IN JUST 7 DAYS, ABOUT 10% OF PEOPLE WHO HAVE A STROKE WILL HAVE ANOTHER

TARGETING HIGH BLOOD PRESSURE IS POSSIBLY THE MOST IMPORTANT INTERVENTION IN PREVENTING ANOTHER ACUTE HEART ATTACK OR STROKE

EXERCISE TRAINING IS ASSOCIATED WITH A 22% REDUCTION IN CARDIAC DEATH IN PATIENTS WITH HEART DISEASE.

$12 BILLION HEART DISEASE REMAINS THE MOST EXPENSIVE DISEASE IN THE COUNTRY. IT COST $12 BILLION IN 2012-13 AND IS ESTIMATED TO RISE TO OVER $22 BILLION BY 2032-33

BAKER HEART AND DIABETES INSTITUTE
IF YOU’VE HAD A HEART ATTACK, YOU ARE TWICE AS LIKELY TO DIE PREMATURELY COMPARED TO THE GENERAL POPULATION

DESPITE CLEAR EVIDENCE OF BENEFIT, ONLY 50% OF PATIENTS WHO SUFFERED A HEART EVENT RECEIVE GUIDELINE-BASED CARE AND REFERRAL TO CARDIAC REHAB

WIDER ACCESS IS CRITICAL

WE NEED TO CONSIDER WIDER ACCESS TO NEW GROUPS OF DRUGS IN AUSTRALIA FOR PEOPLE WHO HAVE EXPERIENCED A HEART EVENT

PEOPLE WHO HAVE SUFFERED A HEART ATTACK OR STROKE ARE AT HIGH RISK. WE NEED A PREVENTION CAMPAIGN TO IMPROVE DEATH AND DISABILITY RATES

NO SECOND CHANCES
OF THE 4.2 MILLION AUSSIES WITH A CARDIOVASCULAR CONDITION, 1.2 MILLION HAVE HEART DISEASE AND ARE 5 TO 7 TIMES MORE LIKELY TO SUFFER FUTURE HEART EVENTS THAN THOSE WITHOUT HEART DISEASE
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Despite major advances in the prevention and management of cardiovascular disease, it remains the leading cause of death in Australia and most costly disease group in the country. This new report shines a light on a critical aspect that demands greater attention in Australia.

There is, and should be, considerable attention given to the primary prevention of cardiovascular disease. We all agree that keeping people healthy and free from disease for as long as possible makes sense when it comes to the health and quality of life of people within our community, and the costs to our health care system.

But for those people in our community who have already experienced a devastating event such as a heart attack or stroke, it is important to understand the increased risks and costs to individuals, their families, the health system and our economy. Importantly, there are opportunities to reduce this burden – over a third of admissions to hospital are followed by another within 3 months.

No Second Chances, written by expert clinician researchers, epidemiologists and health economists, highlights the opportunities to reduce death and disability in people who have already experienced a cardiovascular event, and outlines why an investment in the secondary prevention of cardiovascular disease is not just prudent but critical to the health of Australians. We need strategic leadership and a comprehensive approach to this issue to improve the health of Australians, to save lives, to ensure people are productive for as long as possible and to help reduce the spiralling costs to our health system. This report provides a blueprint for action which we hope will stimulate greater focus, investment and action in the area of secondary prevention of cardiovascular disease.
EXECUTIVE SUMMARY

This report highlights the critical and timely opportunity to invest in secondary prevention in Australia.

An estimated 22% (4.2 million) of Australian adults aged 18 or over have conditions that include any disease involving the heart or circulation. Some of these conditions are risk factors (e.g. hypertension), while others are disease entities (often termed cardiovascular diseases) such as heart attack, heart rhythm disturbance, heart failure, stroke, and peripheral vascular disease. Cardiovascular disease is related to 1.1 million hospitalisations a year, accounting for 11% of all hospitalisations in Australia. It remains Australia’s biggest killer. In 2017, almost 44,000 deaths — many of which may be considered preventable — were attributed to cardiovascular disease in Australia. On average, one Australian dies every 12 minutes from cardiovascular disease. 1

After decades of falling mortality from cardiovascular disease, the trend is beginning to change, likely a consequence of population ageing and improved treatments that have resulted in people living longer with cardiovascular disease. Despite major advances in the prevention and management of cardiovascular disease, the financial burden to Australia remains large. These costs arise from premature death, disability, and costs of treatment in hospital and in the community. In the coming years, cardiovascular disease is likely to remain the most expensive disease group, with a total cost of $12 billion in 2012-13 which is estimated to rise to over $22 billion in 2032-33. 2

When we hear the word “prevention”, most people think of primary prevention - preventing initial heart attacks and strokes by tackling traditional risk factors. However, the people who are at the greatest risk are those who have diagnosed cardiovascular disease — preventing recurrence or progression is the realm of secondary prevention. The tools (including reducing high LDL cholesterol, high blood pressure, diabetes risk, smoking and obesity) are similar for both types of prevention. But the return on investment in prevention is greatest in the secondary prevention group. These people have already experienced a serious event such as a stroke or an acute heart attack and research unequivocally shows they are now at high risk of another cardiovascular event. Preliminary data from the Queensland cardiovascular registry 2010-2015 show a 38.5% rate of readmission to hospital within 3 months, and a rate of 57.3% within one year. These numbers are comparable to Canadian data showing 61.7% were readmitted within a year. 3

Understanding what happens physiologically is important. Cardiac function worsens with every cardiac event, leading to the risk of heart rhythm disturbances due to scarring, heart failure due to loss of muscle and dilation of cardiac chambers, and heart rupture and aneurysms due to the thinning of the infarcted area. To make matters worse, we know that stroke and heart attack share some common risk factors and pathological mechanisms, and therefore patients who survive a stroke or heart attack are also at particularly high risk for other types of cardiovascular events. 4 Such impact has important implications for how we manage and support these people. The cornerstones of treatment of patients with known cardiovascular disease has been relatively static over recent decades, and there are significant opportunities for improvement.

This review reveals how Australia is faring when it comes to secondary prevention of cardiovascular disease, along with what it is costing our community and the opportunities to significantly improve health outcomes and reduce health costs. It opens discussion on modifiable risk factors and targets for medical therapy that should be aimed at high-risk patients, and lifestyle modification in secondary prevention of cardiovascular disease. We define and review secondary prevention, the current approaches to managing risk, and the economic burden associated with known cardiovascular disease. We review recent developments and propose progressive, new pathways that we believe will improve outcomes and reduce costs.

Given the high risk faced by people who have experienced a heart attack or stroke, the worrying global trends about cardiovascular disease and the unabated escalation of costs associated with heart disease, strategic investment has never been more important.

CONTROLLING RISK IN CARDIOVASCULAR DISEASE

RECOMMENDS A RAFT OF MEASURES AS FOLLOWS:

Renewed commitment to proven measures:

1. A secondary prevention campaign with clear strategies and targets
2. Improvement in cardiac rehabilitation funding
3. Strategies to enhance adherence to disease modifying medications
4. Disease management programs, including patient-centred interventions including with mobile devices

Research into new approaches:

1. Development and application of a national standard calculation of post-event risk
2. Recognition of subclinical disease to provide “early secondary prevention”
3. Wider use of new therapies in high risk patients
INTRODUCTION
Cardiovascular disease (CVD) is a term used to describe multiple conditions affecting the heart and blood vessels. CVD is the most common cause of death and disability, especially among people with diabetes. The most common types of CVD are atherosclerosis (coronary heart disease, peripheral arterial disease and stroke, Figure 1.1), heart failure and atrial fibrillation.

PREVALENCE
Approximately one in 20 Australians (1.2 million) had CVD in 2017-18, with a higher prevalence in males (5.4%) than in females (4.2%). The proportion of people with CVD increases with age (Figure 1.2).

MORTALITY
In 2017, almost 44,000 deaths – which contributed to 27% of all deaths and were considered largely preventable – were attributed to CVD in Australia. On average, one Australian dies every 12 minutes from CVD. The leading cause of death was Ischaemic heart disease, accounting for 11.6% of all deaths (Figure 1.3).

CVD accounted for 27% of all deaths in Australia in 2017 (26% and 28% for males and females, respectively). Of all CVD deaths in Australia, 44% were due to coronary artery disease, 18% due to stroke, and 10% due to heart failure and cardiomyopathy.

HOSPITALISATIONS
CVD was the main cause for 556,700 hospitalisations and related to another 576,000 hospitalisations in 2015-16. That means CVD was a factor in more than 1.1 million hospitalisations, accounting for 11% of all hospitalisations in Australia (Figure 1.4). The number of hospital stays due to CVD has increased by 8% during 10 years from 2004-05 to 2014-15.
FIGURE 1.1 ATHEROSCLEROSIS IN DIFFERENT VASCULAR BEDS – CORONARY, PERIPHERAL, CAROTID AND CEREBRAL

A
ISCHAEMIC STROKE DUE TO EMBOLISATION FROM ATHEROSCLEROTIC DISEASE IN THE CAROTID ARTERY

B
CORONARY ARTERY DISEASE (LEADING TO CHEST PAIN, HEART ATTACK, AND HEART FAILURE)

C
PERIPHERAL ARTERY DISEASE (LEADS TO PAIN, NUMBNESS, INFECTION, GANGRENE, AND CAN LEAD TO AMPUTATION)
FIGURE 1.2 PREVALENCE OF CVD BY AGE AND SEX
SOURCE: AUSTRALIAN BUREAU OF STATISTICS 2018, NATIONAL HEALTH SURVEY: FIRST RESULTS, 2017-18. 1

FIGURE 1.3 CAUSES OF DEATH IN CARDIOVASCULAR DISEASE
SOURCE: AIHW NATIONAL MORTALITY DATABASE. 3
FIGURE 1.4 MAJOR CAUSES OF HOSPITALISATION FOR CVD IN AUSTRALIA (2015-16)

SOURCE: AIHW NATIONAL HOSPITAL MORBIDITY DATABASE

BURDEN OF CVD

Globally in 2016, the World Health Organisation (WHO) estimates that over 31% of all deaths were due to CVD.7

Mortality, or death, from heart disease has decreased by >70% since the 1970s in many high-income countries including Australia (Figure 1.6), owing to effective treatment and prevention of premature CVD death.7, 8 However, CVD still remains the number one killer in Australia (Figure 1.5). Ischaemic heart disease is the principle cardiovascular cause of premature death in both men and women, in all states (Figures 1.7 & 1.8).

APPROXIMATELY 22% OF AUSTRALIAN ADULTS ARE LIVING WITH A CARDIOVASCULAR CONDITION

Of the 90 million prescriptions dispensed for cardiovascular medications in 2015, 73% attracted a Pharmaceutical Benefits Scheme subsidy. These subsidies have increased from $558 million in 1993-94 to $1.2 billion in 2016-17.9
FIGURE 1.5 PREVALENCE OF CVD, AMONG PERSONS AGED ≥18 YEARS, IN AUSTRALIA (2014-15)

SOURCE: AIHW ANALYSIS OF ABS MICRODATA: NATIONAL HEALTH SURVEY (NHS), 2014-15.¹

FIGURE 1.6 TOTAL NUMBER OF DEATHS FROM CVD IN AUSTRALIA, 1913-2012

FIGURE 1.7 & 1.8 PROPORTION OF PREMATURE DEATHS (<75 YEARS) FROM CVD IN MALES AND FEMALES RESPECTIVELY (2017)

PROJECTION OF CVD RATES IN THE FUTURE

In the USA, a 2011 report predicted that upwards of 40% of the US population would suffer from CVD in 2035. However, that mark was reached 20 years earlier in 2015. The projected prevalence of CVD was therefore recalculated and now suggests that nearly half of the US population (131.2 million) will suffer from CVD by 2035.

In Australia, the prevalence of CVD is also projected to increase substantially in the coming years, and remain the most costly disease group, with a total cost of $12 billion in 2012-13 expected to rise to over $22 billion in 2032-33.

WHAT IS ATHEROSCLEROSIS?
Atherosclerosis is the pathophysiological process that results in the narrowing of arteries in coronary artery disease, peripheral vascular disease and cerebrovascular disease. It describes a process whereby cholesterol (atheroma) is deposited in plaques within the artery walls. This may lead to the tube of the artery becoming narrow (limiting blood flow), inflammation of the arterial wall, and eventually rupture of the plaque leading to a blood clot and occlusion of the vessel. It is the disease process common to both acute and chronic presentations of coronary artery disease (CAD). Atherosclerosis is a systemic disease.

WHAT IS CORONARY ARTERY DISEASE (CAD)?
CAD, also known as coronary heart disease, happens when atherosclerosis causes the coronary arteries to get narrower and reduce the blood flow to the heart. There are both acute and chronic presentations of CAD. This report focuses on the events after acute presentation of a heart attack with sudden onset chest pain, known as an acute myocardial infarction (AMI) or acute coronary syndrome (ACS). A heart attack is caused by rupture or erosion of the atheroma or plaque, leading to an acute clot blocking the coronary artery, depriving the heart muscle of oxygen and nutrients. This is potentially a life-threatening event that often results in permanent damage to an area of the heart muscle. It can cause dangerous heart rhythms and is the most common cause of sudden cardiac death in adults. Attempts are often made to open the artery mechanically (through a procedure known as ‘stenting’), or by dissolving the blood clot responsible for the event with medication (‘thrombolysis’). The processes of plaque rupture and clotting can recur in the same or another vascular territory.

WHAT IS CEREBROVASCULAR DISEASE?
This entity describes diseases of the blood vessels and, especially, the arteries that supply the brain. Cerebrovascular disease affects large, small blood vessels within the brain resulting in either blockage, haemorrhage or blood vessel rupture. This can lead to a disturbance of blood flow and oxygen supply and subsequent brain tissue injury. Cerebrovascular disease can present as a sudden change in neurological function as a stroke or if the symptoms are brief (and less than 24 hours duration) a mini-stroke or Transient Ischaemic Attack (TIA). Otherwise cerebrovascular disease can begin to appear in a more incipient way, with disconnections in the brain circuitry resulting in cognitive decline and vascular dementia.

Of all strokes, around 85% are caused by ‘blockages’ and are termed ischaemic strokes (IS). The remainder are due to blood vessel rupture and are termed haemorrhagic strokes or spontaneous intracerebral haemorrhage (sICH). Atherosclerosis accounts for 20–30% of ischaemic stroke aetiology – and varies amongst different racial populations. The blockage of blood supply could be because of an atherosclerotic plaque rupturing in a blood vessel that directly supplies the brain. Alternatively, it could be due to a blood clot that formed somewhere else in the circulatory system, for example in the heart during atrial fibrillation. The consequences of stroke will depend upon the part of the brain that is affected and the extent of the brain injury.

In 2017, there were over 56,000 new and recurrent strokes in Australia. That is one stroke every nine minutes. There were 475,000 Australians living with stroke in 2017 – which is predicted to increase to one million in 2050.
WHAT IS PERIPHERAL ARTERY DISEASE (PAD)?

PAD is a group of disorders leading to progressive abnormal narrowing, obstruction or dilation of aorta or blood vessels of the limbs. PAD could provoke a severe, immediate crisis (blocking an artery leading to the possibility of limb amputation) or a chronic condition (reducing blood flow to limbs causing pain during activity).

Atherosclerosis leading to an abnormal narrowing of peripheral arteries, known as stenosis, is the leading cause of PAD in patients >40 years old. Patients notice the symptom of intermittent claudication - the pain that develops in the muscles of the legs when engaging in physical activity, such as walking. Although this symptom is present in 10-30% of PAD patients\textsuperscript{16}, approximately 50% of PAD patients are asymptomatic.\textsuperscript{17,18} Because the symptoms of PAD are often mistaken for other ailments, including ageing, the disease often goes undiagnosed and many people may not be aware they suffer from this disease. A study of patients presenting to an Australian emergency department showed a PAD prevalence of 10.3%, but only 6.4% were symptomatic.\textsuperscript{19} Severe, acute presentations of PAD may result from clots forming in the heart (see AF adjacent) or larger vessels in the chest, abdomen or upper leg. The clots then travel inside the blood vessels in the direction of blood flow (a process known as embolization) until they lodge and block the smaller arteries of the limbs.

The age standardised prevalence of PAD in men aged 65–83 years in Australia is 15.6%.\textsuperscript{20} This may increase up to ~30% in people aged ≥70 years or those aged 50–69 years with a smoking history or diabetes.\textsuperscript{21}

WHAT IS ATRIAL FIBRILLATION?

