HARRY PERKINS INSTITUTE
OF MEDICAL RESEARCH

Harry Perkins Institute North
(QEII Medical Centre)


Harry Perkins Institute South
(Fiona Stanley Hospital)

Perkins Cardiovascular Research
Intensive Mini Symposium
8th November 2022

The Symposium was designed to update attendees on the highlights of Cardiovascular Research in Western Australia

The date was chosen to coincide with the visit of Prof Alex Brown, the 2022 Wesfarmers Perkins Orator

Speakers had only 10 minutes to describe their research, hence “Intensive”

HARRY PERKINS INSTITUTE OF MEDICAL RESEARCH

Prof Shirley Jansen
Head Cardiovascular Science and Diabetes Division

Prof Peter Thompson
Institute Deputy Director

Prof Peter Leedman
Institute Director

Perkins Cardiovascular Research Intensive Mini Symposium 8th 2022

The Symposium is designed to familiarise attendees with current cardiovascular research in Western Australia with a view to enhancing collaboration

The Program combines updates on work in progress from PhD and post doc researchers and state of the art reviews from established investigators.

We hope you enjoy this abbreviated summary of the presentations

HARRY PERKINS INSTITUTE OF MEDICAL RESEARCH

Perkins Cardiovascular Research Intensive Mini Symposium

Introduction	8:00		**Arrival**	**Tea and Coffee**
	8:15	Prof's	**Jansen and Thompson**	**Welcome and Introduction**
Session 1	8:30	**Prof**	**Shirley Jansen**	**Targeted peptides and Atherid**
Atherosclerosis	8:40	**Ms**	**Hanane Belhoul-Fakir**	**Vasa vasorum in atherosclerosis**
	8:50	**Prof**	**Peter Thompson**	**Inflammation in ASCVD**
Keynote Lecture	9:00	**Prof**	**Alex Brown**	**Overcoming CVD inequity among Indigenous Australians**
	9:30		**Discussion**	**Discussion**
Session 2	9:40	**Dr**	**Lee Nedkoff**	**Australian and international trends in coronary heart disease**
Atherosclerosis	9:50	**Dr**	**Mark Nidorf**	**Colchicine clinical trials**
	10:00	**Ms**	**Haritha Kirla**	**Nanoparticle drug delivery**
	10:20	**Prof**	**Gerald Watts**	**Lp(a) and gene silencing therapy**
	10:30		**Discussion**	**Discussion**
	10:40		**MORNING TEA**	**MORNING TEA**
Session 3	11:00	**Mr**	**Benjamin Bartlett**	**Dual disease mouse model**
Atherosclerosis	11:30	**Prof**	**Shirley Jansen**	**PAD and the diabetic foot**
	11:40	**Prof**	**Grant Morahan**	**Genomic prediction of CVD**
	11:50		**Discussion**	**Discussion**
Session 4	12noon	**Prof**	**Girish Dwivedi**	**Cardiac CT Newer imaging biomarkers and Perth experience**
CV Imaging	12:10	**Prof**	**Carl Schultz**	**PET CT and Microcalcification**
	12:20	**A/Prof**	**Ros Francis**	**PET CT and Vascular inflammation**
Session 5	12:30	**Prof**	**Brendan McQuillan**	**Evidence based choice of anti thrombotic for prosthetic valves**
Aortic stenosis	12:40	**Prof**	**Graham Hillis**	**Aortic stenosis and EASY AS**
	12:50	**Dr**	**Elena De-Juan-Pardo**	**3D printed cardiac valves**
	13:00	**Dr**	**Abdul Ihdayhid**	**Computational Modelling to Optimise Outcomes in Aortic Stenosis**
	13:10		**Discussion**	**Discussion**
LUNCH	**13:30**		**LUNCH**	**LUNCH**

Perkins Cardiovascular Research Intensive Mini Symposium

Session 1. Atherosclerosis and Keynote Lecture

- **Shirley Jansen** presents the background to **Atherid,** a drug developed in Juliana Hamzah's lab in the Perkins. This is an exciting development which targets the lipid-laden macrophages in the plaque. It is distinguished from current ant-atherosclerotic agents as it clears, not merely slows, the atherosclerosis.

- **Hanane Belhoul Fakir** is in the final year of her PhD on the role of shear stress in initiating atherosclerosis. Her unique observation that blood injected into the media of an artery rapidly converts to lipid, provides evidence, long suspected but never proven, that rupture of the **vasa vasora**, the fragile vessels in the wall of the artery can initiate atherosclerosis.

- **Peter Thompson** reviews the evidence for inflammation in atherosclerosis and the rapidly evolving international race to find an effective drug to block the inflammation. The established anti-gout drug **colchicine** may be the cheap and readily available answer

- **Alex Brown's** Keynote lecture summarises the continuing and distressing **gap in cardiovascular health** between indigenous and non-indigenous Australians and describes his career-long dedication to tackling the challenge of closing the gap.

ATHERID: A novel medicine to improve blood circulation in patients with peripheral artery disease (PAD)

A/Prof Juliana Hamzah

Head of Laboratory Targeted Drug Delivery, Imaging and Therapy at the Harry Perkins Institute of Medical Research.

Prof Shirley Jansen

Program Head of Cardiovascular Science and Diabetes as well as Director of the Heart and Vascular Research Institute at the Perkins. She is also Head of Dept of Vascular and Endovascular Surgery at Sir Charles Gairdner Hospital

HARRY PERKINS INSTITUTE OF MEDICAL RESEARCH

CURTIN HEALTH INNOVATION RESEARCH INSTITUTE

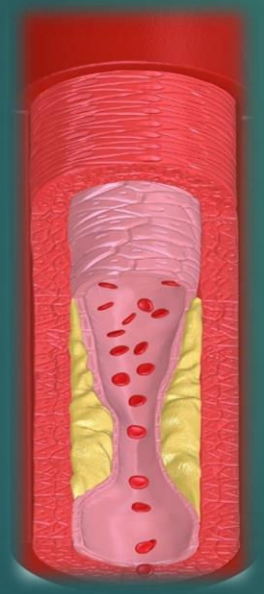
Curtin University

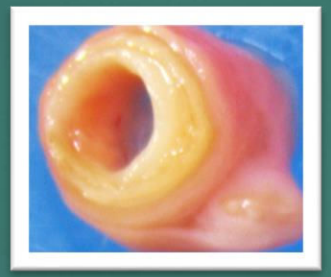
Government of Western Australia
North Metropolitan Health Service
Sir Charles Gairdner Hospital

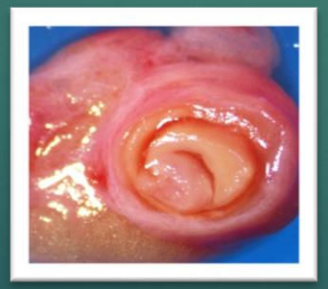
Heart & Vascular Research Institute
Preventing amputation, stroke & heart attack

Clinical Problem-PAD

Progressive arterial stenosis and occlusion leads to end organ events







Intermittent claudication pain

↓

Functional decline

↓

Rest pain
Ulcers/ gangrene

↓

Amputation

Team

LEADERSHIP

IP & COMMERCIAL

Dr. Patty Washer, Biologica Ventures Pty Ltd (WA)

BUSINESS STRATEGY & REGULATORY

Dr. Janet Preuss
QRC Solutions (WA)

A/Prof. Juliana Hamzah

Prof. Shirley Jansen

LABORATORY RESEARCH

Prof. Rod Dilley

Dr. Wen Yeow

Ms. Susan Wu

Ms. Hanane Belhoul-Fakir

ADVOCACY/ CONSUMER INVOLVEMENT

Ms. Briony Williams (WA)

Mr. Peter Miles (WA)

Mr. Trevor Jones (WA)

ADVISORS

Prof. Peter Thompson, Cardiologist (HPI)
Prof. Jianglin Fan, Preclinical (Japan)
Prof. Jon Golledge, Vascular Surgeon (Qln)
Dr. Adam Hill, Electrophysiologist (NSW)
Prof. Kerry-Anne Rye, Lipidologist (NSW)
Prof. Karlheinz Peter, Cardiologist (VIC)
Mr. John Barrington AM, Artrya (WA)

National Biologics Facility

Manufacturing Facility (Vic)

ACvA
Australian Cardiovascular Alliance

linear

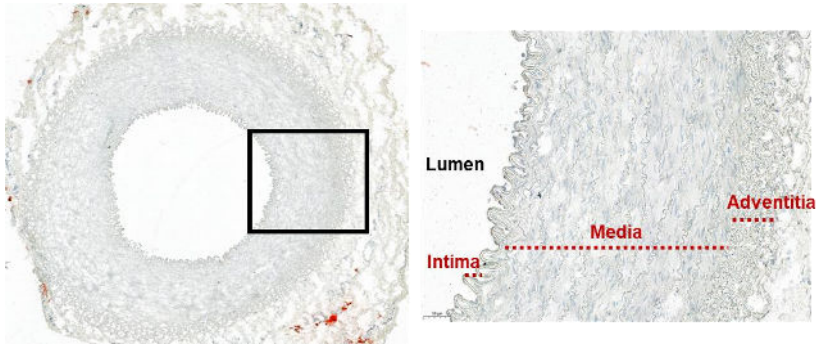
Clinical Trial Facility (WA)

Injury to the arterial media initiates atherogenesis during hyperlipidaemia

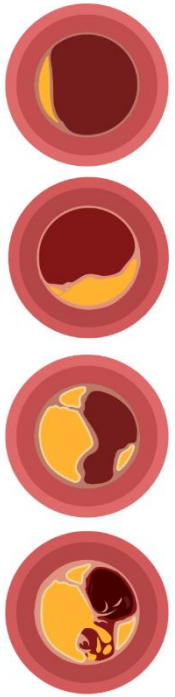
Mrs Hanane Belhoul-Fakir

A final year PhD student at Curtin Medical School and the Harry Perkins Institute of Medical Research. A member of the newly formed WA Cardiovascular Research Alliance EMCR subcommittee and sponsorship lead of the WA branch of the Australian Society for Medical Research.

Carotid artery tissue cross-section



Atherosclerosis stages



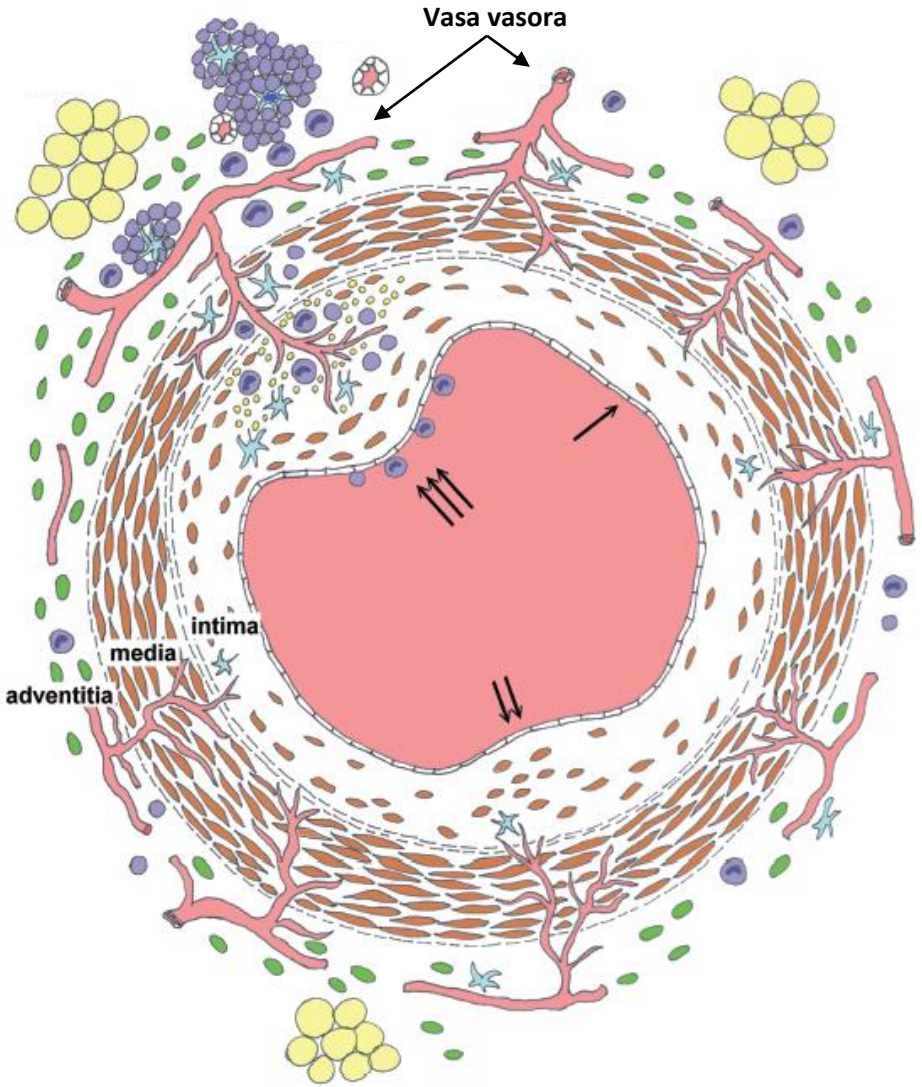
Early

Atheroma

Advanced

Ruptured

Atherosclerosis development through endothelial dysfunction



Aleksandra Milutinović, *et al* modified

Summary

- Injury in the tunica media under hyperlipidaemia induced lipids accumulation, vasa vasora, and immune cell infiltration at the sites of trauma, while the tunica intima remained unaffected.
- Hyperlipidemic diet globally induced disruption of vascular smooth muscle cells in the outer layer of the tunica media adjacent to the tunica adventitia.
- Atheroma was significantly greater in the tunica media than in the tunica intima in 32 % of patients with carotid artery disease.

Conclusion

We show for the first time that Arterial media can be a nidus for atherogenesis, an alternative pathway for atherosclerosis initiation.

Atherosclerosis and inflammation

Peter L Thompson

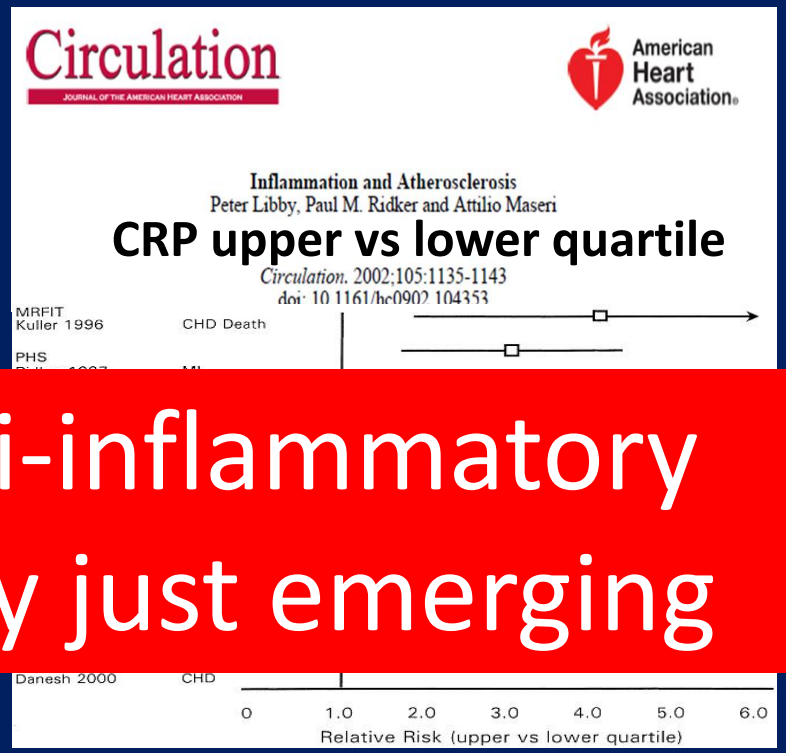
Deputy Director Heart and Vascular Research Institute
Sir Charles Gairdner Hospital
Deputy Director, Harry Perkins Institute of Medical Research
Clinical Professor of Medicine
University of Western Australia

Inflammation in atherosclerosis not a new idea

Citations 33,298!!

1999

Citations 19,991!!



2002

But 20 years on, effective anti-inflammatory treatments for ASCVD are only just emerging

The CANTOS study 2017

Canakinumab (Novartis)

- Development did not proceed,
- FDA application withdrawn
  - CANTOS results were positive but not strong enough to warrant further development
  - Cost was excessive >$200,000 per year
  - Setting the scene for alternatives incl colchicine

Colchicine
Solid RCT evidence of benefit

- RCTs in >11,000 patients with coronary heart disease
- MACE reduced by 25%, MACE+ revascularisation by 33%
- Individual reductions in
  - revascularisation
  - myocardial infarction
  - stroke
- Tolerability excellent apart from 7-10% early GI intolerance

Anti-inflammatory approaches in atherosclerosis

Drug	Mechanism	Trials	Efficacy	Safety	Potential
Untargeted anti-inflammatory agents					
Statins	LDL lowering	Indirect	Uncertain		
Corticosteroids	Non Specific anti-inflammatory	Yes			
NSAIDS	COX inhibition	Yes			
Pexelizumab	Complement inhibition	Yes			
Losmapimod	MAPK inhibitor	Yes			
Darapladib, Varespladib	LpPLA inhibition	Yes			
CRP inhibitors	CRP inhibition	No			
Methotrexate	Multiple sites	Yes			
Targeted anti cytokines					
DMARDS eg etanercept	TNFα inhibition	No			
DMARDS eg tocilizumab	IL6 inhibition	No			
Canakinumab	IL1β inhibition	Yes			
Ziltivekimab	IL6 ligand inhibition	Underway			$$$$
Inflammasome inhibition					
Colchicine	Multiple incl inflammasome assembly	Yes			$

Lack of efficacy proven Efficacy proven Safety under a cloud

Anti-inflammatory agents in atherosclerosis

Conclusions

- Inflammation is now regarded as a major contributor to atherosclerosis
- Untargeted anti inflammatory agents have not been successful
- Downstream targeting of inflammatory cytokines IL1β and IL6 is a valid (but limited?) approach
- Colchicine is a cheap agent with clinical trial “runs on the board”
- Colchicine has anti-NLRP3 inflammasome properties and its full range of anti-atherosclerosis actions is yet to be elucidated
- Upstream direct inhibition of the NLRP3 inflammasome is also under intensive investigation

CVD in Indigenous Australians

Professor Alex Brown (BMed, MPH, PhD, FRACP (hon.), FCSANZ, FAHMS) is the Professor of Indigenous Genomics at the Telethon Kids Institute and The Australian National University. He is an internationally leading Aboriginal clinician/researcher who has worked his entire career in Aboriginal health in the provision of public health services, infectious diseases and chronic disease care, health care policy and research.

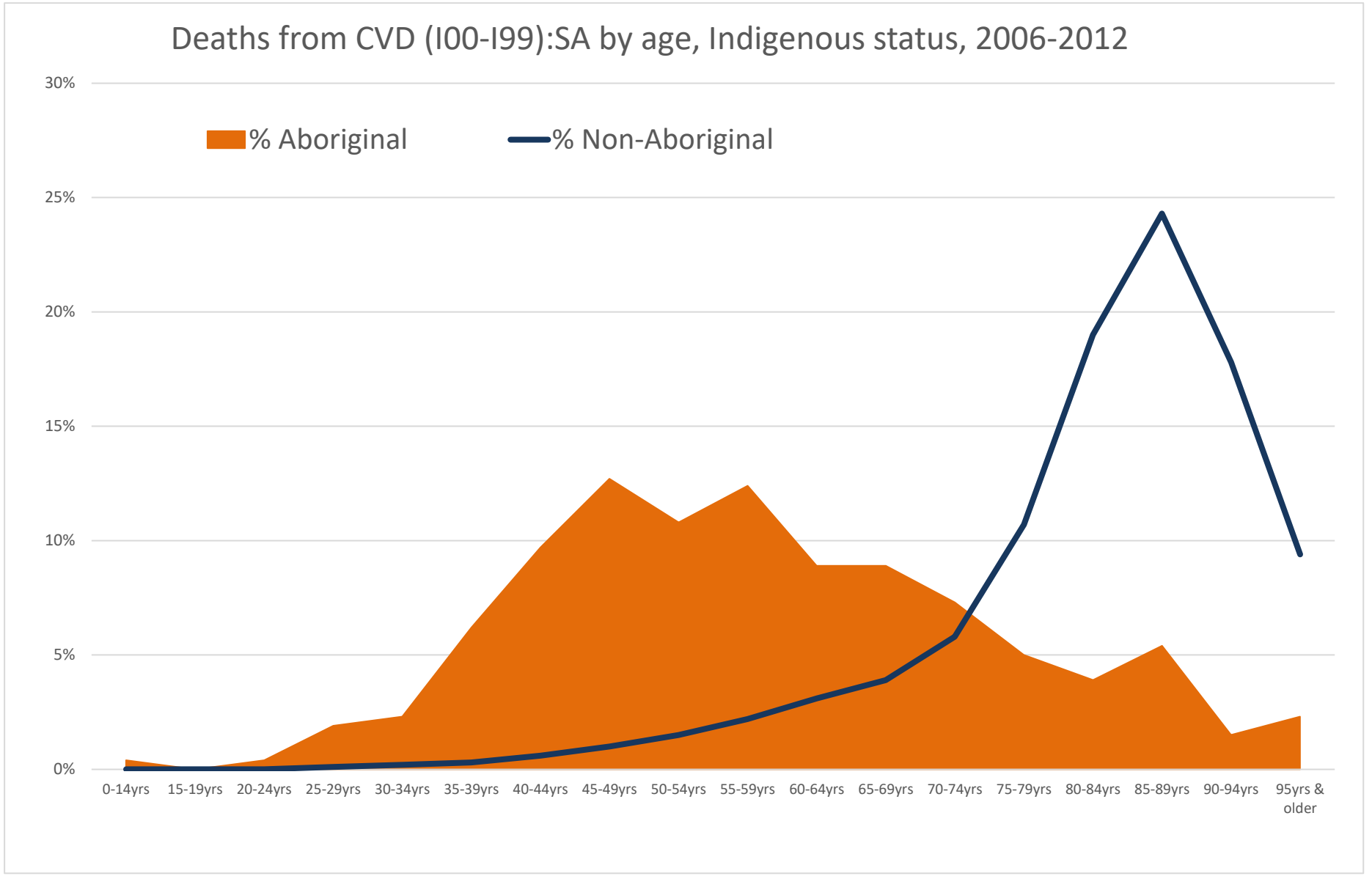
ASHRA

Australian National University

NCIG NATIONAL CENTRE FOR INDIGENOUS GENOMICS

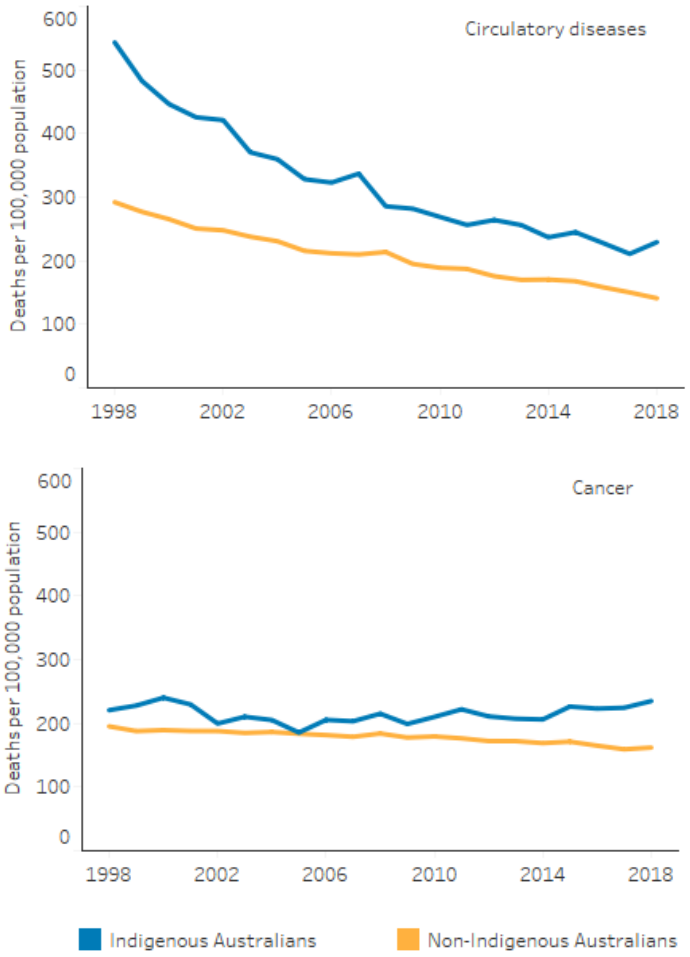
TELETHON KIDS INSTITUTE

Cardiovascular mortality



Acknowledgement: Registries of Births, Deaths and Marriages, the Coroners and the national Coronial Information System.
Data source: Cause of Death Unit Record File for South Australia provided by the Australian Coordinating Registry (unpublished) extracted for the Landscape Project 22 June 2015.

Secular Trends in Leading Causes of Death. Indigenous Australians 2008-2018 (indigenoushpf.gov.au)



Age-standardised mortality rates for selected causes of death, by Indigenous status, NSW, Qld, WA, SA and NT, 1998 to 2018

CVD is the disease group that is the **3rd biggest** health problem for Aboriginal and Torres Strait Islander people.

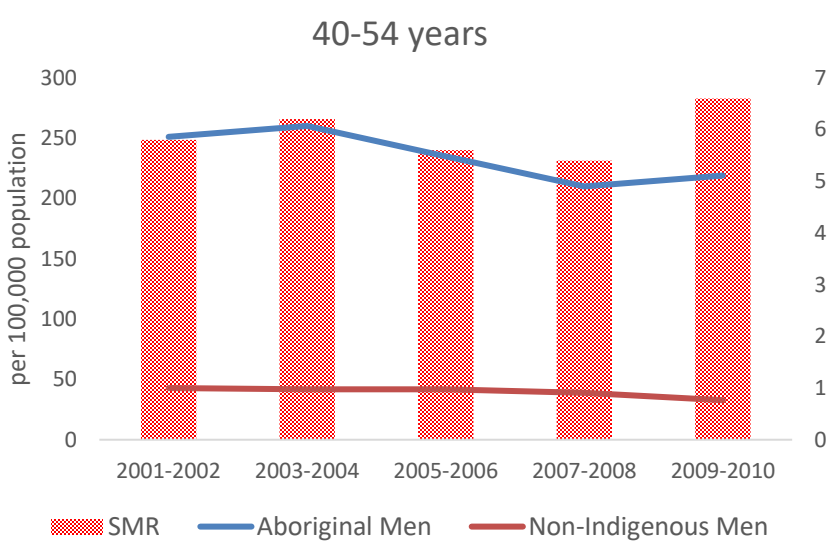
12% *of total burden in 2011 [28]*

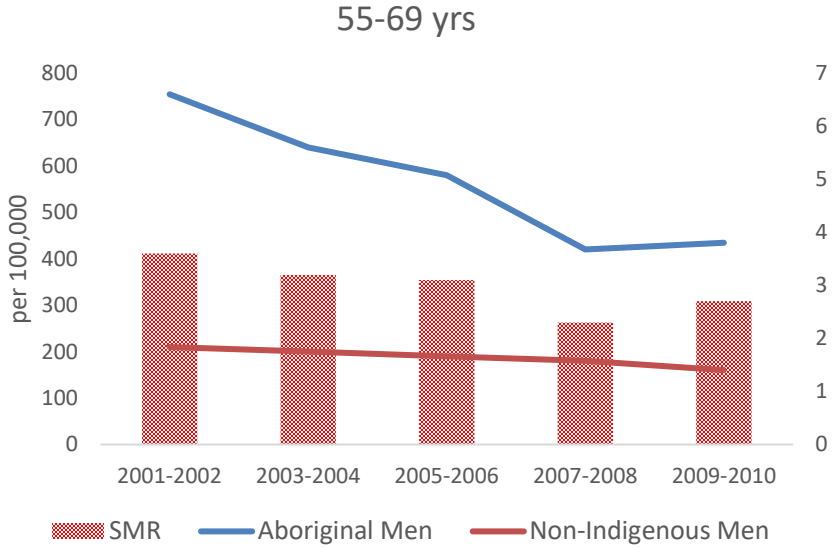
15% of Aboriginal and Torres Strait Islander people said that they had **CVD**, 2018-19 National Aboriginal and Torres Strait Islander Health Survey (NATSIHS) [29].

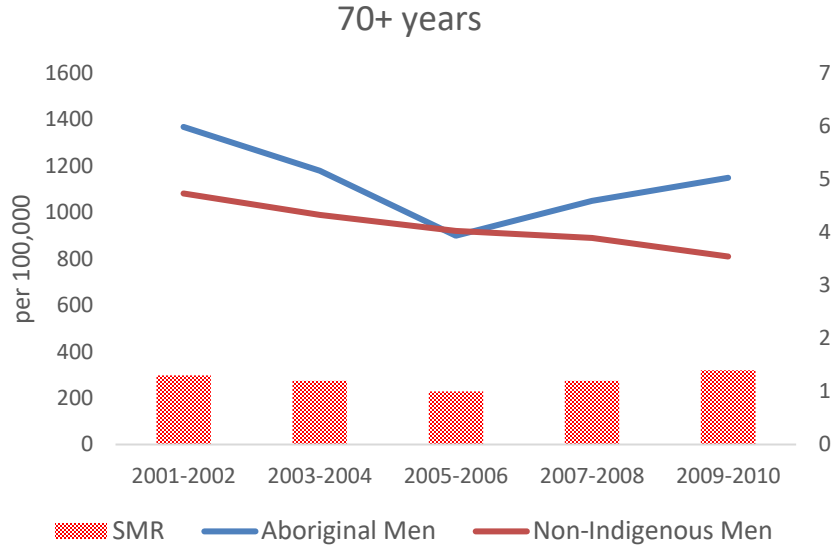
5.4% of all **hospitalisations** among Aboriginal and Torres Strait Islander people were for CVD, 2017-18 (Derived from [30]).

24% **about a quarter of all deaths** of Aboriginal and Torres Strait Islander people were caused by CVD [31].

