Heart failure 2030: Predicting the next decade!

เอกราช อริยะชัยพาณิชย์

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11.12.2020

2-day Cardiology

HF will be more significant in 2030

Epidemiology

During the past half-century, the advances in the prevention, diagnosis, and management of cardiovascular disease (CVD) have been nothing short of spectacular. Age-adjusted CVD-related deaths have declined by about two-thirds in industrialized nations (1). Mortality rates associated with the acute coronary syndromes (ACS), valvular and congenital heart disease, uncontrolled hypertension, and many arrhythmias all have fallen dramatically.

Heart failure (HF) is a notable exception to these encouraging trends. Indeed, after normal delivery, it is the most common cause of hospitalization. Annual hospital discharges in

Aging

Premature CV disease

Better CV care

Better HF care

Table 1. Projections of Crude CVD Prevalence (%), 2010–2030 in the United States

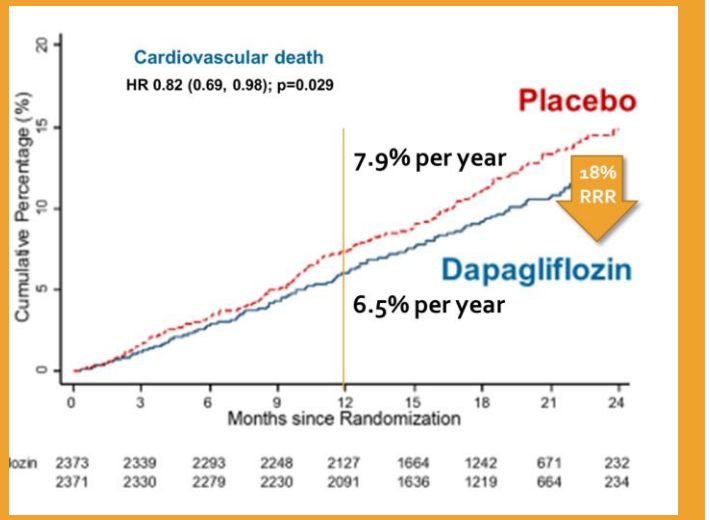
Year	All CVD*	Hypertension	CHD	HF	Stroke
2010	36.9	33.9	8.0	2.8	3.2
2015	37.8	34.8	8.3	3.0	3.4
2020	38.7	35.7	8.6	3.1	3.6
2025	39.7	36.5	8.9	3.3	3.8
2030	40.5	37.3	9.3	3.5	4.0
% Change	9.9	9.9	16.6	25.0	24.9

↑incidence, ↑prevalence resulted in ↑HF hospitalization, ↑CV death, ↑ health care burden and healthcare cost

J Am Coll Cardiol HF 2013;1:1–20
Circulation. 2011;123:933-944.

In 2020, HF is still deadly

DAPAHF

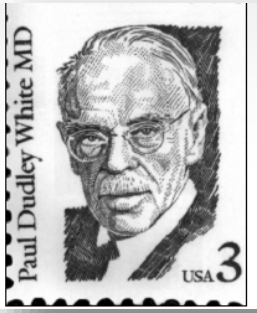


1 in 12 patients with stable HF die within 1 year

N Engl J Med 2019; 381:1995-2008

Modern day of HF

1929



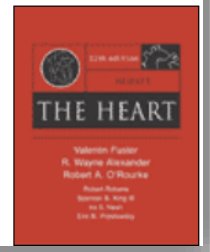
"…and for all this there is only digitalis and rest…"

Paul Dudley White: Textbook in Cardiology, 1929

1974

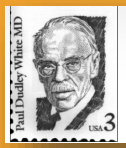
J Willis Hurst
1920-2011

Moderately severe heart failure
- Decrease physical activity
- Institute digitalis
- Give thiazide every day plus potassium
- If not enough use furosemide and if insufficient, combine them



J W Hurst: The Heart 3rd edition, 1974

Modern day of HF



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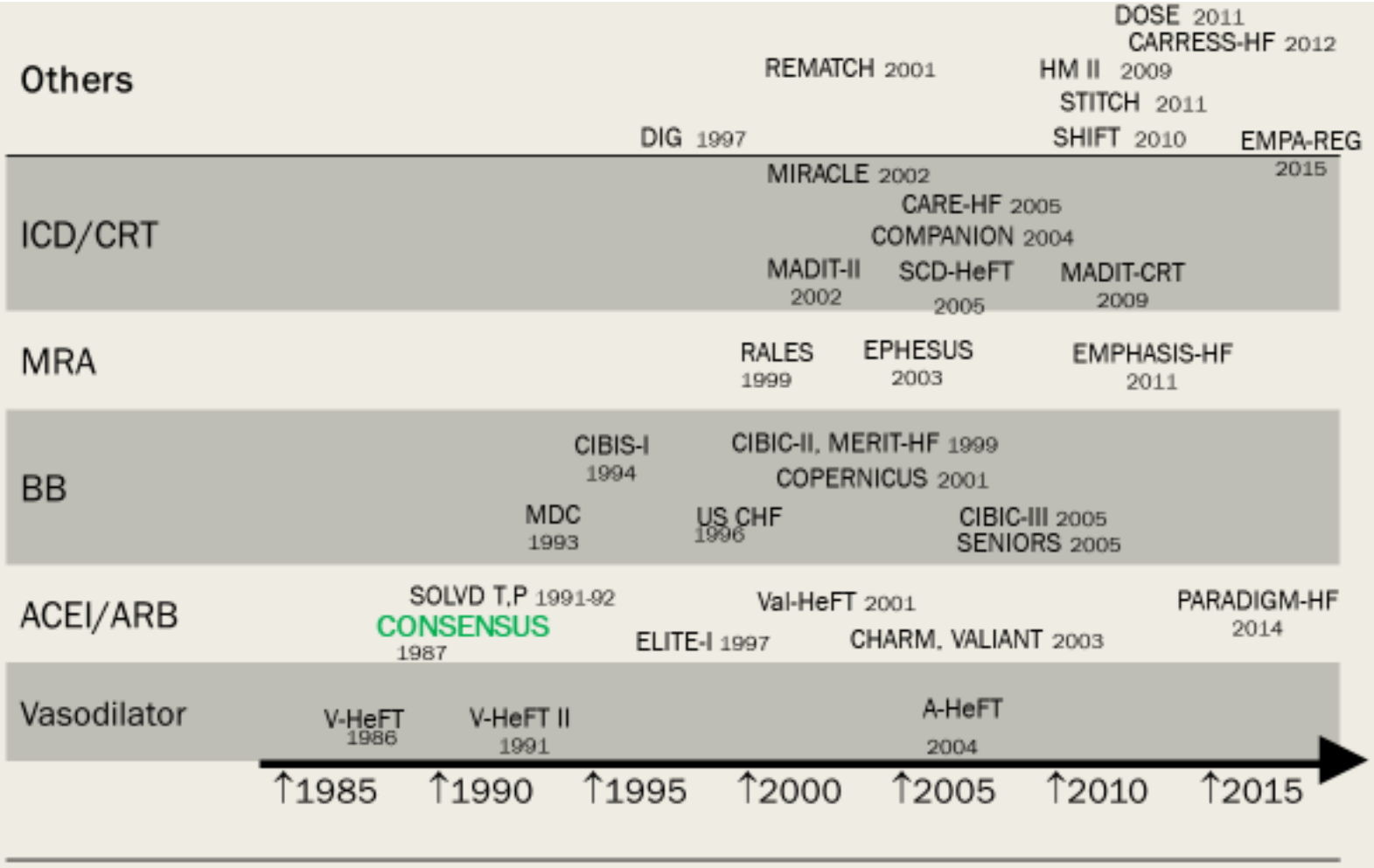
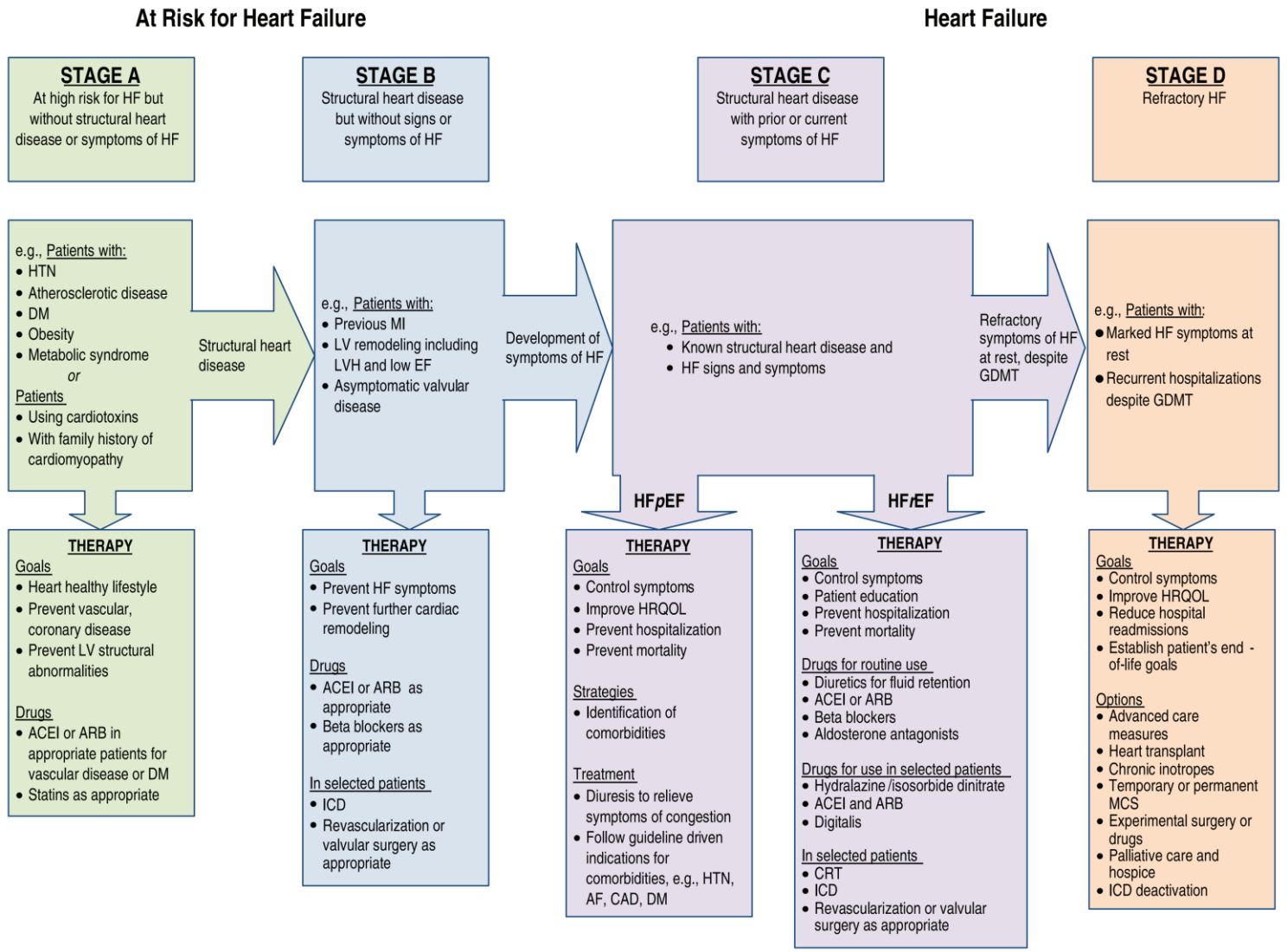


