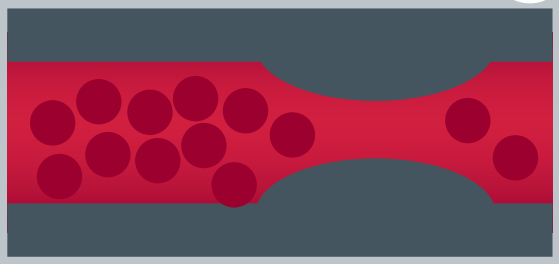
CODE RED:

Overturning Australia's cholesterol complacency

THIS REPORT CONTAINS

New data to paint a picture of Australia's silent cholesterol burden

Baker
HEART & DIABETES INSTITUTE



CARDIOVASCULAR DISEASE HAS NOT BEEN SOLVED. ONE OFTEN NEGLECTED **RISK FACTOR IS ELEVATED CHOLESTEROL**

IN 2017, LOST PRODUCTIVITY DUE TO DEATHS OF WORKING-AGE AUSSIES FROM CONSEQUENCES OF HIGH CHOLESTEROL WAS ESTIMATED AT

$1.55 BILLION

NEW DATA SHOWS THAT NEARLY ONE IN TWO HIGH-RISK PEOPLE WHO HAVE HAD A CARDIOVASCULAR EVENT MAY NOT MEET THE RECOMMENDED TARGET FOR LDL-C OR 'BAD' CHOLESTEROL

56%

OF WOMEN WHO HAVE HAD A CARDIOVASCULAR EVENT ARE NOT BEING OPTIMALLY MANAGED FOR LDL-C OR 'BAD' CHOLESTEROL. THIS COMPARES TO 42% OF MEN.

WHEN IT COMES TO CHOLESTEROL WE NEED GREATER EDUCATION FOR CLINICIANS AND PATIENTS ABOUT THE IMPORTANCE OF TREATING HIGH-RISK PEOPLE TO TARGET

THROUGH OPTIMAL CHOLESTEROL MANAGEMENT

3,738

LIVES COULD BE SAVED

13,742

CARDIOVASCULAR EVENTS PREVENTED

$66.6m

SAVED IN HEALTHCARE COSTS OVER THE NEXT FIVE YEARS

FIRST NEW CHOLESTEROL DATA IN A DECADE EXAMINING AUSTRALIAN ADULTS MOST AT RISK OF CARDIOVASCULAR DISEASE SHOWS **WE ARE FAILING MANY OF THESE PEOPLE**

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Contents

Foreword

Cardiovascular disease is our nation's biggest killer, and has been for decades. In terms of the costs of treating cardiovascular disease on our nation's health system, it is also the most expensive disease group in Australia.

While scientists and health professionals have made major advances in the prevention and management of cardiovascular disease, the high morbidity and mortality statistics remain. What makes this worse is that many of the deaths that occur each year are preventable. Put simply, we need to do more now.

This report, led by clinical and research experts at Baker Heart and Diabetes Institute and Deakin University, shines a light on a critically important aspect of cardiovascular disease, cholesterol, a known risk factor that, if left untreated, can lead to devastating outcomes.

Many of us know something about cholesterol, the type of fat found in our bloodstream. We are familiar with 'good' and 'bad' cholesterol. We understand we need some cholesterol for our body to work effectively but that problems arise when there is too much. Too much cholesterol can clog the arteries supplying blood to the heart and other parts of the body, and lead to critical events such as a heart attack or stroke.

So how is Australia faring when it comes to cholesterol? What is the impact of elevated cholesterol and how much is it costing the community?

For the first time in nearly a decade, this 'CODE RED' report provides new and important data from the MedicineInsight program that highlights the extent of the cholesterol problem observed in patients receiving medical care from a general practice in our country. This report focuses on the cholesterol levels and treatment of Australians with prior cardiovascular disease, who we know are at greater risk of further cardiovascular events such as a heart attack or stroke. These new data, based on the examination of more than 107,000 patients over a 10 year period from 2010 to 2019, highlight cause for concern.

This new report reveals that whilst most of Australia's high risk patients are being treated for elevated cholesterol, worryingly, almost half had a LDL cholesterol result that did not meet recommended target levels, leaving them vulnerable to more cardiovascular events that could result in further disability or death. More women were documented as not achieving recommended target levels compared to men, raising warning signs for women in particular.

Our analysis also looked to understand what could be achieved within the next two decades if cholesterol was managed according to Australia's clinical guidelines, to save lives, prevent cardiovascular events, and reduce healthcare spending – and the figures are concerning.

We must do better for high risk patients. This report provides motivation and renewed action of what can be achieved if we increase awareness, support and advocacy for optimal cholesterol management.

The Baker Heart and Diabetes Institute is grateful to the general practices and general practitioners who participate in the MedicineInsight program, and the patients who allow the use of their de-identified information for MedicineInsight. We also acknowledge the many individuals and organisations with clinical, research, epidemiological and health economic expertise in cholesterol management who have provided guidance and support to develop this report.

FOR THE FIRST TIME IN NEARLY A DECADE, NEW DATA HIGHLIGHTS THE SIGNIFICANT OPPORTUNITY TO REDUCE DEATH AND DISABILITY VIA OPTIMAL CHOLESTEROL MANAGEMENT IN AUSTRALIANS WHO HAVE ALREADY EXPERIENCED A CARDIOVASCULAR EVENT

Abbreviations

CAD
Coronary artery disease

CONCORDANCE
Cooperative National Registry of Acute Coronary care, Guideline Adherence and Clinical Events

CVD
Cardiovascular disease

DALY
Disability-adjusted life year

FOURIER
Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk

GP
General Practitioner

HDL-C
High density lipoprotein cholesterol

IRSAD
Index of Relative Socio-Economic Advantage and Disadvantage

LDL-C
Low density lipoprotein cholesterol

MBS
Medicare Benefits Schedule

PBS
Pharmaceutical Benefits Scheme

PCSK9
Proprotein convertase subtilisin/kexin type 9

PVD
Peripheral vascular disease

QALY
Quality-adjusted life year

VLDL-C
Very low density lipoprotein cholesterol

YLD
Years lived with a disability

YLL
Years of life lost


Many high-risk patients had a LDL cholesterol result that did not reach recommended target levels, making them vulnerable to further cardiovascular events

Executive summary

Cardiovascular disease has not been solved.

The shadow of cardiovascular disease (CVD) continues to be troublesome for Australia despite survival rates from CVD improving over the past 50 years due to new devices, medical procedures and effective drug discovery. Death rates have also declined. Whilst this is good news, CVD remains our biggest killer and the most expensive disease group to treat.

In Australia, more than one in four deaths in 2017 was due to CVD, which claims the life of one Australian every 12 minutes. CVD affects one in six Australians or 4.2 million people, and its impact is far reaching.

One risk factor for CVD is elevated cholesterol. Many of us are aware of it, particularly given the impact of medicines such as statins in the past few decades. But while we are familiar with the topic, community knowledge about cholesterol and optimal management could be improved.

Managing high cholesterol, which includes healthy eating and lifestyle modification, medications, general practice attendances, cholesterol testing and attributable hospital admissions, is already costing the Australian community $1.5 billion in direct healthcare costs each and every year.

Difficulties in controlling elevated cholesterol occur in the context of a challenging backdrop of more Australians living with heart disease than ever before. This means more people are living with disability and their risk of further cardiovascular events, such as another heart attack or stroke, is significantly higher. Effective management of these high-risk Australians is essential.

That is why we have focussed this report on the magnitude of elevated cholesterol in high-risk 'secondary prevention' patients with prior CVD. We also know that elevated LDL cholesterol levels (LDL-C) or 'bad' cholesterol levels are a major risk factor for the occurrence of significant cardiovascular events.

For the first time in nearly a decade, the 'CODE RED' report provides new data highlighting the potential extent of the cholesterol problem amongst high-risk patients in Australia.

This report, which is based on the examination of MedicineInsight data of more than 107,000 patients with prior CVD attending general practice over a 10-year period from 2010, shows that 79% of secondary prevention patients had a prescription recorded for recommended lipid-lowering therapy. Of the 85,352 patients who were prescribed recommended treatment, 40% or 33,857 had a result recorded that did not meet the recommended target for LDL-C or 'bad' cholesterol.

There were also likely gender differences, with women recording higher levels of LDL-C or 'bad' cholesterol than men. LDL-C levels were consistently above Australian guidelines over time and 56% of women had a record of not meeting the recommended target, compared to 42% of men.

Importantly, the report reveals that more than 3,738 lives could be saved, over 13,740 CVD events like heart attacks and strokes prevented, and $66.6 million could be saved in healthcare costs over the next five years through optimal cholesterol management.

With the availability of effective therapeutics and cholesterol management guidelines to implement them, significant potential for optimising cholesterol management has been identified in individuals with prior CVD.

This should be cause to take action. The 'CODE RED' report clearly identifies the critical and timely opportunity to invest in greater awareness and support for cholesterol management in high-risk patients.

NEW MODELLING SHOWS THAT OVER THE NEXT FIVE YEARS THROUGH OPTIMAL CHOLESTEROL MANAGEMENT:

3,738 LIVES COULD BE SAVED

13,742 CARDIOVASCULAR EVENTS PREVENTED

$66.6m SAVED IN HEALTHCARE COSTS

KEY FINDINGS

Records of 107,664 high risk patients with prior CVD who attended a general practice that was participating in the MedicineInsight program were analysed over the period 2010 to mid-2019. This cohort of patients was being managed by general practitioners (GPs) from general practice sites from each state and territory in Australia. The attainment of the recommended LDL-C treatment target of <1.8 mmol/L was reported based on a representative LDL-C result a patient achieved during their follow up period, noting that care provided to patients from clinicians outside of the MedicineInsight program was not captured in this study. LDL-C test results and treatment targets were reported by gender, lipid-lowering medication within 12 months prior to the LDL-C result, age, CVD condition type, geographical region, socio-economic status, state and territory, and primary health networks in Australia.

OF THE STUDY POPULATION

- There were 61% men and the average age of all patients was 64 years.
- The main CVD condition recorded was coronary artery disease (66%) and average duration of CVD was 4.4 years at the participating general practice.
- The majority of patients had 2 or more LDL-C results for evaluation (90,162; 84%).
- The follow-up period was on average 5.3 years.

PRINCIPAL FINDINGS WERE

- The average LDL-C result was 1.87 mmol/L and higher for women (2.03 mmol/L) than for men (1.76 mmol/L).
- There were 52% of patients with a recorded LDL-C result below the target of <1.8 mmol/L and 48% who were above this target.
- There were 85,352 from 107,664 (79%) people who had a recorded prescription for recommended lipid-lowering therapy with statin monotherapy (74,779: 69%), statin therapy combined with ezetimibe (6,918: 6%), ezebimibe alone (3,635: 3%) or adding a PCSK9 inhibitor (20: 0.02%).
- Of those receiving recommended lipid-lowering treatment, there were 33,857 (40%) patients with an LDL-C result that did not meet the recommended LDL-C target of <1.8 mmol/L.
- A higher proportion of patients with a reported LDL-C level ≥1.8 mmol/L (51,452) were women (56%), recorded an index CVD event of cerebrovascular disease (58%) and had a more recent CVD event within the last 5 years (58%).
- In contrast to patients who did not have a LDL-C record that met the recommended target, a higher proportion of patients who achieved the LDL-C treatment target were prescribed with statin plus ezetimibe therapy (72%) or PCSK9 inhibitor (75%) compared with 60% for statin monotherapy and 45% for ezetimibe alone.
- For patients receiving statin monotherapy, the proportion who achieved the LDL-C target of <1.8 mmol/L increased progressively with higher statin intensities from 66% for patients on high intensity, 54% on moderate intensity statin therapy and 34% on low intensity statin treatment.
- Based on a 5-year period and 70% therapy compliance rate, $66.6 million of the total cost burden would be saved with intervention to achieve optimal LDL-C targets for all eligible persons at the national level. Over a longer 10-year horizon, around $70 million would be saved in the total cost burden.
- There would be 3,738 lives saved over 5 years with optimal LDL-C management.
- Around 13,742 CVD events would be averted over a 5 and 10-year period and 31,442 over 20-years with optimal LDL-C management.
- Health gains of 23,444, 63,306 and 124,715 quality adjusted life years over 5, 10 and 20-year timeframes would be achieved with optimal LDL-C management.

Objectives

The primary objective of this Report was to review the magnitude of elevated cholesterol and achievement of secondary targets in high-risk patients with prior CVD. All patients received medical care from a general practitioner between 2010 to 2019 in Australia.

A secondary objective was to estimate the burden of disease over the next 5, 10 and 20 years that can be attributed to elevated cholesterol.

Cholesterol management and attainment of goal LDL-C levels

To quantify exposure to elevated cholesterol in high risk patients, we assessed the broad trends in LDL-C levels from 2010 to mid-2019 in patients with a history of atherosclerotic CVD in general practices across Australia. A representative LDL-C response was assessed according to prescribed lipid-lowering medications and attainment of the goal LDL-C level of 1.8 mmol/L in order to determine gaps in secondary prevention management. Other comparisons were made between sex (men/women), type of CVD condition (coronary artery disease, cerebrovascular disease, peripheral vascular disease), age (<65 years / ≥65 years), geographical region (major cities/ regional/remote), socioeconomic status (SES), location (state or territory) and primary health network.

