

Singapore's Approaching Tsunami of Cardiovascular Disease

NMRC
Research Symposium
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Disclosures

Affiliation/Financial Relationships

- Grant/Research Support
- Consulting Fees
- Speakers Honoraria

Institutions/ Companies

- NMRC
- BMRC
- NUS
- Astra Zeneca
- Alere
- Roche Diagnostics
- Abbott
- Thermo Fisher
- Critical Diagnostics
- Novartis

CVD contribution to Global Burden of Disease

Number 1

cause of death globally more people die annually from CVDs than from any other cause.

17.5 million

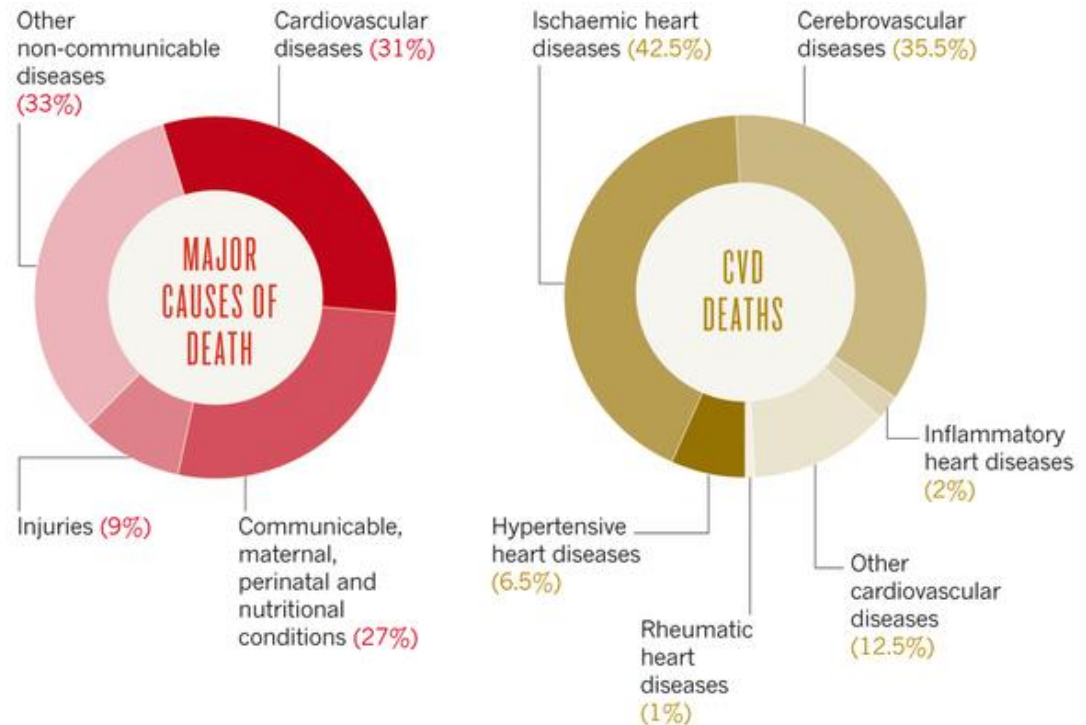
people die each year from CVDs, an estimated 31% of all deaths worldwide.

80%

of all CVD deaths are due to heart attacks and strokes

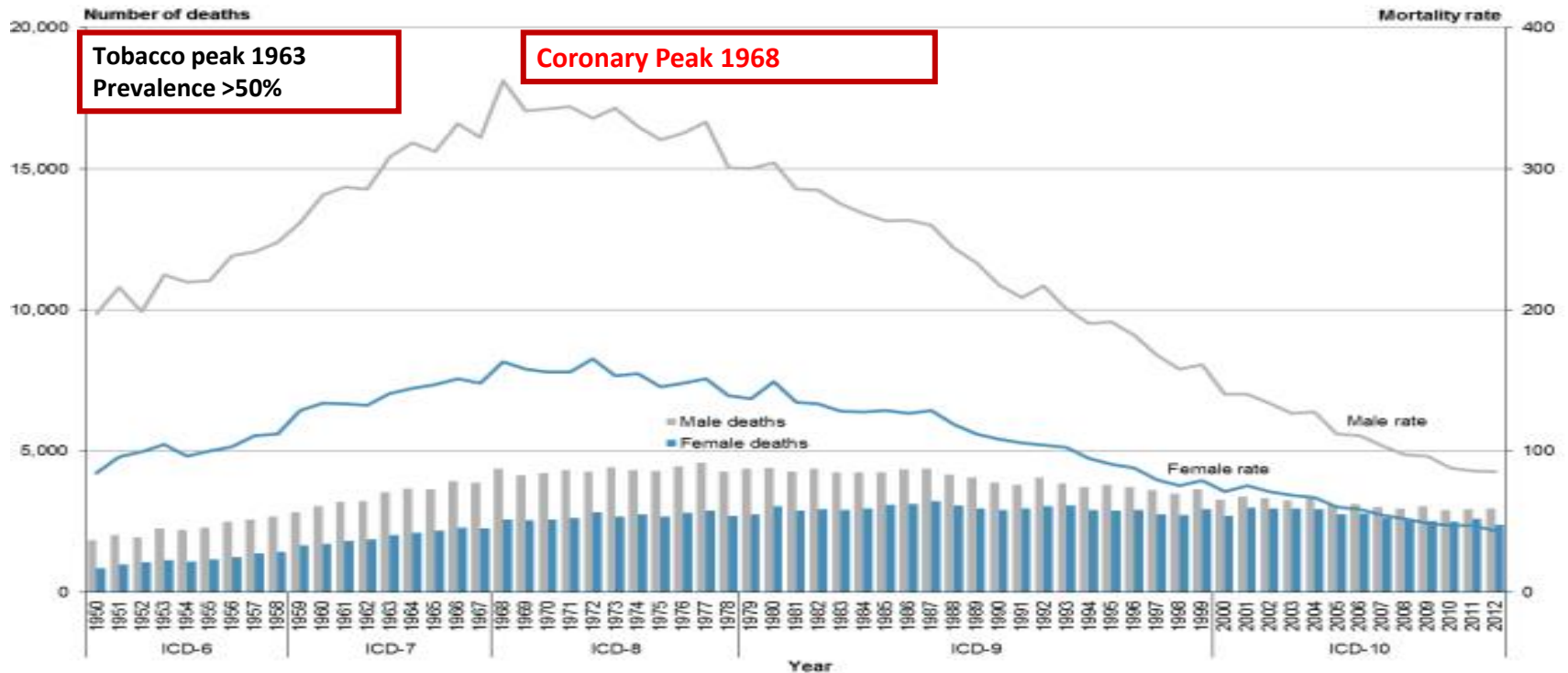
>75%

of CVD deaths occur in low-income and middle-income countries.



Nature 2013

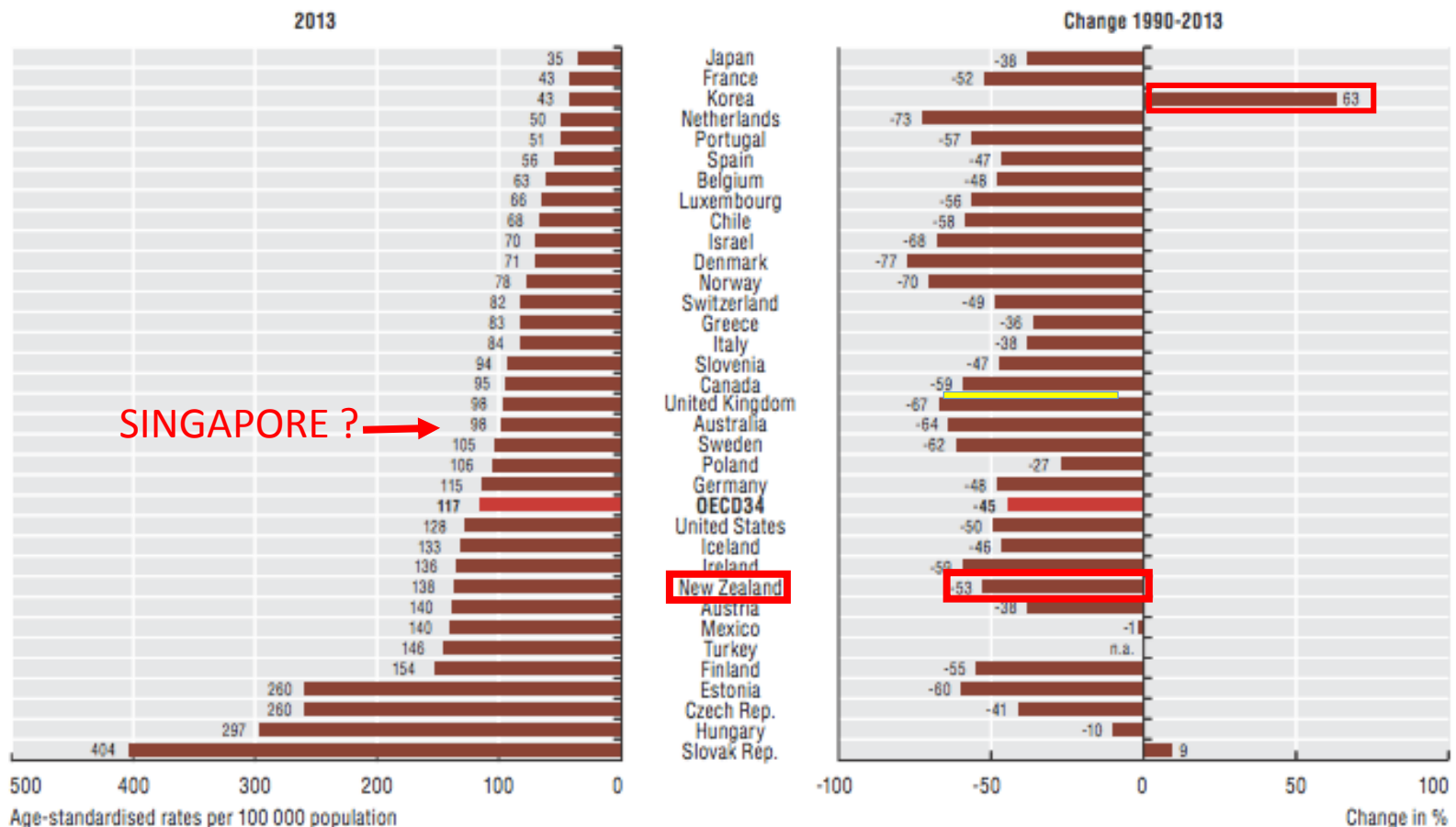
Numbers and age-standardised mortality rates from ischaemic heart disease, by sex, 1950–2012



