THE HARLEY STREET
HEART & VASCULAR CENTRE

CARDIOVASCULAR RISK MANAGEMENT REDEFINED

What else should we be doing for our patients?

15 SEPTEMBER 2018 (SATURDAY)
12.45PM – 3.10PM

REGENT SINGAPORE, PATERSON ROOM AT LEVEL 3
1 CUSCADEN ROAD SINGAPORE 249715

In support of:

Singapore Heart Foundation
Your Heart We Care

SANOFI

Medtronic
Further, Together

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Agenda

1. Risk Reduction In Ischaemic Heart Disease: Lowering Cholesterol to New Depths

   Dr Rohit Khurana

2. Reducing Risk in Heart Failure Patients: New & Traditional Measures

   Dr Peter Ting

3. Interventional and Best Medical Therapy As Complimentary Partners in Carotid & Peripheral Vascular Disease

   Dr Sriram Narayanan

Apologies: Dr Reginald Liew

MEDBULLETIN
SEPTEMBER2018

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From left to right:
Dr. Sriram Narayanan, Dr. Peter Ting, Dr. Rohit Khurana, Dr. Reginald Liew

INTRODUCTION

Greetings from the Harley Street Heart and Vascular Centre! We are pleased to present our second newsletter of 2018 in which we aim to provide the busy clinician with practical updates on the latest advances in the fields of cardiovascular medicine.

In this edition, our cardiologists provide succinct articles shedding new light on how we can best manage both traditional and non-traditional cardiovascular risk factors in our patients with cardiovascular disease. Dr. Reginald Liew addresses the often overlooked lifestyle factors that are important to identify in patients with atrial fibrillation, which can have a significant impact on their overall wellbeing and AF management if successfully implemented. Dr. Rohit Khurana revisits the question of how low we should target cholesterol levels in view of new evidence and treatments available, including the recently introduced PCSK9 inhibitors. Dr. Peter Ting discusses how we can further reduce cardiovascular risk in heart failure patients using a combination of new and traditional measures. Finally, Dr. Sriram Narayanan, our Harley Street vascular specialist, provides an update on how we can best manage patients with carotid disease and decide between medical and interventional therapies.

As usual, the article finishes with an interesting and challenging medical quiz- the answer to the quiz will be posted on our website (www.harleystreet.sg) within a week of the newsletter being sent out.

We hope these articles stimulate and challenge your views on the latest ideas in the treatment of cardiovascular disease. Please feel free to contact us (at enquiries@harleystreet.sg) if you would like to provide any feedback or request a specific topic in future editions.

From The Harley Street Heart & Vascular Centre

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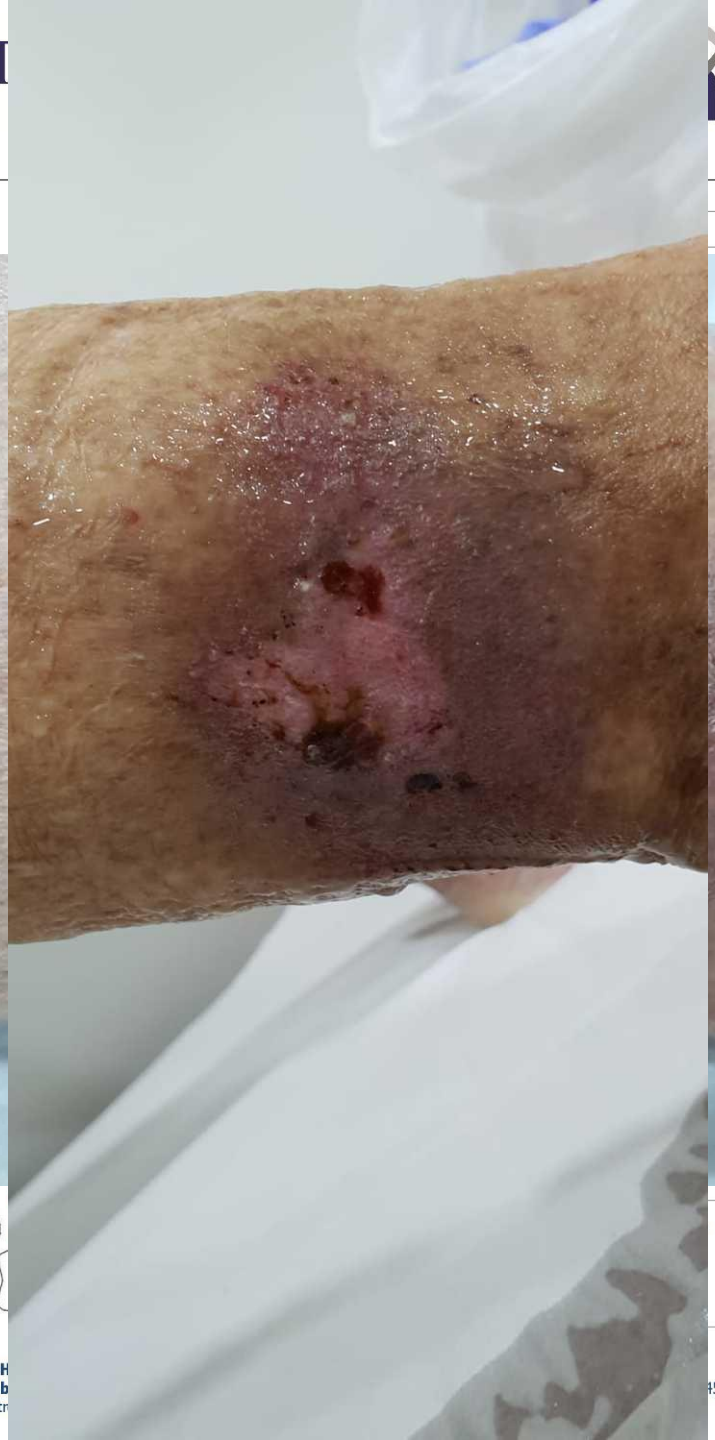

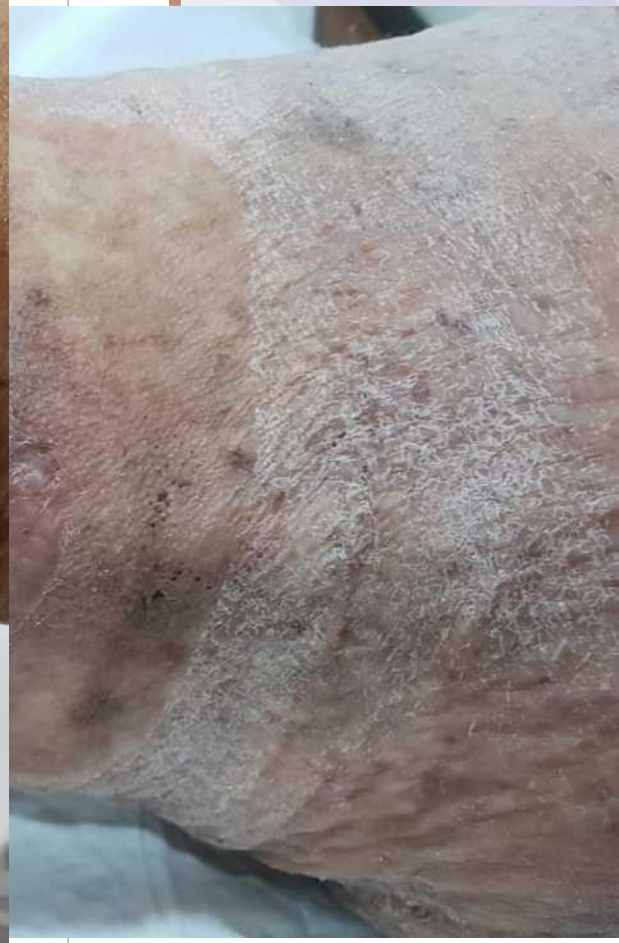

*Answer is availab
http://www.harley
answers/medbulle

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Mount Elizab
www.harleystr

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Dr. Rohit Khurana

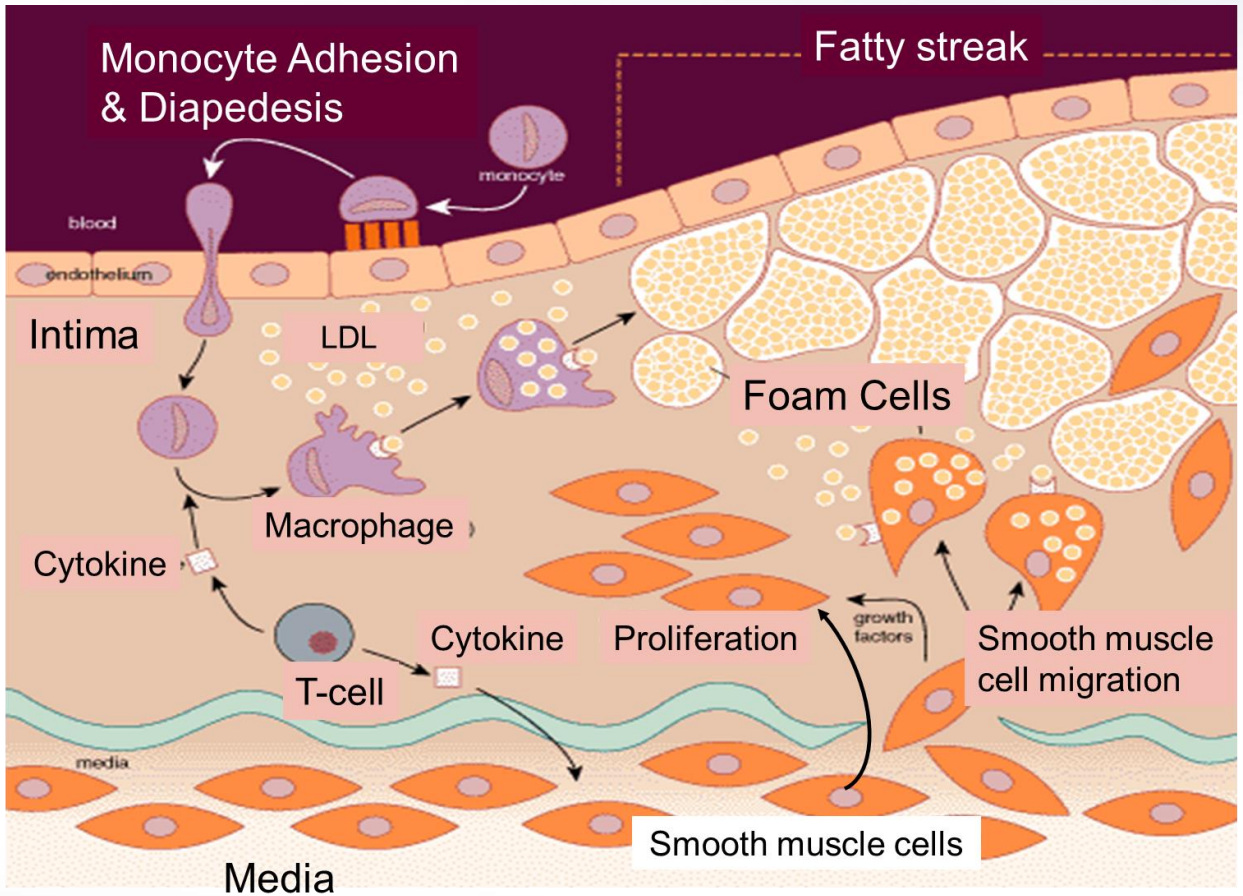
MA (Oxon), BMBCh (Oxon), PhD (Lond)

FRCP (UK), FESC (Europe), FACC (USA)

Consultant Interventional Cardiologist,

Gleneagles Hospital, Singapore

Atherogenesis: The Central Role of LDL-Cholesterol



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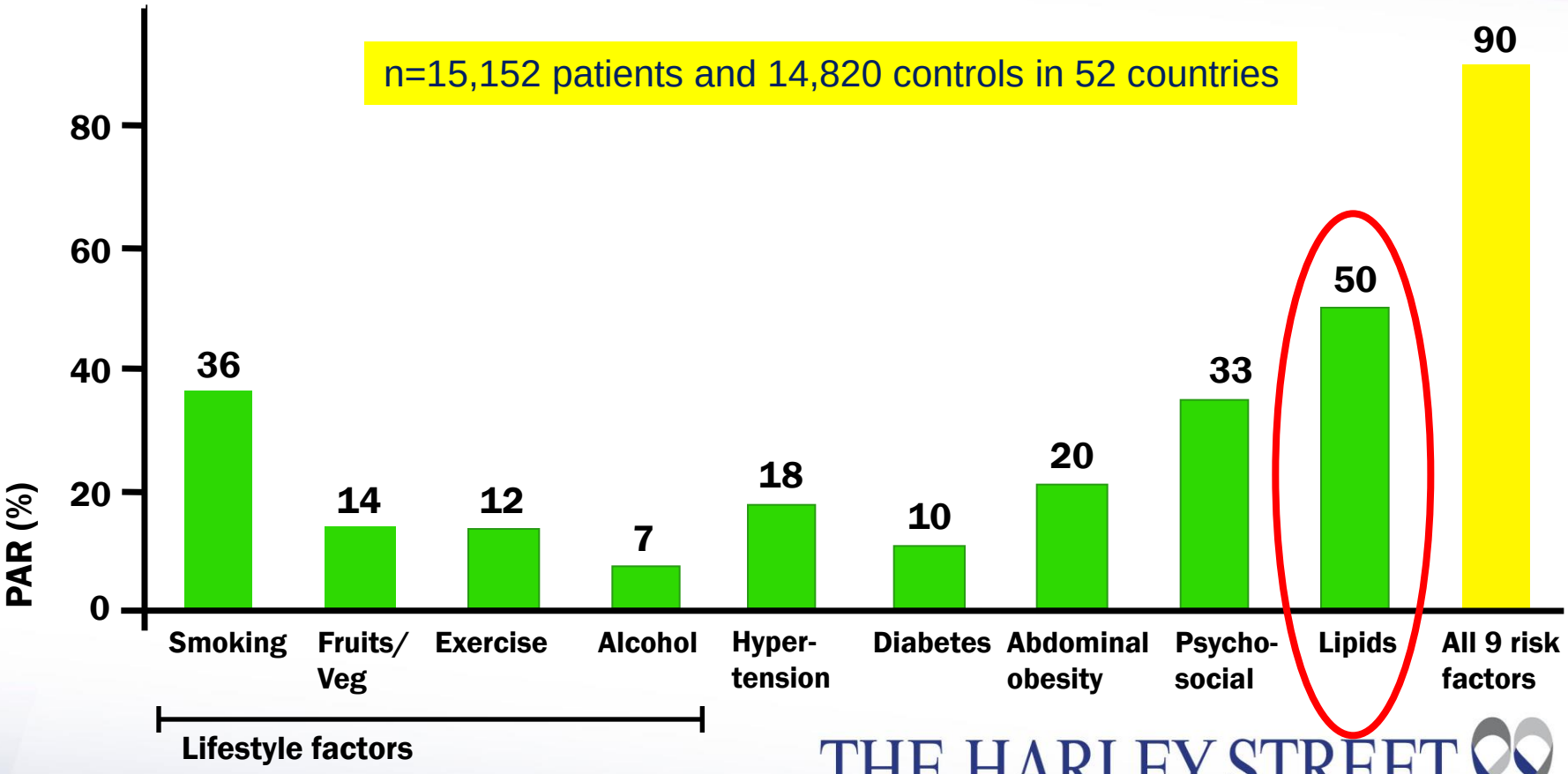
Attributable Risk Factors for a 1st Myocardial Infarction

INTERHEART Study



MI=Myocardial infarction, PAR=Population attributable risk (adjusted for all risk factors)

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Source: Yusuf S et al. *Lancet*. 2004;364:937-952

Therapies to Lower Levels of LDL-C

Class	Drug(s)
3-Hydroxy-3-Methylglutaryl Coenzyme A (HMG-CoA) reductase inhibitors [Statins]	Atorvastatin (Lipitor) Fluvastatin (Lescol XL) Lovastatin (Mevacor) Pitavastatin (Livalo) Pravastatin (Pravachol) Rosuvastatin (Crestor) Simvastatin (Zocor)
Bile acid sequestrants	Cholestyramine (Questran) Colesevelam (Welchol) Colestipol (Colestid)
Cholesterol absorption inhibitor	Ezetimibe (Zetia)
Nicotinic acid	Niacin
Dietary Adjuncts	Soluble fiber Soy protein Stanol esters

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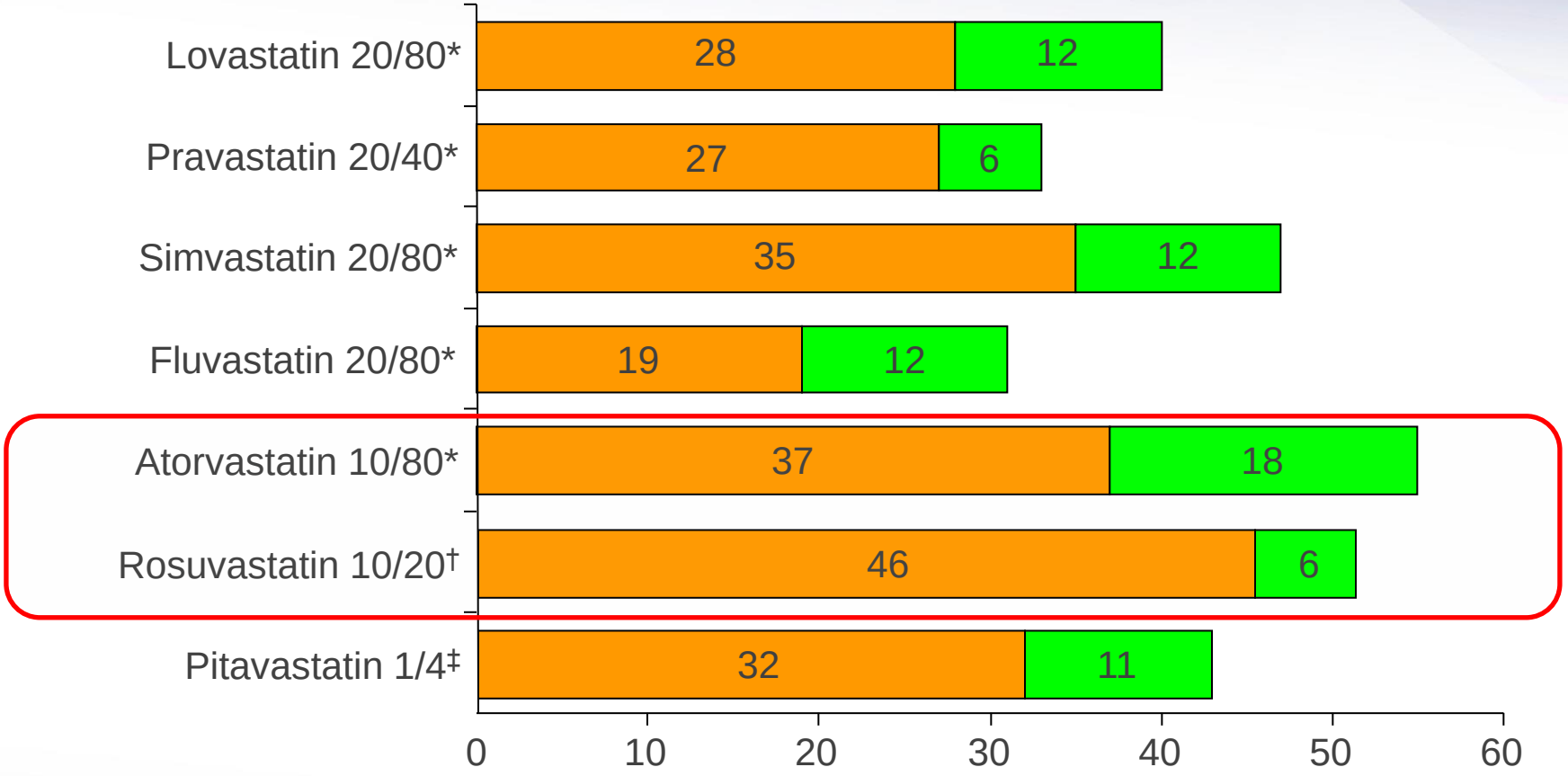
HMG-CoA Reductase Inhibitor: Dose-Dependent Effect

The Rule of 6's



Each doubling of the statin dose produces an approximate 6% reduction in the LDL-C level

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Residual Risk After Acute Coronary Syndrome

- **Remains high despite evidence-based preventive therapies**
- **Is related, in part, to levels of low-density lipoprotein cholesterol (LDL-C)**

- **Is reduced when LDL-C is lowered by**
  - **Statin therapy, compared with placebo[1]**
  - **High-intensity, compared with moderate-intensity statin therapy[2]**
  - **Ezetimibe, compared with placebo, added to statin[3]**

1. Schwartz GG, et al. JAMA 2001;285:1711-8.
2. Cannon CP, et al. NEJM 2004;350:1495-504.
3. Cannon CP, et al. NEJM 2015;372:2387-97.

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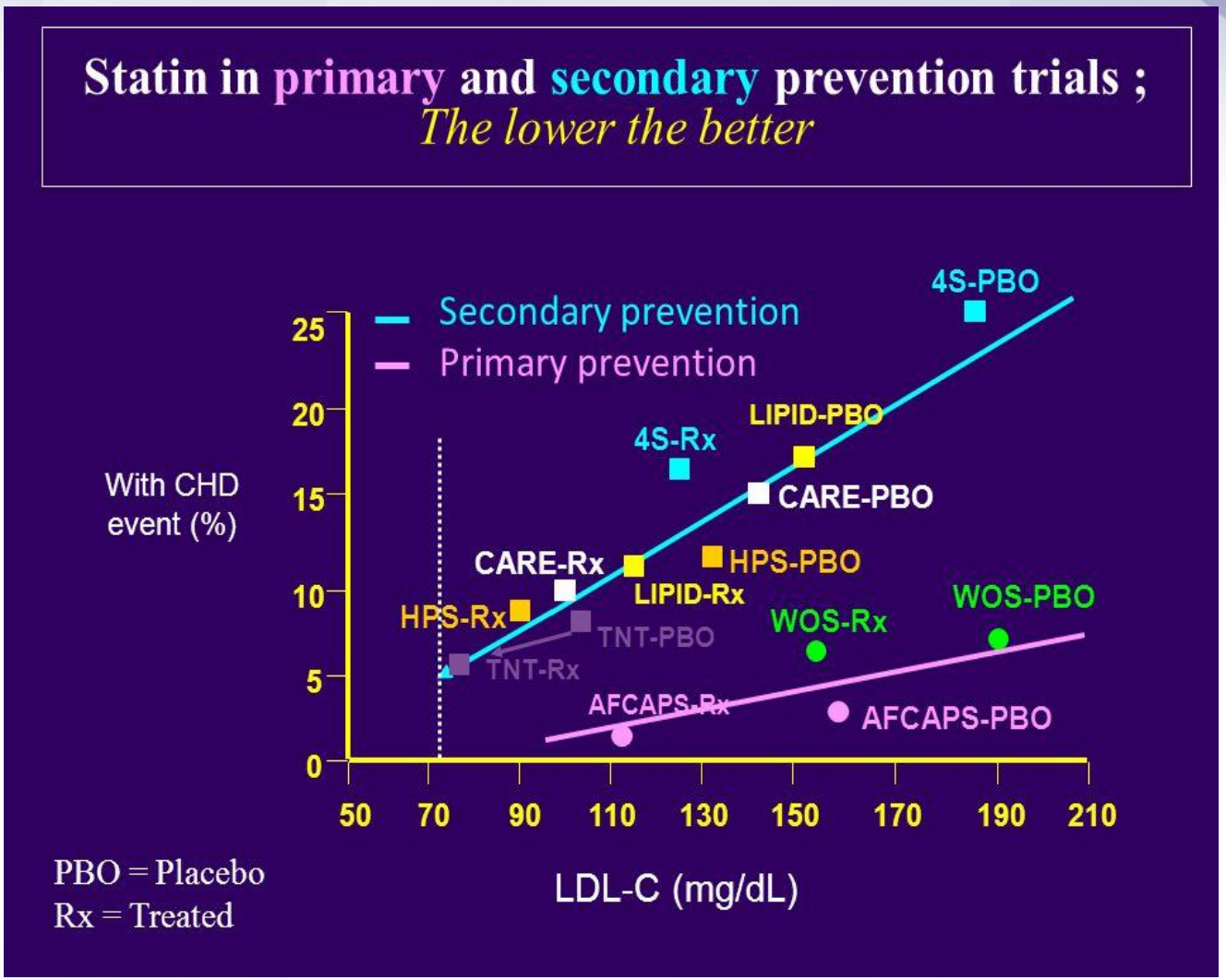
Lower is better: There is no too low!



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Statin Intolerant Patients have worse prognosis after MI

JACC 2017;69:1386-95

- Increased risk for recurrent MI and CHD events
- Statin discontinuation associated with elevated risk of ischemic stroke, all cause mortality, all major events and any hospitalization
- 50% increased risk of MI
- 51% increased risk of all CV events

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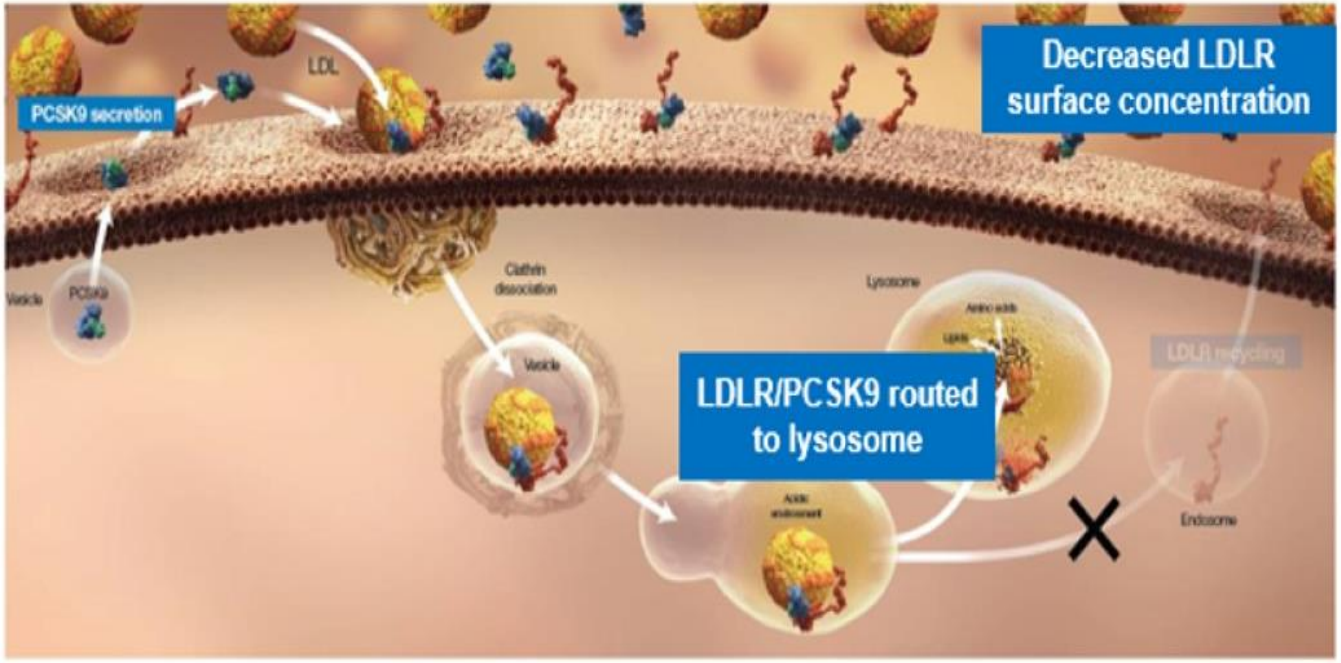
PCSK9 binds to the LDL-R and promotes degradation



- PCSK9 is synthesized in the hepatocyte
- PCSK9 is secreted into the circulation
- Circulating PCSK9 binds to LDL-Rs with high affinity

Blocking PCSK9 increases availability or LDL-R to remove LDL from the circulation

LDL-R: low-density lipoprotein receptor; PCSK9: proprotein convertase subtilisin/kexin type 9.