Economic analyses for the estimation of burden of disease

The health economic modelling aimed to determine the costs of ensuring all persons with CVD in Australia meet the target for LDL-C control, and the cost savings that would accrue to the health system as a result of that action.

The long-term costs and health outcomes of bringing all patients to within the recommended LDL-C levels were estimated separately for 5, 10 and 20 year time horizons. A Markov model was constructed to simulate the long-term cost and health outcomes for patients with histories of CVD from 2017-18 in Australia. Patients meeting or not meeting the optimal LDL-C target were modelled separately to reflect their different profiles in developing CVD in the future.


A new report
shows women are
found to be most at
risk of cholesterol
complacancy

Introduction

It is well known that abnormalities of blood fats or "elevated cholesterol" are not good for your health. This section gives a general overview about cholesterol – it describes how elevated cholesterol is associated with increased risk for CVD and the benefits of cholesterol lowering; it outlines cholesterol target levels and the recommended management of elevated cholesterol in Australia; it summarises how common high cholesterol is; and lastly it provides the economic burden of high cholesterol in Australia.

What is cholesterol?

Cholesterol is a type of fat that is found in all cells in the body. Cholesterol moves through the body inside lipoprotein particles which are made up of two components - lipids and proteins. Major lipids are primarily cholesterol and triglycerides found in the central core of lipoproteins. Because lipids do not interact with water, they are transported in the circulation via proteins. The protein components are called apolipoproteins; they differ in function and in whether or not they can leave a lipoprotein particle for another.

All lipoprotein particles found in blood plasma are divided into seven classes on the basis of size, lipid composition and apolipoprotein (see Figure 1). As illustrated, all lipoproteins excluding high density lipoprotein cholesterol (HDL-C) are "pro-atherogenic", that is they promote the formation of lipid containing lesions (plaques) on the inner walls of arteries. HDL-C is anti-atherogenic.

Chylomicrons and very low density lipoprotein (VLDL) particles are triglyceride rich whereas low density lipoproteins and HDL lipoproteins are composed primarily of cholesterol.

CARDIOVASCULAR DISEASE HAS NOT BEEN SOLVED AND ONE OFTEN NEGLECTED RISK FACTOR IS ELEVATED CHOLESTEROL

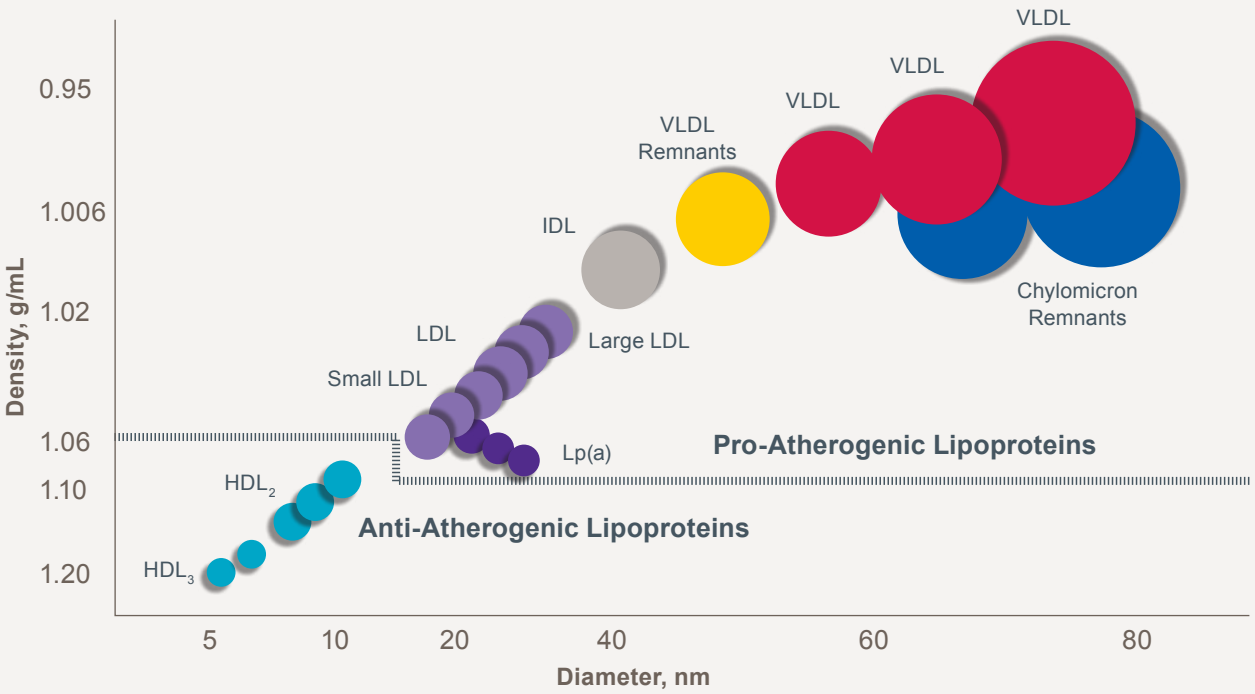
The main types of lipoproteins

LOW DENSITY LIPOPROTEINS (LDL-C)

LDL-C are rich in cholesterol. They carry the majority of the cholesterol that is in the circulation. LDL-C particles vary in size and density (refer Figure 1); small, dense LDL-C particles are deemed to be more pro-atherogenic than larger LDL-C particles and are seen in association with hypertriglyceridemia, low HDL-C levels, obesity, type 2 diabetes and infectious and inflammatory states. For these reasons, LDL-C is often referred to as the "bad" or "unhealthy" cholesterol.

LDL-C is cleared from circulation by LDL receptors that are found on the outside of different cells in the liver. When LDL-C particles circulate, LDL receptors pick them up and get them into the cell where cholesterol is created. Cholesterol is then either used by

FIGURE 1: CLASSES OF LIPOPROTEINS (FIGURE TAKEN FROM (1))



LEGEND: HDL: HIGH DENSITY LIPOPROTEINS; LDL: LOW DENSITY LIPOPROTEINS; IDL: INTERMEDIATE DENSITY LIPOPROTEINS; LP(A): LIPOPROTEIN (A); VLDL: VERY LOW DENSITY LIPOPROTEINS.

the cell, stored or expelled from the body by the liver. A greater number of LDL receptors results in quicker removal of LDL-C from the body. When LDL receptors do not function correctly, LDL-C stays in circulation resulting in elevated LDL-C. In familial hypercholesterolemia, an inherited disorder that causes markedly elevated LDL-C, there is a genetic defect that impedes proper LDL-C clearance leading to accumulation of LDL-C (2). A disturbance to this clearance pathway will never work correctly and familial hypercholesterolemia patients should be treated with effective therapies and diet and lifestyle modifications to drastically improve cholesterol levels (3).

HIGH DENSITY LIPOPROTEINS (HDL-C)

HDL-C are also enriched in cholesterol however they play an important role in transporting excess cholesterol away from peripheral tissues and delivering this back to the liver. Cholesterol is then either broken down in the liver or expelled from the body as waste. HDL-C particles can inhibit atherosclerosis; high levels are associated with a decreased risk of coronary artery disease. Hence, it is often referred to as "good" or 'healthy" cholesterol.

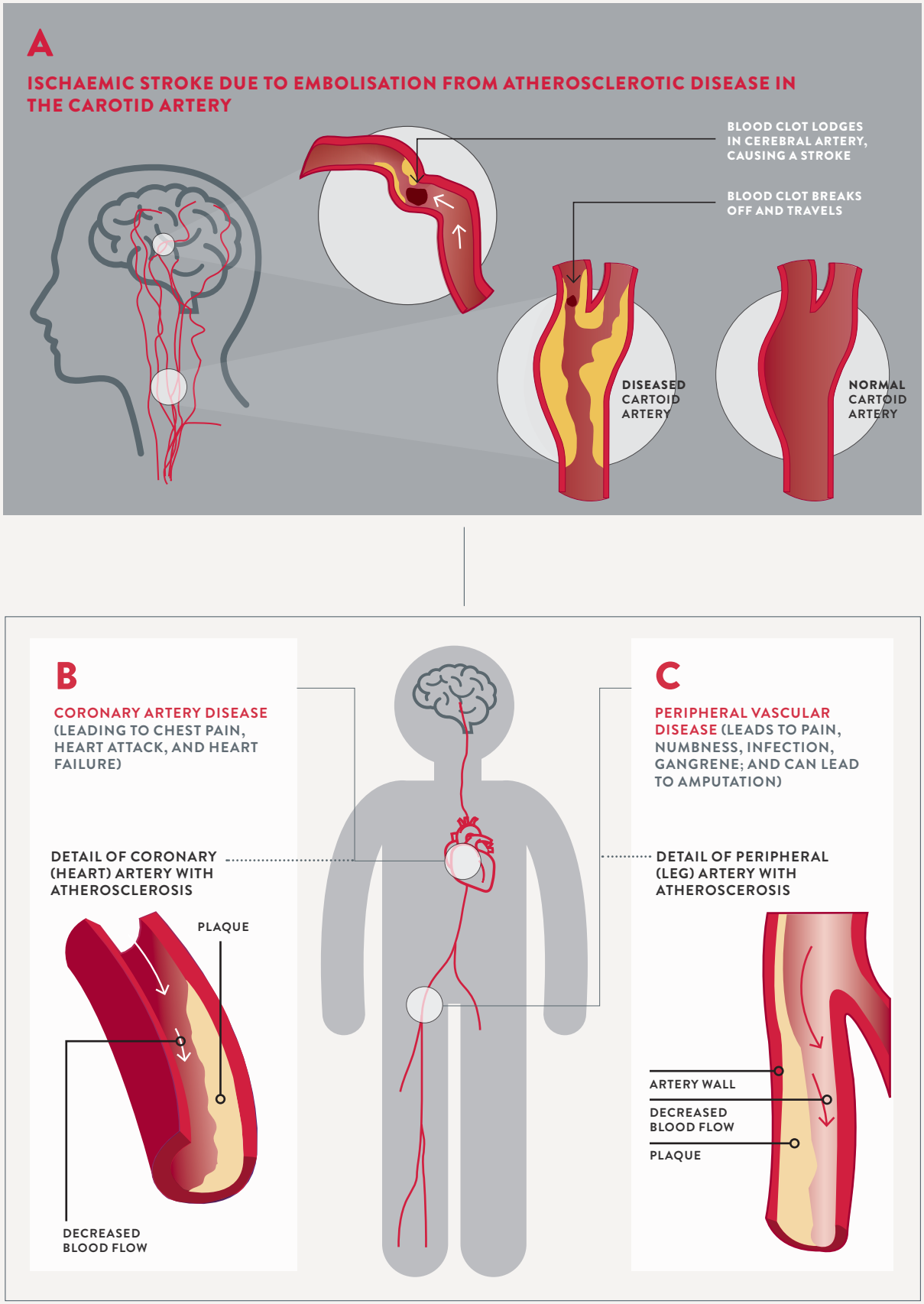
Risk of elevated cholesterol for CVD

Lipoproteins circulating in the blood lead to the build-up of fatty deposits in the blood vessels. This process is called atherosclerosis and it underlies most diseases of the blood vessels. As shown in Figure 2, atherosclerosis results in the narrowing of arteries in coronary artery disease (CAD), cerebrovascular disease and peripheral vascular disease (PVD). In this process, cholesterol is deposited in plaques inside the artery walls that may result in the tube of the artery becoming narrow, thereby restricting blood flow, and may cause inflammation of the arterial wall. Eventually, the plaque may rupture leading to a blood clot and blockage of the blood vessel. The processes of plaque rupture and clotting can recur in the same or another vessel location.

CORONARY ARTERY DISEASE (CAD)

CAD occurs when atherosclerosis causes the coronary arteries to get narrower and reduce the blood flow to the heart. A heart attack is caused by a plaque rupture or erosion that leads to a clot blocking the coronary artery, depriving the heart muscle of oxygen and nutrients. This could

FIGURE 2: ATHEROSCLEROSIS IN CEREBROVASCULAR DISEASE (A), CORONARY ARTERY DISEASE (B), AND PERIPHERAL VASCULAR DISEASE (C)



potentially be life-threatening and often culminates in permanent damage to an area of the heart muscle. A heart attack is the most common cause of sudden cardiac death in adults and can trigger dangerous heart rhythms. CAD can be acute or chronic. Treating arterial blockages involves opening up the affected artery mechanically by inserting a stent (a percutaneous coronary intervention that can be used for acute or chronic disease), redirecting blood flow around the blocked artery by using a healthy blood vessel from another part of the body (coronary artery bypass graft surgery, generally used for chronic disease), or (acutely) by dissolving the blood clot with medication (called thrombolysis) in order to re-establish blood flow.

This report includes patients identified as having CAD and any atherosclerotic related procedure, activity or testing.