In the normal heart, the electrical circuits coordinate the simultaneous contraction of the left and right atrial chambers to pump blood into the left and right ventricular chambers respectively. As the main pumping chambers, the right and left ventricles also contract simultaneously to pump blood into the lungs and the rest of the body. Atrial fibrillation (AF) is the most common type of heart rhythm disorder, or cardiac arrhythmia, and describes disordered electrical activity in the atrial chambers of the heart. The prevalence of atrial fibrillation increases with age and is estimated to be 14.6 per 1,000 in men and 13.6 per 1,000 in women aged 35 and above in Australia.\textsuperscript{22} The disordered electrical activity results in two main problems 1) elevated heart rates and heart failure, and 2) both atria losing their ability to contract and pumping function (known as fibrillation) leading to clots forming in the heart which can embolise or travel to the brain causing stroke – the most devastating and feared complication of AF. Strokes can be prevented with anticoagulants which inhibit clots from forming in the body but increase the risk of bleeding. CAD or heart failure often co-exist with AF and are associated with a doubling of stroke risk in men and trebling of risk in women.\textsuperscript{23}
WHAT ARE SECONDARY CARDIOVASCULAR EVENTS?
SECONDARY CARDIOVASCULAR EVENTS

Secondary cardiovascular events are defined as acute cardiovascular incidents that occur in patients who have already had an event. A study of secondary events after an acute heart attack or stroke has shown that the risk of having an event of the same type is three to five times greater than the risk of having an event of a different type.24

Atherosclerosis is a disease that involves all the arteries in the body. Similar risk factors underlie most forms of CVD, and an event in one vascular territory (e.g. a heart attack) may be followed by a recurrent event in another (e.g. a stroke). However, individual patients may be prone to injury of specific blood vessels – for example the heart vessels (heart attack) or brain vessels (stroke). In other words, the most recent event may predict the next event.

POST MYOCARDIAL INFARCTION

REPEATED HEART ATTACK

There is a high risk of survivors of a first acute heart attack experiencing further cardiovascular events, including repeat heart attacks. Although the incidence rate of repeat heart attacks has declined over the last decade, one in ten heart attack patients develops recurrent events within one year.25

Readmission to hospital is more common after all acute coronary syndromes (i.e. including unstable angina as well as myocardial infarction); in a registry of 4311 patients from Alberta, 61.7% were readmitted, 34.1% as an inpatient, within a year.26 The 30 day inpatient readmission rate was 20.3%, and over half of these were due to a CV problem. The independent predictors were an index length of stay >7 days, the occurrence of non-ST elevation MI, and lack of coronary angiography at the index admission. Recent Australian data are scant, but preliminary data from the Queensland CV registry 2010–2015 (shared by Prof Paul Scurffham, Griffith University) show a 38.5% rate of readmission within 3 months, and a rate of 57.3% within one year. Of those who died, 13.1% died within 3 months and 38.9% died within one year. However, mortality has fallen – only 22.6% of patients with this disease died within the observation period 2010–2015, only 3% within 3 months and 9% within one year. This adds to the picture of ACS being less fatal than previously but producing morbidity and cost.

HEART FAILURE (HF)

Heart failure (HF) is a syndrome that occurs when damage to the heart muscle is severe enough to prevent it from functioning properly as a pump. When this is due to obstruction of the blood supply, typically by a thrombus or embolus, causing death of the heart muscle, or mechanical damage to the heart (e.g. disruption of a heart valve), heart failure can occur suddenly. HF affects 1–2% of the population (approximately 500,000 Australians),26, 27 and is associated with 61,000 deaths per year.27 In developed countries including Australia, HF is the leading cause of hospitalisation and readmission to hospital in persons aged ≥65 years.28, 29
CARDIAC REMODELLING
Cardiac remodelling (or ventricular remodelling) was first described in 1982 to characterise the change in shape of the heart in response to damage and repair. In 2000, an international consensus on cardiac remodelling defined it as a group of molecular and cellular alterations that clinically manifest as changes in size, mass, geometry and function of the heart after cardiac injury. Cardiac remodelling results in poor prognosis because of its association with ventricular dysfunction and malignant arrhythmias.

PROGRESSIVE/RECURRENT DISEASE
Cardiac function worsens with every cardiac event. A progressive loss of cardiac function, asymptomatic at first, will evolve to signs and symptoms of heart failure – which will result in poor prognosis. In addition, a proportion of subsequent deaths after initially surviving an acute heart attack are caused by sudden death. This indicates that a lack of symptoms does not guarantee a good prognosis. Cardiac remodelling after a heart attack is strongly associated with malignant ventricular arrhythmias, including sustained Ventricular Tachycardia (VT) and Ventricular Fibrillation (VF). The thinning of the impacted area of the heart and dilation of cardiac chambers increases the likelihood of heart rupture and aneurysms.

POST STROKE
SECONDARY STROKE
Stroke is a leading cause of disability and a major cause of mortality worldwide. Current registry data in Australia indicate that about 20% of strokes are recurrent and hence potential failures of secondary prevention. This is much less than 15 years ago, when >75% of all secondary CVD events after an incident of stroke were secondary strokes.

RECURRENT NON-STROKE EVENT
Stroke and heart attack share some common risk factors and pathological mechanisms. Therefore, patients who survive a stroke or TIA are also at particularly high risk for subsequent non-stroke cardiovascular events, including heart attack and non-stroke-related vascular death.

POST PERIPHERAL ARTERY DISEASE
RECURRENT PAD AND AMPUTATION
Arterial blockages can be treated by opening the arteries through the insertion of stents or surgical bypass. However, narrowings can recur in the same area or new narrowings can develop in other areas resulting in recurrent claudication. If the blood vessels are too diseased with atherosclerosis, the bypass grafts may not receive enough blood flow to remain open and they can collapse and fail. If limbs don’t receive enough blood flow, patients can experience a recurrence of pain (even at rest), chronic, non-healing ulcers, infection and even gangrene of the limbs. In these cases, limb amputation may be necessary.

STROKE OR CARDIAC EVENT
One third to one half of patients who present with peripheral artery disease have atherosclerosis in other vascular areas including the coronary arteries, and arteries that supply the brain. An acute heart attack or stroke is a major cause of morbidity and mortality in patients who have a history of PAD.
IMPACT OF SECONDARY EVENTS IN CARDIOVASCULAR DISEASE
POST MYOCARDIAL INFARCTION

Coronary artery disease is the leading cause of CVD death, followed by stroke. In 2017, CAD was the underlying cause of approximately 18,590 deaths in Australia (accounting for 12% of all deaths and almost 1 in 2 CVD deaths). Over 40% of CAD deaths were due to acute heart attack. Recurrent heart attack is associated with more hospitalisations and worse prognosis than a single heart attack, and results in substantial long-term cost of care. Survivors of first and recurrent acute heart attacks respectively have 2 and 3-fold risks of all-cause mortality (Figure 3.1), compared with that of the general population of equivalent age.

Although the overall rate of heart attack has declined over time, the magnitude of decline is greater for people who have experienced a single heart attack compared to that of recurrent heart attack. This has led to an increasing proportion of recurrent heart attack over time, which currently accounts for one third of all hospitalised cases of heart attack. The same trend has also been observed for pre-hospital fatal recurrent heart attack. That is, more patients with recurrent heart attack die before arriving at hospital than those who have experienced a single heart attack.

POST STROKE

In 2017, stroke was responsible for over 10,000 deaths in Australia (accounting for 6.3% of all deaths and ranking 3rd in the leading causes of death in Australia). Two thirds of stroke survivors live with long term neurological disability — making stroke a leading cause of disability in Australia. People who survive a stroke or TIA have a greater risk of developing a secondary stroke, especially within a short timeframe. Approximately 10% of people will have another stroke within one week, 14% by one month and 18% by three months. If patients survive for a longer term, their risk falls to approximately 5% per year. Secondary prevention is therefore critical in this high-risk group of patients. Post-stroke patients are also at higher risk of a heart attack or cardiovascular death.

Secondary strokes account for at least 20% of all hospitalised strokes, and often have a higher rate of death and disability because parts of the brain already injured by the original stroke may not be as resilient. One in three stroke survivors is of working age. Approximately 65% of stroke survivors suffer a disability that significantly reduces their quality of life by limiting their ability to carry out activities associated with daily life. The financial cost of stroke to the economy is approximately $5 billion per year in Australia.

PEOPLE WHO SURVIVE A STROKE HAVE A GREATER RISK OF DEVELOPING A SECONDARY STROKE, ESPECIALLY WITHIN A SHORT TIMEFRAME

IMPACT OF SECONDARY EVENTS IN CARDIOVASCULAR DISEASE

PUSHING PAST THE FEAR

Sue Daperis has lost her father, grandfather and three brothers to heart attacks. The 62-year-old aged care worker and mother of two from Melbourne has also had two heart attacks of her own. Her first heart attack six years ago happened while she was driving to work. Luckily, she was one block from her GP and by the time she got there, she was hyperventilating and taken straight to hospital. Three years later, she suffered a second heart attack. At high risk of further heart events, Sue knows a healthy lifestyle is key to ensuring precious years with her family. “Living with the threat of another heart attack can create fear and anxiety,” says Sue. “As you get older, you realise your health is everything.”
FIGURE 3.1 AGE-STANDARDISED MORTALITY RATIOS OVER 7 YEARS IN 30-DAY SURVIVORS OF FIRST MI AND RECURRENT MI.

SOURCE: FIGURE REPRODUCED FROM SMOLINA ET AL. 34

65%
ABOUT 65% OF STROKE SURVIVORS SUFFER A DISABILITY THAT SIGNIFICANTLY REDUCES THEIR QUALITY OF LIFE
OVERVIEW OF RISK FACTORS
The INTERHEART study – a case-control study of acute heart attack undertaken in 52 countries – has described nine risk factors that account for over 90% of these cardiovascular events in both men and women. These risk factors include: hypertension, diabetes, dyslipidaemia, abdominal obesity, smoking, insufficient fruit and vegetable consumption, alcohol consumption, psychosocial factors and lack of regular physical activity. Nine out of ten Australian adults have at least one of these risk factors, and two thirds have three or more (Figure 4.1). Absence of these risk factors reduces the risk on Myocardial Infarction (Figure 4.2). Compounding this are factors specific to Australia that must also be taken into account. There are, for example, ethnic differences in the prevalence of atherosclerosis relevant to Australia’s multicultural society. In 2011-13, Indigenous Australians had higher rates of CVD than non-Indigenous Australians (27% vs 21% respectively). Studies have found South Asian immigrants (e.g. from India and Sri Lanka) tend to have more complex and widespread coronary artery disease, and higher prevalence of cardiovascular disease compared to those of European ancestry. Compared to Europeans, East Asian ethnicities, however, appear to have a more favourable cardiovascular profile with lower rates of atherosclerotic disease. This section will discuss the roles of these risk factors in the development of secondary events in patients with CVD.
### Figure 4.1 Risk of Acute Heart Attack Associated with Exposure to Multiple Risk Factors. Figure Reproduced from the INTERHEART Study. (18)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio (99% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smk (1)</td>
<td>2.9 (2.6–3.2)</td>
</tr>
<tr>
<td>DM (2)</td>
<td>2.4 (2.1–2.7)</td>
</tr>
<tr>
<td>HTN (3)</td>
<td>1.9 (1.7–2.1)</td>
</tr>
<tr>
<td>ApoB/A1 (4)</td>
<td>3.3 (2.8–3.8)</td>
</tr>
<tr>
<td>1+2+3 All 4</td>
<td>13.0 (10.7–15.8)</td>
</tr>
<tr>
<td>Obes + PS</td>
<td>42.3 (33.2–54.0)</td>
</tr>
<tr>
<td>All RFs</td>
<td>68.5 (53.0–88.6)</td>
</tr>
<tr>
<td>All RFs</td>
<td>182.9 (132.6–252.2)</td>
</tr>
<tr>
<td>All RFs</td>
<td>333.7 (230.2–483.9)</td>
</tr>
</tbody>
</table>

### Figure 4.2 Reduced Risk of Acute Heart Attack Associated with Various Risk Factors. Figure Reproduced from the INTERHEART Study. (18)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio (99% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Smoking</td>
<td>0.35 (0.31–0.39)</td>
</tr>
<tr>
<td>Fruit/Veg</td>
<td>0.70 (0.62–0.79)</td>
</tr>
<tr>
<td>Exercise</td>
<td>0.86 (0.76–0.97)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>0.91 (0.82–1.02)</td>
</tr>
<tr>
<td>No Smoking + Fruit/Veg</td>
<td>0.24 (0.21–0.29)</td>
</tr>
<tr>
<td>+Exercise</td>
<td>0.21 (0.17–0.25)</td>
</tr>
<tr>
<td>+Alcohol</td>
<td>0.19 (0.15–0.24)</td>
</tr>
</tbody>
</table>

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Controlling Risk in Cardiovascular Disease
TRADITIONAL RISK FACTORS

HYPERTENSION
Hypertension is a major risk factor for developing CVD, and even more so for developing a secondary event in established CVD. Elevated blood pressure is estimated to cause 7 million premature deaths worldwide and contributes 4.5% of the disease burden (equal to 64 million disability-adjusted life years). High blood pressure is a major risk factor for developing CVD and even more so for developing a secondary event. In 2017-18, one in ten Australians (2.6 million people) reported having hypertension.\(^4\) Findings from a large meta-analysis with over one million adults show a 50% increase in risk of cardiovascular mortality for each 20mmHg increase in systolic blood pressure above 115mmHg.\(^47\)

Targeting hypertension has the highest benefit in reducing CVD burden on a population level and is possibly the most important intervention in secondary prevention of ischemic stroke. The PROGRESS trial – which included 6,105 patients with a history of stroke or TIA – showed a mean blood pressure reduction of 9/4 mmHg and a 4% absolute risk reduction in secondary stroke, regardless of a history of hypertension.\(^48\)

DIABETES
Diabetes has doubled its prevalence in Australia since the 1980s. In 2017-18, 4.9% of the Australian population (1.2 million people) had some type of diabetes (mostly type 2), an increase from 4.5% in 2011–12.\(^4\) Of people aged 75 years and over, almost one in five (18.7%) had diabetes in 2017-18. Pre-diabetes — a condition in which blood glucose levels are higher than normal but not high enough to be diagnosed as diabetes — affects nearly 1 in 6 Australian adults.

Diabetes is associated with accelerated atherosclerosis and confers a two to four times greater risk for acute heart attack and four to six times greater risk for heart failure.\(^49\) People with diabetes are at two to three times higher risk of having a cardiovascular event and 60% of all deaths in people with diabetes are due to CVD.\(^50, 51\) Secondary events are a particular risk in patients with diabetes (Figure 4.3). The same applies to secondary prevention, where poor sugar control and diabetes increase the risk of mortality and recurrent events.\(^52\) Pre-diabetes is not benign either, and is also associated with atherosclerosis.

60% OF ALL DEATHS IN PEOPLE WITH DIABETES ARE DUE TO CVD
DYSLIPIDAEMIA

Dyslipidaemia refers to abnormal levels of blood lipids. “Lipids” is an umbrella term for essential and naturally occurring fats and oils. The two main lipids in the human body include cholesterol and triglycerides, which are formed by the liver from the fats we consume. Cholesterol is central to our understanding of atherosclerosis and its management. Circulating lipids lead to the build-up of fatty deposits in the blood vessels and there is a clear causal relationship between blood cholesterol and the development of atherosclerosis and coronary artery disease.

In 2017-18, 6.1% of all Australians (1.5 million people) reported to have dyslipidaemia, with similar proportions for males and females. In 2011-12, results from biomedical testing suggested that one in three Australians aged ≥18 years (3.6 million people) had dyslipidaemia. However, only 10.1% of this group reported having the condition. This suggests that the majority of people with dyslipidaemia were unaware that they had the condition.

According to the INTERHEART study, dyslipidaemia is the single most powerful cardiovascular risk factor, accounting for over 50% of the attributable risk of heart attack. LDL is a type of particle that contains cholesterol and is primarily responsible for the formation of cholesterol deposits in our blood vessels. Reducing LDL cholesterol levels is an important component of secondary prevention, as every 1 mmol/L reduction in LDL cholesterol concentration will reduce major vascular events by 22%.

OBESITY AND THE METABOLIC SYNDROME

Obesity and the metabolic syndrome is a major health problem worldwide. In Australia, the prevalence of overweight and obesity has steadily increased over the past several decades. In 2017–18, two thirds of Australian adults (67%) were either overweight or obese, an increase from 63.4% in 2014–15. A greater proportion of Australian men (74.5%) were overweight or obes compared with that in women (59.7%). Abdominal obesity is also an emerging problem in Australia, with 98 cm as the average waist circumference for adult men and 87.9 cm for women. The prevalence of severe obesity among Australian adults (9% in 2014–15) has also doubled since 1995 (5%). Obesity appears to originate from a very young age; >20% of children as young as two years were overweight or obese in 2014-15.

HIGH BLOOD PRESSURE IS A MAJOR RISK FACTOR FOR DEVELOPING CARDIOVASCULAR DISEASE AND EVEN MORE SO FOR DEVELOPING A SECONDARY EVENT

CONTROLLING RISK IN CARDIOVASCULAR DISEASE
**FIGURE 4.3** CUMULATIVE RISK OF SECONDARY EVENTS IN PATIENTS WITH AND WITHOUT DIABETES.