1. Qian YW et al. J Lipid Res. 2007;48:1488–1498. 2. Horton JD et al. J Lipid Res. 2009;50(Suppl):S172–S177. 3. Rashid S et al. PNAS 2005;102:5374–5379

PCSK9 monoclonal antibodies (mAbs)

- Highly specific to target PCSK9
- Act outside cell to bind PCSK9
- Metabolized in reticuloendothelial system
  - No hepatic metabolism or renal excretion
- Fully human PCSK mAbs - **Evolocumab & Alirocumab**

Foltz I *et al*. *Circulation* 2013;127(22):2222-30; Nelson AL *et al*. *Nature Reviews Drug Discovery* 2010;9(10):767-74. Roth EM et al. *N Engl J Med.* 2017; online March 17, 2017; Sabatine M, et al. NEJM 2017; online ahead of print March 17, 2017; doi 10.1056/NEJMoa1615664

Monoclonal antibodies to PCSK9

3 taken into large Phase 3 Outcomes trials

All 3 monoclonal antibodies reduce LDL-c substantially (50-60%)

Evolocumab (Amgen)	FOURIER
Alirocumab (Sanofi)	ODYSSEY OUTCOMES
Bococizumab (Pfizer)	SPIRE 1 and 2

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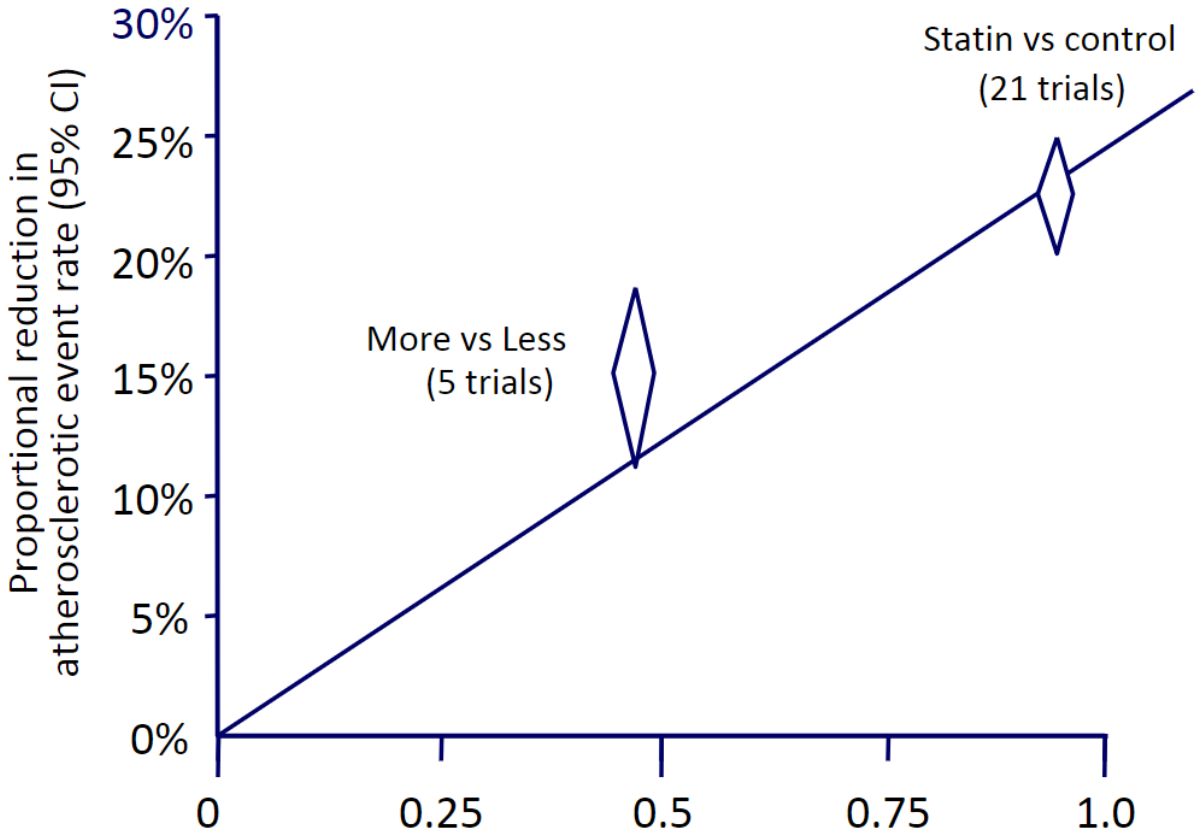
CTT: Impact of LDL lowering on risk depends on the absolute difference in LDL-C



Mean LDL cholesterol difference between treatment groups (mmol/l)

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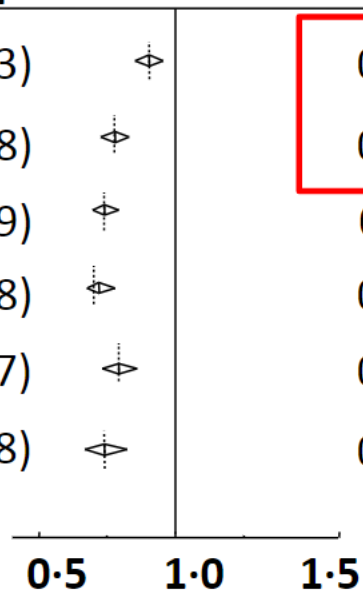
CTT: Effects on major vascular events per mmol/L LDL-c reduction, by year

Endpoint	Events (%) Treatment	Control	Rate Ratio (CI)
YEAR 0-1	1747 (3·9)	1951 (4·3)	0·90 (0.85 – 0·96)
YEAR 1-2	1231 (2·9)	1603 (3·8)	0·78 (0·73 – 0·83)
YEAR 2-3	1151 (2·8)	1543 (3·9)	0·74 (0·69 – 0·79)
YEAR 3-4	946 (2·6)	1306 (3·8)	0·72 (0·67 – 0·78)
YEAR 4-5	811 (2·9)	993 (3·7)	0·79 (0·74 – 0·86)
YEAR 5+	468 (2·8)	598 (3·8)	0·74 (0·67 – 0·82)



◈ RR (95% CI)

p<0.00001

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fourier

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

Marc S. Sabatine, M.D., M.P.H., Robert P. Giugliano, M.D., Anthony C. Keech, M.D., Narimon Honarpour, M.D., Ph.D., Stephen D. Wiviott, M.D., Sabina A. Murphy, M.P.H., Julia F. Kuder, M.A., Huei Wang, Ph.D., Thomas Liu, Ph.D., Scott M. Wasserman, M.D., Peter S. Sever, Ph.D., F.R.C.P., and Terje R. Pedersen, M.D., for the FOURIER Steering Committee and Investigators*

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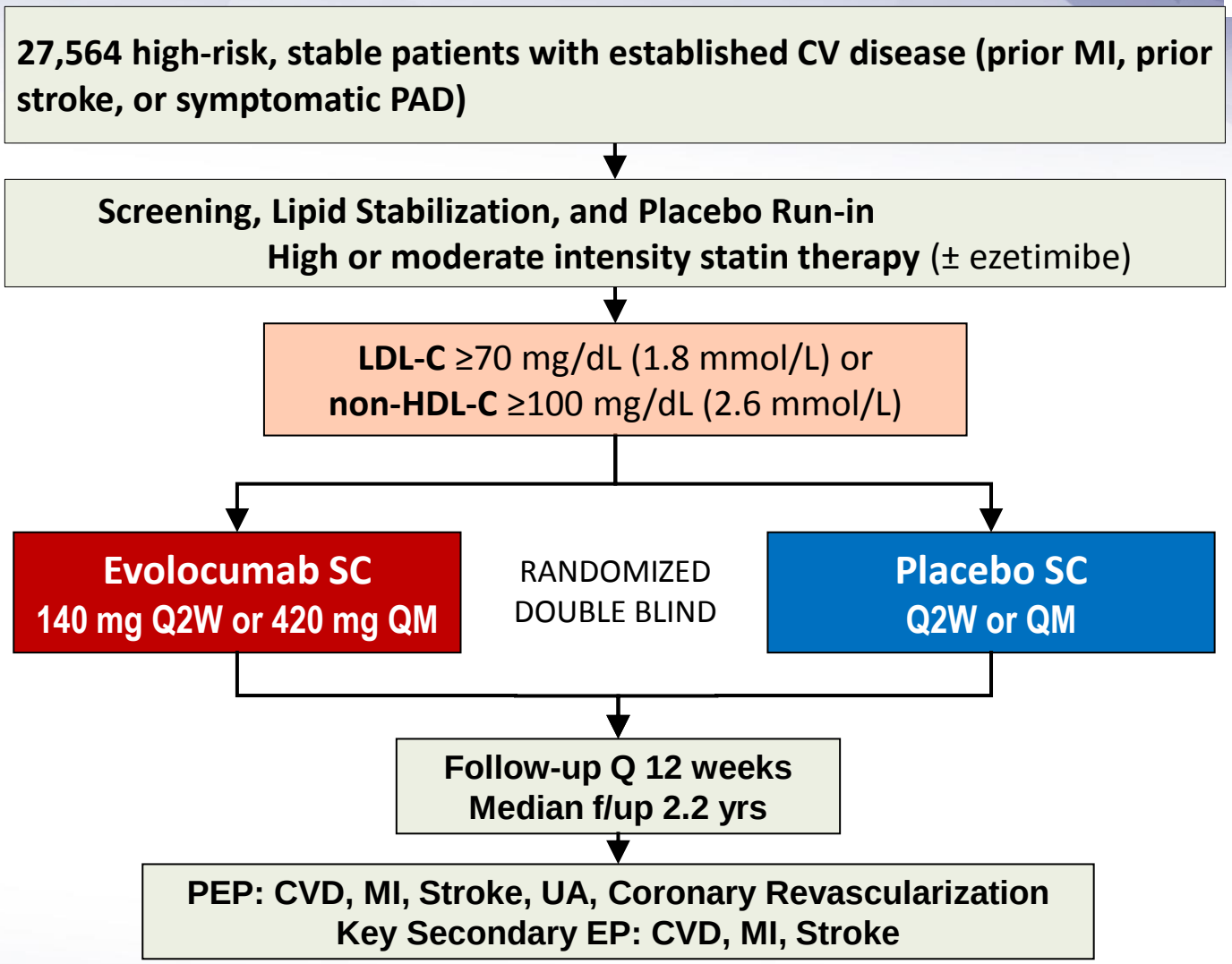
Published March 2017

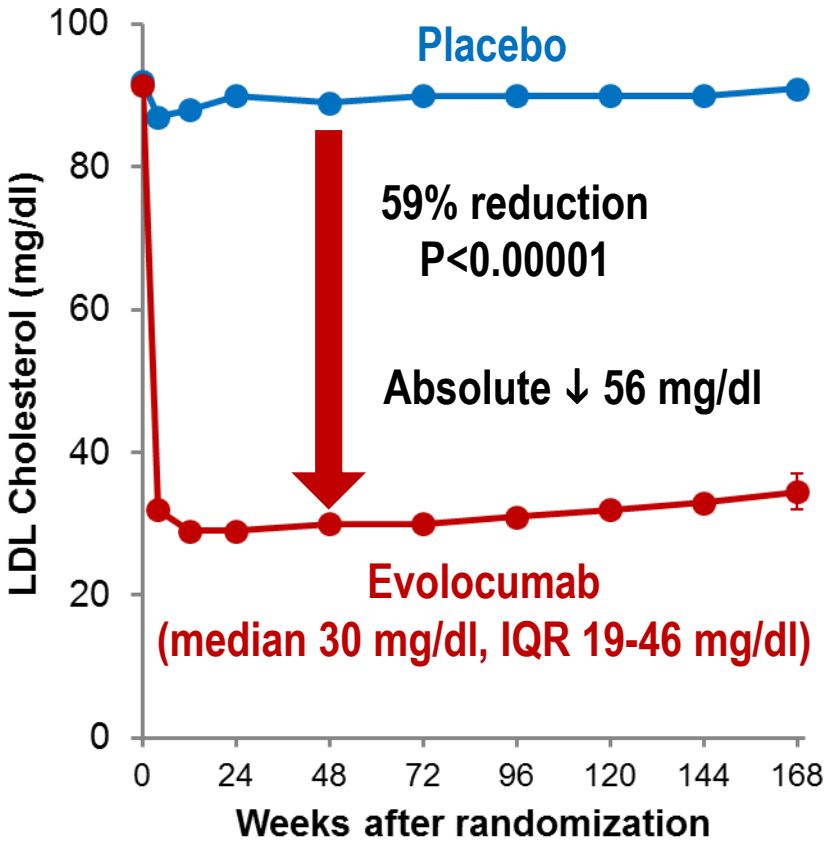
Trial Design

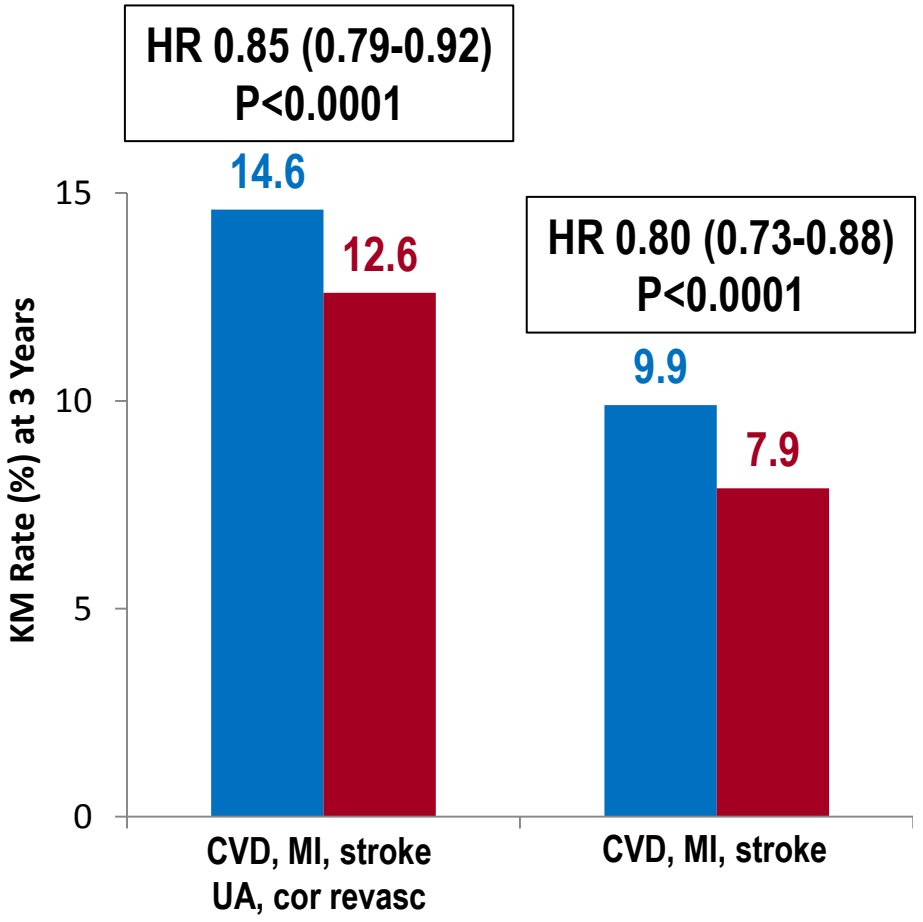


Sabatine MS et al. *Am Heart J* 2016;173:94-101

Summary of Effects of PCSK9i Evolocumab

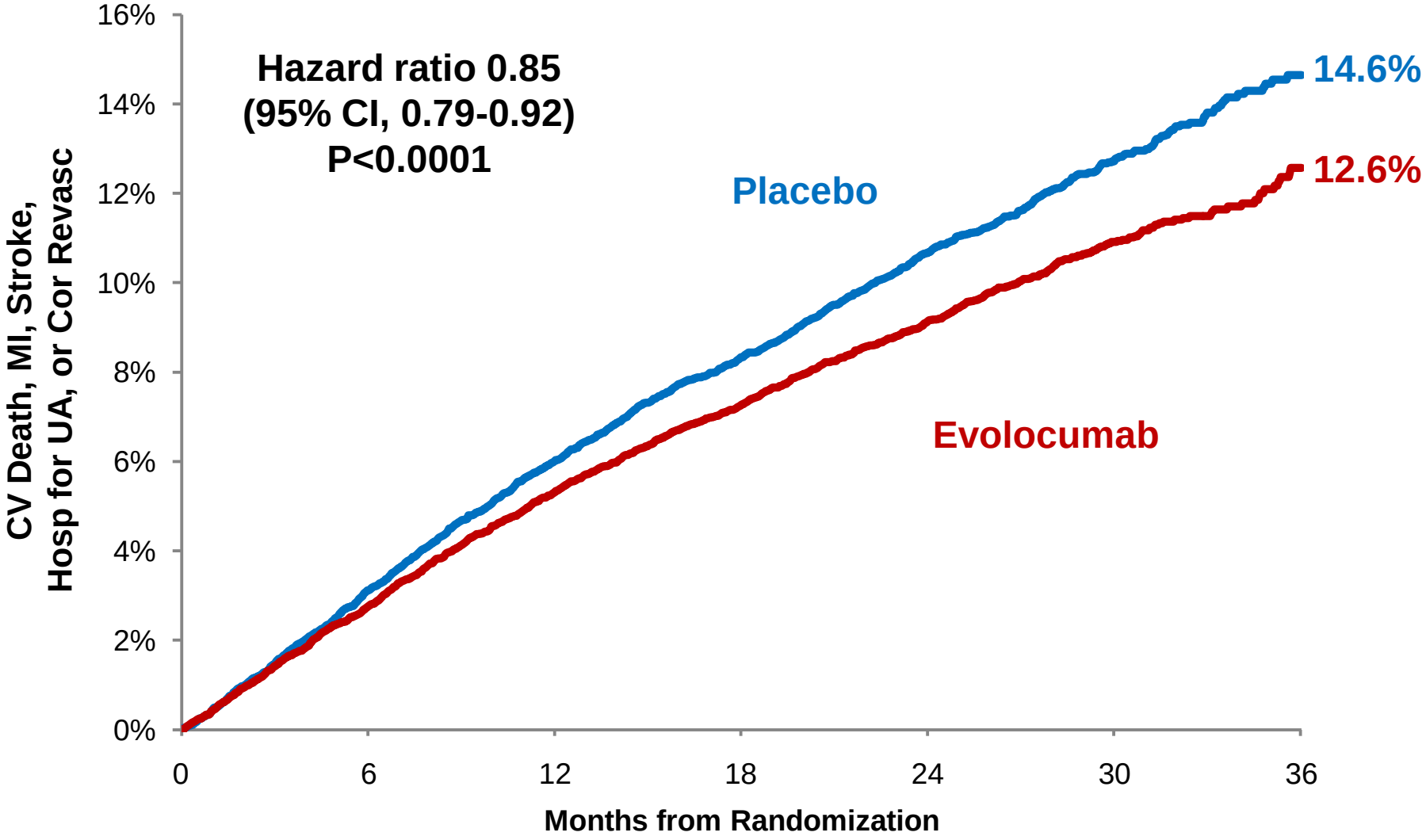
- ↓ LDL-C by 59% to a median of 30 mg/dL
- ↓ CV outcomes in patients on statin
- Safe and well-tolerated





Sabatine MS et al. *NEJM* 2017;376:1713-22

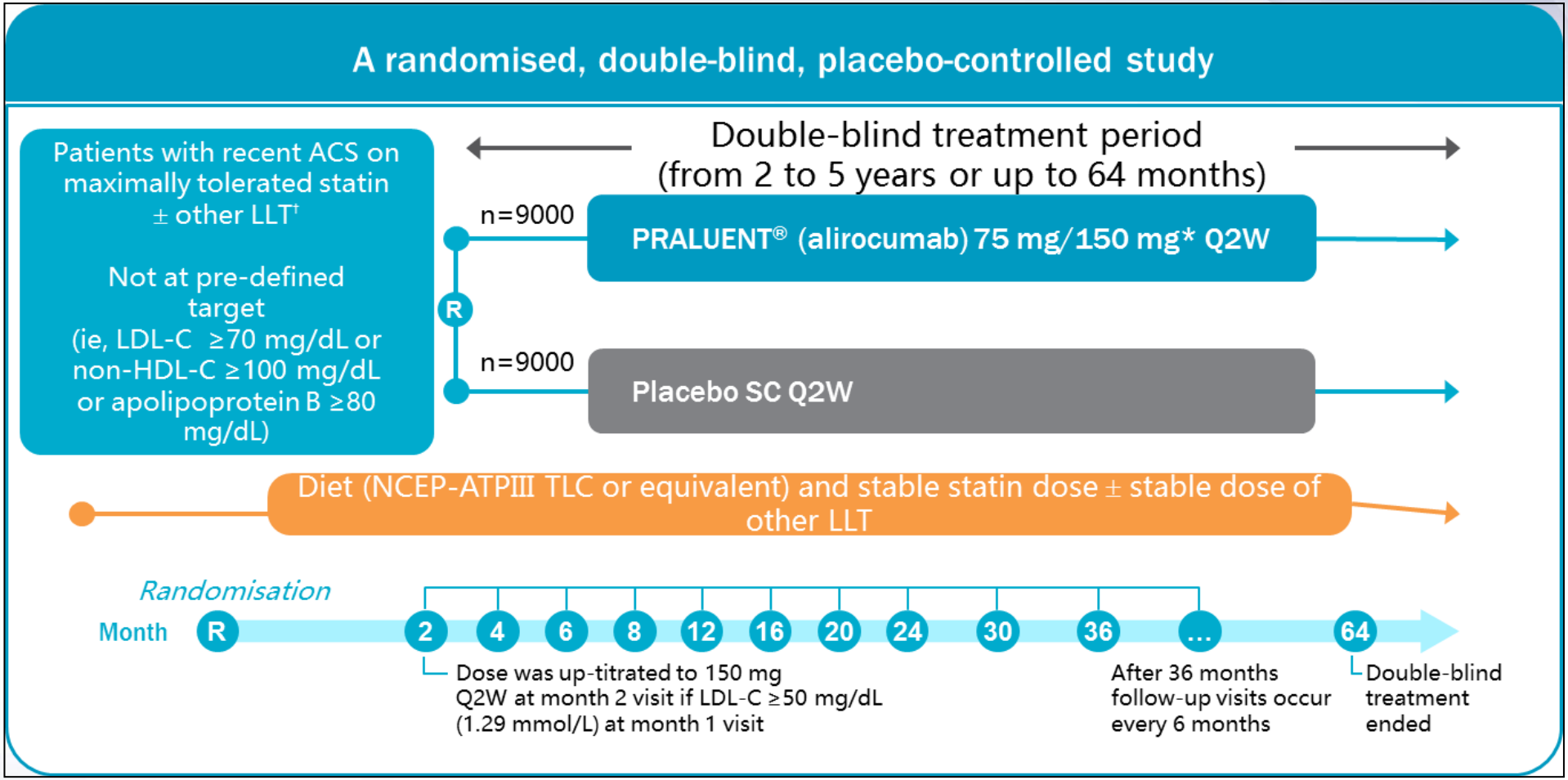
Primary Endpoint



Types of CV Outcomes

Endpoint	Evolocumab (N=13,784)	Placebo (N=13,780)	HR (95% CI)
	3-yr Kaplan-Meier rate		
CV death, MI, or stroke	**7.9**	**9.9**	**0.80 (0.73-0.88)**
Cardiovascular death	**2.5**	**2.4**	**1.05 (0.88-1.25)**
Death due to acute MI	0.26	0.32	0.84 (0.49-1.42)
Death due to stroke	0.29	0.30	0.94 (0.58-1.54)
Other CV death	1.9	1.8	1.10 (0.90-1.35)
MI	**4.4**	**6.3**	**0.73 (0.65-0.82)**
Stroke	**2.2**	**2.6**	**0.79 (0.66-0.95)**

ODYSSEY OUTCOMES



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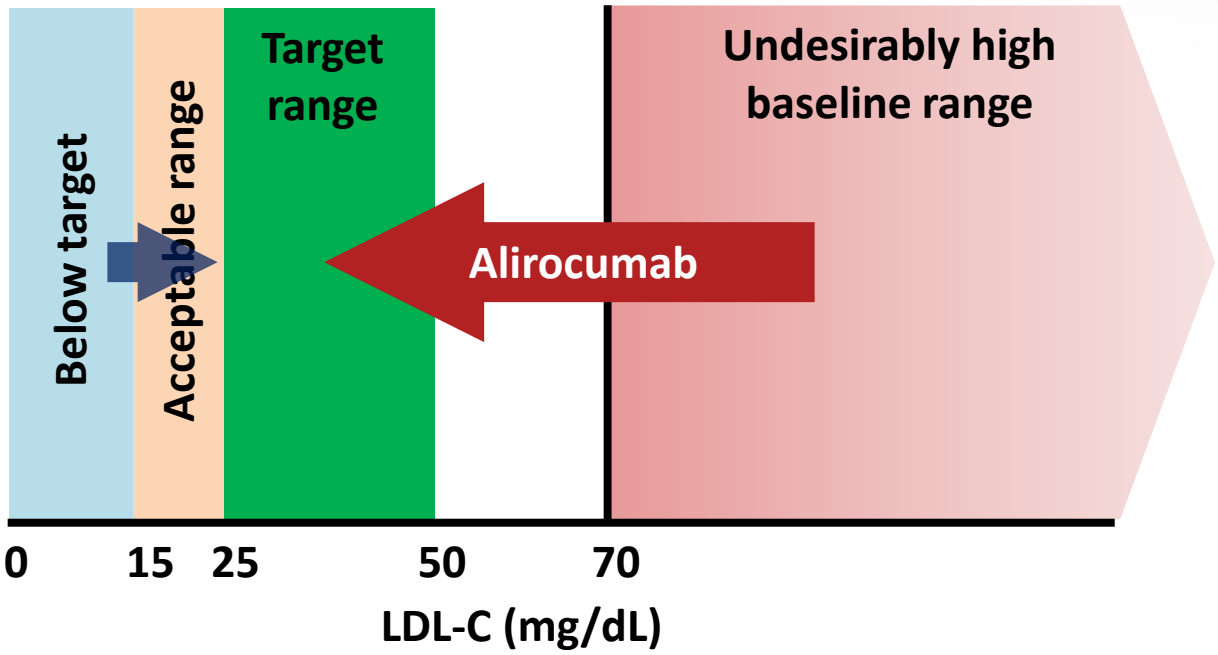
A Target Range for LDL-C

We attempted to maximize the number of patients in the target range and minimize the number below target by blindly titrating alirocumab (75 or 150 mg SC Q2W) or blindly switching to placebo.



Schwartz GG, et al. Am Heart J 2014;168:682-689.e1.

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Main Inclusion Criteria

- **Age** ≥40 years
- **ACS**
  - 1 to 12 months prior to randomization
  - Acute myocardial infarction (MI) or unstable angina
- **High-intensity statin therapy***
  - Atorvastatin 40 to 80 mg daily or
  - Rosuvastatin 20 to 40 mg daily or
  - Maximum tolerated dose of one of these agents for ≥2 weeks
- **Inadequate control of lipids**
  - LDL-C ≥70 mg/dL (1.8 mmol/L) or
  - Non-HDL-C ≥100 mg/dL (2.6 mmol/L) or
  - Apolipoprotein B ≥80 mg/dL

*Patients not on statins were authorized to participate if tolerability issues were present and documented

Schwartz GG, et al. Am Heart J 2014;168:682-689.e1.