Secular Trends in CHD Mortality – Australian Men

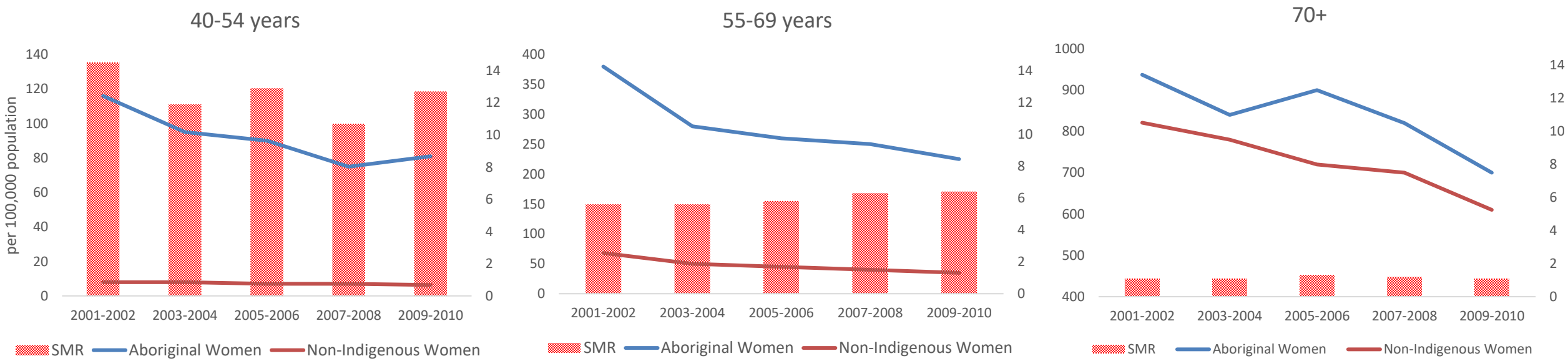






- Reduction in CHD Mortality across all age groups
- Greatest inequalities at young ages
- Persistent inequality over ten-year period
- Some closing of the gap in 55-69 year age group

Secular Trends in CHD Mortality – Australian Women

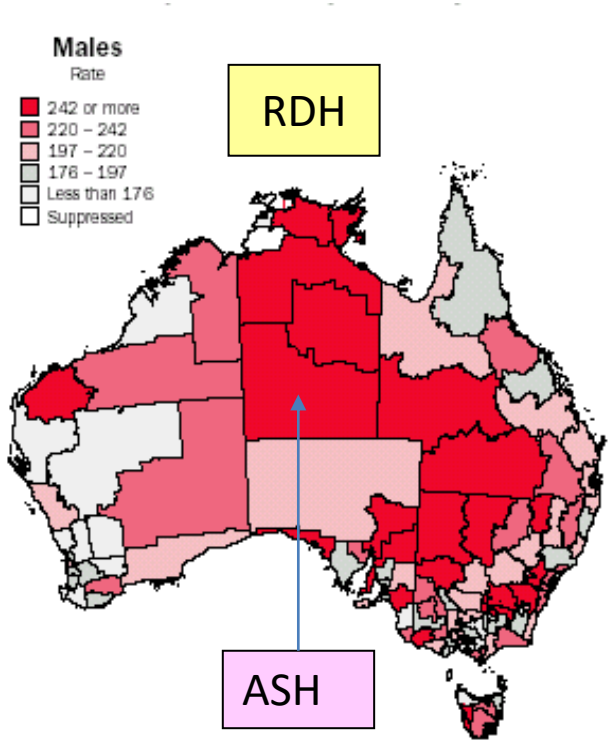


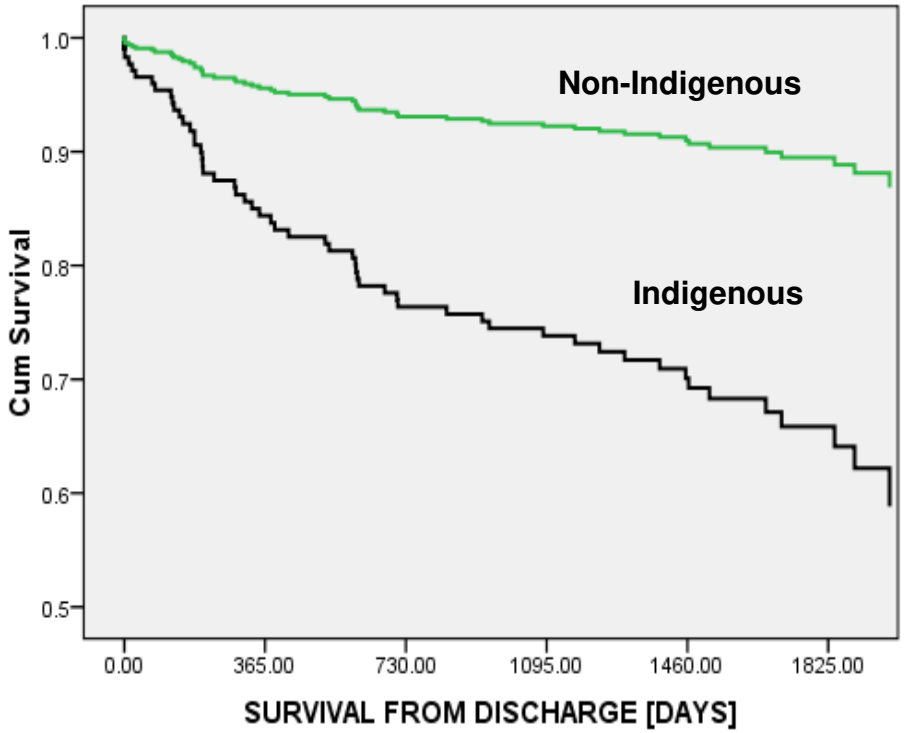
Declining mortality in all age groups

Widest disparities at younger ages (12-14 times)

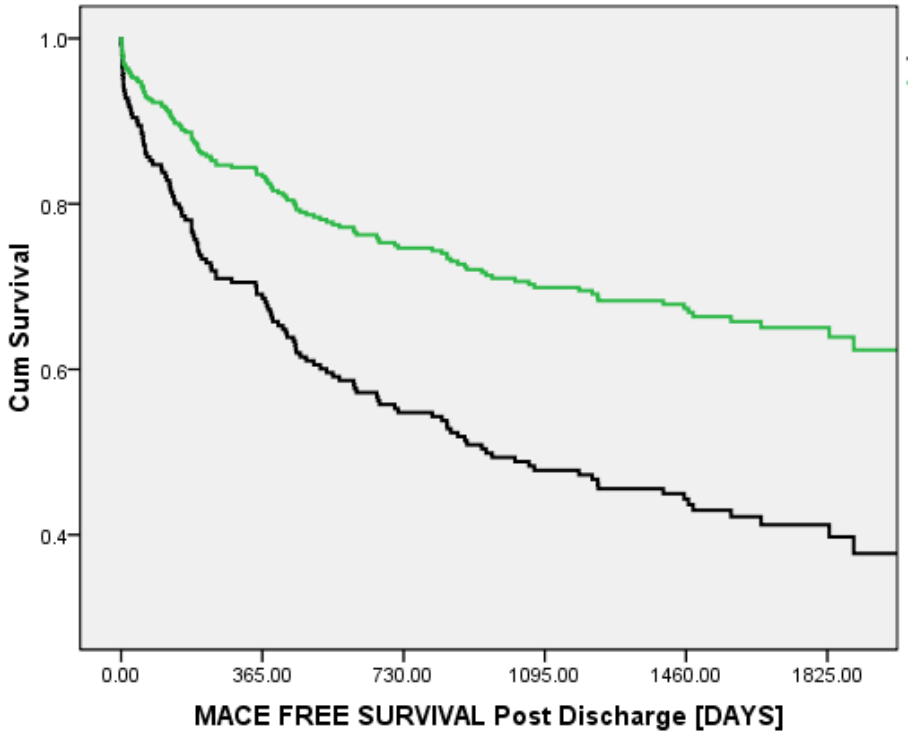
Small rise in inequality among 55-69 year age group

Age Adjusted Survival following Acute Coronary Events – the CASPA Study





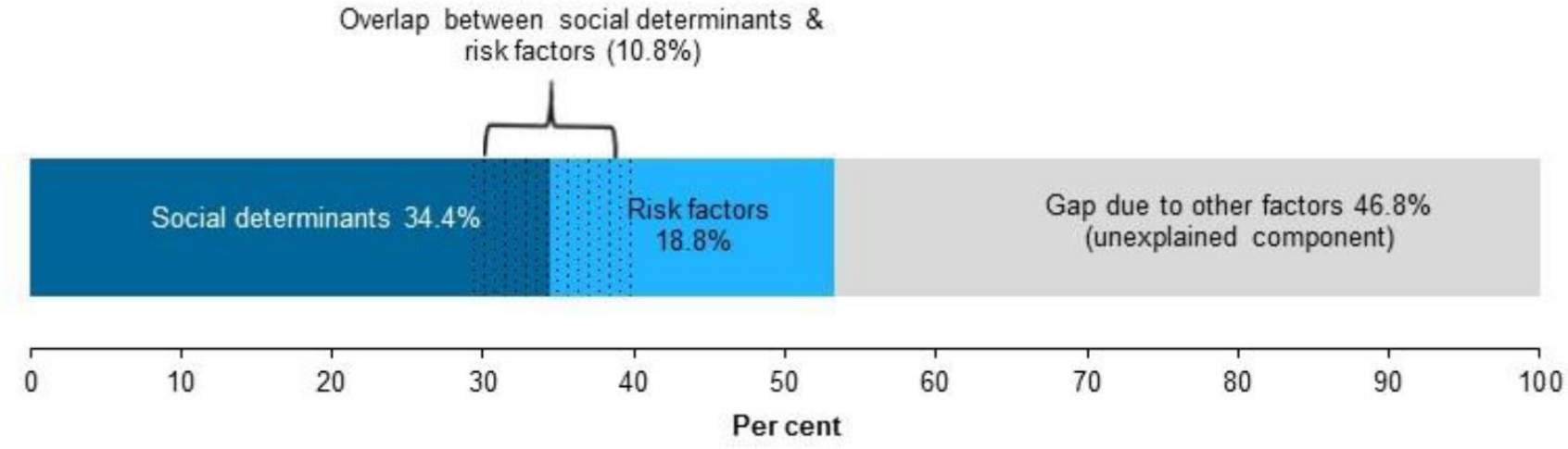
HR = 3.8 [2.15 - 6.58]; p < 0.001

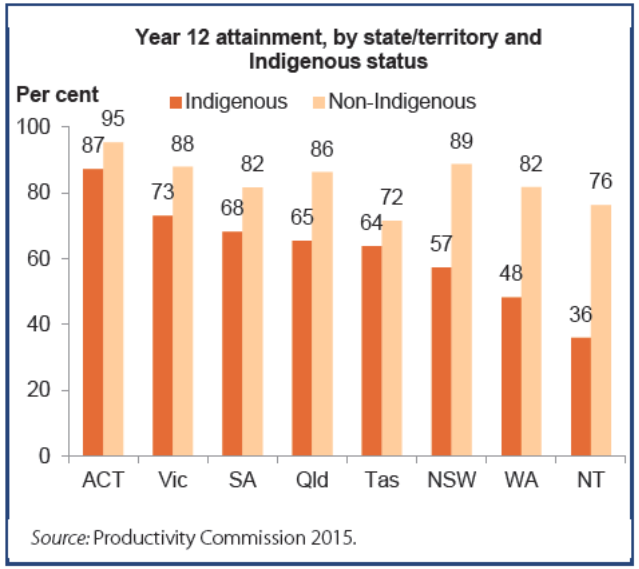


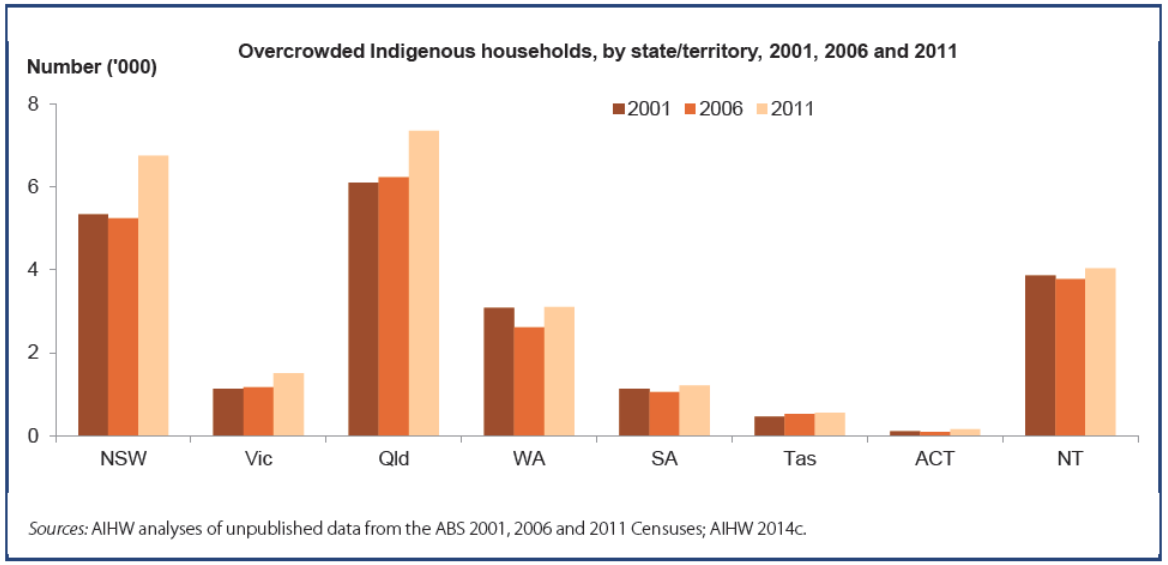
HR = 2.1 [1.40 - 3.02]; p < 0.001

Brown. Heart Lung Circulation 2009.

Contributors to the Gap in the Burden of Disease, 2011-2013







Influencing Policy and Practice

Towards an Exemplar Approach to Close the Gap?
ESSENTIAL SERVICE STANDARDS

1. Trends in and contribution of various conditions to health differentials over time;
2. Equitable service elements and standards of care for all Australians;
3. Mapping which Australians are missing out on various essential elements of care;
4. How best to deliver necessary services and programs to those missing out; and,
5. The costs and likely benefits of delivering essential services and conversely the cost of inaction if inequality is not overcome.

EXPLAINING CVD DISPARITY

- Underlying Risk – Traditional and alternate RFs (Inflammation/Environmental)
- SES/Intergenerational Disadvantage
- Adverse Childhood Experiences
- Social and Historical Factors
- Psychological/Psychosocial Factors
- Inequitable Access and Poor quality of care
- Racism and Adverse Experiences

HARRY PERKINS INSTITUTE
OF MEDICAL RESEARCH

HARRY PERKINS INSTITUTE
OF MEDICAL RESEARCH

Harry Perkins Institute North
(QEII Medical Centre)


Harry Perkins Institute South
(Fiona Stanley Hospital)

Perkins Cardiovascular Research Intensive Mini Symposium 8th November 2022

Session 2.
Atherosclerosis continued

Session 2	9:40	**Dr**	**Lee Nedkoff**	**Australian and international trends in coronary heart disease**
Atherosclerosis	9:50	**Dr**	**Mark Nidorf**	**Colchicine clinical trials**
	10:00	**Ms**	**Haritha Kirla**	**Nanoparticle drug delivery**
	10:20	**Prof**	**Gerald Watts**	**Lp(a) and gene silencing therapy**

Perkins Cardiovascular Research Intensive Mini Symposium

Session 2. Atherosclerosis continued

- **Lee Nedkoff** reviews the recent trends in cardiovascular disease in WA, Australia and internationally. While the decline in age adjusted cardiovascular mortality continues, CVD is still the leading cause of death in men. It has been displaced by dementia in women. There are concerning data that the decline has flattened in younger Australians

- **Mark Nidorf** reviews in detail the clinical trial evidence in >11,000 patients that low dose colchicine ic effective and safe in reducing cardiovascular events, and is ideally suited for long term management of coronary heart disease.

- **Haritha Kirla** describes her work on the use of colchicine loaded nanoparticles to target the atherosclerotic plaque

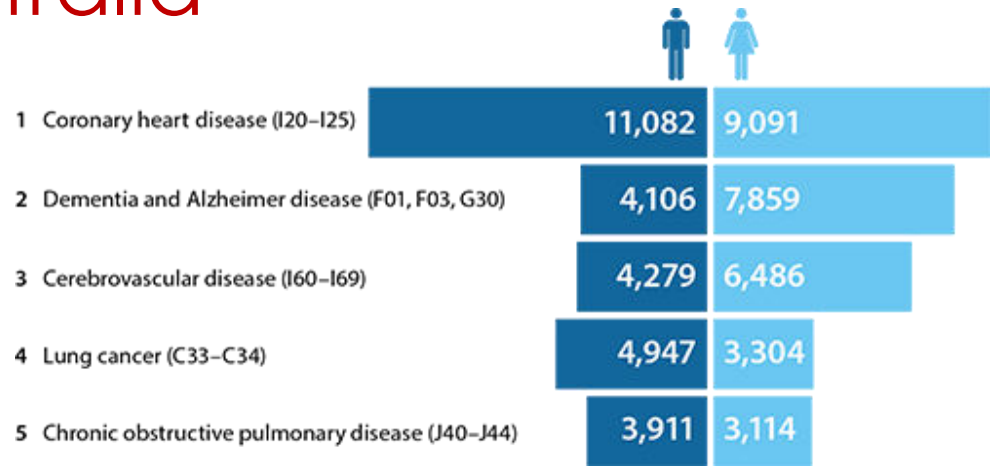
- **Gerald Watts** describes the recent evidence which has shown the importance of Lpa in promoting atherosclerosis and which places it squarely in the sights of new drugs under development to lower it with new RNA technologies.

Australian and international trends in coronary heart disease

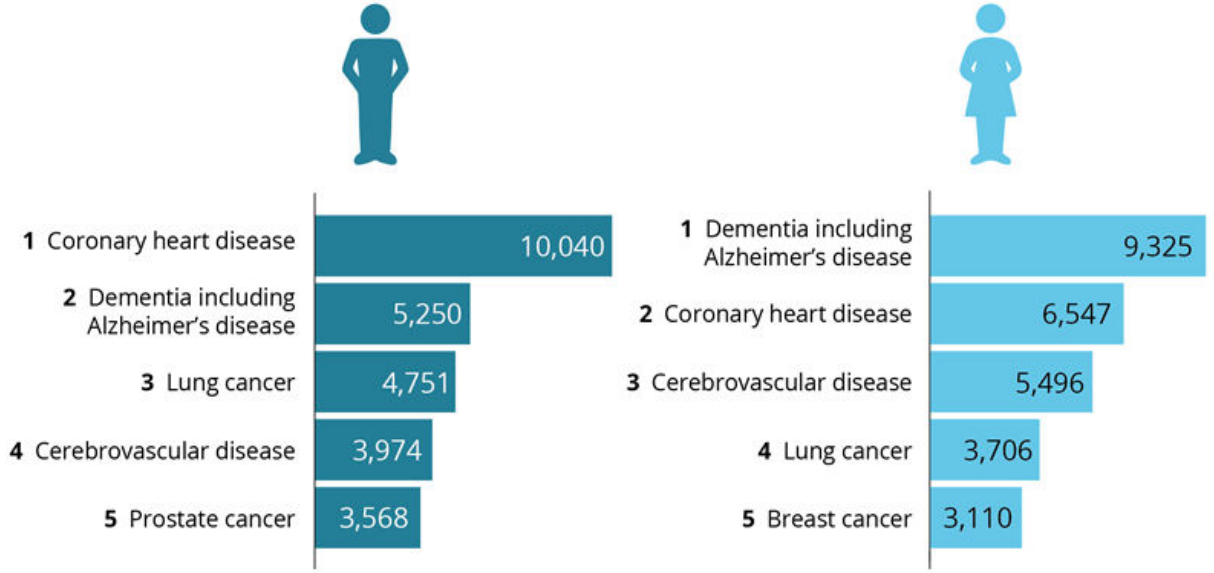
Dr Lee Nedkoff

Co-Director and Senior Research Fellow,
Cardiovascular Research Group (SPGH, UWA)
National Heart Foundation Future Leader Fellow

Leading underlying causes of death in Australia



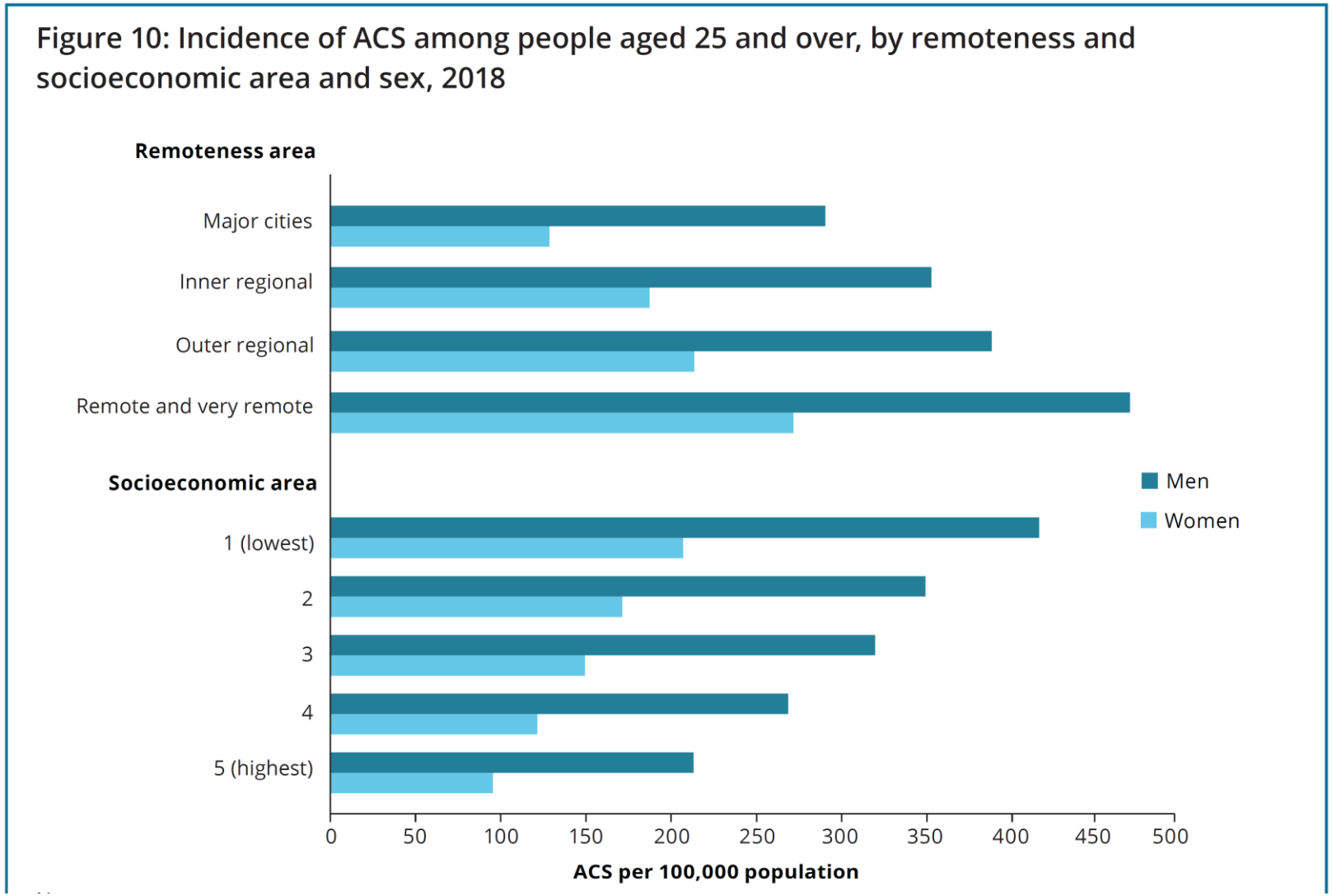
2014



2020

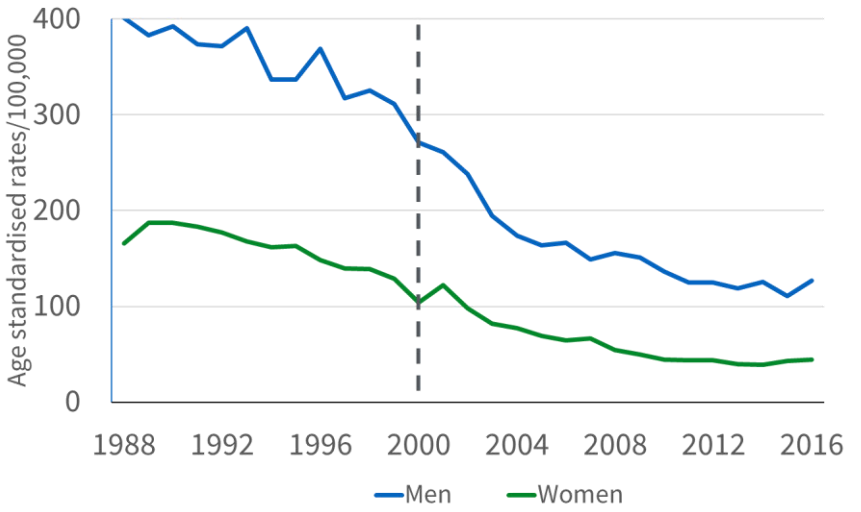
Leading causes of death AIHW
https://www.aihw.gov.au/reports/life-expectancy-death/deaths-in-australia/

Trends in ACS event rates in Australia

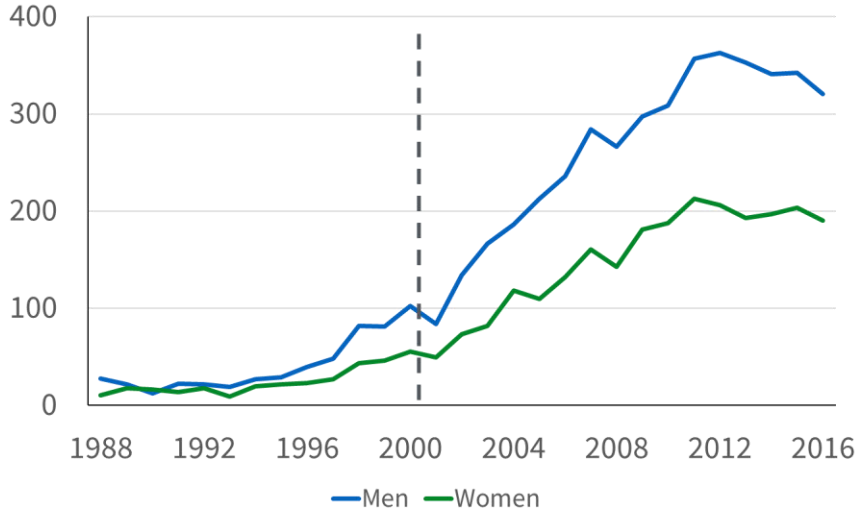


AIHW, 2022

WA hospitalisation rates + age-adjusted trends



STEMI: -5.5%/year since 2000



NSTEMI: +10.2% /year since 2000

Nedkoff et al, BMJ Open 2017

Age-specific trends

Mortality rates

- ❖ Largest declines generally 65-84 year olds
- ❖ ?smaller declines in 30-54 year olds

Case fatality

- ❖ Smallest declines in ≥85 year olds
- ❖ Largest declines 30-54 y.o. women NSW (7%/year)

Event rates

- ❖ Largest declines in 65+ y.o.
- ❖ No decline in 35-54 y.o. women (↑ in England)

Conclusions

- Substantial declines in CHD mortality rates
- ACS incidence declining but at a slower rate

  → driven by declines in STEMI rates

- Continuing concerns re, adverse trends in <55 year olds

  → lack of decline/↑ event rates

  → ↓ mortality completely driven by ↓ in case fatality

  → more targeted CV risk factor prevention in young adults

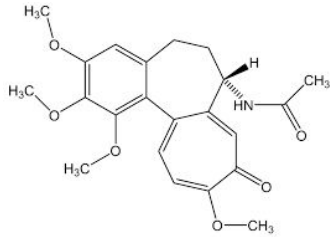
Acknowledgements: Data Linkage Branch (WA Department of Health) for provision of linked hospital and mortality dataset; Co-ordinating Registry, the Registries of Births, Deaths and Marriages, the Coroners, the National Coronial Information System and Victorian Department of Justice and Community Safety.

Seeing Colchicine in a New Light

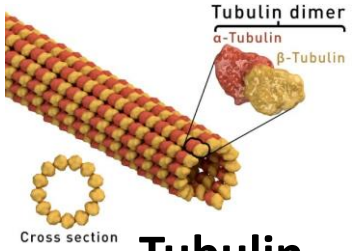
Repurposing colchicine for 2º prevention of coronary disease

Dr Mark Nidorf - Cardiologist

Colchicine has protean cellular actions

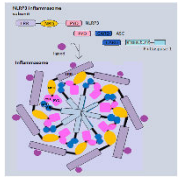


Colchicine



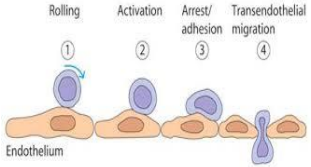
Tubulin

Macrophages



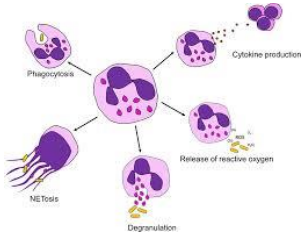
Inflammasome
IL-1β and other ILs

Endothelium



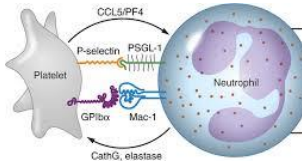
Impair
neutrophil ingress

Neutrophils



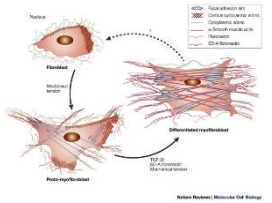
Inhibit release of SO
generation of NETs

Platelets



Interfere with
neutrophil-platelet interaction

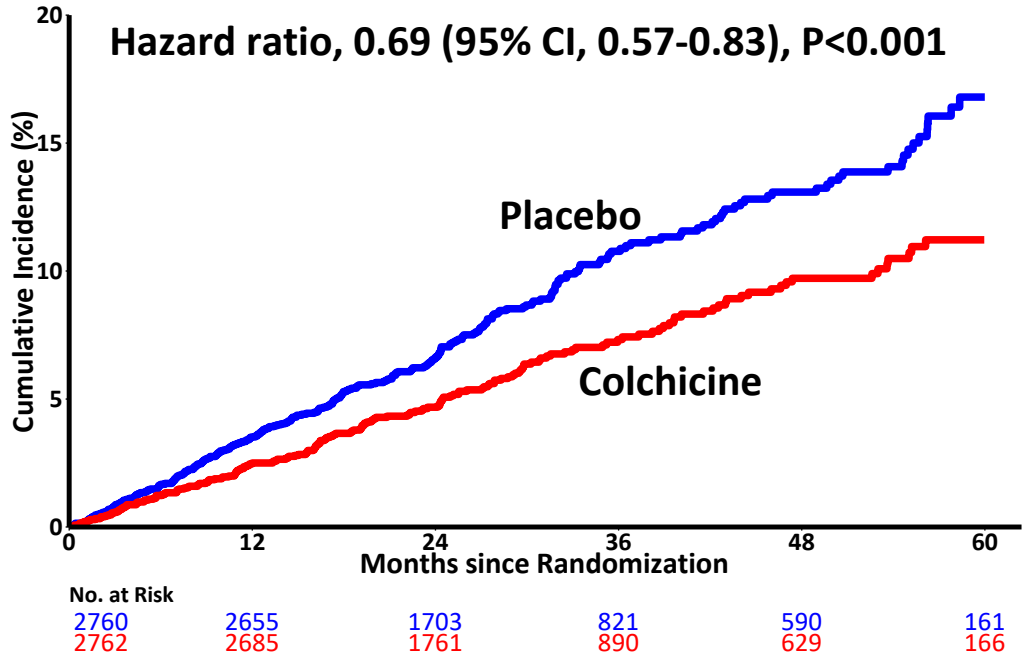
SM Cells/Fibrocytes



limit response
to injury

Colchicine improves event-free survival

Cardiovascular death, myocardial infarction, ischemic stroke or ischemia-driven coronary revascularization



As in LoDoCo

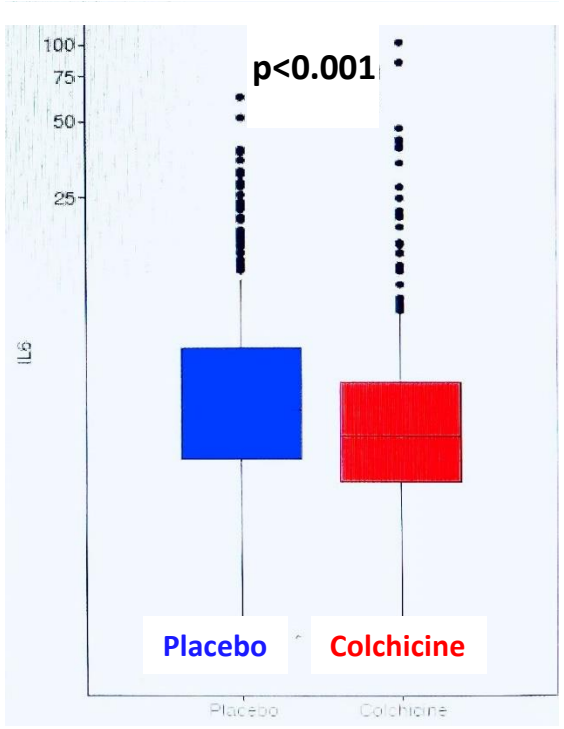
- The ER on placebo ~3.6%pa
- Benefits of colchicine seen early
- Benefits continued to accrue

Nidorf et.al Colchicine in patients with chronic coronary disease August 31, 2020, DOI: 10.1056/NEJMoa2021372