CEREBROVASCULAR DISEASE

Cerebrovascular disease affects the small and large blood vessels that supply blood to and within the brain. A stroke is more often caused by a blocked artery (called ischaemic strokes) than a blood vessel rupture (called haemorrhagic strokes) and this leads to a disturbance of blood flow, oxygen supply and subsequent injury to the brain tissue. A stroke could result from a blood clot that formed somewhere else in the circulatory system, for example in the heart during atrial fibrillation, while passing through the carotid arteries that supply blood to the brain. Atherosclerosis is attributable to approximately 20-30% of ischaemic strokes.

A stroke can be identified as a sudden change in neurological function or if the symptoms are brief (and less than 24 hours duration) a mini-stroke (called a transient ischaemic attack). Otherwise cerebrovascular disease can present more subtly as cognitive decline and vascular dementia due to disconnections in the brain circuitry.

This report includes patients identified as having any type of stroke and carotid stenosis.

PERIPHERAL VASCULAR DISEASE (PVD)

PVD is a form of narrowing or occlusion by atherosclerosis of arteries outside of the heart or brain, most commonly blood vessels of the limbs. PVD can be acute (blocking an artery leading to the possibility of limb amputation) or chronic (reducing blood flow to limbs causing pain during activity) presentations. PVD can be manifested by intermittent claudication - muscle pain that develops in the legs when undertaking physical activity, such as walking. Similar to stroke, PVD could result from a blood clot that formed in the heart or larger vessels in the chest, abdomen or upper leg, then travel inside the blood until they lodge and block the smaller arteries of the limbs.

This report includes patients identified as having PVD.

ELEVATED LDL-C OR 'BAD' CHOLESTEROL LEVELS ARE A MAJOR RISK FACTOR FOR THE OCCURRENCE OF CARDIOVASCULAR EVENTS LIKE A HEART ATTACK OR STROKE.

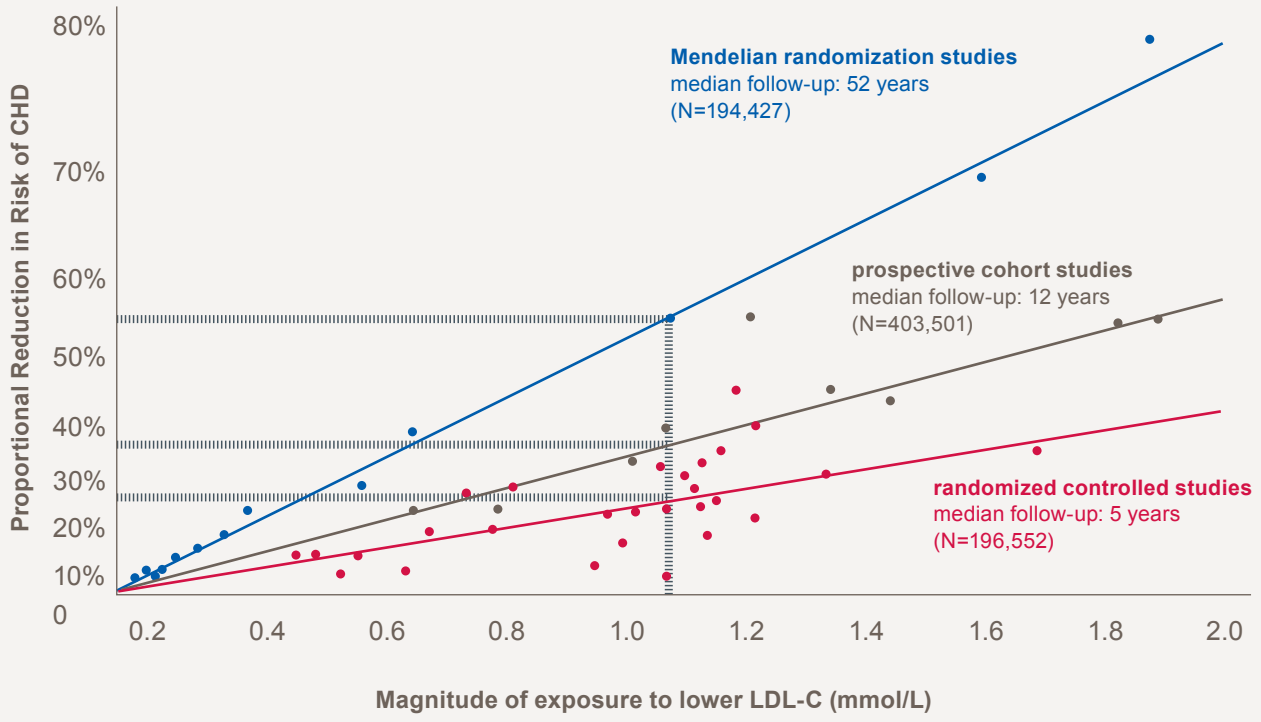
The benefit of lowering cholesterol

In 2017-18, there were 1.15 million Australian adults (4.8%) who reported having a cardiovascular condition including heart, stroke and vascular disease (4). Having pre-existing CAD increases the risk of a future heart attack by 5 to 7 times compared to people without overt CAD (5). Without lipid-lowering medication, an average 6% per year of individuals with CAD will have a repeat heart attack (5).

Elevated LDL-C levels are a major risk factor for the occurrence of major cardiovascular events. Familial hypercholesterolemia, if undiagnosed and untreated, can lead to premature CVD at a very young age due to high LDL-C levels (2). There is a continuous and positive relationship between LDL-C levels and cardiovascular risk that is both causal and cumulative over time. It follows that reductions in elevated LDL-C levels with lipid-lowering modification therapy are accompanied by decreases in CVD risk in a dose-dependent relationship that is proportional to the magnitude of LDL-C lowering. Lipid-lowering treatment improves (pain-free) walking distance and primarily reduces coronary events for patients with PVD (6). It is therefore commonplace to focus on LDL-C lowering as the best guide for therapeutic interventions.

In a meta-analysis of 26 trials (170,000 participants), the Cholesterol Treatment Trialists' Collaboration reported that for every 1.0 mmol/L reduction in LDL-C, there was a 22% proportional reduction (rate ratio 0.78, 95% CI 0.76-0.80) in the risk of major cardiovascular events and 10% reduction in death from all causes (rate ratio

FIGURE 3: ASSOCIATION BETWEEN EXPOSURE TO LDL-C LOWERING AND CAD RISK AS REPORTED IN META-ANALYSES (FIGURE TAKEN FROM (10))



0.90, 95% CI 0.87-0.93) over a median of 5 years of taking statin therapy (7). In the first year of treatment, the effect was a smaller 12% reduction however larger benefits accrued over time for every year of treatment, with an estimated 22% to 24% proportional reduction in the risk of major cardiovascular events per mmol/L reduction in LDL-C during each subsequent year it continued to be taken (7, 8).

More intensive (potent) statin therapy (to achieve ≥50% LDL-C lowering) has greater efficacy compared to less intensive (<50%) regimens and is associated with added improvements in event rates; a 2 mmol/LDL-C lowering reduced risk of major cardiovascular events by about 40% and a 3 mmol/L by about 50% (7). Combination therapy with a statin plus ezetimibe in the IMPROVE-IT trial resulted in reduced risk of major cardiovascular events compared to statin therapy alone in CAD patients who are at high risk of recurrent CVD events (9).

These findings are in accord with Mendelian randomization studies (that use genetic information as a surrogate for randomization) showing the cumulative benefit with longer term exposure to LDL-C lowering in CVD risk reduction (Figure 3). Integrating the evidence from randomised controlled trials and Mendelian randomization studies, Table 1 shows that 5 years of lipid-lowering treatment should reduce the risk of atherosclerotic CVD events by 20% to 25% for every 1.0 mmol/L reduction in LDL-C and 40 years of treatment would reduce atherosclerotic CVD events by around 50% to 55% per mmol/L lower LDL-C (10).

These findings were similar for people with and without established CVD and were independent of baseline LDL-C levels. These incremental benefits can be achieved safely, even with low concentrations of LDL-C of between 1-2 mmol/L (7). There was no threshold below which LDL-C lowering ceased to provide benefit; *the lower the better.*

TABLE 1. EXPECTED PROPORTIONAL RISK REDUCTION AS A FUNCTION OF PRE-TREATMENT LDL-C, ABSOLUTE MAGNITUDE REDUCTION OF LDL-C AND TOTAL DURATION OF LIPID-LOWERING TREATMENT (ADAPTED FROM (8))

Baseline LDL-C (mmol/L)	Absolute reduction LDL-C (mmol/L)	Duration of treatment exposure (years) [expected proportional risk reduction (%)]				
		5	10	20	30	40
7	3.5	58	68	81	89	93
7	3.0	53	62	76	85	90
7	2.5	46	56	70	79	86
7	2.0	39	48	61	71	79
7	1.5	31	39	51	61	69
5	2.5	46	56	70	79	86
5	2.0	39	48	61	71	79
5	1.5	31	39	51	61	69
5	1.0	22	28	38	46	54
3	1.5	31	39	51	61	69
3	1.0	22	28	38	46	54
3	0.5	12	15	21	27	32
2	1.0	22	28	38	46	54
2	0.5	12	15	21	27	32

Controlling blood lipids

Australian guidelines recommend identification of individuals who will benefit most from intervention via an absolute risk approach (11). Use of an absolute CVD risk score, such as the Australian absolute cardiovascular disease risk calculator (cvdcheck.org.au), is recommended in populations who are not known to have CVD (11). Adults with established atherosclerotic CVD (and other high risk population groups) are already known to be at increased absolute risk of CVD and do not require risk stratification. For these individuals, management by lifestyle and pharmacological interventions is recommended to decrease the occurrence of a CVD event and prevent death. For PVD management in particular, the goal is to reduce claudication symptoms and improve exercise capacity to reduce disability and potential limb loss.

Therapeutic targets to achieve a LDL-C reduction vary for people with and without (12) prior CVD and there are stricter (lower) recommendations in secondary prevention and for very high risk individuals (for review refer to (3)). The American College of Cardiology/American Heart Association guideline is to reduce LDL-C by 50% or more in atherosclerotic CVD to achieve a LDL-C level of <1.8 mmol/L (13). In line with these guidelines, the intention of Australian secondary prevention management guidelines was to achieve a LDL-C goal of <1.8 mmol/L. From more recent advice published in the European Society of Cardiology and European Atherosclerosis Society Guidelines, therapeutic LDL-C targets in secondary prevention and for patients at very high risk are notably lower at <1.4 mmol/L (14).

Management of elevated cholesterol for secondary prevention

There are two essential components for the appropriate management of lipids for patients with existing atherosclerotic CVD: **healthy eating and lifestyle advice is a key element of all lipid-lowering treatment strategies. Additionally, pharmacologic treatment must be commenced early after an event. Additional medications may then be added to achieve the recommended LDL-C target.** Lipid-lowering treatment(s) are life-long.

TABLE 2. THERAPEUTIC TARGETS ACCORDING TO CARDIOVASCULAR RISK IN AUSTRALIA

	Primary Prevention Goal (12)	Secondary Prevention Goal
Total cholesterol	< 4.0 mmol/L	
LDL -C	< 2.0 mmol/L	< 1.8 mmol/L
HDL -C	≥ 1.0 mmol/L	≥ 1.0 mmol/L
Triglycerides	< 2.0 mmol/L	< 2.0 mmol/L

LEGEND: LDL-C: LOW DENSITY LIPOPROTEIN CHOLESTEROL; HDL-C: HIGH DENSITY LIPOPROTEIN CHOLESTEROL.

HEALTHY EATING AND LIFESTYLE ADVICE

Healthy eating and lifestyle modification can decrease total cholesterol, LDL-C and triglyceride levels and increase HDL-C levels to reduce the risk of developing CVD. This treatment should be used as an adjunct in high-risk patients who would derive considerable benefit from lipid-lowering drug therapy. Healthy eating includes losing weight by eating less and reducing energy intake, particularly fat. Physical activity is also critically important in keeping excess weight off. Decreasing saturated fat intake and replacing them with polyunsaturated or monounsaturated fats and carbohydrates (excluding sugars and syrup) lowers total cholesterol, LDL-C and triglyceride levels. Plant sterols and stanols and fruit and vegetables may also have a small effect.

LIPID-LOWERING MEDICATION

Statins are the cornerstone and most common medical treatment for lowering LDL-C. However, other non-statin medications can also be effective alone, or in combination with statins in patients who are unable to achieve the desired LDL-C lowering goal (refer Table 3).

The majority of national and international cardiology and cardiovascular societies and health organisations (e.g. The National Heart Foundation of Australia and Stroke Foundation) recommend that all patients with atherosclerotic-related CVD be prescribed a statin, regardless of baseline lipid levels (3, 15). Statin therapy should be initiated preferably whilst in hospital if a hospital admission has occurred. In patients with PVD, management of atherosclerotic risk factors is advocated and statin therapy is recommended to improve exercise capacity and claudication symptoms and decrease the occurrence of CVD events.

For secondary prevention patients at high risk of CVD events, treatment is usually initiated with high intensity statin therapy without beginning or changing from lower intensity statin therapy (3, 15). This contrasts with the stepped approach to statin treatment to lower LDL-C in primary prevention. In both cases, failure to control to target levels with statins should lead to the initiation of additional drugs added as combination therapy. Ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors can be used as third-line therapy for individuals with elevated LDL-C and for whom PCSK9 inhibitors are currently available.

