Characterizing Heart Failure and its Antecedents

NMRC
Awards Ceremony and Research Symposium
18th March 2015

Prof A Mark Richards

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Cardiovascular Research Institute
National University Heart Centre,
NUHS, Singapore

&
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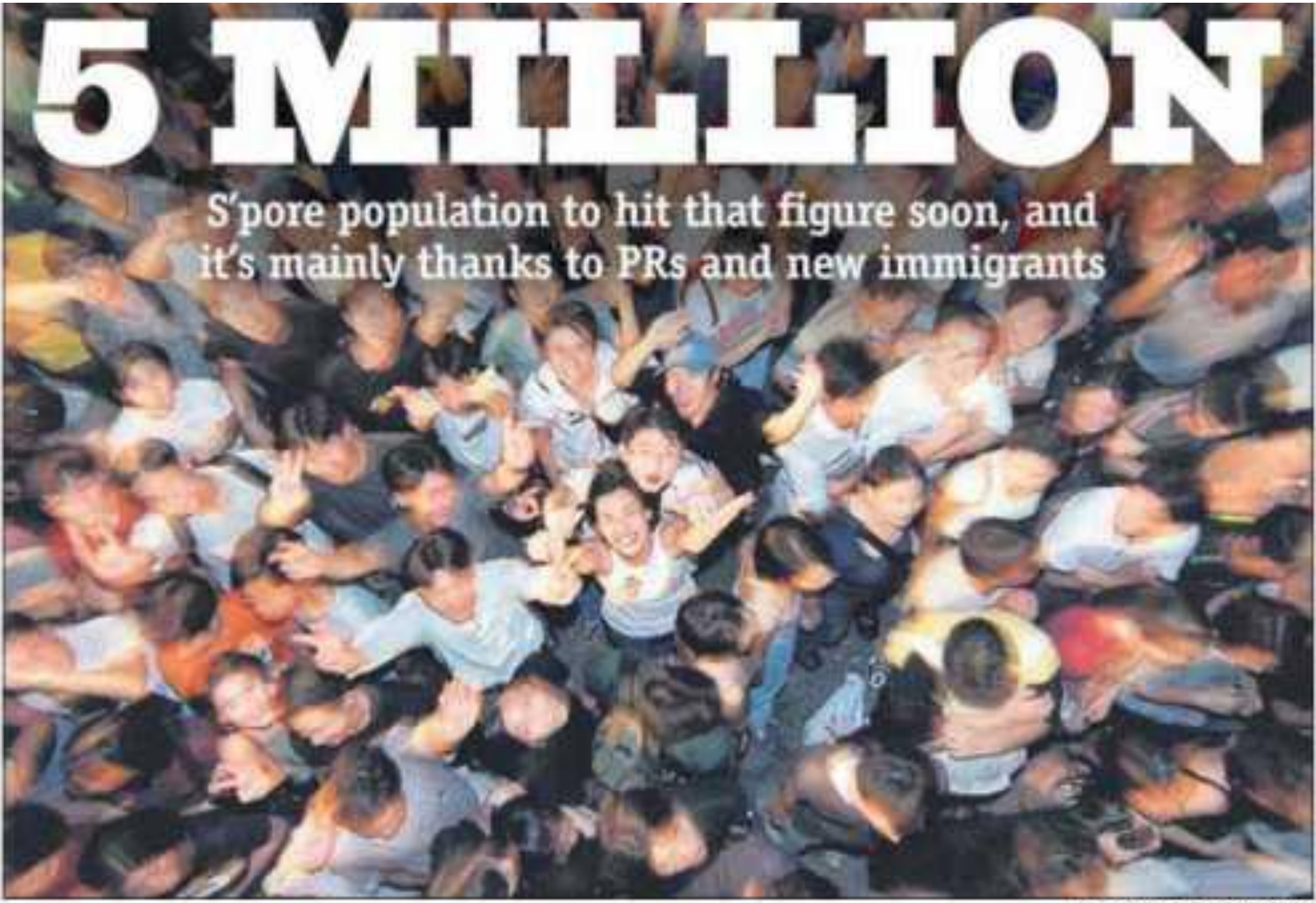
University of Otago , Christchurch,
New Zealand

National University
Heart Centre, Singapore

5 MILLION

S'pore population to hit that figure soon, and it's mainly thanks to PRs and new immigrants



FILE PHOTO: THE STRAITS TIMES

Singapore is Ageing-->

Heart Failure in Singapore

- Commonest cardiac cause of hospitalization
  - ~24% (5,316/22,343) of all cardiac admissions (*source: Casemix Project Office*)
- Age-adjusted HF admission rate rose by ~40% from 1991-8 (*Heart 2003;89:865-70*)
  - Overall burden will increase as society ages
- 5-year mortality remains high at 68%

PEOPLE/SHOP StudyDesign

HF Hospital admission / out-patient visit

↓

Baseline Assessment

Clinical review / Quality of life / echo / bloods

(N = 1250 in NZ plus 1250 in Singapore TOTAL 2,500)

↓

Study Visit (6 weeks and 6 months)

Clinical review / Quality of life / echo (at 6 months) / bloods

↓

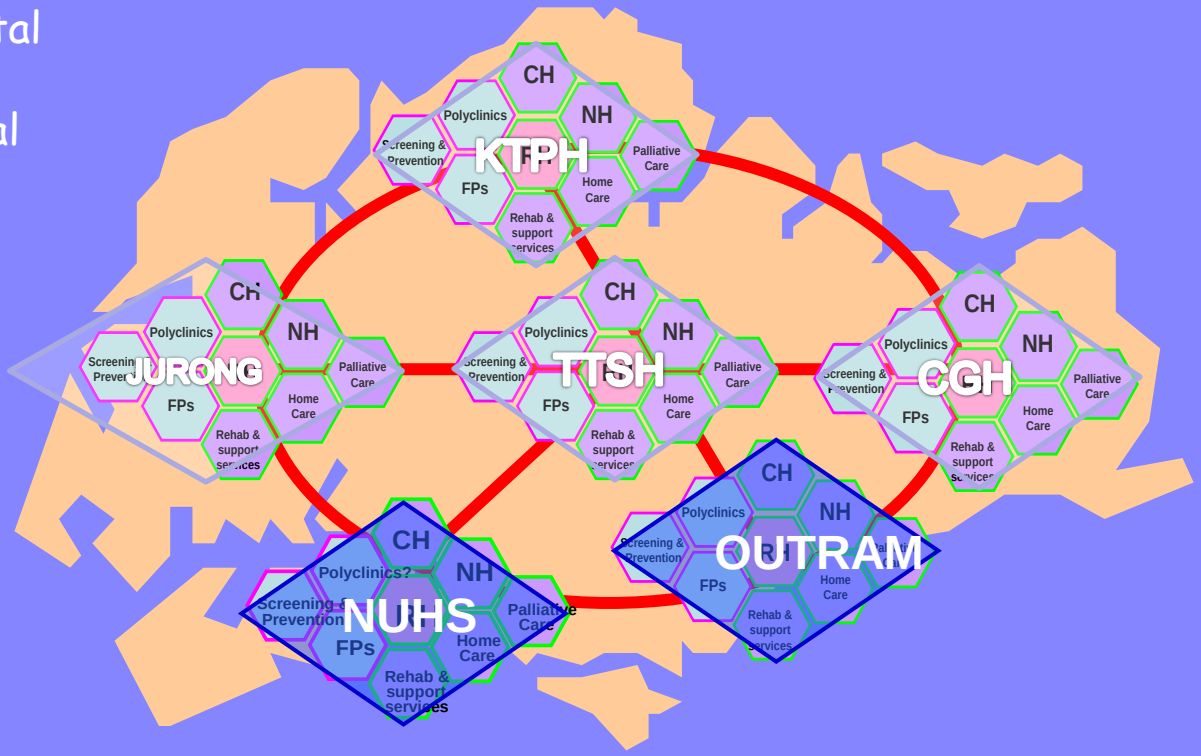
Clinical event follow up for all patients 2 years

