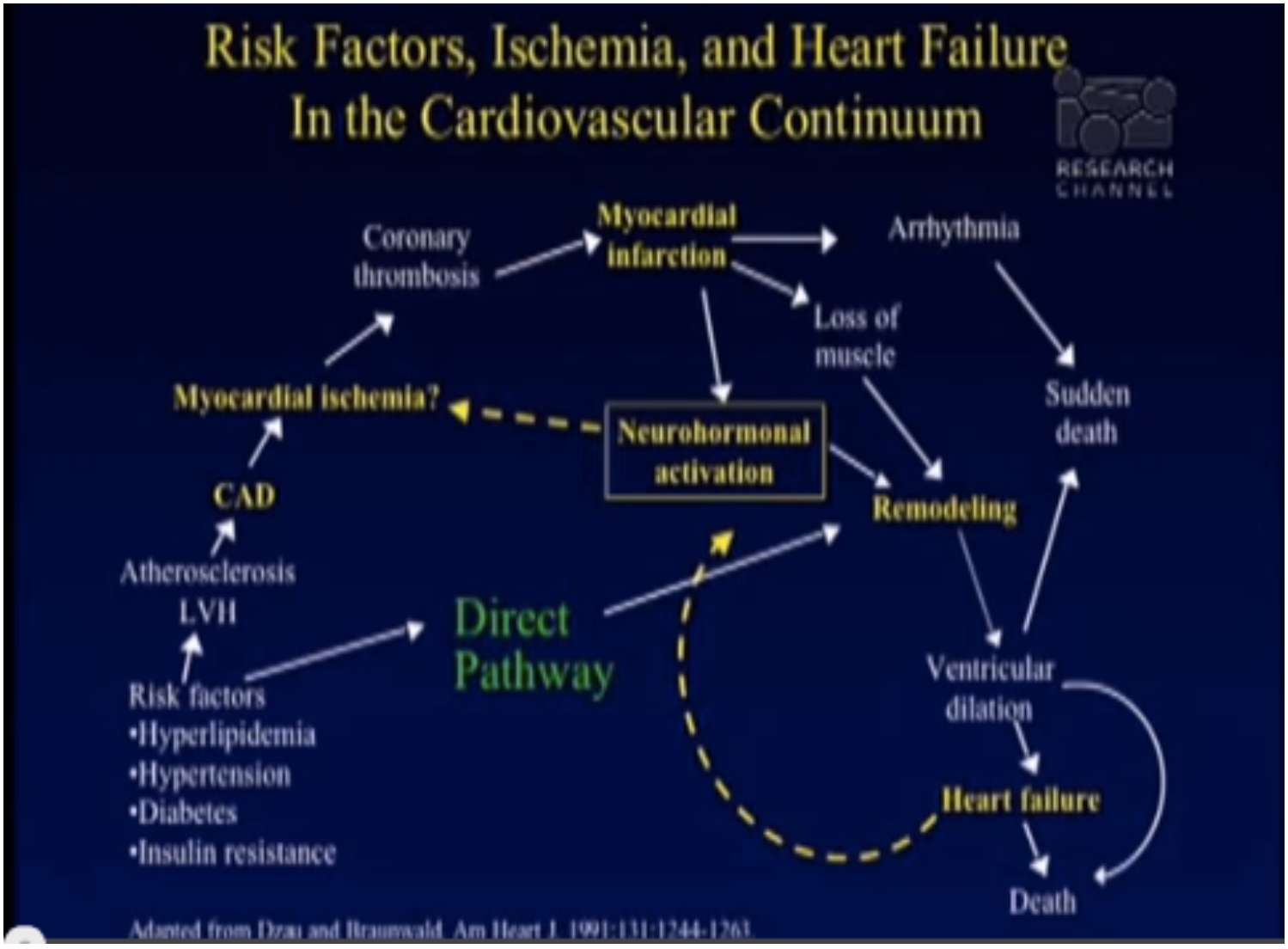
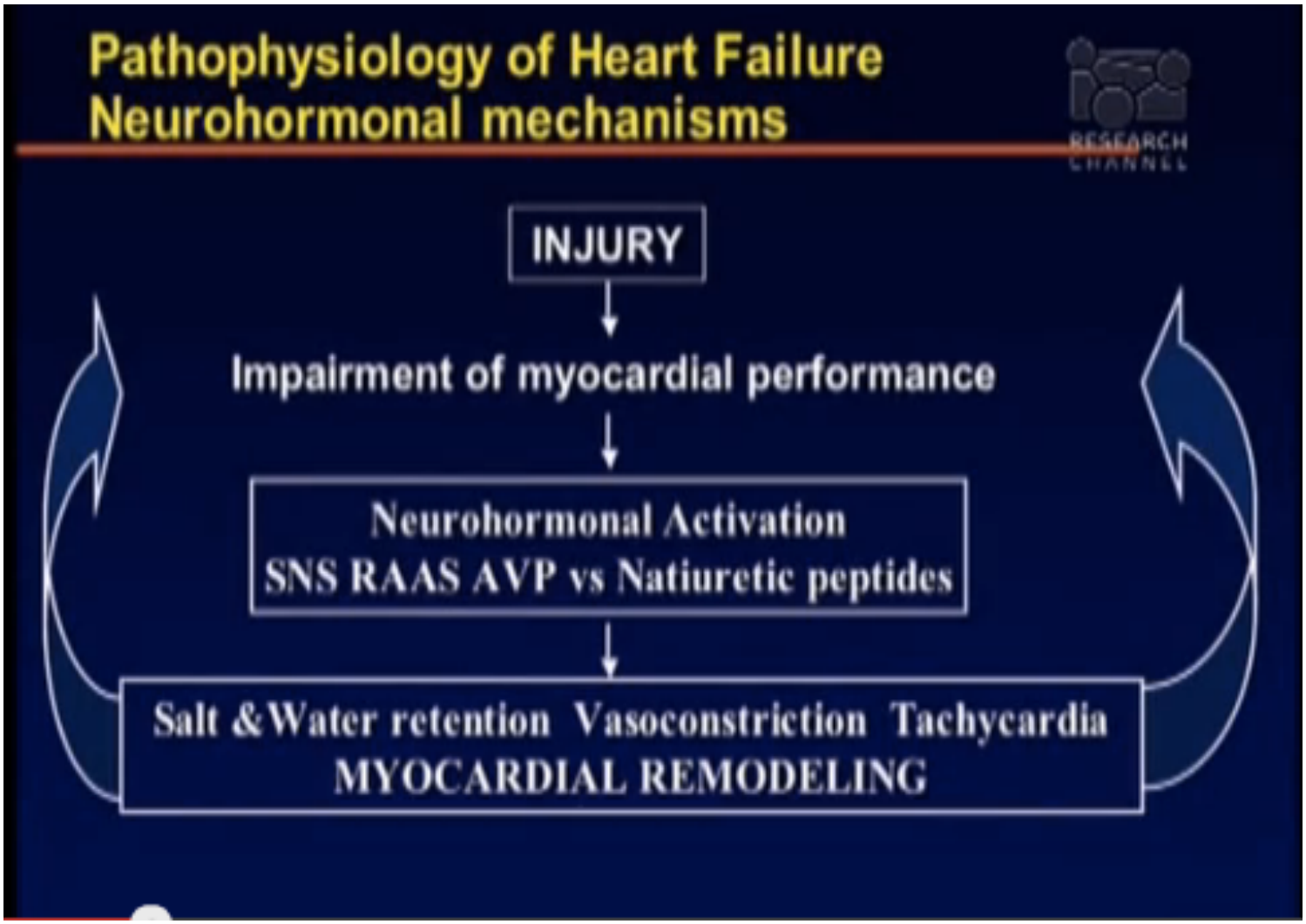
Epidemiology of Heart Failure in the United States