Let the past be behind

HF 2010-2020

- Ivabradine
- ARNI
- SGLT2i in HFrEF
- mid-range EF (EF 40-50%)
- NT-pBNP
- WARM-WET-COLD –DRY
- LVAD & MCS
- ESC 2016
- ACC 2016/2017
- HFCT 2019
- Dedicate HF team and specialist



ACC 2013

NOT COVER TODAY: Now/very near future

ARNI in pEF

SGLT2i in pEF

K binder
Patiromer & SZC

Implantable monitoring

Lung ultrasound

Levosimemdan

Omecamtiv mecabil

Co-Q10

Vericiguat & nitroxyl

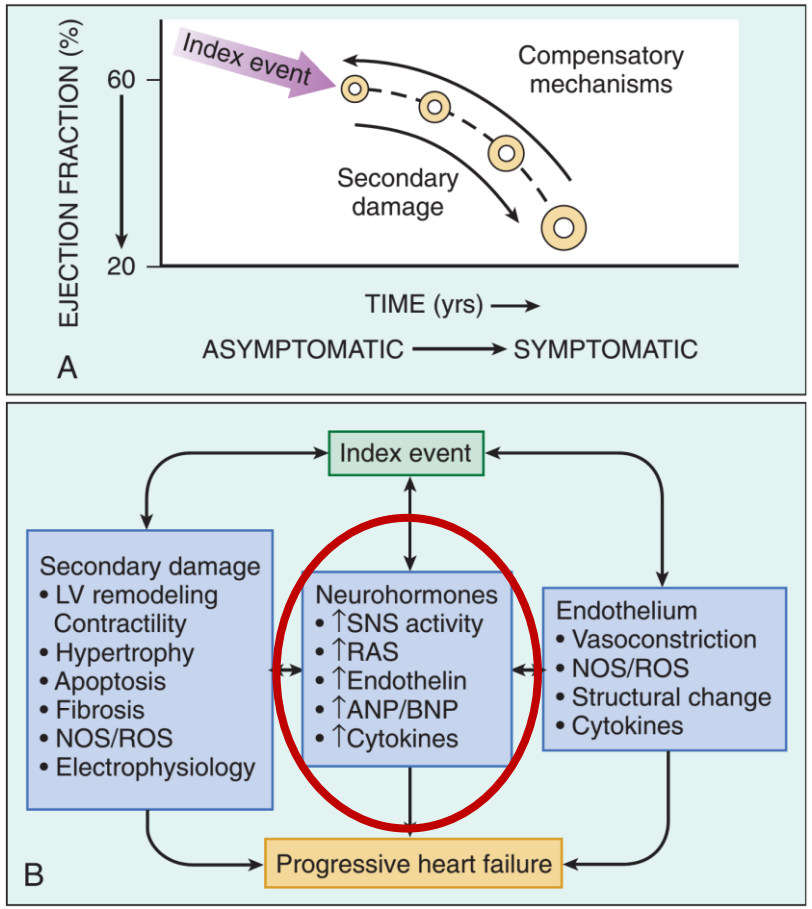
Vagus nerve stim.

Other: influenza vaccine etc

PREDICTION

PREDICTION #1

"HFpEF will be classified by phenotypes and most will be treated with neurohormonal blockage"

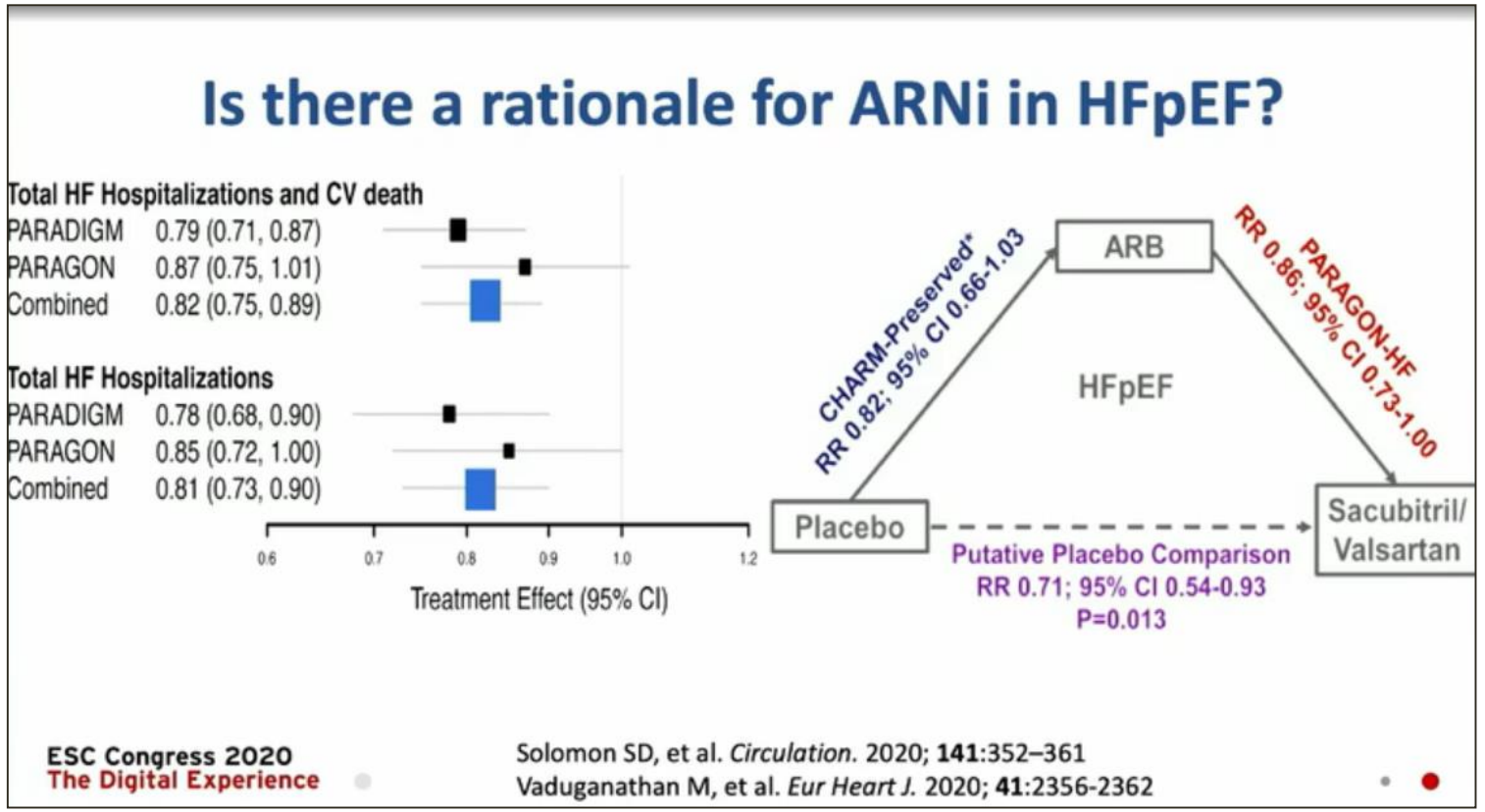


ARNI + MRA + SGLT2 + anti inflammation will be main treatment for HFpEF

European Heart Journal (2018) 39, 5–16 .

PREDICTION #1

"HFpEF will be classified by phenotypes and most will be treated with neurohormonal blockage"

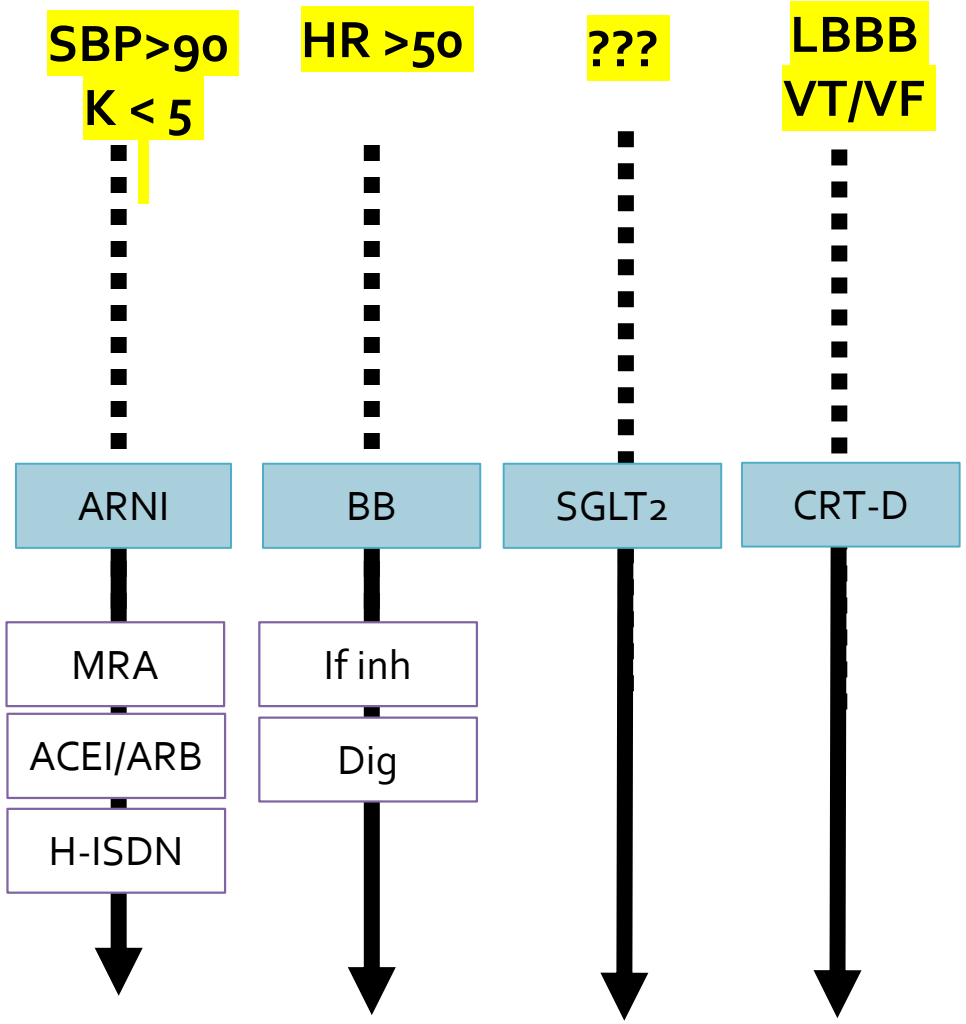


ARNI + MRA + SGLT2 + anti inflammation
will be main treatment for HFpEF

PREDICTION #2

NO MORE
"one size fit all"
"step up approach"

for HFrEF



Step up therapy for poor prog. HF

Focus more on prevention & specific rx for cardiomyopathy

- Amyloid
- HCM
- Peripartum
- etc

Step down therapy
for improve EF

PREDICTION #3

"Stop measuring LVEF"

Structural and Functional Phenotyping of the Failing Heart

Is the Left Ventricular Ejection Fraction Obsolete?

