ACvA Coronary Artery Disease (CAD) Clinical Theme

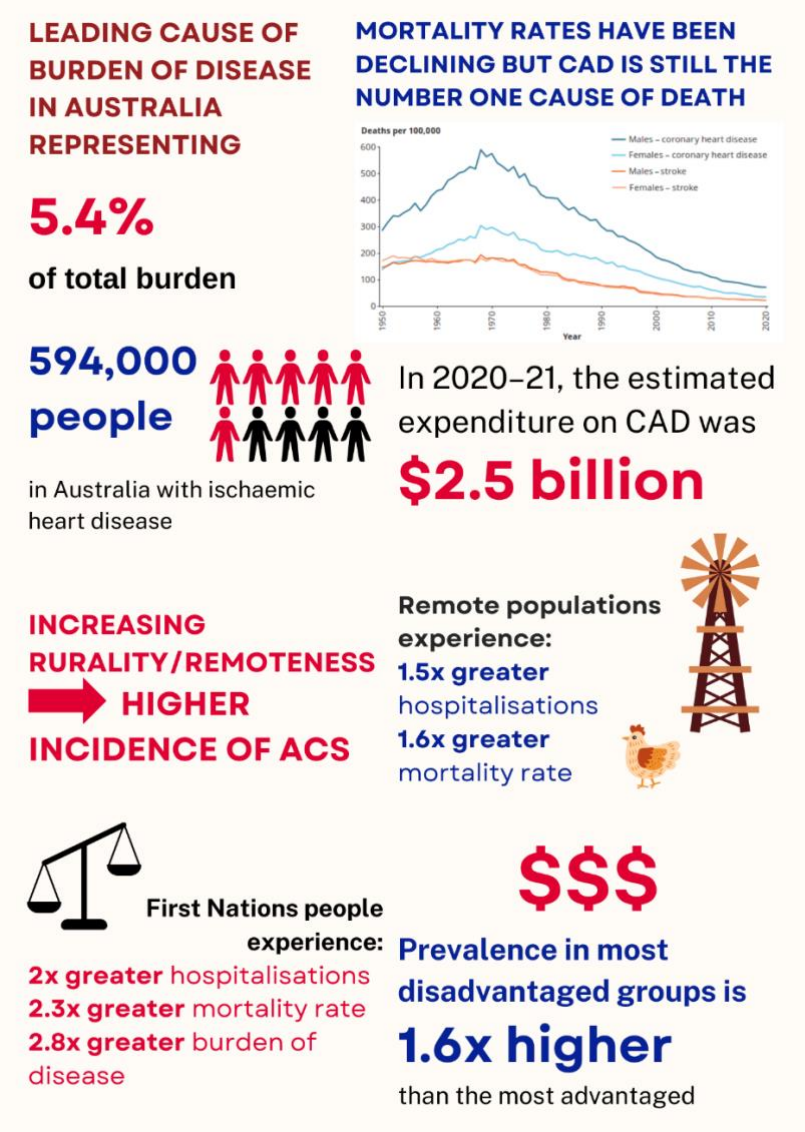
15 February 2024

Workshop 1 Summary

Setting the Scene:

1. Impact of CAD in Australia (Lee Nedkoff)

Since 1968 there has been a steady decline in CAD rates in Australia. Despite this, CAD remains the leading cause of death in males and second leading cause in females (AIHW). Key messages are presented in the below infographic.



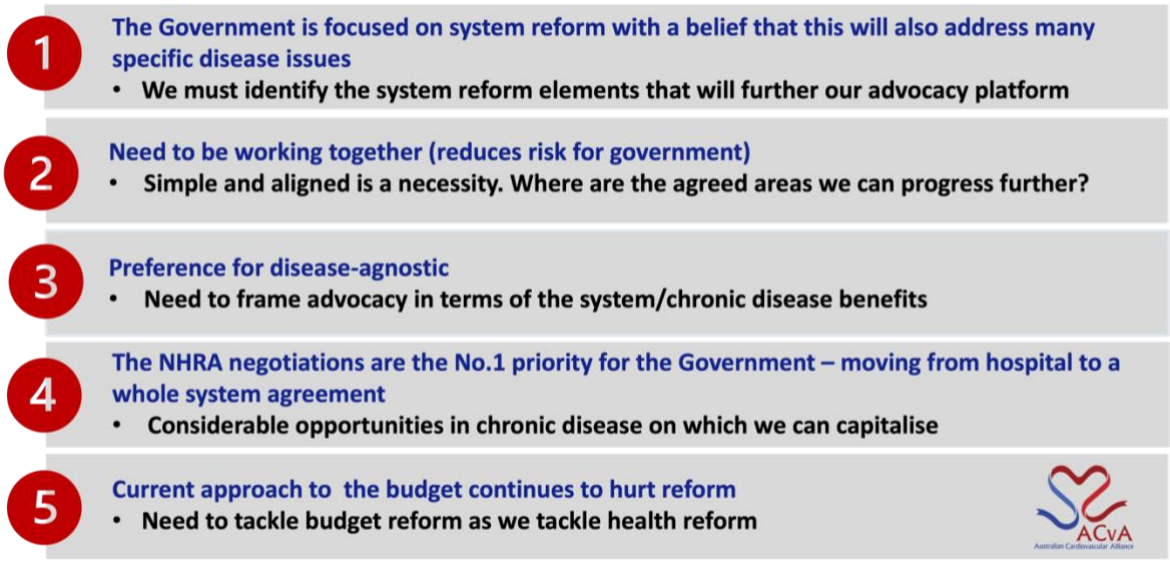
2. Government Policy Agenda and CVD (Kerry Doyle)