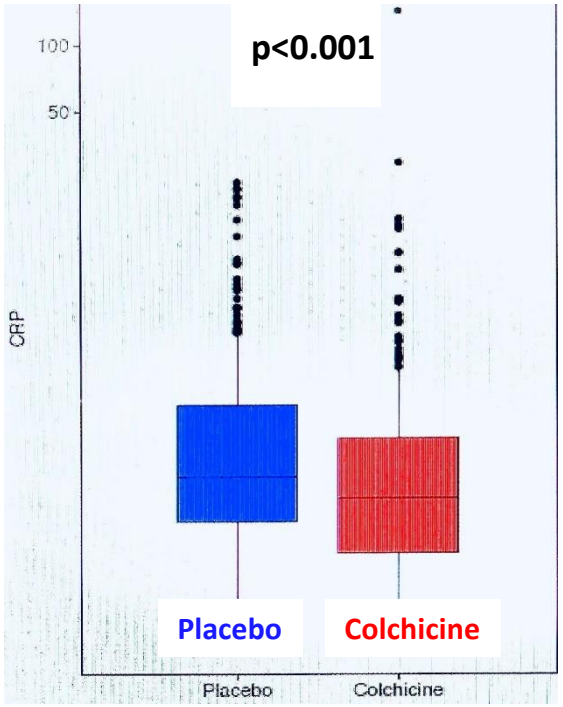
Colchicine reduces inflammatory markers

Close out serum levels in 1776 participants of the LoDoCo2 cohort

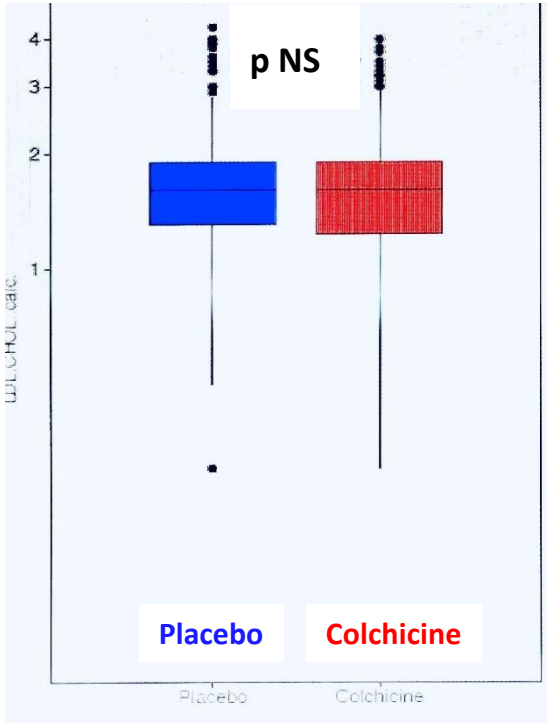
Reduces IL-6



Reduces hs-CRP



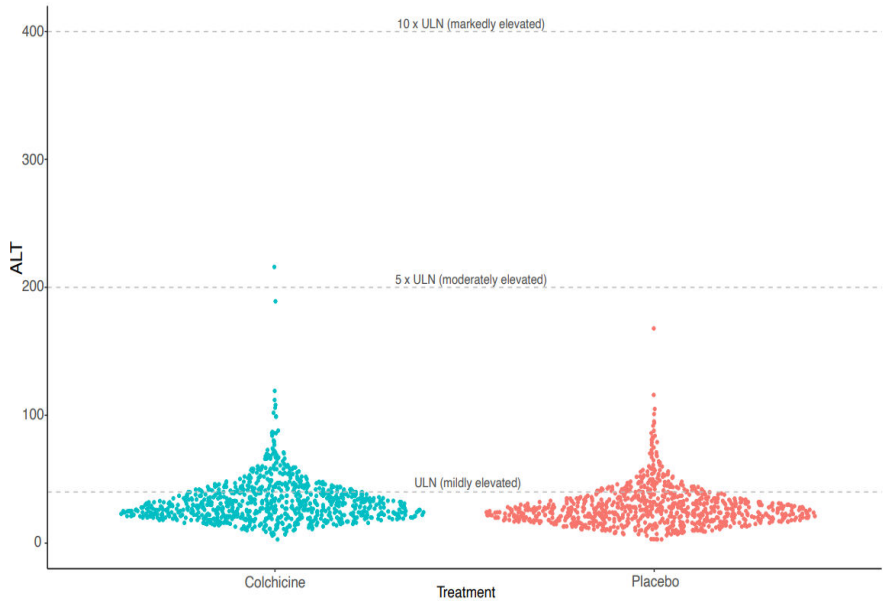
No Effect on LDLc



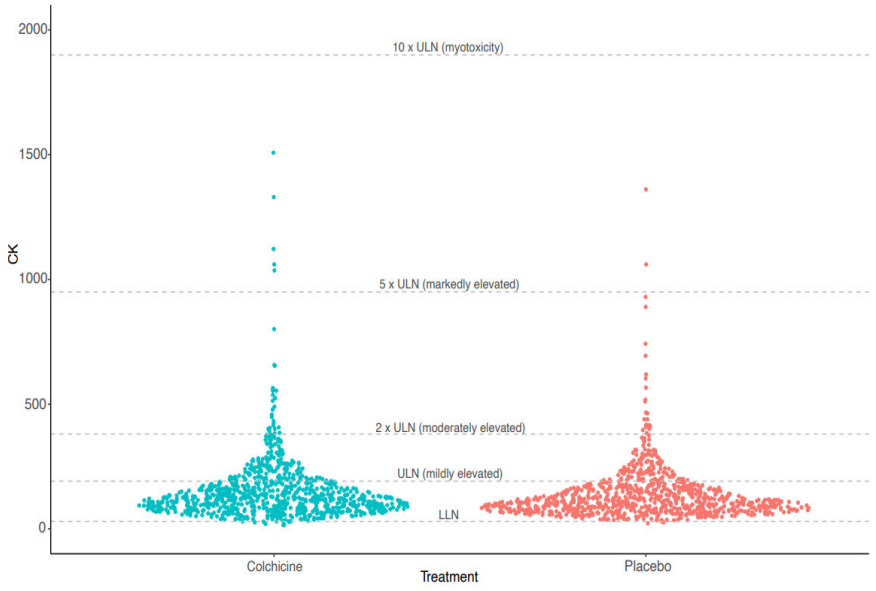
Years-long exposure to low-dose colchicine

associated with occasional mild increase in ALT & CK

Alanine aminotransferase



Creatine Kinase



No myotoxicity or effect on γGT or renal function

Van Broekhoven et.al The Effect of Years-Long Exposure to Low-Dose Colchicine on Renal and Liver Function and Blood Creatine Kinase Levels: Safety Insights from the Low-Dose Colchicine 2 (LoDoCo2) Trial Clinical Drug Investigation DOI: 10.1007/s40262-022-02209-8

Summary

Colchicine is poised to be repurposed for 2º prevention of CV disease*

It is already included in many guidelines as the rationale for using it is clear & the clinical evidence regarding its long-term tolerance, safety and efficacy are strong

Until newer agents are proven more effective than colchicine

It will remain the safest, most widely available, least expensive anti-inflammatory therapy available for 2º prevention of CV disease

* Ridker et.al May 2021: https://www.ahajournals.org/doi/10.1161/CIRCRESAHA.121.319077

Colchicine-loaded Nanoparticles to reduce inflammation in atherosclerotic plaques

Presenter:

Haritha Kirla

Team:

Juliana Hamzah, Peter Thompson, Shirley Jansen, Wen-Shuz Yeow, Susan Wu, David Henry

Funding:

Ray Florence Shaw, Charlies Foundation for Research

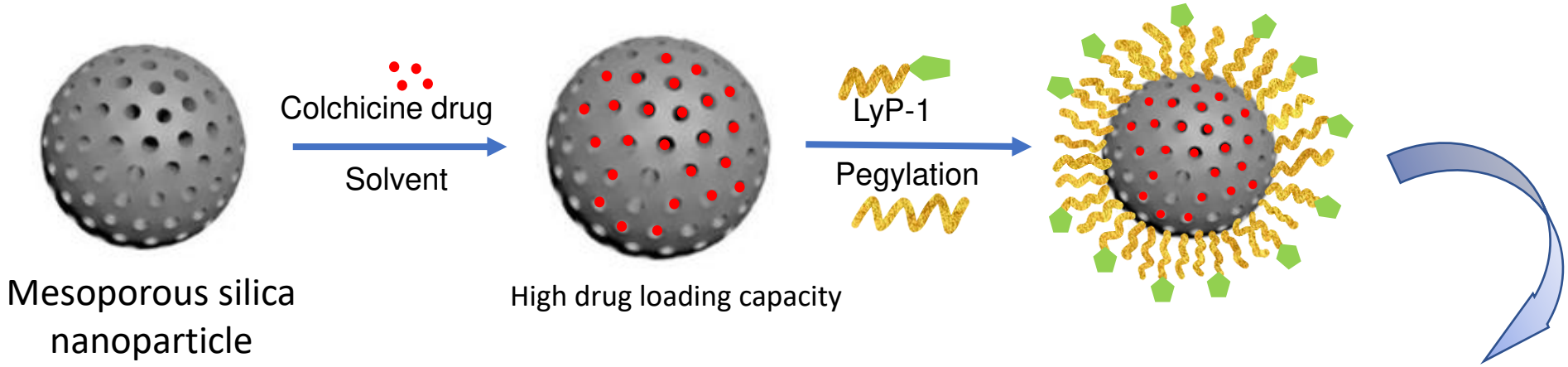
HARRY PERKINS INSTITUTE
OF MEDICAL RESEARCH

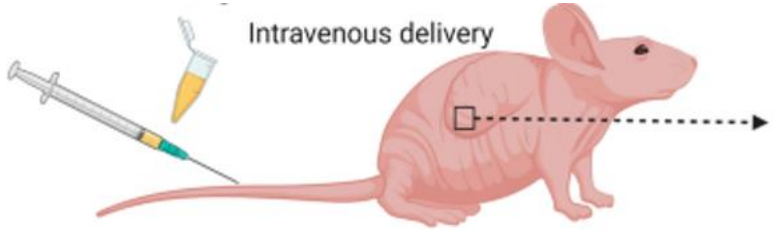
Colchicine to reduce inflammation in atherosclerotic plaques

- Can stabilize plaque lesions by suppressing inflammation
- Current clinical trials showed 25% reduction of cardiovascular events
- Uptake of colchicine is not specific to the atherosclerotic lesions
- High risk medicine if not used correctly and limited to use of low dosage

HARRY PERKINS INSTITUTE
OF MEDICAL RESEARCH

LyP-1 targeted delivery of colchicine loaded MSNs

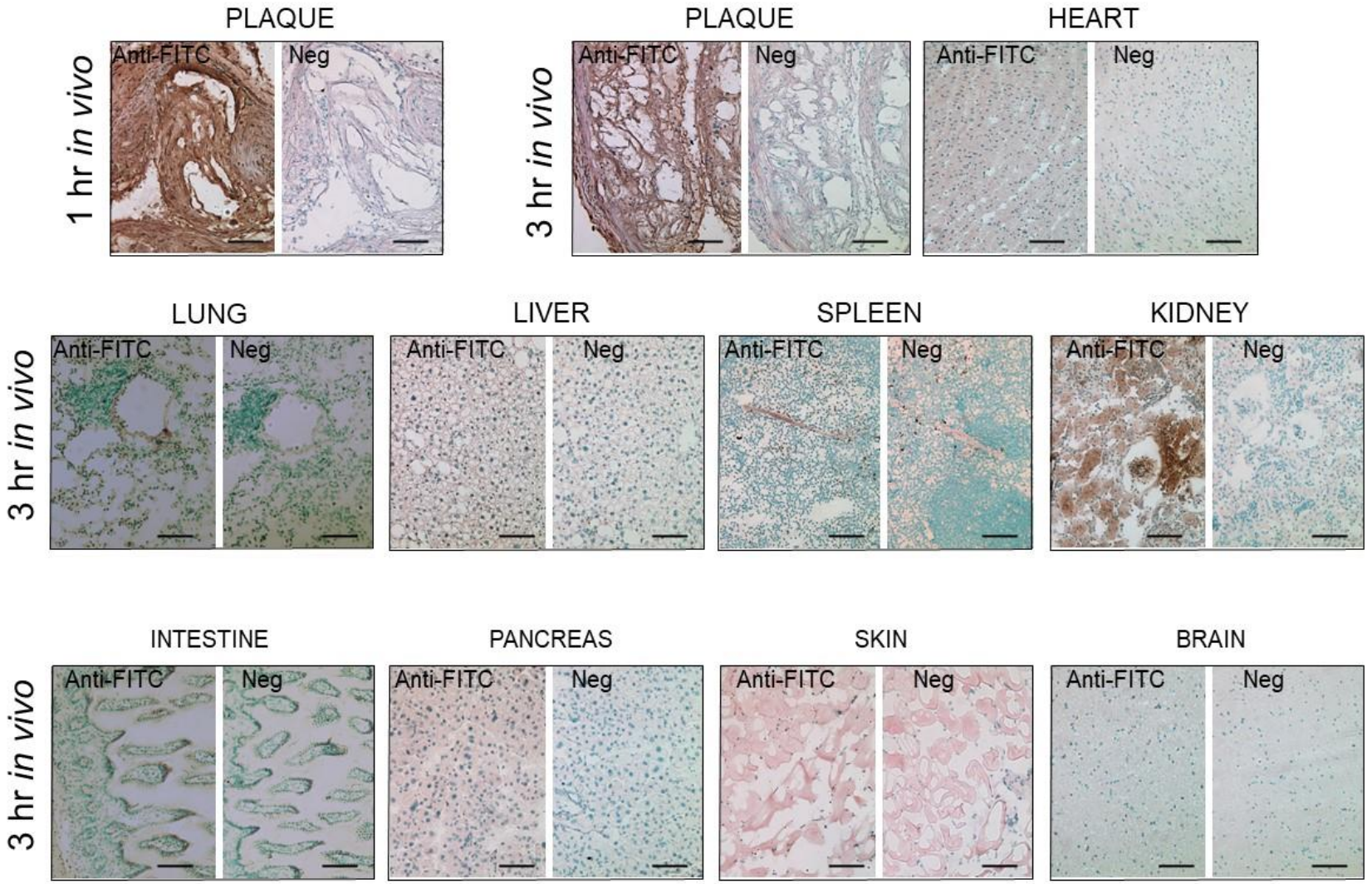




- High surface area
- High pore volume
- Tunable particle size
- Facile surface modification
- High biocompatibility

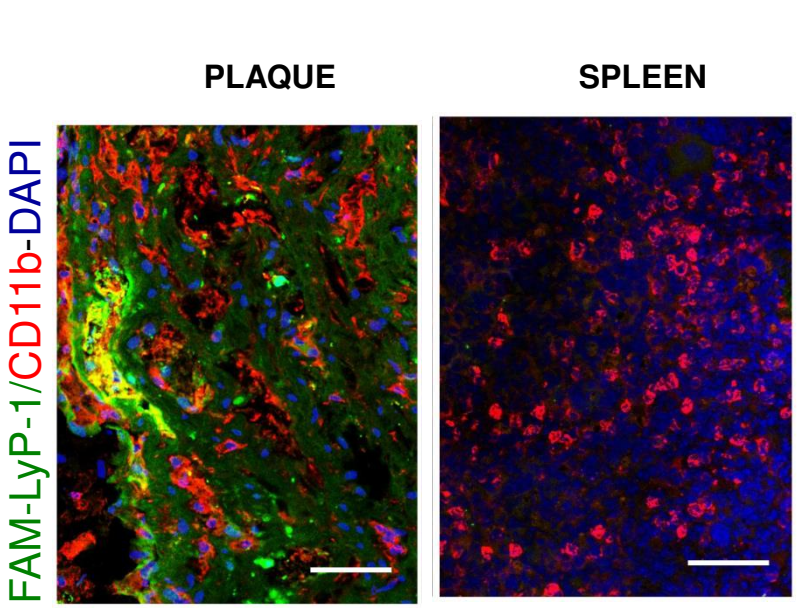
HARRY PERKINS INSTITUTE OF MEDICAL RESEARCH

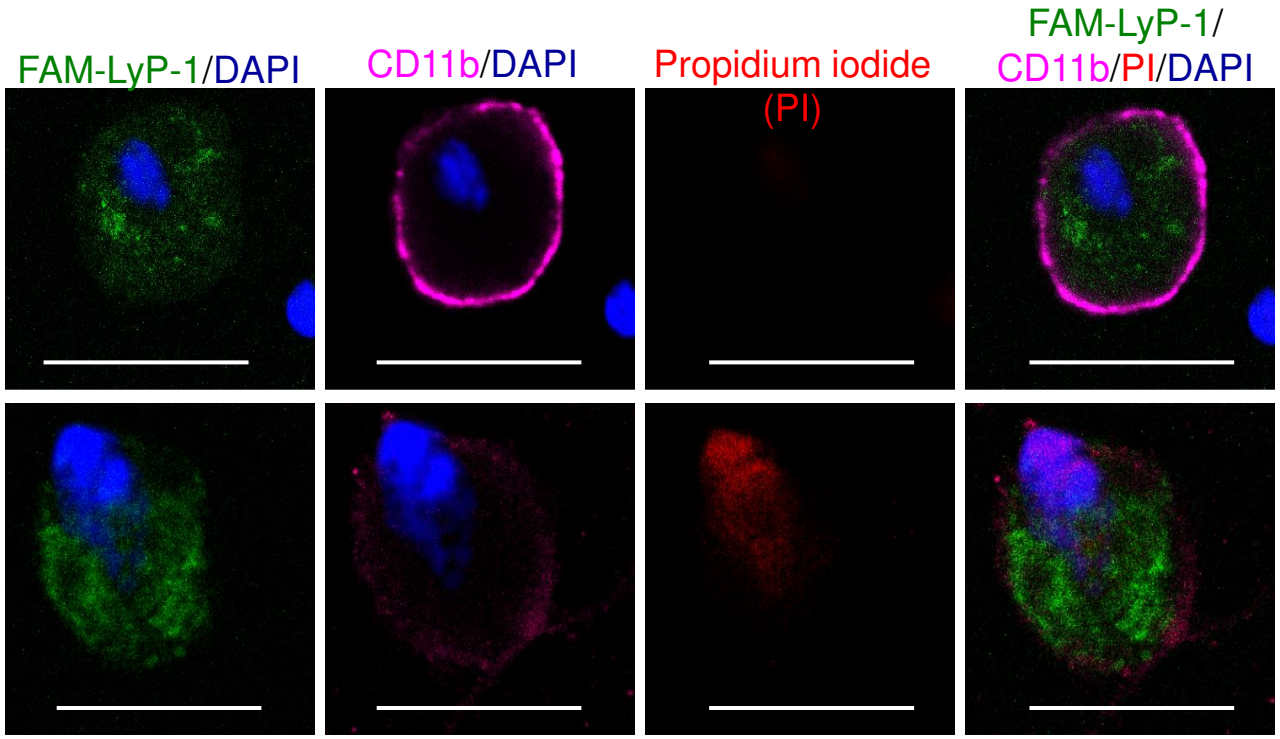
LyP-1 binding to aorta containing plaques following intravenous injection



HARRY PERKINS INSTITUTE
OF MEDICAL RESEARCH

LyP-1 binds and internalises in plaque macrophages





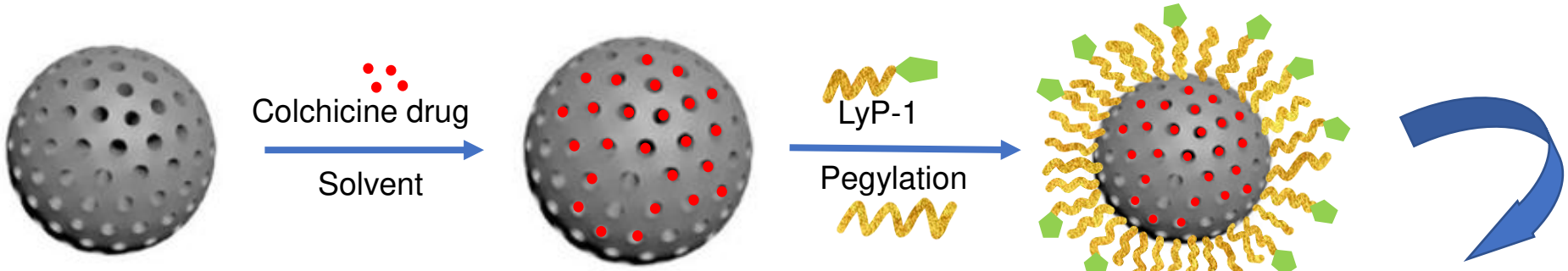
References:

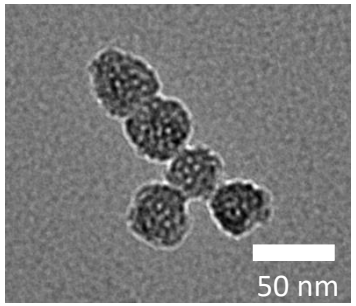
Hamzah J et al., bioconjugate Chem,. 2014, 25 (2), 231-239

Hamzah J et al., Proceedings of the National Academy of Science, 2011, 108 (17), 7154-7159

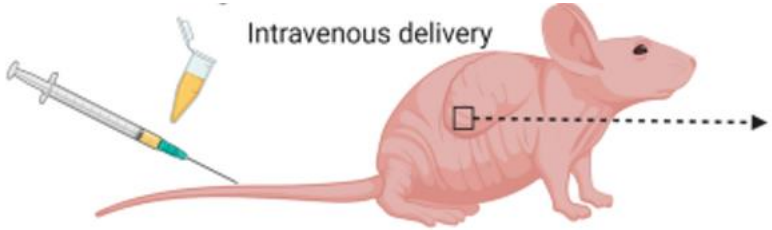
HARRY PERKINS INSTITUTE OF MEDICAL RESEARCH

LyP-1 targeted delivery of colchicine loaded MSNs





Drug loading capacity of ~ 60%
600 mg/ 1 g NPs



Particle diameter: 30 nm

Pore diameter: 3-4 nm

Surface area: 852 m^2/g

Pore volume: 0.88 cm^3/g

1. NP optimisation for colchicine loading
2. NP-colchicine in vitro bioactivity on macrophage cell lines
3. LyP-1-NP biodistribution
4. Optimal doses (safety)
5. Treatment study

HARRY PERKINS INSTITUTE
OF MEDICAL RESEARCH

New Horizons in Coronary Prevention

RNA Therapeutics for Lipoprotein(a)

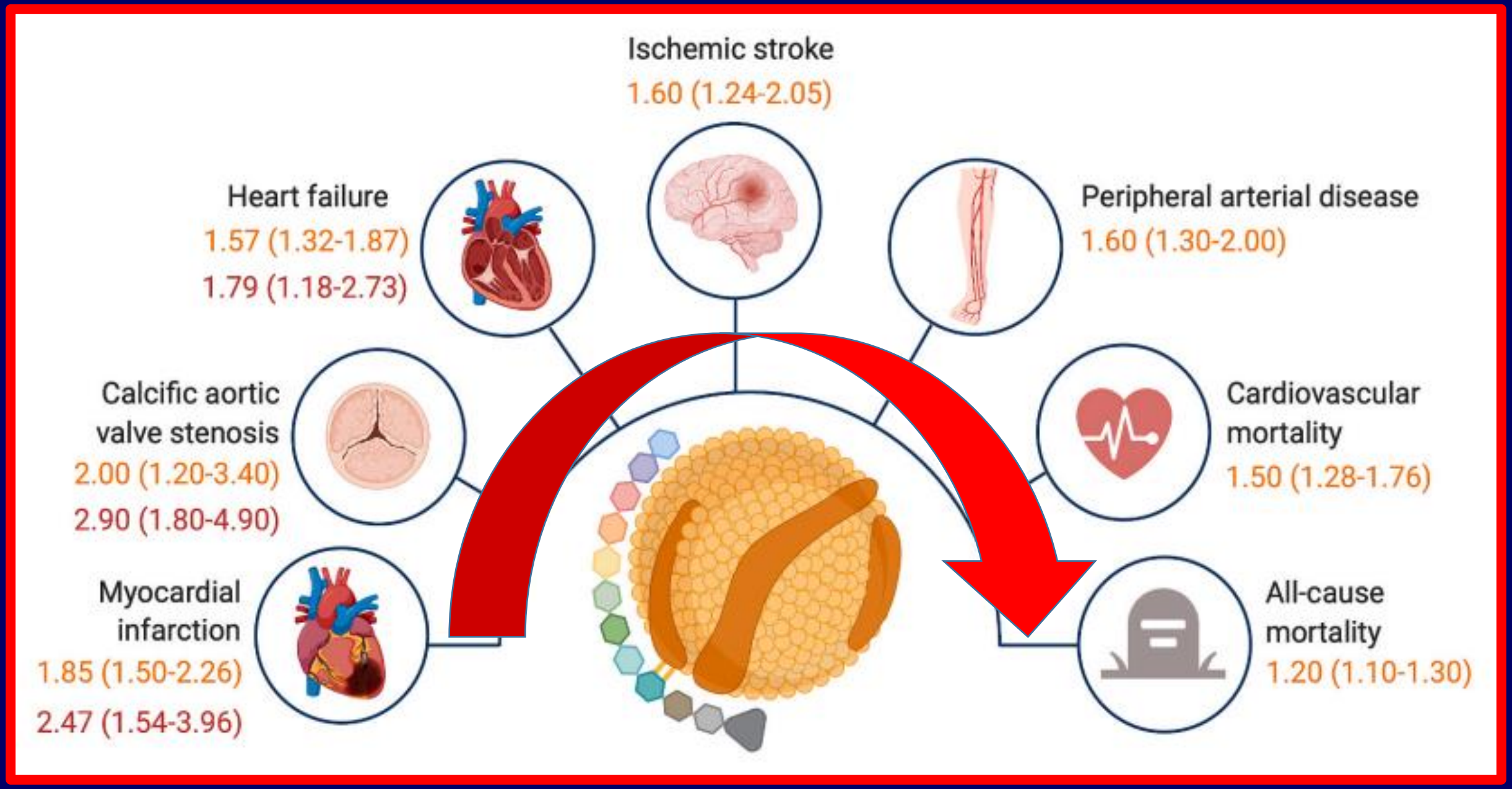
Gerald F Watts
Cardiometabolic Service, Department of Cardiology,
Royal Perth Hospital, School of Medicine,
University of Western Australia

Perkins Intensive Cardiovascular Research Update
November 8th 2022

THE UNIVERSITY OF WESTERN AUSTRALIA

Government of Western Australia

Royal Perth Hospital



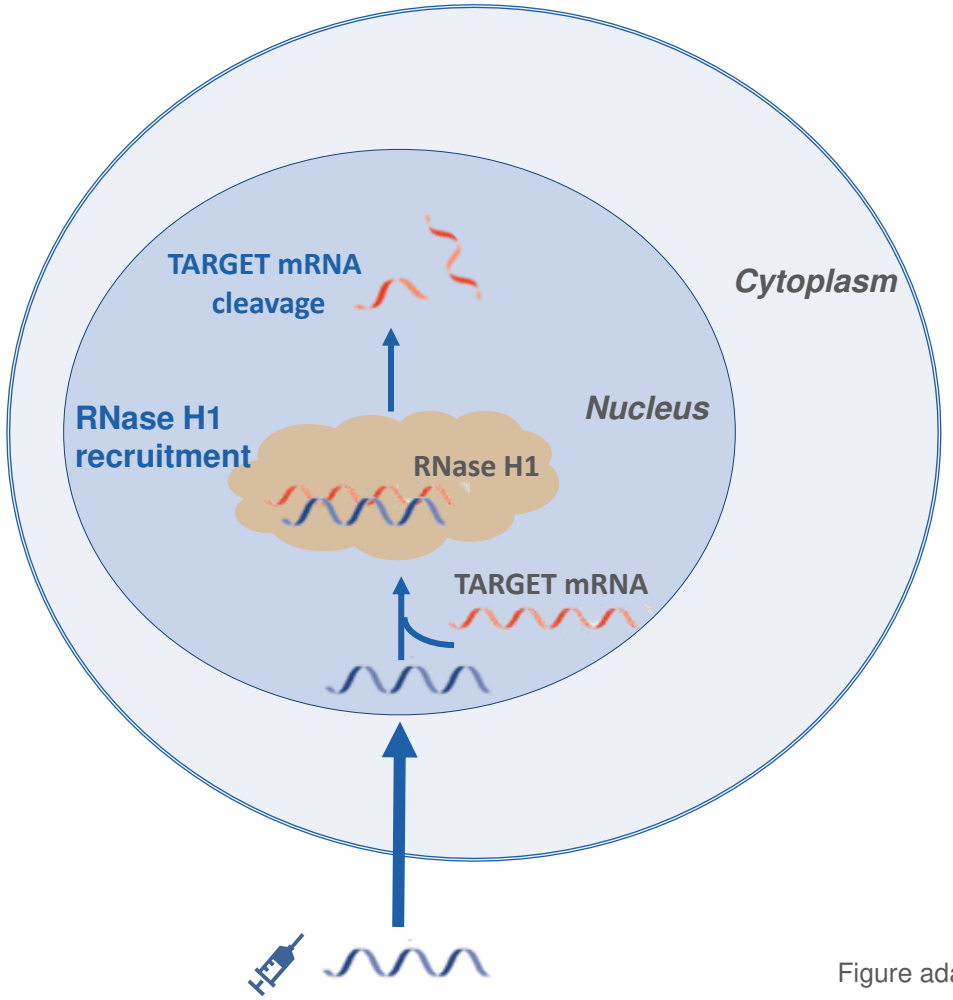
Arsenault & Kamstrup Atherosclerosis 2022; 349; 7-16

Interventions for Lowering Lipoprotein(a)

Therapy	Mechanism	Lp(a) Reduction
Statins	Upregulation of LDL receptor	0-7%
Niacin	Reduced apo(a) transcription or apoB secretion	20%
CETP Inhibitors	Inhibition of apoB lipidation	24-36%
PCSK9 Inhibitors	Upregulation of LDL receptor	25%
Apheresis	Removal of circulating apoB containing lipoproteins	~70% (acute) ~ 25 % (chronic)
Apo(a) RNA Therapeutics	Decreased apo(a) synthesis	~75-90%

A tale of two nucleic acid therapies

ASO Therapy: Pelacarsen



siRNA Therapy: Olpasiran

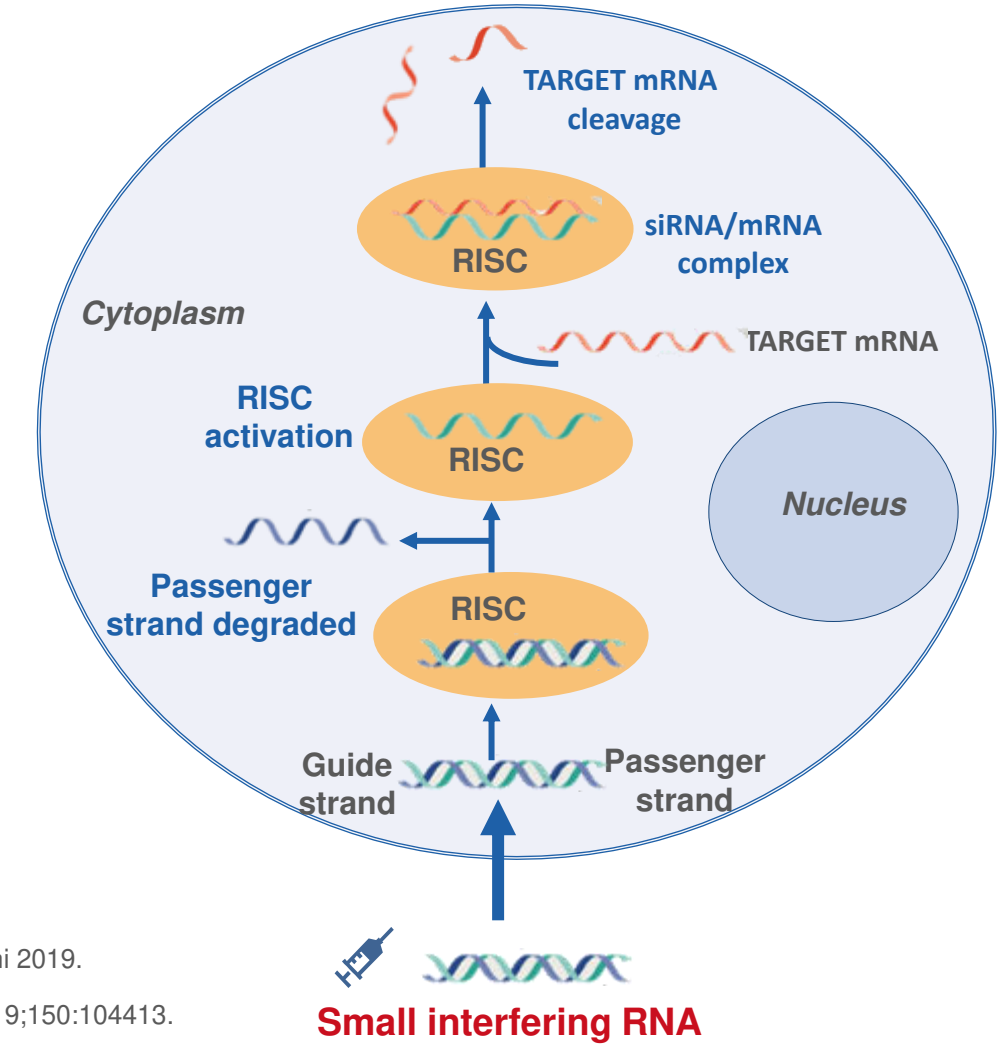
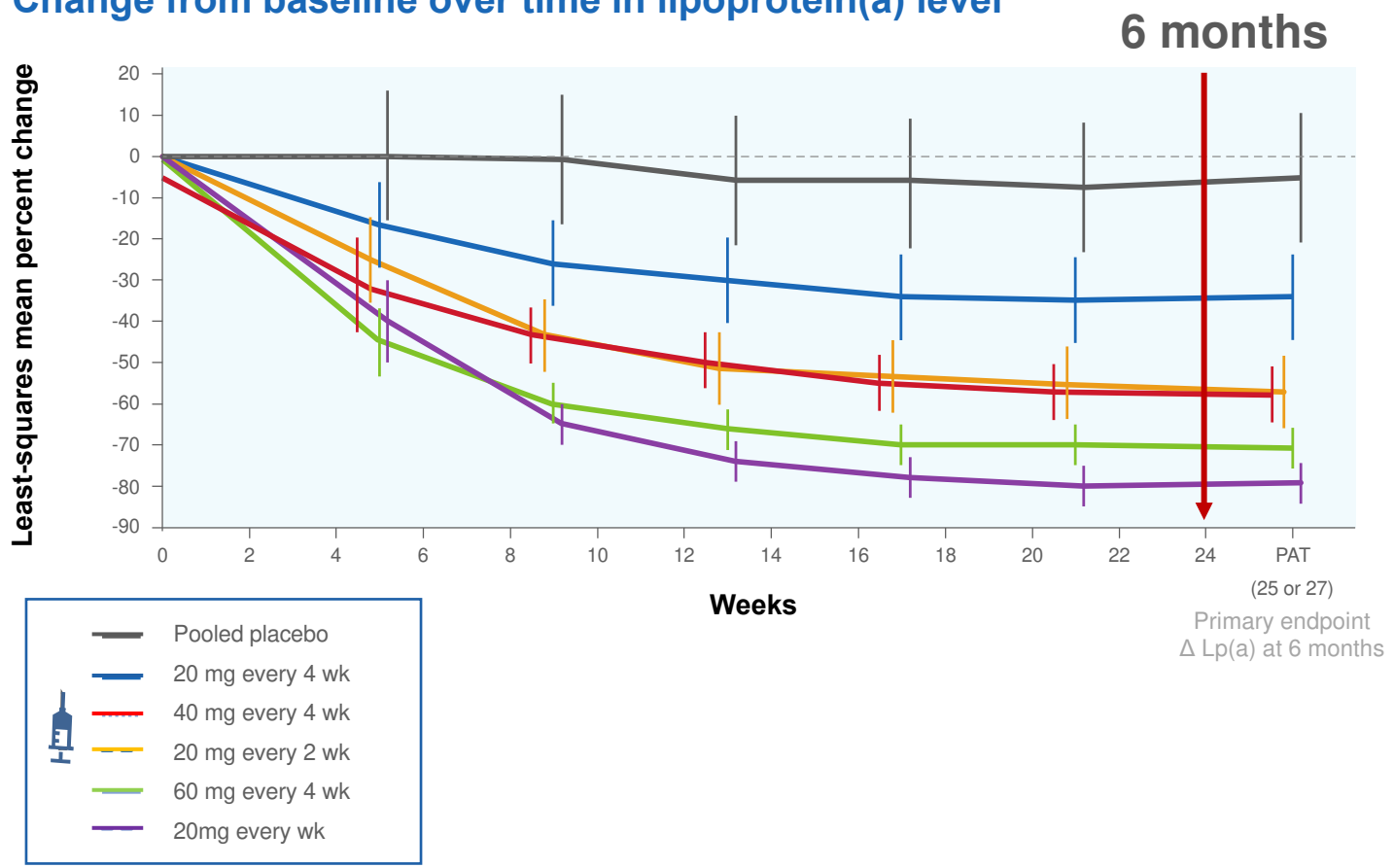


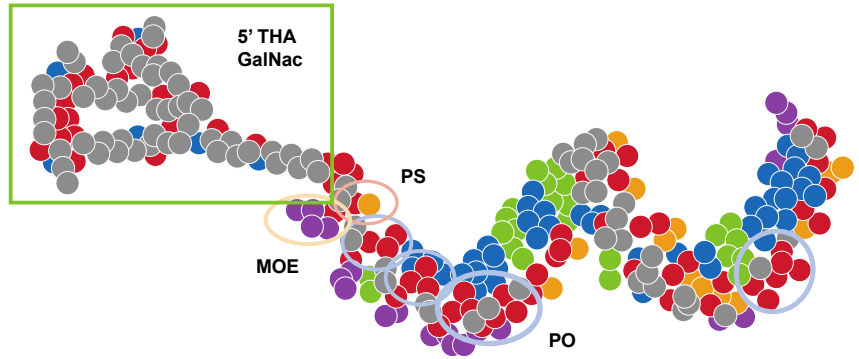
Figure adapted from Macchi 2019.