Michael R. Bristow, MD, PhD,[a] David P. Kao, MD,[a] Khadijah K. Breathett, MD,[b] Natasha L. Altman, MD,[a] John Gorcsan III, MD,[c] Edward A. Gill, MD,[a] Brian D. Lowes, MD, PhD,[d] Edward M. Gilbert, MD,[e] Robert A. Quaife, MD,[a] Douglas L. Mann, MD[c]

EF -Pro

- Easy to do
- Easy to understand
- Associate with LVEDD
- Help select medications

EF-Con

- Not reflect hemodynamics
- Not predict outcomes
- Inter, intra observer variation
- Inter-test variation
- Not reflect physiology

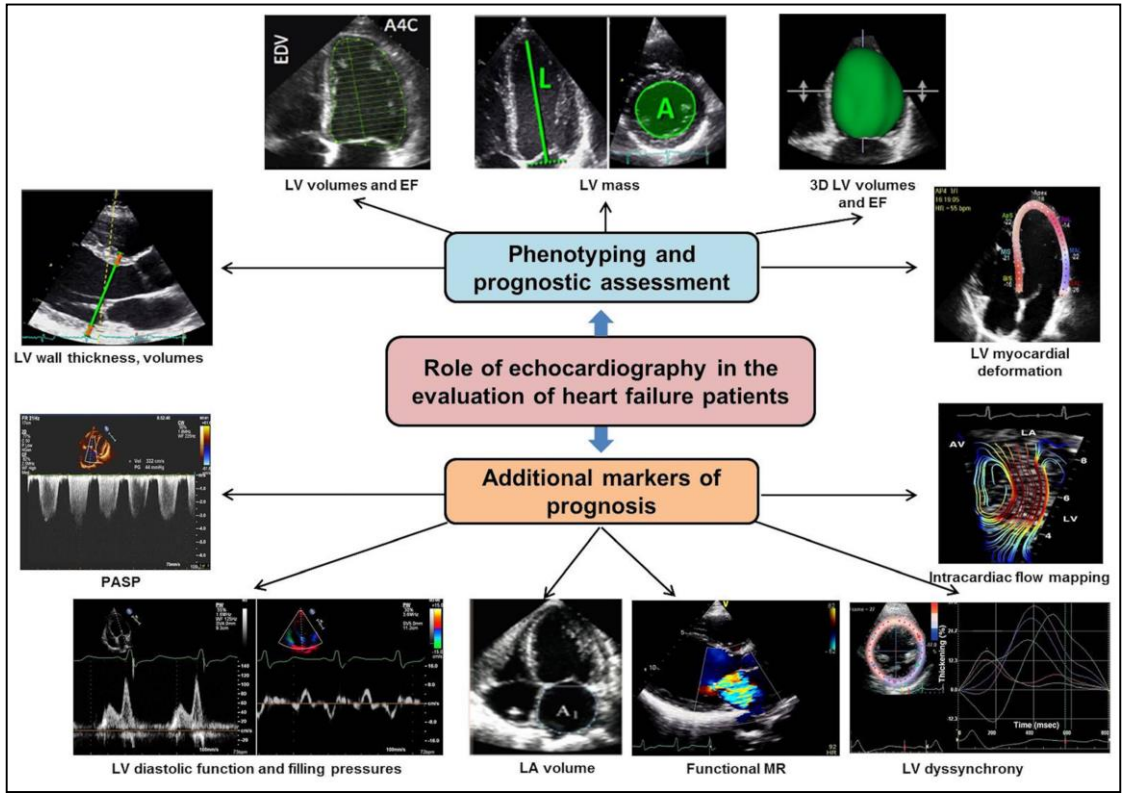
PREDICTION #3

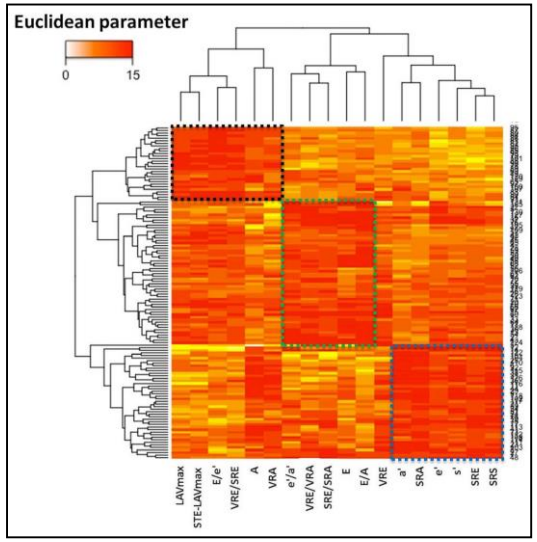
"Stop measuring LVEF"

- AI integrated imaging

Advances in Echocardiographic Imaging in Heart Failure With Reduced and Preserved Ejection Fraction

Alaa Mabrouk Salem Omar, Manish Bansal, Partho P. Sengupta





Circ Res. 2016;119:357.

- Eur Heart J 2016;37:449.
- JACC HF 2017;5:772.

PREDICTION #3

"Stop measuring LVEF"

- AI integrated big data

Clinical Implications of Chronic Heart Failure Phenotypes Defined by Cluster Analysis

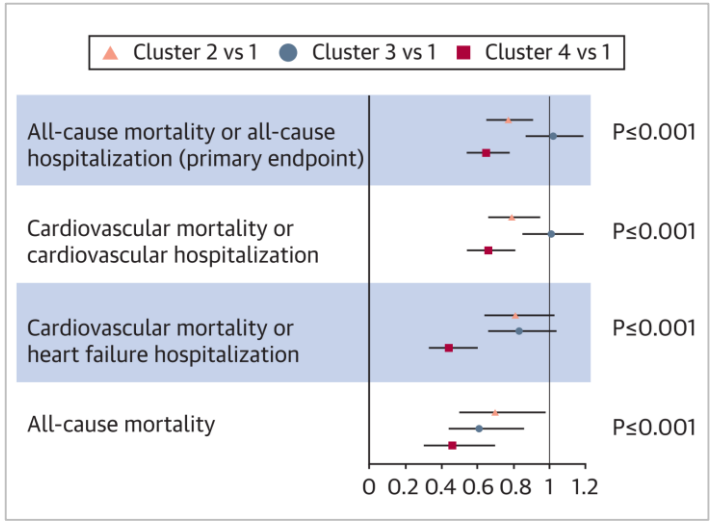
Tariq Ahmad, MD, MPH,*† Michael J. Pencina, PhD,† Phillip J. Schulte, PhD,† Emily O'Brien, PhD,† David J. Whellan, MD,‡ Ileana L. Piña, MD, MPH,§ Dalane W. Kitzman, MD,‖ Kerry L. Lee, PhD,† Christopher M. O'Connor, MD,*† G. Michael Felker, MD, MHS*†

CLUSTER 1: 773 PATIENTS
- Eldest
- Caucasian
- Ischemic CMP
- High Comorbidity Rate
- Advanced Disease
- Highest Mortality Rates

CLUSTER 2: 287 PATIENTS
- Youngest
- Highest BMI
- African American
- Non-ischemic CMP
- High rates of prior rehospitalization
- Lower SES and QOL
- Milder disease on CPET and biomarker assessments

CLUSTER 3: 313 PATIENTS
- Caucasian
- Ischemic CMP
- Severe angina symptoms
- High rates of rehospitalization
- Lower SES and QOL
- Advanced HF based on CPET and biomarkers

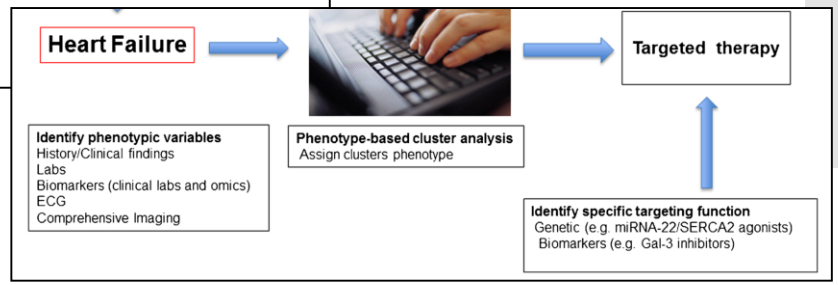
CLUSTER 4: 246 PATIENTS
- Caucasian
- Highest percentage of females
- Non-ischemic CMP
- Low rates of comorbidities
- Low rates of clinical outcomes
- Highest SES and QOL



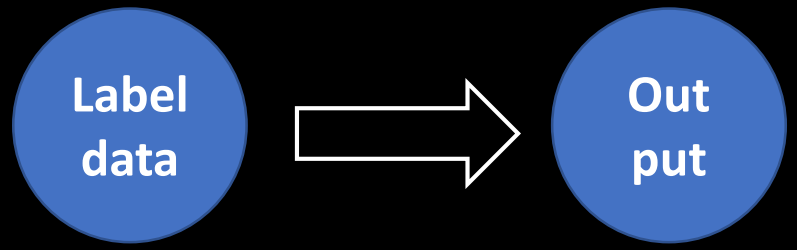
Clinical Phenotyping of Heart Failure with Biomarkers: Current and Future Perspectives

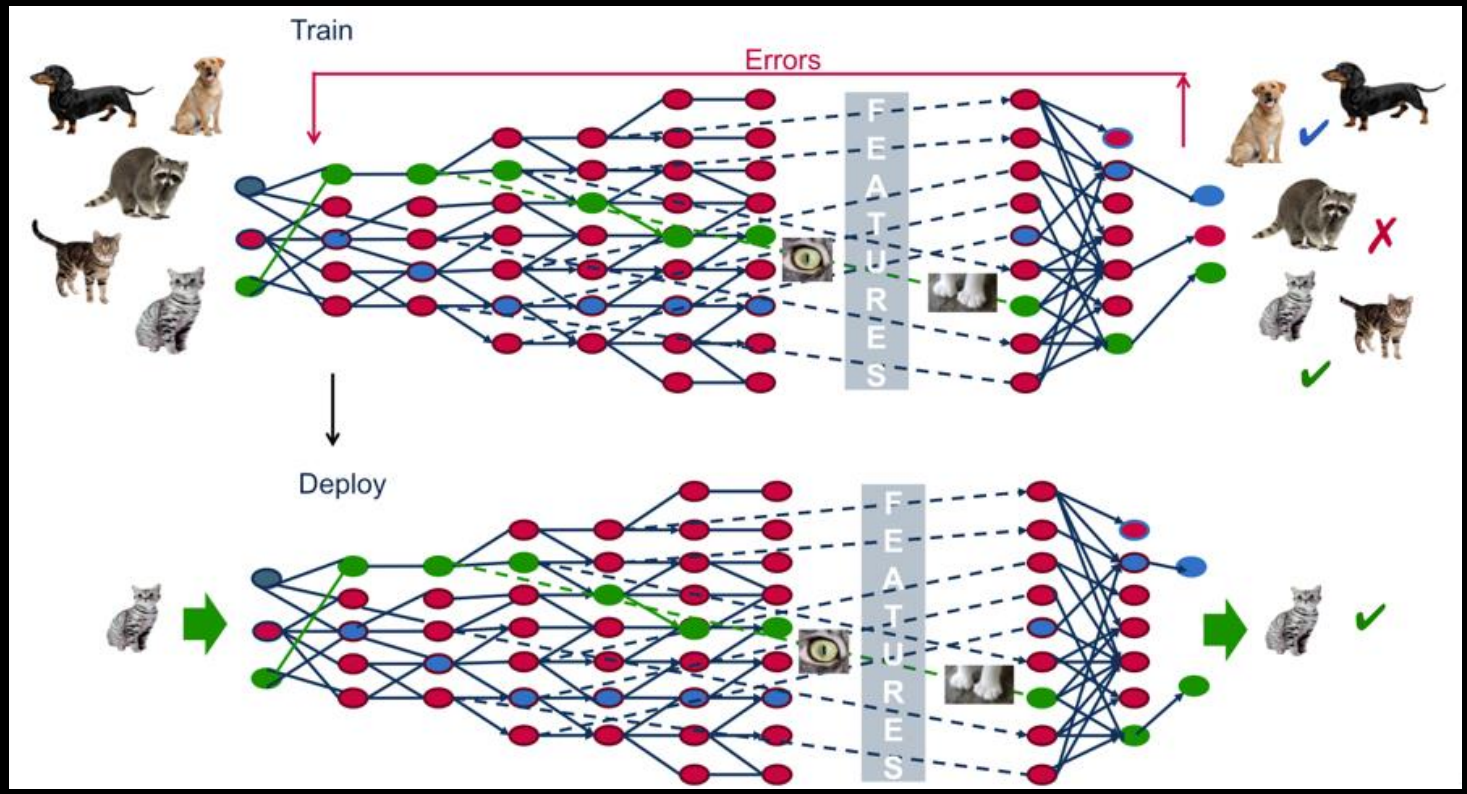
Vichai Senthong[1,2] · Jennifer L. Kirsop[3] · W. H. Wilson Tang[1,3,4]

Curr Heart Fail Rep 2017;14:106.