Statins are well tolerated yet adverse effects can include muscle pain (typically in the first three months after treatment initiation), abnormal liver enzyme levels and increased risk of developing diabetes. The benefits of taking statins outweigh the potential for side effects. Medications that interact with statins include fibrates, calcium channel blockers (to lower blood pressure), anti-coagulants (to thin the blood), anti-arrhythmics (to control irregular heartbeats) and heart failure medications that slow heart rate. These drugs may boost statin levels in the blood, consequently raising the potential for muscle-related side effects, or raise anti-coagulant levels which could increase the risk of bleeding.

FOLLOWING ADVICE ABOUT HEALTHY EATING, LIFESTYLE MODIFICATION AND MEDICATION EARLY AFTER A CVD EVENT ARE CORNERSTONES OF GOOD CHOLESTEROL MANAGEMENT TO REDUCE THE RISK OF SUBSEQUENT EVENTS

TABLE 3. STATIN AND NON-STATIN LIPID LOWERING THERAPIES

Therapy	Description
Statins	
HMG-CoA reductase inhibitors (atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin)	Block the HMG-CoA reductase enzyme which the liver needs to make cholesterol. Statins increase LDL removal and decrease LDL production. Statins lower LDL-C and can lower triglycerides and mildly raise HDL.
Combined with ezetimibe (Atozet, Rosuzet, Vytorin)	
Non-statins	
Nicotinic acid/Niacin	This B-vitamin is available at high doses by prescription to affect the production of blood fats in the liver to lower LDL-C.
Bile acid binding resins (Cholestyramine, Colestipol)	They attach to (cholesterol rich) bile acids in the intestines and prevent it from being absorbed back into the blood. These drugs reduce the supply of cholesterol.
Cholesterol absorption inhibitors (ezetimibe)	Lowers the amount of cholesterol absorbed by the intestines by blocking it to reduce LDL-C.
Fibrates (Fenofibrate, Gemfibrozil)	Fibrates reduce the liver's production of VLDL (the triglyceride carrying particle) and speeds up the removal of triglycerides from the blood. Fibrates lower triglycerides and can modestly increase HDL-C. They are not effective in lowering LDL-C.
Omega-3 fatty acids (alpha-linolenic acid, eicosapentaenoic acid, docosahexaenoic acid)	Taken as supplements or medication to lower triglycerides by producing pro-inflammatory and anti-inflammatory effects. Omega-3s lower triglyceride levels.
PCSK9 inhibitors (evolocumab, alirocumab)	PCSK9 proteins bind to LDL receptors and destroy these liver cell receptors that sweep away excess cholesterol. PCSK9 inhibitors block the PCSK9 protein from binding with LDL receptors to enable more LDL receptor expression and greater capacity to remove more LDL-C. PCSK9 inhibitors lower LDL-C.

PCSK9 INHIBITORS

Recently, PCSK9 inhibitors have shown remarkable results when added to statin therapy. To date, two PCSK9 inhibitor treatments have been developed and tested. In the OSLER trials of 4,465 patients, the use of evolocumab plus standard therapy, as compared with standard therapy alone, significantly reduced LDL-C by 61% during approximately 1 year of treatment (16). In the ODYSSEY LONG TERM trial involving 2,341 patients, alirocumab plus statin therapy lowered LDL-C by 61% over 78 weeks compared to an increase of 0.8% with statin treatment alone (17).

In the latest FOURIER multi-national trial in 27,564 high risk patients, evolocumab in combination with statin therapy lowered LDL-C by a difference of 59% from baseline compared to placebo after 48 weeks (18). The mean absolute reduction was 1.45 mmol/L (95% CI 1.43-1.47 mmol/L) and median LDL-C at baseline was 2.4 mmol/L [IQR 2.1-2.8] reduced to a median LDL-C at 48 weeks of 0.78 mmol/L [IQR 0.49-1.2] (18). The reduction in LDL-C began almost immediately; it was identified as soon as 4 weeks after beginning treatment and was sustained over a median 2.2 year follow-up. The efficacy of this treatment duo corresponded to a 15% relative risk reduction in CVD events (18). New data from the FOURIER study has recently identified the importance of PCSK9 drugs in preventing subsequent cardiovascular events, especially sooner (less than one year) after experiencing an event compared to later than one year (25% vs 15% risk reduction).

FIGURE 4. ELIGIBILITY CRITERIA FOR PCSK9 INHIBITORS SUBSIDISED VIA THE PBS (FOR FULL DETAILS, REFER TO: WWW.PBS.GOV.AU)

	1. LDL-C level	2. Patient diagnosis	3. Optimised therapy†
Non-familial hypercholesterolemia	LDL-C >2.6 mmol/L	Symptomatic atherosclerotic CVD **AND** Any of the following: • ≥2 major cardiovascular events in the last 5 years • Diabetes mellitus plus: – microalbuminuria OR – 60+ years OR – Aboriginal or Torres Strait Islander • Severe multi-vessel CAD (≥50% stenosis) in ≥2 large vessels • Atherosclerotic CVD in ≥2 vascular territories • TIMI risk score for secondary prevention ≥4	≥12 weeks maximised statin* **OR** statin intolerant **OR** statin contraindicated **AND** ≥12 weeks ezetimibe
Familial hypercholesterolemia	**HeFH:** LDL-C >5 mmol/L **OR** LDL-C >2.6 mmol/L + Symptomatic atherosclerotic CVD **HoFH:** LDL-C >2.6 mmol/L	**HeFH:** Dutch Lipid Clinic Network Score ≥6 **HoFH:** Dutch Lipid Clinic Network Score ≥7 **OR** Positive genetic test	**HeFH/HoFH:** ≥12 weeks maximised statin* **OR** statin intolerant **OR** statin contraindicated **HeFH:** **AND** ≥12 weeks ezetimibe

* MAXIMUM RECOMMENDED OR TOLERATED DOSE OF ATORVASTATIN OR ROSUVASTATIN ACCORDING TO THE TGA-APPROVED PRODUCT INFORMATION FOR ≥12 CONSECUTIVE WEEKS †IN CONJUNCTION WITH DIETARY THERAPY AND EXERCISE.

LEGEND: LDL-C: LOW DENSITY LIPOPROTEIN CHOLESTEROL; HeFH: HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA; HoFH: HOMOZYGOUS HYPERCHOLESTEROLEMIA; TIMI: THROMBOLYSIS IN MYOCARDIAL INFARCTION

Thus, there is strong evidence that PCSK9 inhibitors are potent accompaniments to the array of therapies to reduce LDL-C levels. In a simulation model applied to US data from patients with atherosclerotic CVD, it was suggested that after full intensification with statin monotherapy only, LDL-C levels could be reduced to <1.8 mmol/L for 69% of patients (19). Adjunct ezetimibe treatment increased this rate to 86% and adding on a PCSK9 inhibitor increased it further for the remaining 14%. This suggests that over **99% of the population with atherosclerotic CVD could reach recommended LDL-C levels** by using PCSK9 inhibitors when target LDL-C levels were previously unattainable with current standards of care.

PCSK9 inhibitors are a costly lipid lowering therapy (20). As such, the two PCSK9 drugs registered in Australia, Repatha (evolocumab) and Praluent (alirocumab) are currently only subsidised via the Pharmaceutical Benefits Scheme (PBS) for a very select population of patients with genetic high cholesterol (familial homozygous hypercholesterolaemia or familial heterozygous hypercholesterolaemia) and more recently, atherosclerotic CVD with additional risk factors. Detailed eligibility criteria for these prescribed medicines via the PBS are summarised in Figure 4. These agents have been approved by the PBS for wider use in high risk patients with PBS subsidy.

Elevated cholesterol in high risk individuals in Australia

In the CONCORDANCE registry encapsulating data from 42 representative hospitals around Australia on the management and outcomes of patients hospitalised with acute coronary syndrome (21), many patients were receiving some form of lipid-lowering therapy (78%) (22). However there were just over half (55%) of patients who were on optimal management, defined as: ***i)*** intensive statin therapy with or without ezetimibe or, ***ii)*** lower intensity statin therapy with ezetimibe or, ***iii)*** ezetimibe alone, leaving a gap of 45% of people who were not receiving intensive lipid-lowering treatment up to 12 months after their hospitalisation (22). In the latest National Stroke Audit, approximately 80% of ischaemic stoke patients were prescribed lipid-lowering treatment on discharge from hospital (23).

In the community, a recent audit of general practice electronic health records by Lee et al showed gaps in preventative management for patients with

CAD which were larger in women compared to men (24). Women were less likely than men to be prescribed with statin therapy (61.2% vs. 79.4%), a lower proportion of women were assessed for LDL-C at least once during the 2 year study period (69.7% vs. 76.9%) and a lower proportion of women than men achieved the LDL-C target of <1.8 mmol/L (22.7% vs. 37.5%). In the REACH registry of 2,783 subjects enrolled from 273 GP clinics across Australia, 78.8% of secondary CVD patients were on a statin and 80.3% on any lipid-lowering therapy (25). The rates for statin therapy were highest for patients with CAD (81.8%) compared to cerebrovascular disease (62.9%) or PVD (78.8%).

In the Australian population and using self-reported data collected from the National Health Measures Survey (n=635), Banks and colleagues estimated that almost three quarters (73.3%) of people with prior CVD aged between 45-74 years had LDL-C levels ≥ 2.0 mmol/l (26). Among these individuals, around 1 out of 2 (55.7% [47.0%-64.4%]) were likely to be receiving lipid-lowering medication.

As described above, the consequences of living with elevated cholesterol increases the risk of having a subsequent heart attack. Readmission rates remain high (27). In the IMPROVE-IT trial, at least one in three patients still suffered a subsequent major cardiovascular event and 42% of individuals prematurely discontinued treatment after 7 years (9). Therefore, reducing LDL-C continues to be an important objective in secondary prevention by enhancing patient adherence to therapy and guideline-driven lipid-lowering medication utilisation in order to prevent recurrent CVD events.

The economic burden of elevated lipids in Australia

In 2017, 3.4% of the disease burden in Australia was due to elevated cholesterol which contributed to 27.8% of the CVD burden and 13% of stroke burden (28). Accordingly, much of the burden of CVD can be prevented by adequate management and control of elevated LDL-C.

The National Heart Foundation provides the most recent insights into the economic burden of hypercholesterolaemia in Australia (29). In this report, economic burden was comprised of two components:

i. burden associated with the hypercholesterolaemia itself, and

ii. burden associated with diseases caused by hypercholesterolaemia.

Main findings revealed that for 2017-18, the economic burden attributable to hypercholesterolaemia was almost $4 billion. However, importantly costs estimated for medication were determined on 2011-12 prevalence data and therefore, economic costs with up-to-date data are necessary.

DIRECT MEDICAL COSTS

Given that there are no physical symptoms associated with hypercholesterolaemia as a risk factor, the economic burden of the condition itself is confined to the direct cost of lipid-lowering medication and its management. The most recent data from the PBS shown in Table 4 indicated that cholesterol modifying agents (atorvastatin, rosuvastatin, simvastatin and ezetimibe) were listed amongst the top 50 PBS drugs in terms of both number of prescriptions and total cost (30).

A total of 17.87 million PBS subsidised scripts were issued for these four drugs in 2018-19 at a total cost of $312.3 million.

These amounts relate to the cost of medications only, and do not take into account the associated costs of lipid diagnostics, GP or specialist attendance. As a script generally provides for sufficient repeats to last a patient for six months, an average of two visits to the GP were allowed for in the analyses. The issuance of the 17,867,748 prescriptions for lipid-lowering medications shown in Table 4 would entail 2,977,958 GP visits. At a unit cost of $38.20 (Medicare Benefits Schedule [MBS] Item 23), this equates to a cost of $113,757,996 for 2018-19 (31). An average of 1.3 lipid measurement studies per patient per annum, at a unit cost of $11.65 (MBS Item 66503), were costed, equating to a cost of $22,550,587 (31).

There are no data available about the economic burden of high cholesterol on the hospital sector. The Global Burden of Disease data indicates that 51.35% of the DALY burden due to ischemic heart and 13.01% of the DALY burden due to stroke amongst Australians in 2017 were attributable to the risk factor, high LDL-C. These proportions were then applied to the hospital separations for these two disease categories obtained from the National Hospital Cost Data Collection Round 21, 2016-17 (32) to estimate the cost of attributable hospitalisations ($1.025 billion).

Combining these four cost estimates (for medications, GP attendances, cholesterol testing and attributable hospitalisations) gives a total direct health care cost of high cholesterol of $1.47 billion.

TABLE 4. EXPENDITURE ON LIPID LOWERING MEDICATIONS, AUSTRALIA 2018-19 (30)

Drug	PBS subsidised prescriptions	Government cost	Patient contribution[1]	Total cost[2]	Average price[3]	Rank[4]
Atorvastatin	7,388,219	$65,829,038	$38,312,088	$104,141,126	$14.10	1
Rosuvastatin	7,292,825	$89,291,516	$38,881,763	$128,173,279	$17.58	2
Simvastatin	1,920,363	$15,697,416	$9,890,656	$25,588,072	$13.32	24
Ezetimibe	1,266,341	$38,516,852	$15,895,961	$54,412,813	$42.97	48
Total	17,867,748	$209,334,822	$102,980,468	$312,315,290		

LEGEND: PBS: PHARMACEUTICAL BENEFITS SCHEME.