Note: rates per 100,000 population, age-standardised to WHO World Standard Population.

Overall Heart Disease death rates reduced by more than two-thirds since 1968 in the OECD.

IHD Mortality has reduced in most parts of the OECD ...not everywhere

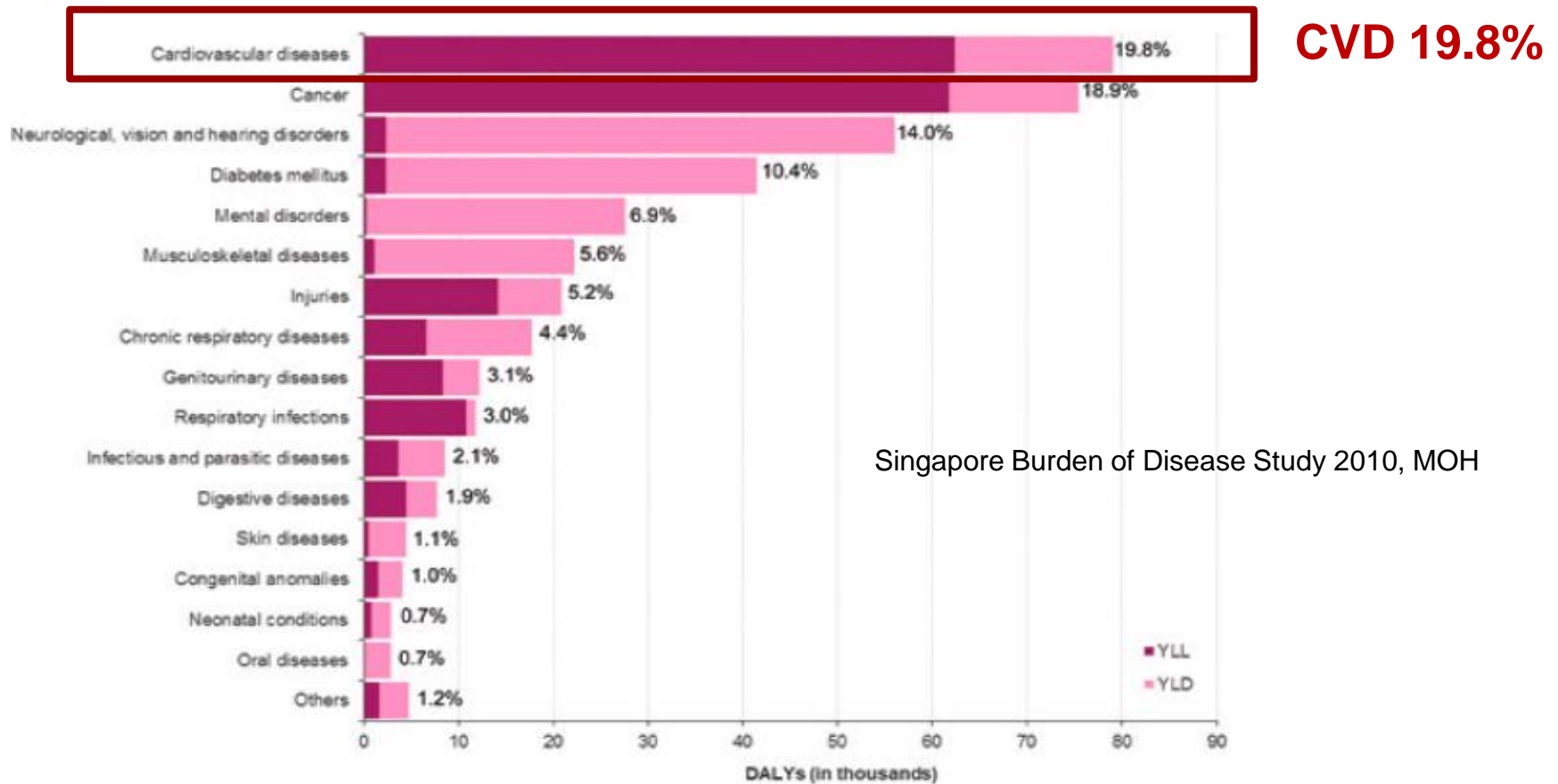


Source: OECD Health Statistics 2015, <http://dx.doi.org/10.1787/health-data-en>.

StatLink <http://dx.doi.org/10.1787/888933280741>

CVD is a Major Local Disease Burden

Figure 4.11: YLL, YLD, and DALYs for each broad cause group, Singapore 2010



Singapore Burden of Disease Study 2010, MOH

The percentage refers to the proportion of total DALYs contributed by the respective broad cause group.

Singapore

Every day, 16 people die from cardiovascular disease (heart disease and stroke) in Singapore. Cardiovascular disease accounted for 29.6% of all deaths in 2015. This means that nearly 1 out of 3 deaths in Singapore, is due to heart disease or stroke.

PRINCIPAL CAUSES OF DEATHS

	2013	2014	2015
Total No. of Deaths	18,938	19,393	19,862
% of Total Deaths			
Ischaemic Heart Disease	15.5%	16.0%	16.7%
Cerebrovascular Disease (including stroke)	8.9%	8.4%	6.8%
Hypertensive Diseases (including hypertensive heart disease)	3.1%	3.6%	3.9%
Other Heart Diseases	2.0%	1.9%	2.2%
Total % of Deaths from Cardiovascular Disease	29.5%	29.9%	29.6%
Total No. of Deaths from Cardiovascular Disease	5,587	5,799	5,879

Population 5,540,000
(mid 2015)