SOURCE: FIGURE REPRODUCED FROM MALMBERG ET AL. 228

<table>
<thead>
<tr>
<th>Event</th>
<th>No Diabetes</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Mortality</strong></td>
<td>0.15</td>
<td>0.20</td>
</tr>
<tr>
<td>RR</td>
<td>1.84 (1.6, 2.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Months</td>
<td>3 6 9 12 15 18 21 24</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiovascular Death</strong></td>
<td>0.15</td>
<td>0.20</td>
</tr>
<tr>
<td>RR</td>
<td>1.78 (1.5, 2.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Months</td>
<td>3 6 9 12 15 18 21 24</td>
<td></td>
</tr>
<tr>
<td><strong>New Myocardial Infarction</strong></td>
<td>0.15</td>
<td>0.20</td>
</tr>
<tr>
<td>RR</td>
<td>1.44 (1.22, 1.68)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Months</td>
<td>3 6 9 12 15 18 21 24</td>
<td></td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td>0.05</td>
<td>0.06</td>
</tr>
<tr>
<td>RR</td>
<td>1.68 (1.27, 2.22)</td>
<td>&lt;0.0002</td>
</tr>
<tr>
<td>Months</td>
<td>3 6 9 12 15 18 21 24</td>
<td></td>
</tr>
<tr>
<td><strong>New Congestive Heart Failure</strong></td>
<td>0.20</td>
<td>0.25</td>
</tr>
<tr>
<td>RR</td>
<td>1.82 (1.60, 2.06)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Months</td>
<td>3 6 9 12 15 18 21 24</td>
<td></td>
</tr>
<tr>
<td><strong>Combined Endpoint</strong></td>
<td>0.15</td>
<td>0.20</td>
</tr>
<tr>
<td>RR</td>
<td>1.56 (1.4, 1.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Months</td>
<td>3 6 9 12 15 18 21 24</td>
<td></td>
</tr>
</tbody>
</table>
Obesity contributes to recurrent cardiovascular events by producing a variety of disorders that influence blood circulation, brain and nerve function, and metabolism (how the body burns food to survive). Indeed, the metabolic syndrome has a widespread impact on various functions and roles within the body. These include inflammation, clotting and disturbances of protective functions of the blood-vessel walls. Metabolic syndrome is associated with a 25-fold increase in risk of type-2 diabetes and a 4-fold increase in risk of atherosclerosis. Those with metabolic syndrome have a 2-fold increase in risk of CVD, myocardial infarction, cardiovascular death and stroke.

The story between obesity and cardiovascular disease is complex. Not all obese or overweight individuals develop metabolic syndrome. Despite the associations with other risk factors, some studies have found overweight and at least mildly obese individuals have a better short- and moderate-term prognosis than thinner patients, known as the ‘obesity paradox’ – though this may be explained by poor cardiorespiratory fitness in underweight individuals. This is an area of ongoing cardiovascular research.

**SMOKING**

Smoking is an important CVD risk factor, second only to dyslipidaemia. Continued smoking after an acute cardiac event is associated with significant adverse effects on the cardiovascular system, including elevated blood pressure, heart rate, peripheral vascular resistance and susceptibility to clotting. Although the smoking rate in Australia has substantially declined since 1995 (23.8%), it remains relatively similar over the recent years (14.5% in 2014-15, 13.8% in 2017-18) (Figure 4.5).
In a contemporary Australian population after heart attack, only 55% of smokers had stopped by 30 days and a quarter of these patients had relapsed by 12 months. There is overwhelming evidence of the relationship of long-term smoking with an increased risk of recurrent cardiovascular events and death in CVD patients. Stopping smoking can reduce the risk of death and heart attack in the medium term by approximately 30%. Compared to quitters, persistent smokers have a 4 fold higher rate of a repeat cardiovascular event as early as 6 months (Figure 4.6).

**FIGURE 4.6 AGE-ADJUSTED 5-YEAR SURVIVAL AFTER FIRST ACUTE HEART ATTACK AMONG MEN (LEFT) AND WOMEN (WOMEN) WHO SMOKED (BLACK CIRCLE) AND DID NOT SMOKE (WHITE CIRCLE), COMPARED WITH THEIR EXPECTED SURVIVAL BEFORE HEART ATTACK (CROSS).**

SOURCE: FIGURE FROM PERKINS ET AL. 65

STOPPING SMOKING CAN REDUCE THE RISK OF DEATH AND HEART ATTACK IN THE MEDIUM TERM BY ABOUT 30%
PSYCHOSOCIAL FACTORS

Depression is about three times more common in patients after an acute heart attack than that in the general community. Of those who are hospitalised due to a cardiac event, approximately 20% meet the criteria for major depression. Depression — either pre-existing or developed following a heart attack — is associated with a worse prognosis and higher risk of recurrent cardiac events. In those hospitalised with heart failure, depression is an independent predictor of readmission and death. Anxiety, stress and those who exhibit personality traits like hostility and anger show similar adverse CVD risk, potentially mediated by biological and behavioural mechanisms. Poor psychological wellbeing may result in chronic activation of the sympathetic nervous system which is cardio-toxic and has a deleterious effect on the action of the heart. Poor mental health is also associated with adverse lifestyle behaviours like smoking, sedentary lifestyle, poor medication compliance and greater burden of cardiovascular risk factors like obesity and hypertension.

INSUFFICIENT FRUIT AND VEGETABLE CONSUMPTION

In 2017-18, just over half of Australians aged ≥18 years (51.3%) reported consuming the recommended daily serves (≥2/day) of fruit, and only one in thirteen (7.5%) met the guidelines for consumption of serves of vegetables (≥5/day). Intake of fruits and vegetables up to 800 g/day is associated with reduced cardiovascular risk. While poor fruit and vegetable consumption generally leads to worse health, whether such consumption contributes to the secondary prevention of cardiovascular events remains uncertain. The link does not appear to be through vitamin and mineral deficiency; randomised clinical trials of vitamin supplementation have failed to show effective prevention of secondary vascular events in CVD patients.

PHYSICAL INACTIVITY

In 2017-18, over half (55.4%) of Australians aged 18-64 years undertook ≥150 minutes of exercise a week. However, only 15% of this group met both the physical activity and muscular strengthening recommendations from guidelines. People aged ≥65 years are recommended to do 30 minutes of physical activity on most, preferably all days, and only a little over a quarter (26.1%) met this target in 2017-18.

Findings from a large cohort study have suggested that physical inactivity is an independent predictor of mortality in patients with coronary heart disease and worldwide accounts for 9% of premature deaths. Physical inactivity is widespread, in 2014-15, it was estimated that only 19% of Australian adults aged 18-64 years did the recommended amount of physical activity and strength-based training. For older Australians, at least three quarters did not do the recommended 30 minutes of moderate physical activity on at least 5 days a week. Poor physical activity increases the risk of obesity, CAD, stroke, cancer, osteoporosis, type 2 diabetes (T2DM), hypertension (HTN) and heart failure. In secondary prevention, those who were more physically active and had better cardiorespiratory fitness had improved survival. Sedentary behaviour appears to increase CVD risk, independent of physical activity, but its role in secondary prevention is unclear.

ALCOHOL CONSUMPTION

One in six Australians aged ≥18 years consumed over two standard drinks/day on average in 2017-18. This was a decline from 17.4% in 2014-15 and 19.5% in 2011-12. When more than two drinks are consumed daily, there is a dose-response relationship between alcohol use and CVD risk factors such as hypertension, atrial fibrillation, cardiomyopathy and diabetes. However, while it is evident that heavy alcohol use increases risk of recurrent cardiovascular events, the role of low-dose alcohol use in preventing secondary events is uncertain. The existence of a J-shaped relationship between alcohol consumption and cardiovascular health is controversial. The protective effect of low-dose alcohol use (up to 1 drink/day for women and 2 drinks/day for men) may be due to improvement of high density lipoprotein (HDL) cholesterol, insulin sensitivity and postprandial glucose levels. However, there is also evidence of a linear relationship between alcohol intake and all cause mortality.
BIOLOGICAL RISK FACTORS

Following a heart attack, there is a activation of cardiovascular neurohormonal systems – such as the renin angiotensin-aldosterone system and the sympathetic nervous system. These are natural responses to the initial physiological shock of the heart attack but, over time, chronic activation of these mechanisms leads to progressive cardiac injury and a reduction in cardiac function (Figure 4.7).

A vicious cycle is formed whereby neurohormonal stimulation results in oxidative stress (an imbalance between free radicals and antioxidants), which in turn aggravates the neurohormonal stimulation. Over time as cardiac injury progresses, patients may develop heart failure or arrhythmias.

FIGURE 4.7 CONTRIBUTION OF NEUROHORMONAL ACTIVATION TO MECHANISMS UNDERLYING THE DEVELOPMENT OF CARDIOVASCULAR DISEASE.
INFLAMMATION

Inflammation is a natural human biological process involved in the protection from threats and repair of tissue. In atherosclerosis, inflammation contributes to the process of plaque rupture and clot formation. Biological markers of low-grade inflammation have been shown to correlate with recurrent cardiovascular risk.  

THROMBOSIS

Thrombosis refers to the process of clot formation inside the body with an acute heart attack caused by a clot forming in the coronary artery. Activation of platelets and clotting factors are necessary to start the process of clot formation. Cholesterol deposits, and even coronary stents, can trigger thrombosis and represent a potential focus of future clots and repeat heart attacks. Antagonists to either platelet activation (aspirin and P2Y12 inhibitors) or clotting (warfarin, rivaroxaban), are known to reduce the risk of heart attacks and stroke, although this beneficial effect always has to be balanced against the risk of bleeding.

RISK FACTORS – WHAT WE DON’T KNOW

Despite the recognition of traditional risk factors for >50 years, much remains unknown. The findings that known risk factors address the majority of population attributable risk in the Interheart study obscure the associations within individuals. Patients with the same risk factor profiles may have completely different courses and outcomes. The reality is that we do not understand the host responses to risk factors that drive the variability in susceptibility to the same risk score. Filling the gaps in our biological understanding is an important research target that would inform better management.

HAVING A HISTORY OF A HEART CONDITION INCREASES THE RISK OF FUTURE EVENTS BY 5 TO 7 TIMES COMPARED TO THOSE WITHOUT A POSITIVE HISTORY
RISK EVALUATION OF SECONDARY EVENTS
A PICTURE OF RISK

A past diagnosis of cardiovascular disease and established atherosclerosis is a common, chronic condition that affects 1.2 million Australians. Having a history of cardiovascular disease increases the risk of future cardiovascular events by 5 to 7 times compared to those without a positive history. The risk of a repeat event persists for many years, though it is highest in the first 6-12 months following the initial heart attack. Untreated, the average annual rate of repeat heart attacks is approximately 6%. A follow-up of 4387 Australians who presented with a heart attack found an overall mortality of 10% at 18 months. But even with treatment, there is significant residual risk in and control of traditional risk factors. In the IMPROVE-IT trial, despite optimal medical treatment, 34% of patients had suffered a major cardiovascular event or non-fatal stroke within 7 years of their first heart attack (Figure 5.1).

AUSTRALIANS WITH A HISTORY OF CORONARY ARTERY DISEASE REPRESENT A VERY HIGH-RISK GROUP AND THERE IS CONSENSUS THAT THIS GROUP REQUIRES AGGRESSIVE MANAGEMENT OF THEIR RISK FACTORS TO PREVENT FURTHER HEART ATTACKS

FIGURE 5.1 RATE OF RECURRENT HEART ATTACKS IN IMPROVE-IT – A CONTEMPORARY CLINICAL TRIAL.

SOURCE: CANNON ET AL. EZETIMIBE ADDED TO STATIN THERAPY AFTER ACUTE CORONARY SYNDROMES. NEJM 2015; 372:2387

CONTROLLING RISK IN CARDIOVASCULAR DISEASE
This is a higher risk group because a) a history of cardiovascular disease indicates patients are likely to have or develop atherosclerosis at other points in the coronary arteries and elsewhere, which could become a focus for subsequent heart attacks, b) some of these patients have a propensity to develop blood clots that block the blood vessel, c) damage to the heart muscle leads to serious consequences such as heart failure and heart rhythm disorders.

Table 5.1 below summarises the many patient and environment-related factors that can contribute to residual atherosclerotic risk in patients.

<table>
<thead>
<tr>
<th>COMORBIDITIES</th>
<th>INDIVIDUAL DISEASE FEATURES</th>
<th>ENVIRONMENT-RELATED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Extent of atherosclerosis in the coronary vessels</td>
<td>Individual socio-economic status</td>
</tr>
<tr>
<td>Gender</td>
<td>History of heart attacks and recurrent heart attacks</td>
<td>Low neighbourhood socio-economic status</td>
</tr>
<tr>
<td>Hypertension</td>
<td>High-risk plaque features</td>
<td>Social isolation and low social support</td>
</tr>
<tr>
<td>Lipid disorders</td>
<td>Left ventricle function</td>
<td>Non-adherence and adverse lifestyle behaviours</td>
</tr>
<tr>
<td>Smoking</td>
<td>Atherosclerosis in other arteries like legs, neck</td>
<td>Access to quality secondary prevention therapy</td>
</tr>
<tr>
<td>Obesity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High cholesterol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history, Genetics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes, metabolic syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic inflammation/hs-CRP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression/Anxiety</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**CLINICAL SCORES, INVESTIGATIONS**

In an acute heart attack, clinical evaluation and investigations confirm the diagnosis, determine the treatment plan, assess for complications and determine prognosis.

**DIAGNOSIS OF ACUTE CORONARY SYNDROME**

The subtypes of Acute Coronary Syndrome (ACS) are characterised upon the basis of symptoms, 12 lead ECG, cardiac troponin and coronary angiography. It is possible that the wider use of plaque burden assessment could stratify the risk of repeat plaque rupture or coronary disease progression. However, at present, coronary CT is not favoured for chest pain assessment in patients with known disease.

**SHORT-TERM RISK SCORES**

All patients following an acute presentation are at increased risk, but within this group, understanding the spectrum of risk may help guide the use of new therapies that carry the risk of complications, increased cost or both. At the simplest level, assessing short term prognosis following a heart attack can guide the patient and clinician to balance the risks and benefits of coronary angiography. These risks can be quantified by using evidence-based scores typically used in clinical practice (Table 5.2). An invasive angiogram can also assess the burden of atherosclerosis by identifying the number and severity of blockages in the main coronary arteries. The greater the burden of atherosclerosis, the higher the risk of having recurrent events. **88**
ASSESSING RESIDUAL, LONGER-TERM RISK

The overall burden of coronary atherosclerotic disease which can be determined from CT, coronary angiogram or invasive angiography, provides a powerful predictor of future risk. There are six important and potentially treatable targets that contribute to future cardiovascular events: residual coronary disease, cholesterol control, inflammation, glucose, thrombosis risk and LV impairment.

RESIDUAL CAD

Individuals who present with an acute heart attack may have narrowings in multiple vessels. The culprit narrowing or obstruction is usually easily identified and fixed first. However, patients may undergo further testing to assess the severity of persistent narrowing of vessels (causing residual ischaemia) to determine if further interventions are required. The presence and extent of high-risk plaque may be an important guide to more aggressive therapy.

LIPIDS: CHOLESTEROL AND TRIGLYCERIDES

LDL-C concentration is a powerful predictor of risk and progressive reductions of LDL-C to even very low levels (as seen with PCSK9 inhibitor therapy) results in proportional reductions in recurrent cardiovascular events and mortality. The “lower is better” strategy for targeting LDL-C in patients with established CVD is supported by findings from many clinical trials. Triglycerides and HDL-C levels have an inverse relationship and elevated triglyceride levels are associated with higher cardiovascular risk. In addition to standard lipid profiles, other lipid species may explain the residual risk of future cardiovascular events.

Table 5.2 Post-ACS risk scores

<table>
<thead>
<tr>
<th>TIMI</th>
<th>GRACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 65 years</td>
<td>Age</td>
</tr>
<tr>
<td>Presence of 3 or more CVD risk factors</td>
<td>Biomarker evidence of cardiac damage</td>
</tr>
<tr>
<td>Known history of CAD</td>
<td>SBP (mmHg)</td>
</tr>
<tr>
<td>Current aspirin use</td>
<td>Heart Rate (bpm)</td>
</tr>
<tr>
<td>2 episodes of angina within 24 hours</td>
<td>Signs of cardiac failure</td>
</tr>
<tr>
<td>ST changes on ECG</td>
<td>Cardiac arrest on admission</td>
</tr>
<tr>
<td>Positive cardiac markers</td>
<td>Presence of ST segment deviation on ECG</td>
</tr>
</tbody>
</table>

TIMI = Thrombosis In Myocardial Infarction

GRACE = Global Registry of Acute Coronary Events

NO SECOND CHANCES

CONTROLLING RISK IN CARDIOVASCULAR DISEASE
INFLAMMATION AND THROMBOSIS

Molecular markers in the blood (eg. high sensitivity C-reactive protein, hs-cRP) reflect chronic, low-grade inflammation and elevated levels are associated with recurrent events. Although it is not routine to measure these markers currently, the availability of newer therapies that target the anti-inflammatory component of atherothrombotic risk may result in a change of practice. Platelet function assessment may help identify those at increased thrombotic risk who may benefit from more potent antithrombotic therapy but more research is required.

RENAL FUNCTION, DIABETES AND METABOLIC SYNDROME

Screening for diabetes and the metabolic syndrome should be routine following an acute heart attack. Disturbances of kidney function are strongly associated with cardiovascular events, so tests of renal function are important also.