Main outcomes for HF-PEF compared with HF-lowEF

PEOPLE / SHOP Study
NZ and Singapore

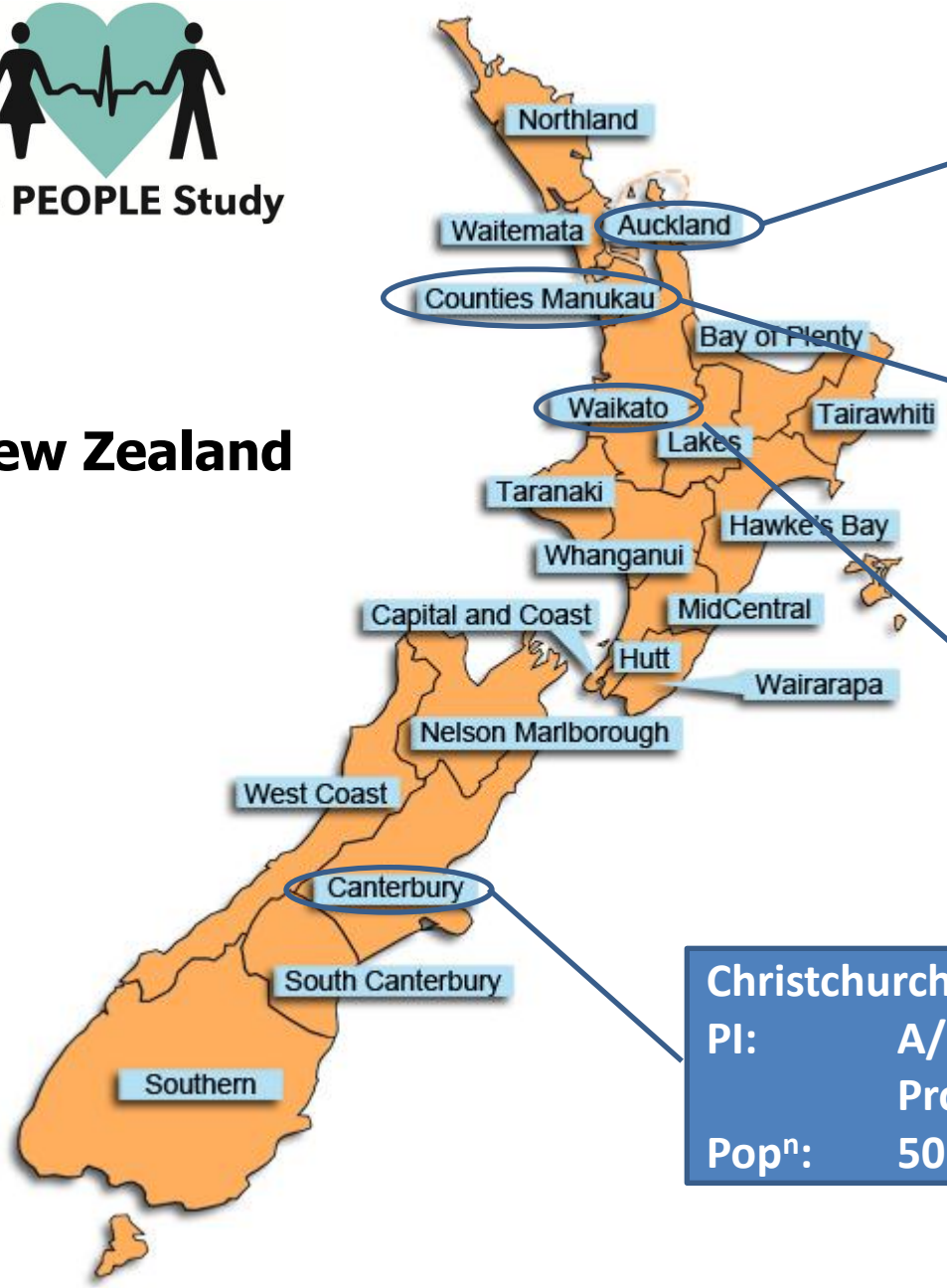
Combined Outcome Study

- National University Hospital
- National Heart Centre
- Singapore General Hospital
- Tan Tock Seng Hospital
- Koo Tek Puat Hospital
- Changi Hospital



The PEOPLE Study

New Zealand



The University of Auckland & Auckland City Hospital
PI: Prof Rob Doughty
Pop^{n}: 456,600

Middlemore Hospital
PI: Dr Mayanna Lund
Pop^{n}: 499,900

Waikato Hospital
PI: Dr Gerry Devlin
Pop^{n}: 367,600

Christchurch Hospital
PI: A/Prof Richard Troughton & Prof Mark Richards
Pop^{n}: 502,700

PEOPLE / SHOP Study
NZ and Singapore

Combined Outcome Study

	New Zealand	Singapore
Population	4.4m	5.3m
Land area	268,000km^2	740km^2
GDP	117,800m	291,900m
Inflation	2.6%	2.8%
Unemployment	6.5%	2.1%
Life Expectancy at birth	80.6yrs	82.1yrs
Ethnicity		
	NZ Euro 67%	Chinese 74%
	Māori 15%	Malay 13%
	Asian 10%	Indian 9.2%
	Pacific 7%	

PEOPLE / SHOP Study
NZ and Singapore

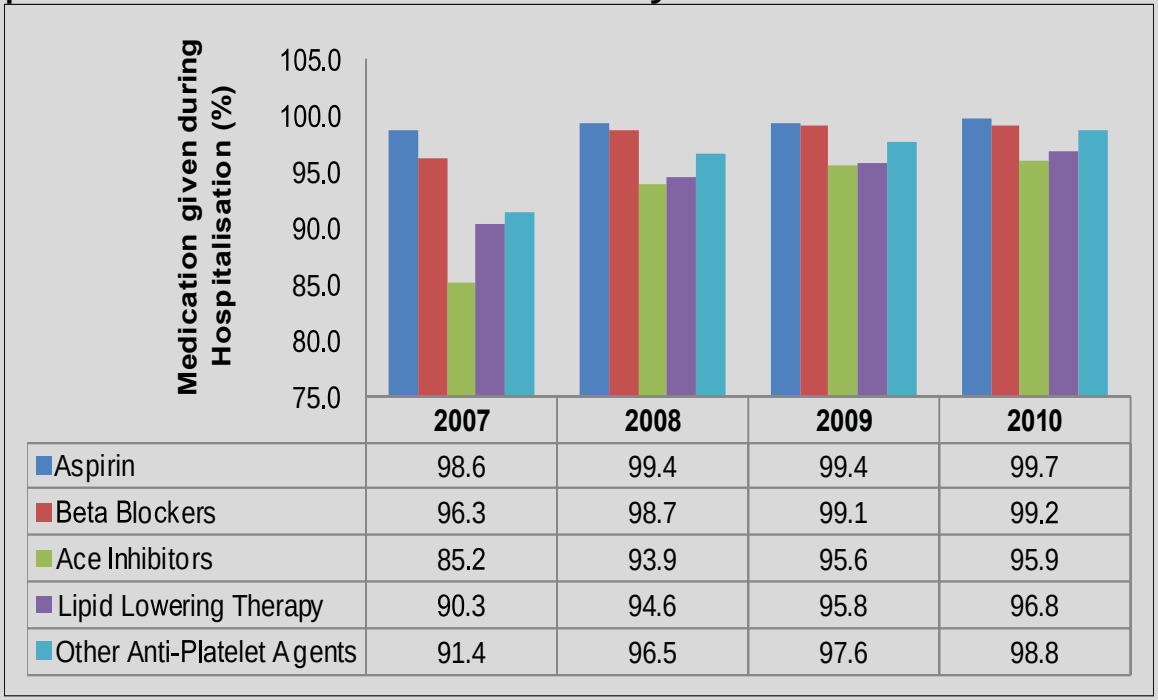
Interim Baseline Data

	PEOPLE Study (NZ)	SHOP Study (Singapore)	MAGGIC Meta-analysis*
N	545	619	50,991
Age	70.5 (39-95)	62 (12)	68 (12)
Women, %	32	23	35
Medical history (%)			
Hypertension	59	72	43
CAD	52	55	52
AF	43	22	21
Diabetes	27	55	23
LVEF, %	43 (17)	33 (15)	36
Heart rate, bpm	73 (15)	76 (14)	79 (18)
SBP, mmHg	122 (24)	123 (21)	131 (23)
DBP, mmHg	72 (12)	70 (23)	77 (13)
LBBB, %	24	7	24

* MAGGIC Meta-analysis. EHJ 2011

Causes of Heart Failure :- Heart Attacks, Hypertension, Valve Disease, Arrhythmia, Congenital, other cardiomyopathies