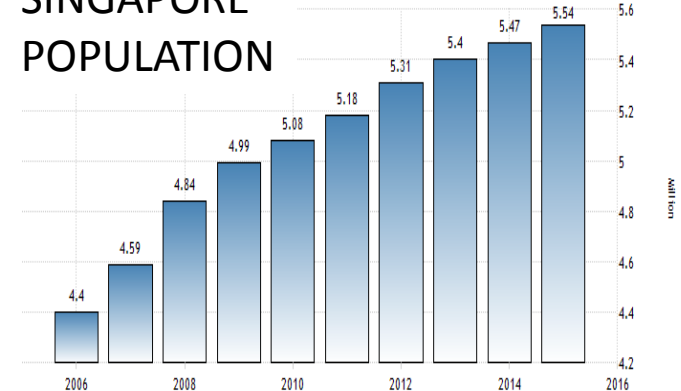
**Raw death rates for
all CV disease**

= 106/100,000

2013-2015

CVD DEATHS ↑ **5.2%**
POPULATION ↑ **2.6%**

SINGAPORE POPULATION

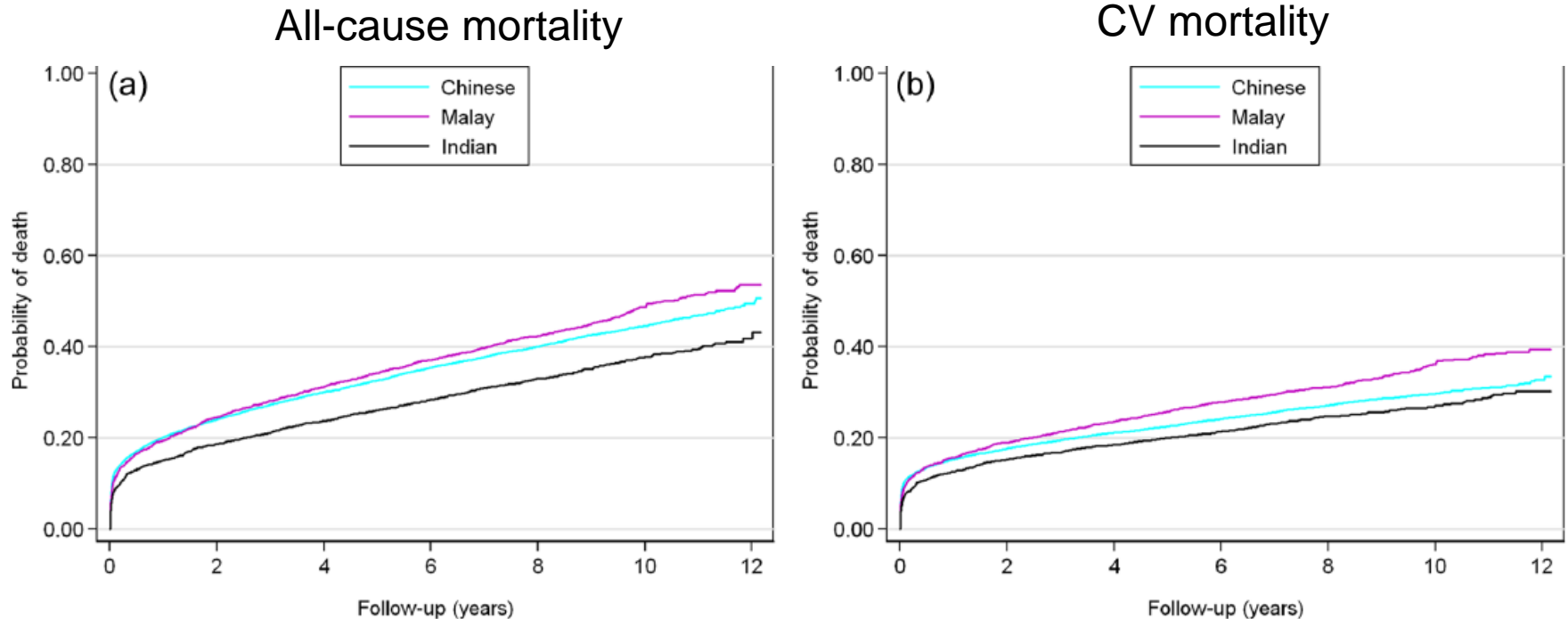


SOURCE: WWW.TRADEINGECONOMICS.COM | STATISTICS SINGAPORE

Characteristics of Patients with Myocardial Infarction

	Chinese (n=10,100)	Malay (n=3005)	Indian (n=2,046)	p-value
Demographic features				
Age (years)	64 (54–74)	61 (51, 71)	58 (49, 70)	<0.001
Male, %	71.0	73.4	77.0	<0.001
Prior history				
Diabetes, %	34.6	42.0	51.0	<0.001
Hypertension, %	60.5	55.2	54.4	<0.001
Hyperlipidemia, %	49.6	46.3	51.9	0.001
Current smoking, %	52.6	59.6	50.8	<0.001
Renal failure, %	6.4	7.2	4.2	<0.001
Family history of premature coronary heart disease, %	11.1	14.5	21.5	<0.001
Prior MI, %	10.5	10.9	14.8	<0.001
Prior PCI, %	4.2	3.6	8.1	<0.001
Prior CABG, %	2.7	1.9	4.7	<0.001
Prior cerebrovascular disease, %	10.5	6.2	7.2	<0.001
Peripheral vascular disease, %	2.6	1.8	2.8	0.037

AMI: Ethnic differences in mortality



Over median follow-up of 7.4 years, 6469 of 15150 (43%) died.

AMI Outcomes: Singapore versus UK-Belgium

Despite younger
Age of onset
(~60y vs 66 yr)
5 year post MI
Mortality is
Higher in
Singapore
Compared with
UK-Belgium

	Singapore	UK-Belgium
	5 Year total no. of death, n=4832/15151 (32%)	5 year total no. of deaths, n=736/3721 (20%)
STEMI	1768/6843 (26%)	269/1403 (19%)
Non-STEMI	3064/8308 (37%)	262/1170 (22%)



European Heart Journal (2010) 31, 2755–2764
doi:10.1093/eurheartj/ehq326

FASTTRACK
ESC CLINICAL TRIAL UPDATE

Underestimated and under-recognized: the late consequences of acute coronary syndrome (GRACE UK–Belgian Study)

Keith A.A. Fox^{1*}, Kathryn F. Carruthers¹, Donald R. Dunbar¹, Catriona Graham², Jonathan R. Manning¹, Herbert De Raedt³, Ian Buyschaert⁴, Diether Lambrechts⁵, and Frans Van de Werf⁴

TRENDS IN ACUTE MYOCARDIAL INFARCTION IN SINGAPORE 2007 – 2013



MINISTRY OF HEALTH

SINGAPORE

Table 4.1.1 Incidence of AMI Per 100,000 Population (95% CI)

Year	2007	2008	2009	2010	2011	2012	2013
No. of cases	6817	7251	6796	7344	8013	9118	9463
CR	234.7 (229.2-240.3)	244.0 (238.4-249.7)	221.6 (216.4-226.9)	235.6 (230.2-241.0)	254.2 (248.6-259.8)	285.7 (279.8-291.6)	293.1 (287.1-299.0)
ASR	208.9 (203.9-214.0)	212.4 (207.4-217.3)	189.4 (184.9-194.0)	194.5 (190.0-199.1)	204.7 (200.1-209.2)	223.1 (218.5-227.8)	221.2 (216.7-225.7)

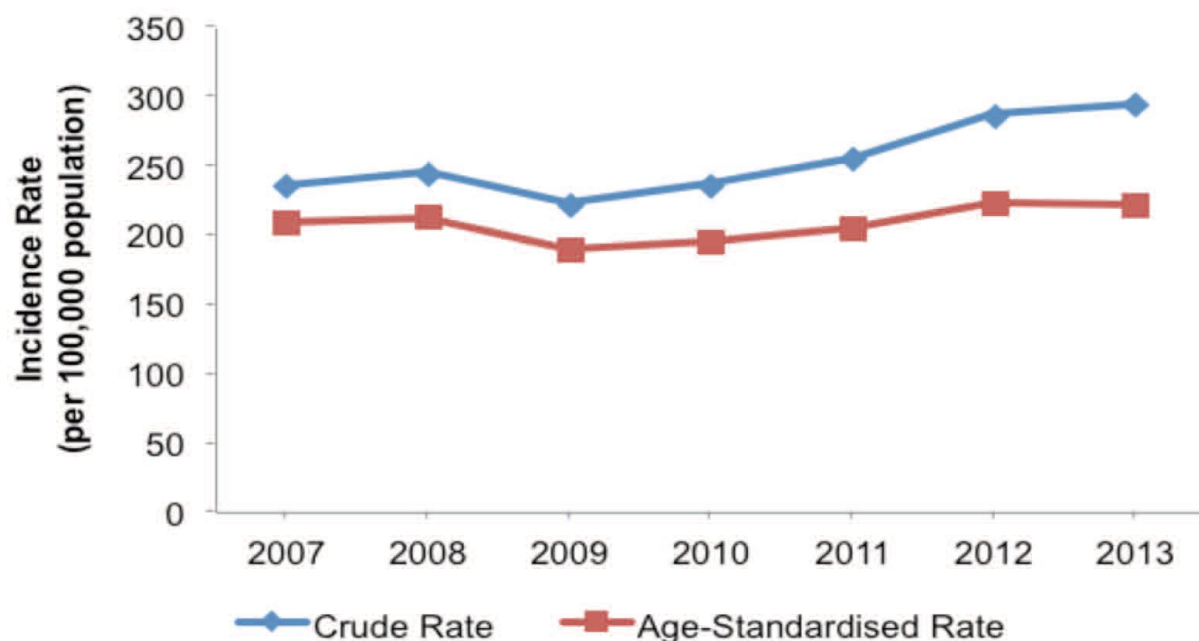
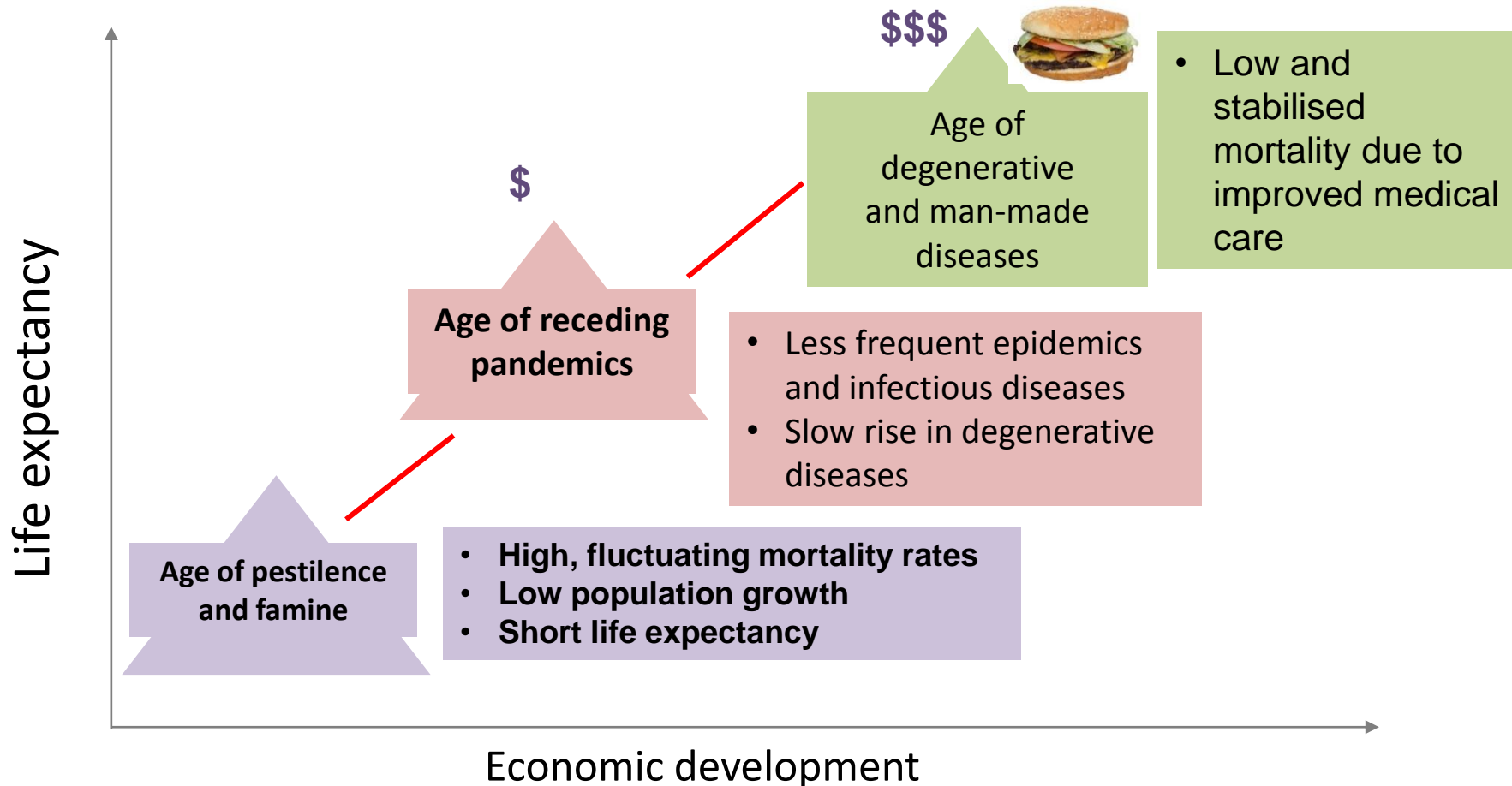