Macchi C et al. Pharmacol Res 2019;150:104413.

Targeting Lp(a) with ASO: Pelacarsen

Change from baseline over time in lipoprotein(a) level



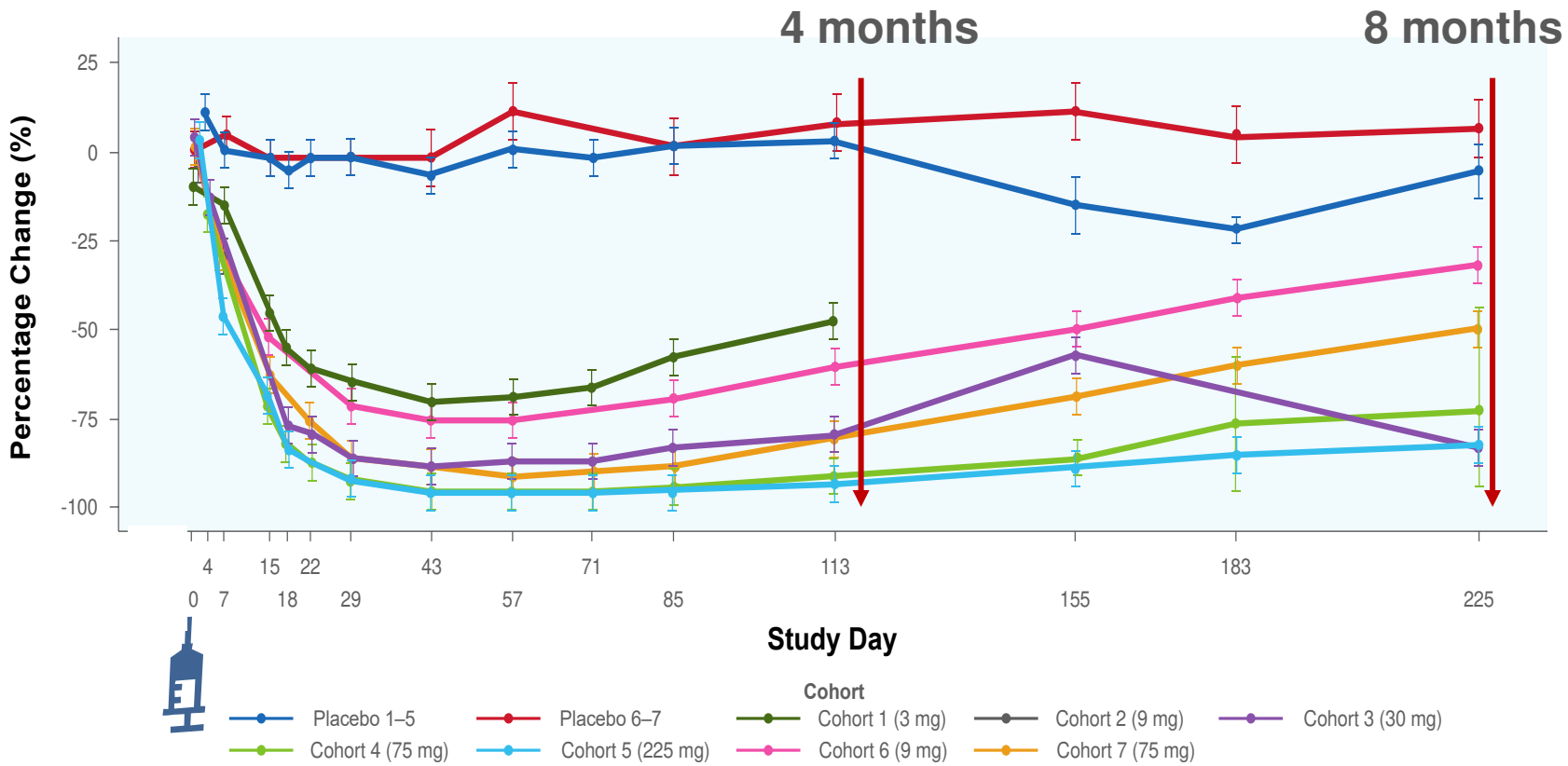


- No changes in platelet, renal or liver function, and no group difference in influenza symptoms
- The most common AEs were injection site reactions, which were generally mild

Phase 2 dose-ranging, randomised, double-blind, placebo-controlled trial showed dose-dependent reductions in Lp(a) in patients with elevated Lp(a) and established CVD.

Adapted from Tsimikas S et al. 2020. **1.** Novartis, data on file **2.** Tsimikas S et al. N Engl J Med 2020; 382: 244–255.

Targeting Lp(a) with siRNA: Olpasiran



- Generally well tolerated
- No serious AEs
- Only one patient (on olpasiran) experienced an injection site reaction
- No relevant changes in liver or kidney function, platelets, coagulation or safety labs
- No abnormal vital signs or ECGs

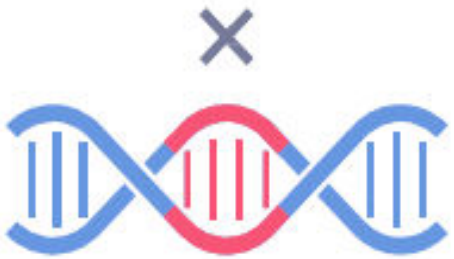
Phase I study (n=64) evaluated the safety, tolerability, pharmacokinetics and pharmacodynamics of olpasiran (AMG 890).

Adapted from Koren MJ el al. 2022. **1.** Koren MJ et al. Nat Med 2022; 28(1): 96–103.

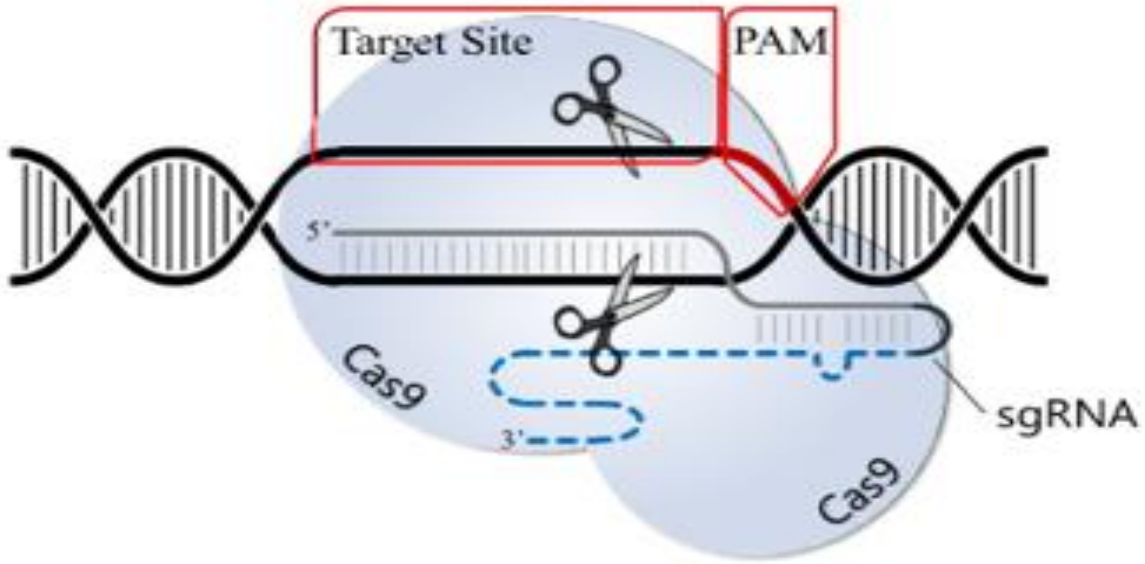
CRISPR-Cas9 Gene Editing

The CRISPR/Cas9 Revolution

A **SPECIFIC**, **EFFICIENT** and **VERSATILE** tool for editing genes



Disrupt



HARRY PERKINS INSTITUTE
OF MEDICAL RESEARCH

HARRY PERKINS INSTITUTE
OF MEDICAL RESEARCH

Harry Perkins Institute North
(QEII Medical Centre)


Harry Perkins Institute South
(Fiona Stanley Hospital)

Perkins Cardiovascular Research Intensive Mini Symposium 8th November 2022

Session 3.
Atherosclerosis continued

Session 3	11:00	**Mr**	**Benjamin Bartlett**	**Dual disease mouse model**
Atherosclerosis	11:30	**Prof**	**Shirley Jansen**	**PAD and the diabetic foot**
	11:40	**Prof**	**Grant Morahan**	**Genomic prediction of CVD**
	11:50		**Discussion**	**Discussion**

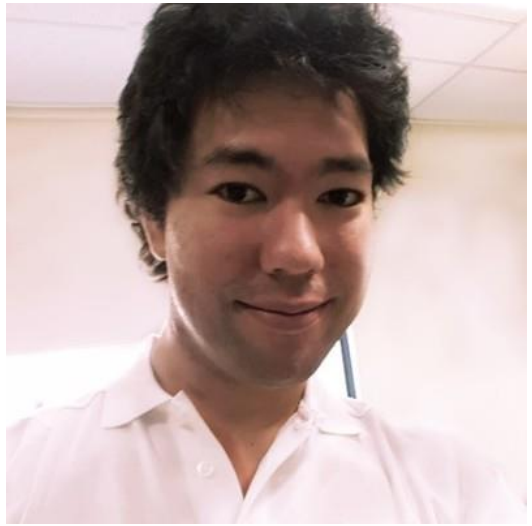
Perkins Cardiovascular Research Intensive Mini Symposium

Session 3. Atherosclerosis Continued

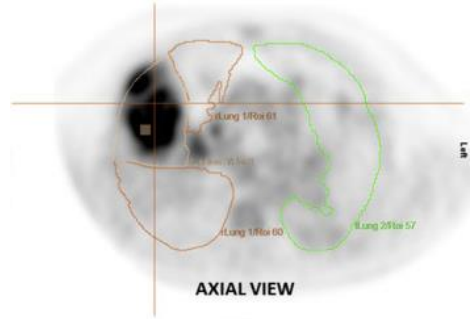
- **Ben Bartlett** describes his development of a model of accelerated atherosclerosis in ApoE knockout high fat diet mice by initiating pneumonia and creating a pro atherogenic inflammatory reaction
- **Shirley Jansen** discusses the clinical challenge of trying to avoid amputation in diabetic foot and the difficulties of reliably assessing foot perfusion with ankle or toe brachial index compared with optical coherence tomography or near infra red spectroscopy and the work she is doing with Prof Danny Green to improve current methods.
- **Grant Morahan** describes his development of genetic risk scores to predict heart attack with more precise accuracy than clinical risk factors. His unique approach relies on identifying genes which are in close relationship with each other. Testing shows remarkable accuracy with a small number of gene variants

Cardiovascular changes after pneumonia in a dual disease mouse model

Benjamin Bartlett[1,2], Herbert P. Ludewick[1], Shipra Verma[5,6], Vicente F. Corrales-Medina[7,8], Grant Waterer[2,9], Silvia Lee[1,4] & Girish Dwivedi[1,2,3]



[1]Department of Advanced Clinical and Translational Cardiovascular Imaging, Harry Perkins Institute of Medical Research, Murdoch, WA, Australia.
[2]School of Medicine, University of Western Australia, Perth, WA, Australia.
[3]Department of Cardiology, Fiona Stanley Hospital, Murdoch, WA, Australia.
[4]Department of Microbiology, Pathwest Laboratory Medicine, Perth, Australia.
[5]Department of Nuclear Medicine, PET CT and Radionuclide Therapy, Fiona Stanley Hospital, Murdoch, WA, Australia.
[6]Department of Geriatric Medicine, Fiona Stanley Hospital, Murdoch, WA, Australia.
[7]Department of Medicine, University of Ottawa, Ottawa, Canada.
[8]Clinical Epidemiology Program, The Ottawa Hospital Research Institute, Ottawa, Canada.
[9]Royal Perth Hospital, Perth, WA, Australia.



THE UNIVERSITY OF WESTERN AUSTRALIA
Achieve International Excellence

FIONA STANLEY hospital

Australian National Phenome Centre

Murdoch University

HARRY PERKINS INSTITUTE OF MEDICAL RESEARCH

Pneumonia increases cardiovascular risk

Association Between Hospitalization for Pneumonia and Subsequent Risk of Cardiovascular Disease

Vicente F. Corrales-Medina, MD, MSc[1,2]; Karina N. Alvarez, MS[3]; Lisa A. Weissfeld, PhD[3,4]; et al

» Author Affiliations | Article Information

JAMA. 2015;313(3):264-274. doi:10.1001/jama.2014.18229

EUROPEAN RESPIRATORY *journal*
FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Is community-acquired pneumonia an independent risk factor for cardiovascular disease?

A. Singanayagam, A. Singanayagam, D.H.J. Elder, J.D. Chalmers

European Respiratory Journal 2012 39: 187-196; **DOI:** 10.1183/09031936.00049111

CURRENT OPINION

Cardiovascular complications following pneumonia: focus on pneumococcus and heart failure

Benjamin Bartlett[a,b], Herbert P. Ludewick[b], Silvia Lee[a,b,c], and Girish Dwivedi[a,b,d]

Chest Infections: Original Research

Persistent Lung Inflammation After Clinical Resolution of Community-Acquired Pneumonia as Measured by ^{18}FDG-PET/CT Imaging

Vicente F. Corrales-Medina MD [a, b], Robert A. deKemp PhD [c, d], Julio A. Chirinos MD, PhD [e], Wanzhen Zeng MD [b], Jerry Wang BSc [c, d], Grant Waterer MD [f, g], Rob S.B. Beanlands MD [c, d], Girish Dwivedi MD, PhD [c, d, g, h, i]

Cardiac Complications in Patients With Community-Acquired Pneumonia

Incidence, Timing, Risk Factors, and Association With Short-Term Mortality

Vicente F. Corrales-Medina, Daniel M. Musher, George A. Wells, Julio A. Chirinos, Li Chen and Michael J. Fine

Originally published 4 Jan 2012 | https://doi.org/10.1161/CIRCULATIONAHA.111.040766 | Circulation. 2012;125:773–781

Research

Risk of heart failure after community acquired pneumonia: prospective controlled study with 10 years of follow-up

BMJ 2017 ; 356 doi: https://doi.org/10.1136/bmj.j413 (Published 13 February 2017)
Cite this as: *BMJ* 2017;356:j413

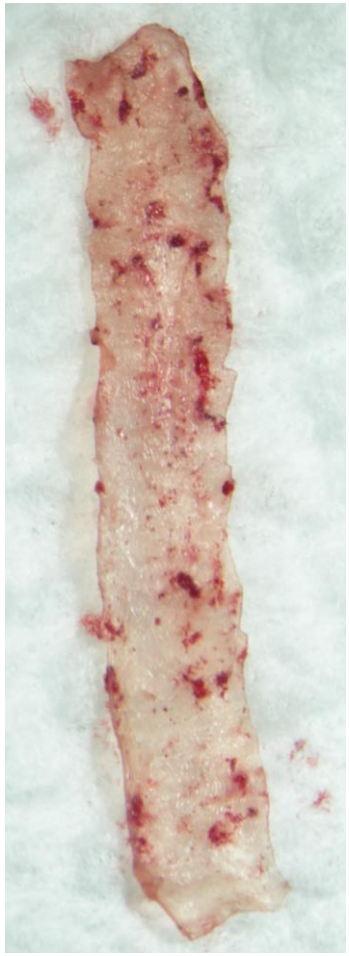
Proposed Project

Develop a longitudinal dual disease (pneumonia-atherosclerosis) mouse model.

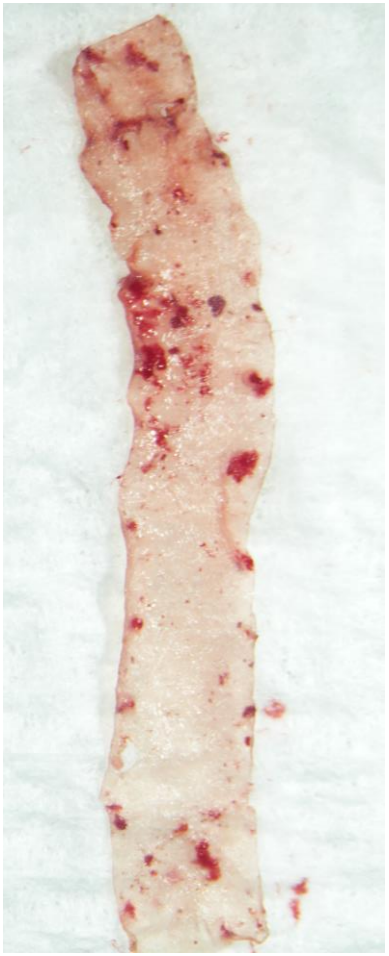
Investigate the mechanisms by which residual inflammation from acute pneumonia increases long-term cardiovascular risk.

1. Assess cardiac and vascular inflammation
2. Assess plaque for markers of stability (i.e., vulnerable plaque)
3. Assess aortic wall integrity

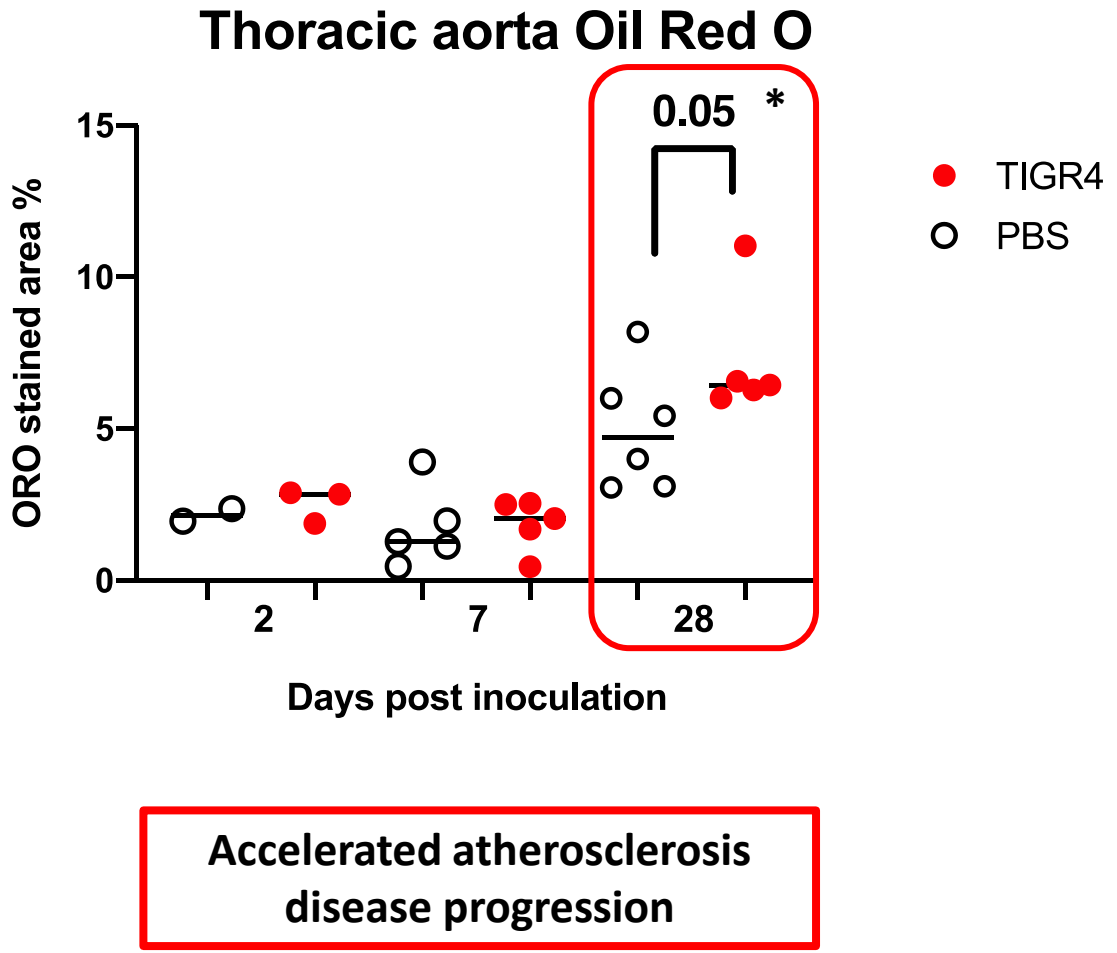
Atherosclerotic disease progression



TIGR4



PBS

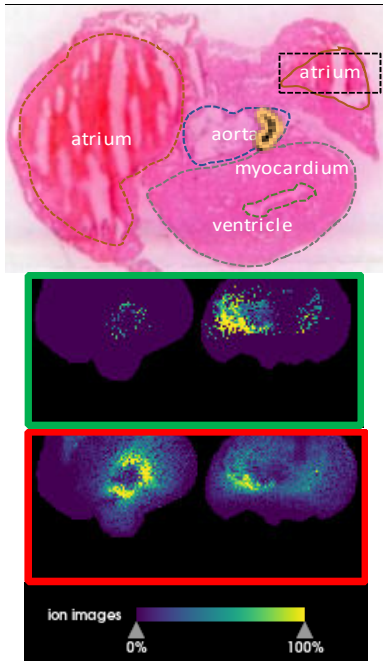


Accelerated atherosclerosis disease progression

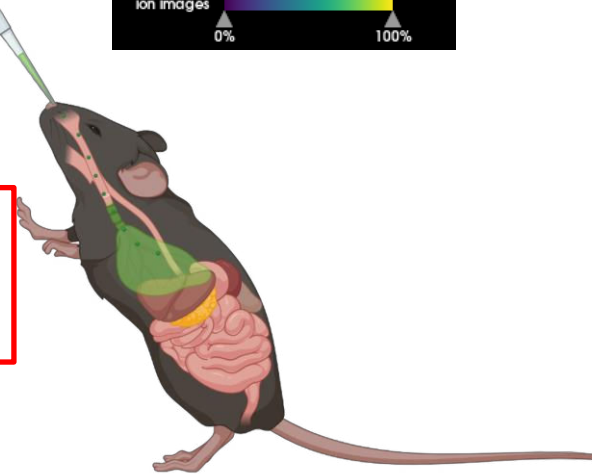
Model Conclusions

Low-dose *Streptococcus pneumoniae* TIGR4 atherosclerosis model demonstrates:

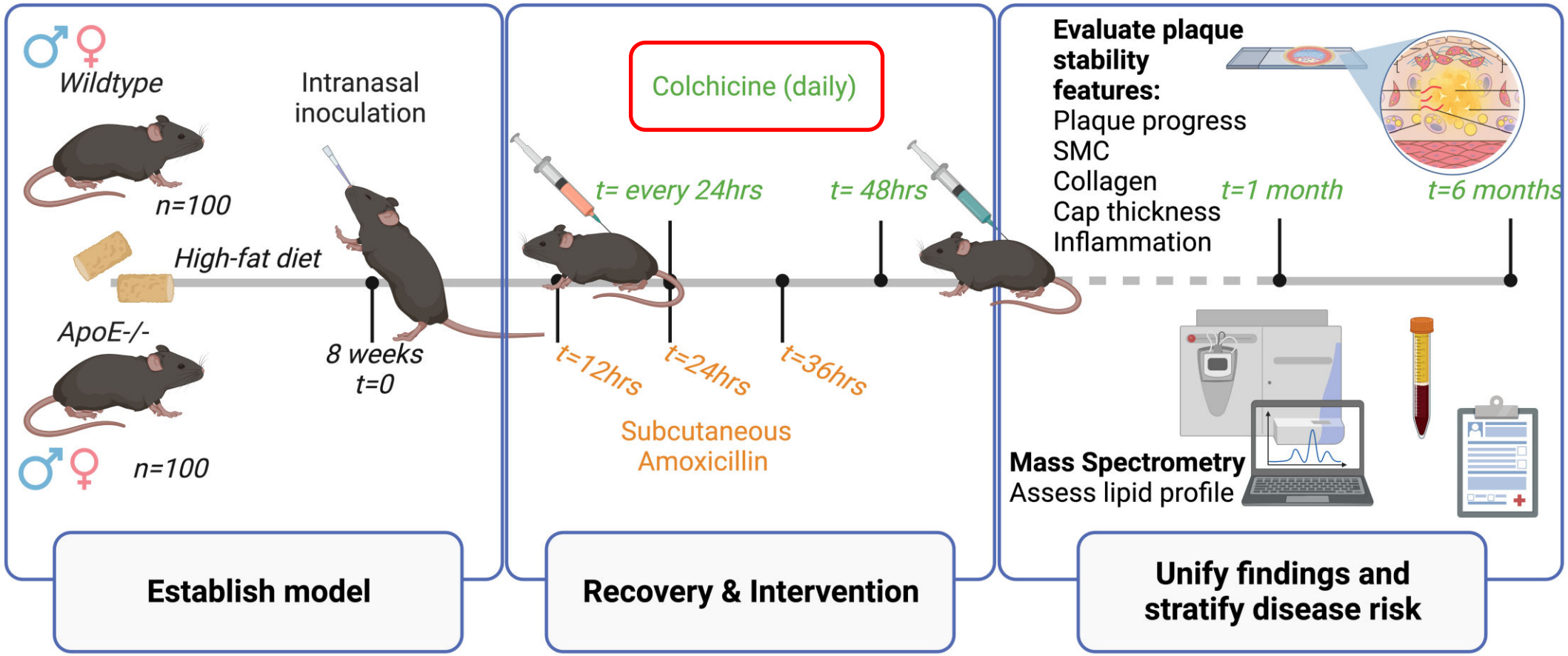
- Persistent lung inflammation (FDG-PET)
- Reduced aortic root plaque collagen and smooth muscle cell content
- Increased aortic root remodeling
- Increased systemic inflammation (MIP-1α)
- Increased atherosclerotic disease progression
- Altered lipid processing



Highlighting several mechanisms that may contribute to increase cardiovascular risk following pneumonia



Future Directions



CI: Prof Girish Dwivedi, Dr Ashish Misra, Dr Abdul Ihdayhid, Prof Peter Thompson, Prof Grant Waterer, Prof Graham Hillis, Prof Sanjay Patel, Dr Vicente Corrales-Medina, Prof Jeremy Nicholson, Dr Silvia Lee, A/Prof Frank Sanfilippo & Prof Yuben Moodley.

PI: A/Prof Berin Boughton & Dr Herbert Ludewick.