To make real progress in tackling cardiovascular disease (CVD) in Australia, we need to take a close look at the policies in place and find ways to influence decision-makers. By understanding the current policies and finding opportunities to make changes, we can make a positive impact on fighting this health problem.

At a recent CVD Health policy briefing session, prepared Ogilvy Health and supported by Amgen the following key points where raised:

- Labor government only took a few health commitments to the 2022 election. In the first Labor government term they have focussed on:
    - Strengthening Medicare
    - Providing 50x urgent care clinics
    - Reducing the PBS co-payment
    - Expanding access to Commonwealth Seniors Health Card
    - Establishing the Australian Centre for Disease Control
    - Expanding newborn screening
    - Strengthening aged care
    - Expanding rural health workforce
- Minister Butler is focussed on several priorities with a longer health reform agenda to future proof the health system.

With a government focused on systems reform, how do we gain traction on CAD reform?



In this workshop, we focussed on six topics areas:

- Biology of CAD progression
- Detecting and treating CAD before a heart attack
- Monitoring CAD at a population, hospital, and primary care level
- Secondary Prevention of CAD
- Identifying new targets for intervention
- Stakeholder engagement

Workshop Topic Discussions

For each topic, speakers were asked to consider "what do we know, what don't we know and where we could go?". A summary of the key discussions from the six topics are provided below.

Topic 1: Biology of CAD progression (Christina Bursill)

Atherosclerosis, the primary process driving plaque formation, was acknowledged as well understood; however, several aspects remain ripe for further investigation, including:

- Strategies for effectively targeting inflammation and oxidation, with particular emphasis on optimal timing for intervention.
- Identification of the disease stage at which regression becomes challenging, offering insights into more targeted therapeutic approaches.
- Recognition of the diverse contributions and sources of immune cells in the progression of CAD, emphasising the importance of understanding their roles for more comprehensive treatment strategies.

In addition, avenues for future research and therapeutic development were discussed, such as:

- Implementing broad-spectrum inhibition of inflammation and oxidation as a potential therapeutic avenue.
- Developing approaches aimed at preventing plaque macrophage apoptosis, thereby supporting processes like emigration, efferocytosis, and cholesterol efflux (e.g., through high-density lipoprotein).
- Exploring plaque-targeted therapies that extend beyond traditional lipid-lowering. strategies, potentially addressing other underlying mechanisms driving disease progression.

Topic 1: What we have learnt about CAD from systems biology (Jason Kovacic)

- Systems biology has "come of age"
    - Now possible to move beyond GWAS and static DNA data that does not account for environmental exposures.
    - System biology approach already given major insights into heritability and causality of CAD and other complex diseases e.g. LDL-glucose paradox.
- Provides an unbiased means to identify powerful therapeutic targets that impact entire networks of genes and proteins.
    - For example, 224 gene regulatory networks explain ~60% CAD heritability.

Topic 1 Exemplar: Infensa Bioscience: Opportunities and Challenges (Nathan Palpant)

Myocardial infarction (MI) and stroke account for 27% of all deaths worldwide yet there are no approved drugs to protect the heart and brain from ischemic damage, despite decades of research into cardioprotective and neuroprotective strategies.

- Most companies in this space are targeting post-infarct remodeling and progression to heart failure.
- Serca Pharmaceuticals and Infensa Bioscience are the only companies targeting initial organ damage caused by MI.

- Value of an MI therapeutic highlighted by Johnson & Johnson's recent acquisition of Abiomed for USD $16.6 billion.