Table 4.1.3 Age-Specific Incidence Rate of AMI Per 100,000 Population

Age Group	2007	2008	2009	2010	2011	2012	2013
15-19	0.0	0.0	0.4	0.0	0.0	0.0	0.0
20-24	0.0	1.3	0.0	1.2	1.2	1.5	1.1
25-29	3.9	2.7	4.4	3.3	3.8	4.3	3.9
30-34	8.5	9.0	9.4	8.4	8.7	10.8	12.1
35-39	30.5	31.2	26.5	28.8	31.6	34.1	34.0
40-44	72.9	71.5	71.6	70.4	69.4	74.8	84.8
45-49	149.0	130.5	131.8	141.5	153.1	153.9	155.9
50-54	230.0	240.3	219.2	247.1	223.3	267.4	269.4
55-59	321.4	334.4	316.3	327.3	325.5	362.8	357.3
60-64	476.8	513.1	462.6	424.2	483.4	536.2	485.6
65-69	711.8	715.9	621.3	602.0	691.3	744.8	718.3
70-74	1090.3	1080.0	947.4	978.4	986.0	1078.5	1054.0
75-79	1573.9	1606.1	1472.4	1413.2	1539.6	1606.5	1578.7
80-84	2126.6	2331.4	1844.1	2025.1	2132.7	2301.6	2333.3
85+	3044.4	2992.5	2465.7	2925.2	3000.0	3250.7	3548.7

Omran's Epidemiological Transition Theory



RESEARCH ARTICLE


Ethnicity Modifies Associations between Cardiovascular Risk Factors and Disease Severity in Parallel Dutch and Singapore Coronary Cohorts

Crystel M. Gijssberts^{1,2}, Aruni Seneviratna³, Leonardo P. de Carvalho³, Hester M. den Ruijter¹, Puwalani Vidanapthirana⁴, Vitaly Sorokin⁴, Pieter Stella⁵, Pierfrancesco Agostoni⁵, Folkert W. Asselbergs^{5,6,7}, A. Mark Richards^{3,8}, Adrian F. Low³, Chi-Hang Lee³, Huay Cheem Tan³, Imo E. Hoefler¹, Gerard Pasterkamp¹, Dominique P. V. de Kleijn^{1,2,4,8*}, Mark Y. Chan^{3,8}



CrossMark
click for updates

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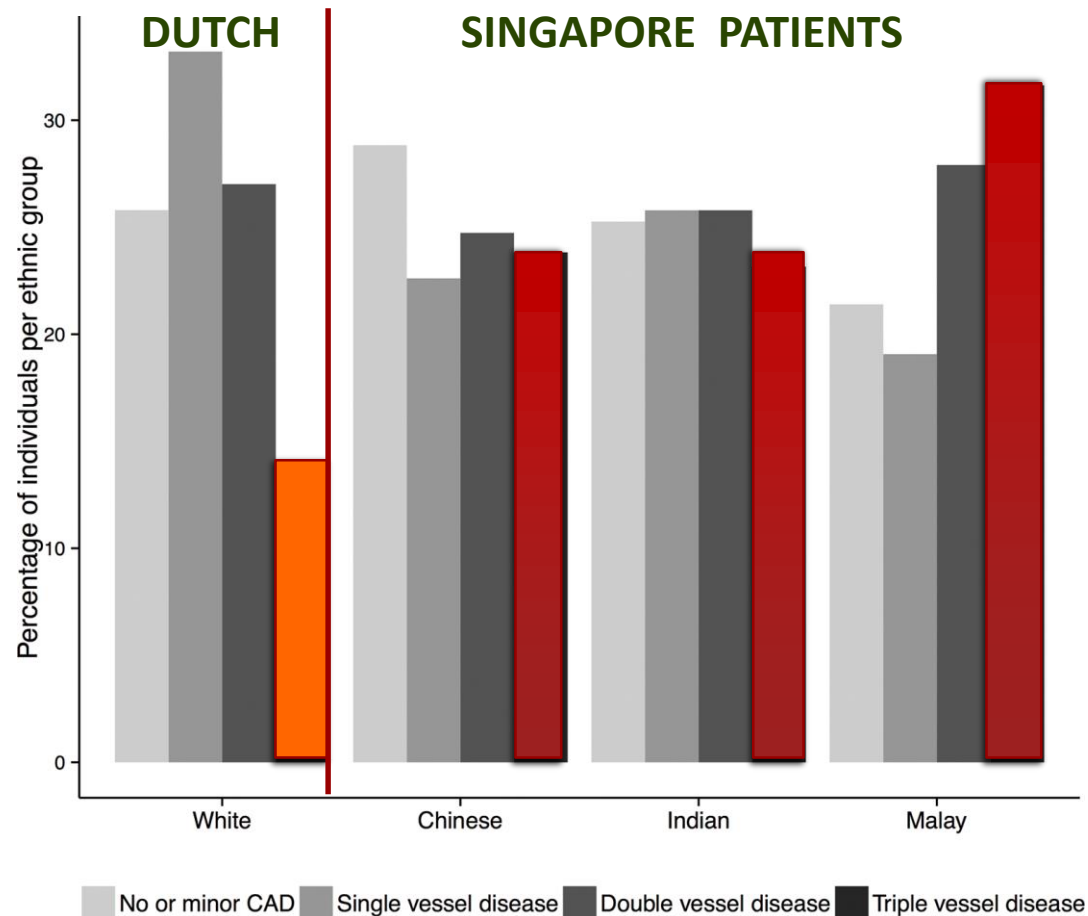
 OPEN ACCESS