CARDIAC IMAGING

Echocardiography or cardiac magnetic resonance can be used to quantify heart function and damage, whilst looking for other abnormalities like valve problems. Poor heart function increases the risk of heart failure, heralds a worse survival and requires consideration of specialised medications and therapies. Impaired cardiac function is used to select post-infarction patients for implantable defibrillators.

RISK SCORES FOR PREDICTING SECONDARY EVENTS

Both Australian and international guidelines classify patients with documented CVD as being at high-risk. This is helpful in emphasizing the need for careful risk factor control and follow-up. However, it does obscure the fact that there is a spectrum of risk in these patients. As we move into an era of costly (eg. PCSK9) or potentially risky (NOAC) therapies, an understanding of risk may be of pivotal importance. A number of risk scores have been developed for secondary prevention patients, but these are not currently widely used.

Risk scores have also been developed to predict the risk of bleeding when patients have been started on stronger blood thinners. Older age, history of bleeding, and anaemia are all associated with higher bleeding complications. Data from the REACH registry found that many of the factors associated with recurrent cardiovascular events were also associated with bleeding, such as heart failure, hypertension, smoking, high cholesterol and peripheral arterial disease.

All patients are at increased risk following an acute event, but the risk is not distributed equally. Table 5.3 lists some risk score models which all identify traditional cardiovascular risk factors as remaining pertinent to future risk. For example, the TIMI Risk Score for Secondary Prevention (TRS2P), which was derived from the results of a secondary prevention trial, includes age, smoking, diabetes and peripheral arterial disease. Many scores also identify the burden and extent of atherosclerosis (e.g. the number of vessels or vascular areas affected by atherosclerosis) as an important predictor. Figure 5.2 shows the risk of recurrent events based on the number of TRS2P risk factors. Both diabetes and polyvascular disease have an important impact on future risk. As risk factors accumulate, the risk of a recurrent cardiovascular event dramatically increases. In the IMPROVE-IT trial, 68% of those with 5 or more risk factors had a recurrent cardiovascular event versus just 9% in those with no risk factors.
### Table 5.3 Comparison of risk factors considered in a variety of tools available to predict cardiovascular events in secondary prevention.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>DAPT&lt;sup&gt;93&lt;/sup&gt;</th>
<th>PARIS&lt;sup&gt;94&lt;/sup&gt;</th>
<th>TRS&lt;sup&gt;2P&lt;/sup&gt;</th>
<th>PEGASUS-TIMI&lt;sup&gt;54&lt;/sup&gt;</th>
<th>REACH&lt;sup&gt;96&lt;/sup&gt;</th>
<th>SMART&lt;sup&gt;97&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sex</td>
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<tr>
<td>Ethnicity</td>
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<tr>
<td>Diabetes</td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Lipid profile</td>
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<tr>
<td>Prior stroke</td>
<td></td>
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<tr>
<td>Prior stent</td>
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<tr>
<td>Prior CABG, multi-vessel CAD</td>
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<tr>
<td>Renal dysfunction</td>
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<tr>
<td>Current smoking</td>
<td></td>
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<td></td>
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<tr>
<td># of vascular beds</td>
<td></td>
<td></td>
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<tr>
<td>MI/ACS presentation</td>
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<tr>
<td>Time since MI</td>
<td></td>
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<tr>
<td>CHF, low EF</td>
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<tr>
<td>Stent diameter</td>
<td></td>
<td></td>
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<tr>
<td>Stent type</td>
<td></td>
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<td></td>
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<tr>
<td>Treated with statins/aspirin</td>
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<tr>
<td>Hs-CRP</td>
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<td></td>
<td></td>
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<tr>
<td>Aortic aneurysm</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Atrial fibrillation</td>
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</tr>
</tbody>
</table>
PERSONALISED MEDICINE

Identifying high risk patients can help target therapy to those most likely to benefit. This is important because interventions providing a consistent risk reduction across a range of risk levels will provide greatest absolute risk reduction in those at the highest risk. For example, European guidelines now recommend the use of expensive PCSK9 inhibitors, which dramatically reduce cholesterol levels, in particular high-risk groups.

Such a risk-based strategy could provide a significant change from the current approach to guideline-based secondary prevention, in which groups of patients are treated much the same. Personalised or precision medicine strives to accurately determine the presence of causal and mediating pathways that lead to disease (Figure 5.2), as well as the extent of disease itself. Identifying the different causes in different people can provide a more refined estimate of risk which would then allow treatments to be personalised. This new frontier of medicine has already arrived, albeit in its infancy. Advances in genetics, medical imaging, biochemistry and pharmacology have already improved the treatment of CAD. For example, anti-inflammatory treatment given to patients with evidence of low-grade inflammation can reduce recurrent event rates. However, these new therapies are not yet available in clinical practice.

FIGURE 5.2 PROPOSED CONCEPTUAL FRAMEWORK FOR ADDRESSING RESIDUAL ATHEROSCLEROTIC DISEASE RISK IN THE ERA OF PRECISION MEDICINE (FIGURE REPRODUCED FROM PATEL ET AL)

LIFESTYLE INTERVENTIONS, GUIDELINE-DIRECTED MEDICAL THERAPY

RESIDUAL RISK TARGET

Lipoproteins Inflammation Metabolism Platelets Coagulation

RESIDUAL RISK-LOWERING THERAPIES

Ezetimibe PCSK9 inhibitor Omega-3 fatty acids Canakinumab Methotrexate Colchicine SGLT2 inhibitor GLP-1 agonist Extended UAP1 Low dose ticagrelor Low-dose rivaroxaban

PRECISION MEDICINE TOOLBOX

Standard lipids (e.g., LDL, HDL, TG), advanced lipid testing, Lp(a), HDL efflux capacity, genetic risk scores, atherosclerosis imaging hs-CRP; biomarkers of inflammation, T cell and immune dysregulation, and clonal haematosis; systemic inflammatory disease (e.g., psoriasis) Prevalent type 2 DM, Hb A1c, HOMA-IR, BMI, visceral adiposity, liver fat Antiplatelet risk scores (e.g., DAPT, PARIS, PRECISE-DAPT), platelet function testing, pharmacogenomics PVD, prior VTE, thrombophilia, bleeding risk scores, coagulation biomarkers
MANAGING RISK TO PREVENT SECONDARY CARDIOVASCULAR EVENTS: LIFESTYLE MODIFICATIONS, PREVENTION AND REHABILITATION
MANAGING RISK TO PREVENT SECONDARY CARDIOVASCULAR EVENTS: LIFESTYLE MODIFICATIONS & PREVENTION

STRATEGIES TO REDUCE CARDIOVASCULAR RISK

The goal of secondary prevention programs is to restore quality of life, maintain or improve functional capacity, prevent recurrence and improve prognosis. This is achieved through comprehensive risk stratification (currently focussed on assessing the amount of cardiac dysfunction), use of referral services and strategies to address risk factors.88

Cardiovascular risk is determined by a combination of multiple factors that can relate to the individual or the health system. Optimising the individual’s modifiable cardiovascular risk factors (hypertension, smoking, obesity, diabetes and high LDL cholesterol) reduces recurrent events. Implementing lifestyle changes and commencing medical treatment can help prevent or slow atherosclerosis.64 Targeting biological processes like inflammation and thrombosis represent new strategies to reduce residual coronary risk.

However, despite strong evidence of benefit and cost-effectiveness, preventative care is often sub-optimal. A significant portion of patients struggle to successfully implement lifestyle changes like smoking cessation and weight loss. Poor medication adherence prevents adequate control of risk factors and up to a third of Australian patients presenting with suspected heart attack are not adherent to optimal therapy.103

Population health initiatives can play an important role in overcoming patient inertia and support them to achieve optimal health. Successful public health strategies have reduced daily smoking rates by half from 24% in 1991 to 12% in 2016.104 National health promotion initiatives like the ‘Canadian Hypertension Education Program’ utilised the collaborative efforts of health experts, health agencies and pharmaceutical companies to successfully increase diagnosis, drug treatment and control of hypertension.105 Similar strategies are needed to address the current epidemic levels of diabetes, hypertension and obesity in Australia.

These challenges are worldwide and health systems must monitor risk factors to identify areas of improvement and support behaviour change. Surveys of secondary prevention patients in Europe found two thirds of patients undertook little or no physical activity, a third were obese, ~40% had high blood pressure and 80% had cholesterol levels above target thresholds.106

POPULATION HEALTH INITIATIVES CAN PLAY AN IMPORTANT ROLE IN OVERCOMING PATIENT INERTIA AND SUPPORT THEM TO ACHIEVE OPTIMAL HEALTH
GOALS OF OPTIMAL MANAGEMENT

HIGH-QUALITY ACUTE MEDICAL CARE AND REvascularisation

In the acute phase, managing symptoms of coronary or carotid artery disease through medications and/or invasive procedures will help restore quality of life and functional capacity. Timely and successful intervention in those presenting with an acute heart attack can limit myocardial damage and improve prognosis. Likewise, timely carotid endarterectomy optimises outcomes of patients that have had a stroke due to symptomatic high grade internal carotid artery stenosis. Residual angina or heart failure will prevent individuals from maximal participation in cardiac rehabilitation and other secondary prevention programs. In those with multivessel disease and diabetes or reduced heart function, coronary artery bypass grafting is superior to percutaneous stent insertion in preventing recurrent cardiovascular events. This is due to the ability to bypass a greater extent of diseased native arteries (figure 6.1). Arterial conduits or grafts have excellent long-term potency and outcomes. Timely carotid endarterectomy is beneficial for patients that have stroke due to symptomatic high grade internal carotid artery stenosis.

While there is a general belief that revascularisation for acute coronary syndromes is well-managed in Australia, a recent registry study of nearly 3000 patients showed that after ST segment elevation myocardial infarction, women were less likely to receive invasive management, revascularisation, or preventive medication at discharge. The reasons for these differences are unclear and need to be addressed.

**FIGURE 6.1 REvascularisation TO IMPROVE THE BLOOD SUPPLY OF HEART MUSCLE. A NARROWED VESSEL CAN BE BYPASSED SURGICALLY, OR THE STENOSIS CAN BE OPENED WITH A STENT.**
COMPREHENSIVE RISK ASSESSMENT TO SET OPTIMAL HEALTH TARGETS

Patients should undergo a comprehensive risk factor assessment and be informed of the optimal targets. Secondary prevention encompasses a high-risk group and target levels for risk factors like blood pressure and are usually more aggressive than for the general population. These interventions can slow or prevent the progression of atherosclerosis. Those at risk of longer-term complications of heart attacks like heart failure and heart arrhythmias should be identified so preventative treatment can be commenced. Other lifestyle aspects to be addressed include healthy diet, weight loss if obese, and low physical activity.

COMMENCE SECONDARY PREVENTION EARLY

Secondary prevention is a continuous lifelong intervention program that should be commenced as soon as possible following the initial event. Patients are more open and receptive to behavioural change following a serious event like a heart attack. Therefore, preventative strategies should begin during the patient’s hospital stay and before discharge. The beneficial effects of necessary lifestyle changes like smoking cessation, diet control and exercise can occur as early as 6 months. There is room for improvement. In 2012 audit of patients admitted for acute coronary syndrome, only 70% received smoking cessation advice and less than half received diet or physical activity advice. Psychosocial co-morbidities which severely impact quality of life and ability to adhere to secondary prevention therapies were screened in only 10% of patients.

ONGOING FOLLOW-UP AND VIGILANT RISK FACTOR CONTROL

In the community setting, secondary prevention programs enter the outpatient and long-term phase of management and require 3 key elements for success: timely surveillance, maintenance of evidence based secondary prevention interventions and equitable access to healthcare. Surveillance is necessary to monitor for risk factors and long-term complications, so clinicians can titrate or supplement therapies accordingly. A strong therapeutic relationship can support a patient’s motivation to maintain healthy lifestyle behaviours and medication adherence. Evidence-based care is continually evolving and regular follow-up is needed to ensure treatment regimens are updated accordingly.

PATIENT EDUCATION, HEALTH LITERACY AND SELF-MANAGEMENT

Improving patient understanding and education is an important management priority that is part of the process of cardiac rehabilitation. This is particularly important in people from non-English speaking background and Indigenous Australians, but as social disadvantage and poor health literacy are also known independent risk factors for cardiovascular disease. Improving health literacy improves individual health outcomes and supports self-management of cardiovascular disease – which is important, as this is a chronic, lifelong condition. Patients exposed to cultural- and language-appropriate education programs have higher compliance rates and control of lifestyle factors. However, recent studies report that only 54% of ACS in indigenous patients were seen by an Indigenous health worker.

PATIENTS ARE MORE OPEN AND RECEPTIVE TO BEHAVIOURAL CHANGE FOLLOWING A SERIOUS EVENT LIKE A HEART ATTACK. THEREFORE, PREVENTATIVE STRATEGIES SHOULD BEGIN DURING THE PATIENT’S HOSPITAL STAY AND BEFORE DISCHARGE
GUIDELINE-BASED APPROACHES – LIFESTYLE CHANGES

Lifestyle modification – including healthy diet, smoking cessation, regular physical activity and weight loss – significantly reduces risk of secondary events in persons with CVD.

SMOKING CESSATION

Stopping smoking is possibly the most effective secondary prevention measure. Guidelines recommend all smoking, including second hand or passive smoking, should be avoided. People who quit smoking after a heart attack or cardiac surgery reduce their risk of death by at least one third, and risk of a secondary heart attack by at least one fifth. Reduced cigarette use that does not lead to cessation is not associated with a decrease in mortality either overall or from tobacco-related diseases. Therefore, stopping smoking altogether should be the primary aim.

There are psychosocial and pharmacological options to support patients to stop smoking. Nicotine replacement therapy (NRT), varenicline and bupropion are available pharmacological options and have shown to improve abstinence rates. There is no clear evidence that NRT, varenicline or bupropion adversely impact CVD event rates in patients with established CAD. E-cigarettes offer a similar harm reduction strategy as NRT, and while they are likely to be less harmful than smoking cigarettes, their long-term consequences for CVD are unknown. Psychosocial interventions and counselling are important adjuncts to pharmacological therapy. Smoking cessation interventions are more successful if commenced before discharge and continued in the community for at least a month. In general, the most comprehensive and intensive smoking cessation programs are the most successful.

DIET AND ALCOHOL

The benefits of a healthy diet are many and profound. Healthy diet can reduce LDL cholesterol, optimise blood sugar levels, reduce weight and lower blood pressure. Adhering to a healthy diet also has protective effects against recurrent coronary events up to four years after the first infarction, and substantially reduces mortality risk. European and Australian guidelines recommend a diet high in fibre, fruits, vegetables with 1-2 servings of fish per week. This is combined with restrictions on saturated fat, trans fatty acids, salt, and sugar-sweetened drinks. Replacing saturated fat with mono- or polyunsaturated fat through for example, olive oil, legumes and tree nuts improve blood lipid profiles. Fish rich in long-chain omega-3 fatty acids improve cardiovascular risk factors like hypertension and dyslipidaemia, and reduce CV death. Guidelines recognise the cardio-protective effect of diets like the DASH and Mediterranean diet. The DASH diet is rich in fruit, vegetables and low-fat dairy products and is known to reduce blood pressure. The Mediterranean diet showed a reduction in 5-year risk of major cardiovascular events by approximately 30%, compared with a low-fat diet alone. However, there is still uncertainty about the ideal diet in secondary prevention. A recent large observational study found higher carbohydrates were associated with cardiovascular disease while higher dietary fats were protective. Nevertheless, the same study confirmed diets high in fruit, legumes, and vegetables were protective.

Alcohol should be limited to 2 standard drinks daily for men and 1 for women. Alcohol consumption may contribute to hypertension and weight gain.

MAINTAINING A HEALTHY DIET CAN PROTECT AGAINST FURTHER HEART EVENTS UP TO FOUR YEARS AFTER THE FIRST HEART ATTACK, AND SUBSTANTIALLY REDUCES THE RISK OF DEATH
WEIGHT CONTROL
Obesity, especially abdominal obesity, is harmful and patients should aim to achieve a BMI <25 kg/m² and healthy waist circumference <94 cm in men and <80 cm in women. Even a modest reduction (≥5%) in body weight may lead to significant improvements in CVD risk factors such as blood lipids, glucose, blood pressure and exercise capacity. In a prospective study of 377 patients with coronary artery disease who enrolled in a cardiac rehab program, weight loss was significantly associated with lower risk of mortality and secondary coronary events, regardless of initial body mass index.

Weight loss should be encouraged with calorie restriction and regular physical activity as first line strategies. Avoiding sedentary behaviour and prolonged sitting (e.g. by using standing desks or physical activity breaks) is important. Most pharmacological interventions target the brain to reduce appetite, prolong satiety and diminish cravings. Selection of which medication should be a shared decision depending on comorbidities, drug-drug interactions and side effects. Due to its high risk and cost, bariatric surgery is usually third-line and limited to those with moderate-to-severe obesity. Mean weight loss at 2-3 years following bariatric surgery ranges from 20-34% of the initial body weight. Bariatric surgery has been associated with improvements in CVD outcomes and improved glycaemic control.