Use of appropriate medications for Acute Myocardial Infarction in Singapore

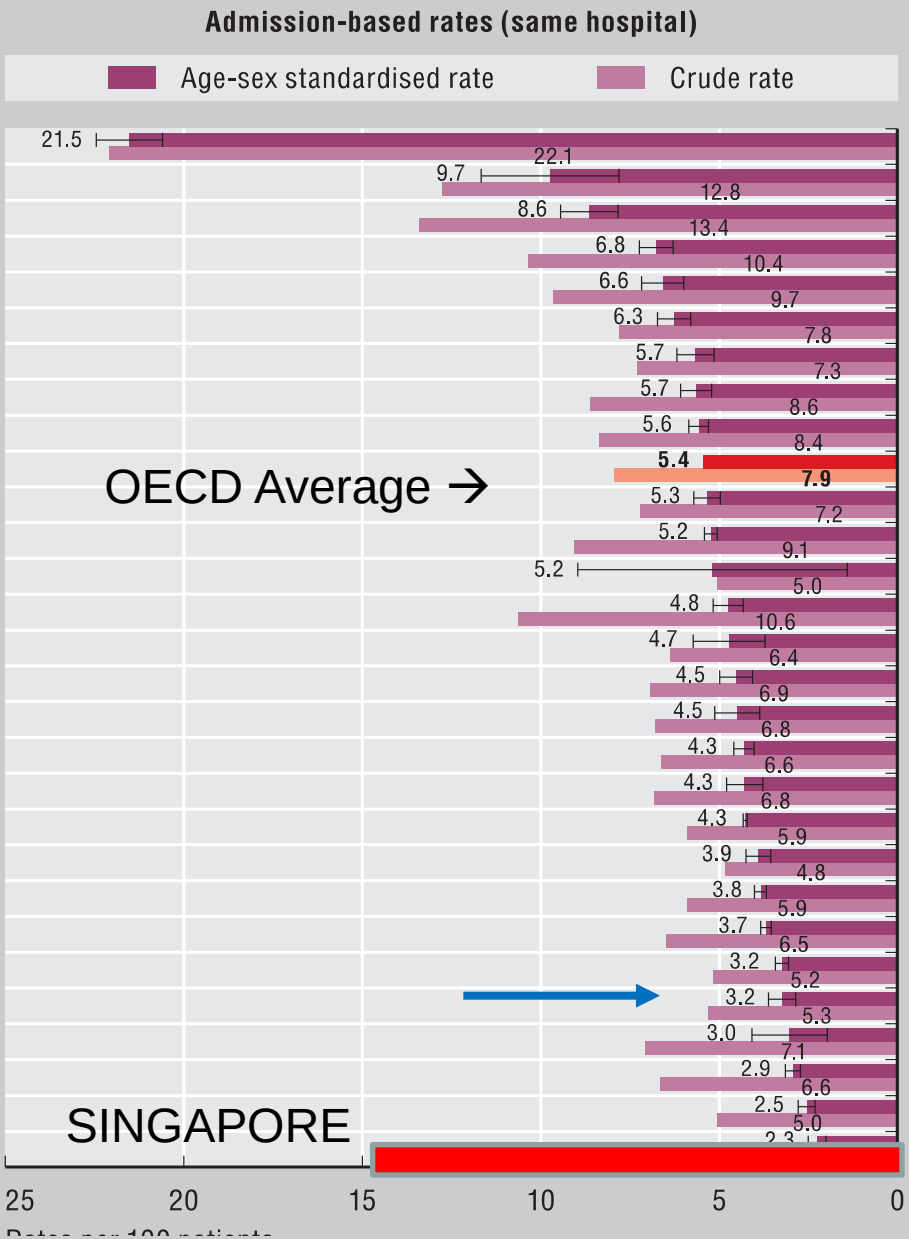


	2007	2008	2009	2010
Aspirin	98.6	99.4	99.4	99.7
Beta Blockers	96.3	98.7	99.1	99.2
Ace Inhibitors	85.2	93.9	95.6	95.9
Lipid Lowering Therapy	90.3	94.6	95.8	96.8
Other Anti-Platelet Agents	91.4	96.5	97.6	98.8

In Singapore emergency and in –hospital management of Acute Myocardial Infarction is excellent by international standards…….but…at NUHC

One year rates of DEATH **and ALL-CAUSE REHOSPITALIZATION** in 2011-12 = **28%**

With HEART FAILURE the number one cause



Mexico
Japan
Belgium
Germany
Portugal
Korea
Slovak Republic
Austria
Spain
OECD
Netherlands
United Kingdom
Luxembourg
Finland
Slovenia
Switzerland
Israel
Czech Republic
Ireland
United States
Poland
Canada
Italy
Australia
New Zealand
Iceland
Sweden
Norway
Denmark

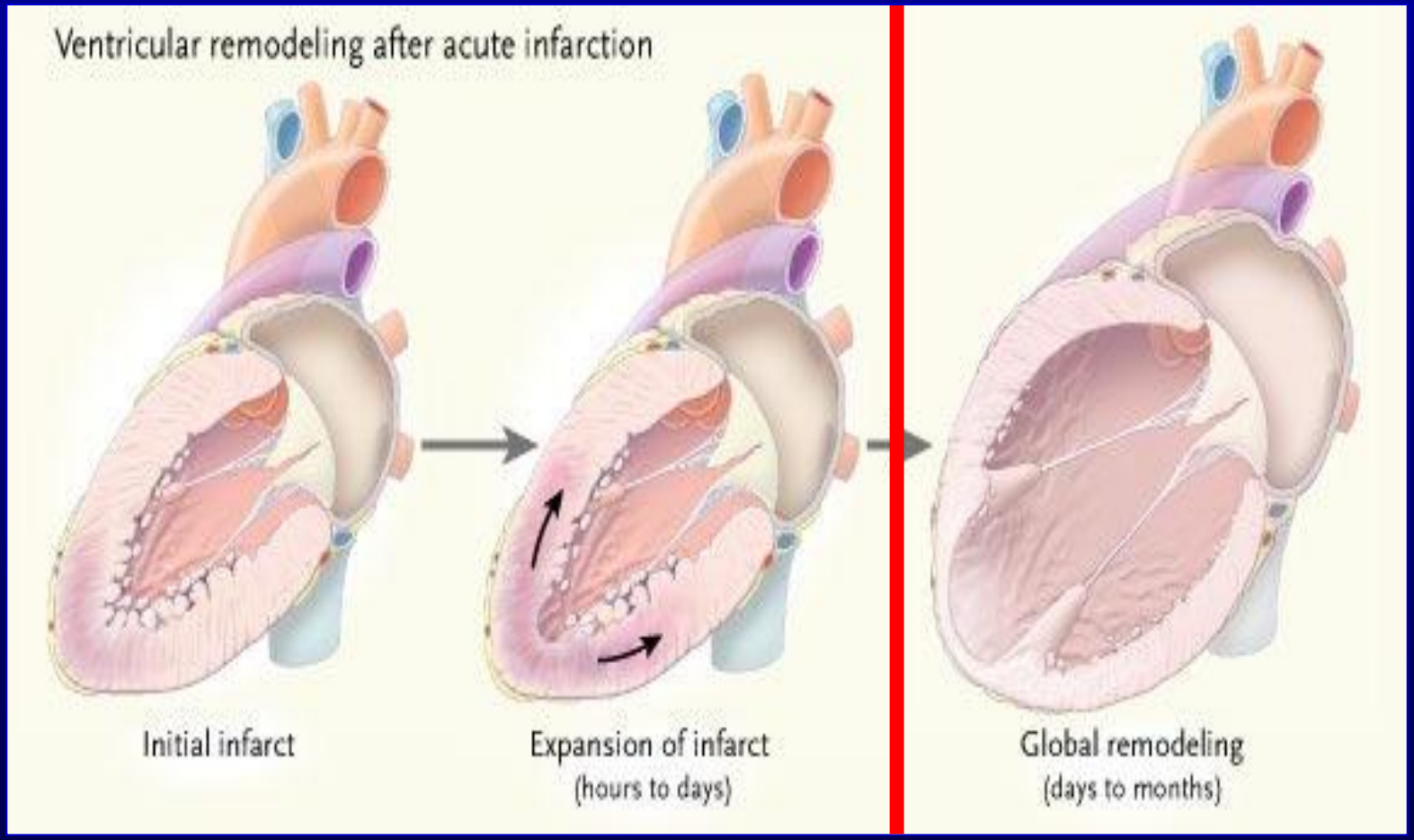
OECD :
Acute Myocardial Infarction
28 Day Case-fatality Rates in 2009.

OECD=organization for economic cooperation and development

SINGAPORE
2007-2012
16.0-12.7 %

Single most common reason for re-admission in the year after AMI
Is Heart Failure.

LV remodeling in Heart Failure



Jessup et al, NEJM 2003, 347, 2007

$(N \cdot m \times g^{-1} \times min^{-1})$

Cardiac tissue efficiency is measured as the ratio of cardiac tissue work to measurements of myocardial oxygen consumption (MVO_2) using ^{11}C-acetate kinetics as a surrogate for energy input [9,10,11]. Strain is determined from tagged or DENSE MRI data [12]. This measurement and estimates of stress are used to calculate myocardial external minute work (MEMW) for a region of tissue in the left ventricle (LV) wall using the expression:

$$MEMW = (HR/\gamma)\int_{ED}^{ES} T d\varepsilon$$

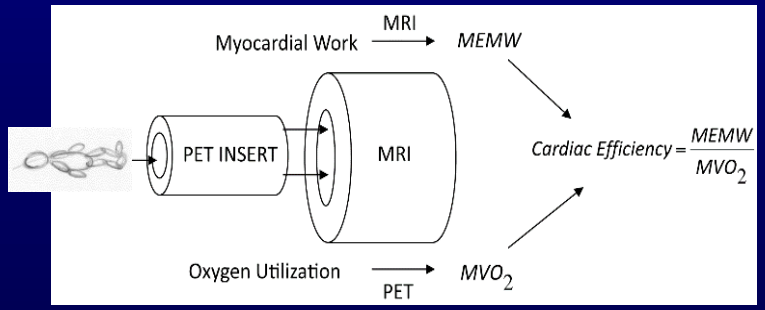


Figure: Hybrid MRI-PET imaging at CIRC. CIRC has installed one of few hybrid MRI-PET systems (Siemens mMR) in the world. Radiolabelling of fatty acid substrates and other tracers can also be done at its in-house GMP facilities.