AI and Machine Learning





Keyword: We will not and cannot understand AI

AI can see the invisible and predicting future

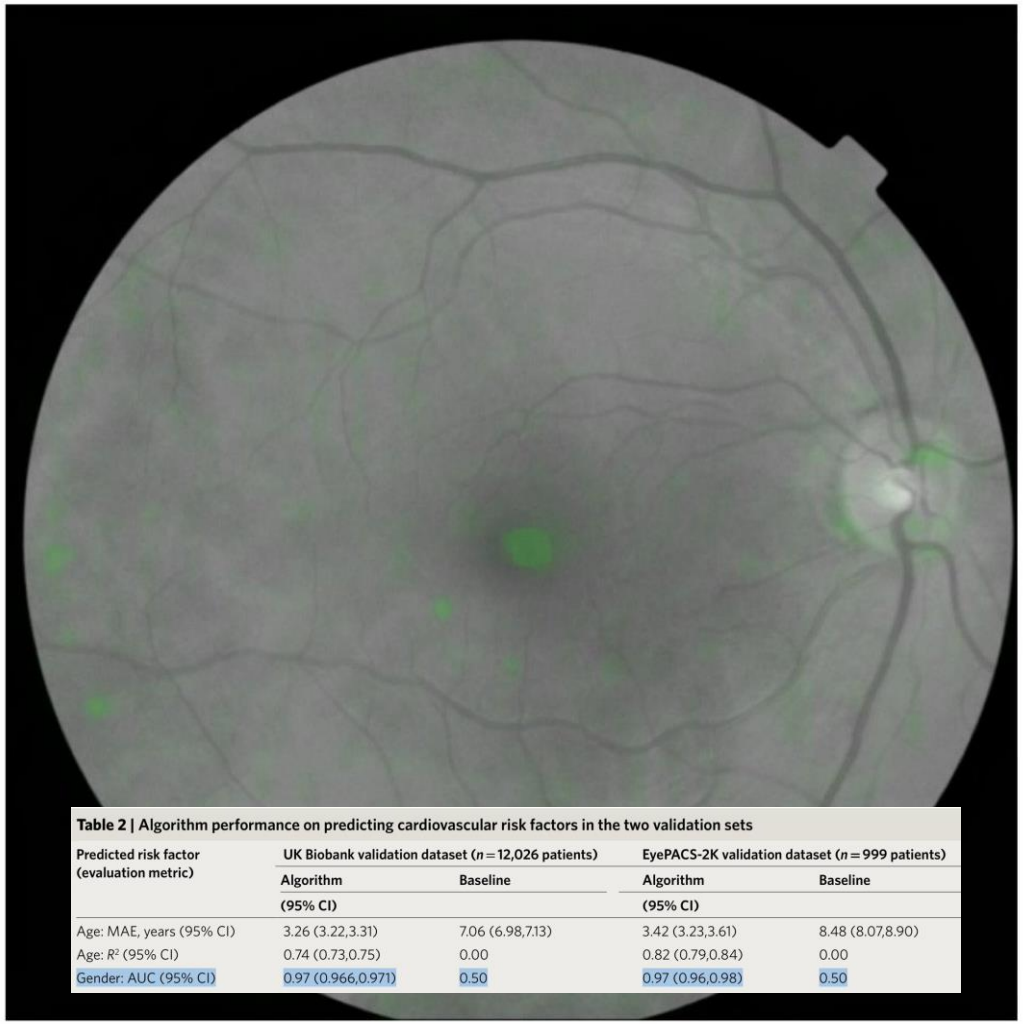


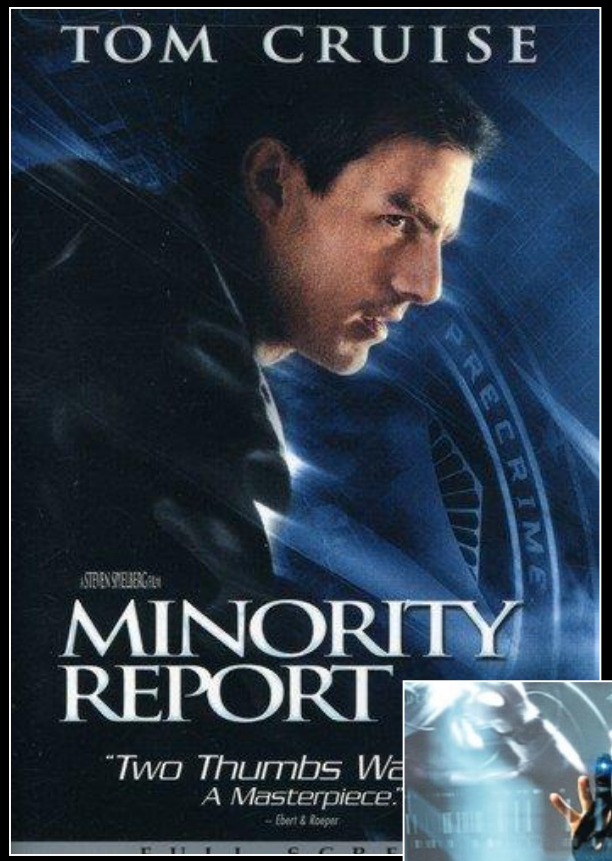
Table 2 | Algorithm performance on predicting cardiovascular risk factors in the two validation sets

Predicted risk factor (evaluation metric)	UK Biobank validation dataset ($n = 12{,}026$ patients)		EyePACS-2K validation dataset ($n = 999$ patients)	
	Algorithm (95% CI)	Baseline	Algorithm (95% CI)	Baseline
Age: MAE, years (95% CI)	3.26 (3.22,3.31)	7.06 (6.98,7.13)	3.42 (3.23,3.61)	8.48 (8.07,8.90)
Age: R^2 (95% CI)	0.74 (0.73,0.75)	0.00	0.82 (0.79,0.84)	0.00
Gender: AUC (95% CI)	0.97 (0.966,0.971)	0.50	0.97 (0.96,0.98)	0.50

Actual: Female

Predicted: Female

Nature Biomedical Engineering **2**, 158–164 (2018)

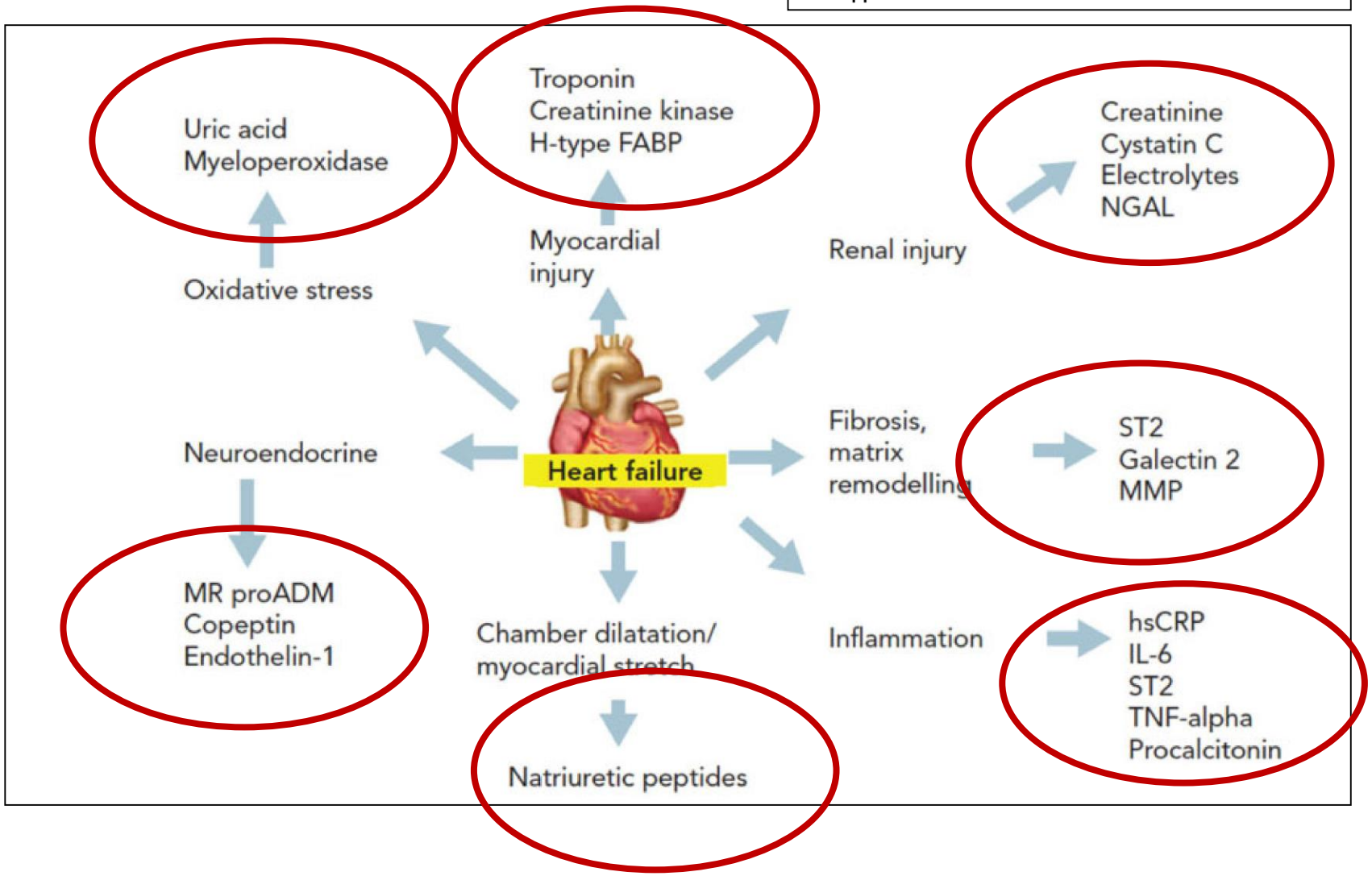


PREDICTION #4

"HF will be treated base on biomarkers phenotype"

Monitoring of biomarkers in heart failure

Ilaria Spoletini[1], Andrew J.S. Coats[1], Michele Senni[2], and Giuseppe M.C. Rosano[1]*