ODYSSEY OUTCOMES

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Primary Efficacy Outcome

Time of first occurrence of:

- **Coronary heart disease (CHD) death, or**
- **Non-fatal MI, or**
- **Fatal or non-fatal ischemic stroke, or**
- **Unstable angina requiring hospitalization***

All outcomes adjudicated by the Clinical Events Committee, under the auspices of the Duke Clinical Research Institute (DCRI). Members were unaware of treatment assignment and lipid levels

*Required all of the following:

1. Hospital admission >23 h for MI symptoms, ↑ tempo in prior 48 hours and/or ≥20 min of chest discomfort at rest
2. New ECG findings consistent with ischemia or infarction
3. Angiographically significant obstructive coronary disease

Schwartz GG, et al. Am Heart J 2014;168:682-689.e1.

ODYSSEY OUTCOMES

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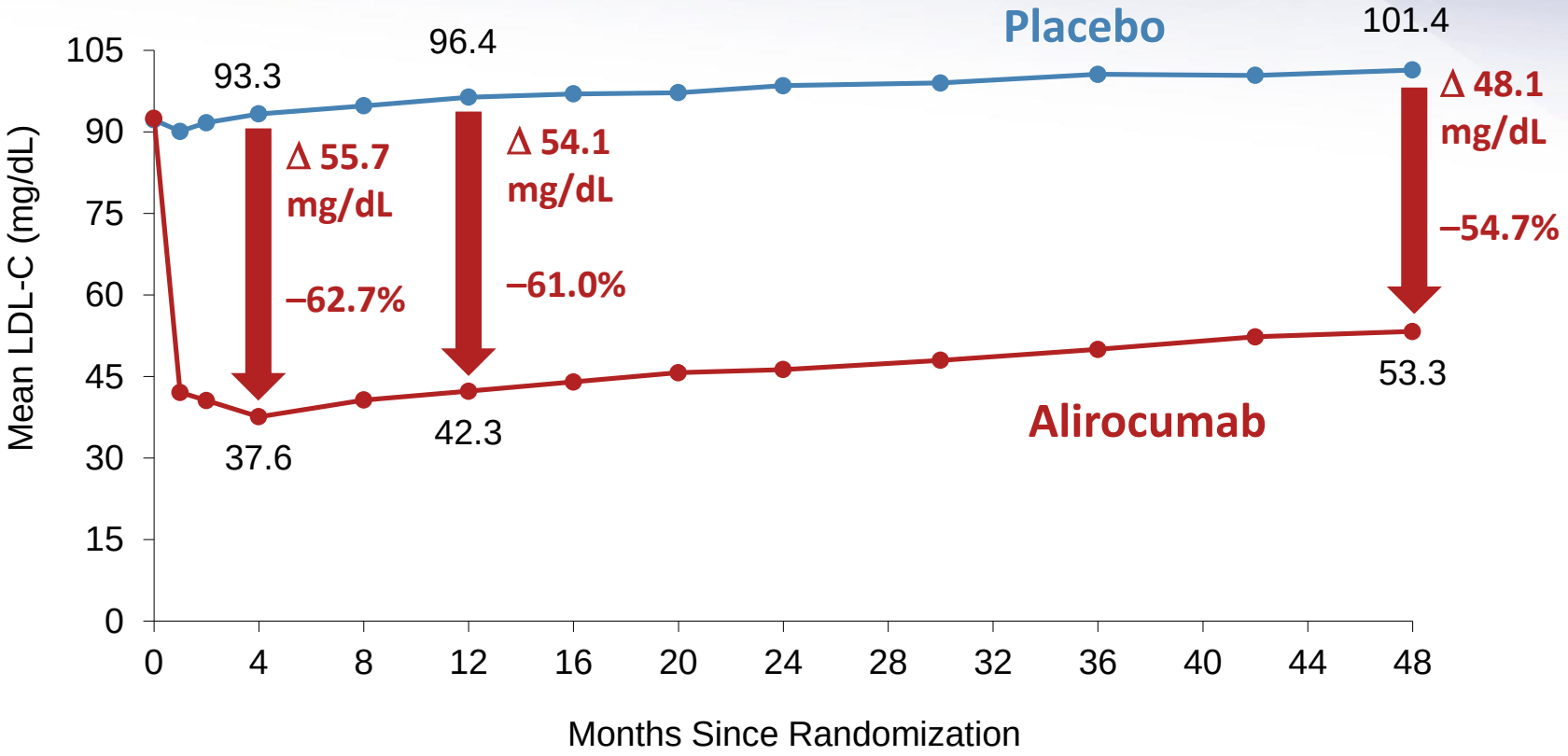
LDL-C: On-Treatment Analysis



Excludes LDL-C values after premature treatment discontinuation or blinded switch to placebo
Approximately 75% of months of active treatment were at the 75 mg dose

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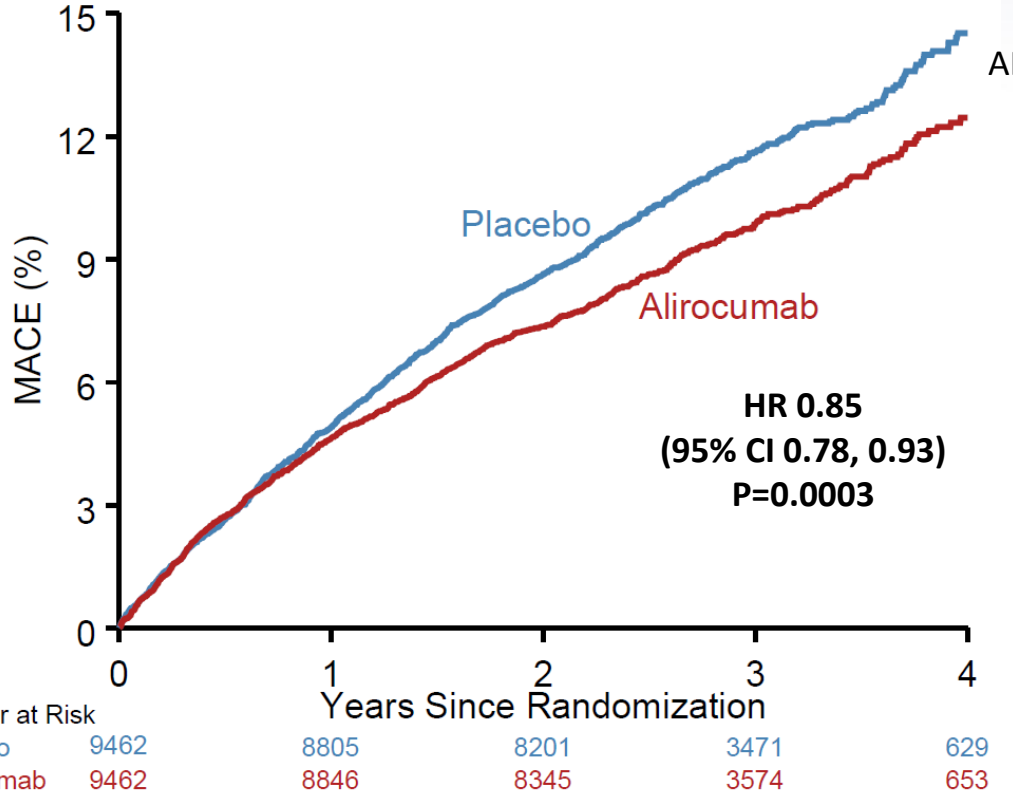
Primary Efficacy Endpoint: MACE



MACE: CHD death, non-fatal MI, ischemic stroke, or unstable angina requiring hospitalization

*Based on cumulative incidence

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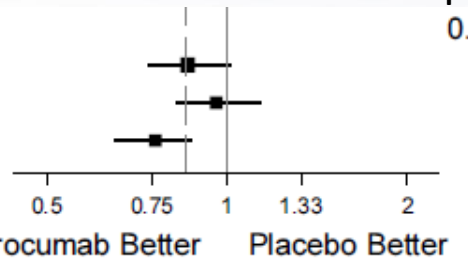
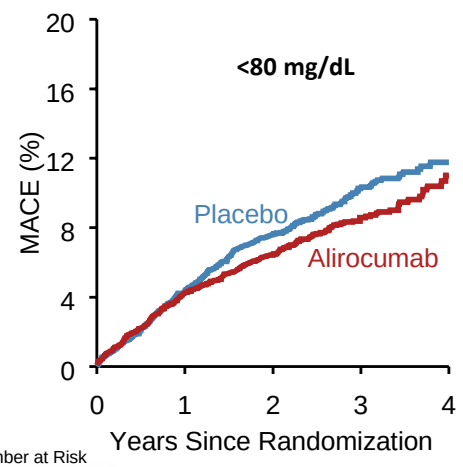
Primary Efficacy in Main Prespecified Subgroups

Subgroup	Patients	Incidence (%) Alirocumab	Placebo	HR (95% CI)	p-value*
LDL (mg/dL)					0.09
<80	7164	8.3	9.5	0.86 (0.74, 1.01)	
80 - <100	6128	9.2	9.5	0.96 (0.82, 1.14)	
≥100	5629	11.5	14.9	0.76 (0.65, 0.87)	

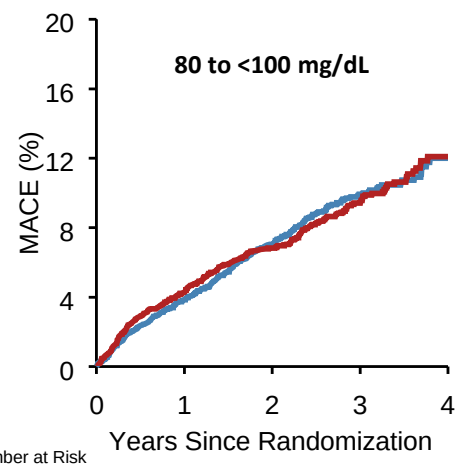


*P-values for interaction



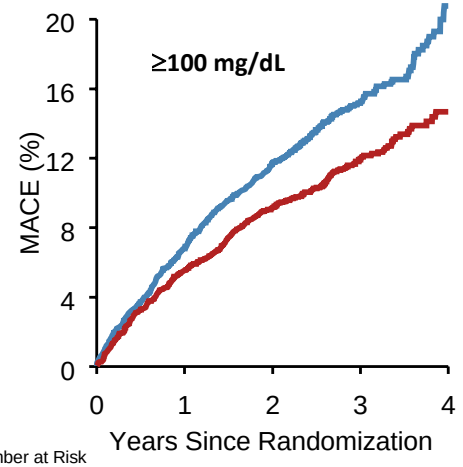
Number at Risk

Placebo	3583	3347	3122	1290	256
Alirocumab	3581	3365	3183	1327	233



Number at Risk

Placebo	3062	2889	2708	1195	195
Alirocumab	3066	2880	2732	1194	213



Number at Risk

Placebo	2815	2568	2371	986	178
Alirocumab	2814	2602	2431	1053	207

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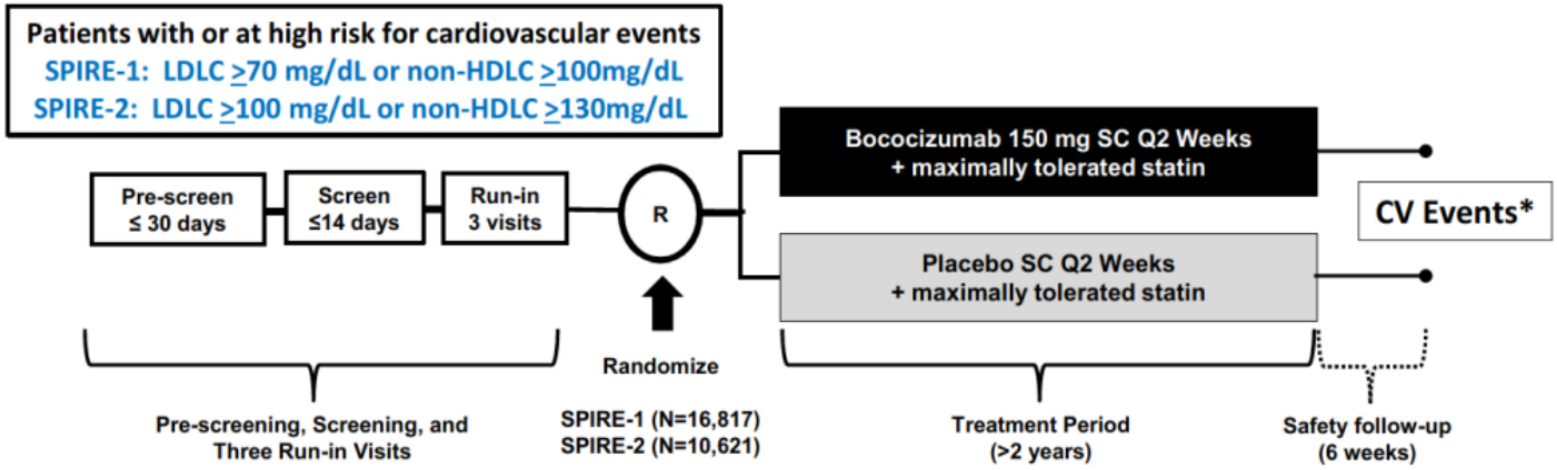
SPIRE trials

SPIRE 1 & SPIRE 2 Cardiovascular Outcome Trials (N= 27,438)



SPIRE trials stopped early – bococizumab program stopped

Ridker P et al. *NEJM* 2017; 376:1527-39

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PCSK-9 Monoclonal Antibody (mAb) Indications Approved by HSA 2017(Singapore)

Alirocumab and Evolocumab

Indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet:

- in combination with a statin or statin with other lipid lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin

OR

- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated

Is PCSK9 inhibition safe?

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Patients Homozygous for PCSK9 Loss-of-function Mutations

- Only a small number of patients who are homozygous (or compound heterozygotes) for PCSK9 have been discovered and studied
- These patients appear to have:
  - Very low LDL-C levels (~10-20 mg/dL)
  - Relatively low TG levels
  - Normal HDL-C levels
  - Otherwise healthy, normal individuals

LOF=loss of function; TG=triglyceride.

Amanda JH, , et al. *Atherosclerosis*. 2007;193:445–448; Cariou B, et al. *Arterioscler Thromb Vasc Biol*. 2009;29:2192–2197; Zhao Z, , et al. *Am J Hum Genet*. 2006;79:514–523.

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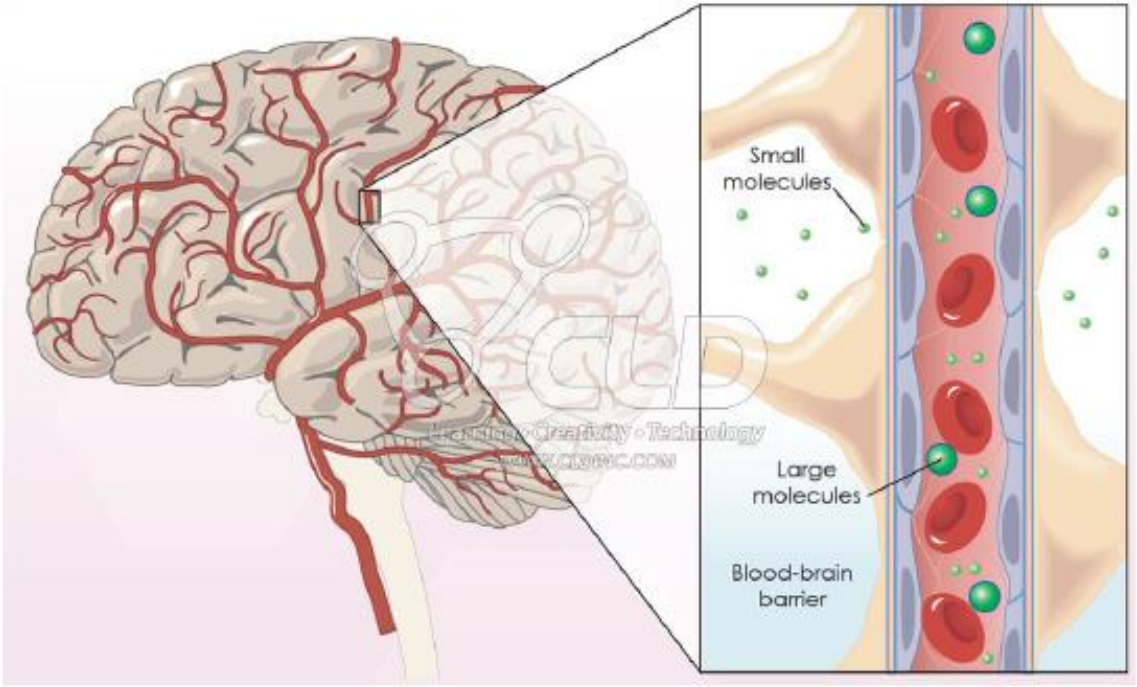
Cognition and PCSK9 Inhibitors

Brain synthesizes cholesterol locally



mAb (e.g., evolocumab) are too large to cross the intact blood-brain barrier

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The ODYSSEY OUTCOMES Trial: Topline Results
Alirocumab in Patients After Acute Coronary Syndrome

Treatment-emergent adverse events, n (%)	Alirocumab (N=9451)	Placebo (N=9443)
Any	7165 (75.8)	7282 (77.1)
Serious	2202 (23.3)	2350 (24.9)

Laboratory value	Alirocumab	Placebo
ALT >3 × ULN, n/N (%)	212/9369 (2.3)	228/9341 (2.4)
Creatine kinase >10 × ULN, n/N (%)	46/9369 (0.5)	48/9338 (0.5)

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The ODYSSEY OUTCOMES Trial: Topline Results

Alirocumab in Patients After Acute Coronary Syndrome

Event	Alirocumab (N=9451)	Placebo (N=9443)
Diabetes worsening or diabetic complications: *pts w/DM at baseline*, n/N (%)	506/2688 (18.8)	583/2747 (21.2)
New onset diabetes; *pts w/o DM at baseline*, n/N (%)	648/6763 (9.6)	676/6696 (10.1)
General allergic reaction, n (%)	748 (7.9)	736 (7.8)
Hepatic disorder, n (%)	500 (5.3)	534 (5.7)
Local injection site reaction, n (%)*	360 (3.8)	203 (2.1)
Neurocognitive disorder, n (%)	143 (1.5)	167 (1.8)
Cataracts, n (%)	120 (1.3)	134 (1.4)
Hemorrhagic stroke, n (%)	9 (<0.1)	16 (0.2)

*HR vs. placebo 1.82 (95% CI 1.54, 2.17)

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Summary: monoclonal antibodies to PCSK9

Lessons learned

- PCSK9 inhibition reduces LDL-c substantially
- Effect on CVD as predicted
- Very low LDL-c achieved
  - Regardless of statin therapy
- Safe
  - Cognition
  - New-onset DM
  - Cancer

Disadvantages

- Hassle
  - Injection each 2-4 weeks (self administered)
  - Storage conditions
- Cost
- Immune reaction
  - Bococizumab
- Not organ specific

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ESC/EAS guidance on PCSK9 in use

PCSK9 inhibitor should be considered in:

- Patients with ASCVD despite maximally tolerated statin with or without ezetimibe
- Patients with ASCVD and at very high risk who do not tolerate appropriate doses of at least three statins and thus have elevated LDL-C levels
- FH without diagnosed ASCVD, at high or very high CV risk, and with substantially elevated LDL-C

LDL-C threshold for consideration of PCSK9 i treatment of 3.6 mmol/l, despite statin with or without ezetimibe therapy or inability to tolerate appropriate doses of at least three statins.

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Conclusions and Next Steps

- Optimal patient selection
- Costs to patients / hospitals / insurers
- More ‘patient friendly options’
- Continued development of safe and effective alternatives to mAbs

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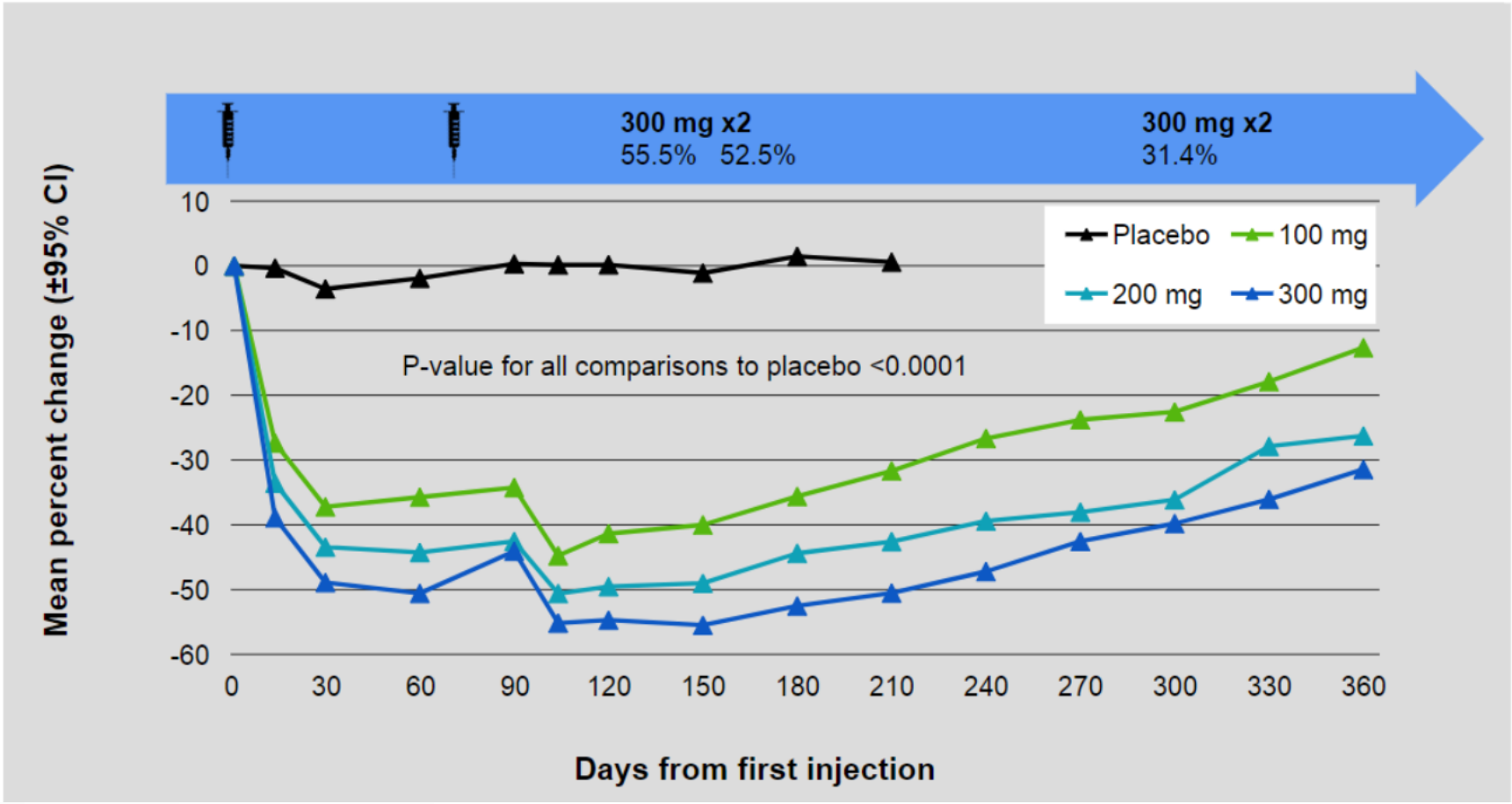
Approaches to PCSK9 inhibition

- Disrupt interaction between PCSK9 and LDL receptor with anti-PCSK9 monoclonal antibody or antigen binding fragment

- Inhibit PCSK9 synthesis with antisense oligonucleotides or small interfering RNAs

Inclisiran efficacy: 2 dose starting regimen

Robust, sustained LDL-C reductions



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ORION-4

- To assess the effect of inclisiran on major cardiovascular events
- ≥15,000 participants aged ≥55 years with pre-existing cardiovascular disease
- Randomized to inclisiran sodium 300 mg and matching placebo (every 6 months)
- 5 year follow-up
- UK and US (Oxford CTSU and TIMI)

UNIVERSITY OF OXFORD

HPS-4
TIMI 65
ORION-4

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Prof Eugene Braunwald, ESC 2018

Made an "outrageous suggestion"

Regarding Inclisiran

Potent inhibitor of PCSK9 production

"Given that inhibition of PCSK9 production will be able to actually prevent CAD If actually begun early enough in one's life, I would propose that such a drug be administered on a regular once or twice yearly basis to everyone over 30 yr old"

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Reducing Risk in Heart Failure: New and Traditional Measures

Dr. Peter Ting
Preventive Cardiology
The Harley Street Heart & Cancer Centre

Agenda

Heart Failure - The Asian challenge
Early diagnosis essential
Management of risk factors
Initiating drug therapy
Newer drug classes
Following up heart failure

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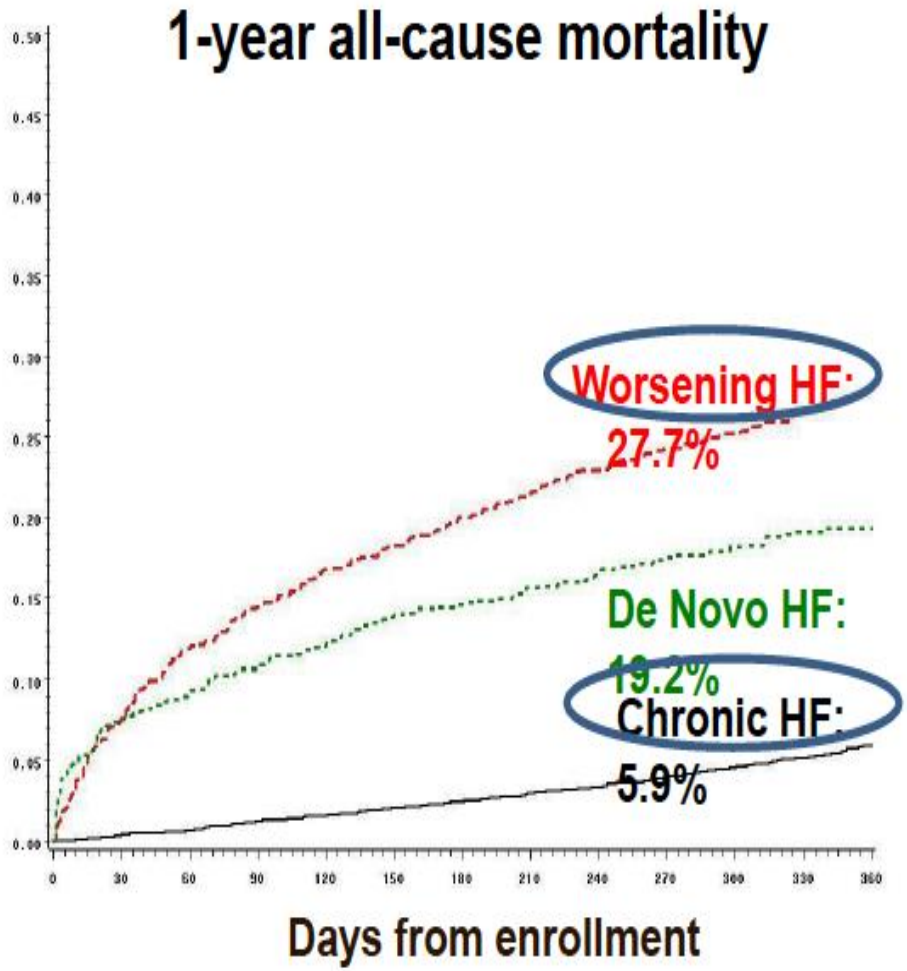
Heart failure in Southeast Asia: facts and numbers