European Heart Journal Advance Access published November 17, 2005

European Heart Journal
doi:10.1093/eurheartj/ehi631

Clinical research

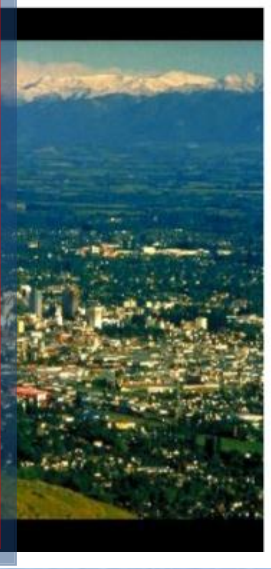
NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients

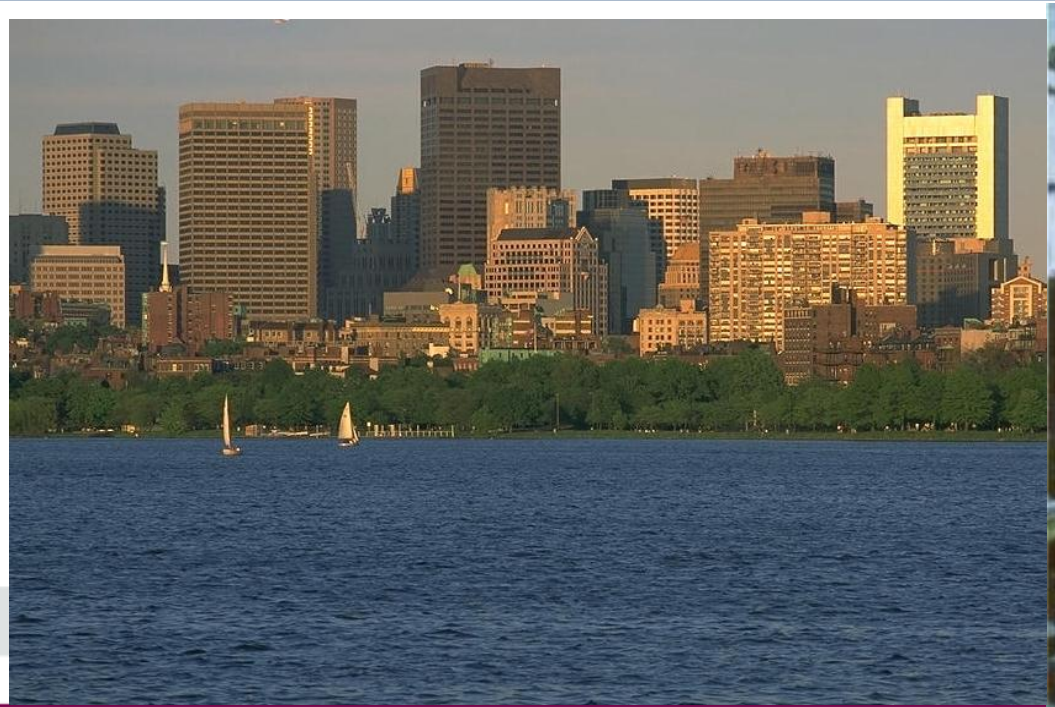
The International Collaborative of NT-proBNP Study

James L. Januzzi[1*†], Roland van Kimmenade[2†], John Lainchbury[3], Antoni Bayes-Genis[4], Jordi Ordonez-Llanos[5], Miguel Santalo-Bel[6], Yigal M. Pinto[2], and Mark Richards[3]

[1] *Cardiology Division, Massachusetts General Hospital, Yawkey 5984, 55 Fruit Street, Boston, MA 02114, USA;* [2] *Cardiology Department, University Hospital, Maastricht, The Netherlands;* [3] *Christchurch Cardioendocrine Research Group, Department of Medicine, Christchurch School of Medicine and Health Sciences, Christchurch, New Zealand;* [4] *Cardiology Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain;* [5] *Biochemistry Service, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; and* [6] *Emergency Medicine, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain*

RCH, NEW ZEALAND





B-type natriuretic peptide guided treatment of heart failure and all cause mortality

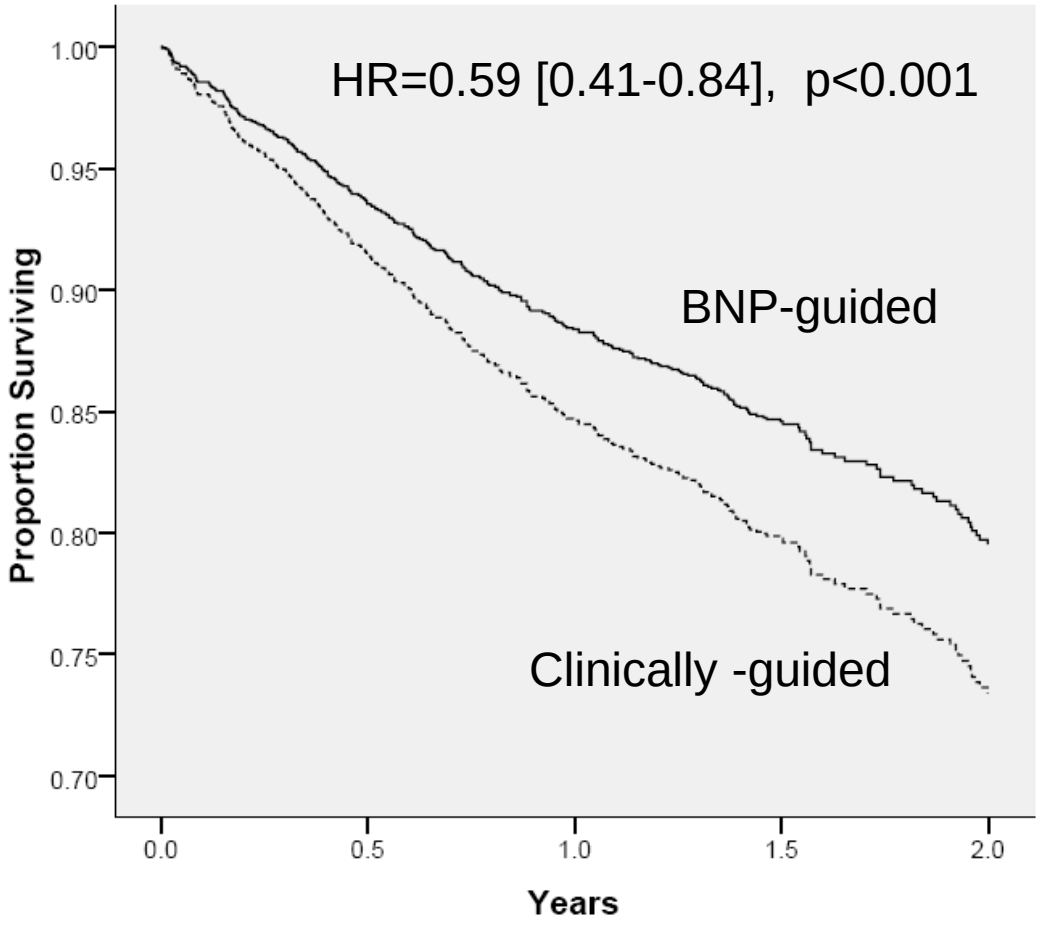
An Individual Patient Data Meta-analysis

Richard Troughton, Hans-Peter Brunner-LaRocca, Chris Frampton, Mark Richards, Rudolf Berger, Chris O'Connor, Hans Persson, Gary Nicholls, Yigal Pinto