SUBMITTED

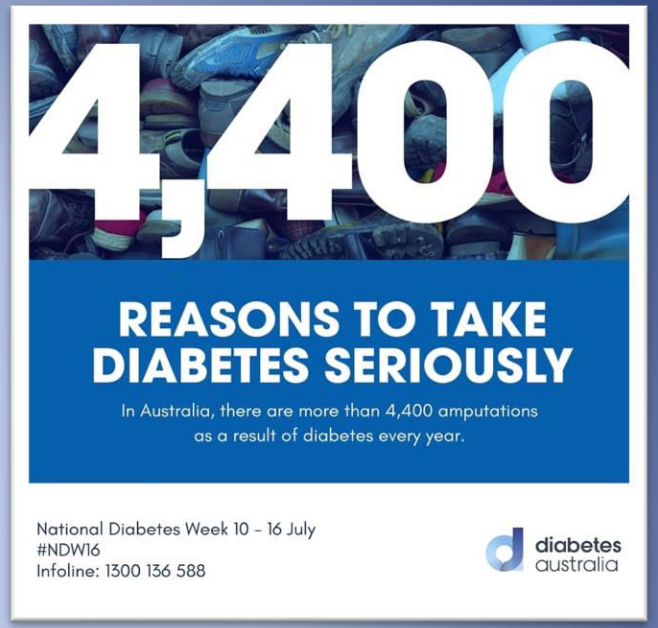
MRFF 2022

PAD and DM

Peripheral Artery Disease and Diabetes Mellitus

Prof Shirley Jansen

Program Head of Cardiovascular Science and Diabetes as well as Director of the Heart and Vascular Research Institute at the Perkins. She is also Head of Dept of Vascular and Endovascular Surgery at Sir Charles Gairdner Hospital



Government of Western Australia
North Metropolitan Health Service
Sir Charles Gairdner Hospital

Heart & Vascular Research Institute
Preventing amputation, stroke & heart attack

CURTIN HEALTH INNOVATION RESEARCH INSTITUTE

Curtin University

Perkins
HARRY PERKINS INSTITUTE OF MEDICAL RESEARCH

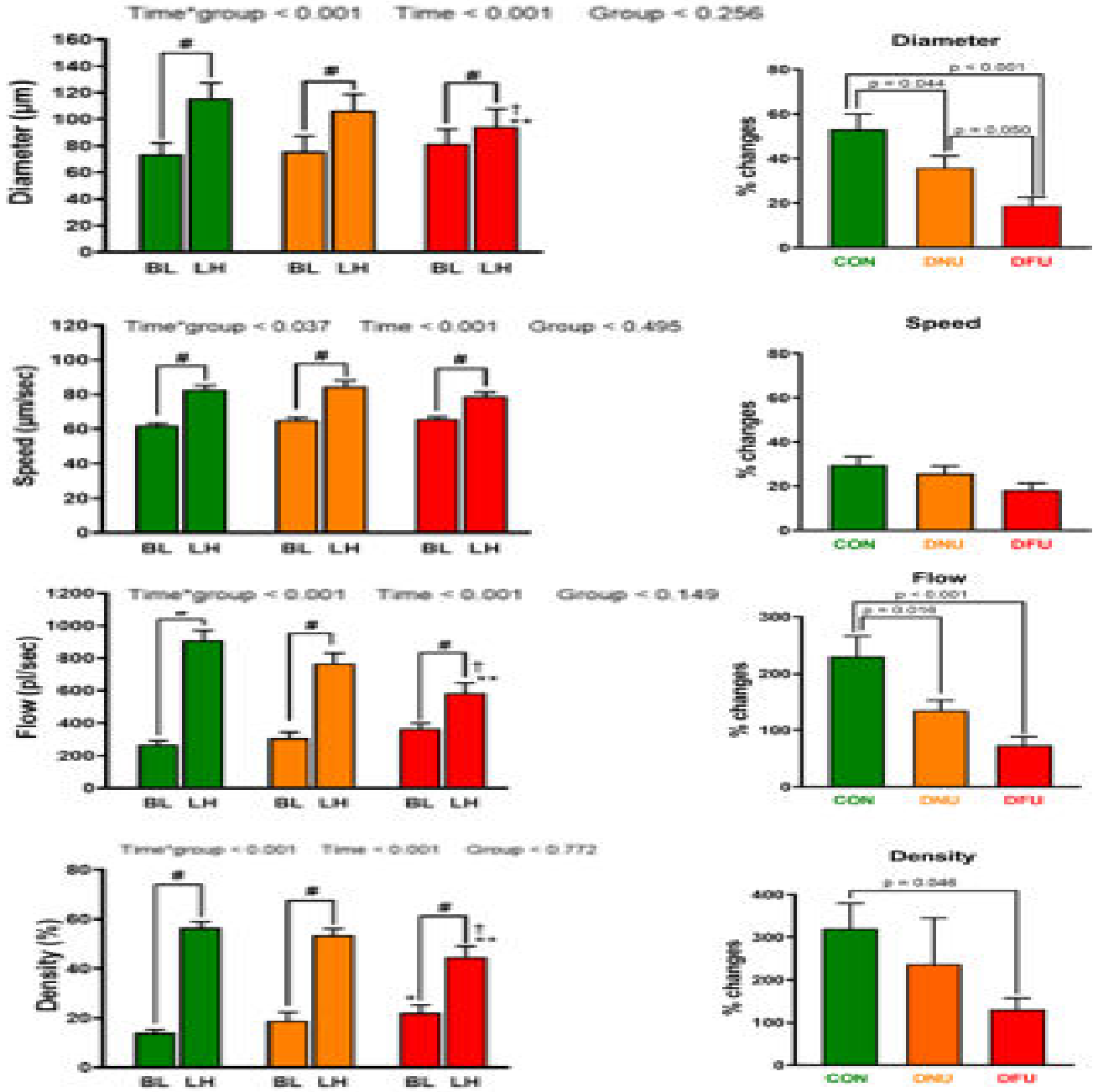
PAD and DM

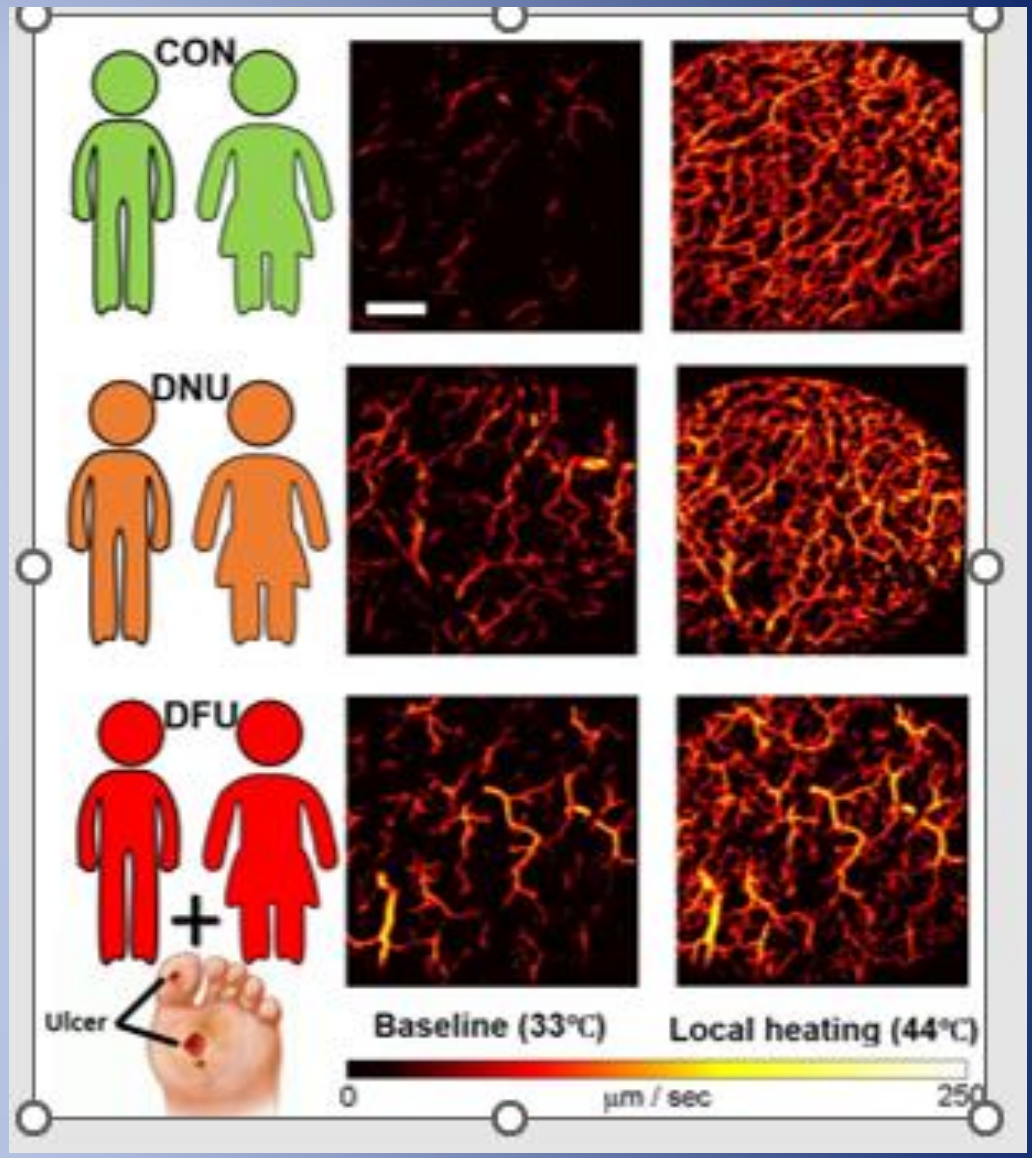
- PAD with diabetes increasing, est 10-40% incidence worldwide.
- Natural history is different:
  - Symptoms not classic progression through claudication to rest pain,
  - more aggressive.
  - > 50% asymptomatic or atypical symptoms from decreased pain perception from peripheral neuropathy.
  - Lifetime risk of DFU is ~25%, PAD is often related in 50%.

It is argued that amputation is largely a preventable complication;

- > 85% of major amputations preceded by DFU
- The risk lower limb amputation 23 x non diabetics
- 5 year mortality with DFU is 2.5x higher

Skin microvasculature: OCT-derived parameters





Limitations of fNIRS

NIRS can assess function BUT affected by:

- Poor skin condition
- Dark skin
- High adiposity
- Oedema

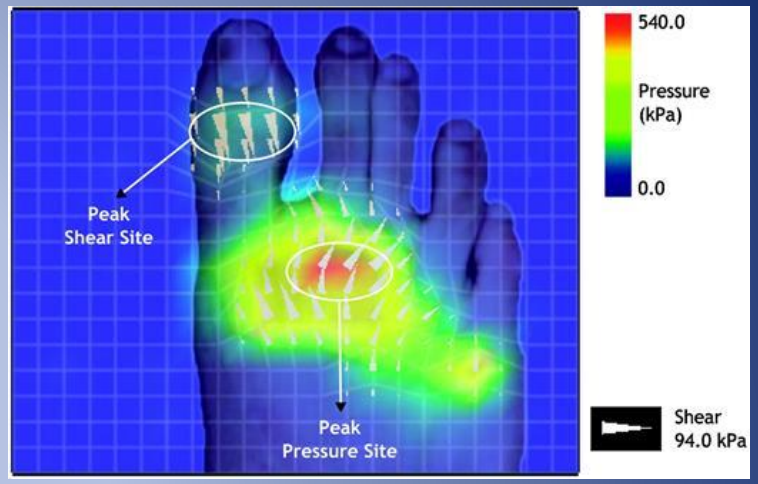
Multiple NIRS probes? Concept of a foot map?

Limitations of OCT

- Expensive equipment that is not portable
- Can only test one area of skin
- Relocation to same testing point is impacted by movement (spasm from neuropathy)
- Needs adapting to a portable POC machine which can be used by untrained people at multiple places on the foot
- BUT unlike NIRS can be used over regions with less muscle

Further research into microcirc perfusion is required to:

- Compare to change in WIFi grade (Wound, Ischemia, and foot Infection)
- Confirm similar utility in severe vessel calcification (dialysis)
- Explore trends with wound healing
- Assess change with pressure load/shear stress on skin/weight bearing time
- Predict limb outcomes



Diabetes Care. 2007

a, Estimate risk of amputation at 1 year for each combination

	Ischemia – 0				Ischemia – 1				Ischemia – 2				Ischemia – 3			
W-0	VL	VL	L	M	VL	L	M	H	L	L	M	H	L	M	M	H
W-1	VL	VL	L	M	VL	L	M	H	L	M	H	H	M	M	H	H
W-2	L	L	M	H	M	M	H	H	M	H	H	H	H	H	H	H
W-3	M	M	H	H	H	H	H	H	H	H	H	H	H	H	H	H
	fI-0	fI-1	fI-2	fI-3	fI-0	fI-1	fI-2	fI-3	fI-0	fI-1	fI-2	fI-3	fI-0	fI-1	fI-2	fI-3

b, Estimate likelihood of benefit of/requirement for revascularization (assuming infection can be controlled first)

	Ischemia – 0				Ischemia – 1				Ischemia – 2				Ischemia – 3			
W-0	VL	VL	VL	VL	VL	L	L	M	L	L	M	M	M	H	H	H
W-1	VL	VL	VL	VL	L	M	M	M	M	H	H	H	H	H	H	H
W-2	VL	VL	VL	VL	M	M	H	H	H	H	H	H	H	H	H	H
W-3	VL	VL	VL	VL	M	M	M	H	H	H	H	H	H	H	H	H
	f-0	fI-1	fI-2	fI-3	fI-0	fI-1	fI-2	fI-3	fI-0	fI-1	fI-2	fI-3	fI-0	fI-1	fI-2	fI-3

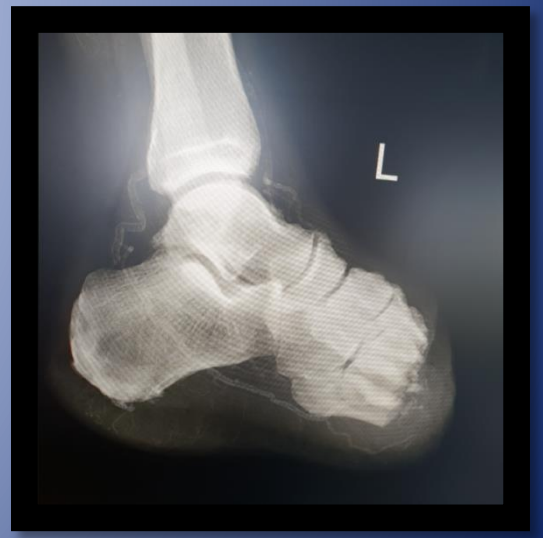
fI, foot Infection; I, Ischemia; W, Wound.

Premises:

1. Increase in wound class increases risk of amputation (based on PEDIS, UT, and other wound classification systems)
2. PAD and infection are synergistic (Eurodiale); infected wound + PAD increases likelihood revascularization will be needed to heal wound
3. Infection 3 category (systemic/metabolic instability): moderate to high-risk of amputation regardless of other factors (validated IDSA guidelines)

Four classes: for each box, group combination into one of these four classes

Very low = VL = clinical stage 1
Low = L = clinical stage 2
Moderate = M = clinical stage 3
High = H = clinical stage 4
Clinical stage 5 would signify an unsalvageable foot



THE UNIVERSITY OF WESTERN AUSTRALIA

Government of Western Australia
North Metropolitan Health Service
Sir Charles Gairdner Hospital

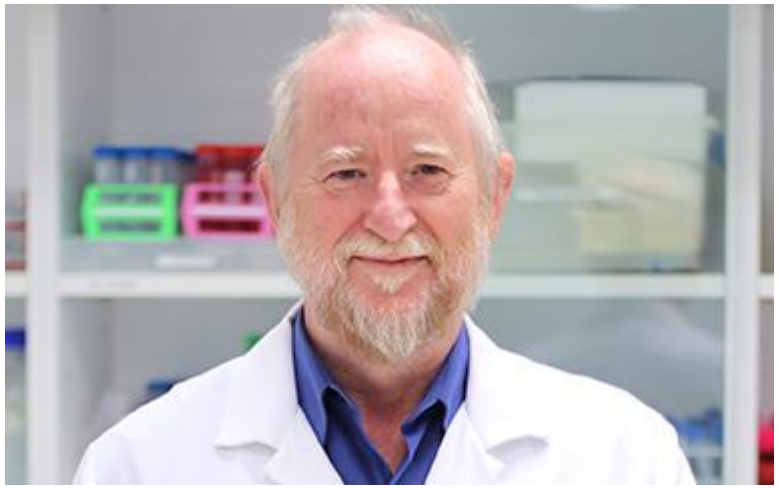
Heart & Vascular Research Institute
Preventing amputation, stroke & heart attack

CURTIN HEALTH INNOVATION RESEARCH INSTITUTE

Curtin University

Perkins
HARRY PERKINS INSTITUTE OF MEDICAL RESEARCH

Genetic Prediction of Risk of Heart Diseases



Grant Morahan

Centre for Diabetes Research

The Harry Perkins Institute for Medical Research

HARRY PERKINS INSTITUTE
OF MEDICAL RESEARCH

Disease Genetics

- Over 1,000 disease "genes" found

BUT:

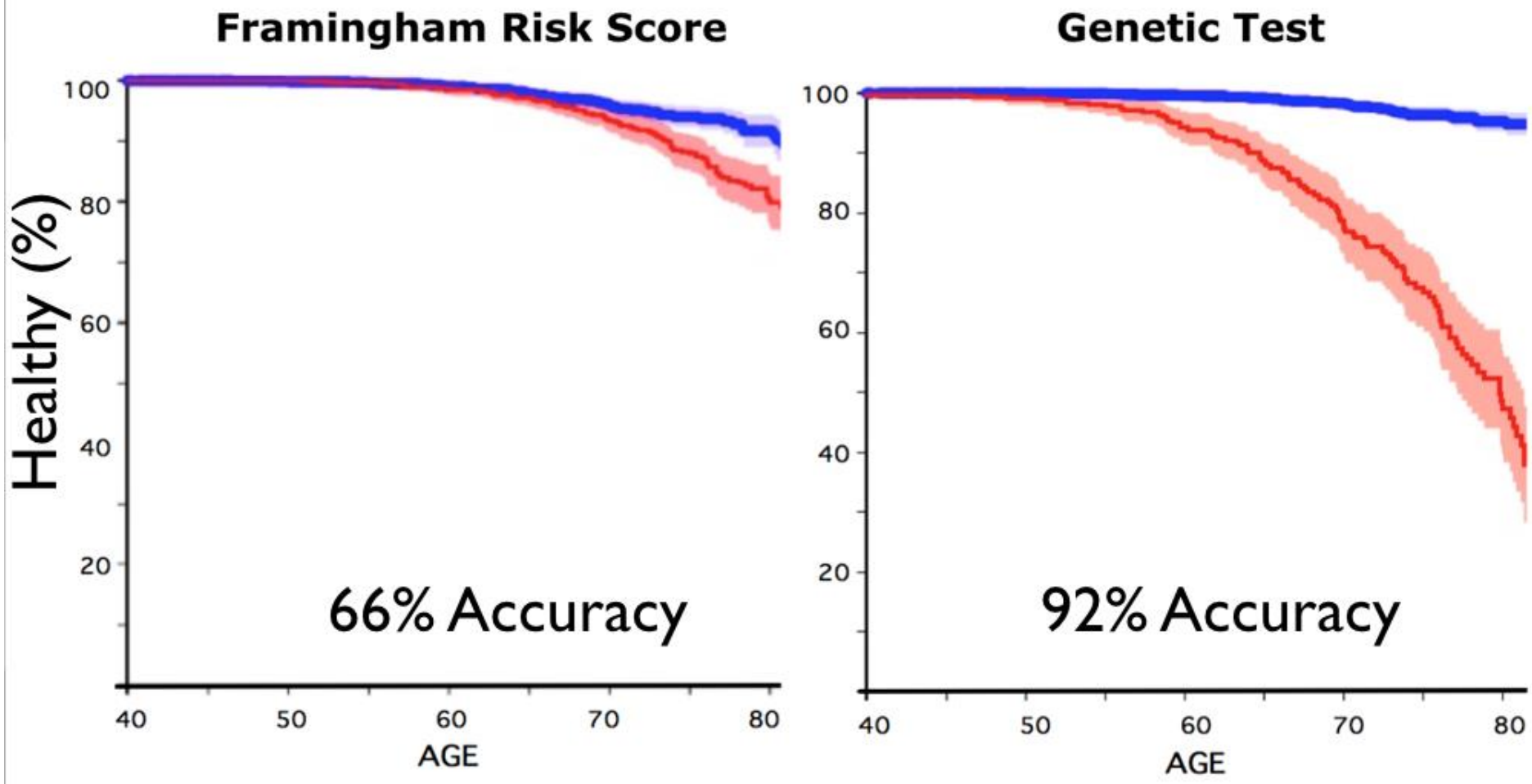
- Most are variants not in genes
- Most have small effects
- Clinical significance doubtful
- Function of most is unknown

=> Need a new approach

Can we predict disease outcomes based on interactions of many low-effect genes?

Heart Attack Risk

(in hypertensive subjects)



Hypertensive Subjects aged 25 to 65 at recruitment; follow-up 15 years

Comparison v Mega test

Statistic	*Lancet* 385:2264	Our Test
Disease Prevalence	10.98%	10.98%
Sensitivity	0.32	**0.74**
Specificity	0.81	0.94
Positive Predictive Value	17.4%	**60.4%**
Negative Predictive Value	90.6%	96.8%
Number Needed to Treat (Benefit)	12.5	**1.75**
Relative risk	1.85	**18.57**
P (Fisher's Exact Test)	7.9e-07	**2.2e-16**

Mega et al. *Lancet* 385:2264-71.

Testing in SCOT- HEART

(David Newby, Girish Dwivedi, Nestor Gahungu)

- benefit of CCTA for CHD patients with angina
- We compared outcomes vs genetic risk in patients with non obstructive CAD
- In setting of low risk CCTA, high genetic risk cases more likely to have adverse events:
  - Low attenuation plaque RR = 18 (P<0.0001)
  - Low (<100) calcium score RR=5 (P=0.03)

SUMMARY

- Our new methods can:
  - identify high-risk people
  - predict disease outcomes
    - *More accurately than best clinical tests*
    - *years before onset of symptoms*
  - *allow personalized medicine*

HARRY PERKINS INSTITUTE
OF MEDICAL RESEARCH

HARRY PERKINS INSTITUTE
OF MEDICAL RESEARCH

Harry Perkins Institute North
(QEII Medical Centre)


Harry Perkins Institute South
(Fiona Stanley Hospital)

Perkins Cardiovascular Research Intensive Mini Symposium 8th November 2022

Session 4.
Advances in Cardiovascular Imaging

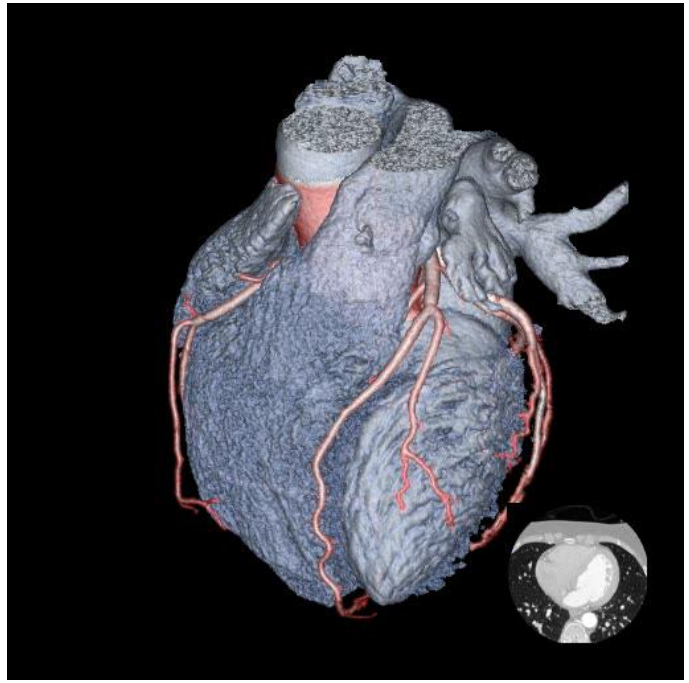
Session 4	12noon	**Prof**	**Girish Dwivedi**	**Cardiac CT Newer imaging biomarkers and Perth experience**
CV Imaging	12:10	**Prof**	**Carl Schultz**	**PET CT and Microcalcification**
	12:20	**A/Prof**	**Ros Francis**	**PET CT and Vascular inflammation**

Perkins Cardiovascular Research Intensive Mini Symposium

Session 4. Advances in Cardiovascular Imaging

- **Girish Dwivedi** discusses the role of cardiac CT in the identification of high risk plaque and pericoronary inflammation and how they determine prognosis in coronary artery disease and familial hypercholesterolemia
- **Carl Schultz** presents data on the importance of microcalcification and its detection with sodium fluoride PET scanning. It is useful in elucidating pathways in progression of atherosclerosis, as a marker of a poor prognosis and as a surrogate for endpoint for clinical trials
- **Ros Francis** discusses the role of FDG PET CT scanning in detecting atherosclerotic inflammation and tracking the response to anti-inflammatory drugs. She also presents an update on the 2023 opening of National Imaging Facility node to be located in the Perkins North building

The Role of Cardiac CT in Patients with cardiometabolic conditions: Focus on newer imaging biomarkers and Perth experience



Professor Girish Dwivedi

Consultant cardiologist, Fiona Stanley Hospital, Perth, Australia
The University of Western Australia
Department of Cardiology and University of Western Australia, Royal Perth Hospital, Perth, Australia
Harry Perkins Institute of Medical Research, The University of Western Australia, Perth, Australia

Chief Scientific Officer – Artrya Lt

FIONA STANLEY hospital

THE UNIVERSITY OF WESTERN AUSTRALIA

HARRY PERKINS INSTITUTE OF MEDICAL RESEARCH

Background

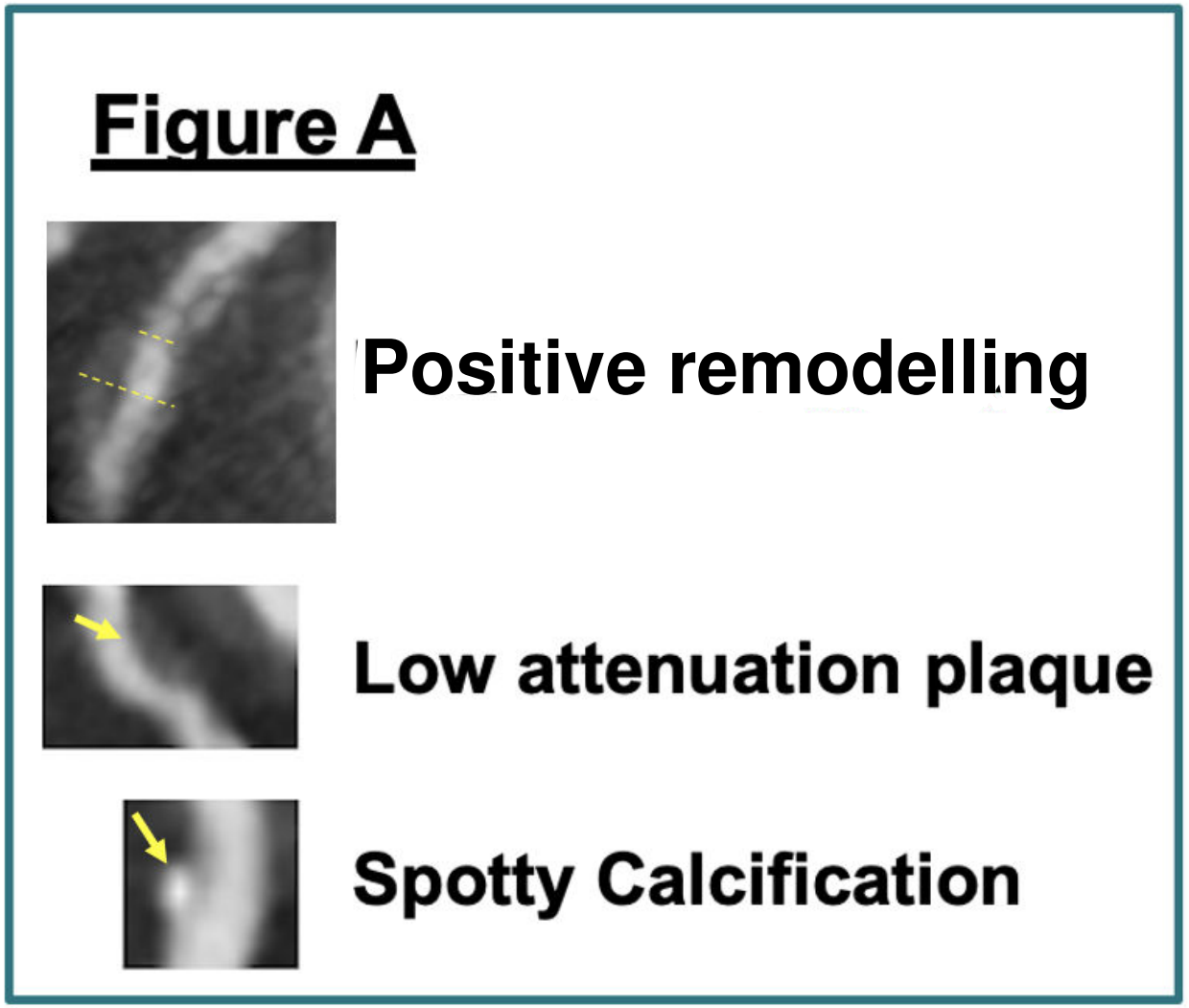
- Coronary computed tomographic angiography (CCTA) presents an opportunity for patient-specific risk stratification

- CCTA assessments of plaque morphology, composition and pericoronary inflammation are recognized prognostic markers in the general population[1,2]

- Role of CCTA plaque biomarkers are yet to be established in FH

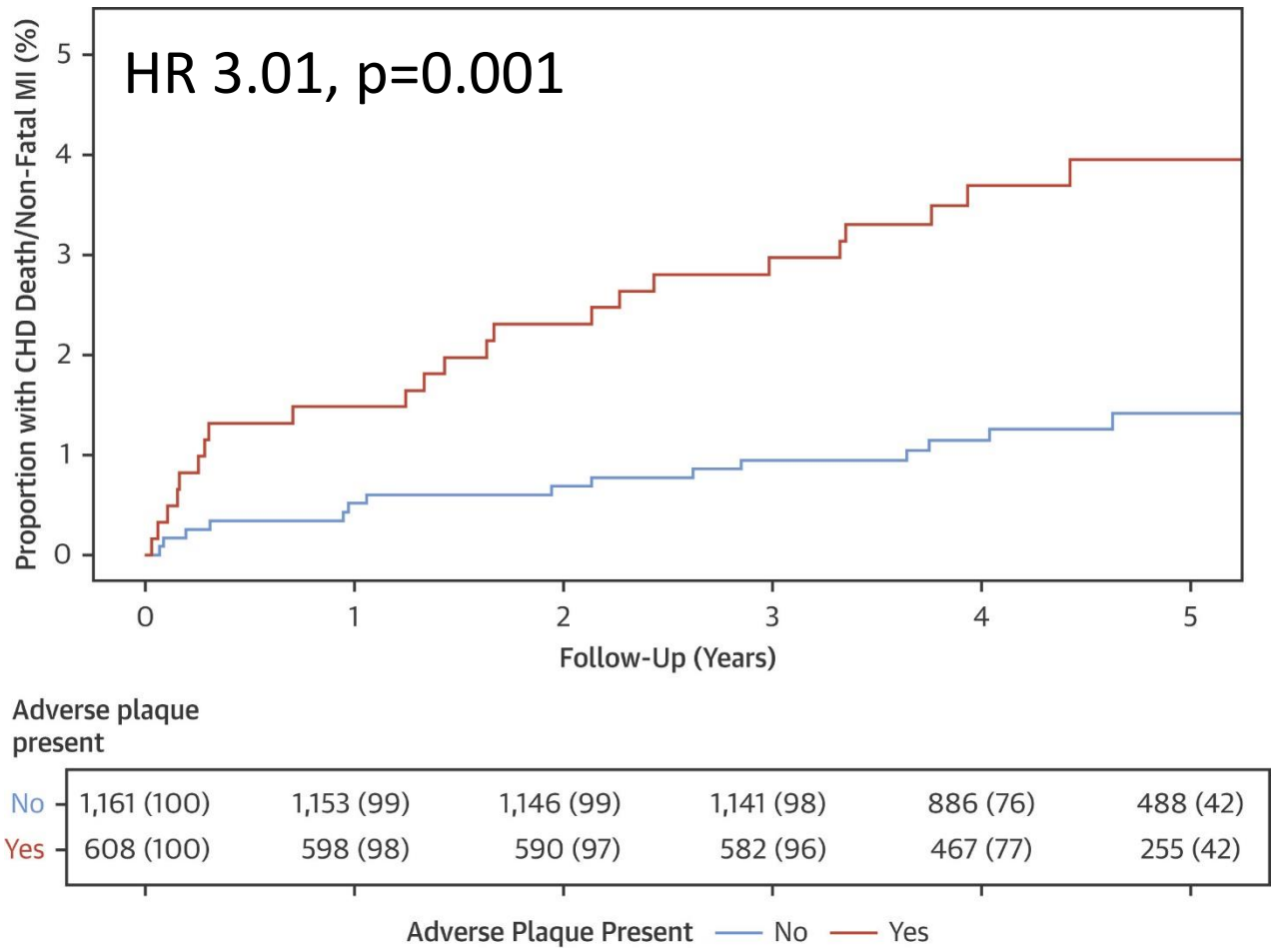
[1]Motoyama S et al, Journal of the American College of Cardiology 2009;54(1):49-57
[2]Oikonomou EK et al, The Lancet 2018;392(10151):929-939

High-Risk Plaque



Williams MC et al, Journal of the American College of Cardiology. 2019;73(3):291-301
Maroules et al, Journal of Cardiovascular Computed Tomography. 2018;12(2):125-130

High Risk Plaque

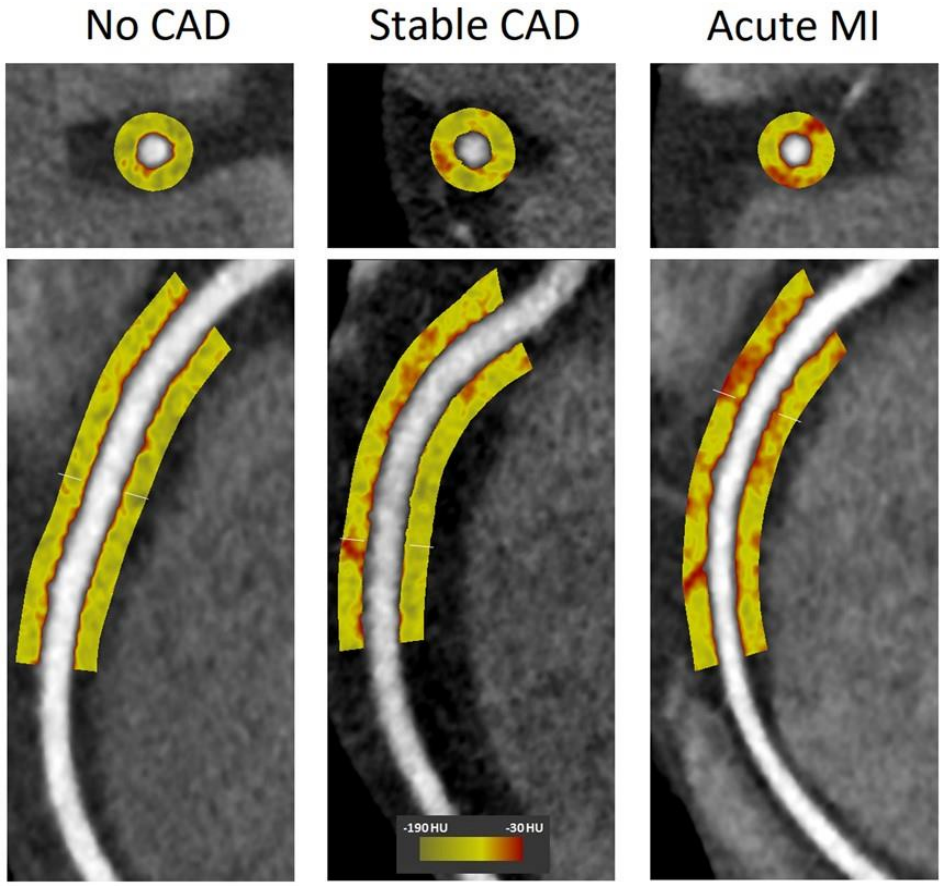


The presence of HRP increases adverse cardiovascular events

Williams MC et al, Journal of the American College of Cardiology. 2019;73(3):291-301.