Proportion of the population living with heart failure in individual countries across the globe

Adapted from: Carolyn S.P. Lam, ESC Heart Failure 2015; 2: 46–49

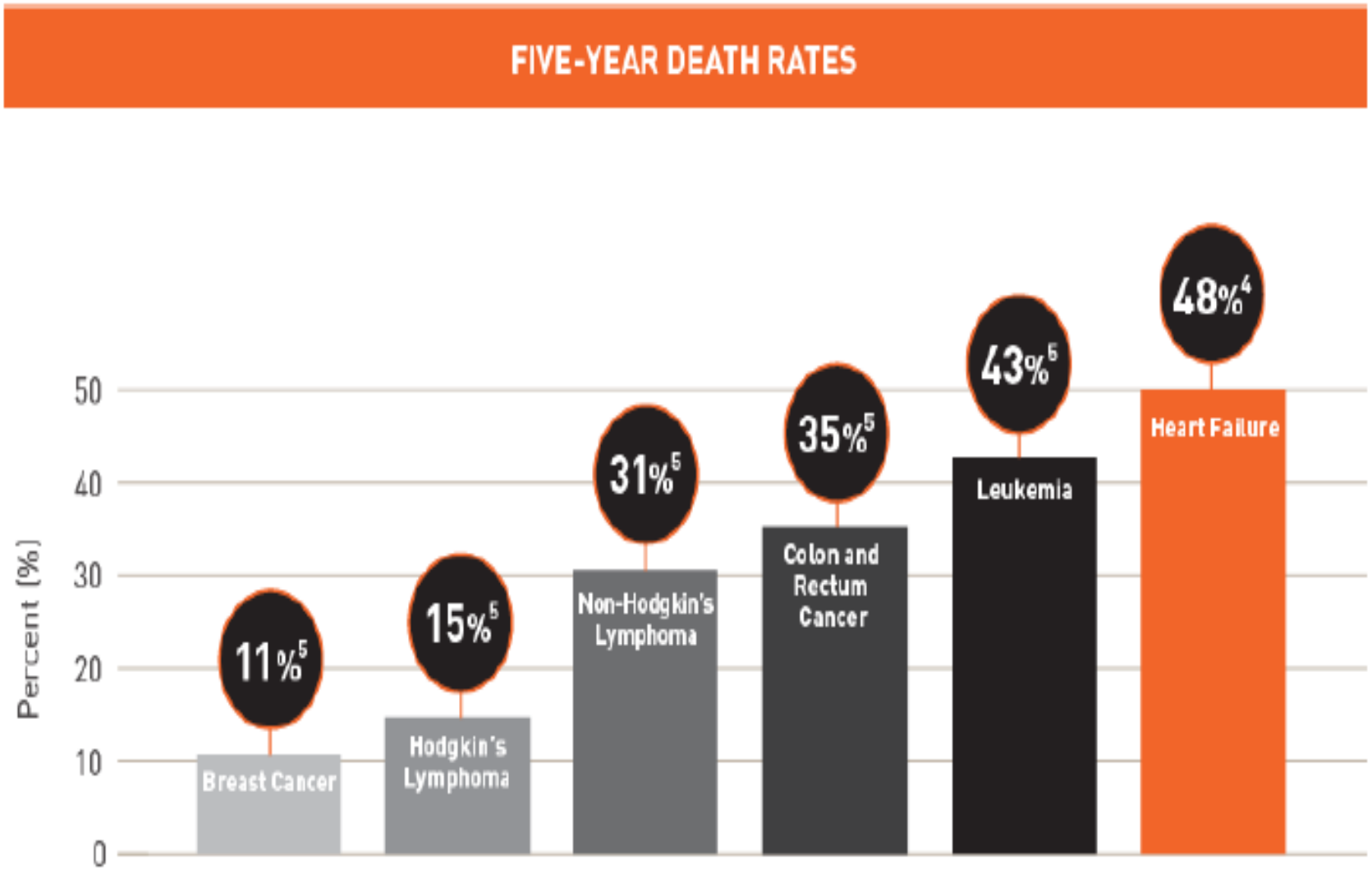
- **Prevalence of HF in Southeast Asian countries is higher compared with countries in the rest of the world (4.5–6.7% vs. 0.5–2% respectively)**
- **Southeast Asian patients present with acute HF at a younger age (54 years) compared with USA patients (75 years) but**
  - have more severe clinical features, higher rates of mechanical ventilation,
  - longer lengths of stay (6 vs. 4.2 days) and
  - higher in-hospital mortality (4.8 vs. 3.0%)
- **Under-usage of disease-modifying HF therapies was reported in the ADHERE Asia-Pacific cohort,**
  - with ACEi or ARBs prescribed upon discharge in 63%,
  - β-blockers in 41% and MRAs in 31% of patients.
- **Important inter-ethnic differences exist, wherein Malay patients appear to fare worse than Indian or Chinese patients, for reasons that are poorly understood**

Prognosis of Heart failure



Tavazzi L, et al Circ Heart Fail. 2013;6:473-481.

Heart failure deadlier than many cancers



DIAGNOSING HEART FAILURE

Early detection and intervention is essential

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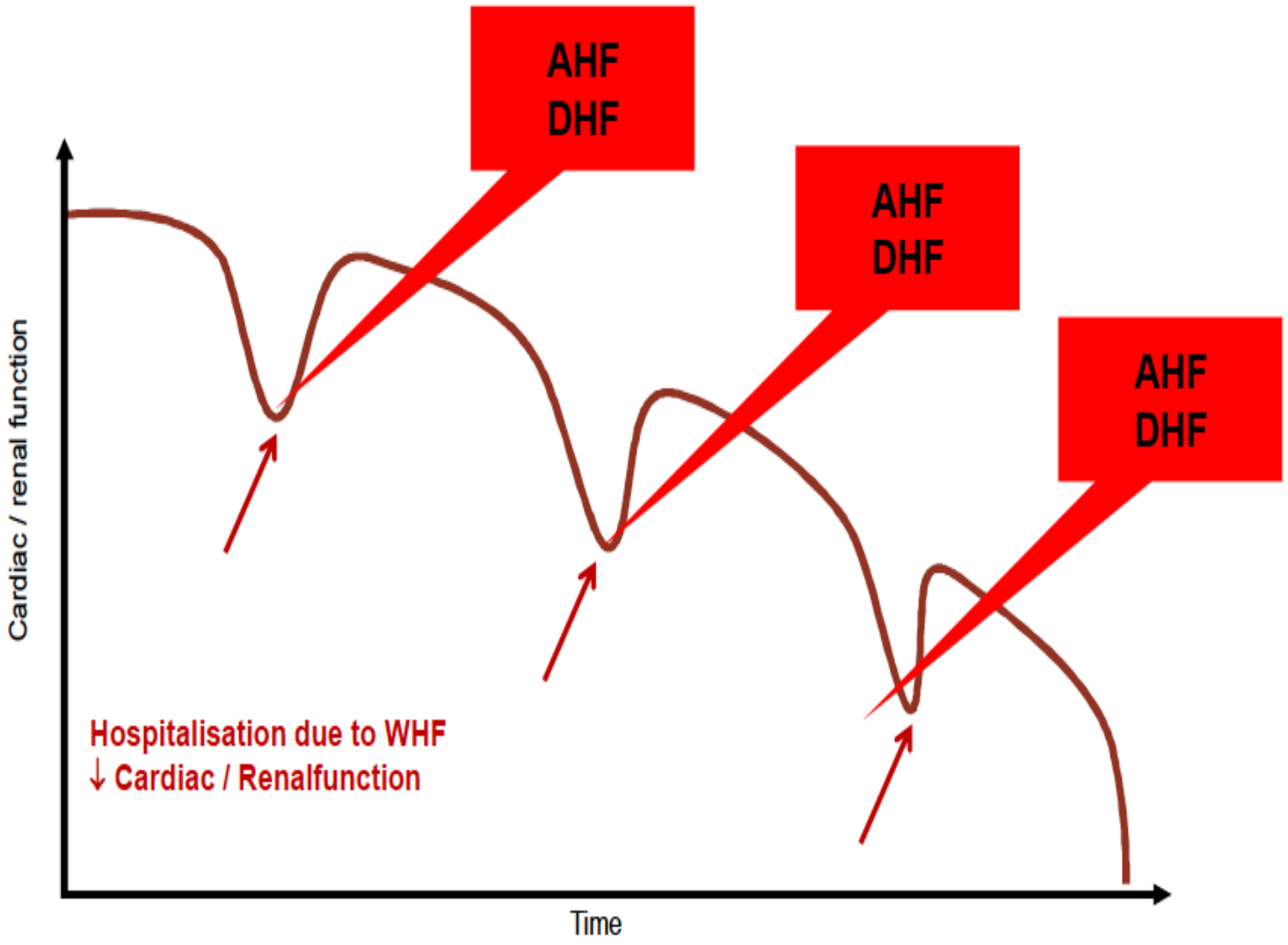
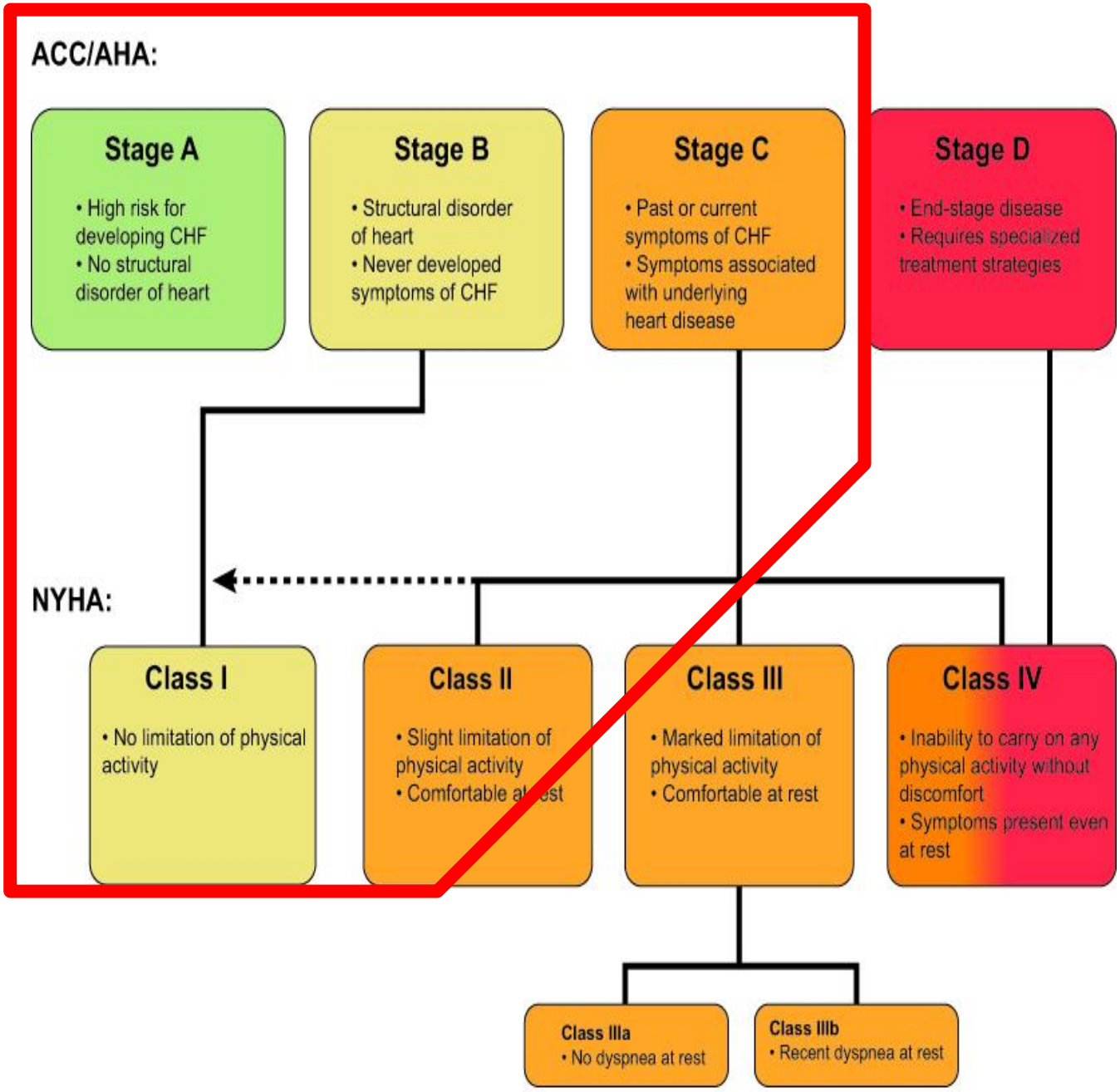
Heart failure is not stable !





GPs see Heart failure at earlier stages, Including the AT RISK PHASE – STAGE A

Symptoms of HF

Symptoms	Signs
Typical	More specific
Breathlessness	Elevated jugular venous pressure
Orthopnea	Hepatojugular reflux
Paroxysmal nocturnal dyspnea	Third heart sound (gallop rhythm)
Reduced exercise tolerance	Laterally displaced apical impulse
Fatigue, tiredness, increased time to recover after exercise	Cardiac murmur
Ankle swelling	
Less typical	Less specific
Nocturnal cough	Peripheral edema (ankle, sacral, scrotal)
Wheezing	Pulmonary crepitations
Weight gain (>2 kg/week)	Reduced air entry and dullness to percussion at lung bases (pleural effusion)
Bloated feeling	Irregular pulse
Confusion (especially in the elderly)	Hepatomegaly
Palpitations	Tissue wasting (cachexia)
Syncope	

Adapted from McMurray JJ, et al. *Eur Heart J.* 2012;33(14):1787-1847.

Suspect HF when…

- Hx of CAD, diabetes, hypertension

- Atrial fibrillation

- Chest infection/URTI that is persistent

- COPD that is deteriorating fast

- Unexplained fatigue or fluid retention in the elderly

Algorithm for Diagnosis of HF

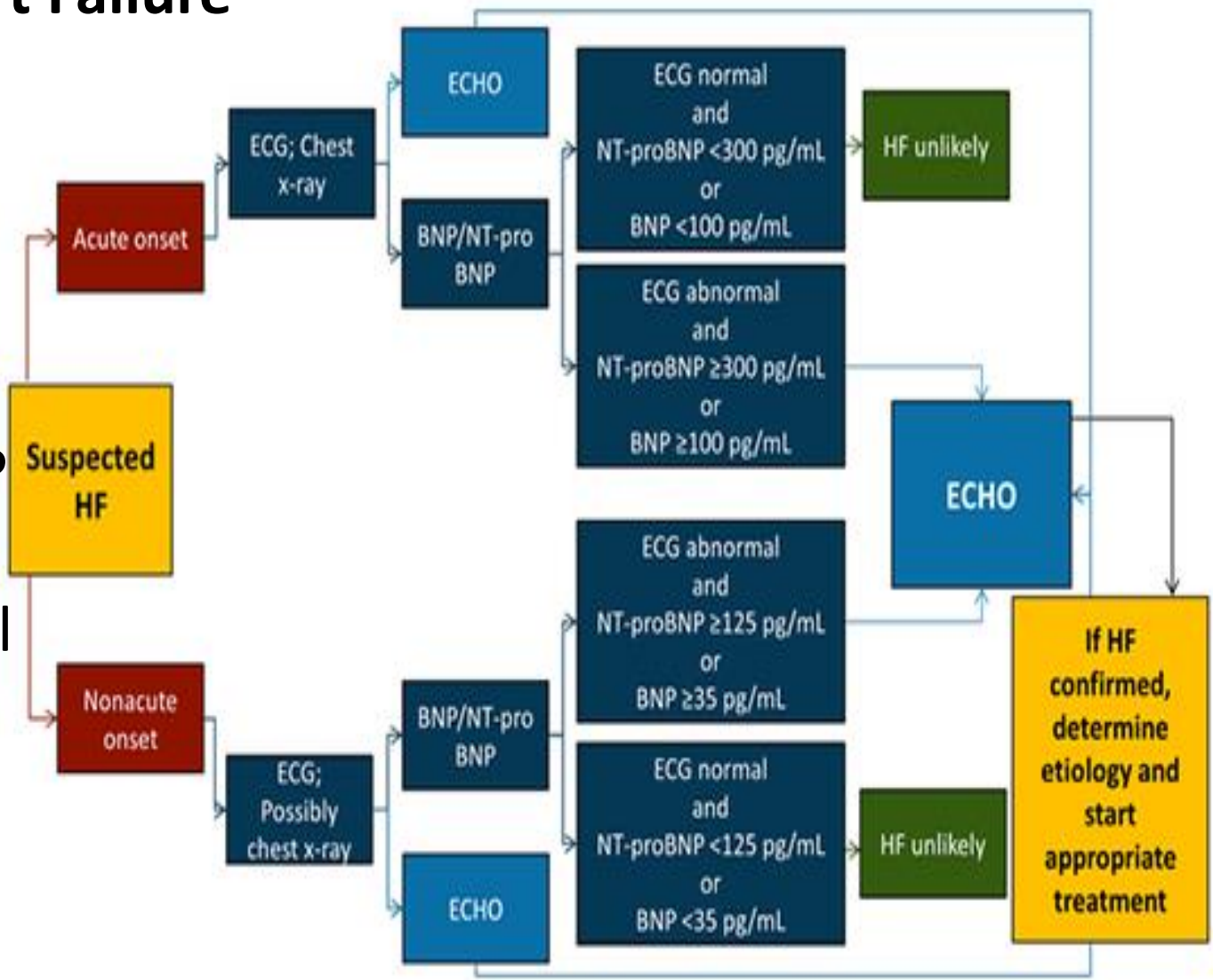
Confirming Heart Failure

ECG

Echo mandatory

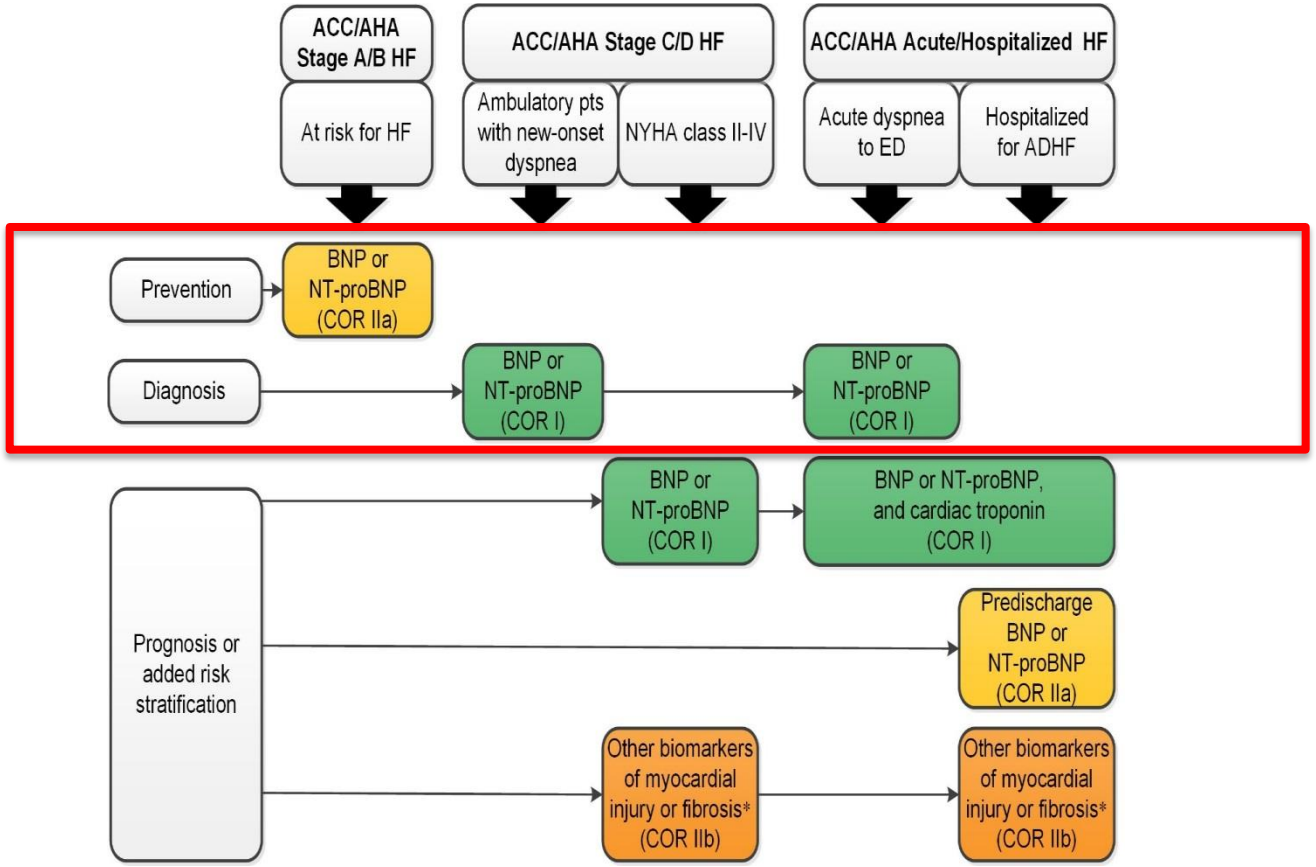
NT-pro BNP/BNP

CXR is less useful



Adapted from McMurray JJ, et al. *Eur Heart J.* 2012;33(14):1787-1847.

Biomarkers Indications for Use



*Other biomarkers of injury or fibrosis include soluble ST2 receptor, galectin-3, and high-sensitivity troponin.

ACC indicates American College of Cardiology; AHA, American Heart Association; ADHF, acute decompensated heart failure; BNP, B-type natriuretic peptide; COR, Class of Recommendation; ED, emergency department; HF, heart failure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; and pts, patients.

Biomarkers

Biomarkers for Diagnosis

COR	LOE	Recommendation	Comment/ Rationale
I	A	In patients presenting with dyspnea, measurement of natriuretic peptide biomarkers is useful to ***support a diagnosis or exclusion of HF.***	MODIFIED: 2013 acute and chronic recommendations have been combined into a diagnosis section.

Biomarkers

Biomarkers for Prognosis or Added Risk Stratification

COR	LOE	Recommendations	Comment/ Rationale
I	A	Measurement of BNP or NT-proBNP is useful for ***establishing prognosis or disease severity in chronic HF.***	2013 recommendation remains current.
I	A	Measurement of baseline levels of natriuretic peptide biomarkers and/or cardiac troponin on admission to the hospital is useful to establish a prognosis in acutely decompensated HF.	MODIFIED: Current recommendation emphasizes that it is admission levels of natriuretic peptide biomarkers th are useful.

MANAGING RISK FACTORS

CAD

Diabetes

Obesity/sleep apnea

Hypertension

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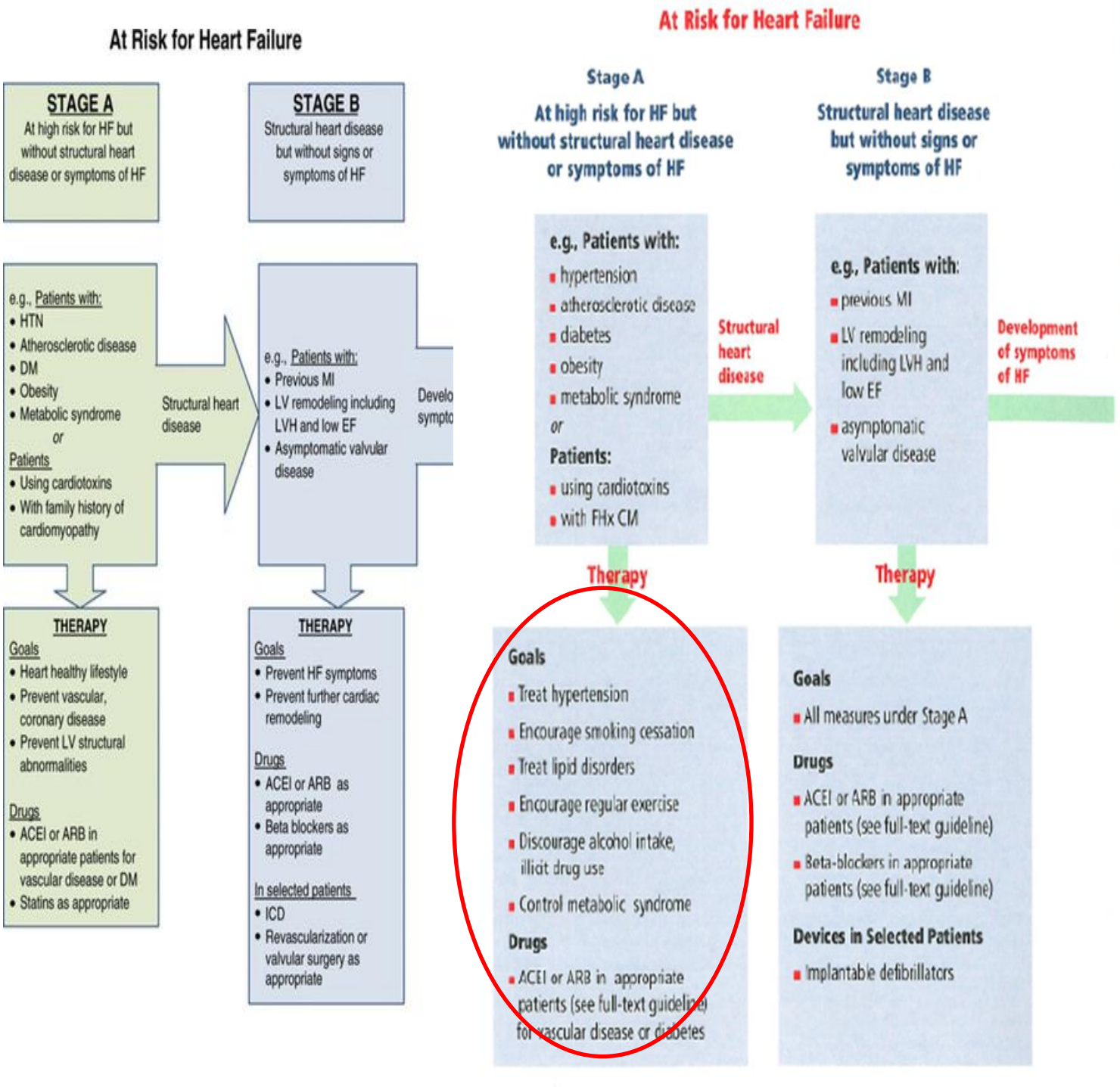

At Risk for Heart Failure
STAGE A
At high risk for HF but without structural heart disease or symptoms of HF
STAGE B
Structural heart disease but without signs or symptoms of HF
e.g., Patients with:
• HTN
• Atherosclerotic disease
• DM
• Obesity
• Metabolic syndrome
or
Patients
• Using cardiotoxins
• With family history of cardiomyopathy
Structural heart disease
e.g., Patients with:
• Previous MI
• LV remodeling including LVH and low EF
• Asymptomatic valvular disease
THERAPY
Goals
• Heart healthy lifestyle
• Prevent vascular, coronary disease
• Prevent LV structural abnormalities
Drugs
• ACEI or ARB in appropriate patients for vascular disease or DM
• Statins as appropriate
THERAPY
Goals
• Prevent HF symptoms
• Prevent further cardiac remodeling
Drugs
• ACEI or ARB as appropriate
• Beta blockers as appropriate
In selected patients
• ICD
• Revascularization or valvular surgery as appropriate
At Risk for Heart Failure
Stage A
At high risk for HF but without structural heart disease or symptoms of HF
Stage B
Structural heart disease but without signs or symptoms of HF
e.g., Patients with:
hypertension
atherosclerotic disease
diabetes
obesity
metabolic syndrome
or
Patients:
using cardiotoxins
with FHx CM
Structural heart disease
e.g., Patients with:
previous MI
LV remodeling including LVH and low EF
asymptomatic valvular disease
Development of symptoms of HF
Therapy
Therapy
Goals
Treat hypertension
Encourage smoking cessation
Treat lipid disorders
Encourage regular exercise
Discourage alcohol intake, illicit drug use
Control metabolic syndrome
Drugs
ACEI or ARB in appropriate patients (see full-text guideline) for vascular disease or diabetes
Goals
All measures under Stage A
Drugs
ACEI or ARB in appropriate patients (see full-text guideline)
Beta-blockers in appropriate patients (see full-text guideline)
Devices in Selected Patients
Implantable defibrillators