For the BNP/NT-proBNP meta-analysis group

ESC Scientific Meeting, August 28th 2011, Paris, France

Primary Endpoint – All Cause Mortality



- Lower mortality in the NT-proBNP-guided group

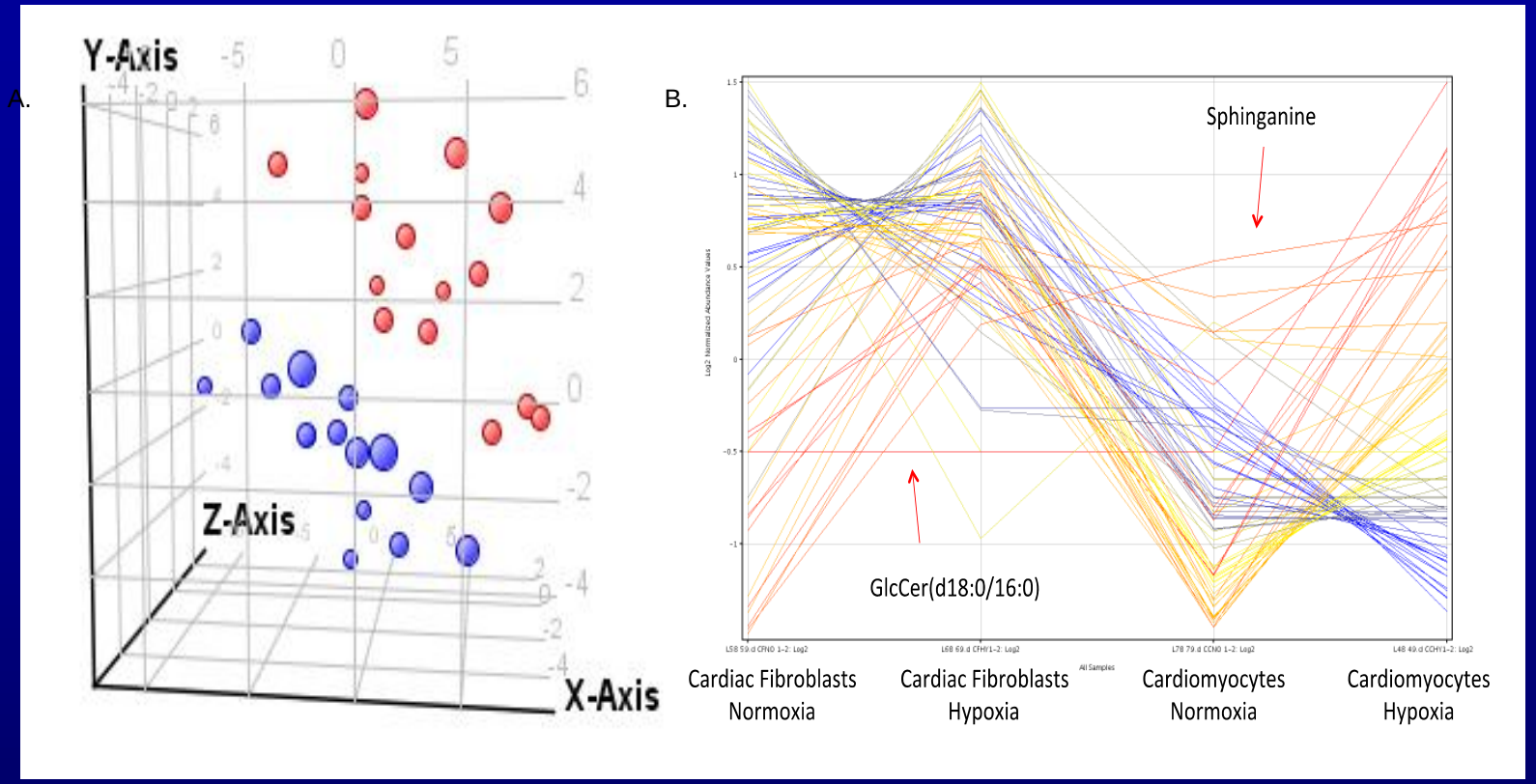
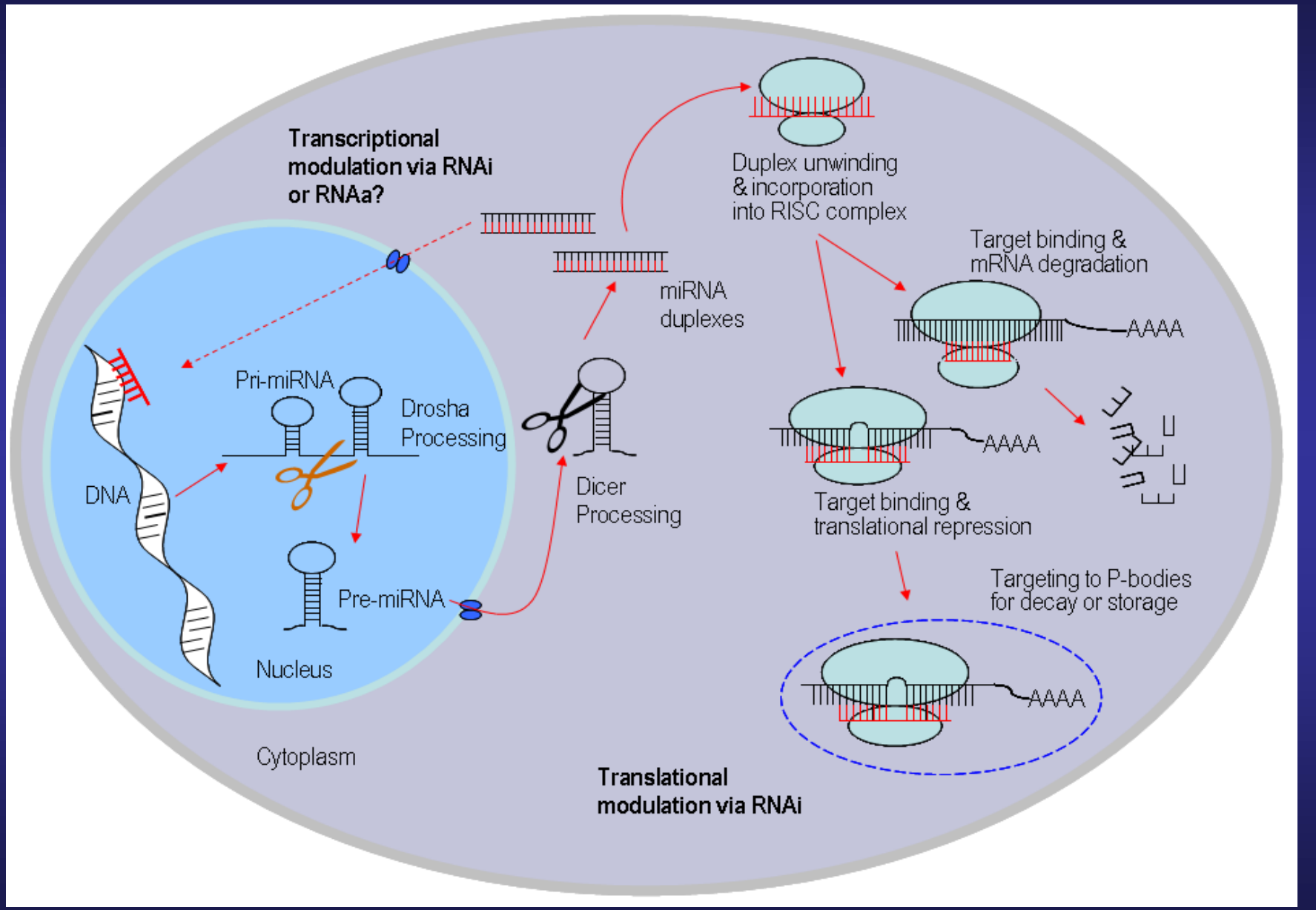
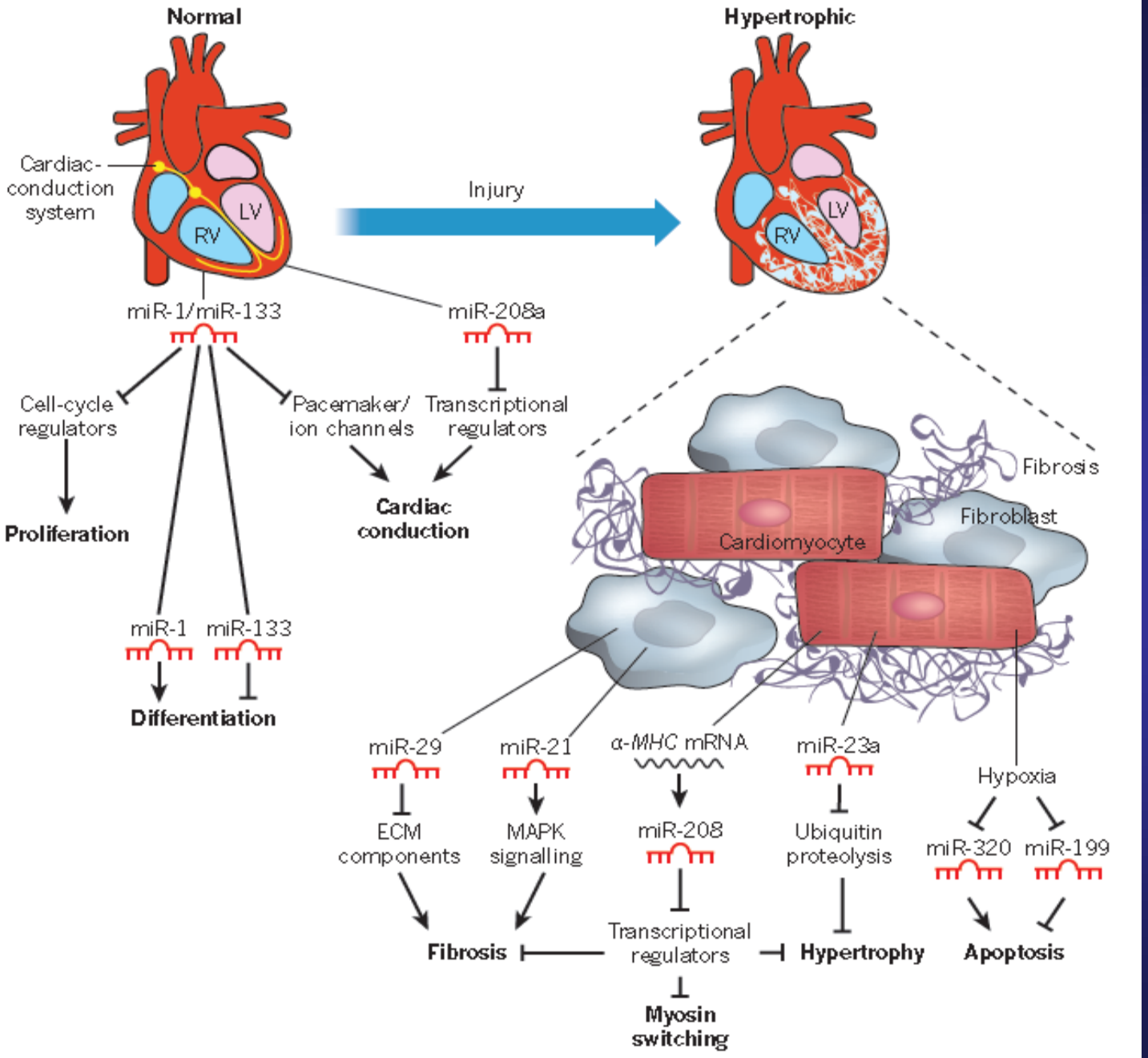