Eur Heart J 2019:Sup21: M5–M8

PREDICTION #4

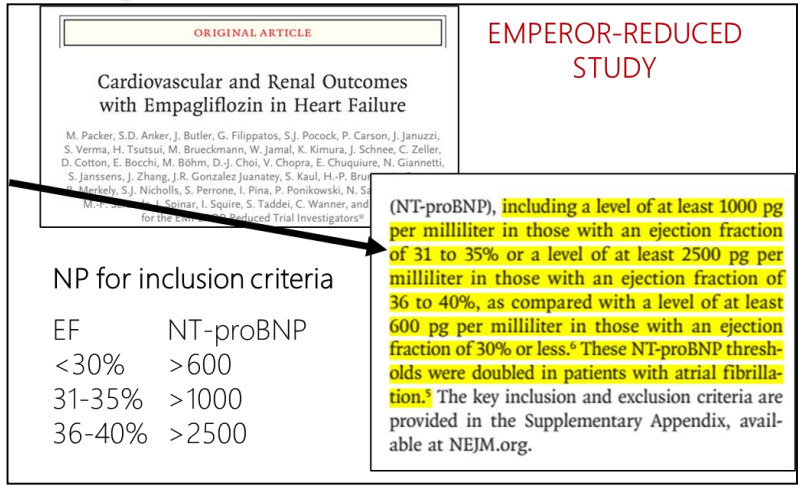
"HF will be treated base on biomarkers phenotype"

HF with high NP

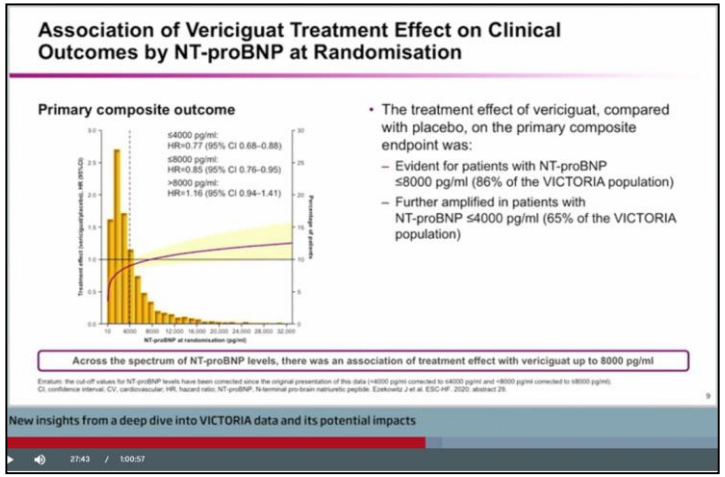
NT-pBNP is used for Diagnosis

Setting	Natriuretic peptide value		Interpretation
Non-acute setting	BNP	<35 pg/mL	HF is unlikely
	NT-proBNP	<125 pg/mL	
Acute setting	BNP	<100 pg/mL	HF is unlikely
	NT pro-BNP	<300 pg/mL	
	BNP	>500 pg/mL	HF is likely
	NT pro-BNP	>450 pg/mL (in patients <50 years)	
	NT pro-BNP	>900 pg/mL (in patients 50 to 75 years)	
	NT pro-BNP	>1,800 pg/mL (in patients >75) years)	

NT-pBNP is used for RCTs enrollment



Δ NT-pBNP, Δ outcomes and response to rx



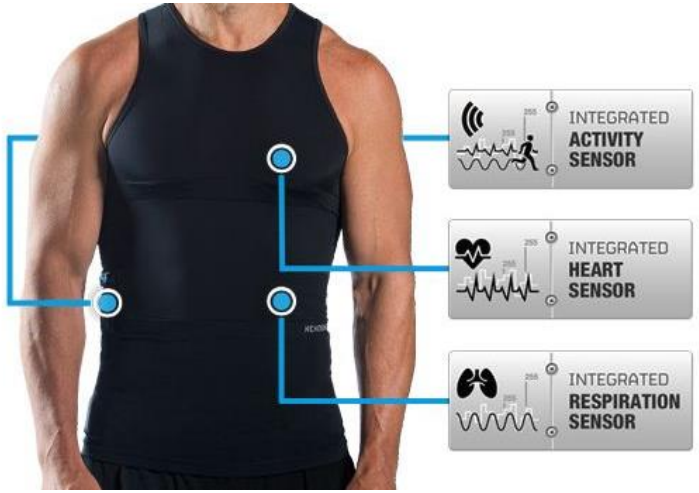
PREDICTION #4

"HF will be treated base on biomarkers phenotype"

+/- bio sensor

Smart watch: Apple watch

Necklace: toSense CoVa

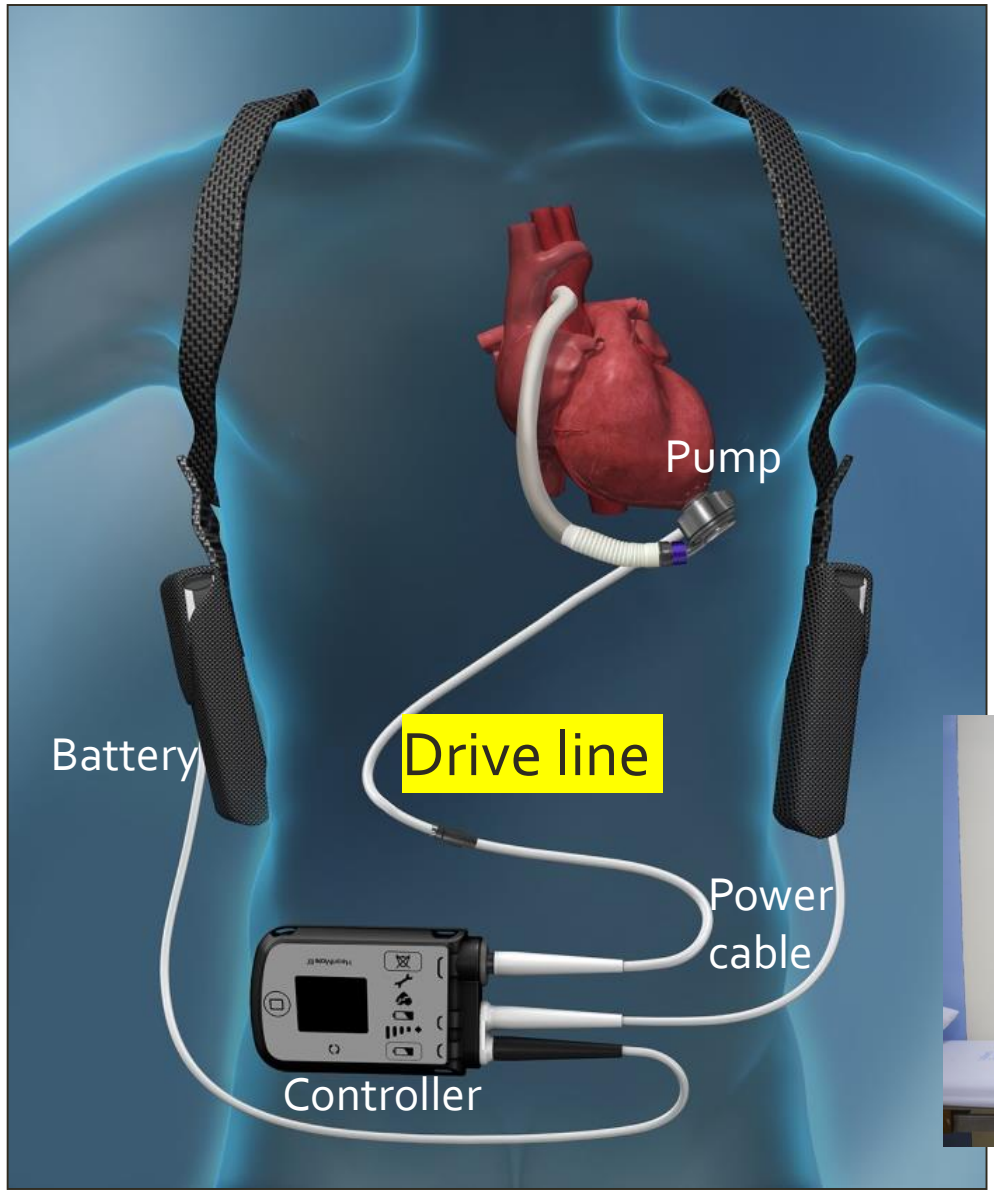


Smart clothing: Hexoskin

Skin patches: VivaLNK

PREDICTION #5

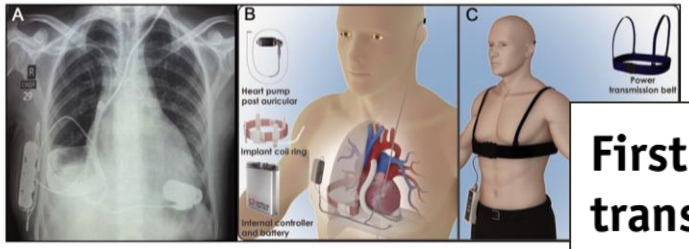
"Palliative patient will be support by fullly implanted LVAD"



Due to driveline,
infection is common

PREDICTION #5

"Palliative patient will be support by fullly implanted LVAD"



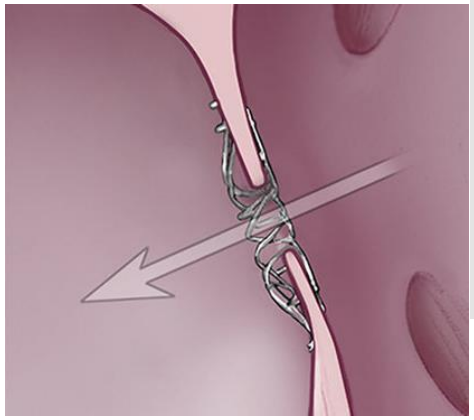
First human use of a wireless coplanar energy transfer coupled with a continuous-flow left ventricular assist device

J Heart Lung Transplant 2019;38:339-343

SIDE NOTE

"More invasive procedure at earlier phase

TAVR in mod AS+ HF	**TAVR-UNLOAD**
MV intervention in mod MR+ HF	**COAPT**
AF ablation in AF + HF	**CASTLE-AF**
Wireless Hemodynamics monitoring	**CHAMPION**

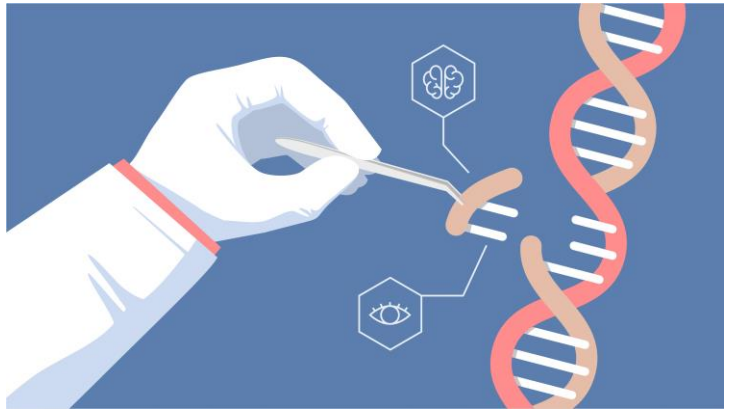


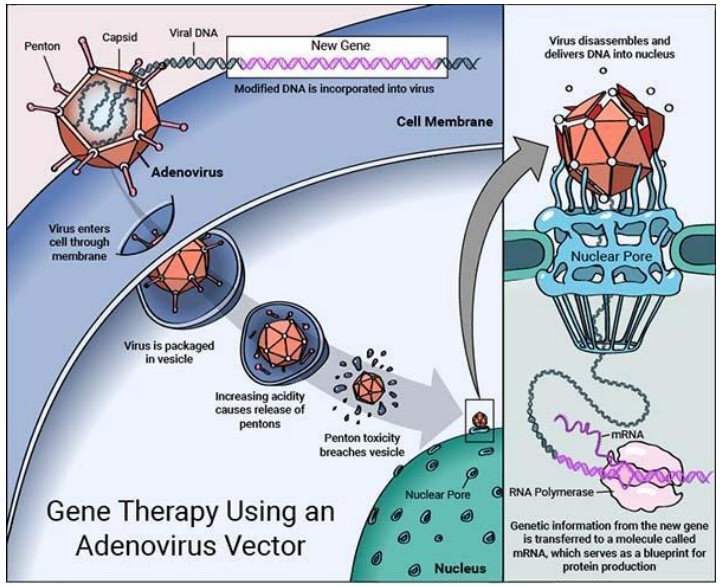
*Others invasive devices e.g. interatrial shunt