EXERCISE AND PHYSICAL ACTIVITY
Physical activity optimises multiple risk factors including blood pressure, endothelial function, insulin resistance, lipid metabolism, obesity, and may even improve psychosocial factors. These beneficial effects contribute to a better quality of life and cardiorespiratory fitness — a strong predictor of prognosis and recurrent events. Following a period of recovery and depending on individual characteristics like age, extent of heart disease and comorbidities, guidelines recommend at least 150/minutes a week of moderate-intensity physical activity.

While physical activity has established health benefits, it is recognised that heavy bouts of physical exertion may transiently increase risk of a cardiovascular event. However, a study of 1228 patients after heart attack showed that <5% of cases appear to be triggered by physical exertion, sedentary patients (defined as heavy exertion less than once per week) are at much higher risk of events.

An exercise-based cardiac rehabilitation program can provide specialised multi-disciplinary support that tailors intervention to the individual patient. Physical activity has positive physiological effects, with exercise training associated with a 22% reduction in cardiac mortality in patients with CAD.

PEOPLE WHO QUIT SMOKING AFTER A HEART ATTACK OR CARDIAC SURGERY REDUCE THEIR RISK OF DEATH BY AT LEAST ONE THIRD

PHYSICAL ACTIVITY HAS POSITIVE PHYSIOLOGICAL EFFECTS, WITH EXERCISE TRAINING ASSOCIATED WITH A 22% REDUCTION IN CARDIAC MORTALITY IN PATIENTS WITH CORONARY ARTERY DISEASE

LIFE IS PRECIOUS
At age 25, and newly married with a young family, Richard Talbot was diagnosed with high cholesterol. “I have a family history of heart disease — with the loss of my grandfather at age 59 and my father at 64 from heart attack,” explains Richard. “I didn’t want to follow in their footsteps so a few years ago I went for a stress test and found I had five blocked arteries. I required immediate surgery to survive.” The grandfather of six has survived a heart attack and a minor stroke and says he makes sure to get regular health checks and lead a healthy lifestyle. “Life is precious and it’s not that difficult to follow the things you should be doing,” he says. “Prevention is always better than cure and I want to be assured that my grandchildren can benefit from my example.”

CHAPTER 6: MANAGING RISK TO PREVENT SECONDARY CARDIOVASCULAR EVENTS: LIFESTYLE MODIFICATIONS, PREVENTION AND REHABILITATION

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BAKER HEART AND DIABETES INSTITUTE
Referral to an exercise-based cardiac rehabilitation service or secondary prevention program is recommended for all patients with symptomatic coronary artery disease. These programs offer lifestyle advice, optimise pharmacological treatment, cardiovascular risk factor control and patient education. Patients who attended a cardiac rehabilitation program had an absolute risk reduction of cardiovascular death, acute heart attack and stroke at 12 months.\(^\text{125}\)

Cardiac rehabilitation (CR) is “the sum of activities required to influence favourably the underlying cause of the disease, as well as to provide the best possible physical, mental and social conditions, so that the patients may, by their own efforts, preserve or resume optimal functioning in their community and through improved health behaviour, slow or reverse progression of disease.”\(^\text{126}\) Patients following an acute coronary event and even those with stable coronary artery disease should be referred for cardiac rehabilitation.\(^\text{111, 127-129}\) With the burden of cardiovascular disease in Australia so great, the importance of providing high quality, accessible cardiac rehabilitation is extremely important.

CR has evolved beyond its foundational purpose of exercise training and safely facilitating a patient’s return to their pre-morbid activity levels. Contemporary CR now represents a bundle of services that can optimise cardiovascular and psychosocial risk, increase physical activity and improve quality of life. At its core is an individualised patient assessment and management plan that addresses the patient’s short and long-term physical, psychological and social needs.\(^\text{130}\) The primary goal of CR is to maximise and maintain everyday function, assist patients to cope with comorbid conditions and prevent recurrent events.\(^\text{131}\) CR also provides essential patient education and counselling that supports chronic disease self-management, medication adherence and lifestyle behavioural change.\(^\text{130}\)

CR programs in Australia are usually delivered in a public hospital or community healthcare setting and offer between 6–12 group education and group exercise sessions.\(^\text{131}\) Alternative delivery formats include home-based, telephone-based or internet-based models.\(^\text{130, 135}\) Most programs deliver comprehensive patient education (including about mental health) but only a minority of Australian CR programs offer individual education or exercise sessions, telephone based support or home visits.\(^\text{131}\) CR providers comprise a multi-disciplinary team including medical practitioners, nurse specialist, physiotherapist, exercise physiologist, dietitian, psychologist, occupational therapist, social worker, pharmacist and clerical staff.\(^\text{130}\) In Australia, nurses, physiotherapists and dietitians are most frequently employed but fewer than half of surveyed Australian CR programs employ exercise physiologists, medical practitioners or psychologists.\(^\text{131}\) In comparison, CR programs in Canada, more frequently coordinated by medical professionals, are more intense and last for a longer duration.\(^\text{131}\)

Evidence from multiple studies and reviews support the benefits of CR in reducing mortality, morbidity, hospital readmission and improved quality of life.\(^\text{132-134}\) The most recent Cochrane systematic review of CR reported 26% and 14% reduction in CV mortality and hospital readmission, but in contrast to previous evidence, found no impact on all-cause mortality. This has raised concerns of a diminishing benefit of CR in the era of contemporary care and changing patient demographic mix. However, the content of the program is important.

Reviews of CR programs restricted to exercise or education components only did not find mortality reductions.\(^\text{135, 136}\) In contrast, comprehensive, multi-component CR programs that targeted at least 6 CVD risk factors reduce all-cause mortality by 37%.\(^\text{137}\) CR programs that provide stress management training provide incremental benefit in medical outcomes over standard CR.\(^\text{138}\) A further two systematic reviews of multi-component CR programs, albeit based on observational evidence, found a 50–70% reduction in all-cause mortality, but without lower rates of recurrent AMI or re-hospitalisation.\(^\text{139, 140}\) Substantial evidence has also established the value of exercise training in improving cardiovascular risk factors, particularly in CR programs that are able to prescribe and monitor medications.\(^\text{141}\) In Europe, a survey of 8000 surviving ACS patients reported a 21% reduction in smoking rates, 24% increase in physical activity levels, better medication compliance and psychological well-being in those that attended CR.\(^\text{142}\) However, these effects did not translate to a greater proportion of patients achieving their diabetic, cholesterol or blood pressure targets.\(^\text{142}\) Heterogeneity in the quality and breadth of CR programs likely account for the variations in mortality and morbidity outcomes, and comprehensive prevention and rehabilitation programs achieve the best patient outcomes. Commencing education early in the acute period, tailored programs that account for the patient’s learning needs and the use of motivational interviewing can improve successful behavioural change.\(^\text{143}\)
Similar to overseas, effective secondary prevention in Australia is undermined by poor rates of referral to CR; only 46% of ACS survivors were referred to CR and only a quarter received optimal secondary preventative care in hospital.\textsuperscript{109} Even in institutions with high referral rates, under 50% attend and far fewer complete a full program – a finding common to many studies.\textsuperscript{144-146} Unfamiliarity of both primary and specialist clinicians with different CR programs is another barrier to higher referral rates.\textsuperscript{147} The one third of Australians that live in rural or remote areas as well indigenous Australians represent particular disadvantaged groups with poorer access to secondary prevention and lower participation rates.\textsuperscript{148, 149} Given the compelling evidence that CR improves outcomes and the dose-dependence of its benefits, maximising patient participation and attendance should be a priority.\textsuperscript{150} Improving uptake of CR from 30% to 50–65% would translate to a net financial saving of $46.7 million and $86.7 million respectively.\textsuperscript{151}

The predictors of poor attendance and utilisation include low educational or socioeconomic status, perceptions of heart disease, older age, female sex, poor fitness and poorly controlled angina.\textsuperscript{152, 153} Poor adherence is often related to practical concerns like the need to return to work, cost, inconvenient hours, distance, transport issues and cultural barriers.\textsuperscript{154, 155} As the burden of cardiovascular disease increases in an ageing Australian population, needs for cardiac rehabilitation will continue to increase and alternatives to group, centre-based program delivery will be required. Astley et al. analysed CR utilisation using an ecological framework and identified barriers and enablers under 5 categories listed in Figure 6.2.\textsuperscript{156}

**Figure 6.2 Factors that impact cardiac rehabilitation adherence and participation**

<table>
<thead>
<tr>
<th>Positive Functions</th>
<th>Negative Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Clear understanding of CR benefits</td>
<td>• Poor understanding of CR benefits</td>
</tr>
<tr>
<td>• First language English</td>
<td>• Language other than English</td>
</tr>
<tr>
<td>• Belief that heart disease is biomedical</td>
<td>• Fatalistic beliefs</td>
</tr>
<tr>
<td>• Belief in the value of CR</td>
<td>• Belief that heart disease is psychosocial</td>
</tr>
<tr>
<td>• Automatic referral</td>
<td>• Belief that there is little to gain from CR</td>
</tr>
<tr>
<td>• Flexible program times</td>
<td>• Chronic pain</td>
</tr>
<tr>
<td>• Program individually tailored</td>
<td>• Contradictory messages in hospital</td>
</tr>
<tr>
<td>• Program culturally suitable</td>
<td>• Physician does not recommend</td>
</tr>
<tr>
<td>• Program available in languages other than English</td>
<td>• ‘Bad’ in-patient experience</td>
</tr>
<tr>
<td>• No carer responsibilities</td>
<td>• Carer responsibilities</td>
</tr>
<tr>
<td>• Family/community support</td>
<td>• ‘Poor’ in-patient experience</td>
</tr>
<tr>
<td>• CR funded by system</td>
<td>• Manual referral</td>
</tr>
<tr>
<td>• Positive media messages for CR</td>
<td>• Fixed program times</td>
</tr>
<tr>
<td>• Support from Heart Foundation, Cardiac Societies</td>
<td>• Program only available in English</td>
</tr>
</tbody>
</table>

**Research shows too much sitting as well as too little exercise places people at much higher risk of a heart attack**

**Chapter 6: Managing Risk to Prevent Secondary Cardiovascular Events: Lifestyle Modifications, Prevention and Rehabilitation**

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**Baker Heart and Diabetes Institute**
Dealing with the challenges and opportunities of CR will require coordination between the multiple stakeholders including government, public hospitals, clinicians and allied health. Reductions in length of stay have resulted in lower inpatient bed stays shifting the burden of secondary preventative care to outpatient settings. As early inpatient referral strongly predicts CR attendance, automated referral systems and improved coordination between hospitals, CR providers and clinicians can improve CR enrolment. High quality medical care before, during and after CR is necessary to reduce cardiac symptoms and improve patient participation. Culturally appropriate and well-designed CR programs have achieved participation rates of up to 80% in especially vulnerable groups like indigenous Australians. Current funding models which favour centre-based care but are not suitable for all ACS participants could evolve to support alternative, equally effective service delivery models like individual case-management, telehealth or home-based care. Information and communication technology innovations like smart-phones, mobile health and high-speed internet can provide CR to patients poorly served by traditional centre-based CR providers. Studies of smart-phone applications, social media networks and remote text-based support have shown improved utilisation and at least equivalent clinical effectiveness compared to traditional centre-based CR. Current data collection systems in Australia do not adequately identify eligible CR patients or measure CR delivery outcomes. Good monitoring and evaluation processes through national registries or minimum datasets can raise standards, minimise quality heterogeneity and improve resource use efficiency. Formal collaboration between State departments and CR service providers in Australia has had success in this area. High quality research that assesses longer-term benefits of CR – especially non-standard aspects of CR – as well as interventions to improve participation and adherence will further advance the field of CR.

### Table 6.1 Barriers to Cardiac Rehabilitation participation, Adapted from Menezes

<table>
<thead>
<tr>
<th>Poor referral rates, especially for certain groups:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Women</td>
</tr>
<tr>
<td>- People from ethnic minority groups</td>
</tr>
<tr>
<td>- Elderly people</td>
</tr>
<tr>
<td>- People living in rural settings</td>
</tr>
<tr>
<td>- People in low socioeconomic classes</td>
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<tr>
<td>Poor patient adherence, leading to low enrolment and high dropout rates</td>
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<tr>
<td>Lack of endorsement by a doctor</td>
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<tr>
<td>Obesity (high body mass index)</td>
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<tr>
<td>Multiple morbidities, leading to poor functional capacity</td>
</tr>
<tr>
<td>Poor exercise habits</td>
</tr>
<tr>
<td>Cigarette smoking</td>
</tr>
<tr>
<td>Depression</td>
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<tr>
<td>Problems with transport</td>
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<tr>
<td>Poor social support</td>
</tr>
<tr>
<td>Lack of leave from work to attend centre-based sessions</td>
</tr>
</tbody>
</table>
Evidence-based pharmacological therapy is integral to secondary prevention, saves lives and should be provided to all patients. Anti-platelet drugs, statins, beta-blockers and angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers are all recommended. Table 4 lists the mechanisms and benefits of these drugs in secondary prevention.

**ANTI-PLATELET AGENTS**

Anti-platelet agents like aspirin reduce secondary events by preventing platelet activation which in turn prevent thrombus formation. They are essential to prevent stent-induced platelet activation and stent thrombosis and occlusion, which may cause a major and potentially fatal heart attack. The benefit of aspirin in reducing secondary coronary events, stroke and cardiovascular death is well-established. It should be prescribed indefinitely for all patients after the diagnosis of coronary artery disease, unless contraindicated. Trial evidence has shown the the addition to aspirin of a second class of potent anti-platelet agents known as P2Y12 inhibitors, further reduce recurrent cardiovascular events including stent thrombosis. The most commonly used agents include clopidogrel, ticagrelor and prasugrel. Guidelines recommend treatment with both aspirin and a P2Y12 inhibitor for up to 12 months following an acute heart attack. Extended duration of therapy with two anti-platelet agents (≥12 months) has been shown to reduce recurrent cardiovascular events but increase bleeding episodes. Those at high risk of recurrent cardiovascular events but low risk of bleeding, will benefit greater from extended therapy.

**ANTICOAGULANT**

Anticoagulants inhibit clotting factors – biological substances in blood that cause thrombus formation once they are activated. Warfarin and novel oral anticoagulants (NOACs; dabigatran, rivaroxaban and apixaban) are the most commonly used outpatient anticoagulant therapy to prevent AF-related stroke. Patients on warfarin need regular blood tests to ensure that anti-coagulant activity is within the desired range to avoid strokes or bleeding events. Warfarin has been largely replaced by NOACs as first-line therapy for stroke prevention in AF, as they are at least equally effective and have a superior safety profile.

In patients who have both AF and a recent heart attack (especially with a stent) the anticoagulation regimen must balance the risk of AF-related stroke, recurrent MI or stent thrombosis with bleeding. A 2018 European expert consensus document recommends initial treatment with three agents: aspirin, clopidogrel and a NOAC. Based on the patient’s individual risk of recurrent CVD events and bleeding, aspirin may be ceased between 1-6 months after the stent insertion and the remaining agents continued until 12 months. At 12 months, clopidogrel can be ceased and the sole anticoagulant continued, unless the patient is at very high risk of recurrent events and clopidogrel can be changed to aspirin.

The place of anticoagulation in the post-infarct patient is controversial. Historical data suggested a potential role for warfarin in reducing risk, but balanced by bleeding risk. The COMPASS trial showed improved cardiovascular outcomes by adding low-dose NOAC (rivaroxaban) to aspirin in high-risk patients, albeit at increased bleeding risk with positive net clinical benefit. All patients after an event are at increased risk, but the bleeding risk of such an intervention might be justified in those at the highest risk.
LIPID LOWERING THERAPY

Controversies about the use of statins in primary prevention do not apply to secondary prevention, where both LDL-C lowering and anti-inflammatory properties are beneficial. Statins result in atherosclerotic plaque regression and reduce future cardiovascular events. Some high-intensity statin medications like atorvastatin and rosuvastatin are more potent at reducing LDL concentration than others. As secondary LDL-C prevention involves high-risk patients, high-intensity statins should be prescribed early at the highest possible tolerated dose irrespective of baseline cholesterol levels to achieve the lowest LDL. If LDL-C remains above target levels (1.8 mmol/L) or an LDL-C reduction of at least 50% is not obtained, then other agents like ezetimibe which further lower LDL-C should be added to prevent cardiovascular events. Statins are similarly indicated in secondary prevention of stroke and can reduce recurrent cardiovascular events by 15%.

Reduction of cholesterol is not the only important lipid intervention. Patients with increased LDL-C triglycerides randomised to a derivative of eicosapentanoic acid (icosapent ethyl) showed a 25% event reduction in the REDUCE-IT trial.

NEUROHORMONAL ANTAGONISTS

Therapies that counteract the harmful neurohormonal pathways following an acute heart attack, can break the vicious cycle and slow down disease progression. They can even reverse cardiac remodelling, improve cardiac function and by doing so, improve survival and quality of life.