Figure 5. A. Principal Components Analysis of Plasma Sphingolipids from Patients with and without AMI. Patients with AMI (n=16) and Patients without AMI (n=16). The 3D-plot shows clear separation of principal components delineating plasma shingolipid signatures of AMI. **B. Individual Shingolipid Levels of Cardiomyocytes and Cardiac Fibroblasts Exposed to Normoxic and Hypoxic Conditions.** Each horizontal line represents a unique sphingolipid. Vertical axis corresponds to normalized intensity values in each cell type/condition. Differential response of individual sphingolipids to hypoxia, compared with normoxia, is observed in the two different cell types (cardiomyocytes and cardiac fibroblasts). For instance, in response to hypoxia, Glc Ceramide(d18:0/16:0) levels remain unchanged in cardiac fibroblasts but increase dramatically in cardiomyocytes. In contrast, in response to hypoxia, sphinganine increases markedly in cardiac fibroblasts but remains unchanged in cardiomyocytes. *(data on file, confidential privileged information)*

MicroRNAs : Biogenesis & Functions



Cardiac miRNA



E M Small & E N

doi:10.1038/nature09783

Brief UltraRapid Communication

MiR423-5p As a Circulating Biomarker for Heart Failure

Anke J. Tijsen,* Esther E. Creemers,* Perry D. Moerland, Leon J. de Windt, Allard C. van der Wal, Wouter E. Kok, Yigal M. Pinto

Rationale: Aberrant expression profiles of circulating microRNAs (miRNAs) have been described in various diseases and provide high sensitivity and specificity. We explored circulating miRNAs as potential biomarkers in patients with heart failure (HF).

Objective: The goal of this study was to determine whether miRNAs allow to distinguish clinical HF not only from healthy controls but also from non-HF forms of dyspnea.

Methods and Results: A miRNA array was performed on plasma of 12 healthy controls and 12 HF patients. From this array, we selected 16 miRNAs for a second clinical study in 39 healthy controls and in 50 cases with reports of dyspnea, of whom 30 were diagnosed with HF and 20 were diagnosed with dyspnea attributable to non–HF-related causes. This revealed that miR423-5p was specifically enriched in blood of HF cases and receiver-operator-characteristics (ROC) curve analysis showed miR423-5p to be a diagnostic predictor of HF, with an area under the curve of 0.91 ($P<0.001$). Five other miRNAs were elevated in HF cases but also slightly increased in non-HF dyspnea cases.

Conclusion: We identify 6 miRNAs that are elevated in patients with HF, among which miR423-5p is most strongly related to the clinical diagnosis of HF. These 6 circulating miRNAs provide attractive candidates as putative biomarkers for HF. (*Circ Res*. 2010;106:1035-1039.)

Key Words: MicroRNAs ■ plasma ■ heart failure ■ biomarker

European Journal of Heart Failure (2015)
doi:10.1002/ejhf.223

Circulating microRNAs in heart failure with reduced and preserved left ventricular ejection fraction

Lee Lee Wong[1,2], Arunmozhiarasi Armugam[3], Sugunavathi Sepramaniam[3], Dwi Setyowati Karolina[3], Kai Ying Lim[3], Jia Yuen Lim[1,2], Jenny P. C. Chong[1,2], Jessica Y. X. Ng[1,2], Yei-Tsung Chen[1,2], Michelle M. Y. Chan[4], Zhaojin Chen[5], Poh Shuan D. Yeo[6,7], Tze P. Ng[2,8], Lieng H. Ling[2,8], David Sim[9], Kui Toh G. Leong[10], Hean Y. Ong[11], Fazlur Jaufeerally[4,12], Raymond Wong[8,13], Ping Chai[8,13], Adrian F. Low[2,8], Carolyn S. P. Lam[1,2,8], Kandiah Jeyaseelan[3,14], and Arthur Mark Richards[1,2,8,15]*