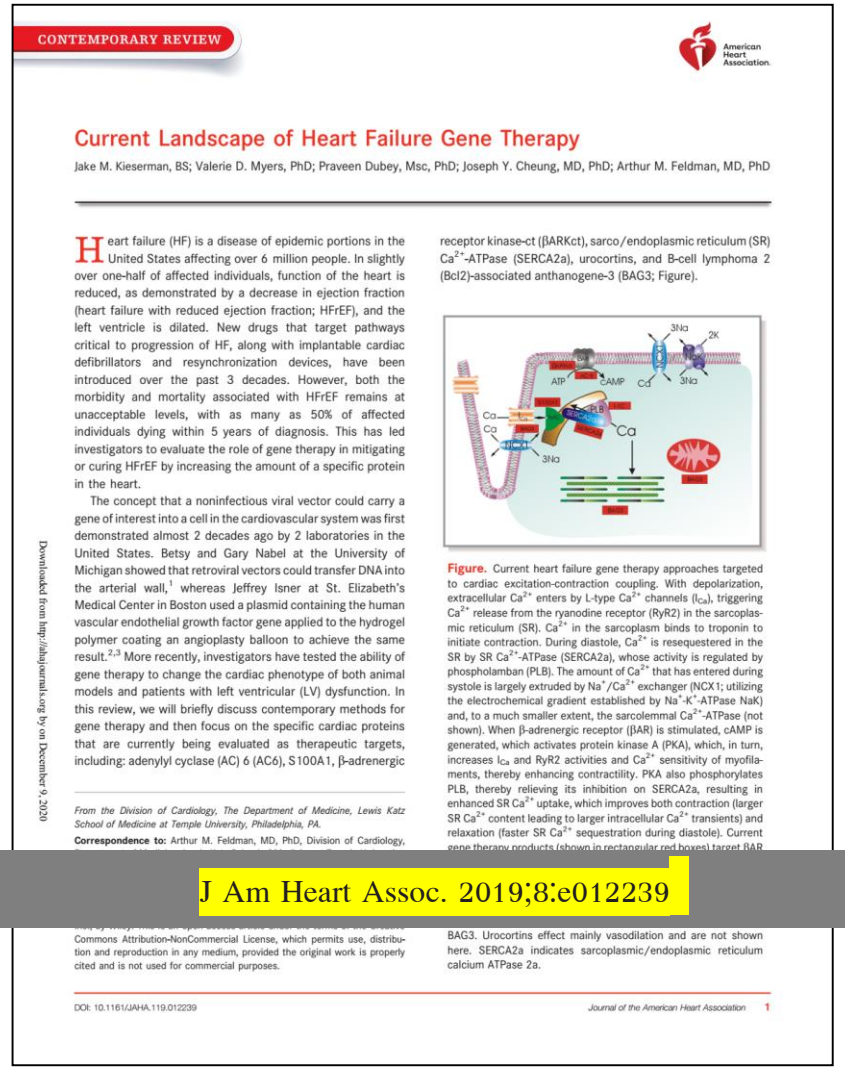
PREDICTION ***minus 1

"Gene/ cell therapy will be a failure"

(at least not in 2030) (maybe for prevent HF)







CONTEMPORARY REVIEW

American Heart Association.

Current Landscape of Heart Failure Gene Therapy

Jake M. Kieserman, BS; Valerie D. Myers, PhD; Praveen Dubey, Msc, PhD; Joseph Y. Cheung, MD, PhD; Arthur M. Feldman, MD, PhD

Heart failure (HF) is a disease of epidemic portions in the United States affecting over 6 million people. In slightly over one-half of affected individuals, function of the heart is reduced, as demonstrated by a decrease in ejection fraction (heart failure with reduced ejection fraction; HFrEF), and the left ventricle is dilated. New drugs that target pathways critical to progression of HF, along with implantable cardiac defibrillators and resynchronization devices, have been introduced over the past 3 decades. However, both the morbidity and mortality associated with HFrEF remains at unacceptable levels, with as many as 50% of affected individuals dying within 5 years of diagnosis. This has led investigators to evaluate the role of gene therapy in mitigating or curing HFrEF by increasing the amount of a specific protein in the heart.

The concept that a noninfectious viral vector could carry a gene of interest into a cell in the cardiovascular system was first demonstrated almost 2 decades ago by 2 laboratories in the United States. Betsy and Gary Nabel at the University of Michigan showed that retroviral vectors could transfer DNA into the arterial wall,[1] whereas Jeffrey Isner at St. Elizabeth's Medical Center in Boston used a plasmid containing the human vascular endothelial growth factor gene applied to the hydrogel polymer coating an angioplasty balloon to achieve the same result.[2,3] More recently, investigators have tested the ability of gene therapy to change the cardiac phenotype of both animal models and patients with left ventricular (LV) dysfunction. In this review, we will briefly discuss contemporary methods for gene therapy and then focus on the specific cardiac proteins that are currently being evaluated as therapeutic targets, including: adenylyl cyclase (AC) 6 (AC6), S100A1, β-adrenergic receptor kinase-ct (βARKct), sarco/endoplasmic reticulum (SR) Ca^{2+}-ATPase (SERCA2a), urocortins, and B-cell lymphoma 2 (Bcl2)-associated anthanogene-3 (BAG3; Figure).

From the Division of Cardiology, The Department of Medicine, Lewis Katz School of Medicine at Temple University, Philadelphia, PA.

Correspondence to: Arthur M. Feldman, MD, PhD, Division of Cardiology,

DOI: 10.1161/JAHA.119.012239

Figure. Current heart failure gene therapy approaches targeted to cardiac excitation-contraction coupling. With depolarization, extracellular Ca^{2+} enters by L-type Ca^{2+} channels (I_{Ca}), triggering Ca^{2+} release from the ryanodine receptor (RyR2) in the sarcoplasmic reticulum (SR). Ca^{2+} in the sarcoplasm binds to troponin to initiate contraction. During diastole, Ca^{2+} is resequestered in the SR by SR Ca^{2+}-ATPase (SERCA2a), whose activity is regulated by phospholamban (PLB). The amount of Ca^{2+} that has entered during systole is largely extruded by Na^+/Ca^{2+} exchanger (NCX1; utilizing the electrochemical gradient established by Na^+-K^+-ATPase NaK) and, to a much smaller extent, the sarcolemmal Ca^{2+}-ATPase (not shown). When β-adrenergic receptor (βAR) is stimulated, cAMP is generated, which activates protein kinase A (PKA), which, in turn, increases I_{Ca} and RyR2 activities and Ca^{2+} sensitivity of myofilaments, thereby enhancing contractility. PKA also phosphorylates PLB, thereby relieving its inhibition on SERCA2a, resulting in enhanced SR Ca^{2+} uptake, which improves both contraction (larger SR Ca^{2+} content leading to larger intracellular Ca^{2+} transients) and relaxation (faster SR Ca^{2+} sequestration during diastole). Current gene therapy products (shown in rectangular red boxes) target βAR BAG3. Urocortins effect mainly vasodilation and are not shown here. SERCA2a indicates sarcoplasmic/endoplasmic reticulum calcium ATPase 2a.

J Am Heart Assoc. 2019;8:e012239

PREDICTION ***minus 1

"Gene/ cell therapy will be a failure"

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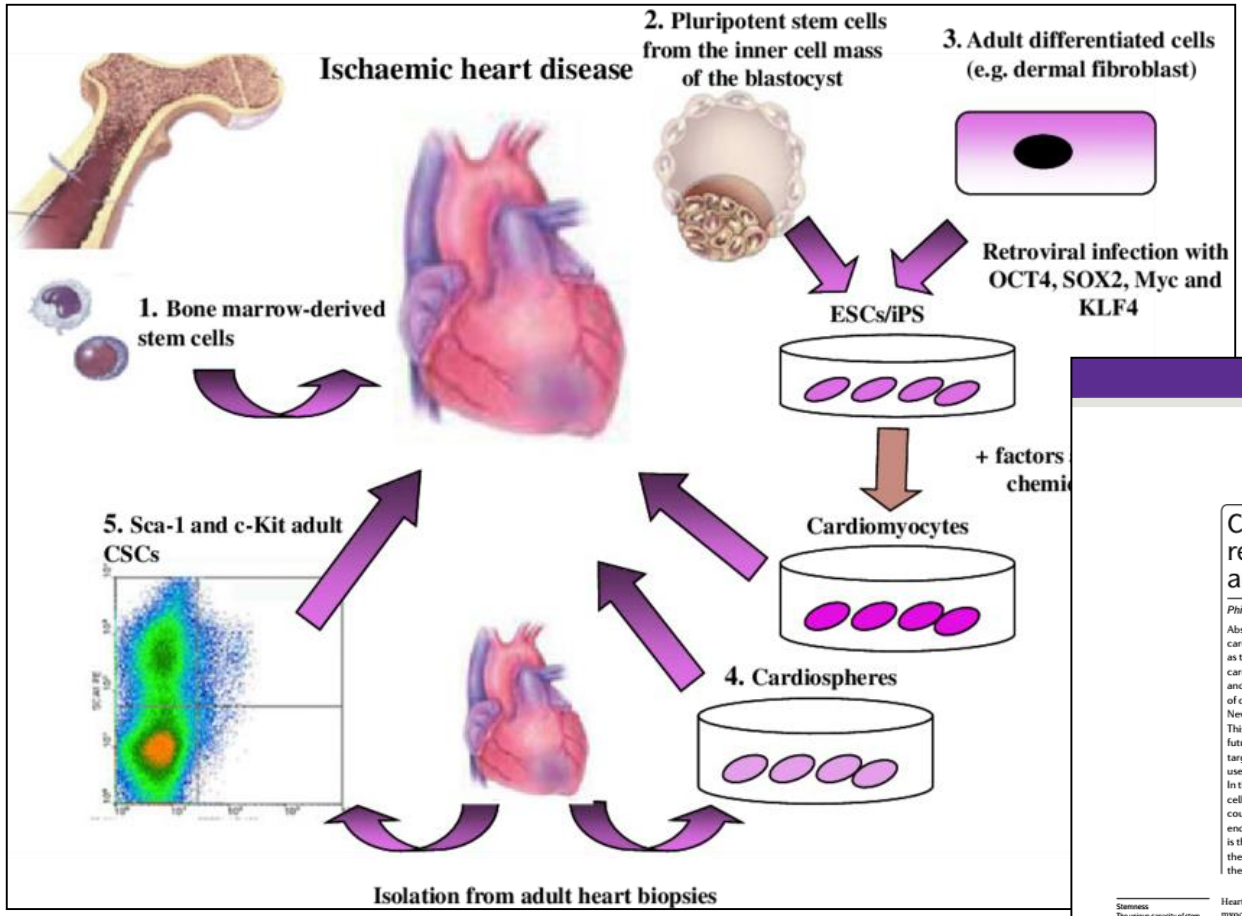



CARDIAC REGENERATION

REVIEWS

Cell therapy trials for heart regeneration — lessons learned and future directions

Philippe Menasché

Abstract | The effects of cell therapy on heart regeneration in patients with chronic cardiomyopathy have been assessed in several clinical trials. These trials can be categorized as those using noncardiac stem cells, including mesenchymal stem cells, and those using cardiac-committed cells, including KIT+ cardiac stem cells, cardiosphere-derived cells, and cardiovascular progenitor cells derived from embryonic stem cells. Although the safety of cell therapies has been consistently reported, their efficacy remains more elusive. Nevertheless, several lessons have been learned that provide useful clues for future studies. This Review summarizes the main outcomes of these studies and draws some perspectives for future cell-based regenerative trials, which are largely based on the primary therapeutic target: remuscularization of chronic myocardial scars by exogenous cells or predominant use of these cells to activate host-associated repair pathways though paracrine signalling. In the first case, the study design should entail delivery of large numbers of cardiac-committed cells, supply of supportive noncardiac cells, and promotion of cell survival and appropriate coupling with endogenous cardiomyocytes. If the primary objective is to harness endogenous repair pathways, then the flexibility of cell type is greater. As the premise is that the transplanted cells need to engraft only transiently, the priority is to optimize their early retention and possibly to switch towards the sole administration of their secretome.