Citation: Gijssberts CM, Seneviratna A, de Carvalho

Stable CAD: Singapore versus Dutch

	Caucasian	Chinese	Indian	Malay	p-value
Stable CAD patients					
N	150	150	150	150	
Males (%)	83.3	81.3	77.3	78.0	0.52
Age (years, mean \pm sd)	63.7 \pm 10.5	62.0 \pm 8.8	56.8 \pm 9.5	57.7 \pm 10.0	<0.001
BMI (kg/m ² , mean \pm sd)	28.0 \pm 4.4	26.5 \pm 4.8	27.4 \pm 5.1	29.2 \pm 4.9	<0.001
Diabetes (%)	23.5	36.0	58.0	52.7	<0.001
Hypertension (%)	64.0	78.0	69.3	71.3	0.06
Dyslipidemia (%)	57.2	77.3	78.0	75.3	<0.001
Current smoker (%)	24.6	28.8	40.0	47.0	0.013*
Previous PCI (%)	46.7	20.7	30.7	20.1	<0.001
Previous ACS (%)	33.3	17.4	26.8	18.0	0.002
CVA/TIA (%)	8.1	10.0	8.0	8.7	0.92
Peripheral arterial disease (%)	10.7	2.7	3.3	2.0	<0.001
Renal failure (%)	4.7	7.3	6.7	6.7	0.80
Anti platelet (%)	94.0	68.0	54.0	59.3	<0.001
Statin (%)	86.0	73.3	65.3	60.7	<0.001
Beta blocker (%)	74.7	40.0	47.3	52.7	<0.001
RAAS (%)	54.7	42.7	41.3	42.7	0.07

Singapore patients Younger but more Multi-vessel Disease than Dutch

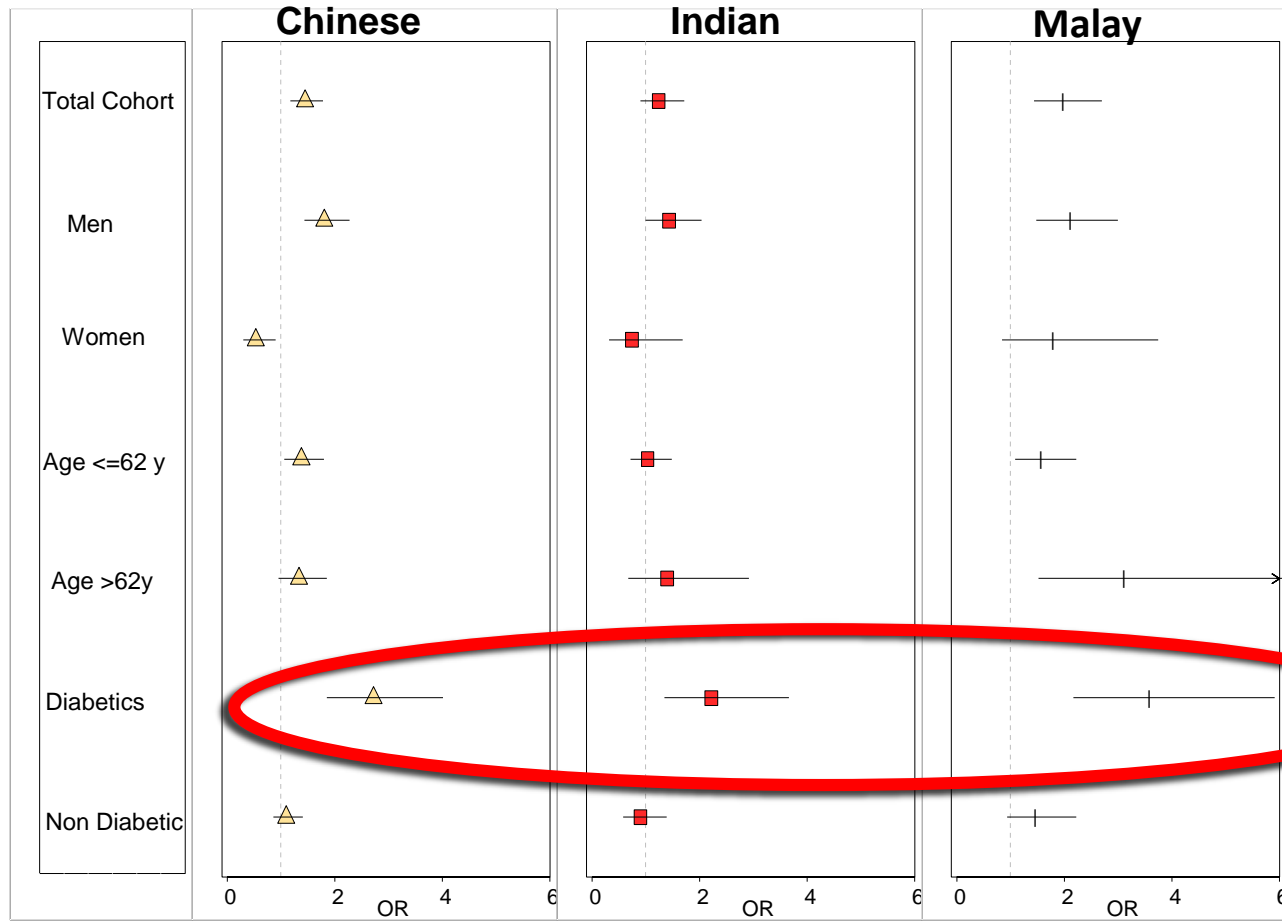


PLoS One. 2015 Jul
6;10(7):e0132278

Fig 1. Severity of CAD by ethnicity. Bar chart depicting the distribution of CAD severity as the percentage of the total number of individuals per ethnic group. Triple vessel disease is significantly more common among Chinese, Indians and Malays than among Whites ($p < 0.001$).

Relative Severity of Coronary Artery Disease by Ethnicity

Odds ratios of Chinese, Indian and Malay ethnicity for the severity of CAD relative to Caucasian.



Gijsberts et al
PLoS ONE
2015

IMproving reModeling in ACute myocardial infarction Using Live and Asynchronous Telemedicine (IMMACULATE)

Principal Investigator: Mark Chan
Study Chairman: A. Mark Richards
Project Lead: Poh Sock Cheng
Telemedicine lead: Karen Koh

Study Sites

National University
Hospital



Tan Tock Seng
Hospital



Changi General Hospital



Sarawak General Hospital
Heart Centre, Malaysia

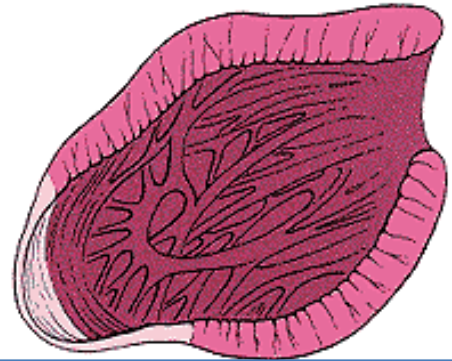
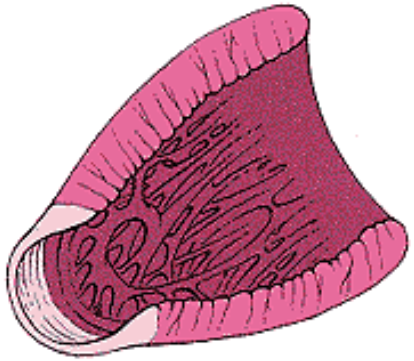
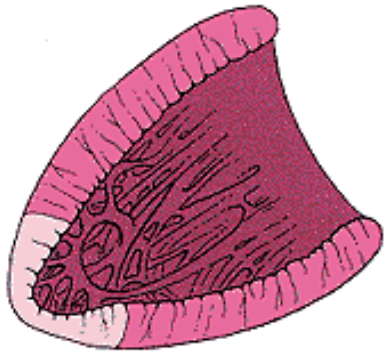
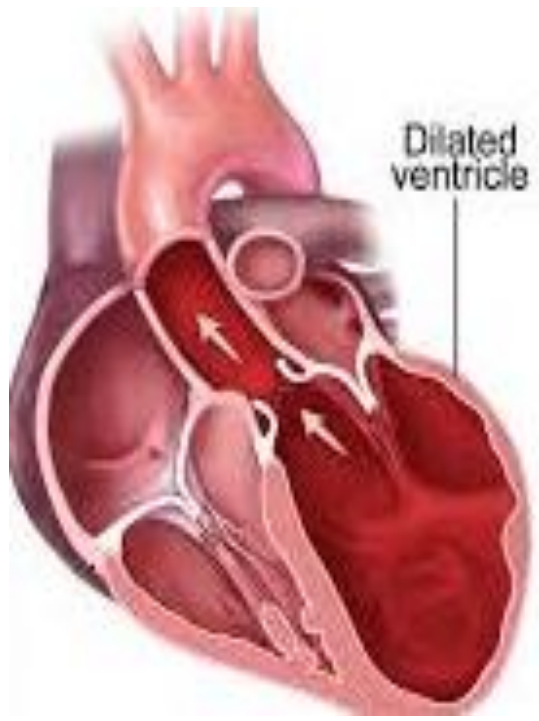
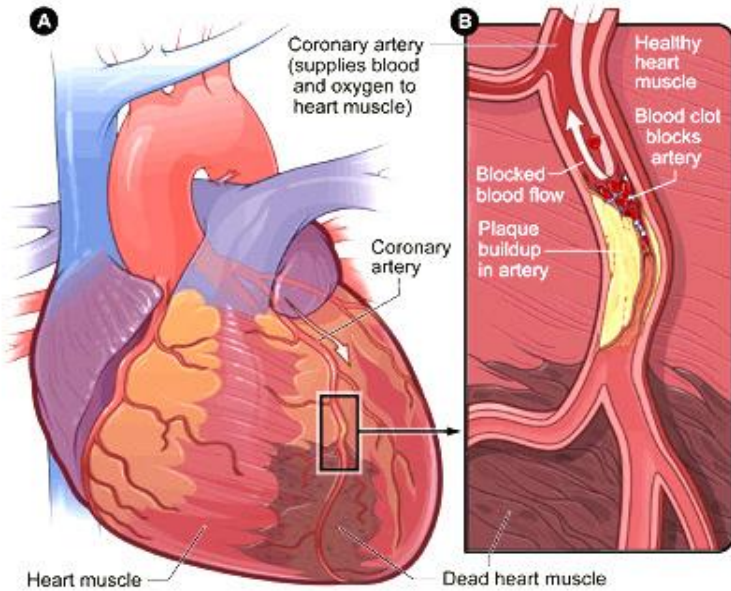