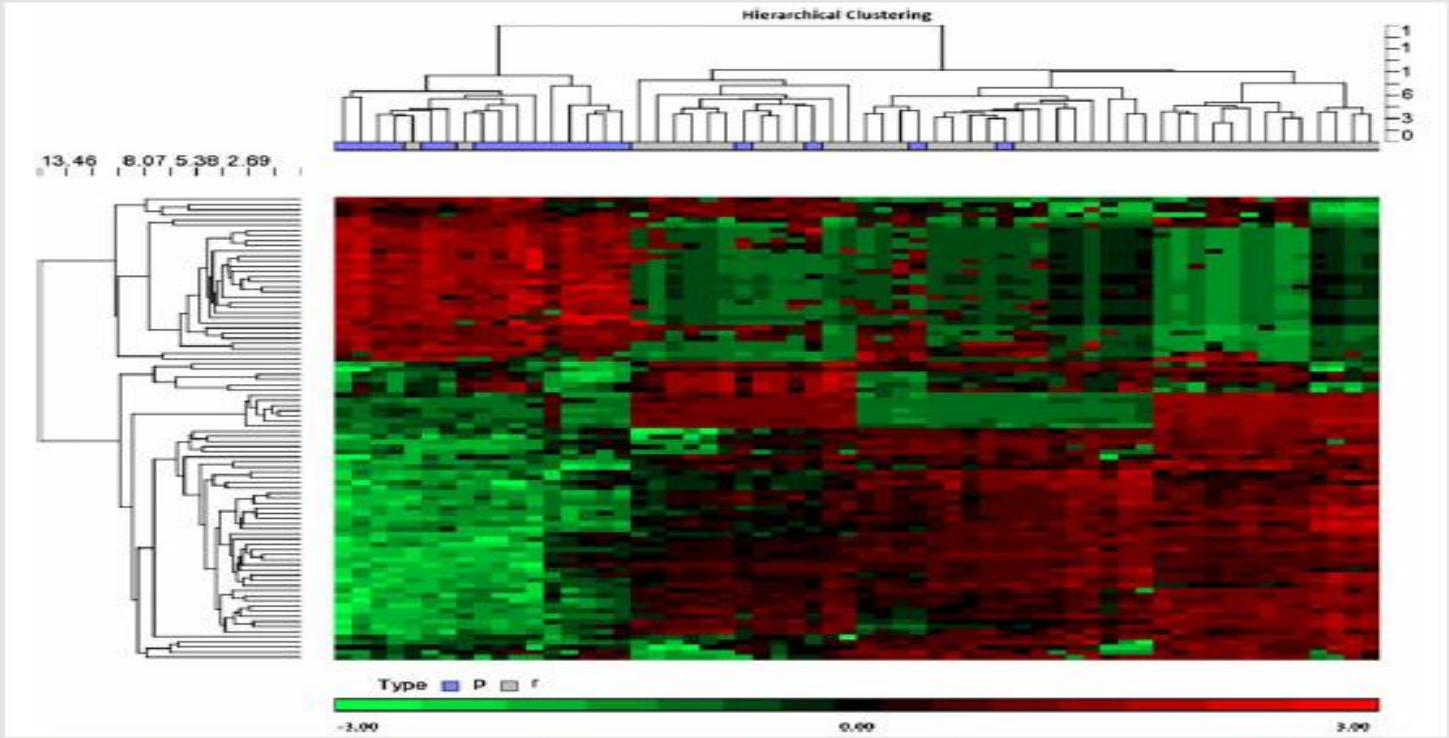
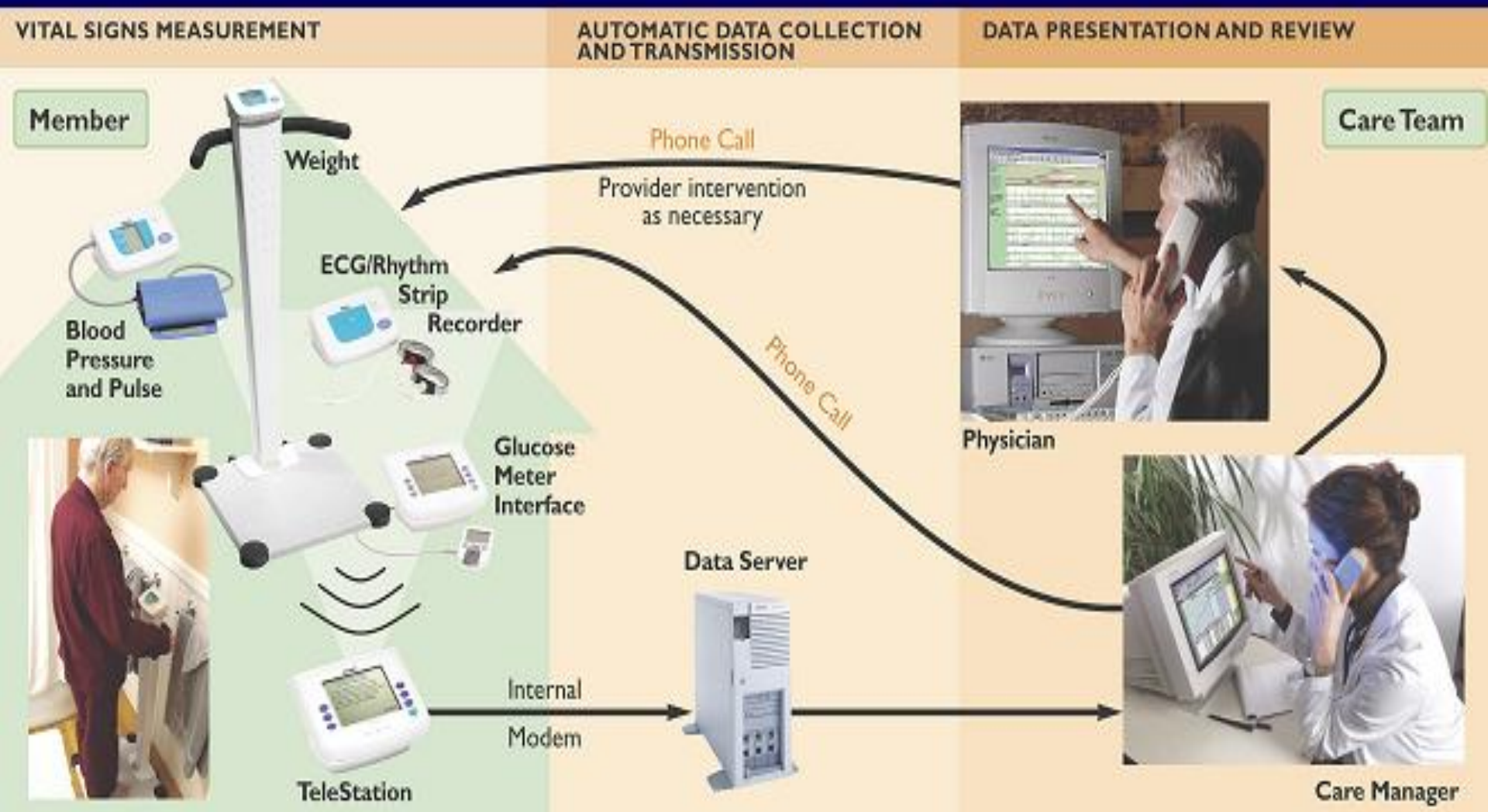


Figure 1 Differentially detected microRNAs (miRNAs) in heart failure relative to controls. Ninety miRNAs were found to be differentially detected (based on receiver operating characteristic (ROC) analysis and Pearson correlation analysis in relation to left ventricular ejection fraction (LVEF) data) in blood profiles of heart failure (HF) patients compared with non-HF controls. Grey denotes patients clinically classified as heart failure with reduced ejection fraction (HFrEF) and purple denotes heart failure with preserved ejection fraction (HFpEF).

Telemonitoring



IMMACULATE RCT: a multi-facetted randomized trial of Intensified Management post-AMI to compare a biomarker-guided strategy of risk stratification, telemedicine and intensive management (systems approach) with usual care following AMI.(Chan MY, D B Matchar, Lam CSP, Koh K, Lee CH, Wong R, Lim TW, Low AFH, Tan HC, Chow KY, Tai BC, Ling LH and Richards AM)

Protocol : Patients will be randomized 1:1 to the IMMACULATE protocol or usual care by sequential block randomization. The **Intervention** will consist of:

(1)Drugs: intensified management with early titration of anti-remodelling drugs

(2) **Contact**: regular telemedicine service consultations.

(3) **Home Tests**: Daily monitoring of BP, HR, weight. Telemedicine treatment titration by advanced nurse practitioners.

(4)Cardiac rehabilitation program will begin early.

(5)Education on medications, smoking, exercise and weight.

Primary Endpoint: Inter-group difference in proportion of patients exhibiting falls in NTproBNP concentrations of < 20% or more from ~72h (36-96) post symptom onset to 6 months.

Secondary End-Points:

1.Incidence of adverse LV remodelling (increase in LVEDVi of >20%) to 6 months.

2.Medication adherence at 12 months.

3. Incidence of death and/or HF at 24 months.

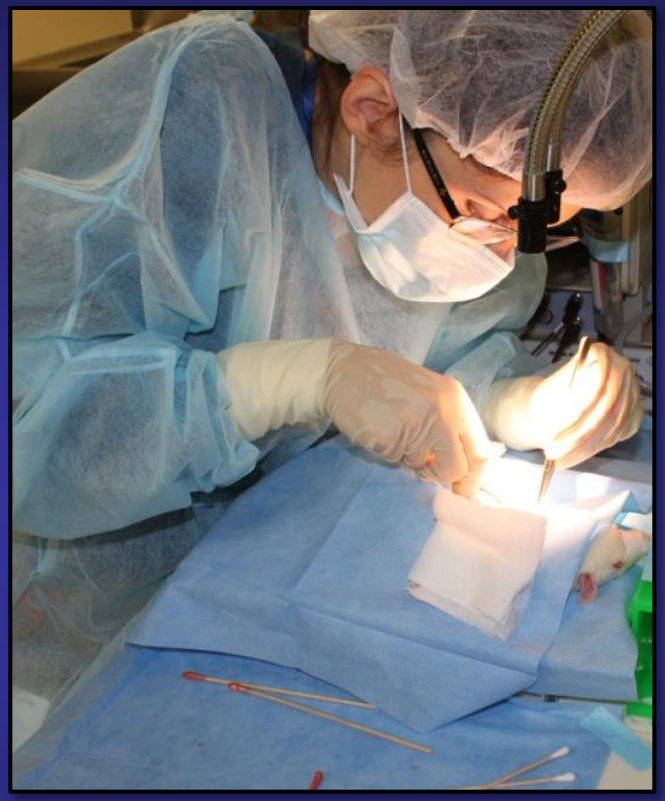
4.Incidence of cardiovascular death and readmission for HF/MI/stroke at 24 months.