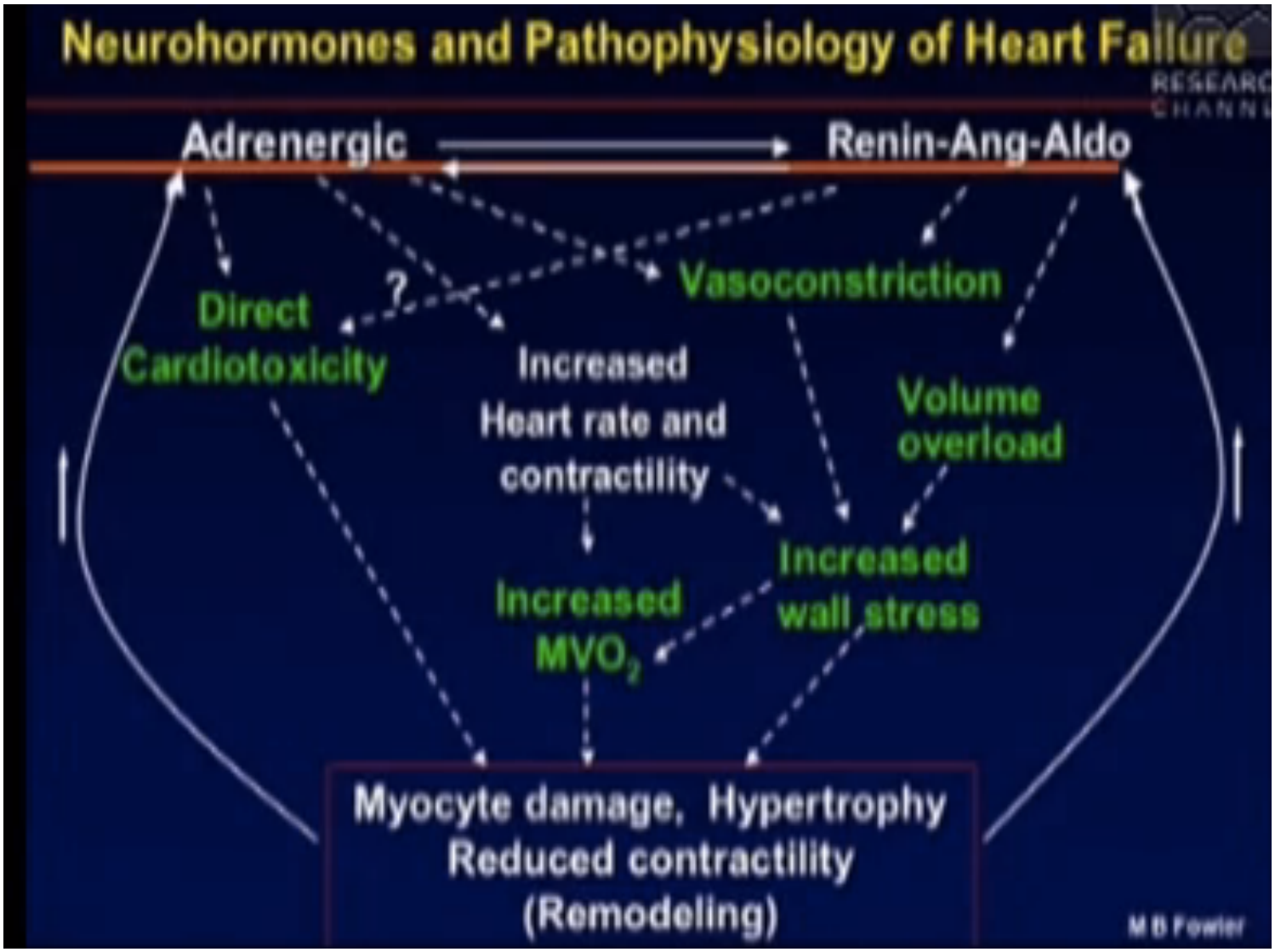


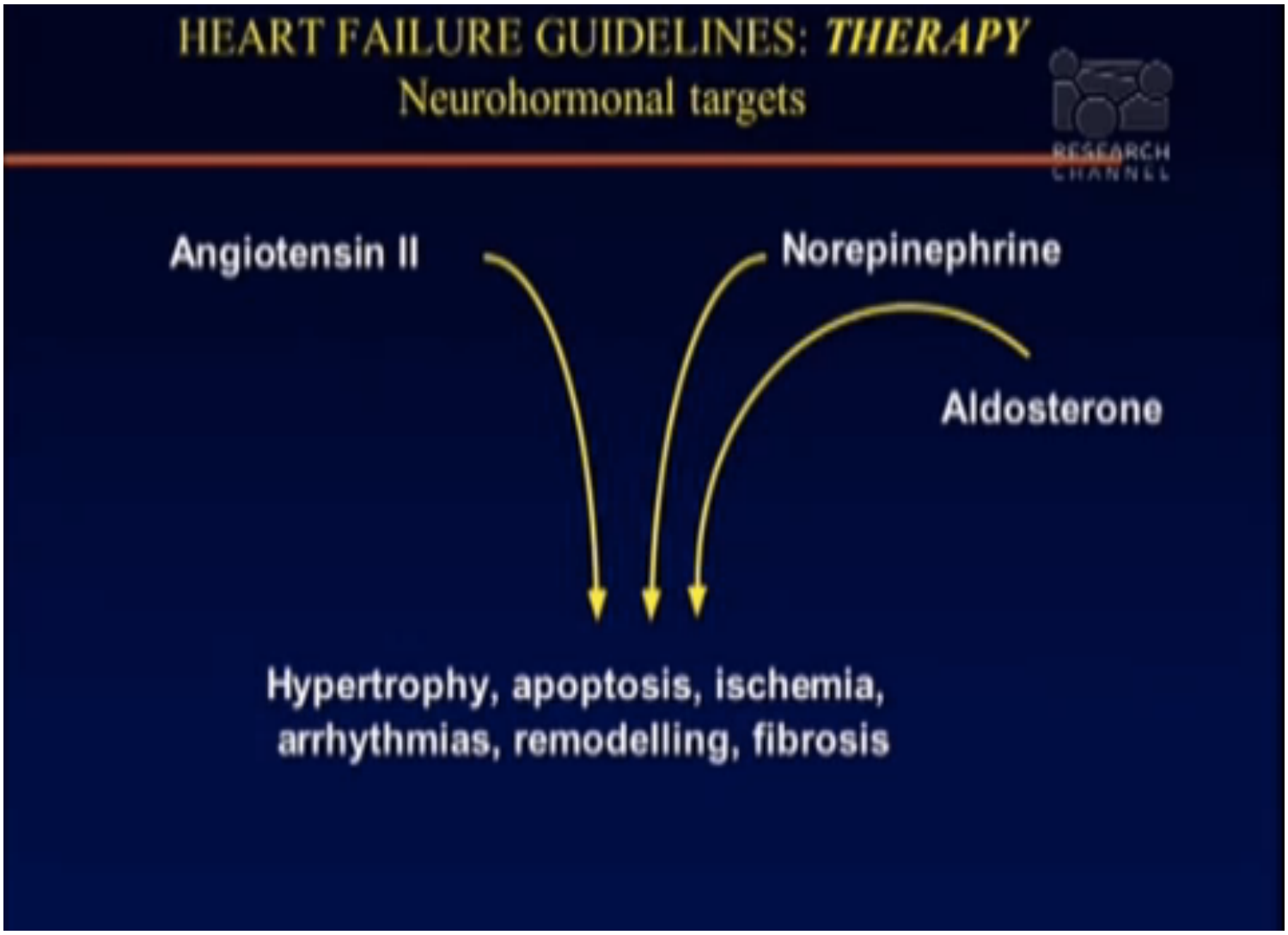
- 5.0 million patients[1]; estimated 10 million in 2037[2]
- Incidence: about 550,000 new cases each year[1]
- Prevalence is 2% in persons aged 40 to 59 years, progressively increasing to 10% for those aged 70 years and older[3]
- Sudden cardiac death is 6 to 9 times higher in the heart failure population[1]