Christchurch Heart
Institute, New Zealand



26/07/2016

Acute Myocardial Infarction



Hours

Days

Months

Aims of IMMACULATE

post-MI LV remodeling program:

- 1. Multicentre registry of patients hospitalised for **acute myocardial infarction (AMI)** with:-
 - Serial cardiac imaging
 - Serial blood sampling to identify biomarkers and therapeutic targets for post-MI ventricular remodeling and heart failure.
- 2. Registry-based randomised trial comparing ventricular remodeling among patients with AMI and elevated NT-pro-B-type natriuretic peptide receiving **comprehensive telemedicine-guided post-MI treatment** (remote intensive management) vs. standard non-telemedicine guided treatment.

Post-MI Remodeling REGISTRY

1200 STEMI and NSTEMI patient with anterior or large inferior MI undergone primary PCI from 5 hospitals

NT-proBNP > 300 pg/ml
regardless of LVEF

Registry-based Randomised Trial

**Nurse-led physician supported
(NLPS)**

Remote intensive

titration of ACE/ARB and BB

versus

STANDARD CARE

Control Group

Standard Care
N = 150

Standard Care :-
Cardiac rehab X 12 sessions,
smoking cessation, face-to-
face cardiologist review 1, 6
and 12 months*

STEMI/NSTEMI with NT-
proBNP > 300pg/ml

CMR (5-10D
post MI)

CMR (6M)

NTproBNP

6-mo
readmission
(ALTRA)

Platelet
reactivity
(TICA)

MR-PET
(Cardiac
efficiency)

QOL and
cost
effectiveness

Intervention group

Telehealth Mx
N = 150

Standard care + 6 month
intervention program.
Telehealth drug titration
weekly (first 2 months) then
Telehealth review every 2
weeks (next 4 months)

IMMACULATE Registry

- NUH, TTSH, CGH, Sarawak, Christchurch
- 911 enrolled as of Dec 2016
- 91 dropouts

IMMACULATE RRCT

- NUH, TTSH
- 177 consented
- 76 NT-proBNP screen failures
- 101 randomized as of Jan 2017

Post-MI Remodeling Registry

Echocardiography characteristics

	Adverse	Reverse
Median Baseline EDV (ml)	92	102
Median Baseline ESV (ml)	40	46
Median Baseline EF %	52	51
Median 6-month EDV (ml)	116	86
Median 6-month ESV (ml)	57	36
Median 6-month EF %	49	56

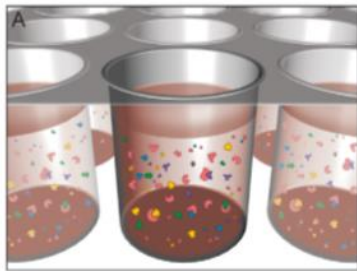
Endpoints

Adverse Remodeling	26.2%	
Reverse Remodeling	25.5%	

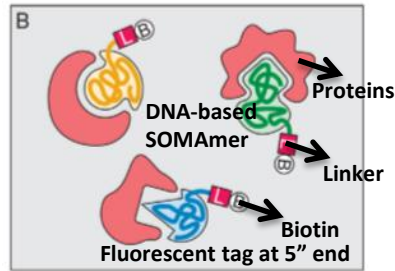
Adverse = increase in left ventricular ESV of 15% over 6 months

Reverse = decrease in left ventricular ESV of 15% over 6 months

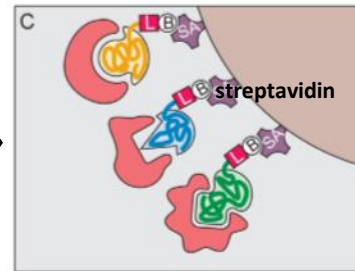
SOMAmer (Slow Off-rate Modified Aptamer) protein-binding reagent consists of **unique short DNA sequence** that incorporates **chemically modified bases** to mimic amino acid side chains and a **5'- fluorescent tag** for use in the [SOMAscan assay](#).



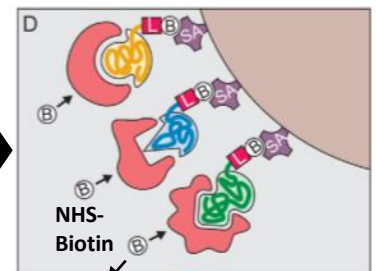
SOMAmers and samples are mixed in 96-well microwell plates and allowed to bind.



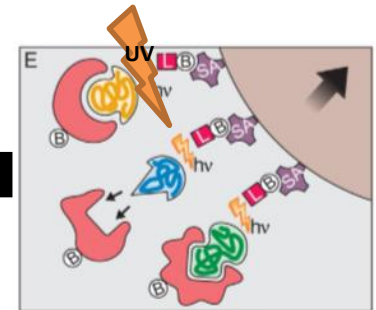
SOMAmer-protein binding: DNA-based SOMAmer molecules bind to specific protein. SOMAmers contain biotin (B), a photo-cleavable linker (L) and a fluorescent tag at the 5'' end.



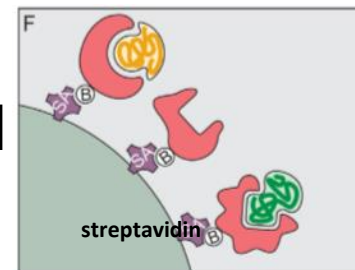
SOMAmers are captured onto a bead coated with **streptavidin** (SA) which binds biotin.



Proteins are tagged with NHS-biotin.



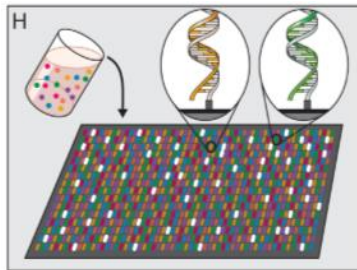
UV light cleaves the linker and SOMAmer-protein complexes are released from beads. Samples are challenged with anionic competitor (dextran sulfate). Non-cognate complexes (blue SOMAmer) preferentially dissociate.



SOMAmer-protein complexes are captured onto **new avidin coated beads** by protein biotin tag.



SOMAmers are released from complexes into solution at high pH



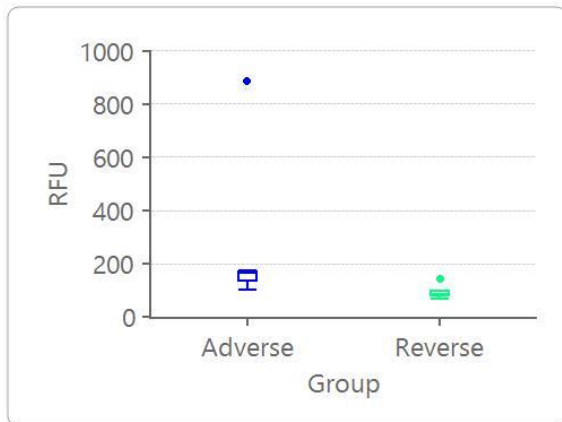
Remaining SOMAmers are quantified by **hybridization** to microarray containing single-stranded DNA probes complementary to SOMAmer DNA sequence, which form a double-stranded helix. **Hybridized SOMAmers are detected by fluorescent tags when the array is scanned.**

Proteomics of post-MI remodelling

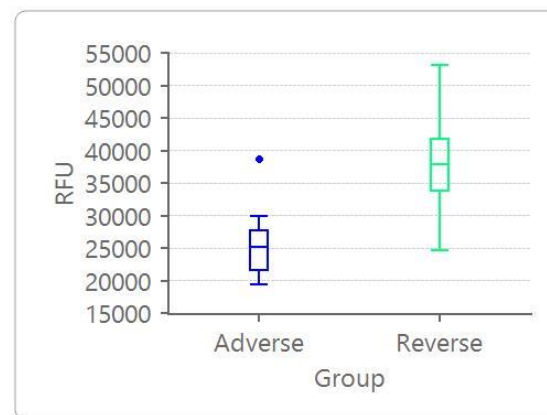
Pilot study (n=24);