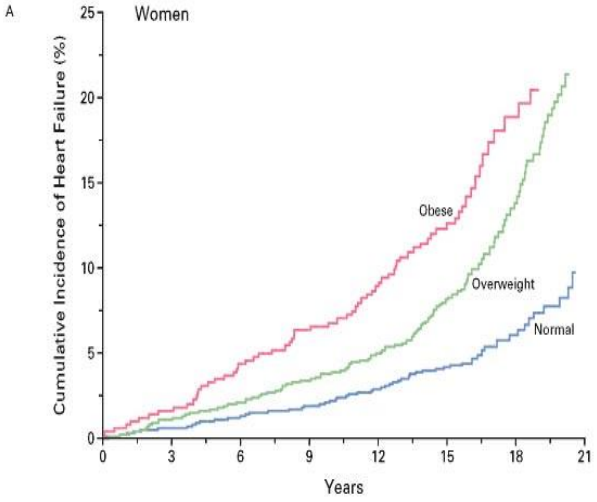
Preventable/Reversible Risk Factors

- Ischemic CMP one of the most common causes of CHF
- Hypertension increased risk of CHF 2-fold in men and 3-fold in women, with a greater impact of the systolic than diastolic blood pressure*
- Diabetes increased CHF risk 2-8 fold with risk ratios twice as large in women as men*

* Corrected for age and other risk factors

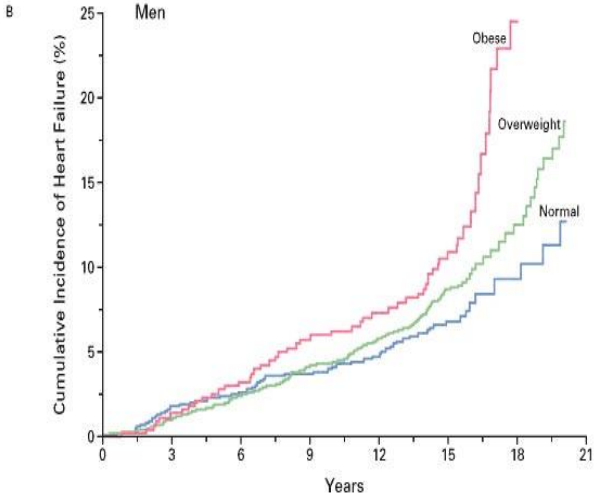
Heart Fail Rev. 2000 Jun;5(2):16

Obesity and heart failure



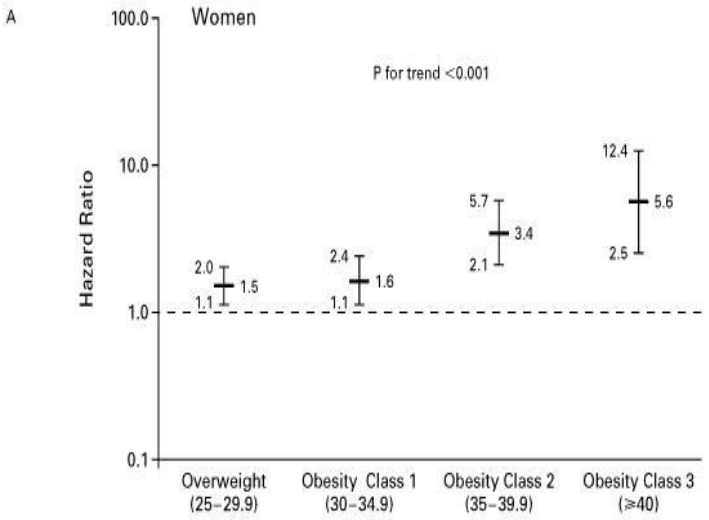
No. at Risk

Normal	1729	1688	1634	1568	1477	1227	295
Overweight	955	929	880	815	757	634	248
Obese	493	477	448	409	372	296	104

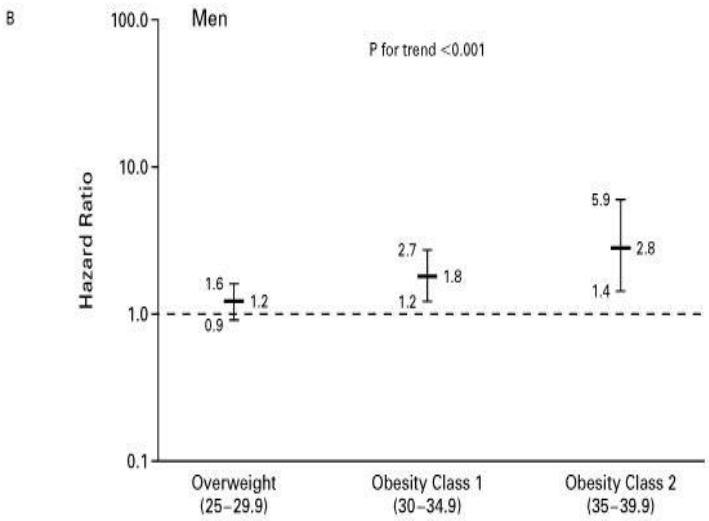


No. at Risk

Normal	869	822	758	690	637	512	105
Overweight	1378	1322	1254	1163	1071	871	171
Obese	457	433	403	370	342	276	51



No. of events	108	40	21	7
No. at risk	955	339	111	43
Person-yr of follow-up	14,232	4909	1540	595



No. of events	125	45	9
No. at risk	1378	391	58
Person-yr of follow-up	19,358	5315	793

Satish Kenchaiah, et al. N Engl J Med 2002; 347:305-

A third of S'poreans 'have sleep apnoea but most are unaware'

Yeo Sam Jo

One in three Singaporeans suffers from moderate to severe obstructive sleep apnoea (OSA), with most of these cases undiagnosed, a recent study has found.

People with this sleep disorder stop breathing repeatedly in their sleep because of a complete or partial blocking in their airway.

This leads to low oxygen levels, which causes symptoms such as daytime fatigue, intellectual impairment and headaches upon waking.

The study by public healthcare group JurongHealth also found that one in 10 Singaporeans has severe sleep apnoea, in which they stop breathing for more than 30 times an hour during slumber.

The study, done between October 2014 and May last year among 250 randomly chosen subjects, was published in the international journal Respirology in March.

Its principal investigator, Dr Adeline Tan, described the high prevalence of the disorder among Singaporeans as worrying. About 90 per cent of the subjects found to have moderate to severe sleep apnoea were unaware of their condition.

Dr Tan, a consultant in respiratory medicine at Ng Teng Fong Hospital, said: "This could be due to low awareness of OSA. The public needs to know the signs so that they or their loved ones know when to seek medical help."

Signs include snoring, choking and gasping during sleep, and frequent urination at night.

Dr Kenny Pang, an ear, nose and throat specialist at Asia Sleep Centre and Mount Elizabeth Hospital, said he diagnoses 30 to 50 cases of sleep apnoea every month.

Patients' airways are blocked because of structural obstructions such as huge tonsils or tongues.

Dr Pang said there has been a huge leap in cases in the past decade, partly due to increased awareness of the condition.

"There is also an increased prevalence in obesity, a risk factor of the disorder," he noted, adding that over half of his sleep apnoea patients are obese or overweight. Those who are obese have more fat in the neck, which extends into their pharynx, or part of the throat, he explained.

Dr Tan's study also showed that Chinese and Malays here have higher rates of moderate to severe OSA, with their estimated population prevalence hitting 32.1 per cent and 33.8 per cent respectively.

Dr Pang said this is partly genetic. "Asians in general have small jaws. When the face is narrow, the tongue has no space in the jaw and falls backwards during sleep, blocking the airway," he said.

Experts said that if left untreated, the condition could lead to hypertension, heart failure, poor job or academic performance and even an increased risk of traffic accidents.

There are three treatment options: surgery of the blocked air passage, wearing an oral appliance to pull out the lower jaw during sleep, or sleeping with a Continuous Positive Airway Pressure (CPAP) machine. This compresses atmospheric air and forces it into the airway through a facial or nasal mask.

Losing weight and avoiding smoking and alcohol help, said Dr Pang.

Sales manager Kenny Tang, 39, was diagnosed with sleep apnoea a year ago. "My wife and reservist bunk mates would say, 'You're not snoring, you're roaring.' "

He removed his left tonsil as it was so huge that it blocked half of his airway. His doctor also said he has a big tongue and small jaw.

Mr Tang, who is overweight, now sleeps with a CPAP machine. "I used to doze off when looking at my laptop in the office. Now I'm not so tired any more."

yeosamjo@sph.com.sg

Sleep apnoea in Singapore

1 in 3
have moderate to severe sleep apnoea

1 in 10
have severe sleep apnoea

Prevalence of moderate to severe sleep apnoea by race

Chinese
32.1%

Malay
33.8%

Indian
16.5%

Top disorders that sleep apnoea patients may have

- Drug-resistant hypertension
- Obesity
- Congestive heart failure
- Type 2 diabetes

Source: JURONGHEALTH
STRAITS TIMES GRAPHICS

Hypertension

Treating Hypertension to Reduce the Incidence of HF

COR	LOE	Recommendations	Comment/ Rationale
I	B-R	In patients at increased risk, ***stage A HF, the optimal blood pressure in those with hypertension should be less than 130/80 mm Hg***.	NEW: Recommendation reflects new RCT data.

Hypertension

Treating Hypertension in Stage C HF*r*EF

COR	LOE	Recommendations	Comment/ Rationale
I	C-EO	Patients with ***HFrEF and hypertension*** should be prescribed GDMT titrated to attain systolic blood pressure less than 130 mm Hg.	NEW: Recommendation has been adapted from recent clinical trial data but not specifically tested per se in a randomized trial of patients wi HF.

Hypertension

Treating Hypertension in Stage C HF*p*EF

COR	LOE	Recommendations	Comment/ Rationale
I	C-LD	Patients with ***HFpEF and persistent hypertension*** after management of volume overload should be prescribed GDMT titrated to attain systolic blood pressure less than 130 mm Hg.	NEW: New target goal blood pressure based on updated interpretation of recent clinical trial data.

Anemia

COR	LOE	Recommendations	Comment/ Rationale
IIb	**B-R**	In patients with NYHA class II and III HF and iron deficiency (ferritin <100 ng/mL or 100 to 300 ng/mL if transferrin saturation is <20%), intravenous iron replacement might be reasonable to	NEW: New evidence consistent with therapeutic benefit.
III: No Benefit	**B-R**	Improve functional status and QoL.	NEW: Current recommendation reflects new evidence demonstrating absence of therapeutic benefit.

In patients with HF and anemia, erythropoietin-stimulating agents should not be used to improve morbidity and mortality.

INITIATING TREATMENT

Evidence based pharmacotherapies

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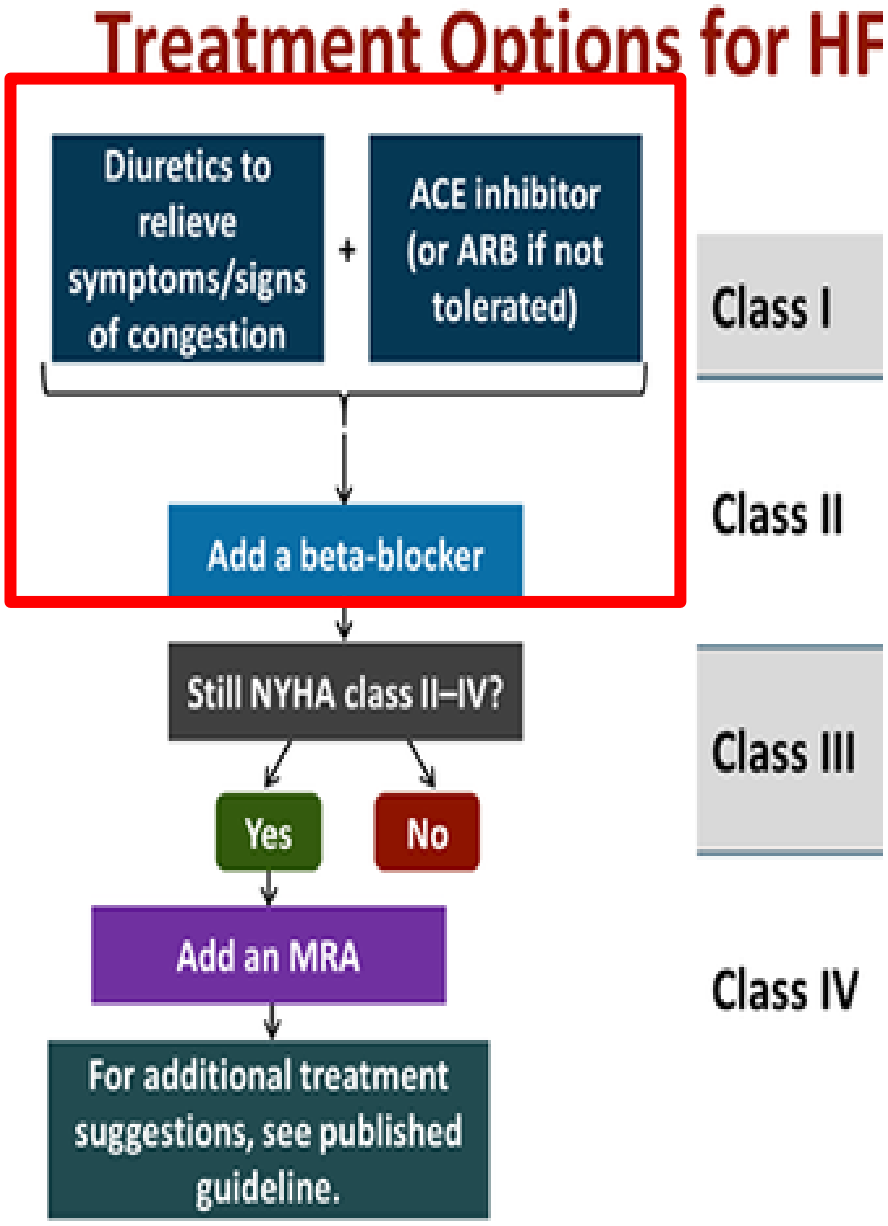
Established Benefits of Guideline-Recommended HF Therapies

Guideline Recommended Therapy	Relative Risk Reduction in Mortality	Number Needed to Treat for Mortality	NNT for Mortality (standardized to 36 months)	Relative Risk Reduction in HF Hospitalizations
ACEI/ARB	17%	22 over 42 months	26	31%
Beta-blocker	34%	28 over 12 months	9	41%
Aldosterone Antagonist	30%	9 over 24 months	6	35%
Hydralazine/Nitrate	43%	25 over 10 months	7	33%
CRT	36%	12 over 24 months	8	52%
ICD	23%	14 over 60 months	23	NA

Fonarow GC, et al. Am Heart J 2011;161:1024-1030.



Adapted from McMurray JJ, et al. *Eur Heart J.* 2012;33(14):1787-1847.

Starting Tips

Start BB and ACEI at lowest doses

Increase every 2 weeks

Use BB proven for CHF – Bisoprolol, Carvedilol and Metoprolol

When initiating ACE/ARB, Cr may increase Between 20-30%

Stop only if causing symptomatic hypotensio
Or sig. hyperkalemia

Lower dose if needed rather than stopping i

Lower doses work better than one alone

MRA: mineralocorticoid receptor anta

Titrating to therapeutic doses

Drug	Initial Daily Dose(s)	Maximum Doses(s)	Mean Doses Achieved in Clinical Trials
ACE Inhibitors			
Captopril	6.25 mg 3 times	50 mg 3 times	122.7 mg/d (421)
Enalapril	2.5 mg twice	10 to 20 mg twice	16.6 mg/d (412)
Fosinopril	5 to 10 mg once	40 mg once	---------
Lisinopril	2.5 to 5 mg once	20 to 40 mg once	32.5 to 35.0 mg/d (444)
Perindopril	2 mg once	8 to 16 mg once	---------
Quinapril	5 mg twice	20 mg twice	---------
Ramipril	1.25 to 2.5 mg once	10 mg once	---------
Trandolapril	1 mg once	4 mg once	---------
ARBs			
Candesartan	4 to 8 mg once	32 mg once	24 mg/d (419)
Losartan	25 to 50 mg once	50 to 150 mg once	129 mg/d (420)
Valsartan	20 to 40 mg twice	160 mg twice	254 mg/d (109)
Aldosterone Antagonists			
Spironolactone	12.5 to 25 mg once	25 mg once or twice	26 mg/d (424)
Eplerenone	25 mg once	50 mg once	42.6 mg/d (445)

Very often Under dosed

Fear of Adverse events

Manageable with careful monitoring, starting lower with progressive increments

Titrating to therapeutic doses

Drug	Initial Daily Dose(s)	Maximum Doses(s)	Mean Doses Achieved in Clinical Trials
Beta Blockers			
Bisoprolol	1.25 mg once	10 mg once	8.6 mg/d (118)
Carvedilol	3.125 mg twice	50 mg twice	37 mg/d (446)
Carvedilol CR	10 mg once	80 mg once	---
Metoprolol succinate extended release (metoprolol CR/XL)	12.5 to 25 mg once	200 mg once	159 mg/d (447)
Hydralazine & Isosorbide Dinitrate			
Fixed dose combination (423)	37.5 mg hydralazine/ 20 mg isosorbide dinitrate 3 times daily	75 mg hydralazine/ 40 Mg isosorbide dinitrate 3 times daily	~175 mg hydralazine/90 mg isosorbide dinitrate daily
Hydralazine and isosorbide dinitrate (448)	Hydralazine: 25 to 50 mg, 3 or 4 times daily and isorsorbide dinitrate: 20 to 30 mg 3 or 4 times daily	Hydralazine: 300 mg daily in divided doses and isosorbide dinitrate 120 mg daily in divided doses	---

NEWER DRUG THERAPIES

3 drugs

- Entresto (Sacubitril/Valsartan)
- Coralan (Ivabradine)
- Jardiance (Empagliflozin)

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European Heart Journal
doi:10.1093/eurheartj/ehw128

ESC GUIDELINES

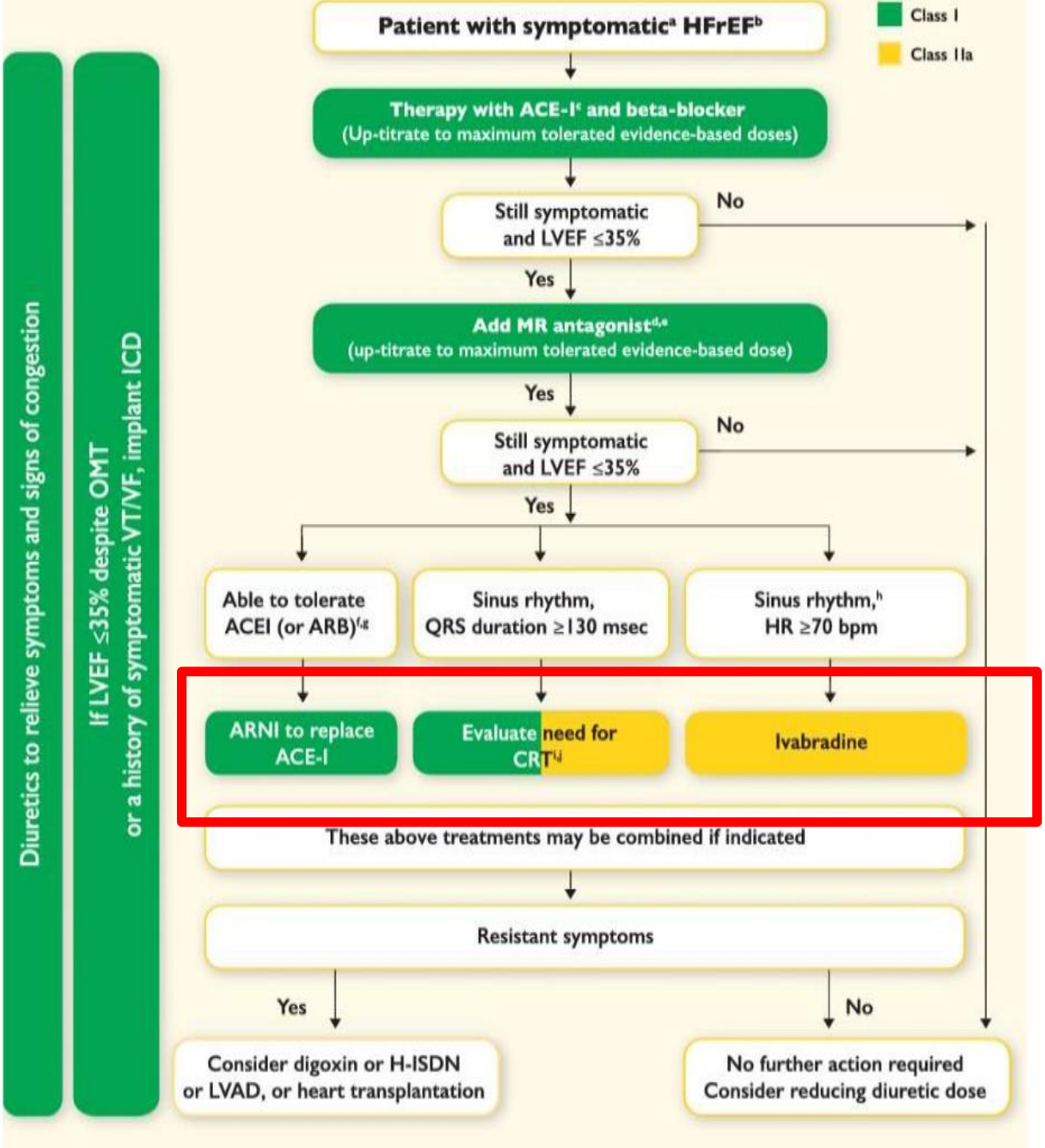
2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

Developed with the special contribution of the Heart Failure Association (HFA) of the ESC

Authors/Task Force Members: Piotr Ponikowski* (Chairperson) (Poland), Adriaan A. Voors* (Co-Chairperson) (The Netherlands), Stefan D. Anker (Germany), Héctor Bueno (Spain), John G. F. Cleland (UK), Andrew J. S. Coats (UK), Volkmar Falk (Germany), José Ramón González-Juanatey (Spain), Veli-Pekka Harjola (Finland), Ewa A. Jankowska (Poland), Mariell Jessup (USA), Cecilia Linde (Sweden), Petros Nihoyannopoulos (UK), John T. Parissis (Greece), Burkert Pieske (Germany), Jillian P. Riley (UK), Giuseppe M. C. Rosano (UK/Italy), Luis M. Ruilope (Spain), Frank Ruschitzka (Switzerland), Frans H. Rutten (The Netherlands), Peter van der Meer (The Netherlands)

Ponikowski P, et *al*. Eur J Heart Fail 2016 & EHJ 2016 (online available)


Class I
Class IIa
Patient with symptomatic[a] HFrEF[b]
Therapy with ACE-I[c] and beta-blocker
(Up-titrate to maximum tolerated evidence-based doses)
Still symptomatic and LVEF ≤35%
No
Yes
Add MR antagonist[d,e]
(up-titrate to maximum tolerated evidence-based dose)
Yes
Still symptomatic and LVEF ≤35%
No
Yes
Able to tolerate ACEI (or ARB)[f,g]
Sinus rhythm, QRS duration ≥130 msec
Sinus rhythm,[h] HR ≥70 bpm
ARNI to replace ACE-I
Evaluate need for CRT[i,j]
Ivabradine
These above treatments may be combined if indicated
Resistant symptoms
Yes
No
Consider digoxin or H-ISDN or LVAD, or heart transplantation
No further action required
Consider reducing diuretic dose
Diuretics to relieve symptoms and signs of congestion
If LVEF ≤35% despite OMT or a history of symptomatic VT/VF, implant ICD

Therapeutic algorithm for a patient with symptomatic HF with reduced ejection fraction

- **ESC-HF guidelines provide strong Class I recommendation for sacubitril/valsartan**
- **Endorsement showing in section 7.3.2 of 2016 Guidelines, discussed in light of PARADIGM-HF**

Pharmacological treatments indicated in patients with symptomatic (NYHA Class II-IV) HFrEF

Recommendations	Class	Level
An **ACEi** is recommended, in addition to a beta blocker, for symptomatic patients with HFrEF to reduce the risk of HF hospitalization and death	I	A
A **beta blocker** is recommended, in addition an ACEi, for patients with stable, symptomatic HFrEF to reduce the risk of HF hospitalization and death	I	A
An **MRA** is recommended for patients with HFrEF, who remain symptomatic despite treatment with an ACEi and a beta-blocker, to reduce the risk of HF hospitalization and death	I	A
Sacubitril/valsartan is recommended as a **replacement for an ACEi** to further reduce the risk of HF hospitalization and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACEi, a beta-blocker and an MRA*	I	B

Estb. Rx

**Patient should have elevated natriuretic peptides (plasma BNP ≥150 pg/mL or plasma NT-proBNP ≥600 pg/mL, or if HF hospitalization within the last 12 months, plasma BNP ≥100 pg/mL or plasma NT-proBNP ≥400 pg/mL) and able to tolerate enalapril 10 mg b.i.d.*

Therapeutic algorithm for a patient with symptomatic HF with reduced ejection fraction

CLASS (STRENGTH) OF RECOMMENDATION

CLASS I (STRONG) — Benefit >>> Risk

Suggested phrases for writing recommendations:
- Is recommended
- Is indicated/useful/effective/beneficial
- Should be performed/administered/other
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is recommended/indicated in preference to treatment B
  - Treatment A should be chosen over treatment B

LEVEL (QUALITY) OF EVIDENCE‡

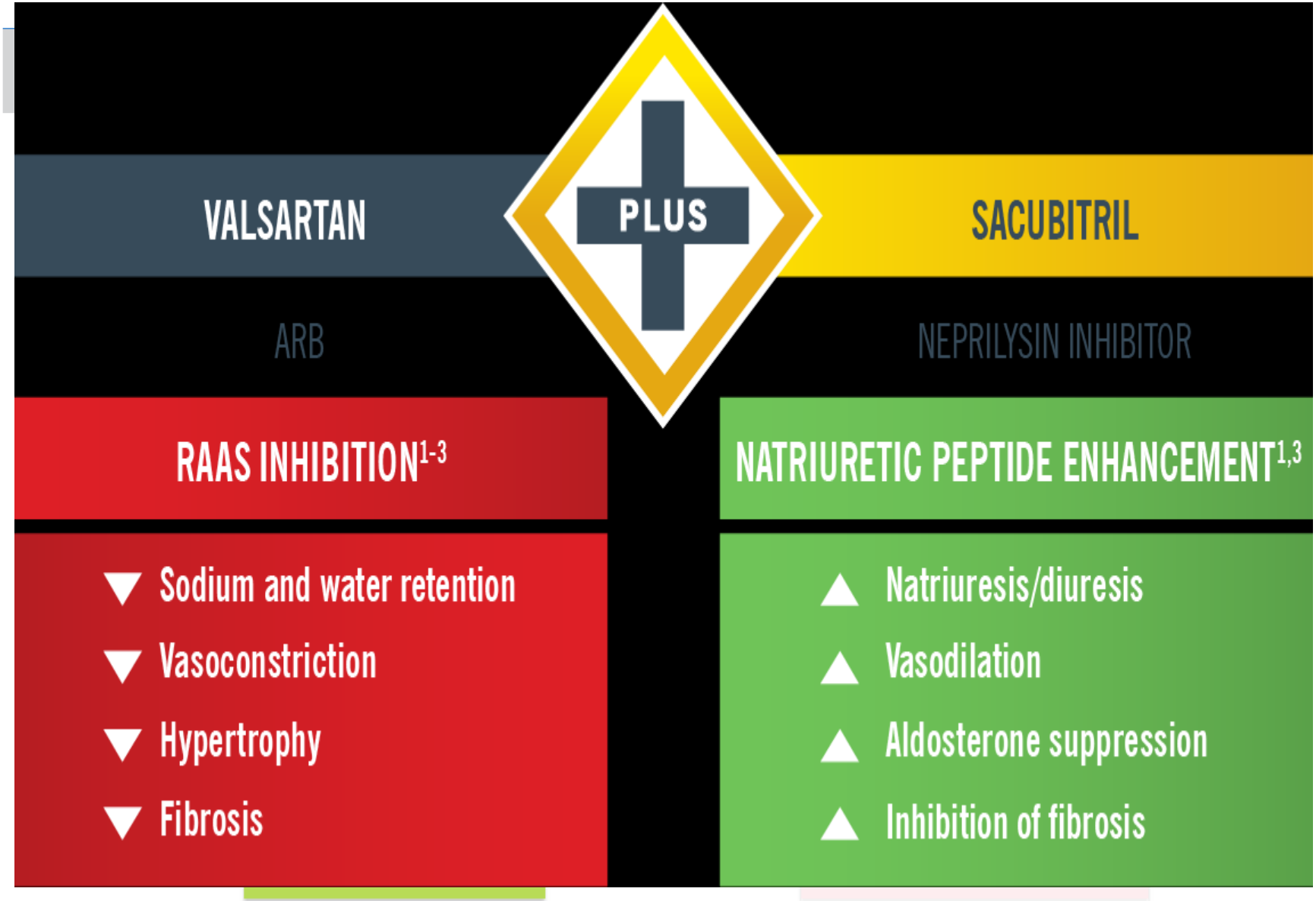
LEVEL A
- High-quality evidence‡ from more than 1 RCT
- Meta-analyses of high-quality RCTs
- One or more RCTs corroborated by high-quality registry studies

LEVEL B-R (Randomized)
- Moderate-quality evidence‡ from 1 or more RCTs
- Meta-analyses of moderate-quality RCTs

Recommendations for Renin-Angiotensin System Inhibition With ACE Inhibitor or ARB or ARNI		
COR	LOE	Recommendations
I	ACE: A ARB: A ARNI: B-R	The clinical strategy of inhibition of the renin-angiotensin system with ACE inhibitors *(Level of Evidence: A)* (9-14), OR ARBs *(Level of Evidence: A)* (15-18), OR ARNI *(Level of Evidence: B-R)* (19) in conjunction with evidence-based beta blockers (20-22), and aldosterone antagonists in selected patients (23, 24), is recommended for patients with chronic HF*r*EF to reduce morbidity and mortality.
I	ARNI: B-R	In patients with chronic symptomatic HF*r*EF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality (19).