1 THE PATIENT CONTRIBUTION DOES NOT INCLUDE THE EFFECT OF THE $1 PBS PATIENT CO-PAYMENT DISCOUNT.

2 TOTAL COST INCLUDES COST TO THE PATIENT AND COST TO THE GOVERNMENT FOR PBS SUBSIDISED PRESCRIPTIONS.

3 AVERAGE PRICE IS TOTAL COSTS DIVIDED BY PBS SUBSIDISED PRESCRIPTIONS.

4 RANK INDICATES THE DRUG'S RANKING IN A LIST OF THE TOP 50 DRUGS SORTED BY HIGHEST SUBSIDISED PRESCRIPTIONS 2018-19.

INDIRECT COSTS – LOST PRODUCTIVITY

A key component of the associated indirect costs of high cholesterol stem from the lost output which arises due to persons not being in the workforce due to either illness or death as a result of the risk factor.

Lost productivity stemming from premature deaths attributable to the risk factor were calculated using two common approaches. The human capital approach measures the working years lost by a worker between the age of death and the average Australian retirement age of 65 years. The friction cost approach, on the other hand, assumes that a deceased worker would be replaced after an average period of thirteen weeks (10 weeks to recruit and three weeks to organise and train the replacement). Deaths of Australians in 2017 attributable to high LDL-C by age (five year age groups) and sex were extracted from the Global Burden of Disease tool (28). Labour force participation rates and average annual salaries by age and sex were obtained from the Australian Bureau of Statistics (33, 34).

The Global Burden of Disease data indicates that 1,576 deaths occurred in Australia in 2017 as a result of high cholesterol amongst persons of working age (15-64 years). **Using a human capital approach, this equated to a loss of nearly 18,000 (17,999) working years and a lost productivity cost of $1.55 billion** (Table 5). The majority of this loss (88.1%) occurred amongst males. This estimate of $1.55 billion in productivity costs is lower than the Heart Foundation estimate of $2.12 billion, which was obtained by applying population attributable fractions of 51% for ischaemic heart disease and 12% for stroke to overall productivity losses estimated for the two disease categories.

Based on the more conservative frictional cost method, productivity losses arising from premature death attributable to high cholesterol were estimated to be $25.7 million in 2017 (Table 5). Whilst the real estimate is likely to lie somewhere between the values provided by these two separate approaches, the human capital approach is the more accepted method and likely to be closer to the real estimate.

Data are not available to enable calculation of lost productivity due to absenteeism and presenteeism attributable to CVD events caused by high cholesterol.

IN 2017, LOST PRODUCTIVITY DUE TO THE DEATHS OF WORKING-AGE AUSTRALIANS FROM THE CONSEQUENCES OF HIGH CHOLESTEROL WAS ESTIMATED AT $1.55 BILLION

TABLE 5. PRODUCTIVITY LOSSES DUE TO PREMATURE DEATHS ATTRIBUTABLE TO HIGH LDL-C, AUSTRALIA 2017

	Productivity losses (human capital method)		Productivity losses (friction cost method)	
15-29 years	$21,137,918	1.36%	$108,400	0.42%
30-39 years	$216,550,463	13.93%	$1,453,850	5.66%
40-49 years	$619,374,171	39.85%	$6,202,292	24.13%
50-64 years	$697,261,323	44.86%	$17,940,903	69.79%
Total	$1,554,323,875	100.00%	$25,705,445	100.00%

BURDEN OF DISEASE COSTS

In addition to the costs to the health system and to the wider economy through lost production, there is also the burden associated with the risk of death or disability as a consequence of high LDL-C. 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.

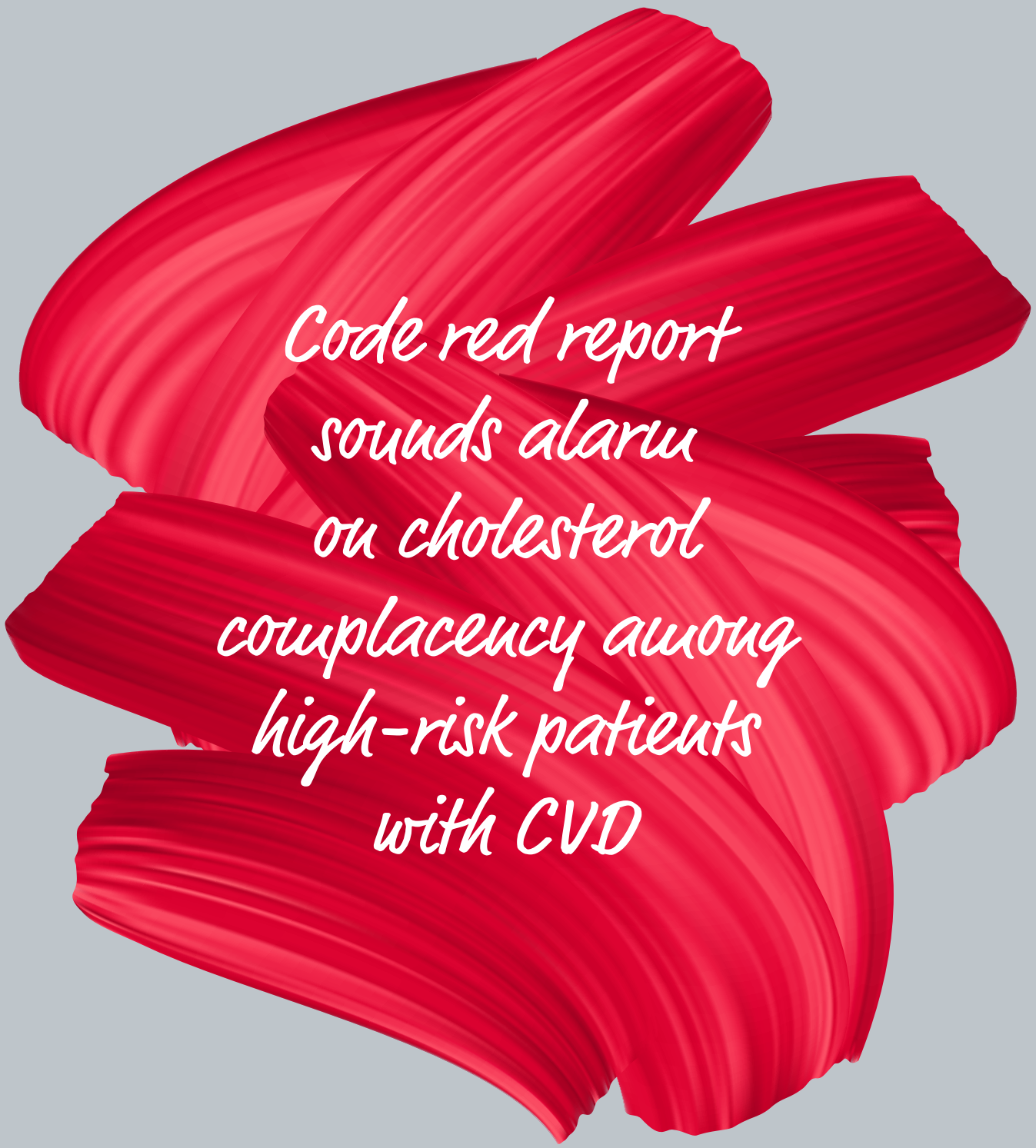
Burden of disease costs are measured in disability-adjusted life years (DALY) which take into account both mortality (years of life lost due to premature mortality [YLL]) and morbidity (years lived with a measure of disability [YLD]) as a result of a disease. DALY, YLL and YLDs due to high LDL-C in the 2017 Australian population Australia were extracted from Global Burden of Disease Data Tool. The commonly used value of $50,000 was assigned to each DALY (35).

The Global Burden of Disease shows that 181,344 DALYs were lost as a result of high cholesterol in the 2017 Australian population. This equates to a loss of $9.07 billion. The majority of this loss (90.4%) was due to premature deaths (Table 6). As a consequence of deaths in 2017 attributable to high cholesterol, some 163,964 years of life were lost incurring a cost burden of $8.2 billion. Males accounted for nearly two thirds of the losses.

MORE THAN 1,570 WORKING-AGE AUSTRALIANS DIED IN 2017 DUE TO THE CONSEQUENCES OF HIGH CHOLESTEROL

TABLE 6. BURDEN OF DISEASE LOSSES ATTRIBUTABLE TO HIGH CHOLESTEROL BY CATEGORY AND SEX

	Years of life lost (YLL)	Years lived with a disability (YLD)	Disability-adjusted life years (DALYs)
Males			
Number	107,753	8,241	115,994
$ losses	$5,387,663,500	$412,029,000	$5,799,692,500
Females			
Number	56,211	9,139	65,350
$ losses	$2,810,530,500	$456,950,000	$3,267,480,500
Persons			
Number	163,964	17,380	181,344
$ losses	$8,198,194,000	$868,979,000	$9,067,173,000


Code red report
sounds alarm
on cholesterol
complacency among
high-risk patients
with CVD

Methodology

High quality care provided by clinicians is important for secondary prevention of CVD. Clinicians play a key role in supporting the management of patients with CVD. The use of large-scale, national data from general practice represents a key opportunity to assess the magnitude of elevated cholesterol and the achievement of recommended target levels in high risk patients with prior CVD in Australia.

Data source

De-identified individual patient data were sourced from the MedicineInsight program (36). In 2011, the Australian Government Department of Health provided core funding to NPS MedicineWise to establish and manage MedicineInsight. NPS MedicineWise is an independent, not-for-profit and evidence-based organisation. It is committed to supporting quality use of medicines to improve decision-making and enhance health outcomes in Australian primary care.

MedicineInsight represents a national, large-scale, primary care data program. Full details about the program have been recently published (37). In brief, longitudinal, de-identified, whole-of-practice information about demographics, medical history, health care and lifestyle is extracted regularly from the clinical software of consenting general practices across Australia.

The majority of Primary Health Networks (organisations that connect health services across a specific geographic region), are represented in MedicineInsight. Characteristics of regularly attending MedicineInsight patients are broadly comparable to patients who visited a general practitioner in the MBS data, in terms of age and sex (37).

Upon joining MedicineInsight, an all-of-practice data collection, incorporating all available de-identified historic and current electronic health records is conducted. Third party data extraction tools to de-identify, extract and securely transmit data are used and applied regularly to collect incremental data to enable a longitudinal database of patients within practices to build over time. These data are housed by NPS MedicineWise, as the Data Custodians, in a secure data warehouse.

The large volume of data allows for a detailed analysis of activities that occur in general practice and the longitudinal nature of the data enables changes over time (sometimes in response to health policy or clinical guidelines) to be monitored. Findings using MedicineInsight can be used by policymakers, health systems and health professionals to inform future health policy and primary care research. Other uses of the data include supporting:

i. quality improvement activities
ii. the safe use of new medicines
iii. a sustainable Pharmaceutical and Medicare Benefits Scheme

MedicineInsight is well suited to provide a greater understanding of general practice activity across Australia and improve health outcomes for all Australians.

A comprehensive list of MedicineInsight data is contained in their Data Dictionary (available on request from NPS MedicineWise).

Data governance and ethics

MedicineInsight data are available to support research that aligns with the NPS MedicineWise mission and is for the public good. There are rigorous governance processes instilled by NPS MedicineWise to mitigate any risk to participants and to ensure that the program is run lawfully, ethically and for the public good. Access to MedicineInsight data is subject to approval by an independent Data Governance Committee that includes consumer advocates, privacy experts and researchers.

Approval from the independent MedicineInsight Data Governance Committee was given for this Report on 21 August 2019 (Project No. 2019-012). Prior low risk review and approval was given by the Alfred Hospital Ethics Committee (Project No. 257/19) on 10 May 2019.

The MedicineInsight program was approved by the Royal Australian College of General Practitioners National Research and Evaluation Ethics Committee in December 2017 for the standard operations and uses by NPS MedicineWise.

Consent

General practices are recruited to MedicineInsight and the owner of, or authorised person for, a general practice consents to participation in the program. Because non-identifiable data are collected, patients are not required to give written consent. Patients are informed about the practice's participation in MedicineInsight through poster displays in the waiting areas (https://www.nps.org.au/assets/NPS1785e_PatientNotification_A3_v5-font-change.pdf) and a Participant Information Sheet if more information is requested (https://www.nps.org.au/assets/NPS1786e_MI_Info_OptOut_Flyer_v5-font-change.pdf).