Stemness
The unique capacity of stem cells to self-renew and to differentiate into multiple lineages.

Heart failure occurs when a large number of cardiomyocytes has been irreversibly damaged, most often after a myocardial infarction but also as a result of a genetic disease, and is further contributed to by alterations in coronary vessels and the extracellular matrix. Although human adult cardiomyocytes are able to divide[1], the spontaneous turnover rate of adult cardiomyocytes cannot compensate for the massive loss of contractile cells that underlies the development of heart failure[2]. However, none of the current therapies for heart failure addresses this fundamental mechanism, as the approaches involve either palliative (drugs) or

the lessons learned from these studies that might help to make next-generation regenerative therapy trials more successful.

Cell trials for cardiac regeneration

Multiple clinical trials have been conducted to test the effects of different cell types on cardiac repair and regeneration, with some of these cells credited to display features of stemness. Comparing the different trials is difficult owing to the vast differences in patient profiles, cell phenotype, dosing (in an early study[3], the reported doses varied from 1.75×10^6 cells

Department of

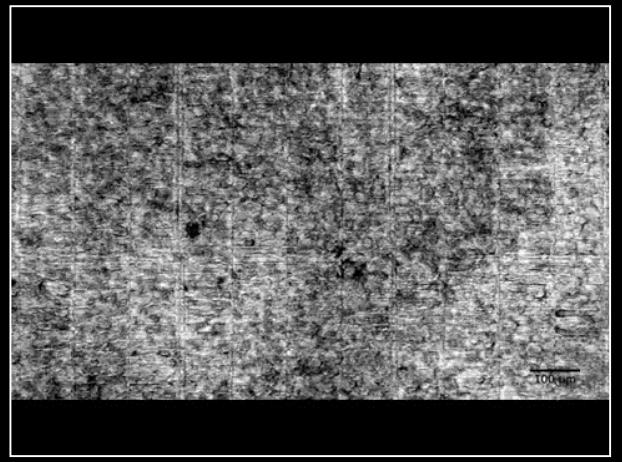
rizes the findings of the major clinical trials of cell therapies for cardiac repair and regeneration, highlighting

markers. Only the latter studies are included in the analysis below.

NATURE REVIEWS | CARDIOLOGY VOLUME 15 | NOVEMBER 2018 | 659

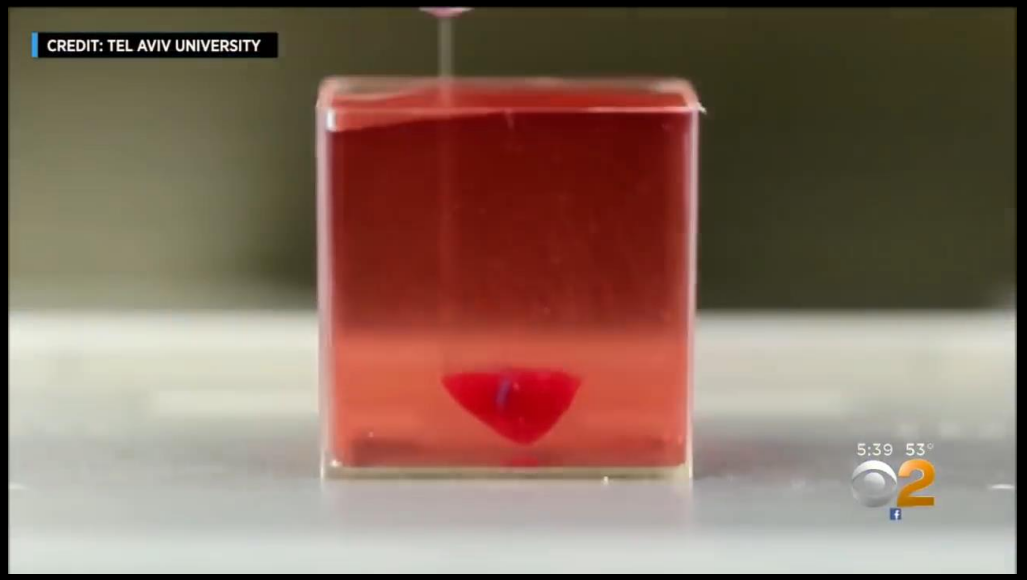
Nature Review Card 2018;15:659

Cell culture



Decellularization

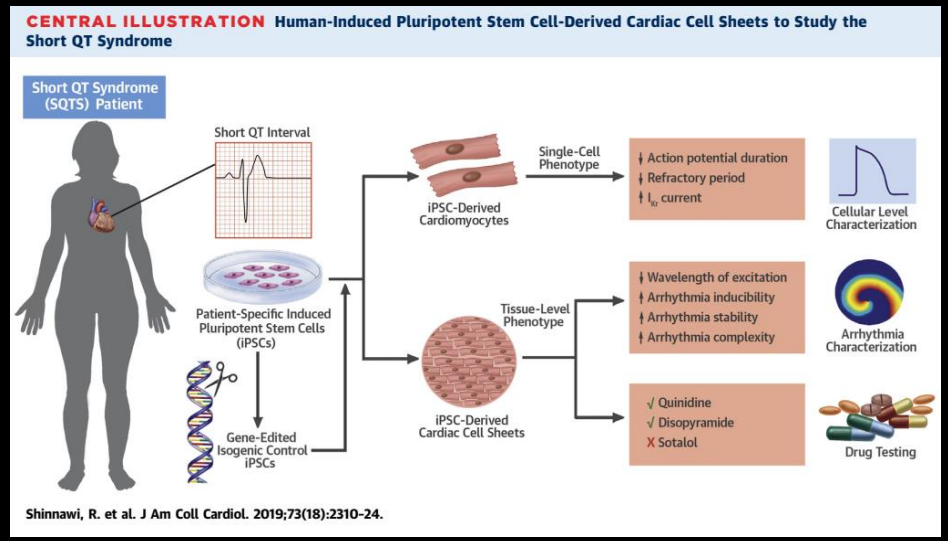
Cardiac patch/sheet



Cardaic bio-3D prinitng

SAVE your patient

Do not recommend stem cell rx for cardiac disease



Stem cell for disease phenotype
Drug development

Heart failure 2030:

1. Neurohormal blockage for HFpEF
2. No one size fit all of HFrEF
3. Stop measure in EF
4. Biomarker guided rx
5. Full implant LVAD

"It has always been the dream of mankind to predict the future"

CONCLUSION

- The 2020-2030 will be just a another decade
  - Change and improvement may happen
  - Stay with the current
- Best treatment is prevention
- Progress depends on how we understand the mechanisms of heart failure
  - AI assisted is inevitable
  - Physicians will play more human role
- No one really know what the future will be like but the future will definitely be a lot different than today.

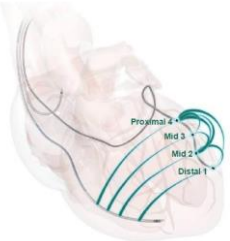
Aekarach.a@chula.ac.th

Thank you for stay current

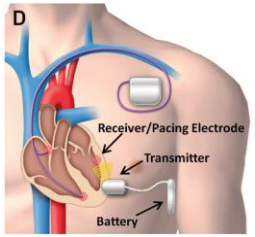
SUPPLEMENT

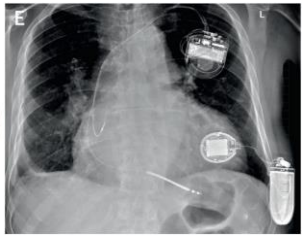
More and more devices

Wearable ICD

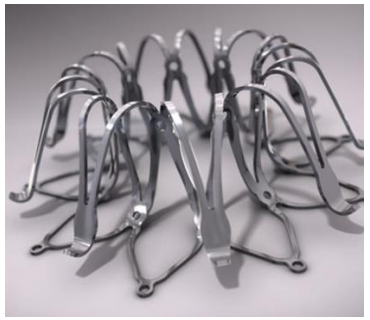


Quadiposition pacing

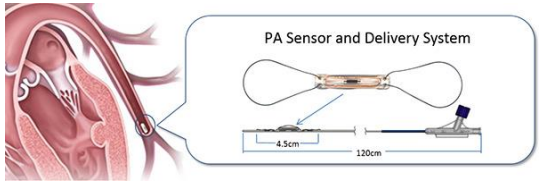




Wireless LV pacing

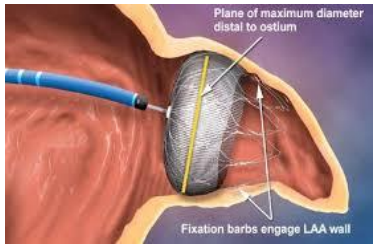


Interatrial device

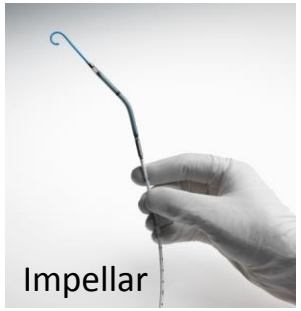


Wireless PA monitoring

21century's Technology make Device safer and Become part of options for treatment

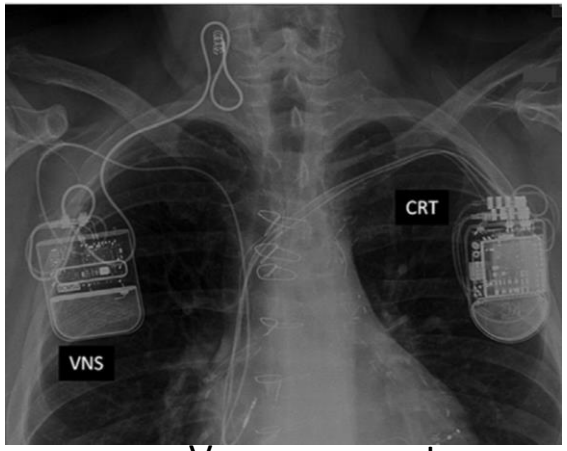


LAA occluder



Short terms VAD

Smaller long term VAD



Vagus nerve stem


72
RECORDINGS
Week
M T W R F S S
72
122/76
98
192

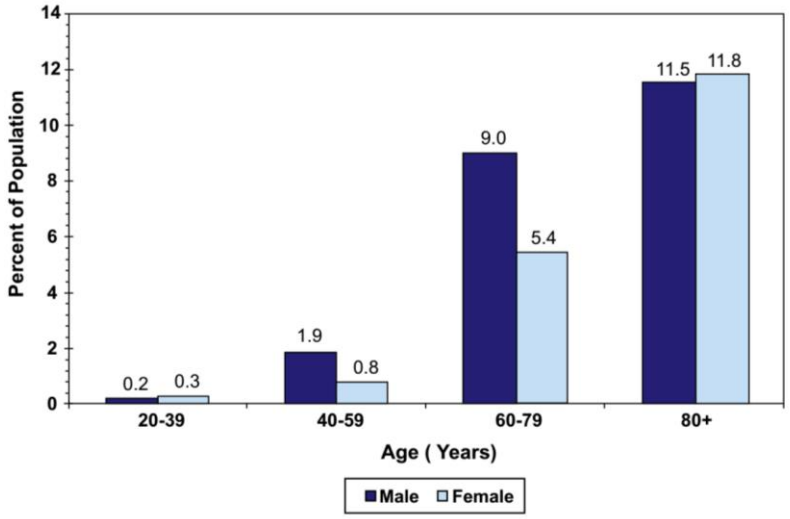


Figure 2 **Prevalence of Heart Failure, by Sex and Age (National Health and Nutrition Examination Survey, 2005–2008)**

Reprinted with permission from: Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics—2012 update. Circulation 2012;125:e12–30. Source: National Hospital Discharge Survey/National Center for Health Statistics and National Heart, Lung, and Blood Institute.