TABLE. Study Schedule of "IMMACULATE" RCT

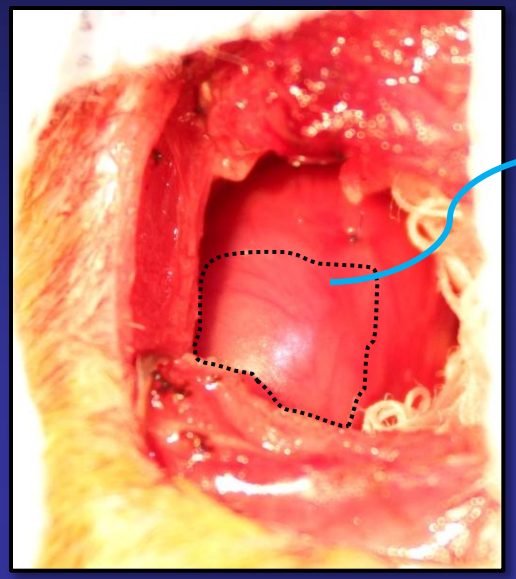
Schedule/ Variables	Initial visit	14 D	30D	2M	3M	4M	5M	6M	1Y	2Y
Visit and Contact	X	X	X	VC	X	VC	VC	X	X	
Clinical evaluation	X		X		X			X		
ECG	X		X		X			X		
Laboratory tests	X	X	X		X			X	X	X
NTproBNP,Sphingolipids, peptides, cytokines	X				X			X	X	X
3-D echocardiogram	X							X		
Cardiac MRI (substudy) (+PET)	X							X		
Exercise stress test		X						X		
Adverse events	X		X		X			X	X	X

Finding novel treatments

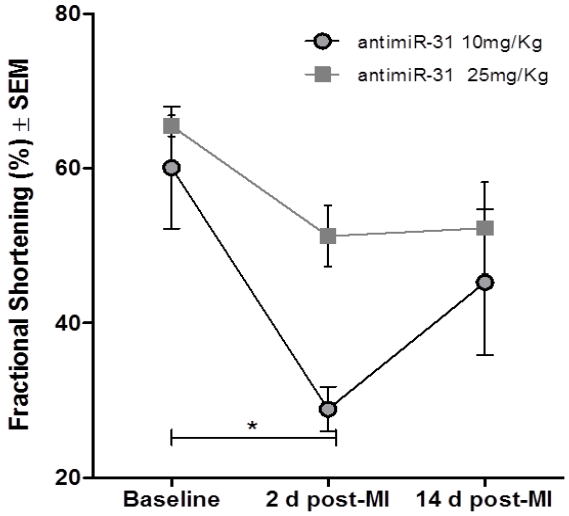
Rat Coronary Ligation myocardial infarction model

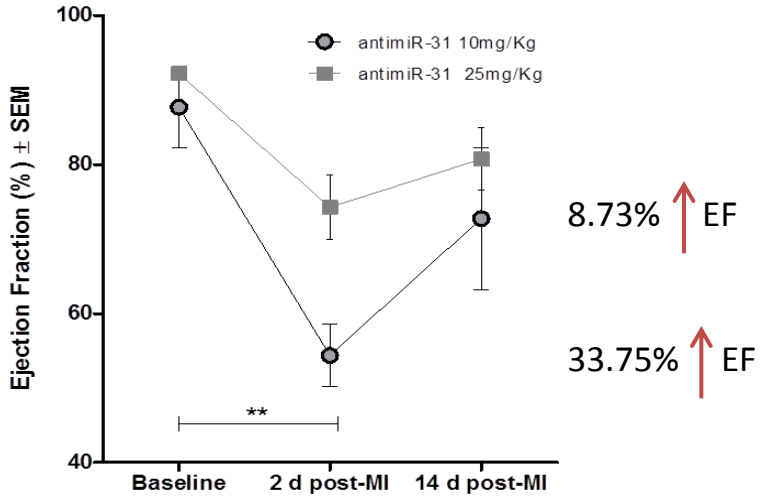


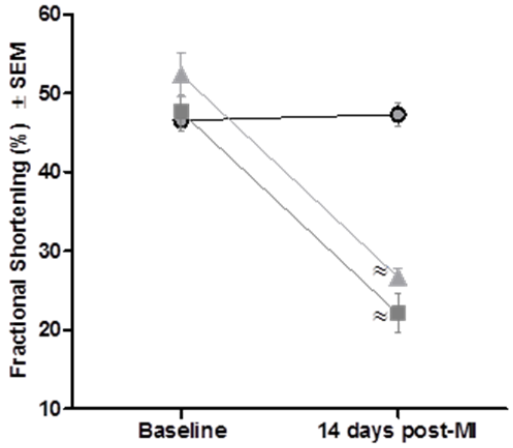
Lateral Thoracotomy and LAD Ligation

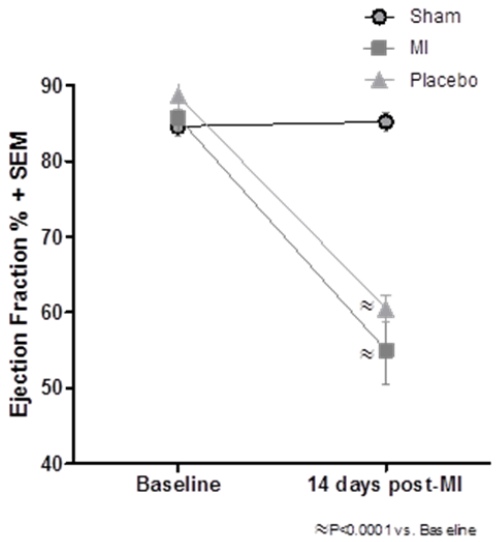


Treatment with LNA mir-31 inhibitor preserves/enhances LV function









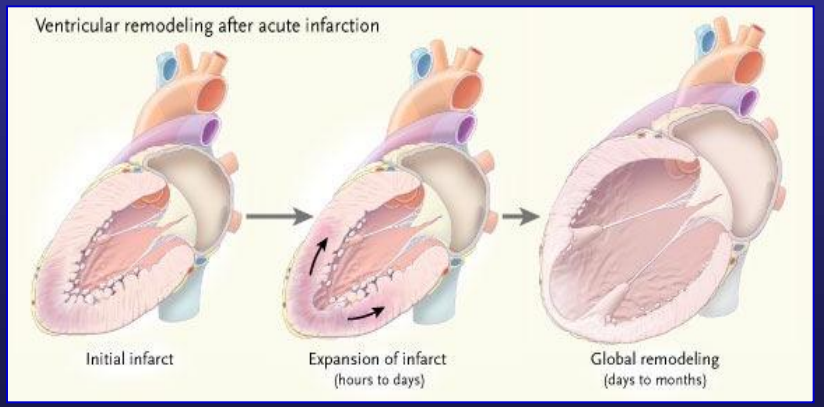
mir-31 inhibition Ameliorates Loss of Ventricular Function Post-MI.

N=3/treatment group

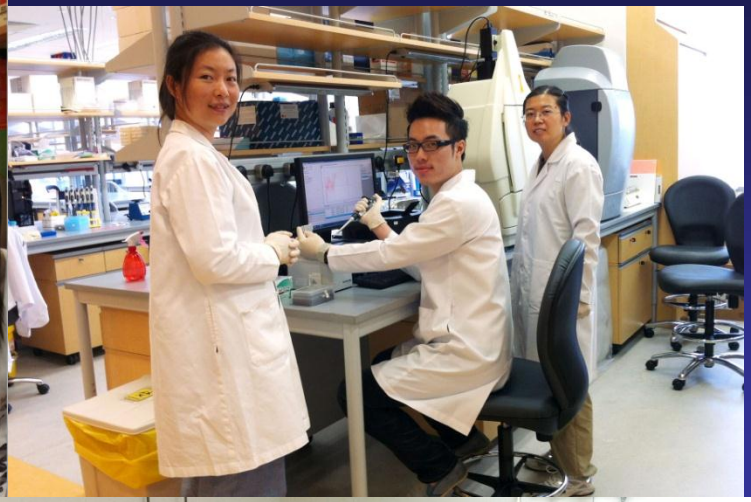
Characterizing Heart Failure and its Antecedents

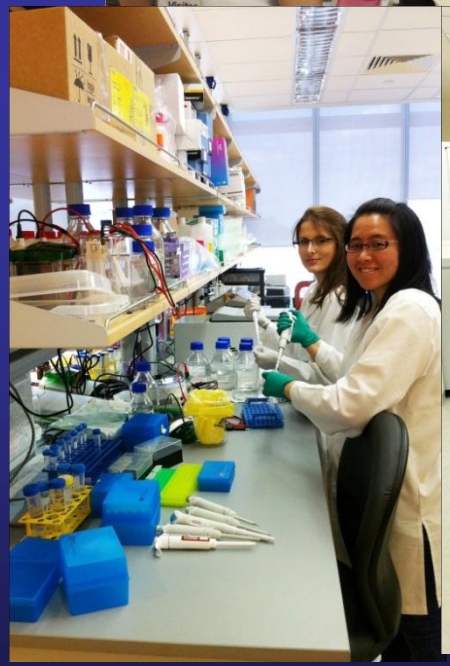
Cardiac remodelling after heart attacks

- Imaging
- Circulating Markers
- Intensified Management
- Novel Therapies



Cardiovascular Research Institute





Singapore Cardiovascular Cohort Studies Collaborative group

CVRI / NUHCS….the people

~ 20 Clinicians and Clinician-Scientists, plus research fellows, ~ 10 post-doctoral scientists, plus Research Assistants and Study Coordinators in multiple centres in Singapore

A Prof Mark Chan
CVRI/NUHCS

Dr Carolyn Lam
NHCS/NUHS

Emerging leaders for NUHCS Clinical research

Links to partner hospitals, AsTAR Institutes and Industry

Pyne Gould Building Chch

It’s hard to make predictions…

Especially about the future

Attributed to both Yogi Berra and to Niels Bohr


Thank you for your attention