Pericoronary Adipose Tissue

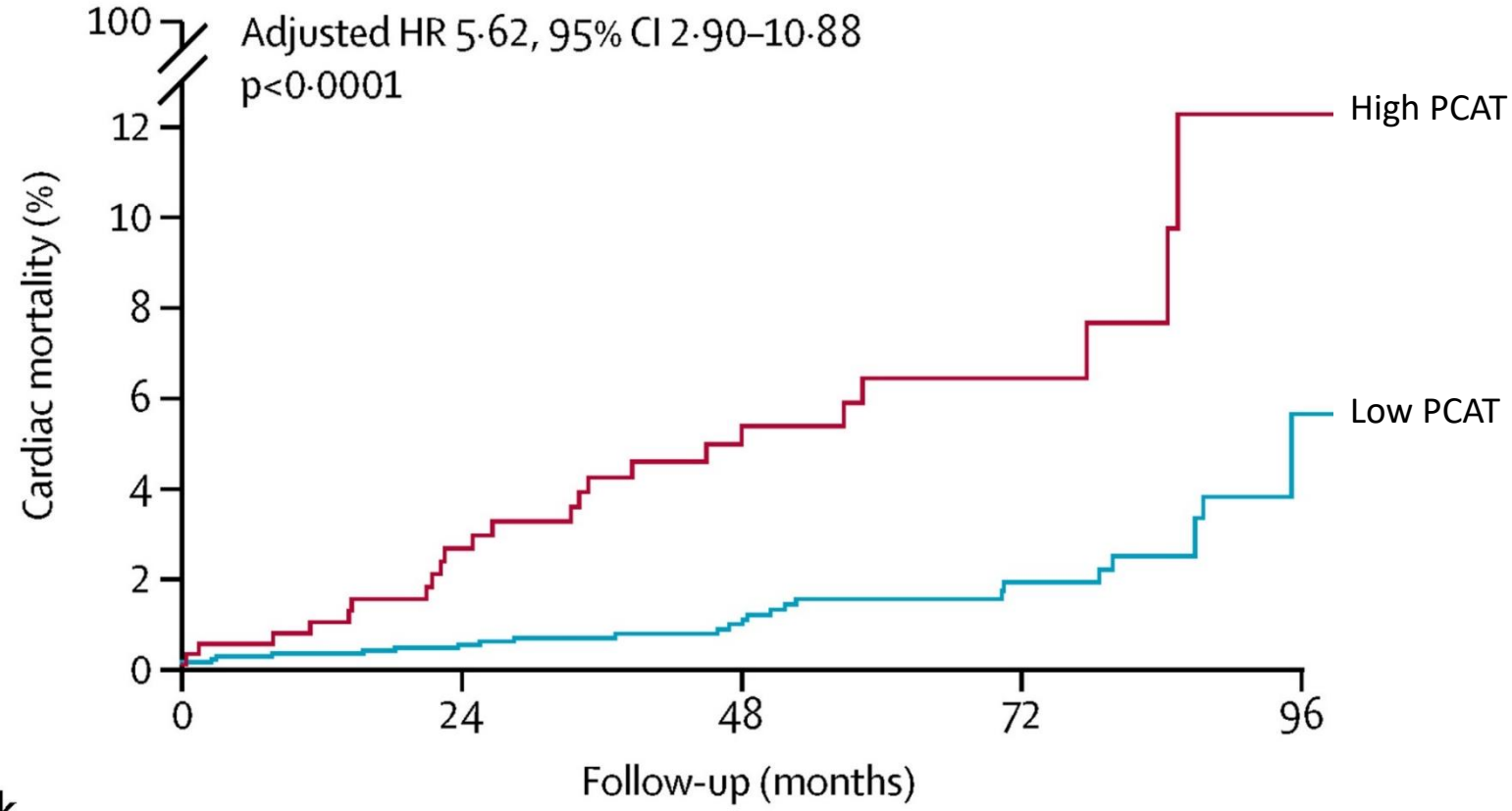
- Atherosclerosis is inflammatory
- hs-CRP lacks specificity
- PET imaging has limitations



Visualising coronary inflammation

Nidorf SM et al, The New England Journal of Medicine 2020; 383:1838-1847
Robson PM, JACC Cardiovascular Imaging 2017; 10:1103-1112
Oikonomou EK et al, The Lancet 2018;392(10151):929-939
Lin et al. European Heart Journal-Cardiovascular Imaging 2021;22(3):298-306

Pericoronary Adipose Tissue



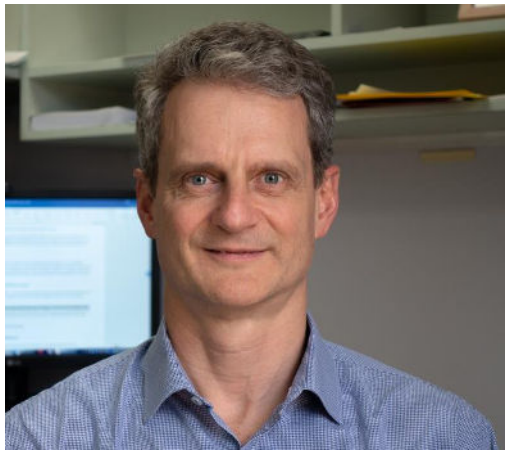
Number at risk					
<–70·1 HU	1623	1337	917	516	113
≥–70·1 HU	417	330	240	114	15

Imaging of coronary inflammation predicts adverse cardiovascular outcomes

Oikonomou EK et al, The Lancet 2018;392(10151):929-939

PET CT and Microcalcification

Improved risk stratification and mechanistic insights of Australia's most dangerous disease

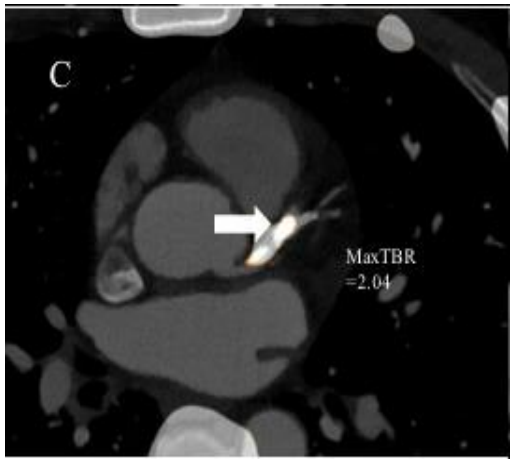


Carl Schultz

Winthrop Professor of Cardiology

Royal Perth Hospital

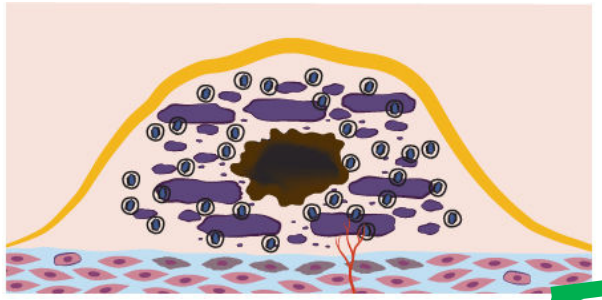
University of Western Australia

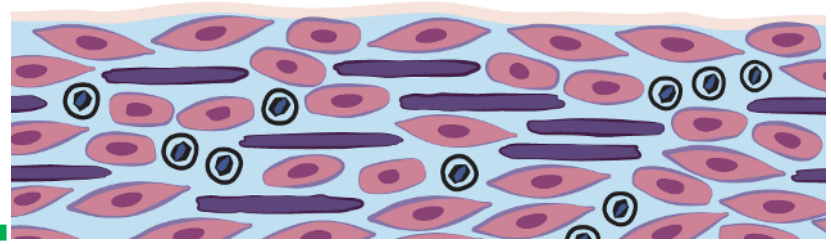


Pathways of arterial calcification pathways

Intimal

Medial





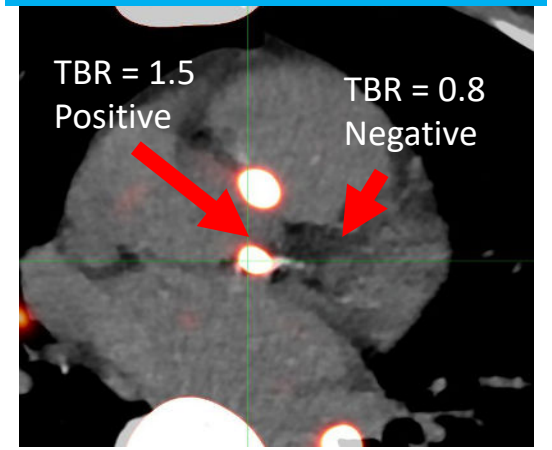
Inflammatory

Matrix vesicles

Transdifferentiation of vascular smooth muscle cells

Apoptotic bodies

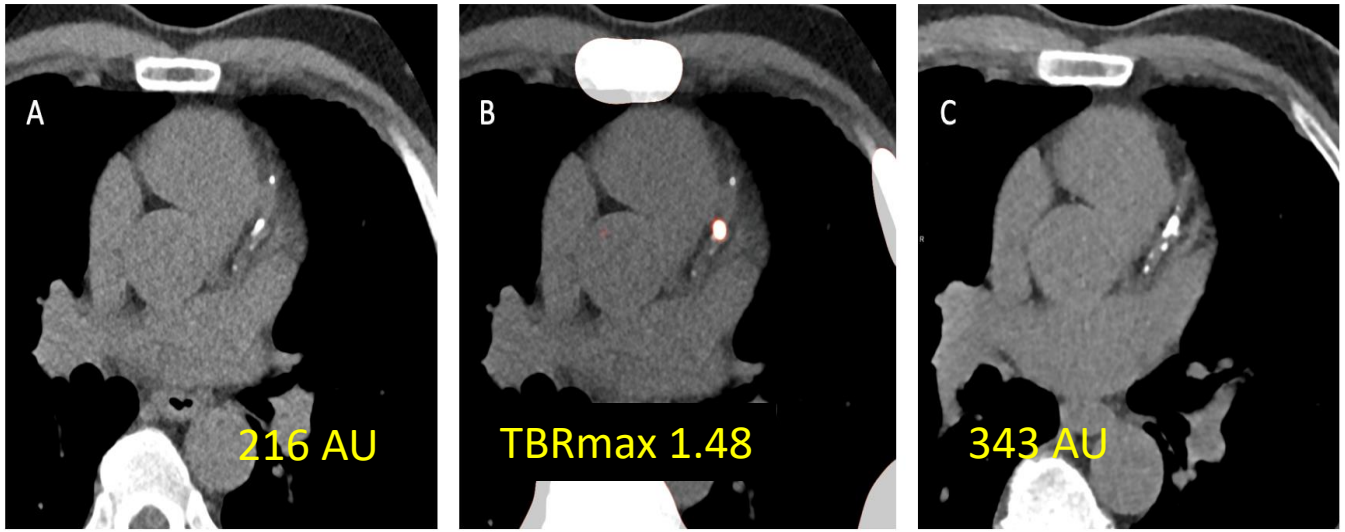
18F-Sodium Fluoride PET



Calcification

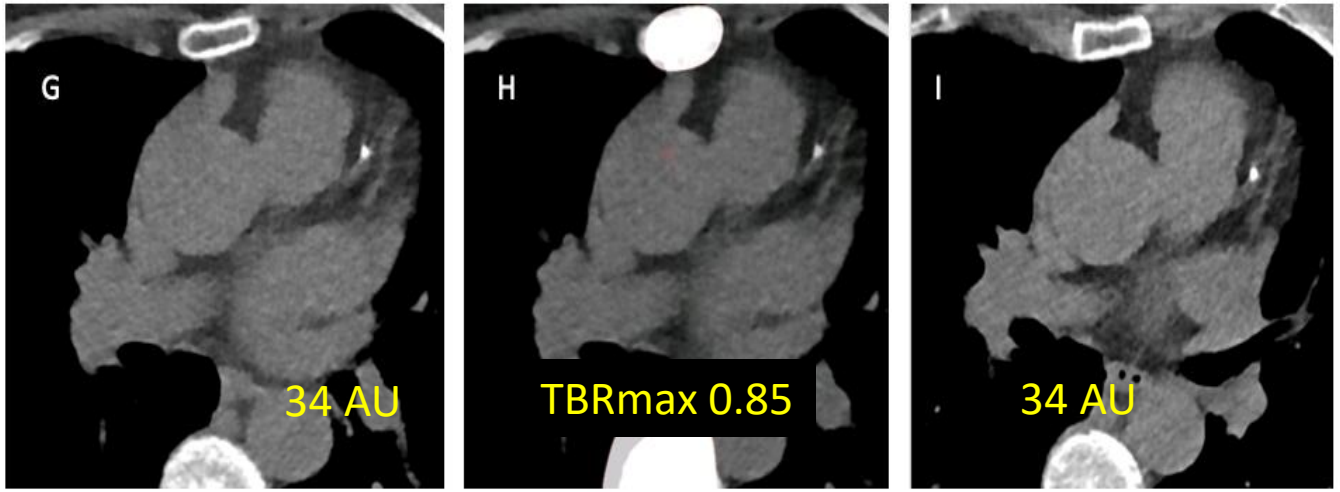
Baseline CT | Baseline PET/CT | Follow up PET/CT

Patient 1



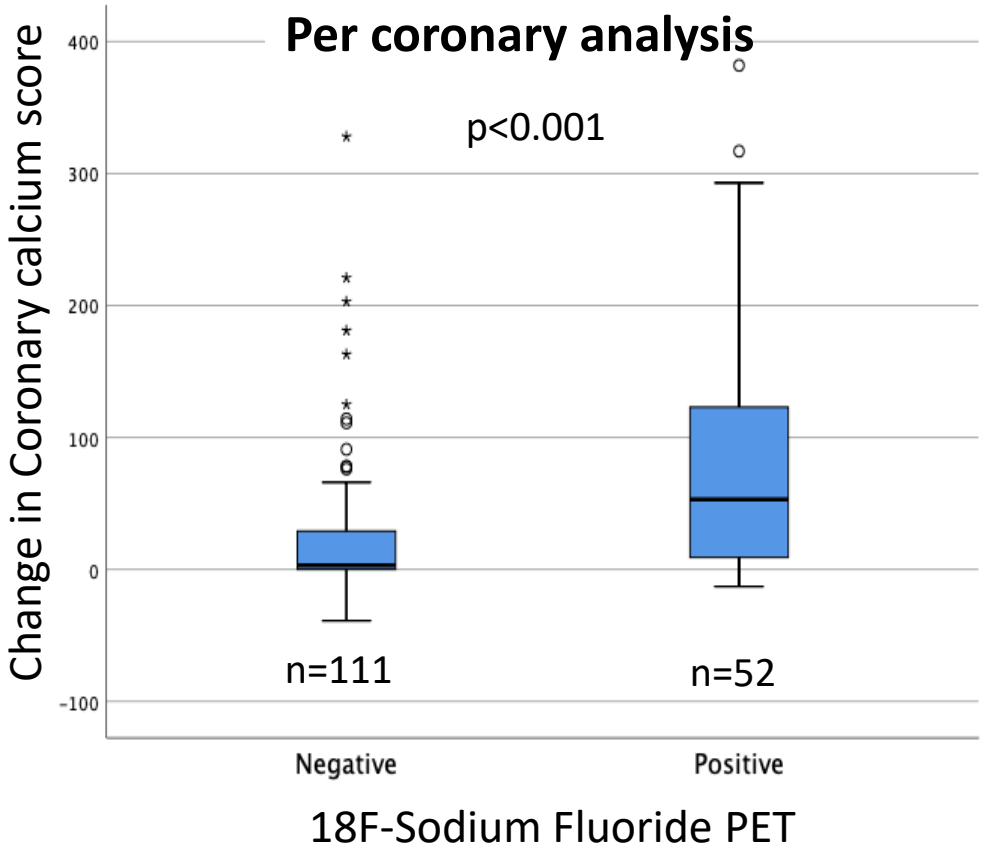
Progressor

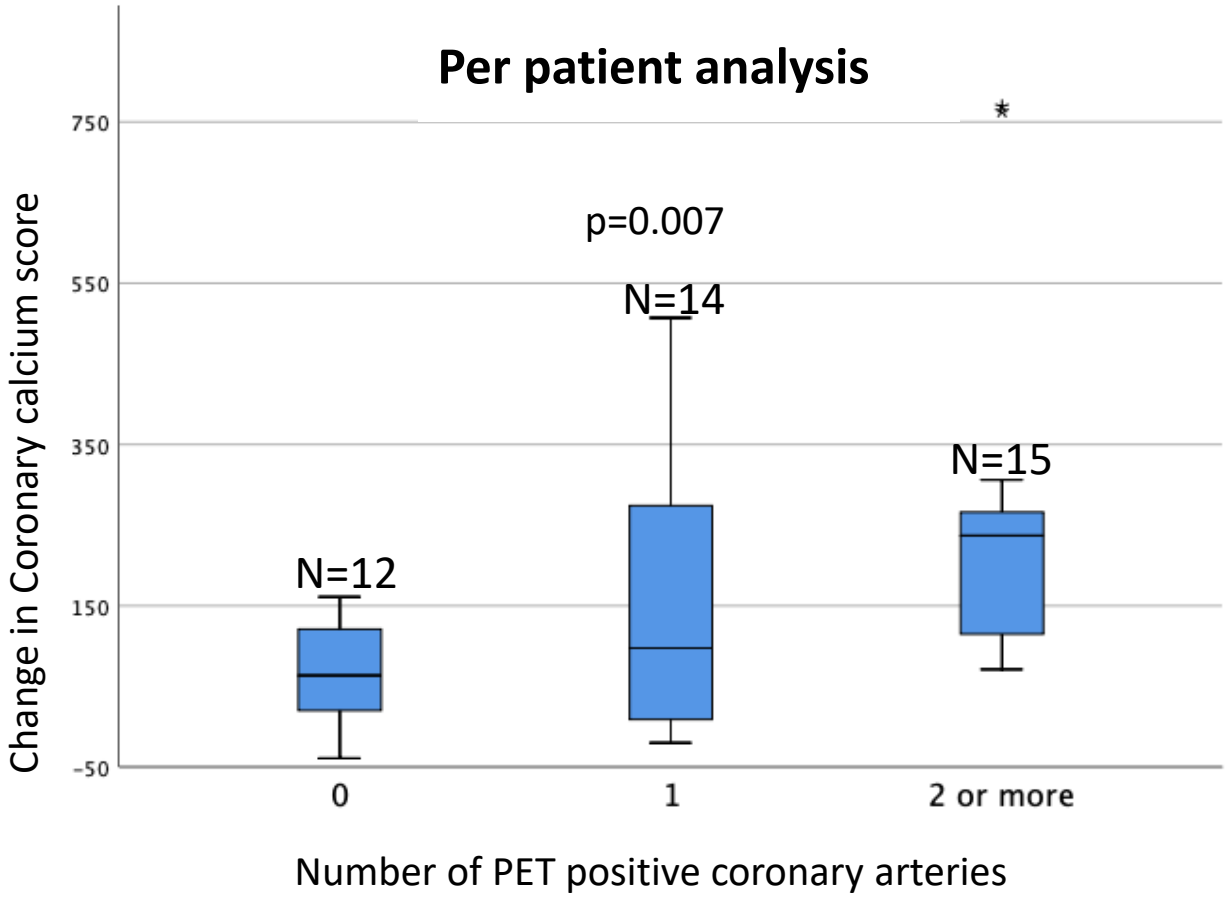
Patient 2



Non-progressor

Bellinge, ATVB 2021





Bellinge, ATVB 2021

Summary

Microcalcification activity detected by 18F-Sodium fluoride PET

- is a powerful risk stratifier in a range of CVD conditions
- Enables novel mechanistic insights as intermediate end-point in trials and observational studies

Thank you

Financial Support
- Royal Perth Hospital Research Foundation
- UWA
- Aspen pharmaceuticals
- Abbott Vascular

Support with 18F-NaF PET
- SCGH PET nurses, technicians and physicians, research nurses
- SCGH physics team

- **Dr Lachlan Kelsey – PhD awarded**
- **Dr Kamran Majeed – PhD awarded**
- **Dr Jamie Bellinge – PhD awarded**
- **Dr Sing Lee – PhD student**
- **Dr Steel Butcher – MSc awarded (UND)**

- A/Prof. Ros Francis
- Dr William Macdonald
- Dr Gerard Chew
- Dr Sen Khee Gan
- Dr Alistair Vickery
- Dr Joshua Lewis
- Prof Gerald Watts
- Barry Doyle

RPH cardiology research nurses

RPH clinical trials pharmacy

RPH medical illustrations and PR

Royal Perth Hospital

RPH Research Foundation

THE UNIVERSITY OF WESTERN AUSTRALIA

FDG PET and vascular inflammation

Perkins Intensive Cardiovascular Research Symposium
8 Nov 2022

A/Prof Roslyn Francis
UWA Medical School
Head of Dept, Nuclear Medicine and WA PET Service, SCGH

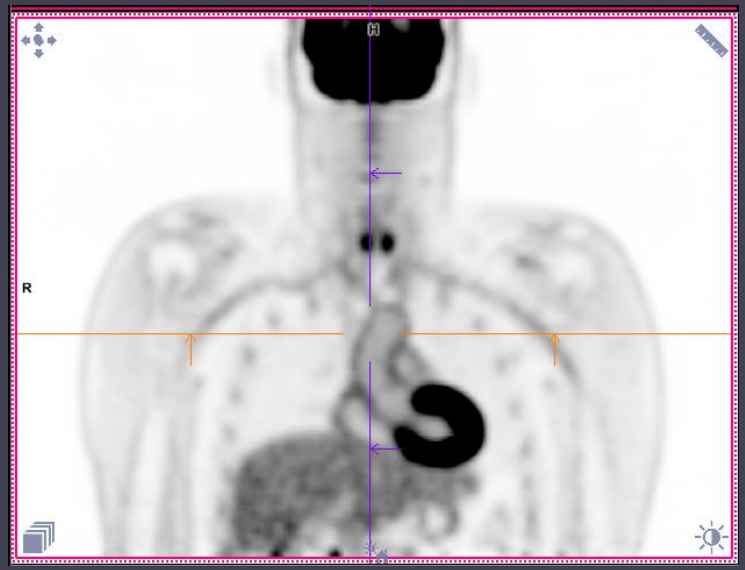
FDG PET and atherosclerosis

- FDG activity in arterial wall reflects inflammation in atherosclerotic plaques.
- Medium and large vessels (aorta, carotid arteries) are suitable for evaluation. Evaluation of coronary vessels is limited by myocardial activity and motion.

Eur J Nucl Med Mol Imaging (2016) 43:780–792
DOI 10.1007/s00259-015-3259-3

GUIDELINES

Position paper of the Cardiovascular Committee of the European Association of Nuclear Medicine (EANM) on PET imaging of atherosclerosis



Vascular inflammation and cardiovascular risk

- The importance of inflammation/inflammatory pathways in atherosclerotic plaque development and progression is increasingly recognized.
- Elevated levels of hsCRP is independently associated with increased cardiovascular risk.
- Modification of vascular inflammation may lead to reduction in cardiovascular risk
  LoDoCo2 study – low dose colchicine associated with 31% lower relative risk of cardiovascular events than placebo (Nidorf et al N Engl J Med. 2020 Nov 5;383(19):1838-1847)

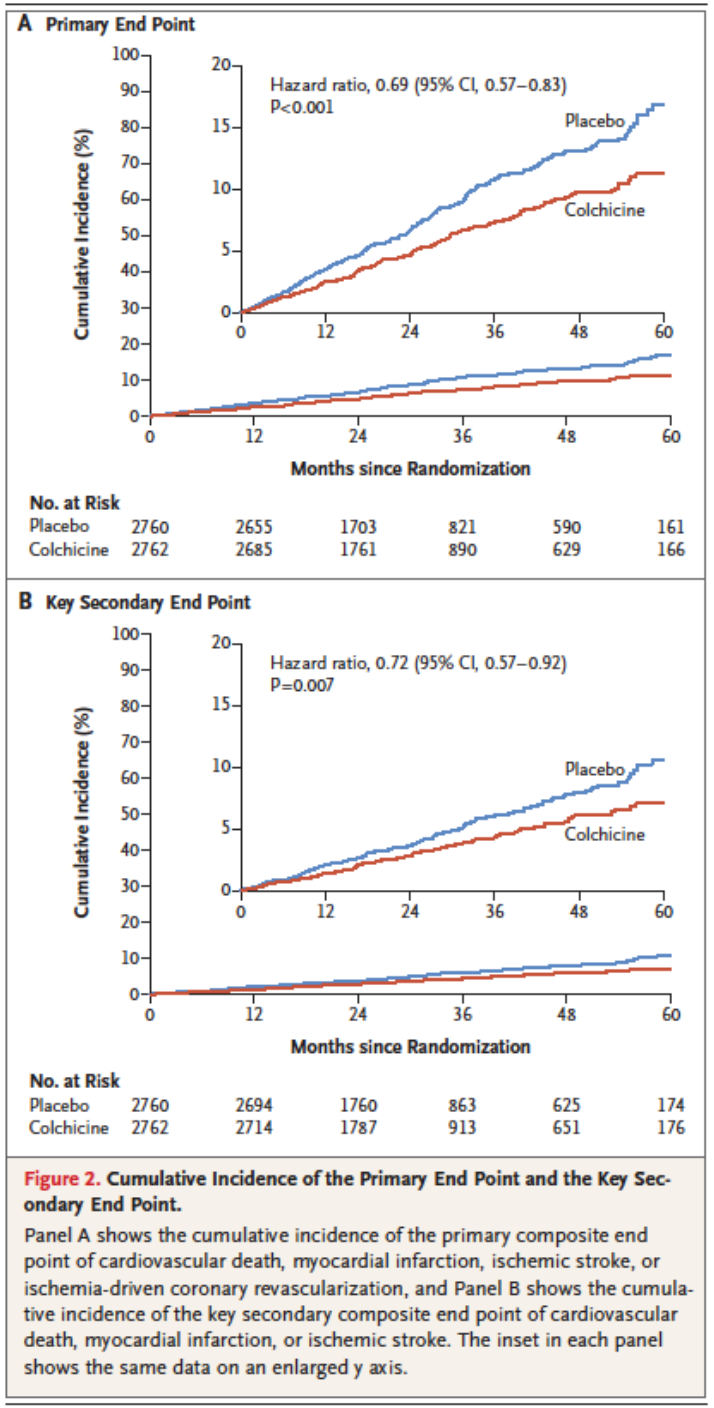


Figure 2. Cumulative Incidence of the Primary End Point and the Key Secondary End Point.

Panel A shows the cumulative incidence of the primary composite end point of cardiovascular death, myocardial infarction, ischemic stroke, or ischemia-driven coronary revascularization, and Panel B shows the cumulative incidence of the key secondary composite end point of cardiovascular death, myocardial infarction, or ischemic stroke. The inset in each panel shows the same data on an enlarged y axis.

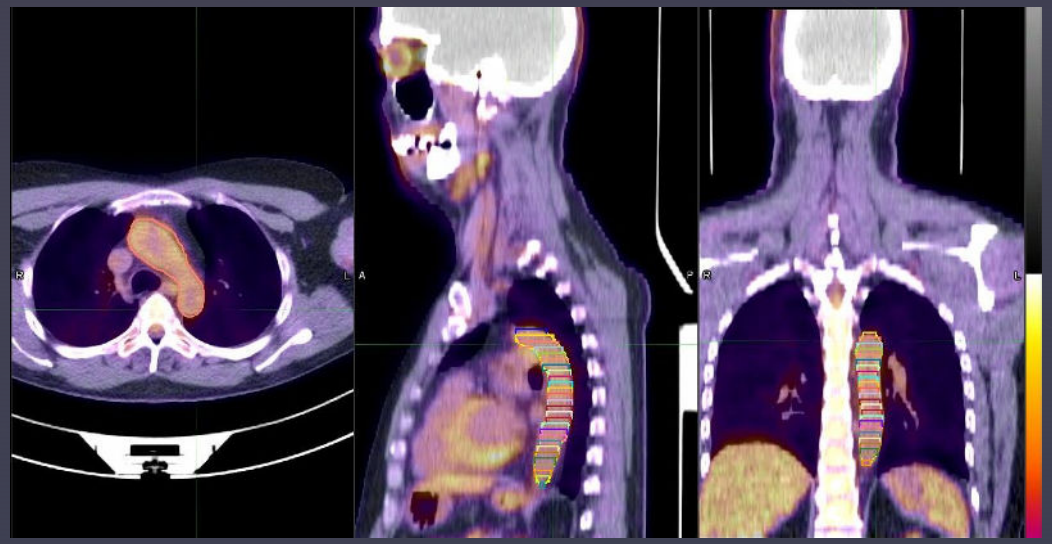
FDG PET quantitation

Bucerius et al EJNMMI 2016 43 780-792

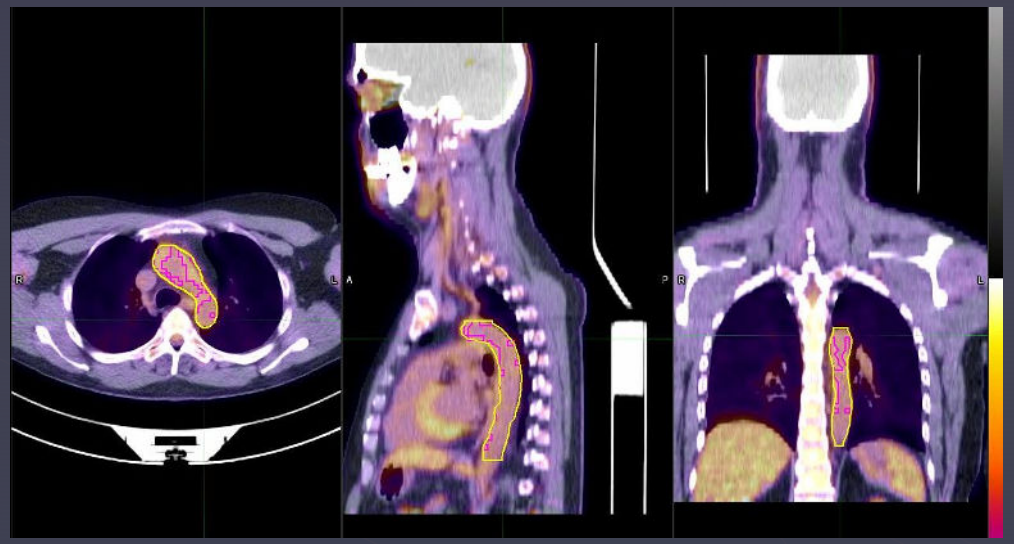
Potential applications of FDG PET quantitative assessment of vascular atherosclerosis

1) Prognosis / prediction of cardiovascular events
2) Surrogate endpoint for interventional studies

MiM Encore workflow



Regions are drawn outlining the aorta on consecutive slices on the PET-CT images

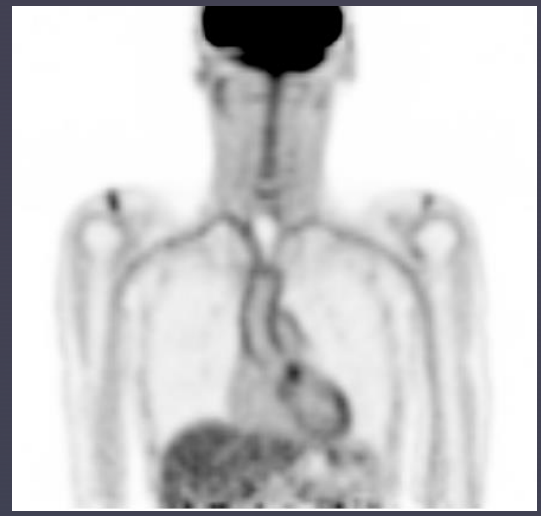


Threshold applied to obtain TBR >1.6 (background = right atrium).