The Target validation pipeline:

- Target identification – Screening of natural compounds that can prevent tissue damage caused by heart attacks and stroke.
- Hit identification – Hi1a protein identified from the K'gari funnel spider venom.
- Lead identification – Hi1a is an inhibitor of the ASIC1a channel.
    - Identified inhibitors of ASIC1a that are both potent (IC_{50} 0.4–1.6 nM) and highly selective and patents filed.
    - Activity found in multiple disease models: heart attack, heart transplantation, and ischemic stroke
    - Efficacy in multiple species: mice, rat, and pig (and human cardiomyocytes)
    - Efficacious at clinically relevant timepoints with delivery before or after onset of cardiac ischemia
    - Genetic association between *ASIC1* and heart disease. Evidence of a genetic association between the target gene and the disease being treated doubles the likelihood of drug approval.

- Lead optimisation – A miniaturised version of Hi1a has been developed and tested in preclinical studies
    - Advantages:
        - Lower developmental costs (6x lower)
        - Less development time
        - Less drug to elicit same effect; lower side-effect risk
        - Stable at room temperature - Enables more patients to be reached
        - Enhances commercial returns

- Preclinical/clinical – The miniaturised version will enter investigational new drug (IND)-enabling preclinical toxicology studies in January 2024, with a view to initiating a Phase I clinical trial in Q4 2024

Topic 2: Detecting & treating CAD before heart attack progression (Gemma Figtree)

- 53 – 57% of CVD events are explained by targetable risk factors, while the remainder of CVD risk is accounted for by other factors, most predominantly genetic and genomic.
    - 25% of heart attacks have no Standard Modifiable Risk Factors ('SMURFless')
- Imaging of CAD provides a new opportunity for diagnostics to detect the disease e.g. through the use of calcium scoring that can be integrated into broader screening programs.
    - There is currently inequity in access to CACS and CCTA for asymptomatic patients.
    - We need equitable access to both screening for risk factors and disease.
    - Important to consider sex-specific imaging that could be used to detect early development of atherosclerosis.
- CAD drug translation has been limited by inability to perform serial non-invasive imaging of the disease itself- focusing heart attack and death.

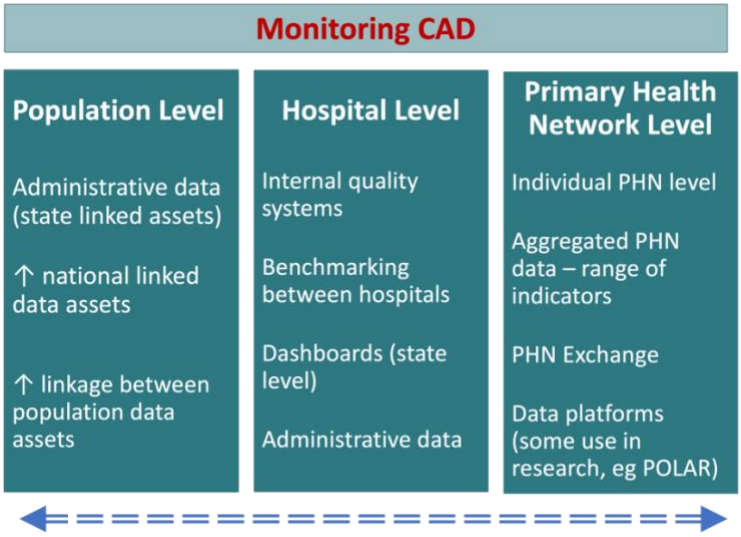
- Coronary Computed Tomography Angiography (CCTA) imaging of plaque in the coronary arteries is highly valuable for assessing cardiovascular risk, as it provides detailed information about plaque characteristics that are strongly associated with future heart events

Topic 3: Monitoring CAD at a population, hospital and primary health network level (Lee Nedkoff)

Need to be clear about what we are monitoring, for example:

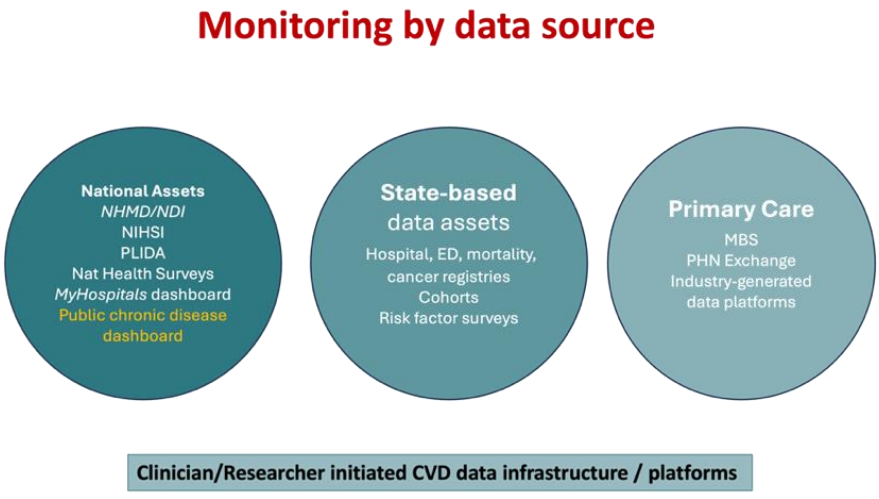
- disease burden
- different levels of disease burden
- quality of care
- service provision

Current data sources for monitoring include:



There are more data assets than ever to monitor CAD. It's unlikely that there will ever be one encompassing system. Each data asset has their own nuances that will need to be overcome.

Data assets currently available include:



Challenges

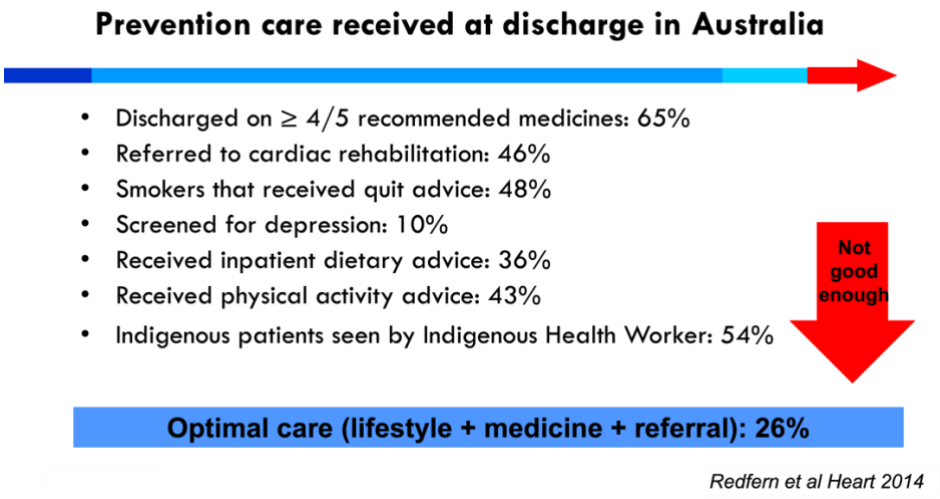
- What is the focus of the monitoring (quality of care, disease burden, investigating disparities). How does this impact on what we need?
- Understanding the metadata behind data assets, dashboards, etc
- Extracting specific CAD/CVD data from some of the data assets
- Keeping track of burgeoning data sources, ensuring limited duplication, consistent data collection/access across regions
- Timely access and cost of access to data
- Overlap with other cardiac, cardiovascular and chronic conditions – need to avoid silos

Topic 4: Secondary Prevention – Treatment Gaps (Mark Nelson)

- There are treatments gaps that occur between hospital discharge and primary care.
- Statically, 61% of patients discharged remain medicated 40-day discharge, this drops to 50% at one year post discharge. This needs to be address and better understood.
- Two achievable therapeutic actions are:
    - The transition of care from hospital to primary care would benefit from better communication and demarcation of roles. E.g. currently discharge summaries are often lacking the necessary information for GPs to continue treatment and up titration leading to therapeutic inertia. Additionally, it is unclear who is responsible for up-titration of medication (GP or cardiologist).
    - To overcome therapeutic inertia educational support is needed to promote the use and adherence to latest guidelines. Currently there is no organisation responsible for providing evidence-based education in primary care.
- Other considerations:
    - Also need to address shortage of GPs, currently only 15% of medical students are choosing general practice. This ideally needs to be more like 50% choosing general practice if we are to improve patient access to GPs.
- Empowering and educating patients is also an important aspect to closing the treatment gap.

Topic 4: Secondary Prevention – Personalised Secondary Prevention (Julie Redfern)

- Secondary prevention is crucial in the patient journey following hospital discharge.
- 56,700 acute coronary events in Australia/year and 13% were fatal (AIHW) (51,000 survived).
- There is an urgent need for improved risk factor management.



- Patients are overwhelmed by medical advice however there is not a one-size fits all.
- Individualised care using different modalities is more effective in improving risk factors.