Mechanism of Action (MoA)

ARNI – angiotensin receptor neprilysin inhibitor

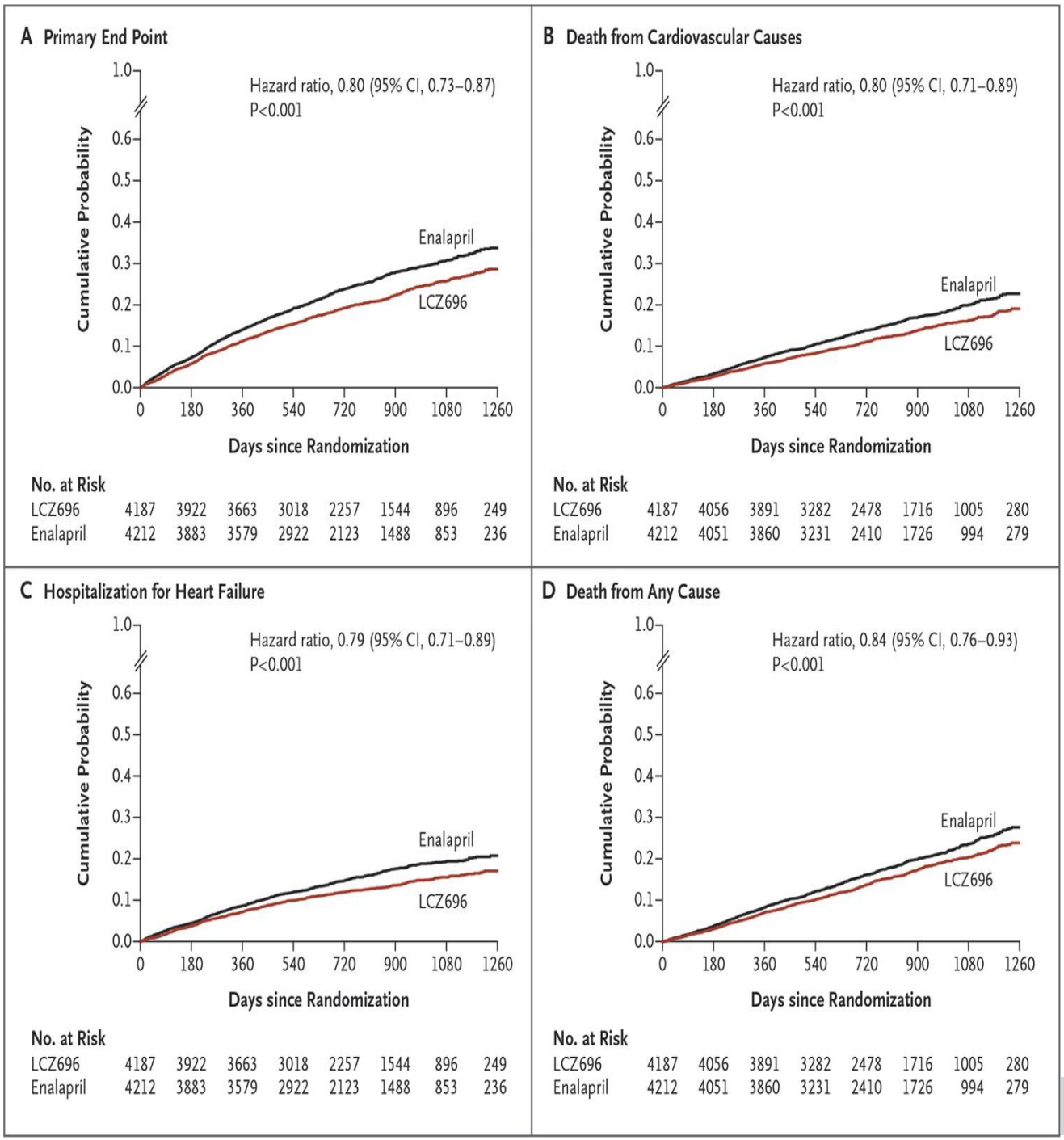


PARADIGM-HF

Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure

A multi-center, randomized, double-blind, parallel-group, active-controlled study to evaluate the efficacy and safety of ENTRESTO® compared with enalapril on morbidity and mortality in patients with chronic HF and reduced ejection fraction

McMurray et al. New Engl J Med 2014;371:993–1004



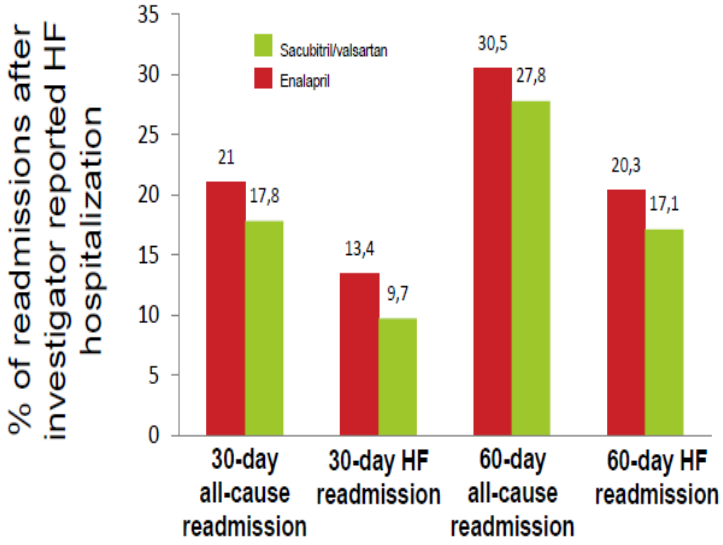
20% reduction in composite e

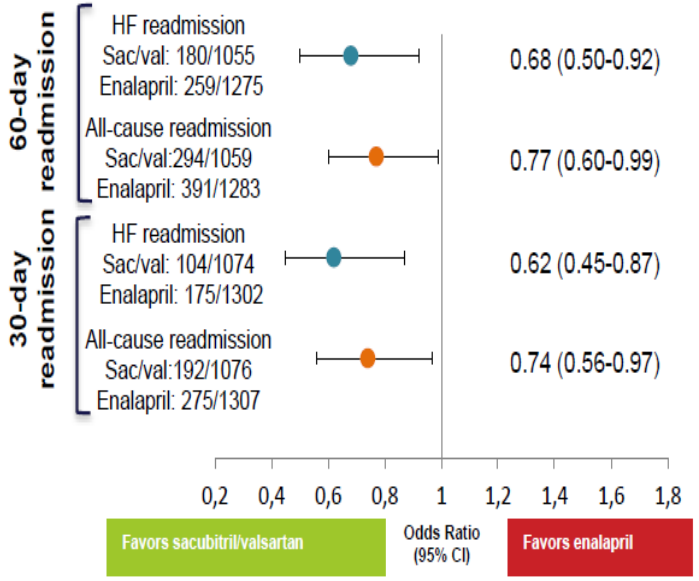
Sig. reductions in CV death, a
Death and hospitalization for

Compared with Enalapril!!

McMurray et al. New Engl J Med 2014;371:993–1004

LCZ 696 significantly reduced the rates of all-cause and HF readmissions compared with enalapril





- readmission for any cause at 30 days (p=0.031)
- readmission for HF at 30 days (p=0.006)
- all-cause (p-0.045) and HF readmission (p=0.01) at 60 days

Desai et al., J Am Coll Cardiol. 2016;68(3):241-8

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

ABSTRACT

BACKGROUND

The effects of empagliflozin, an inhibitor of sodium–glucose cotransporter 2, in addition to standard care, on cardiovascular morbidity and mortality in patients with type 2 diabetes at high cardiovascular risk are not known.

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Recommendations to prevent or delay the development of overt heart failure or prevent death before the onset of symptoms

Recommendations	Class[a]	Level[b]	Ref[c]
Treatment of hypertension is recommended to prevent or delay the onset of HF and prolong life.	I	A	126, 129, 150, 151
Treatment with statins is recommended in patients with or at high-risk of CAD whether or not they have LV systolic dysfunction, in order to prevent or delay the onset of HF and prolong life.	I	A	137–140, 152
Counselling and treatment for smoking cessation and alcohol intake reduction is recommended for people who smoke or who consume excess alcohol in order to prevent or delay the onset of HF.	I	C	131–134
Treating other risk factors of HF (e.g. obesity, dysglycaemia) should be considered in order to prevent or delay the onset of HF.	IIa	C	130, 141, 153–155
Empagliflozin should be considered in patients with type 2 diabetes in order to prevent or delay the onset of HF and prolong life.	IIa	B	130

Heart failure outcomes and all-cause hospitalization

Outcome	Placebo (N=2333)		Empagliflozin (N=4687)		HR (95% CI)	p-value
	n (%)	Rate/1000 pt-years	n (%)	Rate/1000 pt-years		
Heart failure hospitalisation or CV death	198 (8.5)	30.1	265 (5.7)	19.7	0.66 (0.55–0.79)	<0.001
Hospitalisation for or death from heart failure	104 (4.5)	15.8	129 (2.8)	9.6	0.61 (0.47–0.79)	<0.001
Hospitalisation for heart failure	95 (4.1)	14.5	126 (2.7)	9.4	0.65 (0.50–0.85)	0.002
Investigator-reported heart failure*	143 (6.1)	22.0	204 (4.4)	15.3	0.70 (0.56–0.87)	0.001
Investigator-reported serious heart failure*†	136 (5.8)	20.9	192 (4.1)	14.4	0.69 (0.55–0.86)	0.001
All-cause hospitalisation	925 (39.6)	183.3	1725 (36.8)	161.9	0.89 (0.82–0.96)	0.003

Patients treated with at least one dose of study drug.
CI, confidence interval; HR, hazard ratio; MedDRA, Medical Dictionary for Regulatory Activities.
*Based on narrow standardised MedDRA query "cardiac failure".
†Adverse events reported as serious adverse events by investigator.

2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America

Developed in Collaboration With the International Society for Heart and Lung Transplantation

Recommendation for Ivabradine		
COR	LOE	Recommendation
IIa	B-R	Ivabradine can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II-III) stable chronic HF*r*EF (LVEF ≤35%) who are receiving GDEM, including a beta blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of 70 bpm or greater at rest (37-40).

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Other pharmacological treatments recommended in selected patients with symptomatic (NYHA Class II-IV) failure with reduced ejection fraction

Recommendations	Class [a]	Level [b]
Diuretics		
Diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion.	I	B
Diuretics should be considered to reduce the risk of HF hospitalization in patients with signs and/or symptoms of congestion.	IIa	B
Angiotensin receptor neprilysin inhibitor		
Sacubitril/valsartan is recommended as a replacement for an ACE-I to further reduce the risk of HF hospitalization and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACE-I, a beta-blocker and an MRA[d]	I	B
I*f*-channel inhibitor		
Ivabradine should be considered to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm despite treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose below that), ACE-I (or ARB), and an MRA (or ARB).	IIa	B
Ivabradine should be considered to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm who are unable to tolerate or have contra-indications for a beta-blocker. Patients should also receive an ACE-I (or ARB) and an MRA (or ARB).	IIa	C
ARB		
An ARB is recommended to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients unable to tolerate an ACE-I (patients should also receive a beta-blocker and an MRA).	I	B
An ARB may be considered to reduce the risk of HF hospitalization and death in patients who are symptomatic despite treatment with a beta-blocker who are unable to tolerate an MRA.	IIb	C

Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial

Main results

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

Effect of Ivabradine on outcomes

Endpoints	Hazard ratio	95% CI	p value
Primary composite endpoint (CV death or hospital admission for worsening HF)	**0.82**	[0.75;0.90]	p<0.0001
All-cause mortality	**0.90**	[0.80;1.02]	p=0.092
Death from heart failure	**0.74**	[0.58;0.94]	p=0.014
All-cause hospital admission	**0.89**	[0.82;0.96]	p=0.003
Any CV hospital admission	**0.85**	[0.78;0.92]	p=0.0002
CV death/hospital admission for HF or non-fatal MI	**0.82**	[0.74;0.89]	p<0.0001

2010;376(9744):875-885

Conclusion

Ivabradine significantly reduces major risks associated with heart failure:

- 18% reduction in CV death or hospital admission for worsening HF
- 26% reduction in death from heart failure
- 26% reduction in hospital admission for worsening heart failure

Benefits are apparent early, are consistent in predefined subgroups, and have been demonstrated on top of recommended therapy

Treatment is well tolerated

FOLLOWING UP HEART FAILURE

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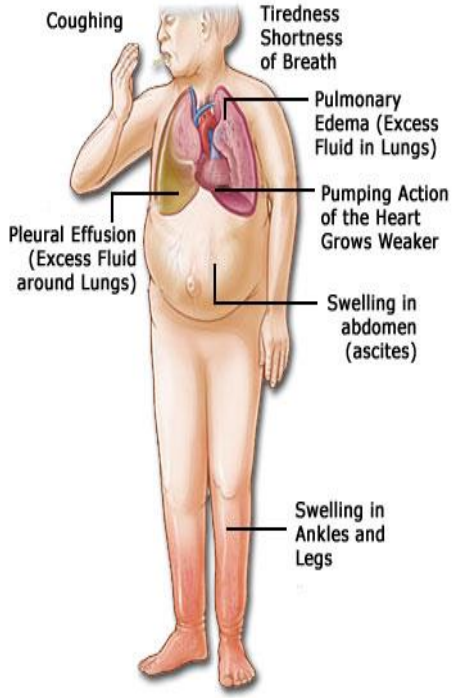
Clinical Events and Findings Useful for Identifying Patients With Advanced HF

Repeated (≥2) hospitalizations or ED visits for HF in the past year
Progressive deterioration in renal function (e.g., rise in BUN and creatinine).
Weight loss without other cause (e.g., cardiac cachexia).
Intolerance to ACE inhibitors due to hypotension and/or worsening renal function.
Intolerance to beta blockers due to worsening HF or hypotension.
Frequent systolic blood pressure <90 mm Hg.
Persistent dyspnea with dressing or bathing requiring rest.
Inability to walk 1 block on the level ground due to dyspnea or fatigue
Recent need to escalate diuretics to maintain volume status, often reaching daily furosemide equivalent dose >160 mg/d and/or use of supplemental metolazone therapy.
Progressive decline in serum sodium, usually to <133 mEq/L.
Frequent ICD shocks.

Adapted from Russell et al. Congest Heart Fail. 2008;14:316-21.

What to assess at each visit



- Functional ability (ADL)
- Volume status and weight
- Use of alcohol, tobacco, illicit drugs, alternative R
- Any new drugs or cardiotoxic drugs
- Dietary/Sodium intake
- Physical activity level

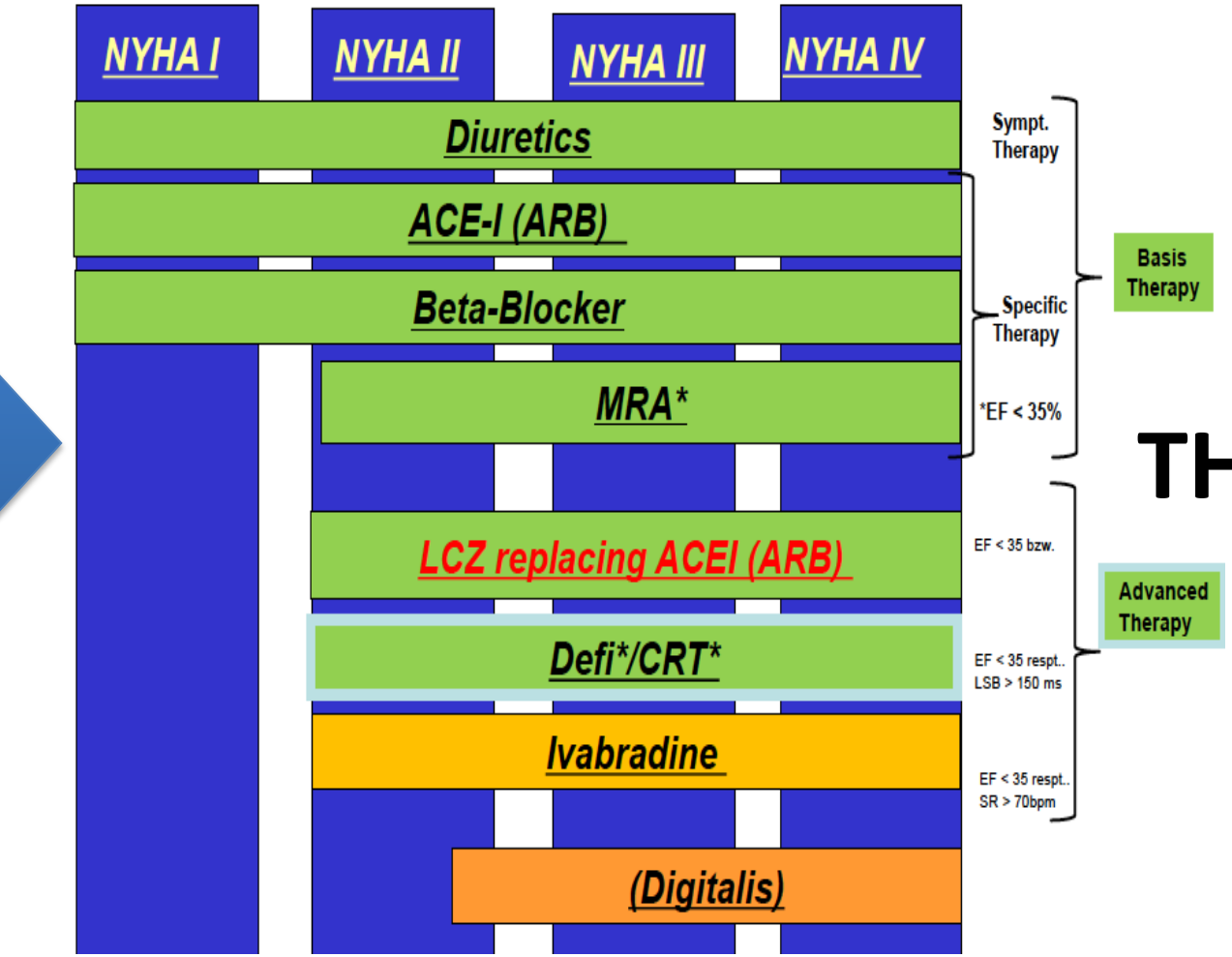
- Any change in clinical status -
  - New Symptoms or findings (e.g. AF, arrhythmias, L[illegible]
  - Recent new clinical event or change in treatment
  - Consider a follow-up echocardiogram to assess left ventricular ejection fraction and structural remodelling

Drugs to take precautions

- NSAIDS, including COX2 inhibitors
- Non-dihydropyridine CCBs
- Some antiarrhythmic – flecainide, dronec
- TCA – may prolong QT and cause arrhyth
- Thiazolidinediones (TZDs) – fluid retentic
- Corticosteroids
- Oncology drugs
- Note: Over the counter medications may also worsen CHF, decongestants, cough mixture, constipation meds.

- Appropriate preventative care includes pneumococcal vaccination and annual influenza vaccination.

Basis – CHF Therapy 2017



Preventive measures focusing on risk factors

Identify early, appropriate use of medications and aggressive lifestyle modification (at times with help of structured lifestyle

THE END

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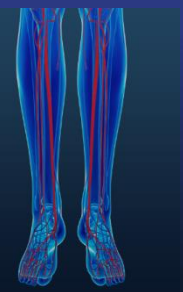
Intervention and Best Medical Therapy

Complementary partners in Carotid and Peripheral Arterial

Dr Sriram Narayanan

Senior Consultant Vascular and Endovascular Surgeon



To intervene or not to intervene

- Driven by perception, passion, pay check
- Selective use of published evidence
- Fear and misinformation of condition and its treatments
- Test if you can't treat – investigating to no avail

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The carotid and peripheral plaque - Cheese and Chalk

Carotid is embolic, Peripheral is occlusive arterial disease

- Softer plaques with lipid core, high inflammatory content in Carotid

  Fibro-calcific plaque, lower lipid and inflammatory content in Femoral
- Clear centre calcification in Carotid

  Sheet-like, nodular calcification and osteoid metaplasia in Femoral

Fanny Herisson, Marie-Françoise Heymann, Maud Chétiveaux, Céline Charrier, Séverine Battaglia, et al.. Carotid and femoral atherosclerotic plaques show different morphology.: Patterns of Peripheral Arterial Disease. Atherosclerosis, Elsevier, 2011, 216 (2), pp.348-54

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Plaque biology - implications for management

Carotid is embolic, Peripheral is occlusive arterial disease

- Inflammatory plaques responds better to systemic medical therapy
- Fibro-calcific plaque respond better to local mechanical therapy
- Plaque biology determines responses to angioplasty, remodelling, stents and drug elution
- Outcomes must look at appropriate end points over the long term
- Atherosclerosis is a systemic disease – so look at systemic outcomes too

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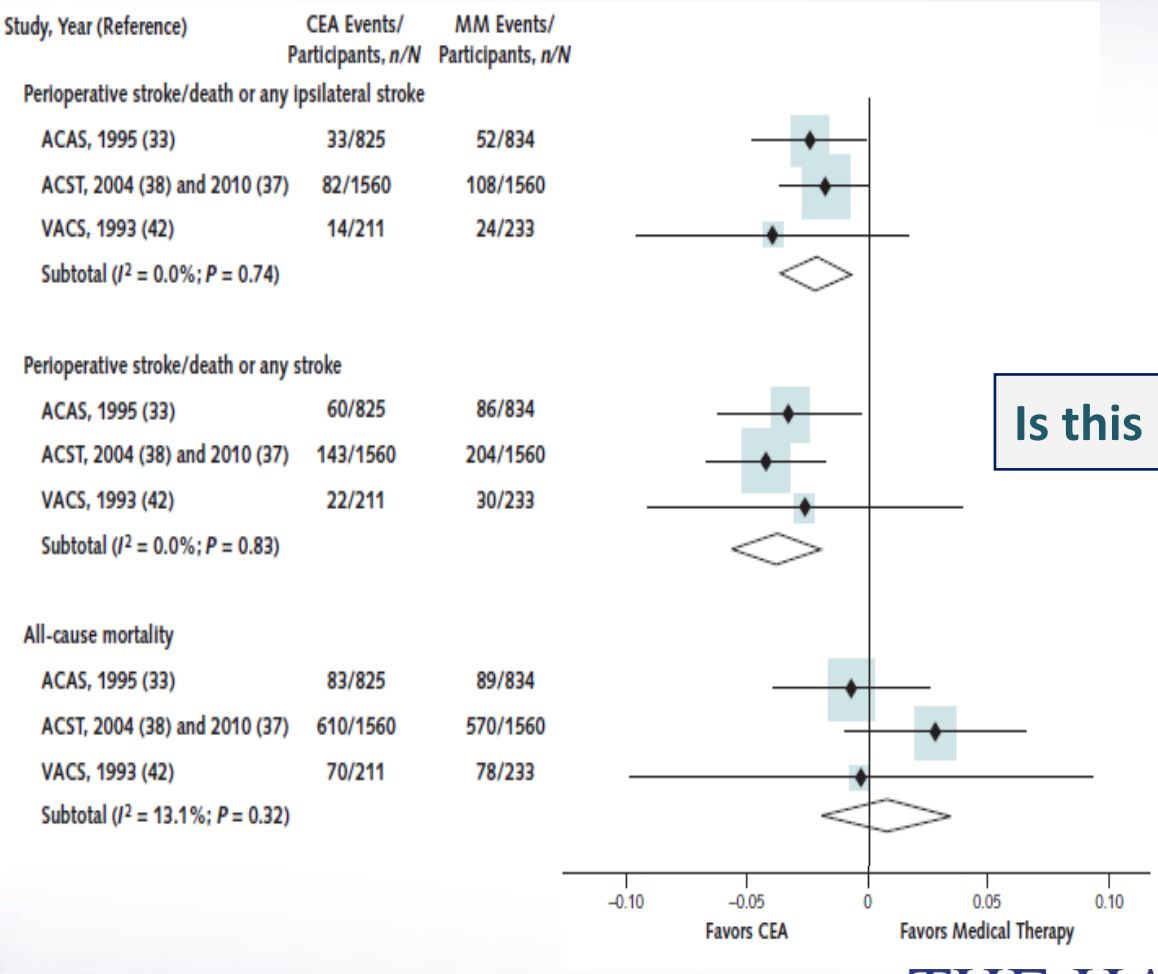
Re-visiting carotid intervention data



Is this historical data still valid ??