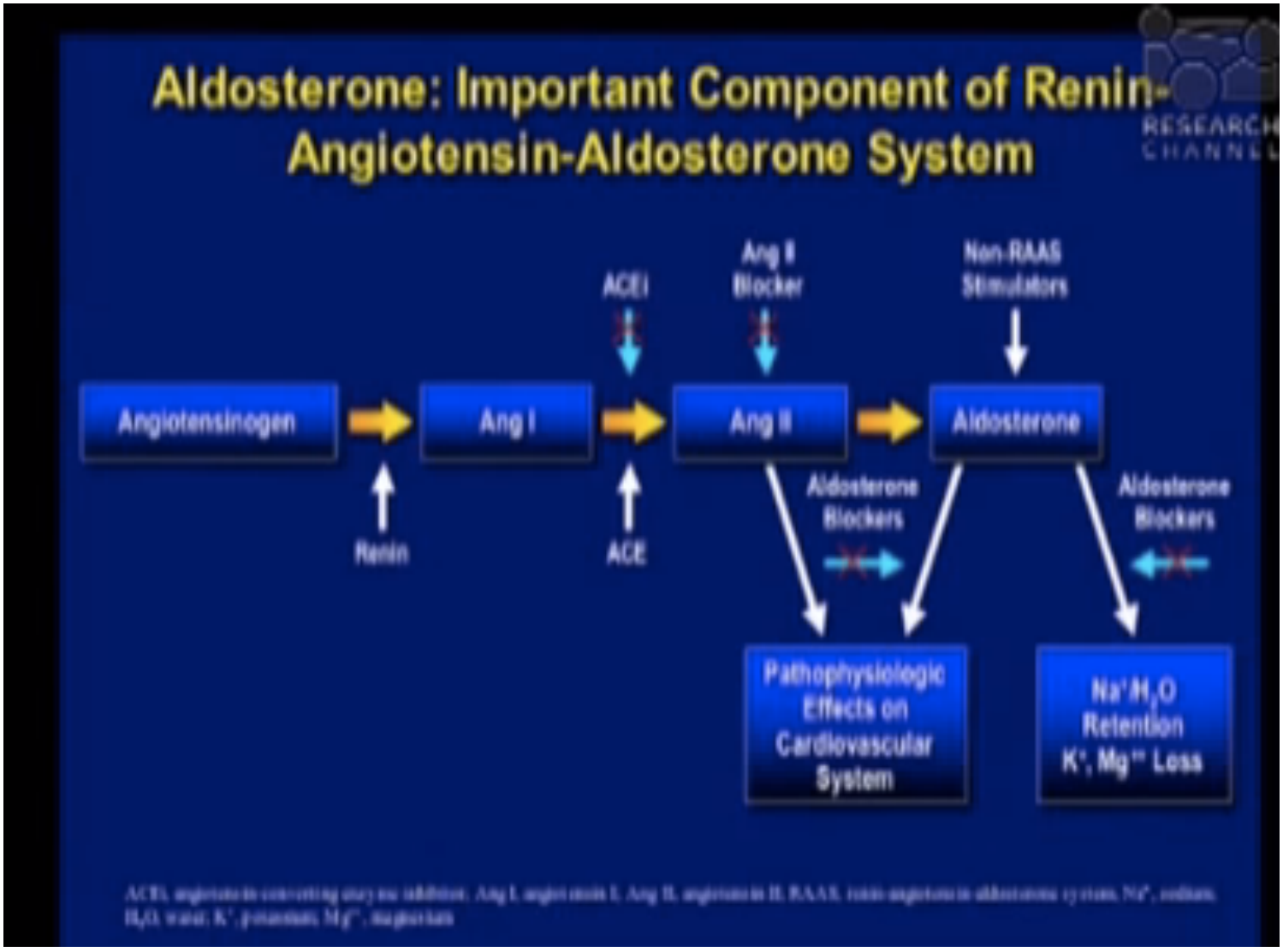
1. American Heart Association. *2004 Heart and Stroke Statistical Update*. 2001.
2. Croft JB et al. *J Am Geriatr Soc*. 1997;45:270-275.
3. National Heart, Lung, and Blood Institute. *Congestive Heart Failure Data Fact Sheet*.