Beta-blockers

Beta blockers blunt the sympathetic nervous system’s effects on the heart. They alleviate angina and reduce heart rhythm problems. They prolong survival in patients who have impaired heart function resulting from their heart attack. Large clinical trials have proven that beta-blockers can reduce secondary cardiovascular events and mortality in patients with prior heart attack, even those without hypertension. It is therefore recommended to initiate and continue beta-blocker therapy for secondary prevention in all patients after having an acute heart attack, unless contraindicated. However, this evidence arose from an era before modern intervention, and most of the benefit likely arose from patients with at least moderate cardiac damage. In these patients, specialised heart failure beta-blockers are indicated on an ongoing basis. In those with preserved heart function, evidence of benefit from beta-blockade is less clear, with at least 3 years of therapy being recommended, although there are variations between guidelines.

Renin-angiotensin antagonists

Similar to beta-blockers, angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) reduce the risk of secondary cardiovascular events, preserve heart function and improve survival. Some evidence also suggests that blocking of specific neurohormonal systems (such as the renin angiotensin-aldosterone system) may counteract the evolution of diabetes and attenuate the adverse effects of hyperglycemia. ACE inhibitors and ARB are also powerful anti-hypertensives and can protect kidney function in patients with diabetes or pre-existing kidney disease.
# CONTROL OF HYPERTENSION

Reducing BP using antihypertensive medications results in significant reduction in secondary cardiovascular events and mortality. As patients following a heart attack are high-risk with established CVD, pharmacological therapy should be commenced in addition to lifestyle changes if their SBP is >140mmHg. Blood pressure targets and the choice of anti-hypertensive should be tailored to the patient’s tolerance and other medical conditions. Care must be taken in the elderly and frail who are more likely to suffer from medication side effects. Hypertension can sometimes be secondary to another, reversible medical cause e.g. sleep apnoea. In those with resistant hypertension, doctors should screen for secondary causes and treat accordingly.

As beta blockers and angiotensin-converting enzymes inhibitors are indicated post heart attack for their neurohormonal benefits (and in the case of beta-blockers anti-anginal effect) they are the preferred anti-hypertensives in secondary prevention of CAD.

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## DIABETES

Current guidelines recommend targeting HbA1c (a marker of 3-month average of blood sugar readings) of <7.0%. However, there is clinical uncertainty about the benefits of intensive glucose lowering as trials have not demonstrated a consistent reduction in cardiovascular events or death. Intensive control can result in recurrent hypoglycaemic episodes which are associated with worse cardiovascular outcomes. Recent guidelines therefore recommend an individualised HbA1c target and to consider relaxing HbA1c goals in the elderly, those with established vascular disease or at risk of hypoglycaemia. Cardiovascular benefits from intensive glucose control are comparatively modest compared to the benefits from intensive control of other risk factors like hypertension, dyslipidaemia, diet, exercise and weight loss.
A history of cardiovascular disease is an important consideration when choosing which glucose-lowering agents to prescribe. Metformin remains the first-line agent; the UKPDS study suggested a lowering of risk for macrovascular disease by 30%. Sulphonylureas are common second-line agents, but meta-analyses have identified an association with increased cardiovascular events (including heart attack and CV death) compared to other agents, however, glimepiride may have a safer cardiovascular profile. Thiazolidinediones like rosiglitazone and pioglitazone have been associated with weight gain and increased heart failure risk tempering their use in cardiovascular patients. Studies of DPP-4 inhibitors (“gliptins”) have not shown either a CVD benefit or harm, but there is concern that some (like saxagliptin, alogliptin) may marginally increase the risk for heart failure. Insulin may be necessary to reduce glucose levels, but weight gain and risk for hypoglycaeemia may mitigate the cardiovascular benefits of improved glycaemic control. There is hope for patients with diabetes and cardiovascular disease with recent trials of SGLT-2 inhibitors and GLP-1 agonists showing a reduction in cardiovascular events. This will be discussed in more detail in the next chapter.

COMPARISON BETWEEN VARIOUS NATIONAL AND INTERNATIONAL GUIDELINES

There a great deal of overlap and consensus between international guidelines in the secondary prevention of coronary artery disease. The Australian guidelines were last updated in 2016. All guidelines stress the importance of cardiac rehabilitation and lifestyle modification in secondary prevention. Guideline-directed medical care includes high-intensity statins, aspirin, P2Y12 inhibitors, beta blockers and renin-angiotensin blockade.

European and US cardiac societies recognise the role of PCSK9 inhibitors in reducing residual cholesterol risk. European guidelines emphasise target LDL levels of 1.8 mmol/L whereas US guidelines aim for a 50% reduction in baseline LDL levels. Both US and European guidelines recommend use of PCSK9 inhibition as adjunctive therapy to meet LDL target goals. The American Association of Clinical Endocrinologists has recommended even lower targets, recognising the benefits of LDL lowering are proportional to absolute LDL levels and continue to very low levels. At present, these agents are used only for familial hyperlipidaemia in Australia.

LIMITATIONS AND GAPS IN EVIDENCE

Management has changed as advances in medical science has revealed more about the complex biology of atherosclerosis and thrombosis. Nonetheless, research is needed into many areas of secondary prevention.

AUSTRALIAN DATA

Local data on recurrence rates and the level of control of risk factors for recurrent events are lacking. Identification of high-risk factors and high-risk groups may allow more costly therapies to be targeted.

IMPROVING GUIDELINE-DIRECTED CARE

The barriers to implementation of guideline-directed care must be investigated and addressed from a patient, clinician and health system level. This includes cost-effective strategies to improve patient education and adherence. Exploring comprehensive systems of care, utilising a multi-disciplinary approach to prevention is required. Expanding the capacity of secondary prevention programs to reach all eligible patients is important – this might involve new platforms such as the internet and social media. Monitoring and evaluation of clinical care and mechanisms to improve poorly performing clinicians may address variations in care.

PSYCHOSOCIAL FACTORS

The role of psychosocial risk factors is widely recognised, and evidence is accruing to show that sympathetic nerve activity is the link between stress-provoked changes in the brain and inflammatory changes mediated by inflammatory cell release from the bone marrow. Means of intervening in this process need to be developed.

INDIVIDUAL RISK STRATIFICATION

Research is needed into the utility and cost-effectiveness of novel biomarkers and targeted therapies to provide personalised medicine, based on the evaluation of risk.
NEW DRUGS AND INTERVENTIONS – WHAT COULD WE DO?
Outcomes following acute heart attack have significantly improved over the last few decades with advances in acute and preventive care. However, survival has plateaued in recent years (figure 7.1). Previous chapters have highlighted opportunities in secondary prevention. Improving compliance by healthcare services and patients with guideline directed care is an obvious and simple strategy to improve outcomes. Research that improves our understanding of causal mechanisms and leads to new therapeutic interventions will help address residual cardiovascular risk. Recently, new interventions and strategies have been shown to provide additional risk reduction. This section will discuss some of these important developments.

**FIGURE 7.1 CHANGES IN SURVIVAL OVER RECENT YEARS – CRUDE, CORRECTED FOR AGE AND GENDER, AND IN-HOSPITAL CORONARY ANGIOGRAPHY**
PCSK-9 INHIBITORS – REDUCING RESIDUAL CHOLESTEROL RISK.

Proprotein convertase subtilisin/kexin type 9 (PCSK-9) is a protein produced by the liver and regulates LDL cholesterol levels. PCSK-9 causes elevated LDL by preventing liver cells from clearing LDL. It was discovered in the early 2000’s by genetic studies which found mutations that increased PCSK-9 activity led to significantly elevated cholesterol levels. This led to the development of PCSK-9 inhibitors (such as PBS-listed evolocumab) which are able to reduce PCSK9 levels to almost unmeasurable amounts and have dramatic reductions in LDL and other lipids including non-HDL cholesterol, apolipoprotein B, Lp(a) and triglycerides. In the FOURIER trial, patients who had a history of CVD, additional risk factors for recurrent events and LDL-C levels above target range despite statin therapy were randomised to evolocumab or placebo. In this high risk group, evolocumab reduced LDL-C levels by an average of 59% (mean LDL-C concentration of 0.78 mmol/L) and the risk of heart attack, stroke or death by 20%.

While these are currently indicated in Australia only for the treatment of familial hyperlipidaemia, European and US guidelines recognise the role of PCSK-9 inhibitors in stable coronary artery disease. The cost-effectiveness of this strategy has provided a barrier to wider use for stable CAD in Australia. However, cost-effectiveness may be optimized by falling costs of the medication (previously ~$8000 per person per year) and selective administration to those most likely to benefit. Indeed, work has been done on the numbers needed to treat for different levels of risk, starting LDL-C level and LDL-cholesterol reduction (Table 7.1).

<table>
<thead>
<tr>
<th>LDL-C mmol/L</th>
<th>High risk (10 year risk 20-29%)</th>
<th>Very high risk (10 year risk ≥ 30%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50% reduction in LDL-C</td>
<td>65% reduction in LDL-C</td>
</tr>
<tr>
<td>4.9</td>
<td>19</td>
<td>15</td>
</tr>
<tr>
<td>4.1</td>
<td>23</td>
<td>18</td>
</tr>
<tr>
<td>3.3</td>
<td>28</td>
<td>22</td>
</tr>
<tr>
<td>2.6</td>
<td>37</td>
<td>28</td>
</tr>
<tr>
<td>1.8</td>
<td>53</td>
<td>40</td>
</tr>
</tbody>
</table>

LDL-C: LOW-DENSITY-LIPOPROTEIN CHOLESTEROL; PCSK9: PROPROTEIN CONVERTASE SUBTILISIN/KEXIN TYPE 9; ACVD: ATHEROSCLEROTIC CARDIOVASCULAR DISEASE.
LOW-DOSE ANTICOAGULANT THERAPY – REDUCING RESIDUAL THROMBOTIC RISK

Combining anti-platelet agents with anticoagulants represents a more potent anti-thrombotic strategy that may reduce cardiovascular risk but increase bleeding. Whether this strategy improves outcomes in CVD was assessed in the COMPASS trial. COMPASS recruited stable CAD and PAD patients at high risk of recurrent events and randomised them to rivaroxaban, rivaroxaban plus aspirin and aspirin alone. Compared to aspirin, low-dose rivaroxaban plus aspirin reduced cardiovascular death, stroke or heart attack by 24%. As expected, it increased major bleeding events, but did not appear to increase fatal events or haemorrhagic stroke. 175

ANTI-INFLAMMATORY THERAPY – REDUCING RESIDUAL INFLAMMATORY RISK

Inflammation in atherosclerotic plaques is thought to play a key role in the process of plaque rupture leading to an acute heart attack. The cardiovascular benefit of statins may partly be mediated by their anti-inflammatory properties. Canakinumab, is an anti-inflammatory agent that blocks a pro-inflammatory molecule (interleukin-1ß) and was shown to reduce inflammatory markers including high-sensitivity-CRP. The CANTOS trial assessed whether these anti-inflammatory effects could reduce recurrent cardiovascular events by randomising patients to canakinumab or placebo. The trial recruited approximately 10,000 patients with established CAD, good medical therapy and elevated hs-CRP. The trial found a 14% reduction in the primary endpoint of heart attack, stroke or CV death with canakinumab, but in individuals whose hs-CRP dropped to target levels the risk reduction was 25%. 102 206 No significant reduction was seen if the hsCRP remained elevated. Elevated hs-CRP is present in up to 60% of secondary prevention patients, highlighting the scope for anti-inflammatory therapies in reducing cardiovascular events. 207

NEWER ANTI-DIABETIC AGENTS

Novel diabetic agents like SGLT2 inhibitors and GLP-1 antagonists have shown benefits in patients with cardiovascular disease. SGLT-2 inhibitors lower blood glucose levels by blocking sodium and glucose uptake by the kidney and increasing their urinary excretion. It also has a diuretic effect, lowers blood pressure and promotes weight loss. The EMPA-REG OUTCOME trial assessed whether empagliflozin improved CVD outcomes in approximately 7000 patients with established CVD and T2DM. Empagliflozin reduced cardiovascular death and may reduce heart failure hospitalisation, though a reduction in recurrent heart attack was not observed. 208 Reductions in heart failure hospitalisation may even extend to patients at high cardiovascular risk, not just those with established CVD as seen in the DECLARE-TIMI 58 trial with dapagliflozin. 209 The cardiovascular safety of GLP-1 receptor agonists, liraglutide and semaglutide, were assessed in the LEADER and SUSTAIN trials. While the effects of GLP-1 agonists are complex, in simple terms they reduce blood glucose by increasing insulin production and suppressing the body’s own glucose production. Both drugs have cardiovascular benefits but these are manifested differently. Liraglutide appears to reduce CV mortality while semaglutide produces reductions in stroke. 210 211 Studies are in progress to better understand the cardio-protective mechanisms of SGLT-2 inhibitors and GLP-1 agonists.

Australian researchers have published the results of a Markov model showing that rivaroxaban in addition to aspirin is cost-effective in Australia. 225 They show an increase of 0.5 years of life saved and 0.4 QALYs gained over 20 years, at a discounted cost of cost of $12,156 per person, providing an incremental cost-effectiveness ratio of $23,560/year of life saved and $31,436/QALY gained.
TELEMEDICINE AND MOBILE (M)-HEALTH

Non-adherence to medications is a major cause of poor risk factor control and limits the impact of improving health system compliance with clinical guidelines. A Cochrane review from 2014 focussed on interventions to improve patient adherence. They identified 17 high quality randomised controlled trials that evaluated intensive, multi-pronged behavioural strategies and found only five improved both adherence and clinical outcomes. Technology-based strategies using text messages or internet-based telemonitoring were identified but only a minority were considered to be at low risk of bias, and many did not show improvements in clinical outcomes or adherence. The potential for technology to improve adherence for a large patient population cost-effectively is great but more research is required to determine its role in best practice secondary prevention.

Similarly, technology can play an important role in supporting cardiac rehabilitation. A meta-analysis of smartphone use in secondary prevention of cardiac disease found smartphone health applications had high rates of participant engagement, acceptance, usage and adherence. The effectiveness of cardiac rehabilitation to improve risk factors like blood pressure when delivered remotely was comparable to that of traditional centre-based cardiac rehabilitation or usual care. Ongoing research is required to see whether tele-medicine or internet based interventions that improve cardiovascular risk profiles in patients translate to reductions in recurrent cardiovascular events.

THE POTENTIAL FOR TECHNOLOGY TO IMPROVE ADHERENCE FOR A LARGE PATIENT POPULATION COST-EFFECTIVELY IS GREAT BUT MORE RESEARCH IS REQUIRED
ECONOMIC BURDEN OF SECONDARY CARDIOVASCULAR EVENTS
DIRECT MEDICAL COSTS
Cardiovascular disease incurs the highest level of health care sector expenditure in Australia. Consistently, in recent years, around 11-12% of total allocated healthcare expenditure has been incurred by patients with cardiovascular disease.

HOSPITALISATIONS
Of these costs, the majority were attributed to hospital-admitted patient services. Cardiovascular disease resulted in more than 1.1 million hospitalisations in 2015-16, which equated to 11% of all hospitalisations in Australia. This number is based on admitted patient episodes, which means that multiple events experienced by the same patients are counted separately.

In 2015-16, there were 556,700 hospitalisations where cardiovascular disease was the principal diagnosis or the primary reason for the hospital admission. A further 576,000 hospital admissions cited cardiovascular disease as an additional diagnosis to the principal diagnosis. Acute hospitalisations for cardiovascular disease as the principal diagnosis rose by 20% over the decade between 2005-06 and 2015-16, despite the age-standardised rates for acute care falling from 1944 to 1824 per 100,000 persons over the same period. Hospitalisations were 1.6 times higher in males than females, and the majority (82%) involved persons aged 55 years and over.

The two most expensive cardiovascular diseases are coronary heart disease and stroke. According to Round 20 of the National Hospital Cost Data Collection (2015-16, Table 8.1), the 147,047 separations for coronary heart disease entailed 521,377 bed-days at a total cost of $1.135 billion. Stroke accounted for 40,095 separations with a marginally higher average length of stay, resulting in a cost of $338.5 million. Peripheral artery disease accounted for 9,142 separations, 37,977 bed-days and a total cost of $72.64 million.

ECONOMIC BURDEN OF SECONDARY CVD EVENTS

CARDIOVASCULAR DISEASE INCURS THE HIGHEST LEVEL OF HEALTH CARE SECTOR EXPENDITURE IN AUSTRALIA

<table>
<thead>
<tr>
<th>Separations</th>
<th>Days</th>
<th>Cost</th>
<th>% separations</th>
<th>% days</th>
<th>% cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary heart disease</td>
<td>147,047</td>
<td>521,377</td>
<td>$1,135,585,427</td>
<td>74.92</td>
<td>69.2</td>
</tr>
<tr>
<td>Stroke</td>
<td>40,095</td>
<td>194,043</td>
<td>$338,510,072</td>
<td>20.43</td>
<td>25.76</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>9,142</td>
<td>37,977</td>
<td>$72,644,340</td>
<td>4.66</td>
<td>5.04</td>
</tr>
<tr>
<td>Total</td>
<td>196,284</td>
<td>735,397</td>
<td>$1,546,742,839</td>
<td>100.0</td>
<td>100.0</td>
</tr>
</tbody>
</table>

TABLE 8.1 SEPARATIONS, DAYS AND COSTS FOR CARDIOVASCULAR DISEASE.
SOURCE: COMPILED FROM NATIONAL HOSPITAL COST DATA COLLECTION ROUND 20, 2015-16
MEDICINES

After hospital-provided care, pharmaceutical costs are the next largest category of expenditure on cardiovascular disease. In 2016, a total of $1.844 billion was spent on cardiovascular medicines (including $396 million on antithrombotic agents), which represented 20% of Australia’s total expenditure on pharmaceuticals.