*Jonas DE, Feltner C, Amick HR, Sheridan S, Zheng ZJ, Watford DJ, et al. Screening for asymptomatic carotid artery stenosis: a systematic review and meta-analysis for the U.S. Preventive Services Task Force. Ann Intern Med. 2014;161:336-346.

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Re-visiting carotid intervention data

(Negative value = CEA favored)	Difference between CEA and Medical Rx	95% CI
Perioperative stroke/death or subsequent ipsilateral stroke	-2.0	-3.3 to -0.7
Perioperative stroke/death or any subsequent stroke	-3.5	-5.1 to -1.8
All-cause mortality	1.0	-2.0 to 3.0
Any stroke or death	-2.7	-5.1 to -0.3
Ipsilateral stroke (nonoperative)	-4.1	-5.4 to -2.7
Perioperative stroke/death	1.9	

Is this historical data still valid ??

DJ, et al. Screening for asymptomatic carotid artery stenosis: a systematic review and meta-analysis for the U.S. Preventive Services Task Force. Ann Intern Med. 2014;161:336-346.

What was missed in the historical data

- **Control of hypertension**
  - Each 10mmHg drop in BP decreases stroke risk by 33%
- **Smoking cessation**
  - Current smokers RR 4
  - Ex-smokers RR 1.7

*Lawes CM, Bennett DA, Feigin VL, Rodgers A. Blood pressure and stroke: an overview of published reviews. Stroke. 2004;35:776-785.
*Wannamethee SG, Shaper AG, Whincup PH, Walker M. Smoking cessation and the risk of stroke in middle-aged men. JAMA. 1995;274:155-160.

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What was missed in the historical data – lipid lowering therapy

- **LDL**
  - Stroke risk drops >15% for each 10% drop in LDL
- **Statins**
  - Decrease risk 15-30%

*Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, et al; Cholesterol Treatment Trialists' (CTT)
Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis
of data from 90,056 participants in 14 randomised trials of statins. Lancet. 2005;366:1267-1278.
*Bucher HC, Griffith LE, Guyatt GH. Effect of HMGcoA reductase inhibitors on stroke. A meta-
analysis of randomized, controlled trials. Ann Intern Med. 1998;128:89-95.
*Amarenco P, Bogousslavsky J, Callahan A 3rd, Goldstein LB, Hennerici M, et al; Stroke Prevention

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What was missed in the historical data – Anti-platelets

- No studies in asymptomatic patients
- Multiple studies show benefit for symptomatic carotid disease
- AHA/ASA/USPSTF recommends ASA for men > 45 women > 55 w/ >3% anticipated cardiac morbidity

E.g.

Carotid stenosis

*Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE,et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. N Engl J Med. 2006;354:1706-1717.
*Collaborative overview of randomised trials of antiplatelet therapy--I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. Antiplatelet Trialists' Collaboration. BMJ. 1994;308:81-106.
*Diener HC, Bogousslavsky J, Brass LM, Cimminiello C, Csiba L, Kaste M,et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic

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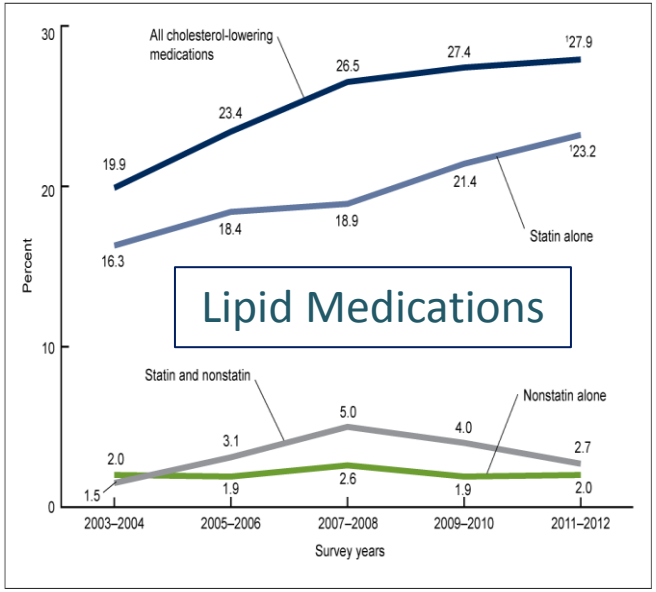
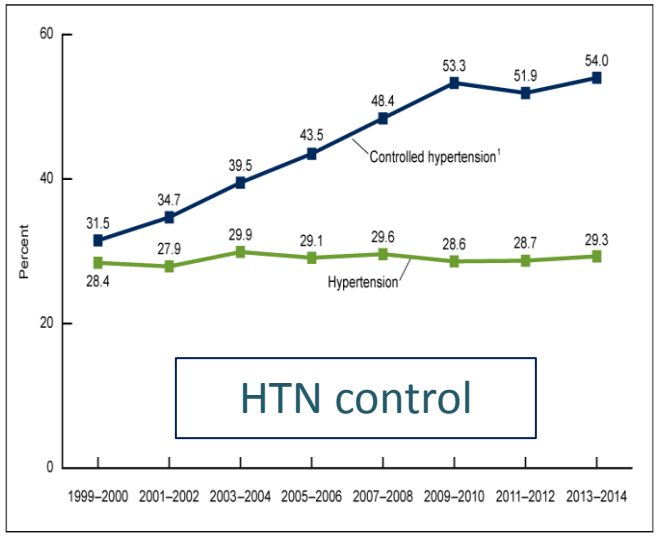
Changing risk factor landscape

Figure 1. Percentage of adults aged 40 and over who reported using a prescription cholesterol-lowering medication: United States, 2003–2012

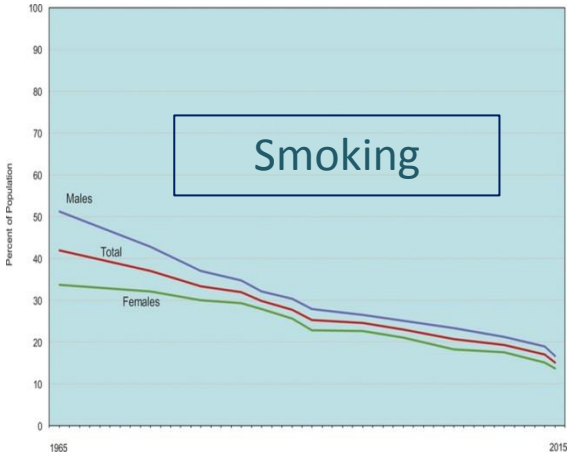


¹Significant linear trend ($p < 0.01$).
NOTE: Age-adjusted by direct method to the year 2000 projected U.S. population.
SOURCE: CDC/NCHS, National Health and Nutrition Examination Survey, 2003–2012.

Figure 5. Age-adjusted trends in hypertension and controlled hypertension among adults aged 18 and over: United States, 1999–2014



¹Significant increasing linear trend, $p < 0.0001$.
NOTES: Hypertension estimates are age-adjusted by the direct method to the 2000 U.S. census population using age groups 18–39, 40–59, and 60 and over; see reference 9. Controlled hypertension estimates are age-adjusted by the direct method using computed weights based on the subpopulation of persons with hypertension in the 2007–2008 National Health and Nutrition Examination Survey; see reference 7.
SOURCE: CDC/NCHS, National Health and Nutrition Examination Survey, 2011–2014.



*Gu Q, Paulose-Ram R, Burt VL, Kit BK. Prescription cholesterol-lowering medication use in adults aged 40 and over: United States, 2003–2012. NCHS data brief, no 177. Hyattsville, MD: National Center for Health Statistics. 2014.

*Yoon SS, Fryar CD, Carroll MD. Hypertension prevalence and control among adults: United States, 2011–2014. NCHS data brief, no 220. Hyattsville, MD: National Center for Health Statistics. 2015.

*Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, et al; American

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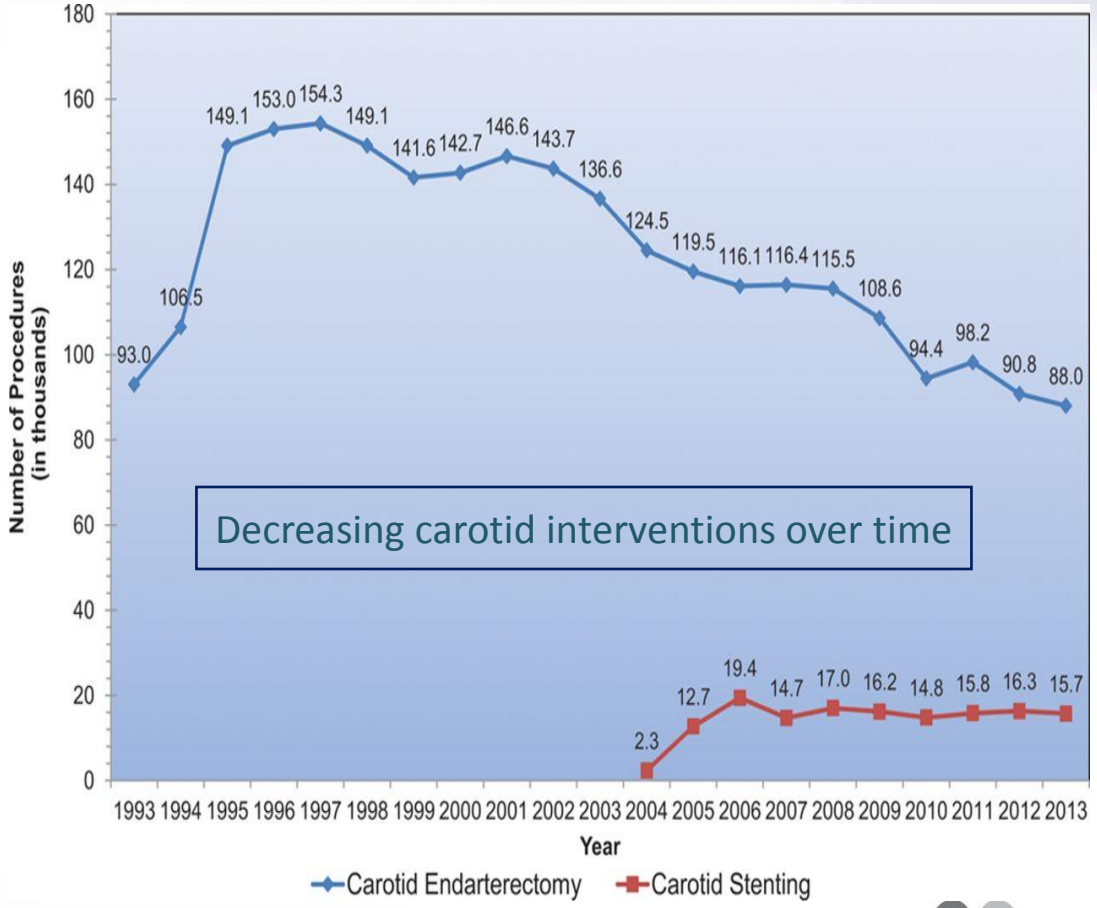
Minimally invasive may be maximally damaging

- **ACT**
  - CAS 2.9% vs CEA 1.7%
- **CREST**
  - CAS 2.5% vs CEA 1.4%



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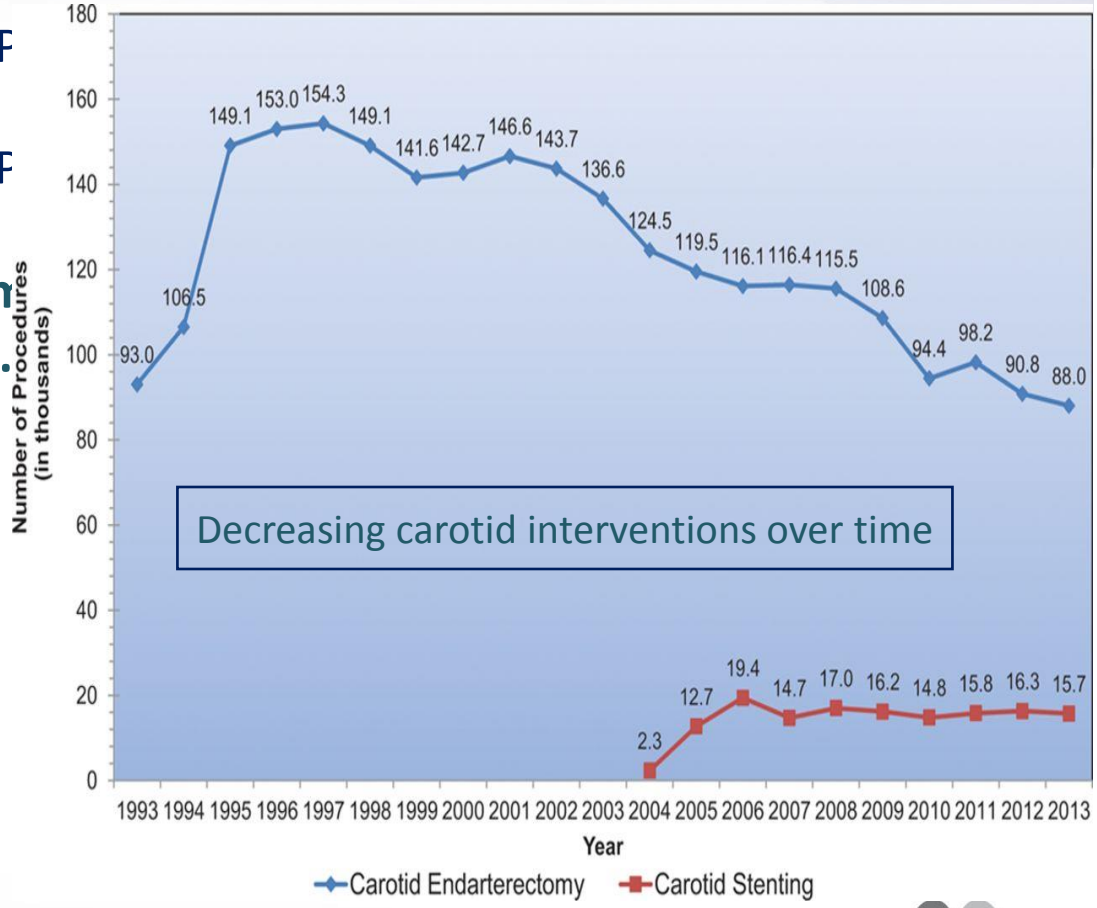
*Rosenfield K, Matsumura JS, Chaturvedi S, Riles T, Ansel GM, et al; ACT I Investigators. Randomized Trial of Stent versus Surgery for Asymptomatic Carotid Stenosis. N Engl J Med. 2016;374:1011-1020.

*Brott TG, Howard G, Roubin GS, Meschia JF, Mackey A, et al; CREST Investigators. Long-Term Results

Non invasive most beneficial ?

- **ACT**
  - CAS 2.9% vs CEA 1.7%
- **CREST**
  - CAS 2.5% vs CEA 1.4%

Annual risk of stroke in asympton
Plaque with 70% stenosis approx.



Decreasing carotid interventions over time

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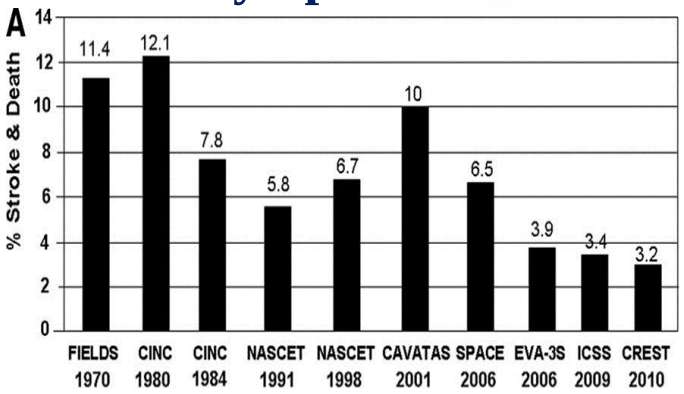
*Rosenfield K, Matsumura JS, Chaturvedi S, Riles T, Ansel GM, et al; ACT I Investigators. Randomized Trial of Stent versus Surgery for Asymptomatic Carotid Stenosis. N Engl J Med. 2016;374:1011-1020.

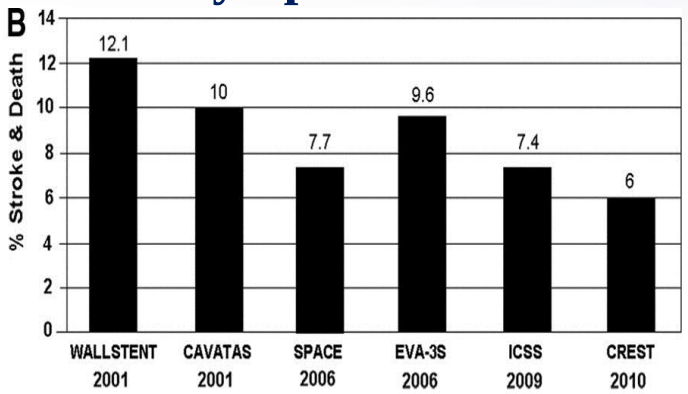
*Brott TG, Howard G, Roubin GS, Meschia JF, Mackey A, et al; CREST Investigators. Long-Term Results

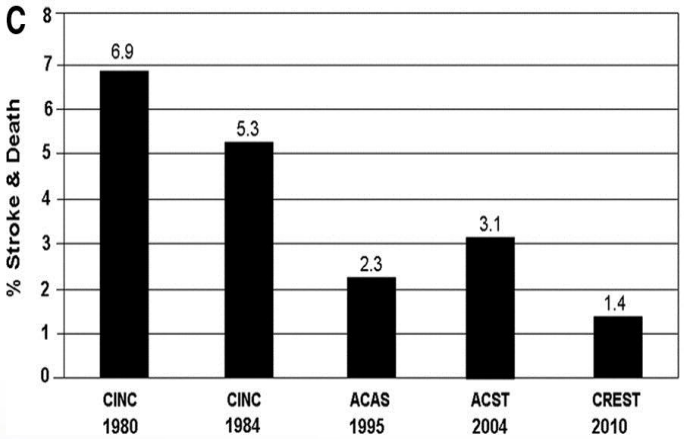
Carotid intervention – CEA and CAS are also improving

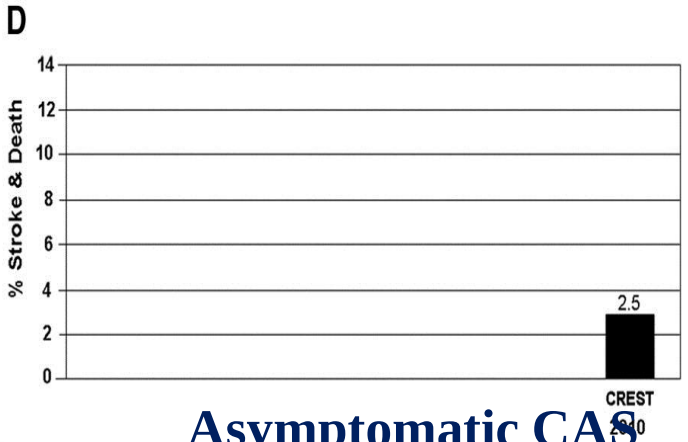
Symptomatic CEA



Symptomatic CAS







Asymptomatic CAS

Asymptomatic CEA

Annual risk of stroke in asymptomatic Plaque with 70% stenosis approx. 0.5%

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*Silver FL, Mackey A, Clark WM, Brooks W, Timaran CH, Chiu D, et al; CREST Investigators. Safety of stenting and endarterectomy by symptomatic status in the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST).

Stroke. 2011 Mar;42(3):675-680. http://stroke.ahajournals.org/content/42/3/675.long

Why screen, who to screen

- Detectable pre-clinical phase - Asx Carotid Stenosis
- Test is inexpensive, accurate - Duplex
- Disease has serious consequences – Stroke, cardiovascular events
- Treatment is more effective prior to symptoms - 85% have CVA w/o antecedent TIA
- Screening determines treatment options - CEA, CAS, Medical Therapy
- Prevalence is high

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The Harley Street Duplex scan

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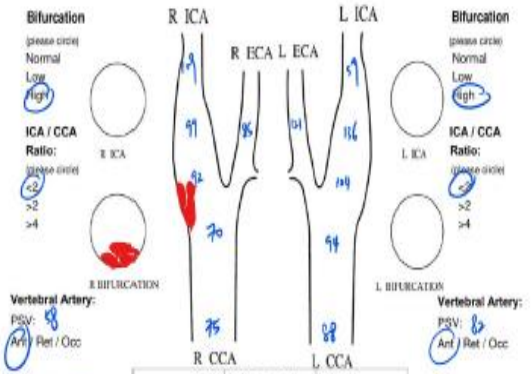
Carotid and Vertebral Duplex Ultrasound Report



RIGHT ICA Stenosis Grading	ICA Stenosis Grading Criteria (NASCET Criteria, Radiology 1998)	LEFT ICA Stenosis Grading
0 - 15%	No plaque (normal) OR Minimal thickening of wall or mild plaque, PSV <125cm/s	0 - 15%
16 - 49%	Moderate plaque, Hemodynamically significant Stenosis, PSV <125 cm/s, ICA/CCA < 2	16 - 49%
50 - 69%	Hemodynamically significant Stenosis, Prominent Plaque, Hemodynamically significant Stenosis, PSV >125cm/s AND EDV >150cm/s OR ICA/CCA >2	50 - 69%
70 - 79%	Subtotal plaque, Hemodynamically significant Stenosis, PSV ≥ 230cm/s OR EDV > 100cms OR ICA/CCA >4	70 - 79%
80 - 99%	AS ABOVE, EDV >140cms, Critical Stenosis	80 - 99%
OCCLUDED	NO Flow, Terminal Stump, Total Plaque	OCCLUDED

Reference - Oates C.P et. al., Joint Recommendations for reporting carotid ultrasound investigations in the United Kingdom (2008), doi:10.1016/j.ejvs.2008.10.015

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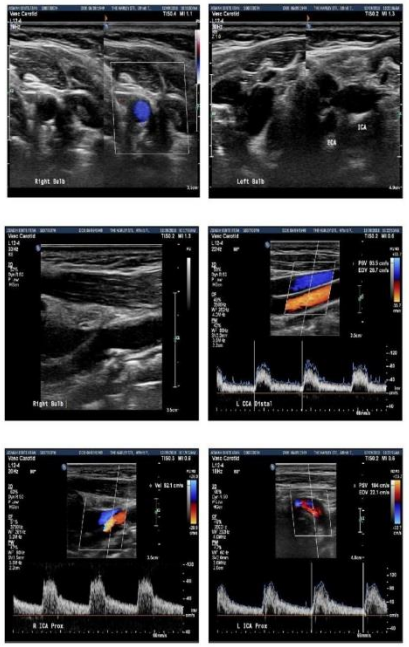
Patient Name	: ASMAH BINTE ATAN	Study Date	: 12 September 2018
NRIC/ID	: S0077007H	Reading Physician	: Dr Sriram Narayanan
Date of Birth	: 06-09-1949	Sonographer	: Yee Jia Ng
Gender / Age	: Female / 69		

IMAGES



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FINDINGS

Marked intimal thickening noted, left worse than right. There has been significant progression in the intimal thickening since July 2017.

On the grayscale images, both common carotid arteries demonstrate patency with normal laminar flow. There is prominent irregular plaque of mixed echogenicity noted in the right carotid bulb. Colour Doppler does not show signal in the echolucent area within the plaque suggesting an intraplaque haemorrhage. This is highly vulnerable in nature. Pansystolic spectral broadening in the proximal internal carotid artery. Peak systolic velocities remain under the acceptable limit of 125cm/s.

No atheromatous plaque in the left carotid bifurcation. The ICA and ECA show normal forward flow on doppler. No pan-systolic broadening with normal PSV.

Patent vertebral arteries with antegrade flow.

IMPRESSION

Sonographic features of a vulnerable plaque in the right carotid bulb.
16-49% Rt ICA stenosis. 0-15% Lt ICA stenosis.