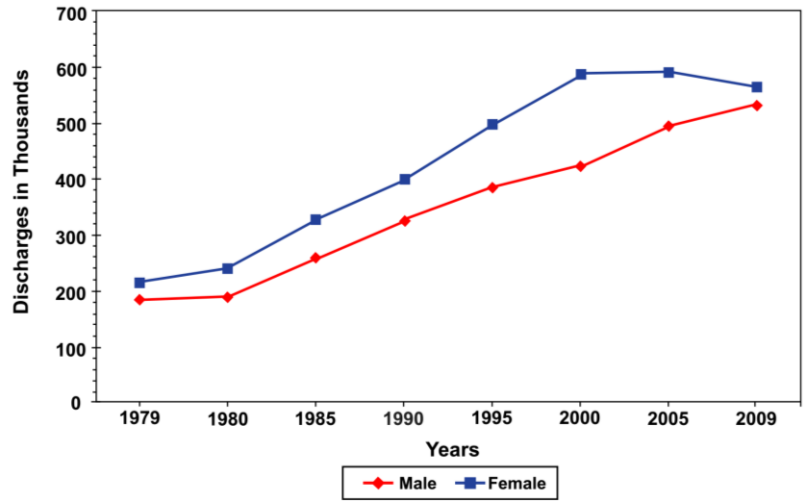
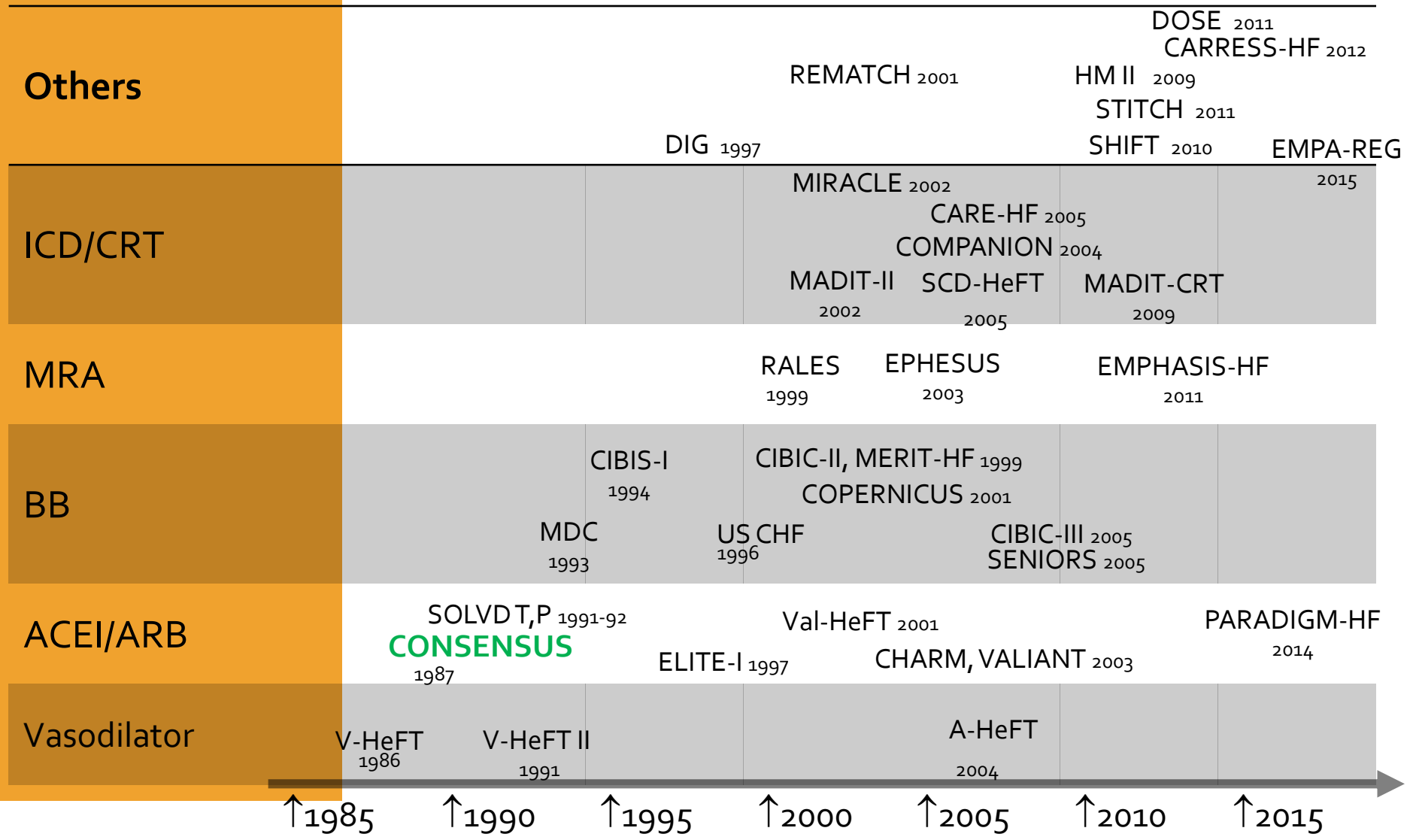
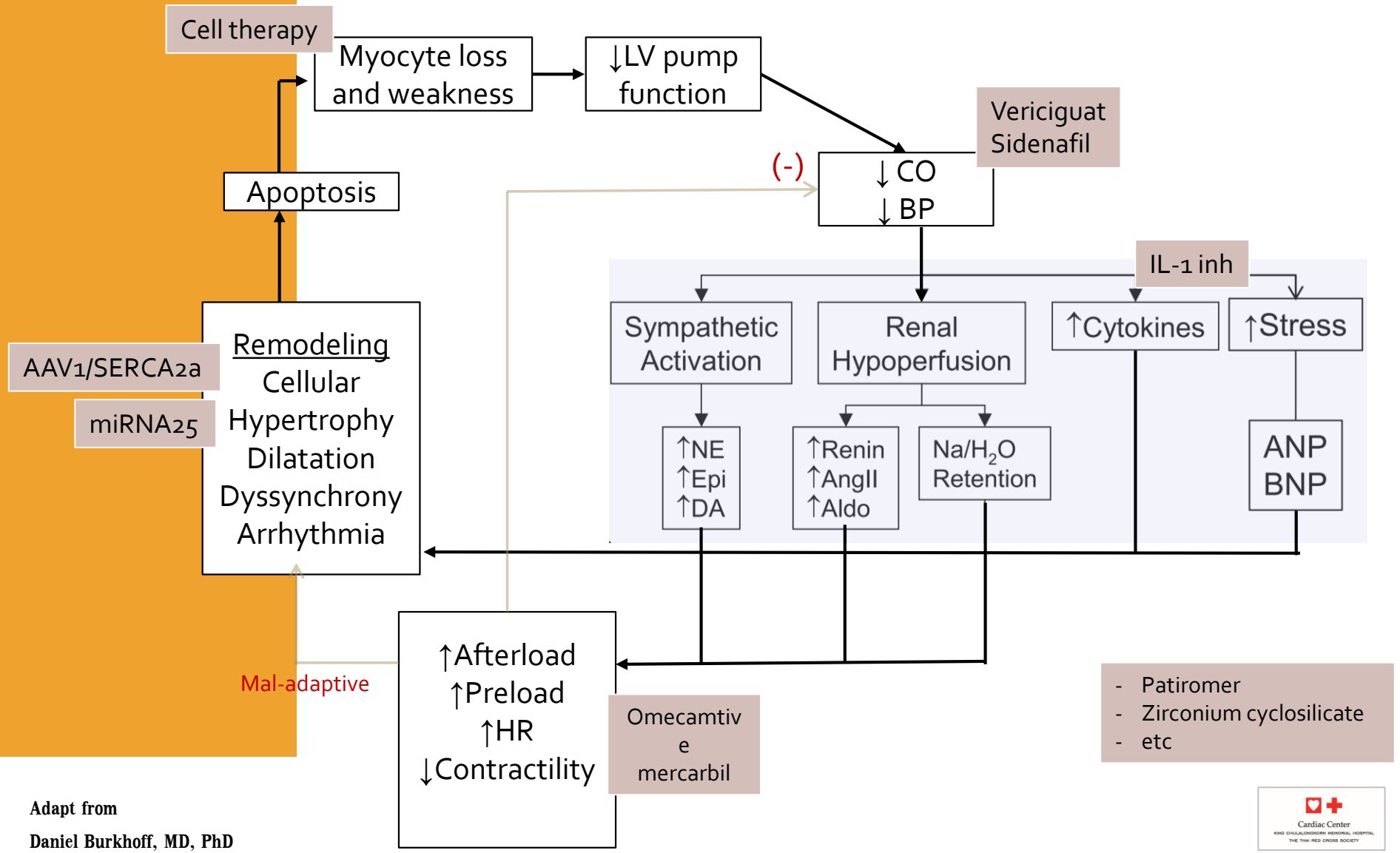


Figure 1 **Discharges From Hospitalization Due to Heart Failure, by Sex (United States, 1979–2009)**

Reprinted with permission from: Roger VL, Go AS, Lloyd-Jones DM et al. Heart disease and stroke statistics—2012 update. Circulation 2012;125:e12–30. Source: National Hospital Discharge Survey/National Center for Health Statistics and National Heart, Lung, and Blood Institute.


Others
DOSE 2011
CARRESS-HF 2012
REMATCH 2001
HM II 2009
STITCH 2011
DIG 1997
SHIFT 2010
EMPA-REG 2015
ICD/CRT
MIRACLE 2002
CARE-HF 2005
COMPANION 2004
MADIT-II 2002
SCD-HeFT 2005
MADIT-CRT 2009
MRA
RALES 1999
EPHESUS 2003
EMPHASIS-HF 2011
BB
CIBIS-I 1994
CIBIC-II, MERIT-HF 1999
COPERNICUS 2001
MDC 1993
US CHF 1996
CIBIC-III 2005
SENIORS 2005
ACEI/ARB
SOLVD T,P 1991-92
CONSENSUS 1987
Val-HeFT 2001
PARADIGM-HF 2014
ELITE-I 1997
CHARM, VALIANT 2003
Vasodilator
V-HeFT 1986
V-HeFT II 1991
A-HeFT 2004
1985
1990
1995
2000
2005
2010
2015



Adapt from

Daniel Burkhoff, MD, PhD