Clinical research projects

- **Prognosis / prediction of cardiovascular events**
  Persistent lung and arterial inflammation post COVID-19
  DOH WA / WAHTN COVID 19 research grants program &
  Australia-India Strategic Research Fund Scheme
  R Francis, G Dwivedi, M Schlaich, C Reid, G Hillis, F Sanfilippo, G Waterer

- **Surrogate endpoint for interventional studies**
  Effect of high-dose fish oil supplementation on arterial inflammation in patients with elevated lipoprotein (a)
  Royal Perth Hospital Medical Research Foundation
  G Watts, D Chan, N Ward C Schultz, G Dwivedi, R Francis



WA NIF node expansion project

- NIF: National Imaging Facility. WA NIF node is hosted by UWA
- Dedicated research imaging facility located on 3rd floor Harry Perkins Nth
  - 3T MRI
  - digital PET-CT
  - radiochemistry production facilities (‘GMP’)

Planned operational date –2023

NIF MRI Fellow
Dr Sjoerd Vos

NIF Radiochemistry Fellow
Dr Joseph Ioppolo

NIF PET Fellow
Dr Heidi Espedal

HARRY PERKINS INSTITUTE
OF MEDICAL RESEARCH

HARRY PERKINS INSTITUTE
OF MEDICAL RESEARCH

Harry Perkins Institute North
(QEII Medical Centre)


Harry Perkins Institute South
(Fiona Stanley Hospital)

Perkins Cardiovascular Research Intensive Mini Symposium 8th November 2022

Session 5.
Cardiac valves/Aortic Stenosis

Session 5	12:30	**Prof**	**Brendan McQuillan**	**Evidence based choice of anti thrombotic for prosthetic valves**
Aortic stenosis	12:40	**Prof**	**Graham Hillis**	**Aortic stenosis and EASY AS**
	12:50	**Dr**	**Elena De-Juan-Pardo**	**3D printed cardiac valves**
	13:00	**Dr**	**Abdul Ihdayhid**	**Computational Modelling to Optimise Outcomes in Aortic Stenosis**
	13:10		**Discussion**	**Discussion**

Perkins Cardiovascular Research Intensive Mini Symposium

Session 5. Cardiac valves/Aortic stenosis

- Brendan McQuillan reviews the evidence base for antithrombotic treatment of patients with artificial cardiac valves. Older anticoagulants are still needed for mechanical valves, over aggressive treatment has warranted caution with bioprosthetic valves and data is still coming in to guide the management of TAVI valves
- Graham Hillis describes the importance of aortic stenosis and how current approaches to intervention delayed intervention may be costing lives , and an update on the EASYAS trial which compares the standard wait and see approach with early intervention
- Elena de Juan Pardo describes her work on 3D printing of cardiac valves with the unique insight that she respects and learns from the biology of the native valve in her design and choice of biomaterial
- Abdul Ihdayhid explains computational modelling to guide treatment strategy in very large aortic annulus to optimise outcomes in aortic stenosis.

Evidence based choice of anti thrombotic for prosthetic valves

The University of Western Australia acknowledges that its campus is situated on Whadjuk Noongar land, and that Noongar people remain the spiritual and cultural custodians of their land, and continue to practice their values, languages, beliefs and knowledge.

Bubble, bubble, boil and trouble...

Dr Brendan McQuillan

Dean, Head of School, UWA Medical School
University of Western Australia

Cardiologist, Director of Echocardiography,
Department of Cardiovascular Medicine
Sir Charles Gairdner Hospital

Cardiovascular Seminar
Harry Perkins Institute for Medical Research
Nov 2022

Mechanical prosthetic valves

THE UNIVERSITY OF WESTERN AUSTRALIA
Dr Brendan McQuillan

Warfarin

- For (modern) mechanical AVR, an INR of 2.0 – 3.0 offers similar protection against stroke and systemic emboli with a lower risk of bleeding than an INR of 3.0 – 4.5 [1 - 3]
- For AVR with higher risk of thromboembolism (AF, prior embolism, LV impairment, ball-in-cage prosthesis) the INR should be maintained at 3.0 (range, 2.5–3.5) [3 – 4]
- For MVR, an INR of 3.0 (range 2.5 – 3.5) is a reasonable compromise between efficacy and risk [5]

1. Hering D, et al. Thromboembolic and bleeding complications following St. Jude Medical valve replacement: results of the German Experience With Low-Intensity Anticoagulation Study. Chest. 2005;127:53–9.
2. Acar J, et al. AREVA: multicentre randomized comparison of low-dose versus standard-dose anticoagulation in patients with mechanical prosthetic heart valves. Circulation. 1996;94:2107–12.
3. Whitlock RP, et al. Antithrombotic and thrombolytic therapy for valvular disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141:e576S–600S.
4. Horstkotte D, Scharf RE, Schultheiss HP. Intracardiac thrombosis: patient related and device-related factors. J Heart Valve Dis. 1995;4:114–20.
5. Pruefer D, et al. Intensity of oral anticoagulation after implantation of St. Jude Medical mitral or multiple valve replacement: lessons learned from GELIA (GELIA 5). Eur Heart J Suppl. 2001;3:Q39–43.

Surely the DOACs are better…

THE UNIVERSITY OF WESTERN AUSTRALIA

Oral antithrombin and anti-Xa agents are ***not*** approved for use in these patients.

RE-ALIGN Investigators: The use of dabigatran in patients with mechanical heart valves was associated with increased rates of thromboembolic and bleeding complications, as compared with warfarin, thus showing no benefit and an excess risk [1,2].

Artivion Follows Recommendation to Stop PROACT Xa Clinical Trial…
Apixaban vs warfarin for patients with an On-X mechanical aortic valve
"The DSMB found that blood clots, resulting in stroke, occurred more frequently in patients receiving apixaban and that continuing the trial was unlikely to achieve the primary endpoint while possibly exposing patients to increased risk." [3]

1. Eikelboom JW, et al. Dabigatran versus warfarin in patients with mechanical heart valves. N Engl J Med. 2013;369:1206–14.
2. Van de Werf F, et al. A comparison of dabigatran etexilate with warfarin in patients with mechanical heart valves (REALIGN). Am Heart J. 2012;163:931–7.e1.
3. Artivion Follows Recommendation to Stop PROACT Xa Clinical Trial - Drugs.com MedNews Accessed 30 Oct 2022

Antiplatelets and mechanical prosthetic valves

THE UNIVERSITY OF WESTERN AUSTRALIA
Dr Brendan McQuillan

- Uncertainty over prior recommendation to add low-dose aspirin to therapeutic VKA therapy for a mechanical valve prosthesis ,
- Based on studies performed with older-generation prostheses who also had additional thromboembolic and vascular risk factors.
- Compared with anticoagulation alone, the addition of an antiplatelet agent may reduce the risk of thromboembolic events and mortality but at the cost of an increased risk of major bleeding.
- An individualized approach that takes the risk of bleeding into account is required.
- Room for further trials…

- Massel DR, Little SH. Antiplatelet and anticoagulation for patients with prosthetic heart valves. Cochrane Database Syst Rev. 2013;CD003464.
- Puskas J, Gerdisch M, Nichols D, et al. Reduced anticoagulation after mechanical aortic valve replacement: interim results from the prospective randomized on-X valve anticoagulation clinical trial randomized Food and Drug Administration investigational device exemption trial. J Thorac Cardiovasc Surg. 2014;147:1202–10.
- Puskas JD, Gerdisch M, Nichols D, et al. Anticoagulation and antiplatelet strategies after On-X mechanical aortic valve replacement. J Am Coll Cardiol. 2018;71:2717–26.

Bio-prosthetic valves

THE UNIVERSITY OF WESTERN AUSTRALIA
Dr Brendan McQuillan

- Patients who undergo surgical implantation of a bioprosthetic mitral or aortic valve do not require lifelong anticoagulation in the absence of an independent indication (e.g., AF).
- There is an increased risk of ischaemic stroke in the first 3 – 6 months after either bioprosthetic AVR or MVR
- Anticoagulation early after valve implantation is intended to decrease the risk of thromboembolism until the prosthetic valve is fully endothelialized.
- The potential benefit of anticoagulation therapy must be weighed against the risk of bleeding.

- Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361:1139–51.
- Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013;369:2093–104.
- Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365:883–91.
- Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365:981–92.

Antiplatelet therapy after TAVI

Among TAVI patients who do not have an indication for OAC:

- The routine use of dual-antiplatelet therapy for 6 months after TAVI, has been not been rigorously assessed.
- Aspirin is safer and non-inferior post TAVI c.f. aspirin plus clopidogrel [1]

Among TAVI patients with an indication for OAC:

- DOACs are (probably) non-inferior to VKA (small studies)
- The addition of clopidogrel to warfarin after TAVI increases bleeding risk without clear clinical benefit [2]

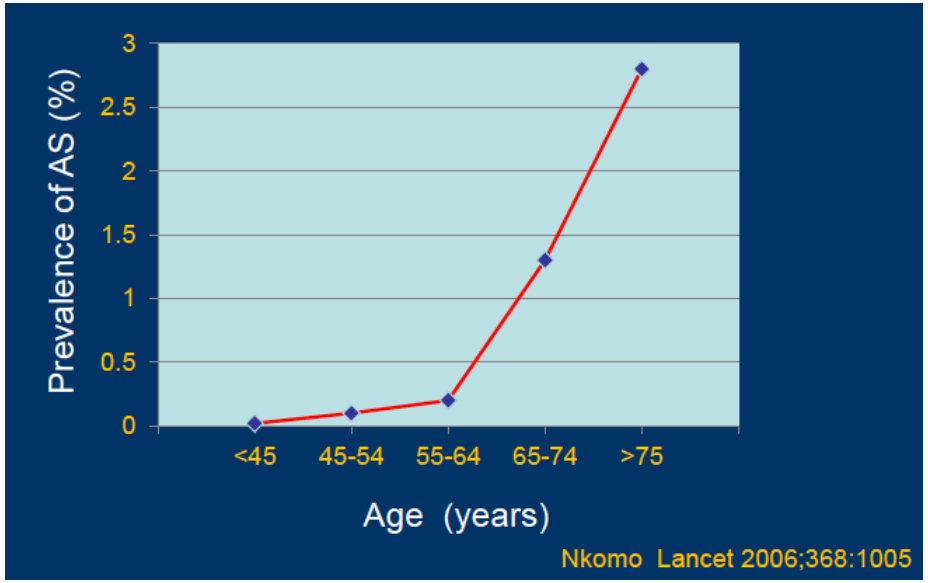
1. Brouwer J, et al. Aspirin with or without Clopidogrel after Transcatheter Aortic-Valve Implantation. N Engl J Med 2020;383:1447-57. DOI: 10.1056/NEJMoa2017815
2. Nijenhuis VJ, et al. Anticoagulation with or without Clopidogrel after Transcatheter Aortic-Valve Implantation. N Engl J Med 2020;382:1696-707. DOI: 10.1056/NEJMoa1915152

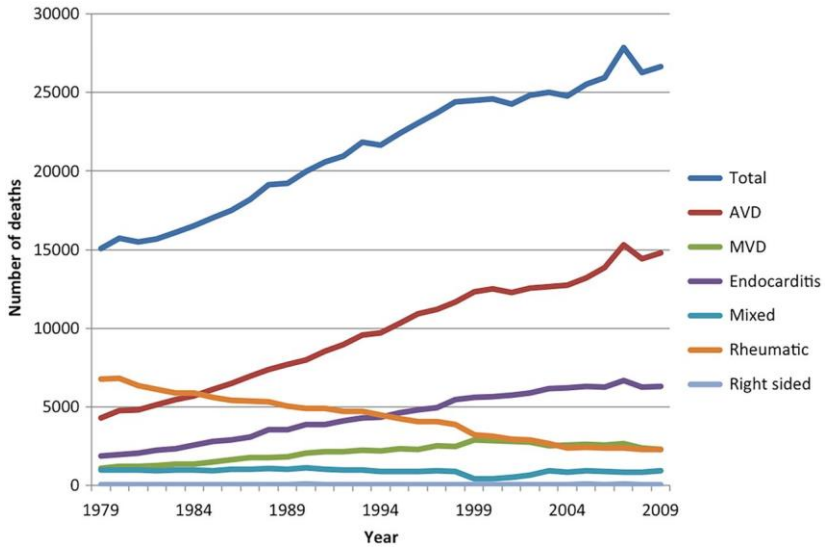
A RANDOMISED CONTROLLED TRIAL OF EARLY VALVE REPLACEMENT IN SEVERE ASYMPTOMATIC AORTIC STENOSIS

Graham Hillis
Department of Cardiology, Royal Perth Hospital

BACKGROUND

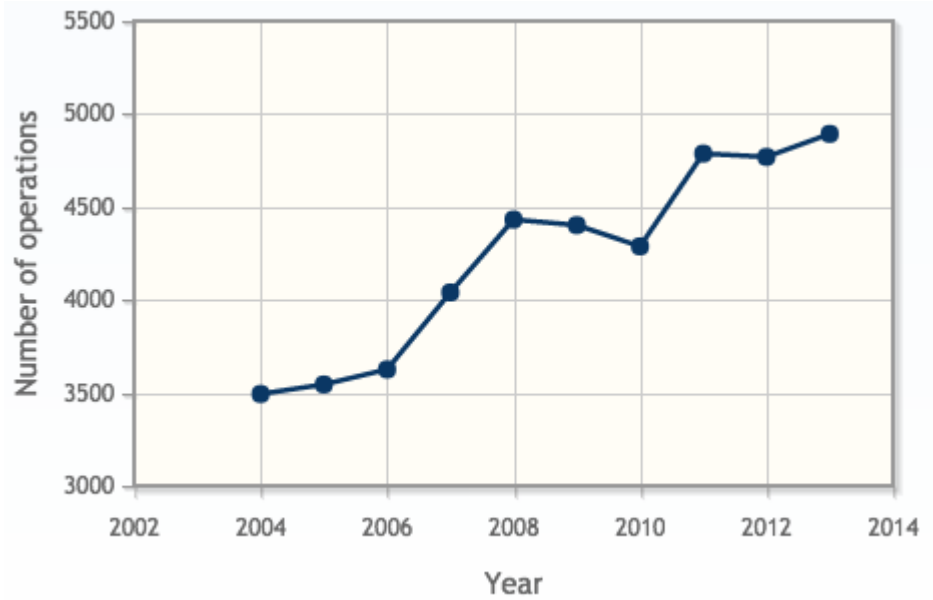
- Aortic stenosis is the commonest valve condition requiring intervention in the developed world
- Prevalence is growing rapidly
- Mainly a condition that affects the middle aged and elderly





Mortality from valvular heart disease in USA

Heart 2016;102:75-85



First time isolated AVR in UK

Blue book- online: http://bluebook.scts.org/

THE UNIVERSITY OF WESTERN AUSTRALIA

AIM & PRIMARY CLINICAL OUTCOME

- **Aim:** To determine whether early AVR results in better clinical outcomes and cost-effectiveness than a strategy of expectant management in asymptomatic patients with severe AS

- **Primary Outcome:** A combined measure of CV death and hospitalisation for heart failure, measured in days from randomisation until end of study (minimum 3 years)

CURRENT TRIAL UPDATE

- 290 participants randomised (as of 4th November 2022)
  - UK: 219
  - Australia: 51
  - New Zealand: 20

  - Already second largest study addressing this important question
  - Recruitment rate strongly accelerating post-COVID peak
  - UK recently met their vanguard phase funding milestone
    - Full £2.72M BHF funds now available
    - Currently 30 sites, but can now add an additional 50-60
  - Study expansion to several other countries underway

REFLECTIONS SO FAR

- **Many challenges**
  - Funding, COVID, recruitment, lack of infrastructure for investigator initiated trials in Australia
- **Many things learned**
  - Establishment of international trial infrastructure, trial management and support
- **Many people to thank**
  - Colleagues locally, nationally and internationally, patients and families, Curtin CTC, Tom Gilbert
- **Many great experiences!**

3D printed cardiac valves

Dr. Elena Juan Pardo

Head, T3mPLATE, Harry Perkins Institute of Medical Research

Senior Lecturer, The University of Western Australia

Current Clinical Solutions: Heart Valves' Substitutes

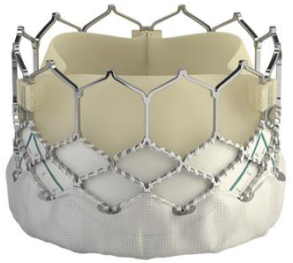
Mechanical valves

Bileaflet mechanical valve
(St Jude)

- ✓ Durability: ~20 years
- ✗ Lifelong anti-coagulation therapy
- ✗ Open heart surgery required
- ✗ Sudden failure – catastrophic outcome

Bio-prosthetic valves

Stented porcine bioprosthesis
(Medtronic Mosaic)

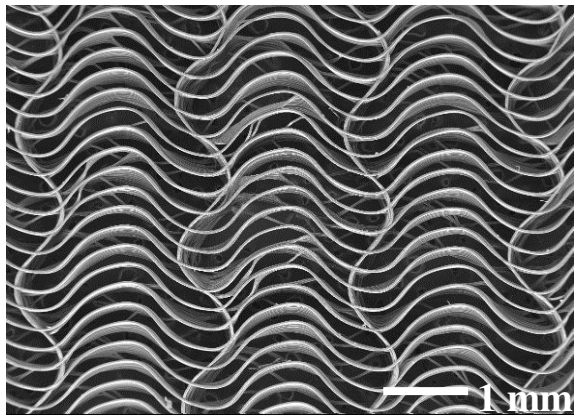


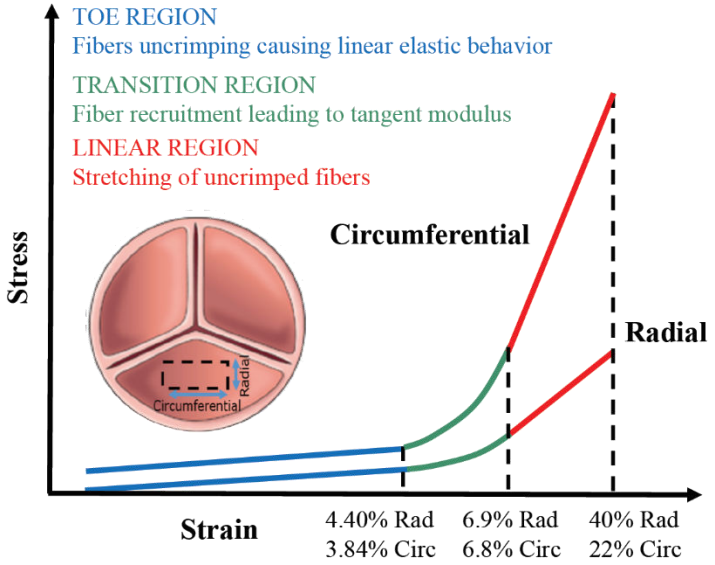
TAVR bioprosthesis
(Edwards Sapien 3)

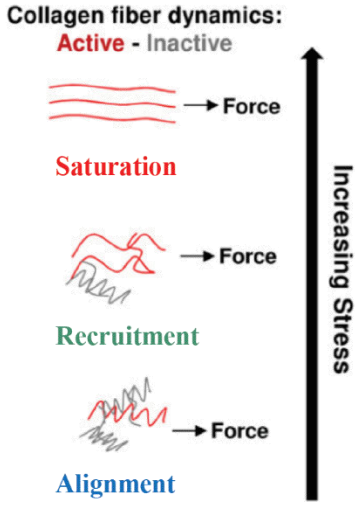
- ✓ TAVR compatible with minimally invasive surgery
- ✓ No anti-coagulation therapy
- ✗ Durability: ~5 years in younger patients

Unique Patented Biomimetic Scaffold Design

From biology → **TO** → **Matched mechanical properties**

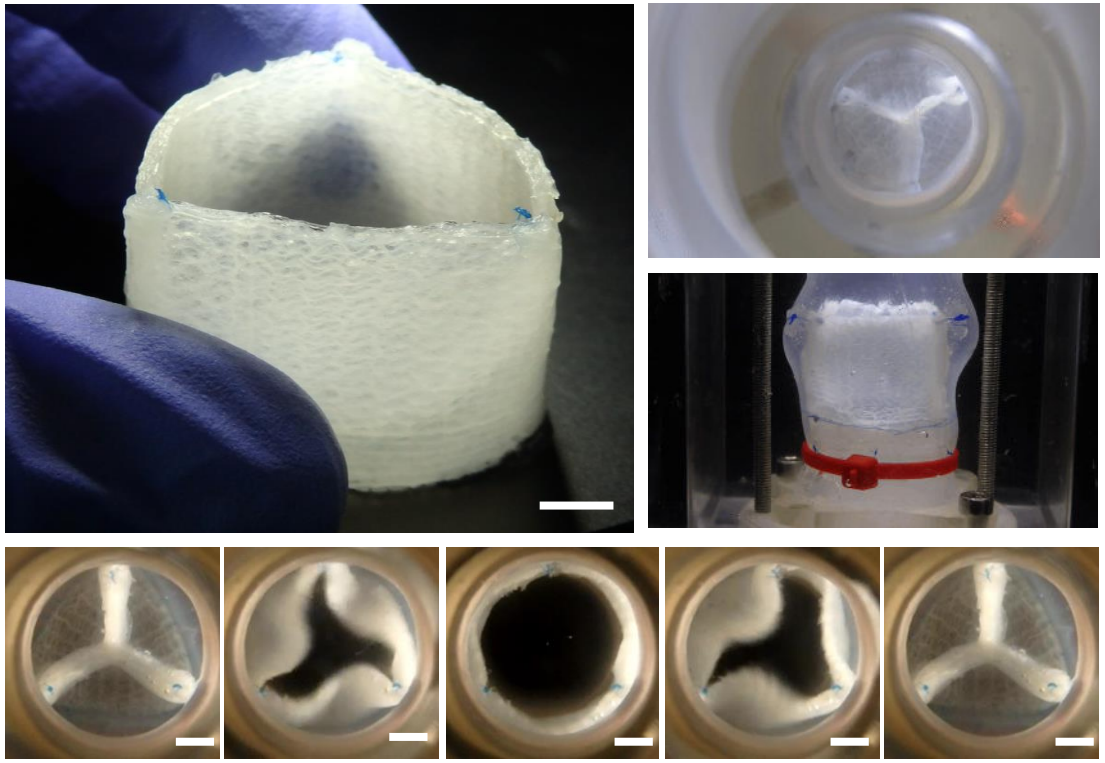




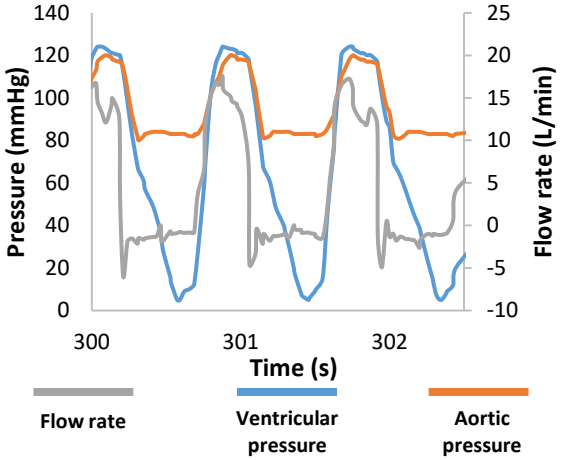


Saidi, … Mela & De-Juan-Pardo. Small (2019)

Spatially Heterogeneous Heart Valve Scaffolds



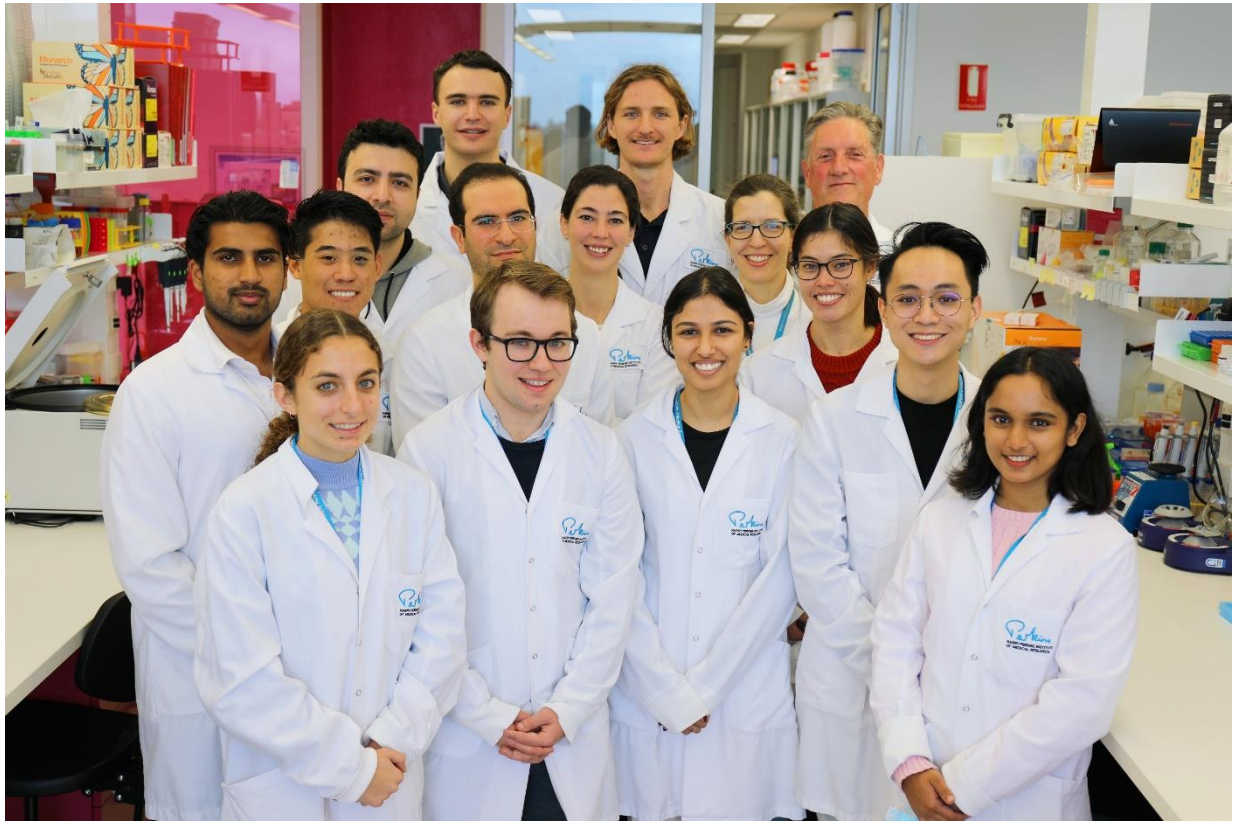
Scale bars = 5 mm



✓ISO Standard 5840 (Cardiovascular Implants – Cardiac Valve Prosthesis)

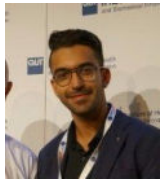
Saidy, … De-Juan-Pardo* & Mela*. Adv. Functional Mater. (2022)

Acknowledgements








Patient-Specific CT-Derived Computational Modelling to Optimise Outcomes in Aortic Stenosis

Abdul Rahman Ihdayhid

MBBS (Hons), PhD, FRACP

Interventional Cardiologist | Cardiac CT Specialist | Fiona Stanley Hospital
Group Leader, Harry Perkins Institute of Medical Research
Research Leader in Cardiovascular Biology, Curtin University

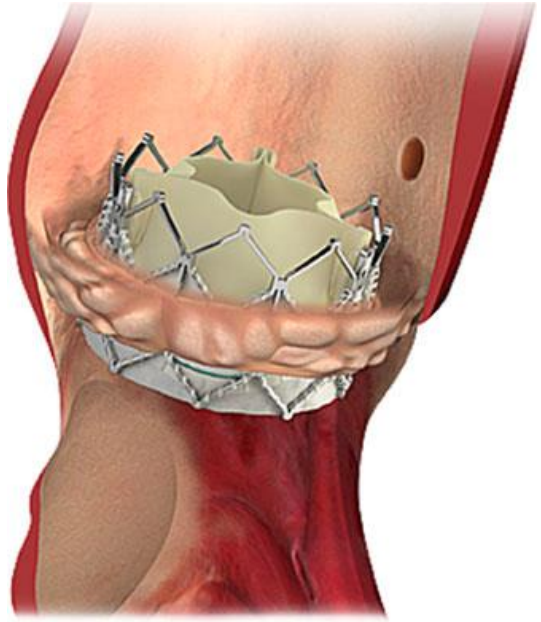
FIONA STANLEY hospital

Curtin University

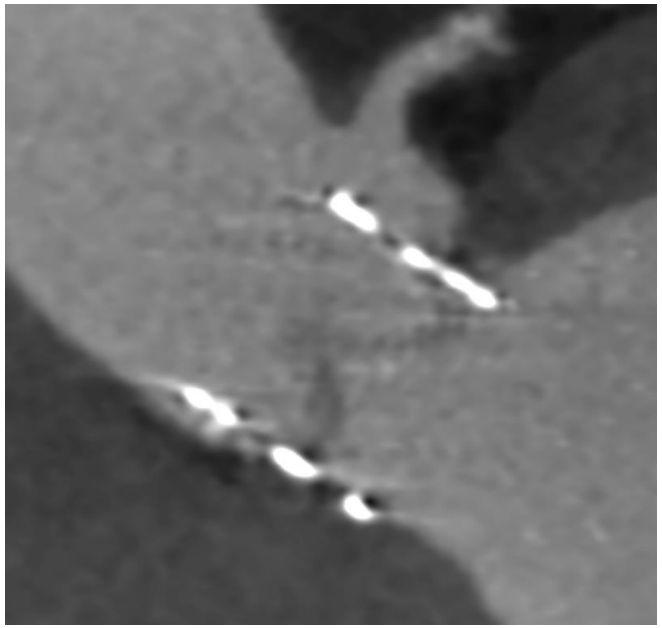
Perkins
HARRY PERKINS INSTITUTE OF MEDICAL RESEARCH