Assessed and written by: Yee Jia Ng
Senior Vascular Sonographer
Accredited by Australian Sonographer Accreditation Registry (ASAR)

Reviewed and approved by: Dr Sriram Narayanan
Senior Consultant Vascular Surgeon
This report has been electronically signed

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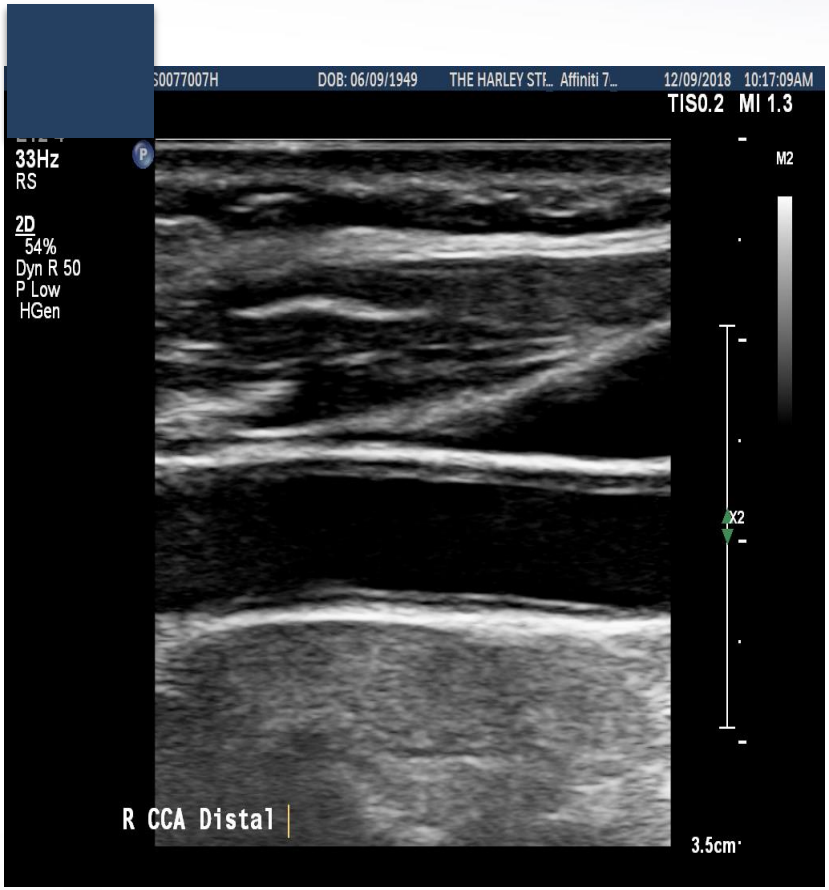
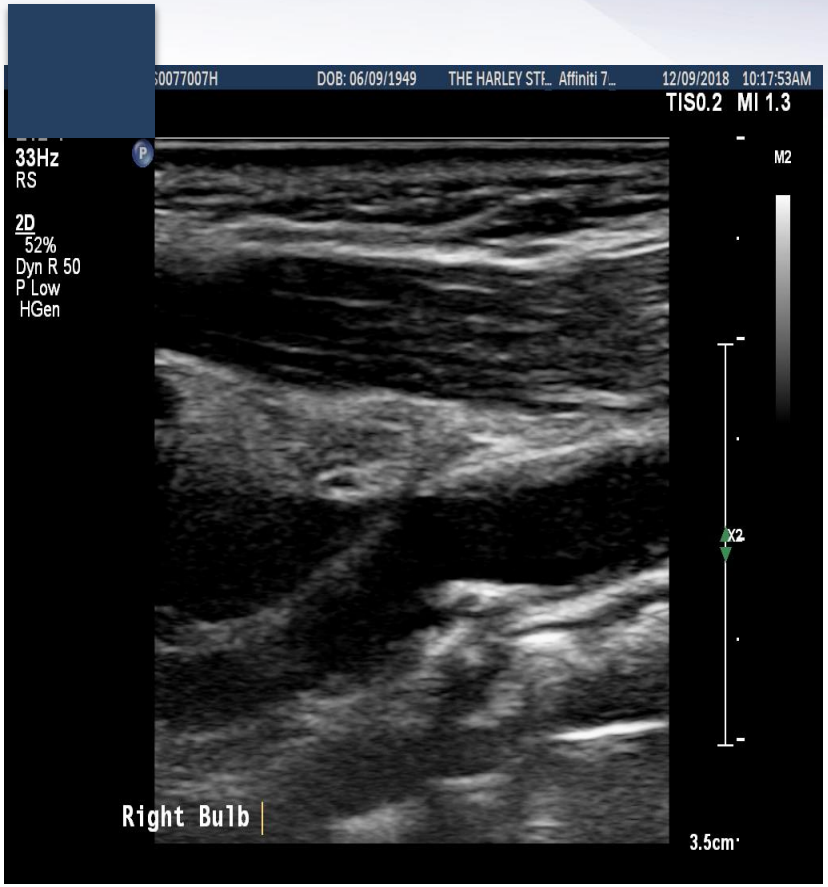
The Harley Street Duplex scan





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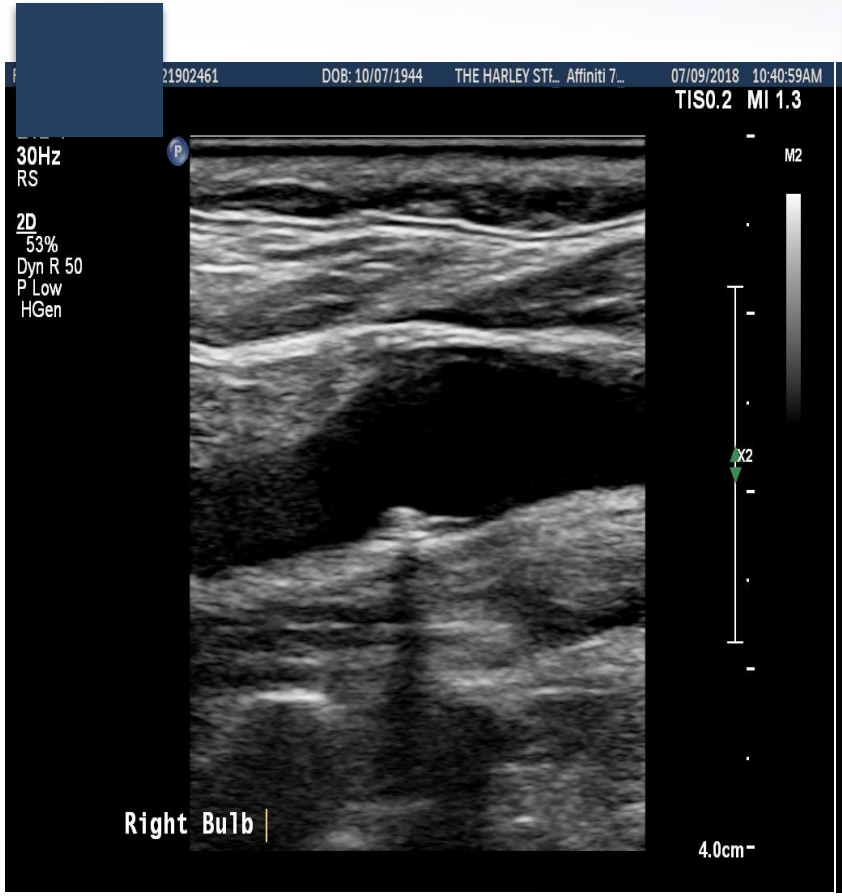
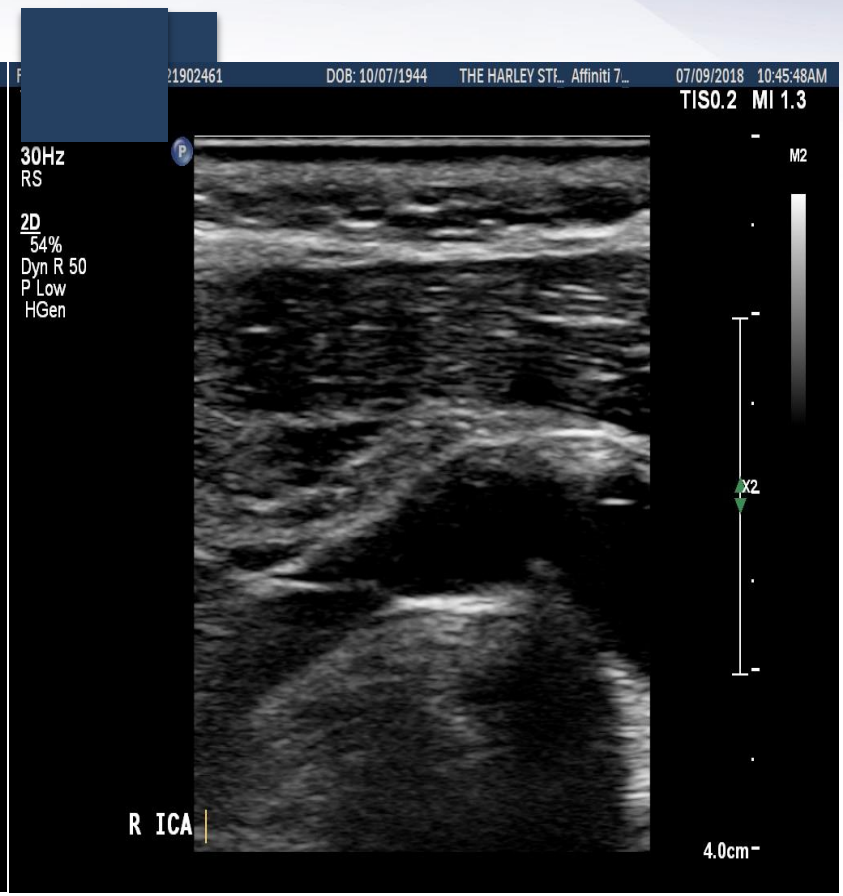
The Harley Street Duplex scan





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When to intervene, what intervention

- Be conservative in carotid intervention – BMT , BMT
- Asymptomatic with high risk plaque – DAPT / ASA-Rivaroxaban
- Symptomatic – 70% stenosis – consider intervention
- Symptomatic - not 70 % - IMT

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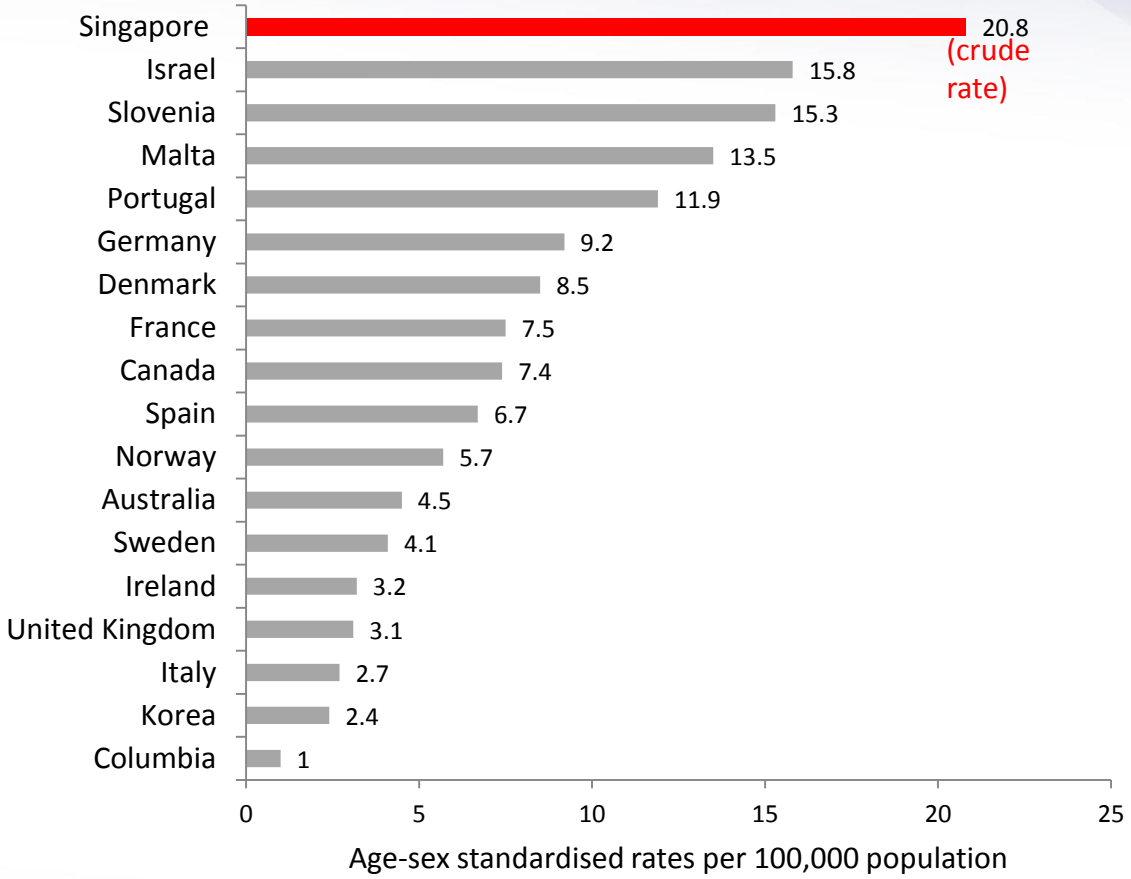
PAD – greetings from the amputation capital of the world

Major LEA* in diabetes patients, per 100,000 population aged 15+, 2013



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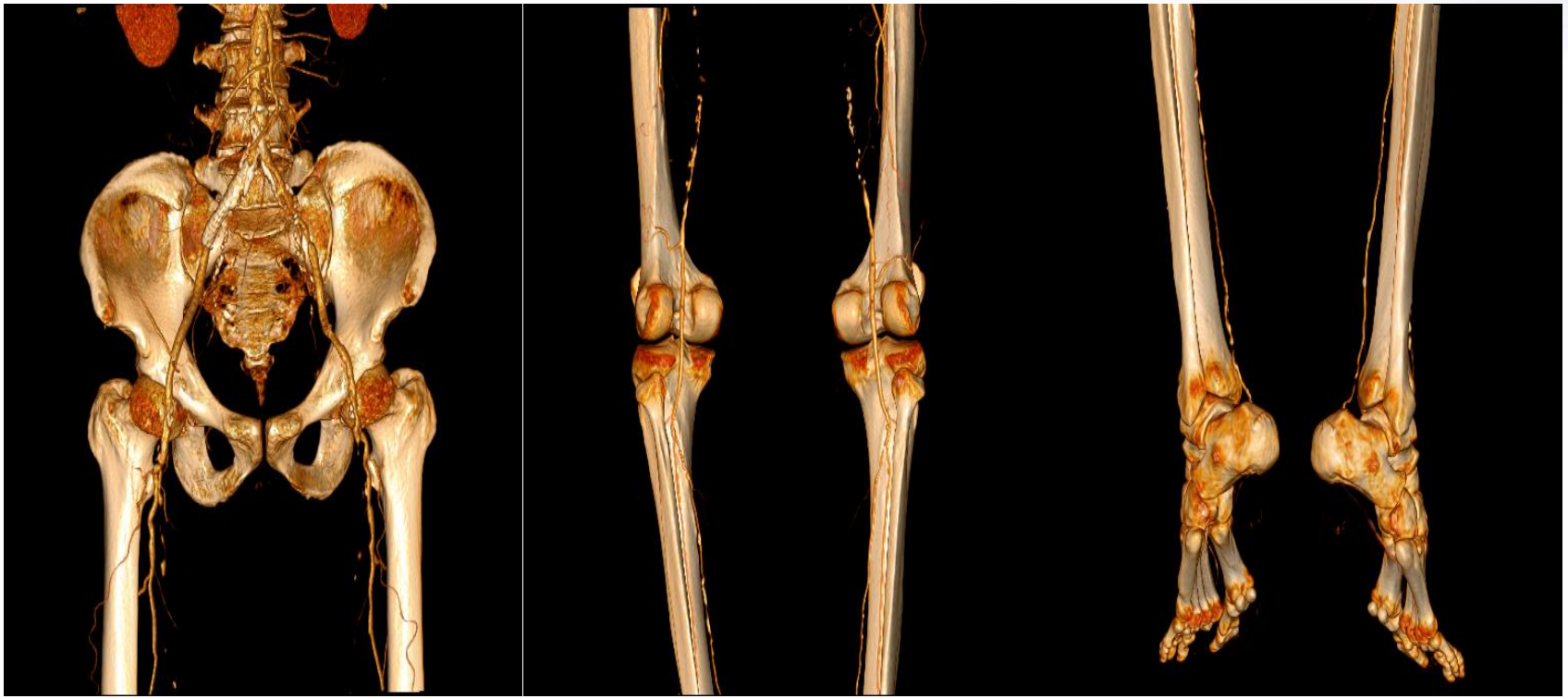
*exclude toe and ray amputation

Source: Health Care Quality Indicators: Primary Care. Diabetes lower extremity amputation. OECD Stats.

Asian PAD is very different



Occlusive disease in Iliac, femoral, tibial, peroneal and foot arteries – in a sin

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Late interventions – poorer outcomes in Diabetic BTK disease

- Presents with critical limb ischaemia and not intermittent claudication
- Serious co-morbidities like diabetes and renal failure
- Both intimal and medial disease
- Small arteries, calcified arteries, and long segment disease
- Often associated with proximal femoro-popliteal disease

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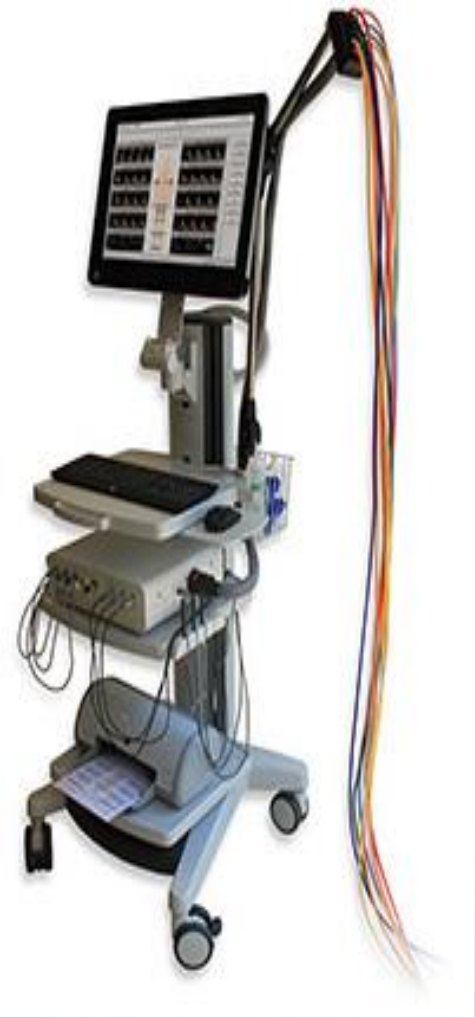
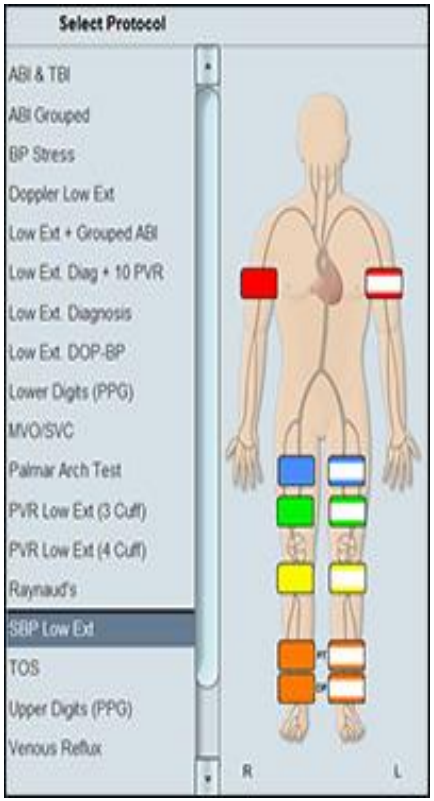
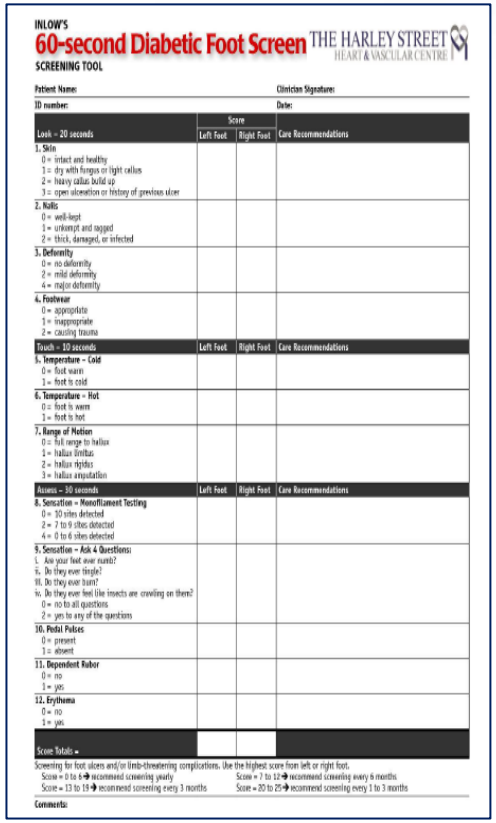
Early hemodynamic assessment – cheaper easier intervention







INLOW'S
60-second Diabetic Foot Screen THE HARLEY STREET HEART & VASCULAR CENTRE
SCREENING TOOL

Patient Name: Clinician Signature:
ID number: Date:

Look – 20 seconds	Score: Left Foot	Score: Right Foot	Care Recommendations
1. Skin 0 = intact and healthy 1 = dry with fungus or light callus 2 = heavy callus build up 3 = open ulceration or history of previous ulcer			
2. Nails 0 = well-kept 1 = unkempt and ragged 2 = thick, damaged, or infected			
3. Deformity 0 = no deformity 2 = mild deformity 4 = major deformity			
4. Footwear 0 = appropriate 1 = inappropriate 2 = causing trauma			
Touch – 10 seconds	**Left Foot**	**Right Foot**	**Care Recommendations**
5. Temperature – Cold 0 = foot warm 1 = foot is cold			
6. Temperature – Hot 0 = foot is warm 1 = foot is hot			
7. Range of Motion 0 = full range to hallux 1 = hallux limitus 2 = hallux rigidus 3 = hallux amputation			
Assess – 30 seconds	**Left Foot**	**Right Foot**	**Care Recommendations**
8. Sensation – Monofilament Testing 0 = 10 sites detected 2 = 7 to 9 sites detected 4 = 0 to 6 sites detected			
9. Sensation – Ask 4 Questions: i. Are your feet ever numb? ii. Do they ever tingle? iii. Do they ever burn? iv. Do they ever feel like insects are crawling on them? 0 = no to all questions 2 = yes to any of the questions			
10. Pedal Pulses 0 = present 1 = absent			
11. Dependent Rubor 0 = no 1 = yes			
12. Erythema 0 = no 1 = yes			
Score Totals =			

Screening for foot ulcers and/or limb-threatening complications. Use the highest score from left or right foot.
Score = 0 to 6 → recommend screening yearly
Score = 7 to 12 → recommend screening every 6 months
Score = 13 to 19 → recommend screening every 3 months
Score = 20 to 25 → recommend screening every 1 to 3 months

Comments:

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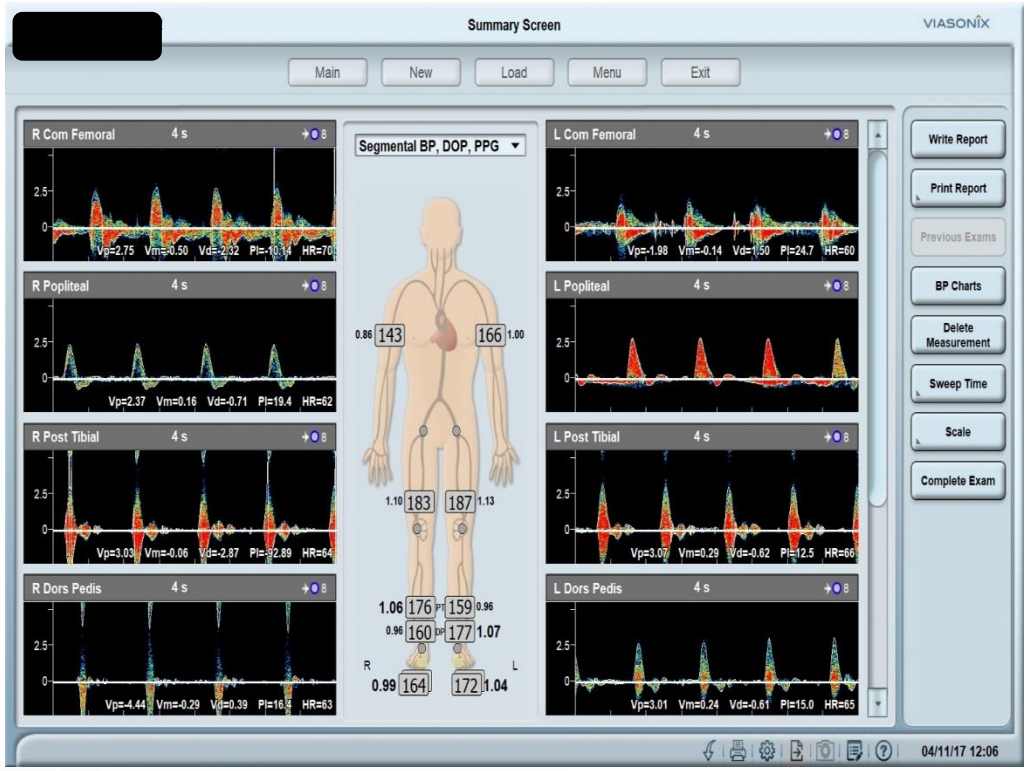
The long standing diabetic – **PAD screen**



- Cardiopaths
- PAD silent marker for CAD
- ABI alone poor marker in diabetics

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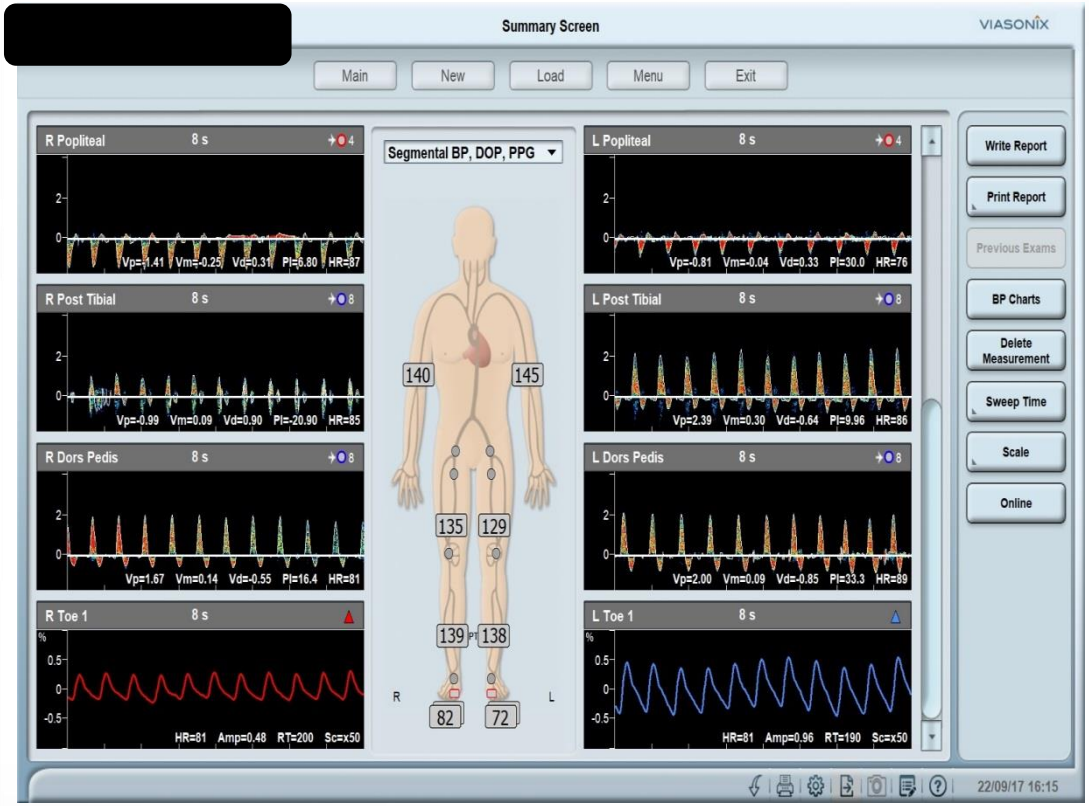
The long standing diabetic – **PAD screen**



- Toe pressures needed
- Screen positive patients – Toe pressure < 50 mmHg
- Risk of foot ulcers, heel pressure injury

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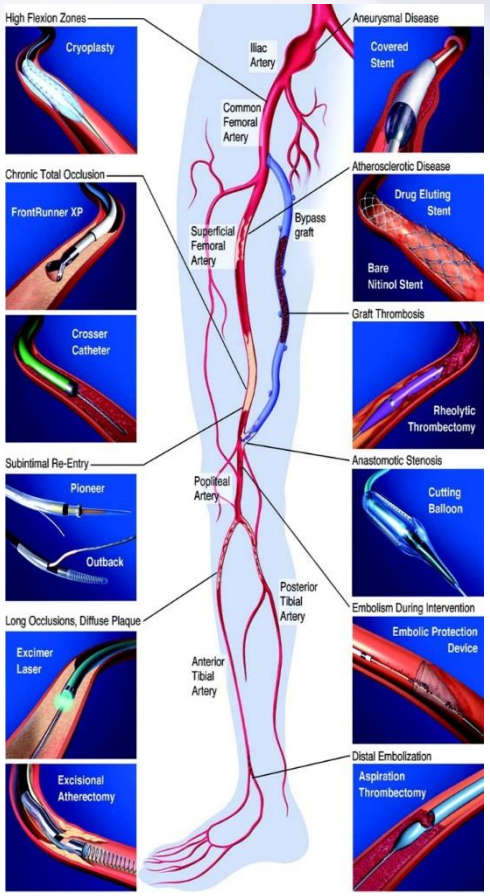
Blessed with state of the art endovascular kits in Sg

- Newer safer devices for recanalising difficult occlusions
- Better data that stents do not work below knee
- Drug coated balloons for below knee angioplasty
- Retrograde recanalization techniques



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PVD in diabetics has a poor prognosis

- PVD is 20 x more common in diabetics than non diabetics
- **lower limb amputation is 15 x more common in diabetics**
- ten year cumulative incidence of lower limb amputation is 5.4% in
  type I diabetes and 7.3% in type II
- 10% of diabetics get an ulcer (10% are purely ischaemic, 45% are ischaemic with associated neuropathy, infection, biomechanical abnormalities and Charcot deformity)

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Increased risk of CVD, CAD, nephropathy, retinopathy and death

Summary

- Carotid, peripheral and coronary artery disease are part of an atherobiologic
- Differences in plaque biology determine best approach
- Best medical therapy remains the mainstay of management
- Conservative therapy in carotid plaques, early intervention in peripheral dis
- Screen for carotid and peripheral arterial disease in all cardiovascular groups

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Questions ??

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