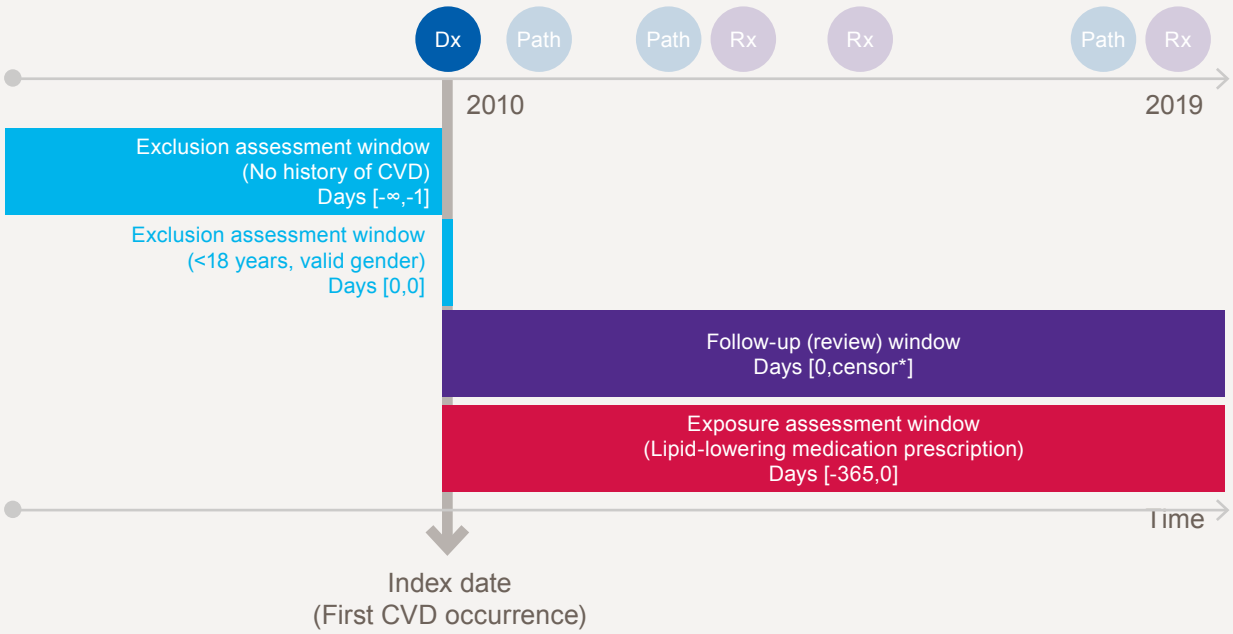
Patients can opt out and deny any information from their medical record to be shared with MedicineInsight by signing a form.

Study design and setting

This Report is a retrospective data audit based on MedicineInsight data extracted in August 2019. The source data range covers 1 January 1955 (for first CVD diagnosis) to 23 July 2019 (for LDL-C measurements and lipid-lowering medication prescriptions).

As shown in Figure 5, the study implementation was oriented around a diagnosis of CVD (refer to Study Population) and anchored to the date of the first recorded CVD occurrence. This date was taken as the index date (cohort entry date) following which time data could be assessed as potentially analysable study data. Patients who met the high risk cohort selection criteria were included

FIGURE 5: ILLUSTRATION OF STUDY DESIGN IMPLEMENTATION



LEGEND: DX: DIAGNOSIS; PATH: LDL-C TEST RESULT; RX: LIPID-LOWERING MEDICATION PRESCRIPTION.

* LATEST OF RECORDED LDL-C TEST RESULT OR LIPID-LOWERING MEDICATION PRESCRIBED.

if they had a sex recorded and a valid age (at index condition date) of 18 years or above. Patients without a recorded history of the occurrence of a CVD condition, or anybody below 18 years of age or who did not have a valid sex recorded at the date of the index condition were excluded.

The follow up window for reviewing LDL-C test results was January 2010 to July 2019 and for lipid lowering prescription medications, the follow-up window was within 12 months before their representative LDL-C test result, (i.e. January 2009 to July 2019). Patients without any lipid-lowering prescribed medication within the 12 month assessment window but had exposure to lipid-lowering treatment before or after this period were excluded.

Therefore, the observation period was not of a fixed duration for all patients and began when patients had their first recorded LDL-C measurement after 1 January 2010 and ended at the latest of either their final recorded LDL-C test result or lipid-lowering medication prescribed.

Study population

To obtain a **high risk cohort, patients were eligible for inclusion if they were identified as having a diagnosis of CVD**. A patient was considered to have CVD if any one or more of the condition terms specified in Table 8 was identified throughout their medical records.

Patients who were identified by age (over 18 years) and sex with a recorded history of the occurrence of a CVD condition satisfied the selection criteria. These eligibility criteria are summarised in Table 7 below (and as discussed above).

Variables

CVD CONDITION

CVD was identified according to the conditions a patient was classified with in MedicineInsight. Condition terms/flags within MedicineInsight were derived by NPS MedicineWise based on defined criteria, taking into account information selected in drop down lists by GPs and/or free text terms in designated data fields (specifically diagnosis/ medical history, reason for encounter and reason for prescription). The defined list of condition terms were then categorised into three main diagnostic groups; ***i)*** traditional atherosclerotic CAD; ***ii)*** cerebrovascular disease; and ***iii)*** PVD. Exposure to CVD was defined as at least one recorded CVD diagnosis in patient's longitudinal data stream. If there were multiple CVD exposures,

TABLE 7. IDENTIFICATION OF HIGH RISK PATIENTS BASED ON RECORDED DIAGNOSES

Diagnosis	Included condition terms
Coronary heart disease and atherosclerosis	Coronary heart disease and atherosclerosis OR
	Coronary heart disease related procedure and atherosclerosis OR
	Coronary heart disease and atherosclerosis related activity OR
	Coronary heart disease related procedure OR
	Coronary heart disease related activity
Cerebrovascular disease	Transient ischaemic attack OR
	Stroke ischaemic OR
	Stroke lacunar OR
	Stroke thrombotic OR
	Stroke haemorrhagic OR
	Stroke migrainous OR
	Carotid artery stenosis OR
	Carotid artery stenosis related procedure OR
	Stroke unspecific
Peripheral vascular disease	Peripheral vascular disease

TABLE 8. STUDY ELIGIBILITY CRITERIA

Inclusion criteria	Exclusion criteria
Diagnosis of CVD	No diagnosed CVD
At the index date	
Aged ≥18 years	Aged <18 years
Valid sex	No valid sex
During follow-up period	
Lipid-lowering treatment exposure within 12 month assessment window	Lipid-lowering treatment exposure outside of 12 month assessment window

the first/earliest CVD occurrence was taken as the index event date.

LDL-C MEASUREMENTS

LDL-C test results were searched for within MedicineInsight. All cholesterol test results were performed by an accredited laboratory using standard assays and may have been requested by the consulting general practitioner or carbon copied to the practice from an external provider for input into the clinical information system. All available LDL-C records for a patient after their index CVD condition date and between 2010 and mid-2019 were retrieved for analyses. If there were multiple eligible LDL-C measurements during the follow-up period, the minimum LDL-C result a patient achieved during their follow-up period was chosen as the representative LDL-C measurement, otherwise the single LDL-C test result available, in the case of only one eligible LDL-C record, was used.

LIPID-LOWERING MEDICATION PRESCRIPTIONS

Lipid-lowering medication prescriptions were searched for within MedicineInsight in two ways. Firstly, exposure to

TABLE 9: CLASSIFICATION OF LIPID-LOWERING MEDICATION PRESCRIPTIONS

0 Non-recommended therapy	1 Low Intensity (statin monotherapy)	2 Moderate Intensity (statin monotherapy)	3 High Intensity (statin monotherapy)	4 Combination statin therapy	5 Cholesterol absorption inhibitors	6 Very high intensity
Nicotinic acid/niacin	Simvastatin 10 mg	Atorvastatin 10-20 mg	Atorvastatin 40-80 mg	Statin combined with ezetimibe e.g. Vytorin	Ezetimibe	PCSK9 inhibitors
Bile acid binding resins	Pravastatin 10-20 mg	Rosuvastatin 5-10 mg	Rosuvastatin 20-40 mg			
Fibrates	Fluvastatin 20-40 mg	Simvastatin 20-40 mg	Simvastatin 80 mg			
Omega 3 fatty acids		Pravastatin 40-80 mg				
		Lovastatin 40-80 mg				
		Fluvastatin 40-80 mg				

No treatment: Patients with no evidence of any lipid-lowering medication prescription after the index condition date and within 12 months prior to their representative LDL-C test result date, or the latest prescribed lipid-lowering therapy for patients without a recorded LDL-C test result

lipid-lowering treatment was defined according to script item details of individual prescriptions printed for patients. Secondly, for patients who did not have any evidence of specific scripts for any lipid-lowering medication prescription, their more general medication histories were used to identify lipid-lowering treatments prescribed by specialists, hospitals, or other health professionals and recorded in MedicineInsight.

Prescription data, including medicine active ingredient, medicine trade name and strength, were sought for all lipid-lowering medication prescriptions listed in Table 9. All available lipid-lowering medication prescriptions for a patient were retrieved for analyses. Prescriptions were then categorised according to the following, as outlined in Table 9; ***i)*** non-recommended lipid-lowering therapy; ***ii)*** statin monotherapy (low, moderate and high intensity); ***iii)*** statin therapy combined with ezetimibe; ***iv)*** ezetimibe alone; and ***v)*** more potent (i.e. non statin or ezetimibe) lipid-lowering therapy. Since lipid-lowering medication could be prescribed multiple times during the follow-up period, the most recent prescription(s) within 12 months before the representative LDL-C result and after their index CVD condition date was reflective of lipid-lowering treatment assignment.

SOCIO-DEMOGRAPHIC INFORMATION

Socio-demographic information that could be evaluated with MedicineInsight and obtained for analyses included sex, age, smoking status, SES (Index of Relative Socio-Economic Advantage and Disadvantage, IRSAD) and the geographical region (major cities, regional and remote), location (state and territory) and primary health network (PHN) within the area of the GP clinic.

Study size

Raw data of 7,330,343 records of medical conditions associated with CVD dated between January 1955 and July 2019 were received for 434,710 patients. Following the exclusion of patients without a history of CVD and duplicate records, a total of 134,799 patients were aged 18 years or older at the time of diagnosis of atherosclerotic-related CVD (see Figure 6).

As shown in Figure 6, from 134,799 eligible patients with CVD, there were 107,664 individuals who had at least one LDL-C test result following their index CVD condition date and between 2010 and 2019. A total of 12,063 patients did not have a LDL-C result recorded during the follow-up window and were excluded. The remaining 15,072 patients were also excluded due to having no lipid-lowering prescribed medication within the 12 month assessment window (but exposure prior to or after this period).

There were 91,187 from 107,664 patients with a LDL-C record that were prescribed lipid-lowering medication within 12 months prior to the representative LDL-C test result.

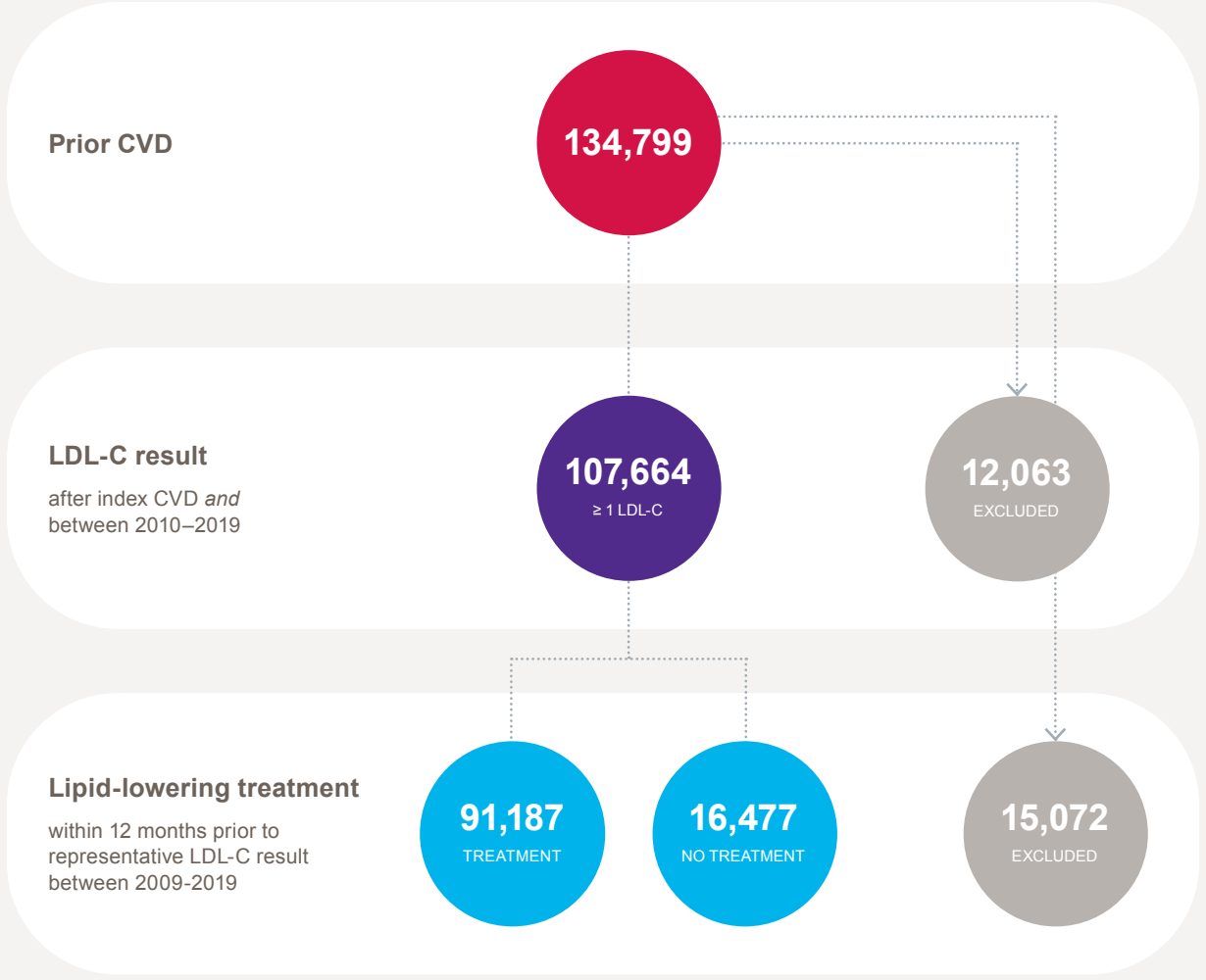
This cohort of patients was being managed by GPs from each state and territory in Australia. As shown in Figure 7, over the decade commencing in 2010, most patients included in the study attended a GP clinic located in New South Wales (40%), Victoria (21%) or Queensland (16%). An additional 9% and 8% were located in Western Australia and Tasmania, respectively. There were fewer patients from the remaining states and territories.