Translational Vision

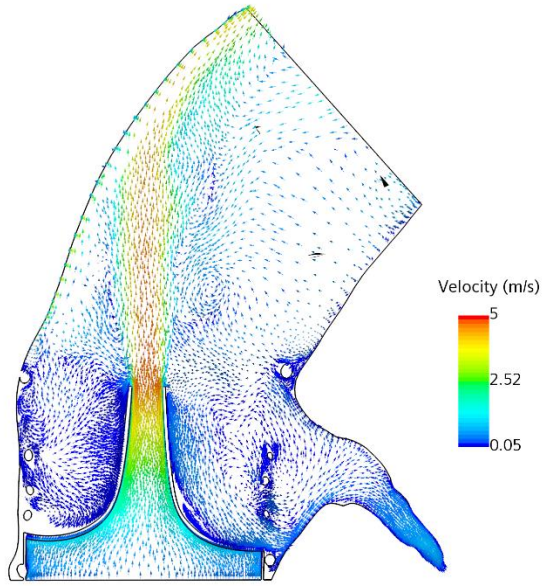
TAVR



Post TAVR CT



Computational Modelling



High Risk

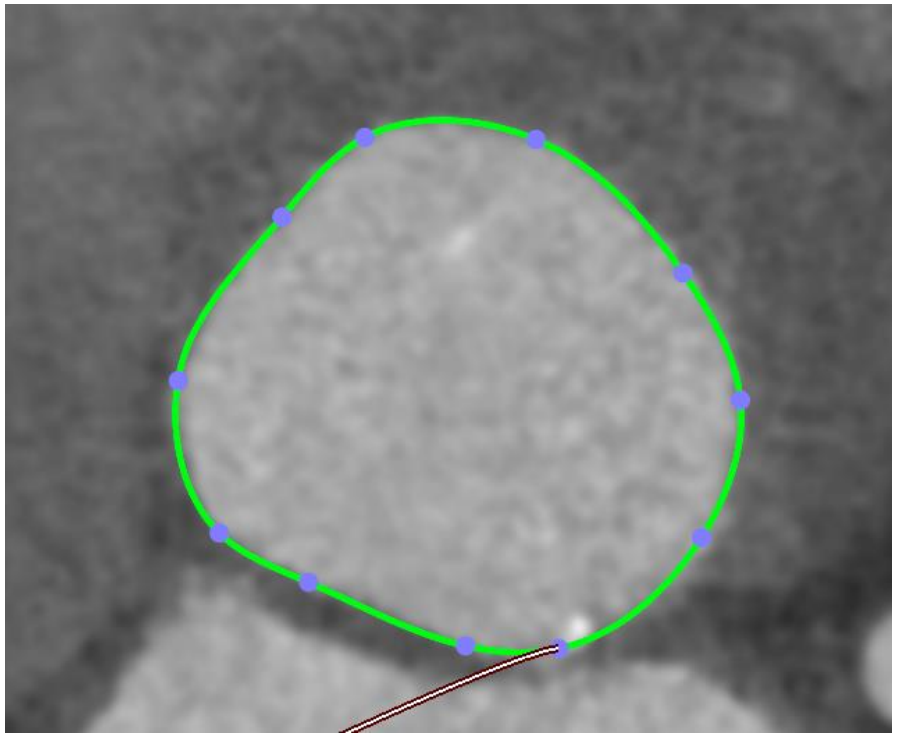
NOAC

Low Risk

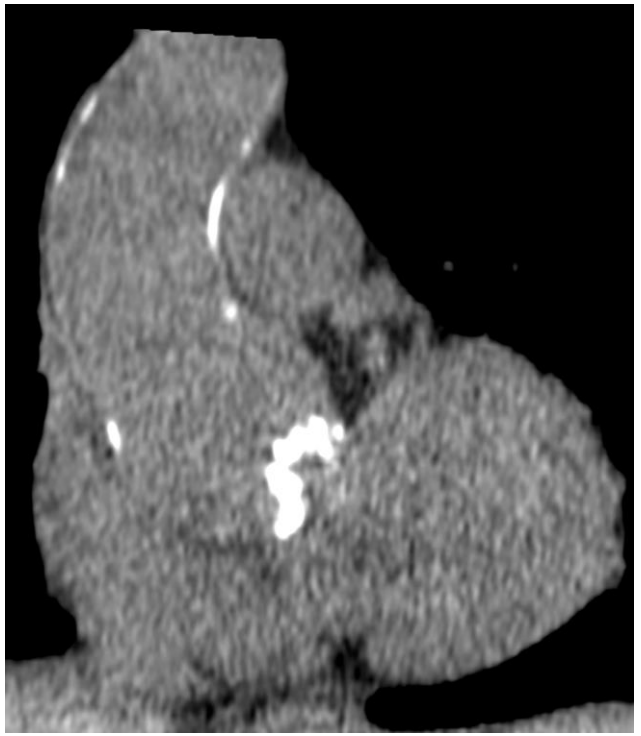
Monitor

Computational Modelling to Guide Treatment Strategy in Very Large Aortic Annulus

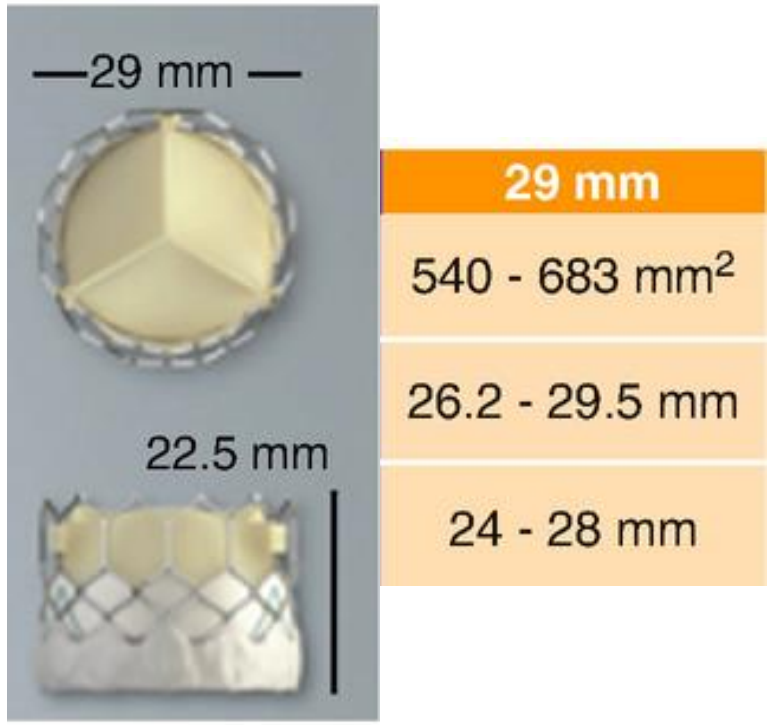
78 year old male
Severe symptomatic aortic stenosis | Bicuspid Aortic Valve



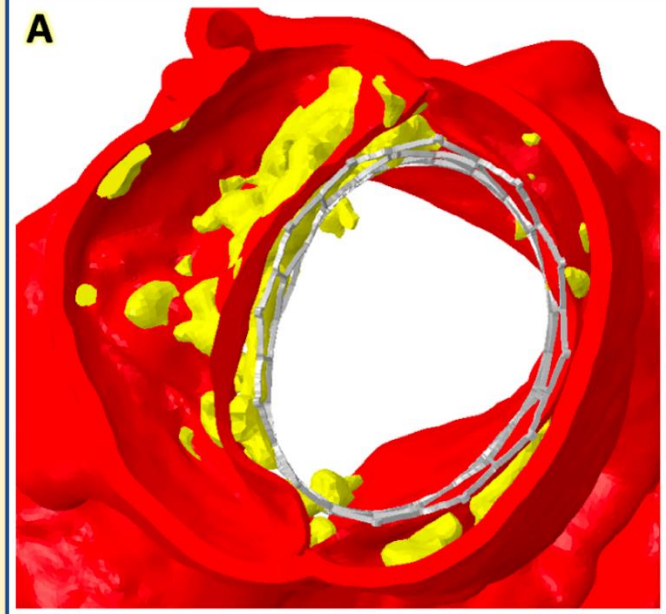
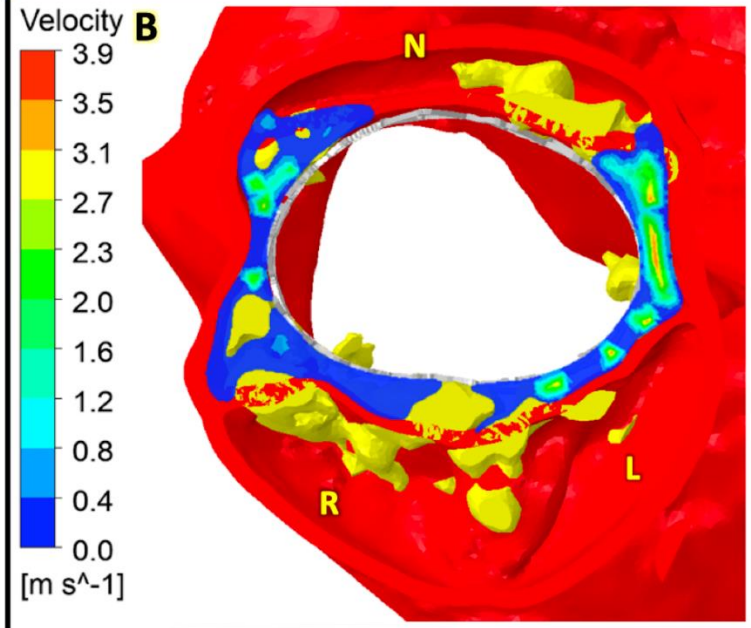
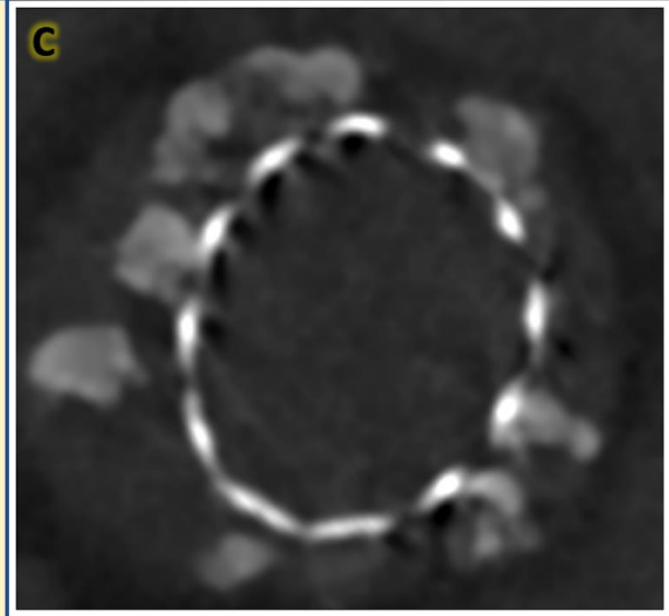
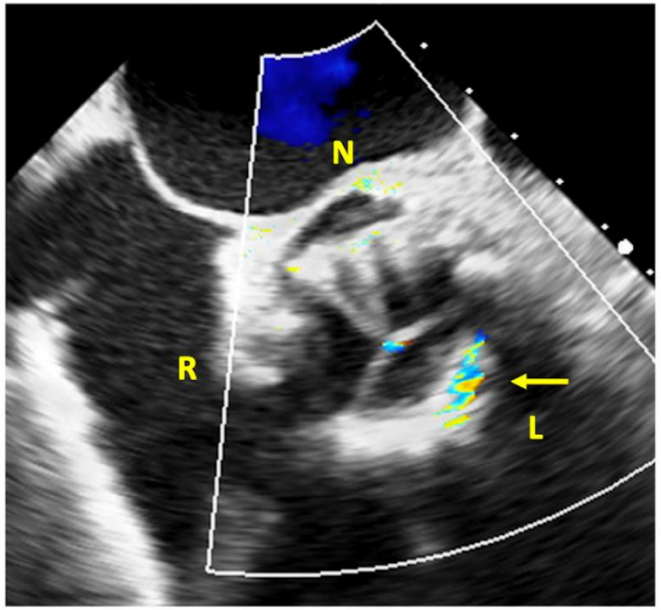
Annulus Area: 1023 mm²
Dimensions: 37 x 36.8 mm
Perimeter 115



Heavily Calcified Aorta
High risk stroke/dissection with surgery



Largest Valve: 29 mm Sapien 3
??Patient anatomy too big for TAVR

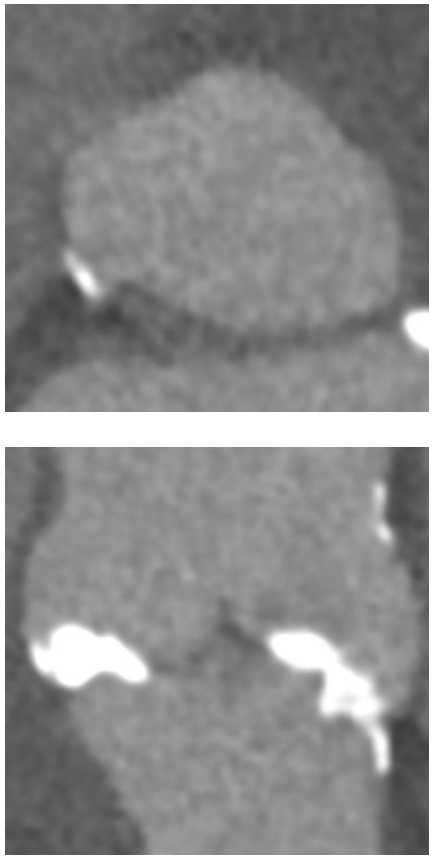
	Frame Expansion	Paravalvular Regurgitation
Pre-TAVR CT Modelling	A 	B 
Post-TAVR CT + Echo Imaging	C 	D 

Av. Diameter (mm)	30.4
Area (mm²)	678
Perimeter (mm)	94.0
Ellipticity Index	0.28

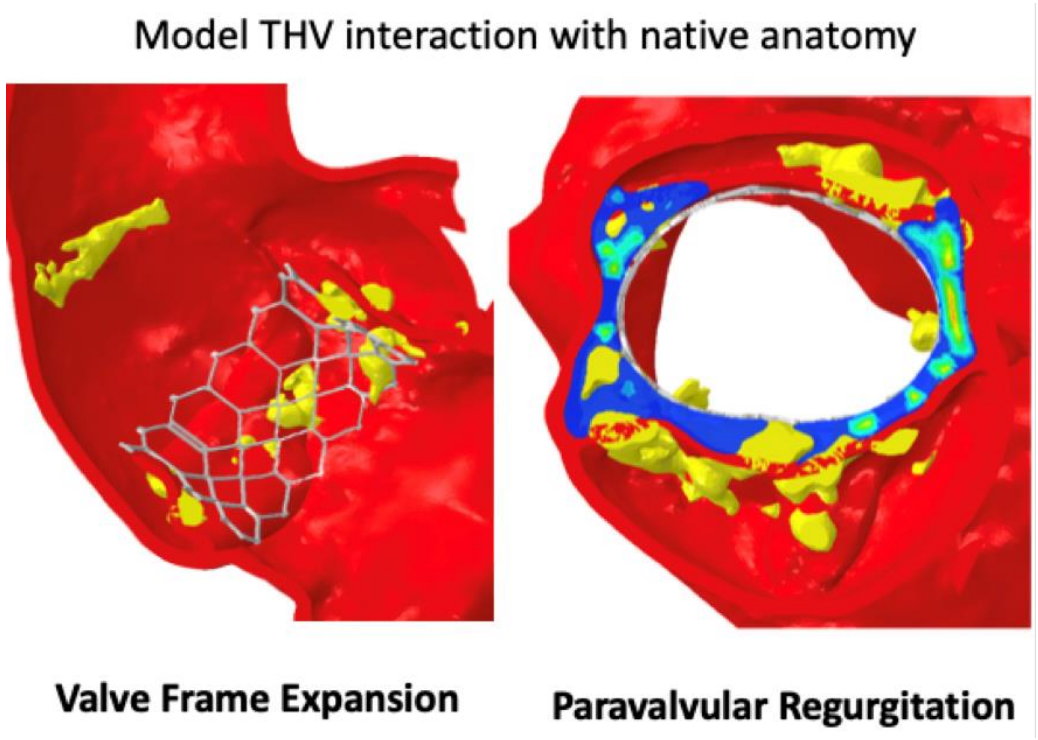
Av. Diameter (mm)	29.3
Area (mm²)	670
Perimeter (mm)	92.4
Ellipticity Index	0.24

Translational Vision

Pre-TAVR CT



Computational Modelling

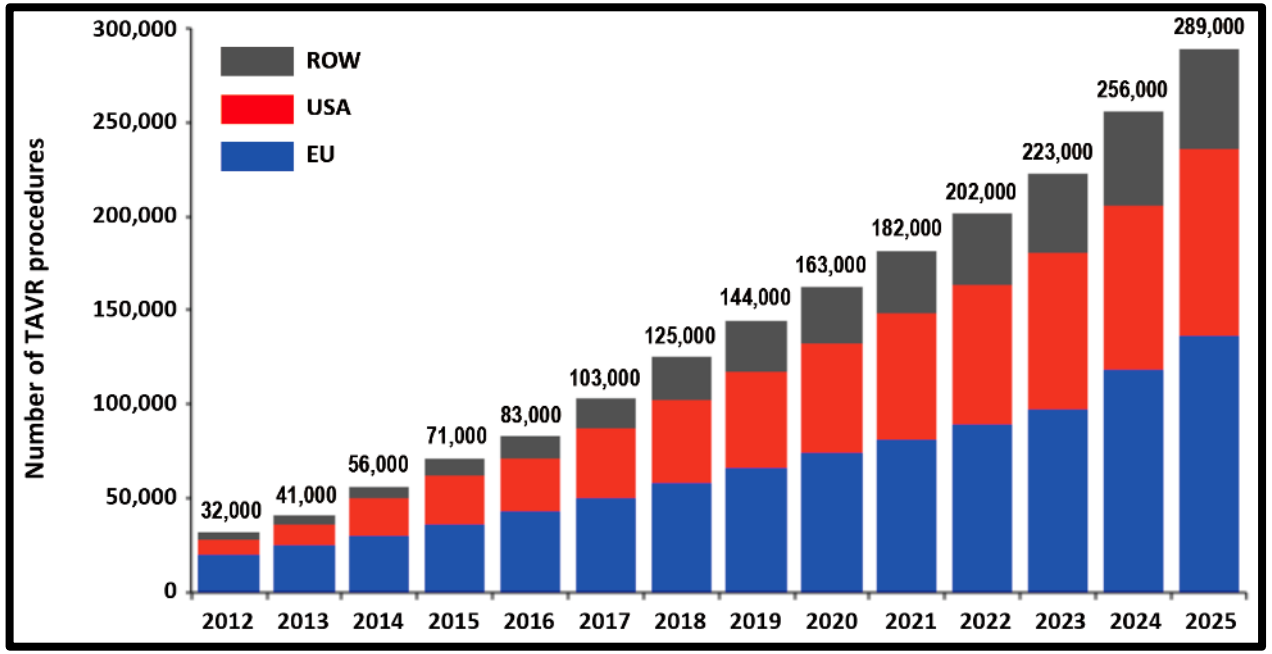


Refine Procedural Strategy

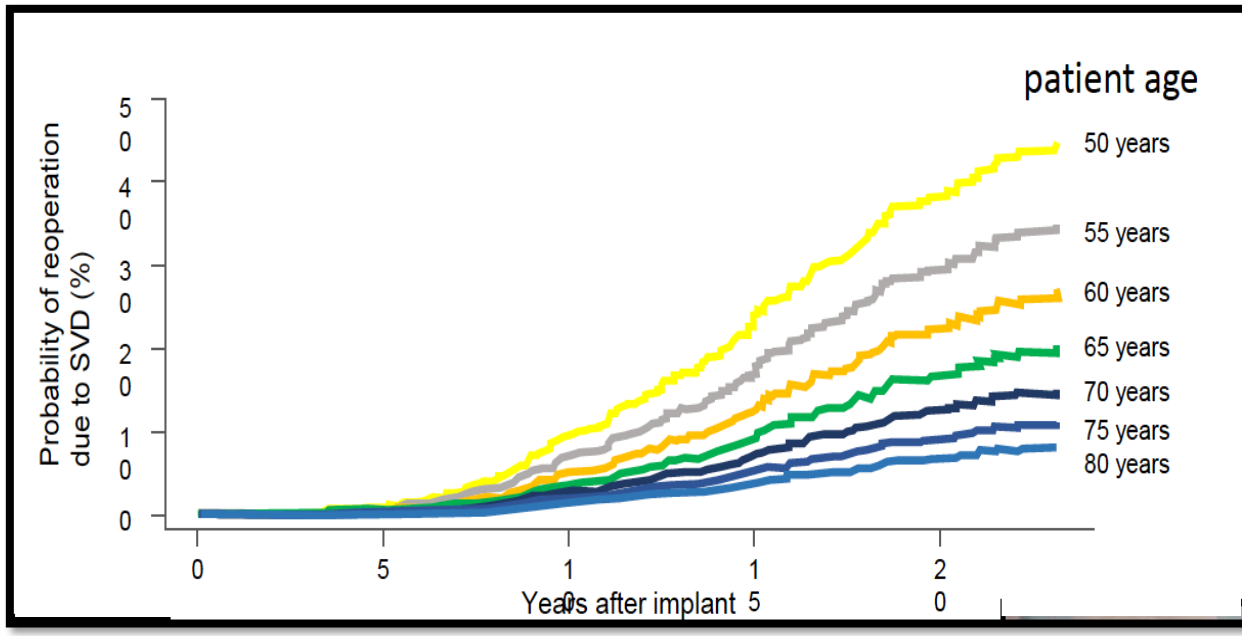
- **Valve Type**
- **Valve Size**
- **Deployment Height**
- **??SAVR**

TAVR: Increasing Utilization | Unresolved Problems

Rapidly rising use of TAVR



Bioprosthetic TAVR Valves eventually degenerate ~20% require repeat intervention



TAVR Degeneration will became a major clinical issue in the future

Younger patients will require a second TAVR (THV in THV) as anticipated life-expectancy > life-span of initial TAVR

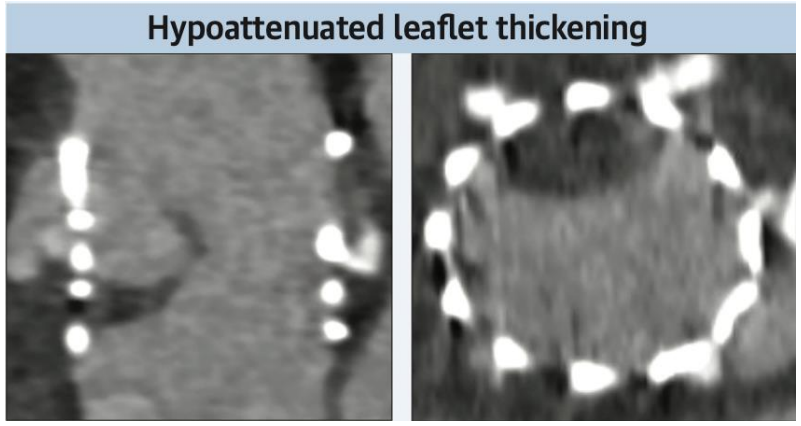
Cesna et al. Journal of Thoracic Disease. 2017

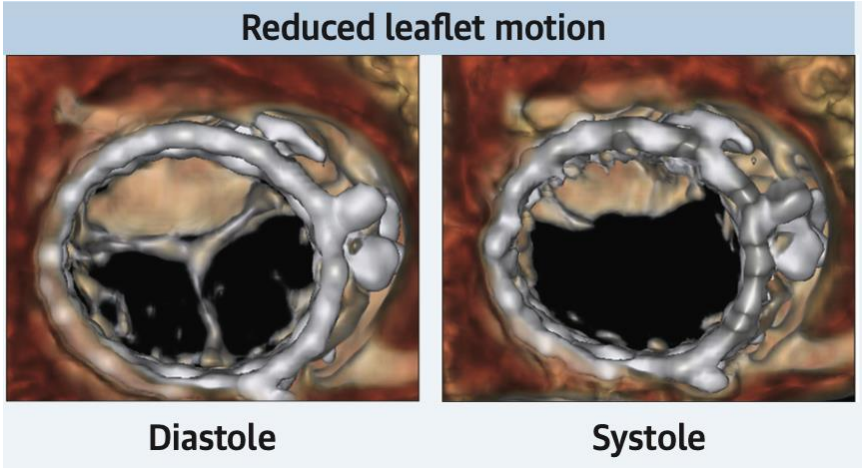
Bourguignon T etal. Ann Thorac Surg. 2015

Bioprosthetic Valve Leaflet Thrombosis

- Subclinical leaflet thrombosis is frequently (10-15%) identified on CT imaging of TAVR + SAVR bioprosthesis

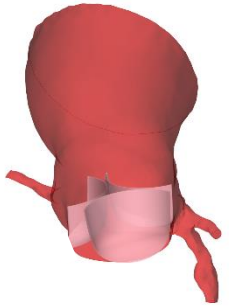
- **Leaflet thrombosis:** Presence of hypoattenuated leaflet thickening + reduced leaflet motion.



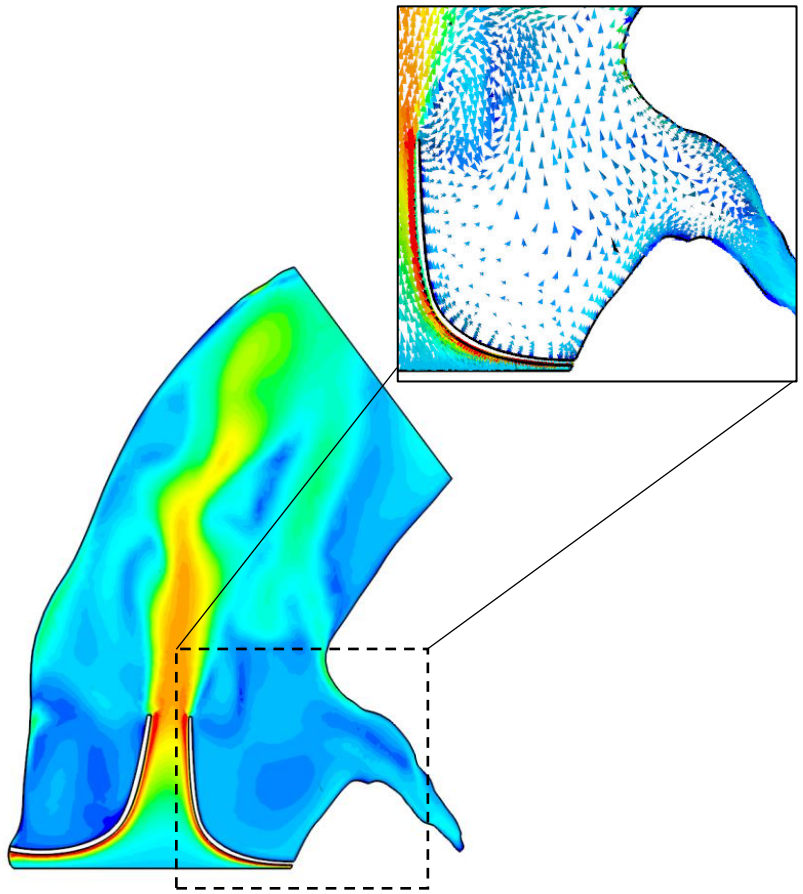


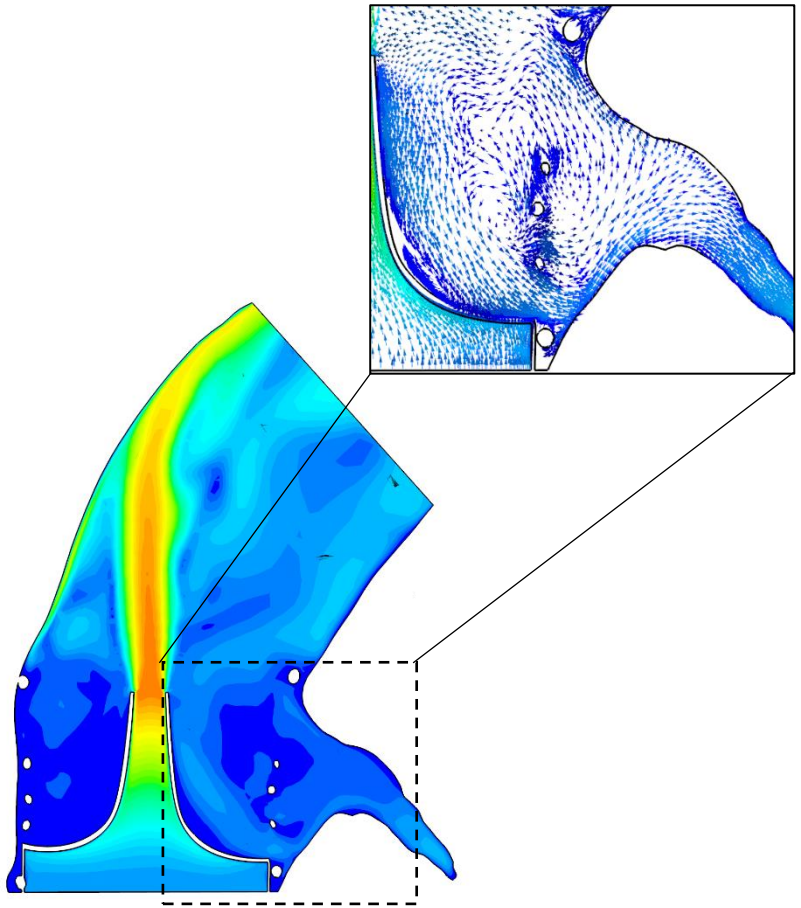
Makkar et al. JACC 2020; Rashid et al. Eurointervention 2018

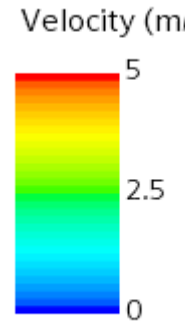
Scenario 1: No TAVI

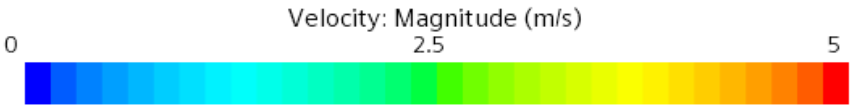


Scenario 2: First TAVI



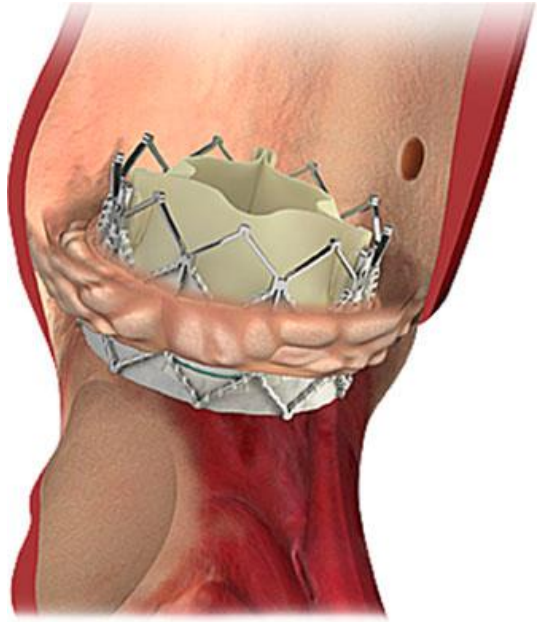




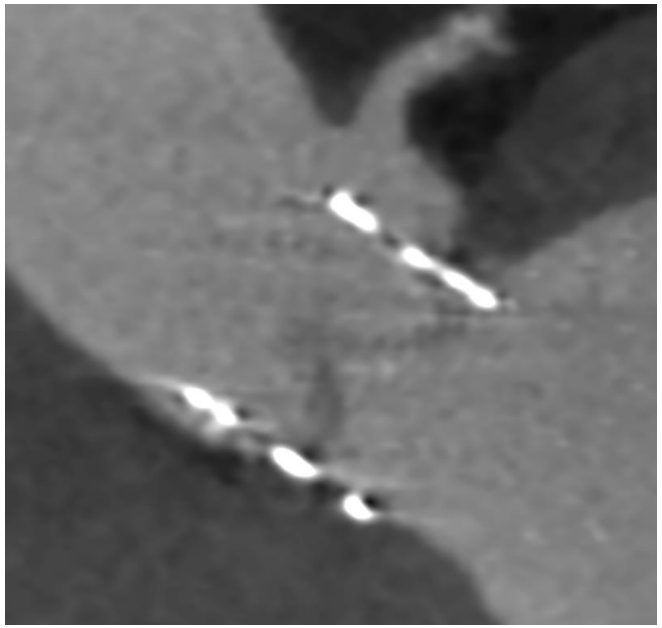


Translational Vision

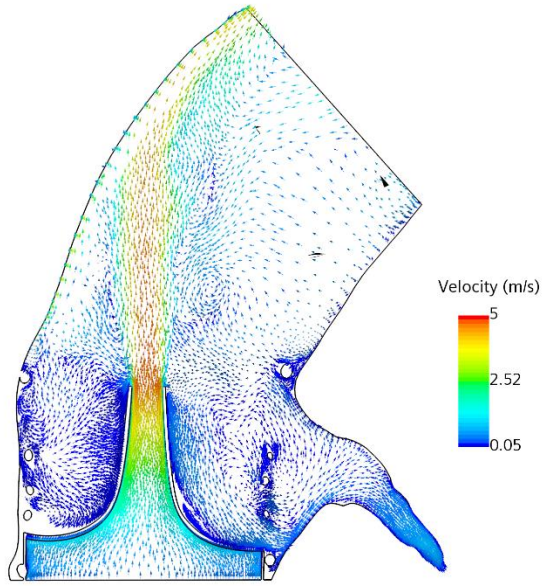
TAVR



Post TAVR CT



Computational Modelling



High Risk

NOAC

Low Risk

Monitor