Risk Factors, Ischemia, and Heart Failure
In the Cardiovascular Continuum
RESEARCH CHANNEL
Coronary thrombosis
Myocardial infarction
Arrhythmia
Loss of muscle
Myocardial ischemia?
Neurohormonal activation
Sudden death
CAD
Remodeling
Atherosclerosis
LVH
Direct Pathway
Ventricular dilation
Risk factors
•Hyperlipidemia
•Hypertension
•Diabetes
•Insulin resistance
Heart failure
Death
Adapted from Dzau and Braunwald. Am Heart J. 1991;131:1244-1263


Pathophysiology of Heart Failure
Neurohormonal mechanisms
INJURY
Impairment of myocardial performance
Neurohormonal Activation
SNS RAAS AVP vs Natiuretic peptides
Salt &Water retention Vasoconstriction Tachycardia
MYOCARDIAL REMODELING

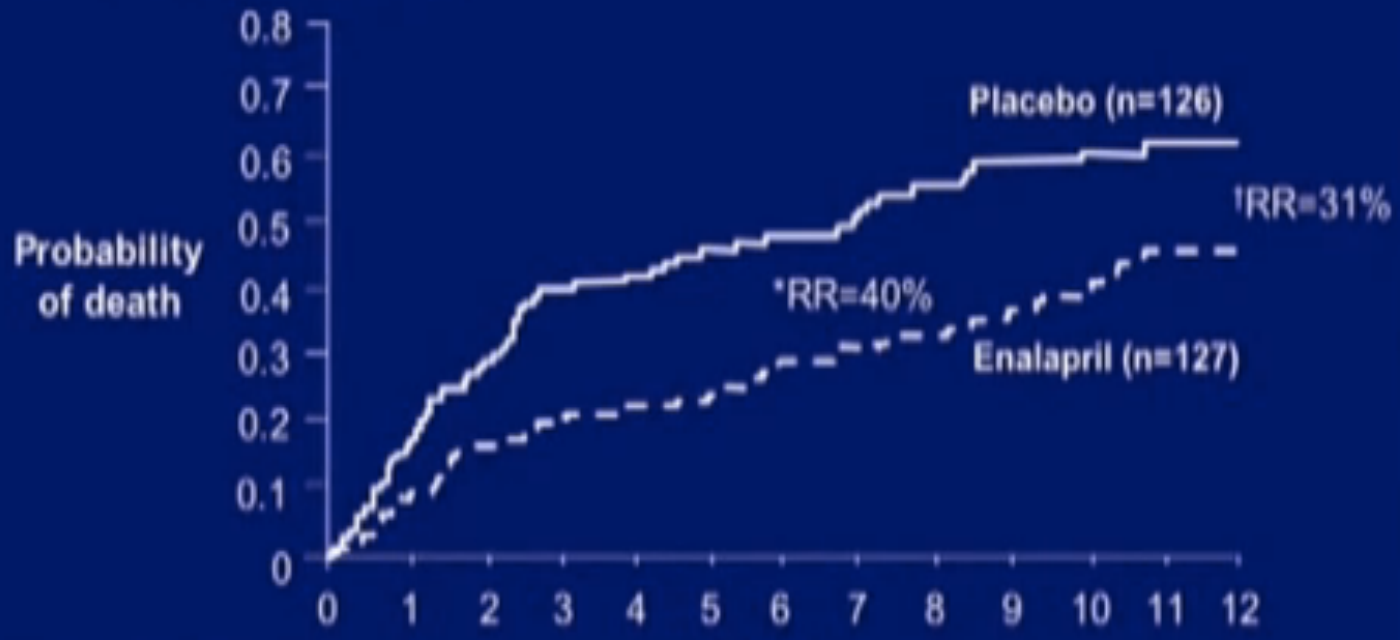

Neurohormones and Pathophysiology of Heart Failure
Adrenergic
Renin-Ang-Aldo
Direct Cardiotoxicity
?
Vasoconstriction
Increased Heart rate and contractility
Volume overload
Increased MVO_2
Increased wall stress
Myocyte damage, Hypertrophy
Reduced contractility
(Remodeling)
M B Fowler


HEART FAILURE GUIDELINES: THERAPY
Neurohormonal targets
RESEARCH CHANNEL
Angiotensin II
Norepinephrine
Aldosterone
Hypertrophy, apoptosis, ischemia,
arrhythmias, remodelling, fibrosis


Aldosterone: Important Component of Renin-Angiotensin-Aldosterone System
ACEI
Ang II Blocker
Non-RAAS Stimulators
Angiotensinogen
Ang I
Ang II
Aldosterone
Renin
ACE
Aldosterone Blockers
Aldosterone Blockers
Pathophysiologic Effects on Cardiovascular System
Na+H2O Retention K+, Mg++ Loss

CONSENSUS I

All-Cause Mortality



Mean age 70.5 years
*P<0.002 enalapril vs placebo at 6 months
†P<0.001 enalapril vs placebo at 12 months

Adapted with permission from CONSENSUS Trial Study Group. *N Engl J Med* 1987;316:1429

Aldosterone Biology[1-3]

Multiple Modulators of Aldosterone Secretion
Angiotensin II–K^+ –ACTH- Norepinephrine – Serotonin – Endothelin-NO