Data analyses

Age was calculated as the difference between year of birth and year of index condition date to denote age at condition occurrence. We assigned a duration of CVD for each person, calculated as the time difference from the date of the index CVD condition and the initial LDL-C test result for an individual. Length of follow up was calculated as the time difference from the first LDL-C test result to the latest of either their last recorded LDL-C test result or lipid- lowering medication prescribed.

The attainment of the LDL-C treatment target of <1.8 mmol/L was evaluated based on the representative LDL-C result a patient achieved during their

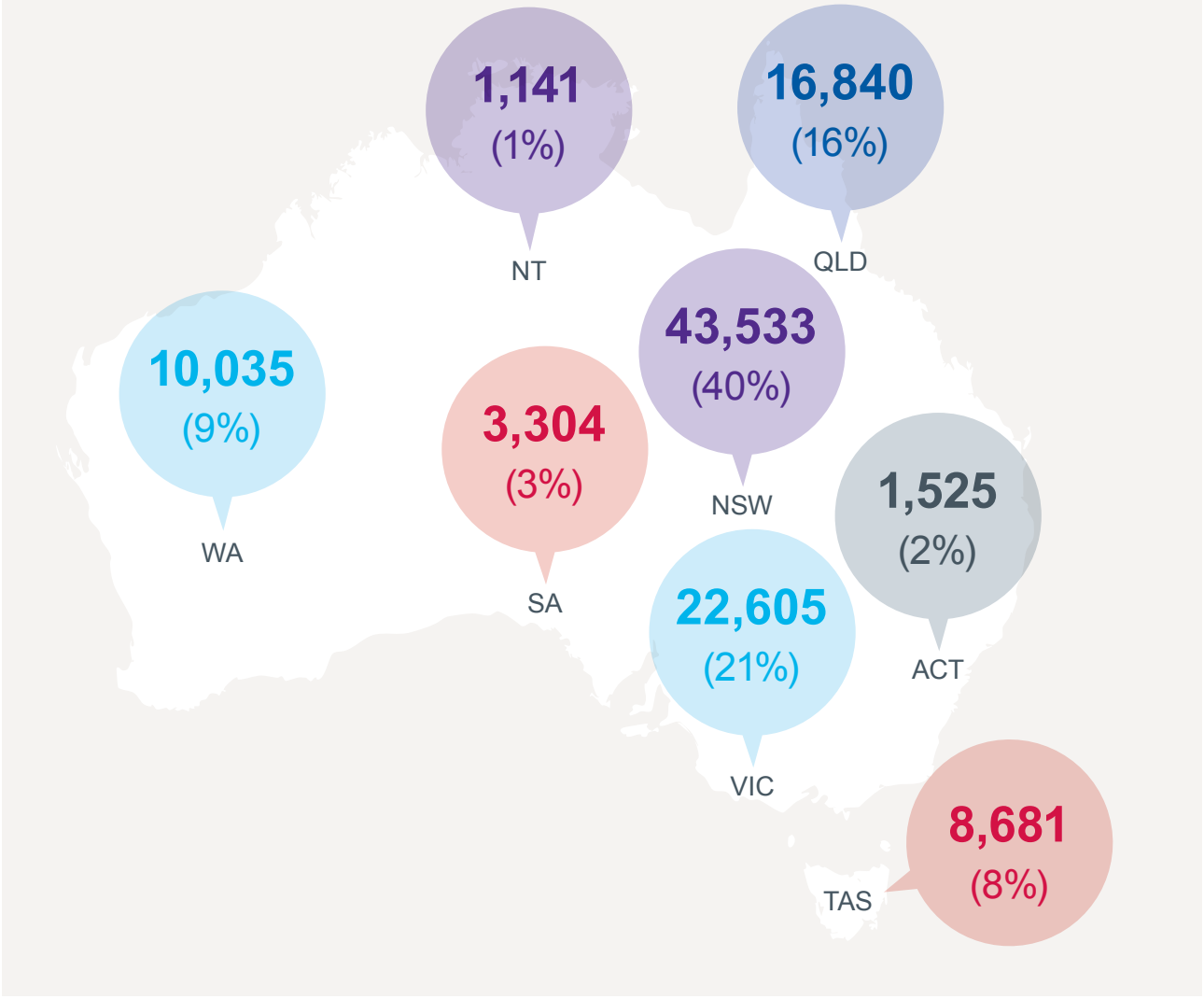
FIGURE 6: STUDY FLOW CHART OF ELIGIBILE PATIENTS WHO HAVE PRIOR CVD BASED ON LDL-C TEST RESULTS AND LIPID-LOWERING PRESCRIBED TREATMENT



follow up period. The LDL-C results, histograms and proportions achieving target were analysed for the overall study cohort and according to gender. Furthermore, LDL-C test results and treatment targets are reported by lipid-lowering medication type, CVD condition type, age groups and geographical region. Descriptive statistics using the mean and standard deviations (continuous variables) and frequencies and proportions (discrete variables) were calculated to describe the sample and characterise lipid levels and treatment goals. Results are not adjusted for possible confounding variables which might influence the amount of association between outcomes.

Data were analysed using Stata version 16 (StataCorp LP).

FIGURE 7: TOTAL NUMBER OF PATIENTS PER STATE AND TERRITORY WITH AT LEAST ONE LDL-C TEST RESULT BETWEEN 2010 AND 2019 WHO HAVE PRIOR CVD



HEALTH ECONOMIC ANALYSES

The health economics modelling aimed to determine the costs of ensuring all persons with CVD in Australia meet the target for LDL-C control, and the cost savings that will accrue to the health system as a result of that action.

Model: The number of Australian adults (persons aged 18 years and over) who had at least one CVD event (heart, stroke or vascular disease) amounted to 1,150,200 and was obtained from the AIHW (4).

A Markov microsimulation model was constructed to simulate the long-term outcomes of optimally managing the LDL-C levels of all patients with CVD compared to the current scenario where not all patients in the target group meet the LDL-C control target (i.e. <1.8 mmol/L). Allocation of persons to each group was based on the proportions of the MedicineInsight sample of 107,664 persons (those who had at least one LDL-C cholesterol test between 2010 and 2019 after an initial CVD occurrence) meeting or not meeting the recommended cholesterol level target of 1.8 mmo/L.

Age and representative LDL-C measurement of each simulated subject were defined by the MedicineInsight database. Each patient started in the 'no event' state while facing the annual risk of experiencing recurrent fatal/ non-fatal CVD event or dying from non-CVD causes. Patients who had another CVD event then incurred the similar risk of experiencing recurrent CVD event over the course of remaining time horizon.

A 100% compliance to statin therapy is unrealistic. In our base case, 70% compliance from 7 years onwards was adopted to model the long-term benefits of continuing the optimal treatment. Colantonio et al. (38) and Cannon et al. (9) reported that at 7 years, around 60-70% of people would still be on statin treatment, and this was further supported by Romanelli and Segal (39). As a result, in our base case, 70% compliance from 7 years onwards was adopted to model the long term benefits of continuing the optimal treatment. Scenario analyses of 60% and 80% adherence were modelled as sensitivity analyses.

Transition probabilities: The probability of recurrent fatal/non-fatal CVD was determined by the LDL-C measurement of each subject (i.e. meeting the LDL-C control target lowers the risk of recurrent CVD and vice versa). The reduction of relative risk of recurrent CVD through the use of statins was sourced from a meta-analysis of data from 174,000 participants in 27 randomised controlled trials (40). The background non-CVD mortality was informed by the Australian Bureau of Statistics causes of death by subtracting the CVD mortality rate from the overall mortality rate (41). The mortality due to non-CVD causes was inflated to reflect patients' history of CVD (42).

Costs: An Australian healthcare system perspective was adopted to measure the cost of optimal LDL-C management. Costs related to statin utilisation, outpatient consultations for statin management, acute hospitalisation for CVD events, and post-CVD management were included. Acute hospitalisation for CVD (fatal or non-fatal) was calculated as the weighted average according to major causes of CVD (i.e. number of hospitalisations by primary diagnosis for the hospital episode) based on the national statistics (43). The same approach was followed to estimate the post-CVD management cost.

The costs of statin utilisation and outpatient consultation for LDL-C management were based on the resource use from the MedicineInsight cohort data. All patients were analysed based on the level of LDL-C (meeting or not meeting the LDL-C control target) to estimate the number of scripts for the lipid-lowering medications and the number of outpatient consultations for LDL-C management by the LDL-C status.

Utility weights: Utility or preference weights representing the strength of desirability towards different health states (i.e. more preferred health states will have greater weight) were measured on a cardinal scale of 0-1 (where 0 indicates death and 1 indicates perfect health). Utility weights post CVD were calculated as the weighted average in accordance with each major type of CVD event (i.e. myocardial infarction, stroke, heart failure, PVD, etc.) (32). A decrement in utility weight (i.e. disutility) was immediately applied to patients following an acute recurrent CVD event.

Long-term modelled cost-effectiveness analysis: The long-term costs and health outcomes of bringing all patients to within the recommended LDL-C levels were estimated separately for 5, 10 and 20 year time horizons. Utility weights were utilised to estimate the Quality-adjusted life years (QALYs). An incremental cost-effectiveness ratio was reported to determine the value for money of the proposed intervention of bringing all patients in the target group within the recommended target level for LDL-C cholesterol. Costs and benefits were discounted at a rate of 3% per annual. Cost-effectiveness was measured against the often quoted willingness to pay per QALY threshold of AUD $50,000 (35).

Findings

Records of 107,664 high risk patients with prior CVD were analysed over the period 2010 to mid-2019. Table 10 summarises the characteristics of patients in the study.

There was a predominance of men in the study population (61%) and just under half of all patients were aged over 65 years.

An index diagnosis of CAD was documented for most patients (66%) and around two in five patients had CVD for at least 10 years and for a period of 5 to 10 years, while one in five had CVD more recently, as recorded at the participating general practice. The number of LDL-C test results per patient available for evaluation ranged from 1 to 46 during the study period and most patients had a minimum of two LDL-C measurements (90,162; 84%). The majority of patients were receiving some form of lipid-lowering therapy (91,187) and 85,352 (79%) were prescribed recommended treatment, defined as statin monotherapy, statin combination therapy with ezetimibe, ezetimibe alone or a PCSK9 inhibitor; of these individuals, most were prescribed statin monotherapy. At least 50% of patients had a history of smoking and 10% remained current smokers. There were 58% of patients who attended a GP practice located in a major Australian city compared to 40% of patients in inner and outer regional locations. There was an approximately equal split of patients who attended a GP practice in the lower (deciles 1 to 5) and upper (deciles 6 to 10) deciles of the IRSAD. The average length of follow up was just over 5 years.