- 12 adverse post MI remodelling (% change ESV > 15%)
- 12 reverse post MI remodelling (% change ESV > -15%)
- The SOMAscan® 1.3k Assay (SOMALogic, Boulder, CO) was used for hypothesis-free biomarker discovery 1,310 proteins measured simultaneously in 150 microliters of EDTA plasma (collected 30 days after MI)
- 191 proteins with $P < 0.05$ and 48 proteins with $p < 0.01$ and 5 proteins with $P < 0.001$

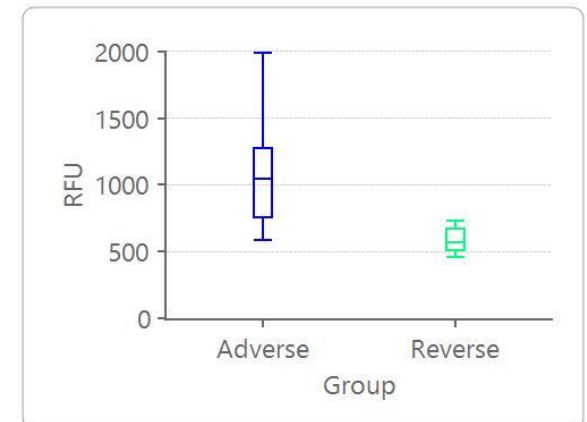
Angiotensin-2 **P=8.61E-05**



Myokines, human **P=0.0003**



ANP **P=0.0003**

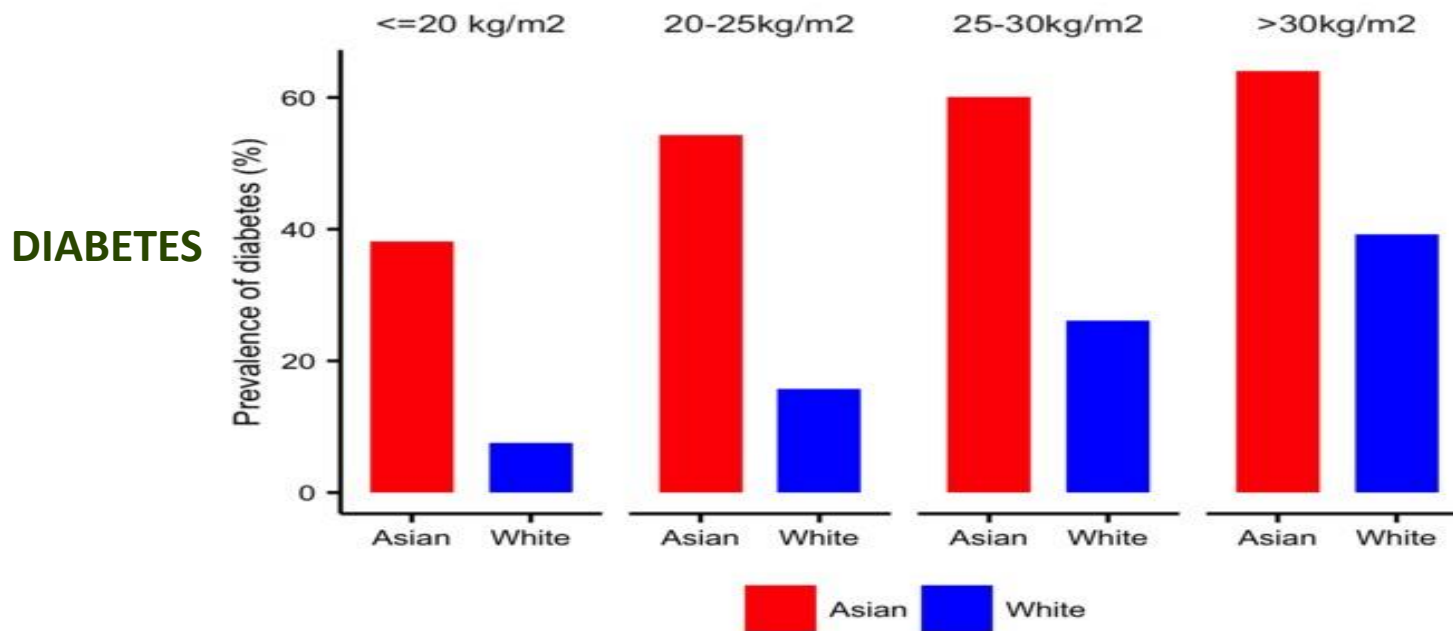


Is Singapore facing cardiovascular Catastrophe ?

Comparison of HF in Singapore and Sweden

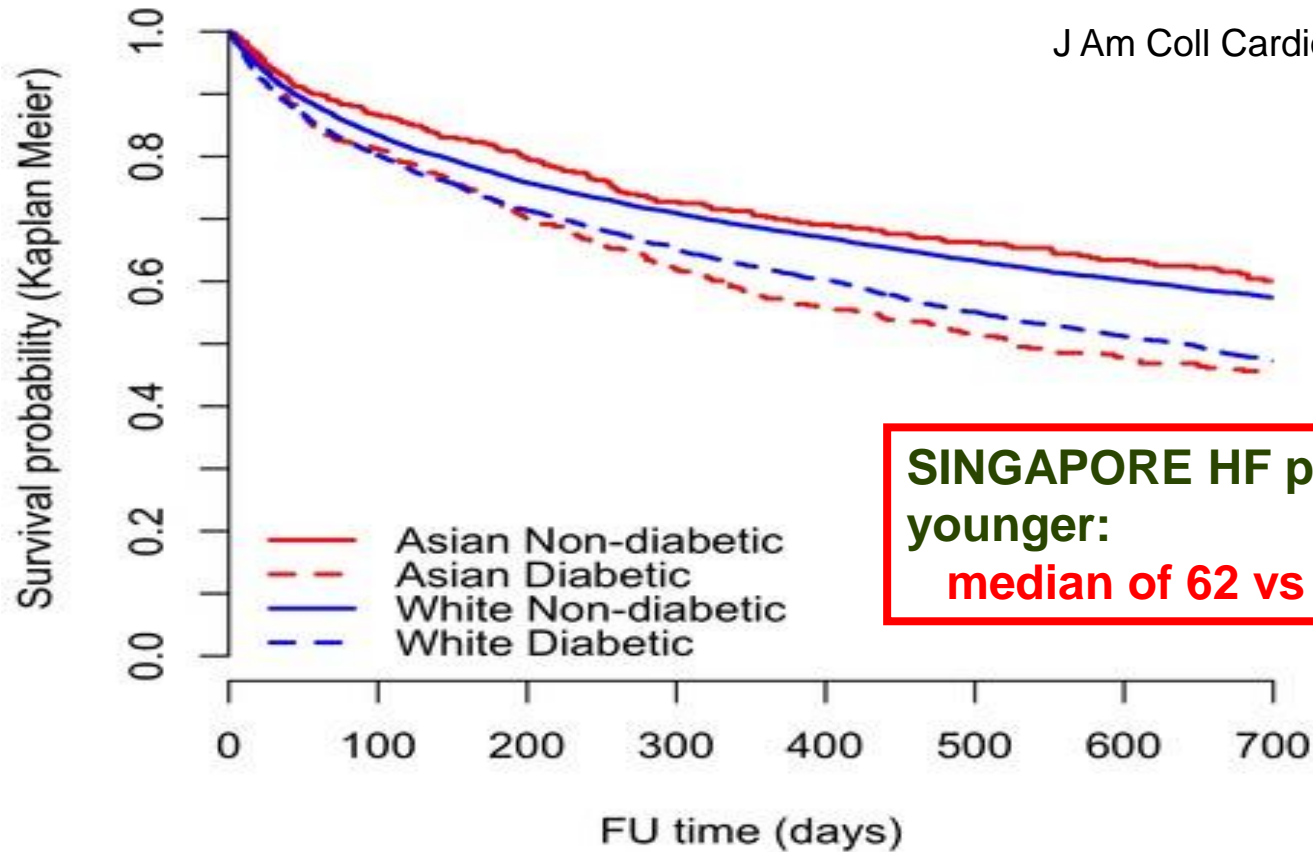
Methods Two contemporary population-based HF cohorts were compared:

- 1) Singapore n=1,002, 62 [54-70] yr, 76% men, 19.5% obese
- 2) Sweden n=19,537, 77 [68-84] yr, 60% men, 24.8% obese



Heart Failure and Survival in Singapore and Sweden

J Am Coll Cardiol: Heart Failure 2016



Number of patients at risk

Asians	1001	806	705	630	479	423	396	334
Whites	19537	14809	12250	10224	8407	6674	5341	3884

Is Singapore facing cardiovascular Catastrophe ?

Comparison of HF in Singapore and Sweden

Methods Two contemporary population-based HF cohorts were compared:

- 1) Singapore n=1,002, 62 [54-70] yr, 76% men, 19.5% obese
- 2) Sweden n=19,537, 77 [68-84] yr, 60% men, 24.8% obese

Results

Diabetes was present in 569 (57%) Asians versus 4680 (24%) Whites ($p < 0.001$).

Diabetes was more strongly associated with increased HF hospitalization and all cause mortality in :-

Asians (adjusted HR 1.50, 95% CI 1.21-1.87) than Whites (HR 1.29, 95% CI 1.22-1.36) ($p = 0.045$).