↓

Aldosterone Production

Adrenal Gland, Brain, Heart, Blood Vessels

↓

Locations of Aldosterone Receptors

- **Previously Known**
- **Recently Discovered**

Kidneys

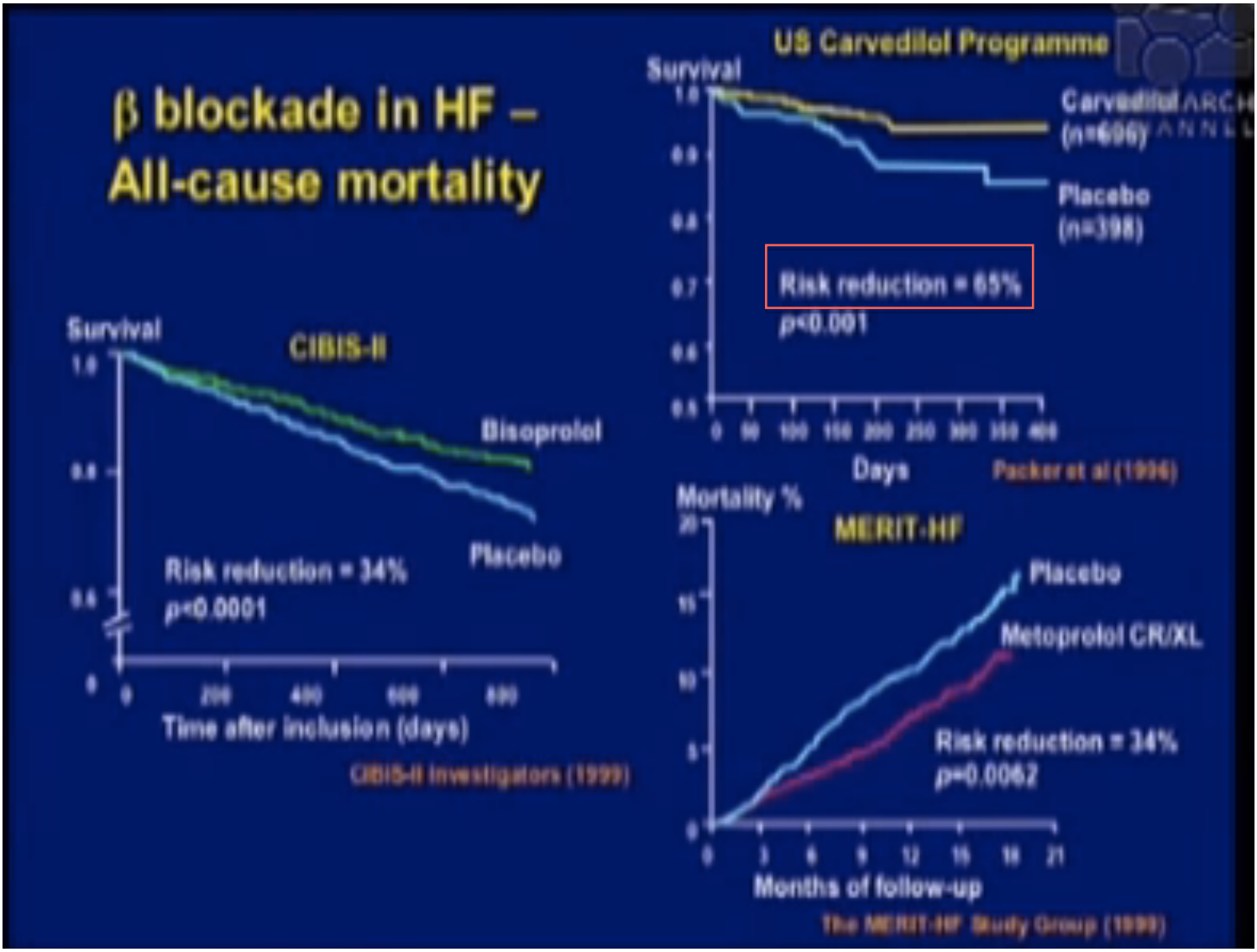
Brain

Heart

Blood Vessels

ACTH=adrenocorticotropic hormone; NO=nitric oxide

1. Colucci and Braunwald. Pathophysiology of Heart Failure. In: Braunwald, ed. *Heart Disease: A Textbook of Cardiovascular Medicine*. Philadelphia, Pa: WB Saunders Co;1997:394-420; 2. Lombès et al. *Ann Endocrinol (Paris)*. 2000;61:41-46; 3. Brown. *Circulation*. 2003;107:2512-2518.


β blockade in HF –
All-cause mortality
Survival
CIBIS-II
Bisoprolol
Placebo
Risk reduction = 34%
p<0.0001
Time after inclusion (days)
CIBIS-II Investigators (1999)
US Carvedilol Programme
Survival
Carvedilol
(n=696)
Placebo
(n=398)
Risk reduction = 65%
p<0.001
Days
Packer et al (1996)
Mortality %
MERIT-HF
Placebo
Metoprolol CR/XL
Risk reduction = 34%
p=0.0062
Months of follow-up
The MERIT-HF Study Group (1999)

Ventricular Dysynchrony and Cardiac Resynchronization

- Ventricular Dysynchrony[1]
  - **Electrical:** Inter- or intraventricular conduction delays typically manifested as left bundle branch block
  - **Structural:** disruption of myocardial collagen matrix impairing electrical conduction and mechanical efficiency
  - **Mechanical:** Regional wall motion abnormalities with increased workload and stress—compromising ventricular mechanics

- Cardiac Resynchronization
  - Therapeutic intent of atrial synchronized biventricular pacing
    - Modification of interventricular, intraventricular, and atrial-ventricular activation sequences in patients with ventricular dysynchrony
    - Complement to optimal medical therapy

[1] Tavazzi L. *Eur Heart J* 2000;21:1213-1214

COMPANION: *Secondary Endpoint of All-Cause Mortality*