Whilst this expenditure was largely incurred by the Australian government, patient contributions accounted for 24%. Over the ten-year period between 2005-06 and 2015-16, total expenditure on cardiovascular system medications fell by 31%; this was primarily due to the availability of lower price drugs. During the same period, expenditure on antithrombotic agents rose by 78%.

Lipid-modifying agents (mainly statins) accounted for 43% of total cardiovascular disease medication expenditure, followed by agents acting on the renin-angiotensin system 31%, beta-blockers 8% and calcium channel blockers 7%. The average dispensed price per cardiovascular system medication prescription in 2015-16 was $22.25, and $47.39 for an antithrombotic agent.

OTHER HEALTHCARE EXPENDITURE

Whilst hospital-provided care and medications account for the bulk of health care expenditure on cardiovascular disease, medical services provided out of hospital, aged care homes, and allied health services make up the balance.

The most recent apportionment of health care expenditure by the Australian Institute of Health and Welfare on cardiovascular disease was for 2008-09. Of the total health care expenditure on cardiovascular disease ($7,605 million), hospitals and prescription medicines accounted for 59% and 22% respectively. The other category of expenditure itemised was medical services provided outside of hospitals (20%) which covered general practitioners, specialists, pathology tests, screening and other diagnostic services. These three categories did not account for all expenditure on cardiovascular disease as some expenditure categories could not be allocated by disease. Exclusions included non-admitted patient hospital services, over-the-counter drugs, other health practitioner services, community health services, expenditure on public health programs, health aids and appliances and patient transport.

AN ESTIMATED TOTAL OF 30,717 WORKING YEARS WERE CALCULATED TO HAVE BEEN LOST IN 2016 FROM CVD DEATHS OF PEOPLE WHO WOULD OTHERWISE HAVE BEEN EMPLOYED. THE COST OF THIS LOST PRODUCTIVITY TOTALS AN ESTIMATED $1.57 BILLION

INDIRECT COSTS – LOST PRODUCTIVITY

A significant driver of lost output in any economy is the loss of labour due to illness or early death resulting from disease. The prevalence of cardiovascular disease directly affects both the size and quality of the labour force through premature death, illness or disability of workers.

LOST PRODUCTIVITY DUE TO PREMATURE DEATH

Lost productivity as a result of persons in the workforce dying prematurely as a result of cardiovascular disease has been measured in two ways: firstly, the human capital approach, which measures all working years lost between age of death and an average retirement age of 65 years, and secondly, the friction cost approach, which assumes a deceased worker will be replaced after an average period of three weeks. Deaths by disease group by age and gender were obtained from the Global Burden of Disease data for 2016 and labour force participation rates and average annual salaries by age and gender were obtained from the Australian Bureau of Statistics. No multipliers were included in the calculations of future earnings, but a discount rate of 3% was applied to future losses.

Based on the commonly used human capital approach, an estimated total of 30,717 working years were calculated to have been lost from CVD deaths in 2016 of people who would otherwise have been employed. The cost of this lost productivity totals an estimated $1.57 billion (Table 8.2). The largest losses result from deaths from ischemic heart disease ($1.25 billion), whilst stroke would result in losses of $318.4 million and peripheral artery disease $6.3 million. The vast majority of the working years (76.9%) lost are incurred by males.
TABLE 8.2 PRODUCTIVITY LOSSES DUE TO PREMATURE DEATH BY AGE AND GENDER GROUP (BASED ON HUMAN CAPITAL METHOD), 2016

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Ischaemic Heart Disease</th>
<th>Stroke</th>
<th>Peripheral Artery Disease</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-29 years</td>
<td>$10,719,654</td>
<td>$8,053,695</td>
<td>$0</td>
<td>$18,773,349</td>
</tr>
<tr>
<td>30-39 years</td>
<td>$102,351,559</td>
<td>$33,844,726</td>
<td>$0</td>
<td>$136,196,285</td>
</tr>
<tr>
<td>40-49 years</td>
<td>$415,955,169</td>
<td>$109,780,275</td>
<td>$846,225</td>
<td>$526,581,670</td>
</tr>
<tr>
<td>50-64 years</td>
<td>$721,450,818</td>
<td>$166,744,820</td>
<td>$5,490,803</td>
<td>$893,686,441</td>
</tr>
<tr>
<td>Total</td>
<td>$1,250,477,201</td>
<td>$318,423,517</td>
<td>$6,337,028</td>
<td>$1,575,237,746</td>
</tr>
</tbody>
</table>

Based on the more conservative frictional cost method, productivity losses arising from premature death are estimated to total a more modest $39.79 million.

LOST PRODUCTIVITY LOSSES DUE TO ABSENTEEISM

Absenteeism refers to the cost of lost productivity when employees are absent from work due to illness. Absenteeism costs to the Australian economy as a consequence of the three categories of CVD have been estimated based on lost wages. The number of cases of people living with each disease was estimated by subtracting the number of deaths in each age range from the prevalence. Age- and gender-specific workforce participation rates were then applied to these surviving cases, to estimate the number of persons with each disease who were likely to be working. The expected annual number of days taken off work was calculated by multiplying the number of surviving cases in the labour force by the average number of days of absence due to a disease. Estimates of an average of 7.89 days lost for ischemic heart disease and 17.94 for stroke were obtained from Anesetti-Rothermel and Sambamoorthi 2011. The days lost for heart disease were also used in the calculations for peripheral artery disease.

An estimated total of 3,117,653 working days are estimated to be lost annually due to the three CVD categories. This amounts to a productivity loss to the Australian economy of $1.01 billion (Table 8.3). This loss would be fairly evenly spread across the three disease categories. By far the greatest losses from absenteeism arose from persons in the later working years (aged 50-64 years).

TABLE 8.3 PRODUCTIVITY LOSSES DUE TO ABSENTEEISM BY AGE AND DISEASE (BASED ON HUMAN CAPITAL METHOD), 2016

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Ischaemic Heart Disease</th>
<th>Stroke</th>
<th>Peripheral Artery Disease</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-29 years</td>
<td>$8,280,034</td>
<td>$10,363,200</td>
<td>$0</td>
<td>$18,643,233</td>
</tr>
<tr>
<td>30-39 years</td>
<td>$221,138,720</td>
<td>$24,893,232</td>
<td>$0</td>
<td>$47,031,953</td>
</tr>
<tr>
<td>40-49 years</td>
<td>$415,955,169</td>
<td>$68,378,314</td>
<td>$89,049,421</td>
<td>$231,670,629</td>
</tr>
<tr>
<td>50-64 years</td>
<td>$263,653,646</td>
<td>$187,730,181</td>
<td>$267,088,568</td>
<td>$718,472,394</td>
</tr>
<tr>
<td>Total</td>
<td>$368,315,294</td>
<td>$291,364,926</td>
<td>$356,137,989</td>
<td>$1,015,818,209</td>
</tr>
</tbody>
</table>
TABLE 8.4 PRODUCTIVITY LOSSES (IN $) DUE TO PRESENTEEISM BY AGE AND DISEASE, 2016

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Ischaemic Heart Disease</th>
<th>Stroke</th>
<th>Peripheral Artery Disease</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-29 years</td>
<td>$14,615,047</td>
<td>$7,696,495</td>
<td>$0</td>
<td>$22,311,542</td>
</tr>
<tr>
<td>30-39 years</td>
<td>$39,076,946</td>
<td>$18,487,596</td>
<td>$0</td>
<td>$57,564,542</td>
</tr>
<tr>
<td>40-49 years</td>
<td>$131,045,765</td>
<td>$50,782,904</td>
<td>$157,180,693</td>
<td>$339,009,362</td>
</tr>
<tr>
<td>50-64 years</td>
<td>$465,373,747</td>
<td>$139,422,622</td>
<td>$471,436,711</td>
<td>$1,076,233,079</td>
</tr>
<tr>
<td>Total</td>
<td>$650,111,504</td>
<td>$216,389,617</td>
<td>$628,617,403</td>
<td>$1,495,118,525</td>
</tr>
</tbody>
</table>

LOST PRODUCTIVITY DUE TO PRESENTEEISM

Presenteeism refers to the cost of lost productivity resulting from people who are present at work but not working at full capacity. Productivity losses due to presenteeism are difficult to measure; it is further problematic to determine the extent to which presenteeism losses are attributable to a worker’s disease. Goetzel et al. estimated that a worker with heart disease lost 0.5 working hours per day, which equates to around 6% of their working hours. In the absence of other data, these losses were also applied to stroke and peripheral artery disease. Presenteeism as a result of the three categories of CVD is estimated to result in productivity losses amounting to $1.49 billion (Table 8.4).

INDIRECT COSTS – INFORMAL CARE

Cardiovascular disease may result in further costs and productivity losses as a result of carers leaving the workforce or taking time off work to provide informal care to a person who is recovering from a cardiovascular event. Informal carers may be partners, other family members or friends, who provide a range of tasks such as basic nursing and personal care, cooking, shopping, transporting, administering medications and monitoring the patient’s condition.

Australian data related to the costs of informal care associated with cardiovascular disease are scarce. Access Economics estimated that around 22.3 million hours of informal care were provided to persons with acute coronary syndrome in Australia in 2009. This was estimated to equate to a total cost of informal care of $691.1 million in 2009.

Besides lost wages, caring for a person with cardiovascular disease may result in other costs. Out of pocket costs may be incurred for the purchase of special equipment, or for home modifications necessary to cope with the person at home. Carers may also experience intangible costs for loss of their own quality of life given their confinement to home and inability to participate in activities outside of the home. There may result in long term adverse economic and social impacts for themselves; for example, where children are taken out of school to look after a sick relative, their education may be compromised. There are no data available to facilitate quantification of such costs to carers.

INDIRECT COSTS – TAXATION LOSSES

As a result of the lost production time resulting from the prevalence of cardiovascular disease amongst workers (through reduced work hours, absenteeism or premature death), taxation revenue collected by the government will be reduced. This will stem from two components. Firstly, as a result of the loss of total personal earnings through lost wages – conservatively estimated at $2,496.4 million in 2016 – of workers dying from three categories of cardiovascular disease (ischemic heart disease, stroke and peripheral artery disease). If it is assumed that net tax as a proportion of taxable income approximates half of the average personal income tax rate (say 22.5%), then the potential income tax revenue foregone by the government would equate to $561.6 million. Secondly, premature death leads to a fall in indirect consumption tax as a consequence of the loss of personal income and the flow-on effects on expenditure on goods and services. If an indirect tax rate of 10% (equivalent to the current GST rate) is applied, this would result in an estimated loss of indirect taxation of $249.6 million.
BURDEN OF DISEASE COSTS

In addition to the impact of coronary artery disease and peripheral artery disease on the health care system and on the wider economy through lost production, there is also the economic burden associated with the risk of death and disability as a consequence of NCDs. Burden of disease losses relate to an individual’s loss of healthy life years - a value is placed on the quality of life that an individual loses through death or chronic illness. These are different costs to productivity costs which relate to losses to the economy of lost engagement in the workforce.

Burden of disease costs are measured in DALYs or disability-adjusted life years, which take into account both mortality (years of life lost due to premature mortality [YLL]) and morbidity (years lived with a measure of disability [YLD]) as a result of a disease. DALY, YLL and YLDs due to ischemic heart disease, stroke and peripheral artery disease for Australia in 2016 were extracted from Global Burden of Disease Data Tool http://ghdx.healthdata.org/gbd-data-tool (167). The commonly used value of A$50,000 was assigned to each DALY.

These three cardiovascular disease categories accounted for 530,869 DALYs, which equated to nearly 10% of the total DALYs experienced by Australia’s 2016 population from all causes (Table 9). The DALY losses from the three categories of CVD events totalled $26.04 billion. Ischemic heart disease accounted for 349,641 or 65.9% of the losses followed by stroke 170,962 or 32.2%.

The vast majority of DALY losses (86.7%) were due to premature deaths (Table 8.5). Some 460,715 years of life were lost incurring a cost burden of $23 billion. Years lived with a disability totalled 70,164, at a cost of $3.5 billion (or only 13.4% of the total DALY burden). Whilst the majority of losses (62.6%) occurred in the age groups 70 years and over, some 28.9% of the burden occurred during the ages of 50-69 years.

<table>
<thead>
<tr>
<th>ISCHAEMIC HEART DISEASE</th>
<th>STROKE</th>
<th>PERIPHERAL ARTERY DISEASE</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years of life lost</td>
<td>323,150</td>
<td>129,549</td>
<td>8,005</td>
</tr>
<tr>
<td>Years lived with disability</td>
<td>26,491</td>
<td>41,413</td>
<td>2,260</td>
</tr>
<tr>
<td>DALYs</td>
<td>349,641</td>
<td>170,962</td>
<td>10,266</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cost burden ($ billion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years of life lost</td>
</tr>
<tr>
<td>Years lived with disability</td>
</tr>
<tr>
<td>DALYs</td>
</tr>
</tbody>
</table>

TABLE 8.5 BURDEN OF DISEASE LOSSES BY CATEGORY, 2016

SOURCE: COMPILED FROM GLOBAL BURDEN OF DISEASE DATA TOOL HTTP://GHDX.HEALTHDATA.ORG/GBD-DATA-TOOL (167)
REDUCING ECONOMIC COSTS ASSOCIATED WITH SECONDARY PREVENTION

It is estimated that up to 10% of patients with a history of cardiovascular disease will have a recurrent event. As discussed in Chapter 6, there is a range of potential strategies targeting secondary prevention, each of which offers the capacity to lower the economic burden associated with cardiovascular disease.

Statins have been widely used in secondary prevention, but many patients are intolerant or take inadequate doses, leading to reduced efficacy in preventing disease progression. As discussed in the previous chapter, PCSK9 inhibitors are highly effective, but costly. A recent Australian study examined the cost-effectiveness of PCSK9 use in Australia, if it were used in a similar population to the FOURIER trial – a population aged 62.5 years, 25% female, with inadequate control of lipid status, and with clinically evident atherosclerotic CVD or at high risk of CVD (81% with MI, 19% with non-haemorrhagic stroke and 13% with symptomatic peripheral artery disease). At current Australian prices (~AU$8000/year), the incremental cost effectiveness ratio was over AU$300,000 per QALY saved, and prices would have to fall to AU$1500/year to reach the usual threshold of AU$50,000/QALY. Of course, cost/QALY could also be optimised if the use of the agent were restricted to patients at higher risk.

Aspirin has been commonly used as a secondary prevention strategy, and has been shown to result in a 19% lower risk of major adverse cardiovascular events and a 9% lower risk of cardiovascular death than placebo. The COMPASS trial showed improved outcomes in stable cardiovascular disease patients when they were prescribed low dose rivaroxaban (2.5 mg twice daily) plus aspirin (100 mg daily) versus aspirin alone. Based on a Markov model, Ademi et al. established that from an Australian healthcare perspective, that rivaroxaban in combination with aspirin, was likely to be cost-effective in preventing recurrent cardiovascular events in patients with stable atherosclerotic vascular disease. It would result in an additional cost of $12,156 per patient, but lead to 0.516 years of life saved and 0.386 QALYs gained over a 20 year period. This would equate to an incremental cost-effectiveness ratio of $31,436/QALY gained, against the commonly held benchmark of cost-effectiveness of $50,000/QALY gained. Despite an estimated small increase in bleeding events, there would be potential for significant savings in CVD events, for a relatively modest increase in costs.

The next section summarizes the current guidelines, and how we might consider the selection of patients for these new and expensive therapies. Inherently, selective use of these agents is dependent on a process that recognises risk as being non-uniform in the secondary prevention population – this represents a significant change to current Australian practice.
CURRENT GUIDELINES

Guidelines for clinical practice are built on compelling evidence-based results from clinical research, and support the provision of optimal patient care. All international guidelines stress the importance of lifestyle interventions in reducing CVD risk, particularly in those with prior cardiovascular events. The differences among guidelines for secondary prevention of CVD in Australia, United States and Europe are summarised in Table 9.1.

PROPOSED CONCEPTUAL FRAMEWORK FOR RISK-TARGETED APPROACH

Patients with established CVD or a prior cardiovascular event have for years been treated with the same core group of medications (statins, anti-platelets and ACE inhibitors) that are prognostically beneficial, safe and cost-effective. Nonetheless, despite use of the highest tolerated dose of these evidence-based therapies, substantial residual risk for secondary events persists, particularly for high-risk patients.

The addition of other treatments will carry additional cost and/or risk of side-effects. On the other hand, clinical trials of new pharmacological agents have provided evidence that these drugs support the current risk-reduction therapies. The efficient use of these new therapies will require a more sophisticated risk evaluation strategy than is currently considered in the secondary prevention setting. At present, all such patients are considered “high risk”.