Conclusions Diabetes was > TWO-fold more common in Southeast Asian compared to White HF patients, in spite of younger age and less obesity, and more strongly associated with poor outcomes in Asians than Whites.

**PEOPLE / SHOP Study
NZ and Singapore**

Combined Outcome Study

New Zealand

Singapore



Population

4.6m

5.5m

Density n/km²

7.8

7,829

Land area

268,000km²

740km²

GDP

174,000m

293,000m

Unemployment

5.6%

3.0%

Life Expectancy

80.6yrs

82.1yrs

Ethnicity

NZ Euro

67%

Chinese

74%

Māori

15%

Malay

13%

Asian

10%

Indian 9.2%

Pacific

7%



Superior performance of N-terminal pro brain natriuretic peptide for diagnosis of acute decompensated heart failure in an Asian compared with a Western setting

**Irwani Ibrahim^{1,2}, Win Sen Kuan^{1,2}, Chris Frampton³, Richard Troughton³,
Oi Wah Liew^{4,5}, Jenny Pek Ching Chong^{4,5}, Siew Pang Chan^{4,5}, Li Ling Tan^{4,5},
Wei Qin Lin^{4,5}, Chris J. Pemberton³, Shirley Beng Suat Ooi^{1,2}, and
A. Mark Richards^{3,4,5*}**

¹Emergency Medicine Department, National University Hospital, National University Health System, Singapore; ²Department of Surgery, Yong Loo Lin School of Medicine, National University of Singapore, Singapore; ³Christchurch Heart Institute, University of Otago, Christchurch, New Zealand; ⁴Cardiovascular Research Institute, National University Heart Centre Singapore, National University Health System, Singapore; and ⁵Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

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Is Singapore facing cardiovascular Catastrophe ?

		COUNTRY		P-value
		Singapore n=606	NZ n=500	
AGE (yr)	Mean	55.1	70.6	<0.001
	(SD)	15.2	13.0	
BMI (kg/m ²)	Mean	27.4	27.3	0.806
	(SD)	6.9	7.5	
Sa O ₂ (%)	Mean	97.3	94.4	<0.001
	(SD)	3	6	
eGFR (ml/min/1.73 m ²)	Mean	82.4	61.2	<0.001
	(SD)	29.3	20.7	

Is Singapore facing cardiovascular Catastrophe ?

Breathless People with a Diagnosis of Acute Heart Failure

Comparison (NZ) (n=180/500) EDS.

		COUNTRY		P-value
		Singapore n=148	NZ n=180	
AGE (years)	Mean	62.0	75.4	P<0.001
	(SD)	11.5	11.4	
BMI (kg/m ²)	Mean	28.4	27.5	0.277
	(SD)	7.4	6.8	
Sa O ₂ (%O ₂)	Mean	96.3	94.1	<0.001
	Std. Deviation	3.8	6.0	
eGFR (ml/min/1.73m ²)	Mean	63.9	53.9	<0.001
	Std. Deviation	27.7	18.8	

Acute heart Failure cases In the Emergency Department are not the same in Singapore & New Zealand

Ibrahim et al
Eur J Heart Fail
2016

Is Singapore facing cardiovascular Catastrophe ?

Breathless People with a Diagnosis of Acute Heart Failure

	COUNTRY				P-value
	Singapore (N=148)		NZ (N=180)		
	Count	%	Count	%	
Gender (F)	40	27.0%	64	35.6%	0.099
COPD	10	6.8%	46	26.0%	<0.001
CHF	60	40.5%	89	50.6%	0.071
TOBACCO	46	31.1%	16	8.9%	<0.001
PND	74	51.4%	110	63.6%	0.028
ELEVJVP	54	37.2%	115	67.6%	<0.001
DIABETES	80	54.1%	43	24.2%	<0.001
HYPERLIPIDEMIA	85	57.4%	79	46.2%	0.045
DYSPREST	95	65.5%	138	77.1%	0.021
ECGAFIB	33	22.3%	64	44.1%	<0.001
ECGLBBB	7	4.7%	18	13.3%	0.011

Acute heart Failure cases In the Emergency Department are not the same in Singapore & New Zealand

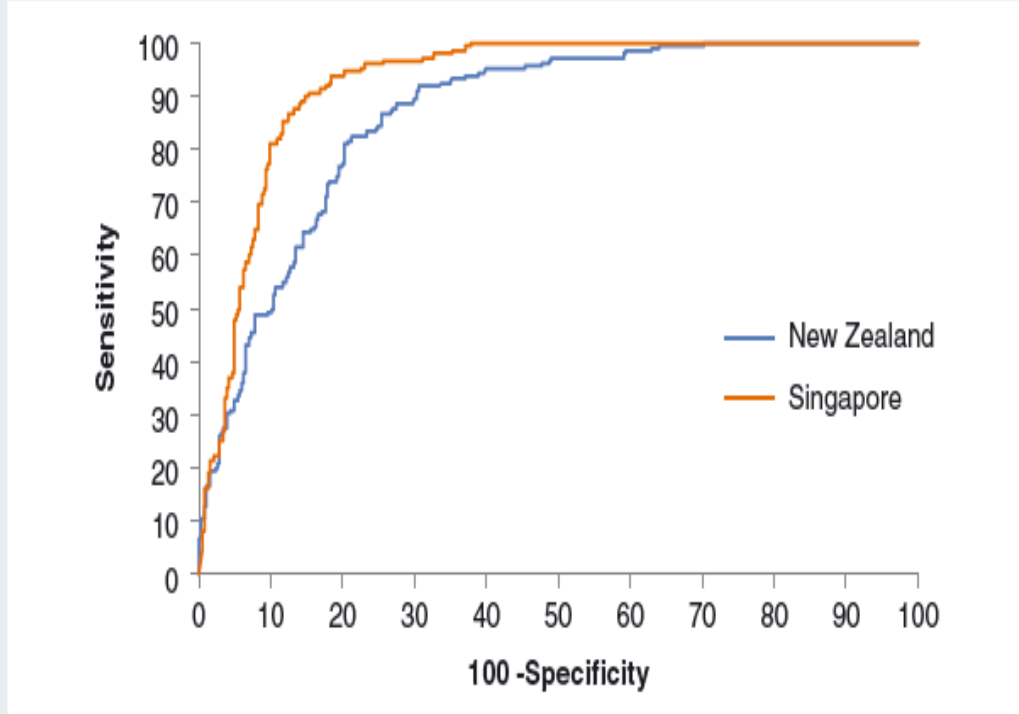


Figure 1 Receiver operating characteristic curves for discrimination of acute decompensated heart failure. Areas under the curve for Singapore (0.926) and New Zealand (0.866) differ significantly ($P = 0.012$).

Diagnostic Test Performance of NT-proBNP for Diagnosis of Acute Heart Failure



Single threshold (300pg/ml)

Singapore			
Diagnosis	NTPBNP		Total
	<= 300.00	300.01+	
No	334	124	458
Yes	5	143	148
Total	339	267	606
	Estimate	LL	UL
Sensitivity	96.62	92.29	98.89
Specificity	72.93	68.61	76.94
PPV	53.56	47.38	59.66
NPV	98.53	96.59	99.52
Accuracy	78.71%		

Christchurch			
Diagnosis	NTPBNP		Total
	<= 300.00	300.01+	
No	135	185	320
Yes	5	175	180
Total	140	360	500
	Estimate	LL	UL
Sensitivity	97.22	93.64	99.09
Specificity	42.19	36.71	47.81
PPV	48.61	43.34	53.91
NPV	96.43	91.86	98.83
Accuracy	62.00%		

Age adjusted thresholds
 <50 years >450pg/ml
 50-75 yr >900pg/ml
 >75 years >1800pg/ml

Singapore			
Diagnosis	NTPBNP		Total
	Below	Above	
No	393	65	458
Yes	17	131	148
Total	410	196	606
	Estimate	LL	UL
Sensitivity	88.51	82.25	93.16
Specificity	85.81	82.27	88.87
PPV	66.84	59.77	73.38
NPV	95.85	93.44	97.57
Accuracy	86.47%		

Christchurch			
Diagnosis	NTPBNP		Total
	Below	Above	
No	228	92	320
Yes	21	159	180
Total	249	251	500
	Estimate	LL	UL
Sensitivity	88.33	82.72	92.63
Specificity	71.25	65.95	76.15
PPV	63.35	57.06	69.32
NPV	91.57	87.40	94.70
Accuracy	77.40%		



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CONCLUSIONS

- Myocardial Infarction occurs **early** in Singapore.
- Outcomes may be **worse** than in the West.
- Incidence in **younger (30-60 years) age groups** appears to be rising.
- Risk factors including **Diabetes** and **Hypertension** are highly prevalent within the AMI population. Disease for given burden of risk is worse than in the west.
- Heart Failure ...a key consequent morbidity after AMI occurs early and is characterized by **high prevalence of diabetes and worse outcomes**.
- Research in to the burden of risk leading to AMI and the biology and medical management post-AMI warrant research and development of effective interventional strategies.

Thank you for your attention