> "Evidence-based care is not about telling patients to participate in evidence-based care BUT *engaging* patients in evidence-based care…" Professor Julie Redfern

Topic 5: Can we develop a vaccine for CAD? – (Steve Nicholls)

- Fifteen years ago, there was optimism surrounding a vaccine targeting oxidized LDL as a potential cure for coronary artery disease (CAD). However, this therapeutic approach has yet to materialise.
- Adopting a vaccine-like approach to treat conventional risk factors may lead to earlier success.
- While statins have been effective, the field is rapidly evolving, with numerous new therapeutics emerging, some offering the potential for biannual treatment regimens.
- Below is a summary of current therapeutics:

On the Pathway to Personalised Prevention of Cardiometabolic Risk

Biology	Cholesterol	TG	HDL	Inflammation	Thrombosis	Diabetes	Lp(a)	Obesity
Biomarker	LDL-C	TG	HDL-C efflux	CRP	None	HbA1c	Lp(a)	BMI
Strategy	Lower apoB or LDL-C	Lower TG Raise or promote HDL	Raise HDL or enhance lipid transport	Target inflammatory mediators	Reduce platelet or thrombotic activity	Improve glycemic control	Lower Lp(a)	Weight reduction
Trial Evidence	Ezetimibe PCSK9 mAb PCSK9 RNAi Bempedoic acid	High dose EPA ?ApoC3 ?ANGPLT3/4	?HDL mimetics ?LCAT agonists ?Endothelial lipase inhibitors	IL-1 mAb IL-6 mAb Colchicine	DAPT COMPASS	SGLT2 GLP-1 RA GLP/GIP	?antisense ?RNAi ?disruption	Surgery GLP-1 RA GLP/GIP

- It was emphasized that patients at high risk, particularly those who have experienced a myocardial infarction (MI), are susceptible to flu and should receive the influenza vaccination to mitigate their risk.

Topic 6: Stakeholder Engagement
Australian Atherosclerosis Society key initiatives & opportunities (Judy de Haan)

- Collaborations with international Societies:
    - Korean Society of Lipids and Atherosclerosis
        - 13th International Congress on Lipid and Atherosclerosis (26-28 Sep, Seoul, South Korea.
    - European Atherosclerosis Society (EAS)
- Bi-monthly virtual seminar program
- NHF-AAS-ACvA led position statements in lipid management.

Topic 6: Stakeholder Engagement
Australian Cardiovascular Health and Rehabilitation (ACRA)

- The Australian Cardiovascular Health and Rehabilitation Association (ACRA) is the peak body that provides support and advocacy for multidisciplinary health professional to deliver evidence-based best practice across the continuum of cardiovascular care.

- Vision: empower health professionals to achieve optimal and equitable outcomes for all affected by cardiovascular disease.

Strategic Plan
2023-2026

- While many Cardiac Rehabilitation programs have vastly different needs, resources and other operational constraints there is a need for benchmarking, standardisation and certification. Currently there are:
    - No training requirements for CR clinicians in Australia
    - No national benchmarks or criteria for CR programs in Australia
    - No national data registry for CR program outcomes

- ACRA's National Certification & Data Strategy approach:
    - Ensure that all cardiac rehabilitation clinicians are certified to an internationally recognised standard, as defined by the Cardiac Rehab Foundation certification program of the International Council of Cardiovascular Prevention and Rehabilitation (ICCPR).
    - Phase II Outpatient Cardiac Rehabilitation (CR) programs must adhere to the following requirements:
        - Fulfill three mandatory standards and achieve 70% compliance with all standards outlined in the global ICCPR Cardiac Rehabilitation Clinical Quality Standards.
    - Post program & progress data – available to every registered program.
        - Data to also be collated into a national Australian data registry to support the CR programs around the country to deliver best practice based on international standards.

Next Steps

The workshop was a significant first step towards identifying a shared objective within the CAD Clinical Theme. Although a specific common goal wasn't defined, there's agreement that this would be a focus that the CAD Clinical Theme could collaboratively pursue in the future. In light of this, it's important to continue and expand upon the discussions from the workshop.

The next steps include:

- Continue to build this CAD Clinical Theme Platform of exchange and interaction across Australia.
    - Reconvene virtually in April/May and plan for a satellite F2F meeting (potentially 31st July - TBC) at CSANZ (1-4 August, Perth).
- At the next meetings, focus on:
    - Learning from other Clinical Themes: Invite Alta Schutte/Markus Schlaich to the next CAD Clinical Theme Meeting to discuss the Hypertension Taskforce model and Roadmap and how it could be adapted for the CAD Clinical Theme
    - Work toward identifying a common goal and the data required to support delivery of that goal.
    - Working on ways to develop and improve data and data-dashboards related to CAD.