But there is a huge difference in risk between one patient who has undergone an effective and timely primary percutaneous intervention for a first heart attack, with minimal atherosclerosis apart from the target lesion, little if any heart muscle damage or functional impairment, and with effective management of all risk factors, with another patient with a late intervention for recurrent heart muscle damage, impaired function, extensive atherosclerosis, and inability to treat to target. In light of the growing body of evidence and novel medications, we propose a conceptual framework that targets treatment to the level of risk, so that higher intensity treatment is targeted at high-risk patients who are most likely to benefit (Table 9.2).

ALL INTERNATIONAL GUIDELINES STRESS THE IMPORTANCE OF LIFESTYLE INTERVENTIONS IN REDUCING CARDIOVASCULAR DISEASE RISK, PARTICULARLY IN THOSE WITH PRIOR CARDIOVASCULAR EVENTS.
GAPS IN EVIDENCE
There are limited data regarding which interventions are most effective in specific groups of patients (eg. young vs old, high vs low socioeconomic status, normal vs impaired cognition) and how to improve their adherence to treatment.

The introduction of new agents is likely to be most beneficial and cost-effective if it is targeted to risk. However, risk evaluation is focused on LV dysfunction (harking back to a former era of common LV dysfunction post MI). Other markers of risk in the current era may be plaque burden or inflammation.

Our proposed conceptual framework relies on a number of risk tools to determine initiation of treatment and evaluate treatment response. While some are supported by existing data, most still require further research. Taking lipid lowering therapy as an example, LDL-C levels have long been a guide for treatment, the underlying risk may pertain to atherosclerotic burden.

POLICY
In October 2018, the Federal Government announced funding to support the development of a plan for heart disease and stroke and to outline a better way to diagnose, treat and manage these conditions in Australia. The National Heart Foundation of Australia received $170,000 to develop a National Strategic Action Plan, with assistance from the National Stroke Foundation. This plan will go to the Federal Government in April 2019.

It is critical that secondary prevention of cardiovascular disease is comprehensively addressed in this action plan, given the return on investment in terms of improved quality of life, productivity and healthcare cost savings that this report outlines.

Cardiovascular disease remains the leading cause of death in Australia and global data indicates that this is not likely to change anytime soon. It also remains the most costly disease group. This is troubling for many individuals and organisations in Australia’s health and scientific sectors in particular, and has led to the establishment of leadership groups such as the Australian Cardiovascular Alliance. The Alliance was started in 2015 by concerned scientists and scientific institutions that saw a need to increase the visibility of cardiovascular diseases as a National Health Priority Area.

The fight against Australia’s biggest killer is far from over and now more than ever, we need strong leadership in cardiovascular disease. This latest insight into secondary prevention of cardiovascular disease provides a blueprint for action, which we hope will lead to greater support to improve adherence to treatment, access to new medicines, access to new technologies to pursue a risk-based approach to treatment, and more funding for research.

Countries such as the United States have set audacious national goals when it comes to primary and secondary prevention of heart disease. The Million Hearts campaign in the US seeks to prevent one million deaths from heart attack and stroke over a five-year period.

Australia too has the opportunity take a leadership role in tackling cardiovascular disease, and in particular, secondary prevention.

AUSTRALIA HAS THE OPPORTUNITY TAKE A LEADERSHIP ROLE IN TACKLING CARDIOVASCULAR DISEASE, AND IN PARTICULAR, SECONDARY PREVENTION
## Table 9.1 Comparison among guidelines for secondary prevention of CVD after MI

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Australian Guideline</th>
<th>US Guideline</th>
<th>European Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antiplatelet therapy</strong></td>
<td>- Aspirin 75-150mg/d indefinitely unless contraindicated (in which case, replace aspirin by clopidogrel) for SIHD</td>
<td>- Aspirin 81-162mg/d indefinitely unless contraindicated</td>
<td>- Aspirin recommended for patients with SIHD</td>
</tr>
<tr>
<td></td>
<td>- DAPT in patients with recurrent events</td>
<td>- P2Y12 inhibitor added to aspirin after PCI (≥1 month for bare-metal stent and ≥6 months for drug-eluting stent in SIHD, and ≥1 year in ACS)</td>
<td>- P2Y12 inhibitor added to aspirin in ACS patients for ≥12 months</td>
</tr>
<tr>
<td></td>
<td>- Dual-antiplatelet therapy with aspirin and a P2Y12 inhibitor (clopidogrel or ticagrelor) should be prescribed for up to 12 months in patients with ACS</td>
<td>- In DAPT, use aspirin 81mg/d</td>
<td>- In patients with non-cardioembolic ischaemic stroke or TIA, use aspirin only, or dipyridamole plus aspirin, or clopidogrel alone</td>
</tr>
<tr>
<td></td>
<td>- Low-dose aspirin, clopidogrel or combined low-dose aspirin and modified release dipyridamole for all patients with ischaemic stroke or TIA</td>
<td>- Aspirin 81-325mg/d or clopidogrel for all patients following a non-cardioembolic ischaemic stroke</td>
<td></td>
</tr>
<tr>
<td><strong>Anticoagulant therapy</strong></td>
<td>- Anticoagulation recommended in patients with AF, mural thrombus or previous embolization</td>
<td>- For patients with AF:</td>
<td>- Oral anticoagulation to prevent thromboembolism for all AF patients with CHA2DS2-VASC ≥2 (male) or CHA2DS2-VASC ≥3 (female)</td>
</tr>
<tr>
<td></td>
<td>- Non-vitamin K oral anticoagulant (NOAC) – apixaban, dabigatran or rivaroxaban – is recommended in preference to warfarin</td>
<td>- NOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) are recommended over warfarin in NOAC-eligible patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve)</td>
<td>- NOACs preferred over warfarin</td>
</tr>
<tr>
<td><strong>Neurohormonal blockade</strong></td>
<td>- Start ACEi/ARB and beta-blocker early post-MI event</td>
<td>- ACEi/ARB indefinitely in all patients with LV dysfunction, and in those with hypertension, DM or chronic renal disease</td>
<td>- Warfarin recommended for AF patients with moderate mitral stenosis or mechanical heart valves</td>
</tr>
<tr>
<td></td>
<td>- Aldosterone blockade early post-MI in patients with LV systolic dysfunction or HF</td>
<td>- Beta-blocker in all patients with LV dysfunction, HF or prior MI</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Aldosterone blockade in post-MI patients with LV systolic dysfunction, diabetes or HF, and without significant renal dysfunction</td>
<td></td>
</tr>
<tr>
<td><strong>Lipid lowering therapy</strong></td>
<td>- Statin for all patients with established CVD</td>
<td>- High-intensity statin</td>
<td>- Statin as first choice</td>
</tr>
<tr>
<td></td>
<td>- PCSK9 inhibitors are recommended only for patients with familial hypercholesterolemia</td>
<td>- If LDL-C ≥1.8mmol/l, non-HDL-C ≥2.6mmol/l, and high risk for another event (e.g., TIMI risk score for secondary prevention &gt;3) after trial of highest tolerated dose of a high-intensity statin, consider ezetimibe [Class IIa] and/or PCSK9 inhibitors [Class IIb].</td>
<td>- Combination with ezetimibe (or PCSK9 inhibitors) when a specific goal is not achieved with a maximal tolerated dose of statin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- If triglycerides &gt;5.6mmol/l, then fibrates [Class I] and/or high-dose omega 3</td>
<td>- Fibrates added to statin if triglycerides remain high and/or HDL-C is very low</td>
</tr>
</tbody>
</table>

**Abbreviations:** PCI (Percutaneous Coronary Intervention), SIHD (Stable Ischemic Heart Disease), ACS (Acute Coronary Syndrome), DAPT (Dual Antiplatelet Therapy)
Table 9.2 Proposed conceptual framework for risk-targeted approach in secondary prevention of CVD

<table>
<thead>
<tr>
<th>THERAPEUTIC TARGETS</th>
<th>RISK TOOL</th>
<th>INTERVENTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lifestyle</strong></td>
<td>Lipoproteins</td>
<td>Lifestyle intervention in all patients</td>
</tr>
<tr>
<td></td>
<td>Lipid measurements, atherosclerosis imaging, genetics</td>
<td>Moderate-intensity statin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High-intensity statin Ezetimibe</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PCSK9 inhibitor Omega-3 fatty acids</td>
</tr>
<tr>
<td><strong>Platelets and coagulation</strong></td>
<td>Antiplatelet risk scores (eg. DAPT, PARIS)</td>
<td>ASA DAPT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Extended DAPT Ticagrelor Low-dose rivaroxaban</td>
</tr>
<tr>
<td><strong>Neurohormonal activation</strong></td>
<td>Echocardiogram, MRI, DAPT, PARIS, PRECISE-DAPT</td>
<td>BB + ACEi/ARB BB + ACEi/ARB</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BB, ACEi/ARB, MRA Entresto</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>Type 2 DM, HbAIC levels, abdominal obesity</td>
<td>Metformin Multiple therapies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SGLT2 inhibitor Entresto GLP-1 agonist</td>
</tr>
<tr>
<td><strong>Inflammation</strong></td>
<td>Unclear, possibly Hs-CRP</td>
<td>Canakinumab</td>
</tr>
</tbody>
</table>

**Abbreviation:** CAD, coronary artery disease; MI, myocardial infarction; ACS, acute coronary syndrome; PCSK9, proprotein convertase subtilisin/kexin type 9; DAPT, dual antiplatelet therapy; PARIS, patterns of non-adherence to anti-platelet regimen in stented patients; ASA, aspirin; PRECISE-DAPT, predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy; BB, beta blocker; ACEi/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; HbA1C, glycated haemoglobin; SGLT2, sodium-glucose cotransporter 2; GLP-1, glucagon-like peptide 1; Hs-CRP, high-sensitivity C-reactive protein

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CHAPTER 9: CURRENT CARDIOVASCULAR DISEASE POLICY & GUIDELINES

Baker Heart and Diabetes Institute
CONCLUSION AND RECOMMENDATIONS
Both the consequences and treatment of CVD remain a significant social and financial burden to the Australian community, and much of this is avoidable. The higher risks of patients in a secondary prevention setting represent an opportunity with a potentially high return on investment. Although current Australian evidence is limited, it seems likely that this is an area of underachievement, in part related to the fragmentation of the Australian healthcare system.

Despite strong evidence of benefit and cost-effectiveness, preventative care remains sub-optimal. In contrast to primary prevention, secondary prevention involves the management of a relatively small number of patients at high risk. While there are potential disadvantages to intervening too late in the course of the disease, investments in secondary intervention may nonetheless be more efficient than those in primary prevention.

**RENEWED COMMITMENT TO PROVEN MEASURES:**

1. A secondary prevention campaign with clear strategies and targets to improve death and disability rates. Countries such as the US have set audacious national goals, such as the Million Hearts campaign which is focused on primary and secondary prevention of heart disease and seeks to prevent one million deaths in a five-year period. By bringing together 120 official partners and 20 US Federal Agencies, there is significant collective power to drive change.

2. Improvement in cardiac rehabilitation following acute presentations. Funding for rehabilitation is often limited, leading to “thin” programs that have been shown to be less effective than multidisciplinary care. Optimal delivery of secondary prevention might be achieved with system redesign to integrate general practice and cardiologists, as well as providing career pathways in preventive cardiology.

3. Strategies to enhance adherence to disease modifying medications. The evidence is that the adherence of patients to these treatments, just like their attendance at cardiac rehabilitation, is suboptimal. The current medical therapies for controlling disease progression, including statins, aspirin, and neurohormonal modulation are highly effective, and there are well-defined treatment targets, but many patients are not treated to target. The greatest areas of need are around high blood pressure and cholesterol.

4. Disease management programs, similar to those used in heart failure, m-health and new delivery mechanisms for rehabilitation should also be considered for widespread adoption by hospitals and healthcare organisations nationally. There are opportunities to improve adherence around self-management with better education and health literacy targeted at different ethnicities. Research strongly supports the benefits of these programs in reducing further cardiovascular risk. Patient-centred interventions such as SMS prompts, home monitoring, and the use of software including avatars to educate and motivate patients will be important areas of m-health, applied to cardiology.

**CONCLUSION AND RECOMMENDATIONS**

Despite strong evidence of benefit and cost-effectiveness, preventative care remains sub-optimal.
CONSIDERATION OF NEW MEASURES

New groups of treatments are promising but have had limited impact on the guidelines to date. Several new developments warrant consideration about inclusion into national policy;

1. **Development and application of a national standard calculation of post-event risk** would be valuable in developing cost-effective and targeted strategies around preventive care. Effective treatment needs to be targeted to the level of risk.

2. **Recognition of subclinical disease.** The classic distinction between primary and secondary prevention is being blurred by the development of highly accurate imaging tests that identify individuals with clear evidence of cardiovascular disease, who have not yet developed symptoms. We might consider such an entity “early secondary prevention”. These patients include individuals with a positive coronary calcium score or carotid plaque (indicating the presence of atherosclerosis), abnormal left ventricular function (a prelude to heart failure), asymptomatic atrial fibrillation (indicating risk of stroke) and evidence of previous myocardial scarring on cardiac MRI (signifying undiagnosed coronary disease). Unlike in primary prevention, where patients have risk factors but may never develop disease, this group already has disease, and the only uncertainty pertains to the timing of its eventual presentation. Research is needed to understand the benefits, risks and economic implications of managing these patients.

3. **Wider use of PCSK9 inhibitors.** Although expensive, these agents are the most effective means of reducing LDL cholesterol, are very potent for reducing high atherosclerotic plaque burden, and impact survival. Knowledge of the efficacy of these agents has been available for >5 years, and the initial approvals for clinical use were made in 2015. In Australia, their use is confined to individuals with familial hypercholesterolemia. The benefit of their broader use could follow a risk-based approach. This would require recognition of a gradient of risk in secondary prevention.

4. **Novel oral anticoagulants (NOACs).** There is emerging evidence that the use of low-dose NOACs could be helpful in secondary prevention. These findings are congruent with the benefits of warfarin in secondary prevention, but with a lower risk of bleeding complications. There is clinical familiarity with NOACs, which have replaced warfarin in many patients with atrial fibrillation or thrombotic problems.

5. **New groups of antidiabetic drugs** appear to have cardiovascular benefits, particularly the SGLT2 inhibitors (reduction of heart failure) and to some extent the GLP-1 agonists (reduction of heart attack).

6. **Additional evidence regarding the use of anti-inflammatory treatments.** It seems unlikely that canakinumab will be widely adopted, although other anti-inflammatory therapies will be forthcoming.

New treatments are potentially expensive and more research is urgently needed to progress opportunities and strategies to efficiently tackle secondary prevention, and make inroads in the treatment of the most deadly and costly disease in Australia. There is a need to personalise intervention to ensure that those at highest risk are the most likely to be treated. In the setting of atherosclerotic vascular disease, much attention in defining risk has been devoted towards measuring the consequences of an event, such as a heart attack or stroke. In the current era of early invasive intervention, this is probably less useful than it was previously. However, we now have new tools for examining the burden of atherosclerosis, which is likely to be an important determinant of a further event. Patients with a high atherosclerotic burden would probably benefit from therapy designed to induce plaque regression, including the PCSK9 inhibitors. Similarly, patients with a high plaque burden are more likely to develop plaque rupture and therefore thrombosis, so further consideration might be given to low-dose anticoagulation. The analyses presented in this review should lead us to reconsider the evaluation of risk and treatment in secondary prevention.

THERE IS A NEED TO PERSONALISE INTERVENTION TO ENSURE THAT THOSE AT HIGHEST RISK ARE THE MOST LIKELY TO BE TREATED

CONTROLLING RISK IN CARDIOVASCULAR DISEASE
AUTHORS

Prof Tom Marwick MBBS, PhD, MPH is the Director of Baker Heart and Diabetes Institute and practises as a cardiologist at Alfred Health and Western Health. He has research interests in the detection and management of early disease.

Dr Quan Huynh MB, PhD is an epidemiologist at the Baker Heart and Diabetes Institute. He has research interests in the epidemiology of cardiovascular disease.

Dr Prasanna Venkataraman MBBS, FRACP is a clinical cardiologist and current PhD student at the Baker Heart and Diabetes Institute. His academic and clinical interests cover general cardiology including preventative cardiology, cardiac imaging and health economics.

Prof Dianna Magliano B.AppSci (Hons), MPH, PhD is an epidemiologist at the Baker Heart and Diabetes Institute. She has research interests in the epidemiology of diabetes and its complications.

Prof Marj Moodie BA (hons), Dip Ed, Dip TRP, DrPH is a Health Economist & Deputy Head, Deakin Health Economics at Deakin University. Her research interests centre on the economics of non-communicable diseases, with a particular focus on the economics of obesity and stroke.

Prof Geoffrey Cloud MBBS, BSc, FRCP (London) FRACP FESO is Director of Stroke Services, The Alfred Hospital, Adjunct Professor, Stroke, Monash Central Medical School and a Consultant/Physician.

Prof Bronwyn Kingwell BSc(Hons), PhD, FAHA, FAICD, FAHMS is Head of the Translational Research Domain and the Metabolic and Vascular Physiology Laboratory at Baker Heart and Diabetes Institute.
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