Overall, 56,212 of 107,664 (52%) patients had a recorded LDL-C result below the target of <1.8 mmol/L and 51,452 (48%) were above this target level (Table 11). On an unadjusted basis, a greater proportion of men achieved the recommended LDL-C target. Between 10% and 15% more patients with CAD met

PATIENTS WHO HAD MORE RECENT DOCUMENTATION OF CVD WERE LESS LIKELY TO MEET THE TARGET FOR LDL-C OR 'BAD' CHOLESTEROL

TABLE 10. CHARACTERISTICS OF PATIENTS IN THE HIGH RISK STUDY COHORT (N= 107,664)

CHARACTERISTIC	
Sex:	
Women	42,326 (39%)
Men	65,331 (61%)
Transfer gender	7 (<1%)
Age:	64.0 (sd 12.3) years
18-65 years	56,552 (52%)
> 65 years	51,112 (48%)
Index CVD occurrence:	
CAD	71,322 (66%)
Cerebrovascular disease	30,740 (29%)
Peripheral vascular disease	5,602 (5%)
Duration of CVD:	4.35 (sd 6.38) years
Pre 2010	45,227 (42%)
2010 to 2015	40,727 (38%)
2016 to 2019	21,710 (20%)
Number of LDL-C test results:	
1	17,502 (16%)
2	16,119 (15%)
3	13,739 (13%)
4	12,021 (11%)
5 or more	48,283 (45%)
Prescribed lipid-lowering medication:	
Recommended therapy	85,352 (79%)
Other therapy	5,835 (5.5%)
No evidence of treatment	16,477 (15.5%)
Smoking status:	
Current smoker	10,231 (10%)
Ex smoker	45,364 (42%)
Non-smoker	47,808 (44%)
Missing	4,261 (4%)
Geographical region:	
Major cities	62,017 (58%)
Inner regional	30,620 (28%)
Outer regional	13,381 (12%)
Remote/very remote	1,192 (1%)
Missing	454 (<1%)
Socio-economic status (IRSAD):	
Decile 1-5	54,863 (51%)
Decile 6-10	52,149 (48%)
Missing	652 (1%)
Length of follow-up	5.3 (sd 3.83) years

TABLE 11. PATIENTS WITH A REPRESENTATIVE LDL-C RESULT THAT ACHIEVED TARGET (<1.8 MMOL/L) AND DID NOT ACHIEVE TARGET (≥ 1.8 MMOL/L)

GROUP	ACHIEVED TARGET LDL-C <1.8 mmol/L (n= 56,212, 52%)	DID NOT ACHIEVE TARGET LDL-C ≥1.8 mmol/L (n= 51,452, 48%)
Sex*:		
Women	18,442 (44%)	23,884 (56%)
Men	37,767 (58%)	27,564 (42%)
Age		
18-65 years	28,859 (51%)	27,693 (49%)
> 65 years	27,353 (54%)	23,759 (46%)
Index CVD diagnosis		
CAD	40,597 (57%)	30,725 (43%)
Cerebrovascular disease	13,000 (42%)	17,740 (58%)
Peripheral vascular disease	2,615 (47%)	2,987 (53%)
Duration of CVD		
Pre 2010	26,832 (59%)	18,395 (41%)
2010 to 2015	20,256 (50%)	20,471 (50%)
2015 to 2019	9,124 (42%)	12,586 (58%)
Lipid lowering medication		
Recommended:	***51,495 (60%)***	***33,857 (40%)***
Statin therapy alone	44,855 (60%)	29,924 (40%)
Statin therapy and ezetimibe	5,000 (72%)	1,918 (18%)
Ezetimibe alone	1,625 (45%)	2,010 (55%)
PCSK9 inhibitor	15 (75%)	5 (25%)
Non-recommended/none:	***4,717 (21%)***	***17,595 (79%)***
Other therapy	3,103 (53%)	2,732 (47%)
No evidence of treatment	1,614 (10%)	14,863 (90%)
Geographical region		
Major cities	33,203 (54%)	28,814 (46%)
Inner regional	15,513 (51%)	15,107 (49%)
Outer regional	6,681 (50%)	6,700 (50%)
Remote/very remote	597 (50%)	595 (50%)
Socio-economic status (IRSAD)		
Decile 1-5	28,396 (52%)	15,428 (38%)
Decile 6-10	27,492 (53%)	26,467 (48%)

* excludes transfer gender cases due to small count

the ideal LDL-C goal level than patients with PVD and cerebrovascular disease. There were proportionally more patients who achieved the recommended LDL-C target with a longer duration of CVD. There were 60% of patients prescribed recommended lipid-lowering treatment who achieved the ideal LDL-C target and 40% who did not meet this cut off value. In regards to geographical regions and SES, approximately half of patients met the goal LDL-C level.

Cholesterol management and attainment of goal LDL-C levels

The representative LDL-C result by year of result date between 2010 and 2019 (Panel A) and histogram of LDL-C measurements (Panel B) are shown in Figure 8. The average LDL-C measurement was 1.87 mmol/L (SD 0.80 mmol/L). The LDL-C levels were below the secondary prevention target (shown by the horizontal line at 1.8 mmol/L in Panel A) before 2013 but not in any subsequent years. Tabulated below Figure 8, the percentage of patients who achieved the LDL-C treatment target ranged from 50% to 60%.

FIGURE 8: LDL-C LEVELS (A) AND HISTOGRAM OF LDL-C LEVELS (B), 2010 TO 2019

A

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Year	Total patients (n= 107,664)	Achieved target (%)
2010	2,945	1,642 (56%)
2011	3,600	2.040 (57%)
2012	4,967	2,956 (60%)
2013	6,304	3,560 (56%)
2014	10,118	5,307 (52%)
2015	11,318	5,896 (52%)
2016	13,213	6,750 (51%)
2017	15,941	7,984 (50%)
2018	24,534	12,367 (50%)
2019	14,724	7,710 (52%)

B

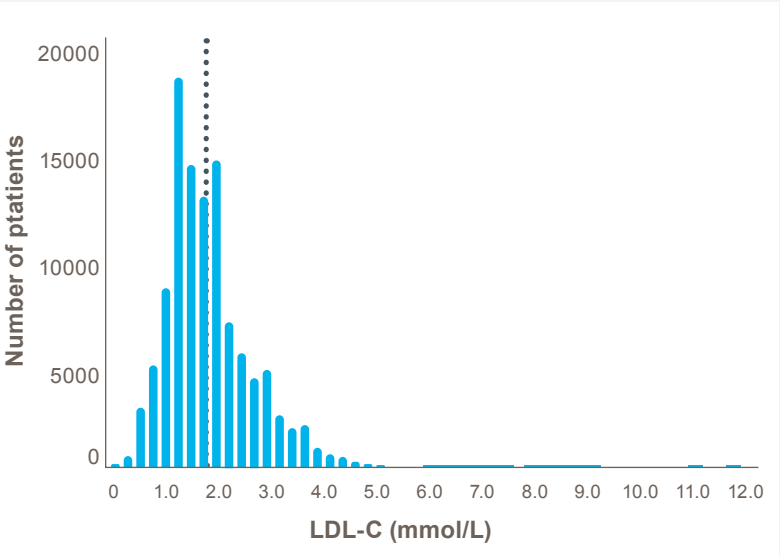
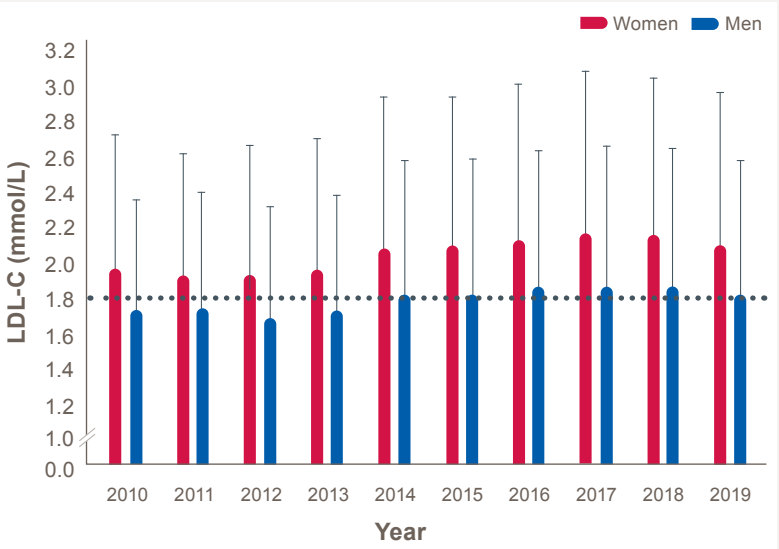


Figure 9 shows average LDL-C values recorded by year of result and gender between 2010 and 2019 (Panel A) and histograms of LDL-C results (Panel B). In any year, LDL-C was higher for women (2.03 mmol/L, SD 0.86 mmol/L) than men (1.76 mmol/L, SD 0.75 mmol/L). In all years, the LDL-C levels were above the secondary prevention target (shown by the horizontal line at 1.8 mmol/L in Panel A) for women and at or below the secondary prevention target in every year for men. The percentage who achieved the LDL-C treatment target ranged from 41% to 51% for women and 55% to 65% for men.

AT LEAST 44% OF AUSTRALIAN WOMEN WITH PRIOR CVD ARE BEING OPTIMALLY MANAGED FOR LDL-C OR 'BAD' CHOLESTEROL. THIS COMPARES TO 58% OF AUSTRALIAN MEN.

FIGURE 9: LDL-C LEVELS (A) AND HISTOGRAM OF LDL-C LEVELS (B) BY GENDER, 2010 TO 2019

A



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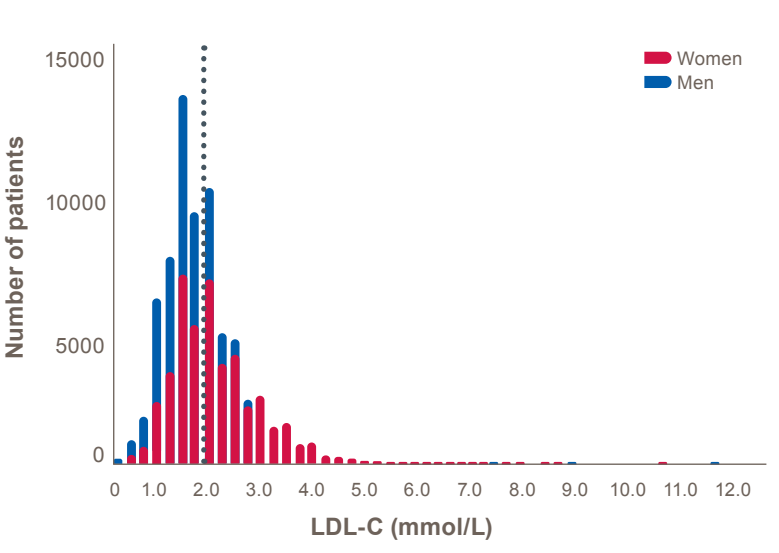
Year	Men (n= 65,331)	Achieved target (%)	Women (n= 42,326)	Achieved target (%)
2010	1,777	1,092 (61%)	1,168	550 (47%)
2011	2,174	1,334 (61%)	1,426	706 (50%)
2012	2,997	1,954 (65%)	1,970	1,002 (51%)
2013	3,735	2,324 (62%)	2,569	1,236 (48%)
2014	5,985	3,473 (58%)	4,132	1,834 (44%)
2015	6,694	3,898 (58%)	4,622	1,998 (43%)
2016	8,088	4,567 (56%)	5,124	2,182 (43%)
2017	9,661	5,347 (55%)	6,279	2,637 (42%)
2018	15,046	8,451 (56%)	9,487	3,915 (41%)
2019	9,174	5,327 (58%)	5,549	2,282 (41%)

B

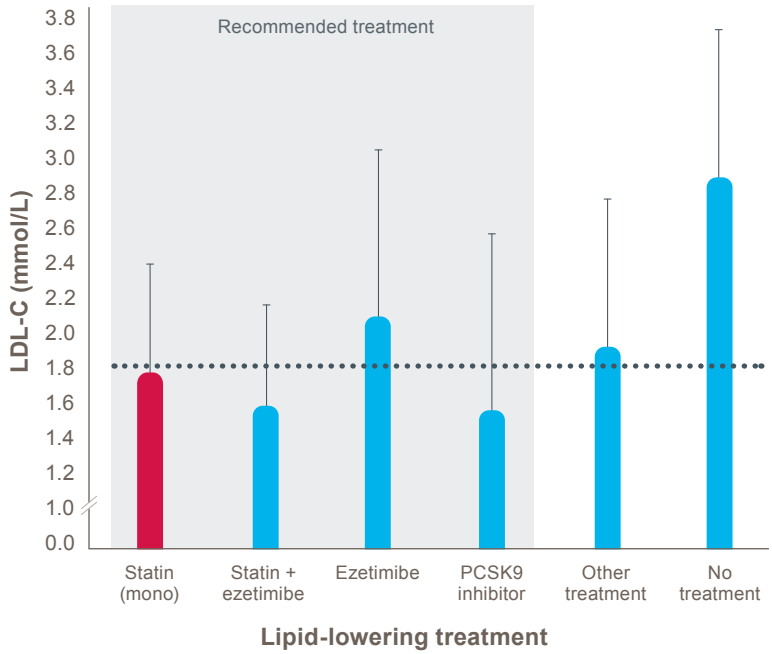


Representative LDL-C test results according to lipid-lowering treatment are shown in Figure 10 (Panel A) and intensity of statin monotherapy (Panel B). LDL-C levels were lower on average for patients who were prescribed recommended lipid-lowering modification therapy (1.69 mmol/L, SD 0.66 mmol/L) compared to non-recommended treatment (1.84 mmol/L, SD 0.83 mmol/L) or no therapy (2.81 mmol/L, SD 0.84 mmol/L). The LDL-C levels were below the secondary prevention target (shown by the horizontal line at 1.8 mmol/L in Panel A) for all recommended lipid-lowering therapies, except for patients prescribed ezetimibe therapy alone. Whereas LDL-C levels were marginally above target for patients prescribed non-recommended lipid-lowering treatment but more substantially above threshold by 1.0 mmol/L for patients who were not prescribed any lipid lowering therapy.

Overall, Figure 10 and Table 11 indicate that the proportion of patients who were receiving recommended lipid-lowering therapy and who were treated to the LDL-C target level (shown by the horizontal line at 1.8 mmol/L) was 60% compared to 21% of patients who were either prescribed non-recommended treatment or not prescribed any lipid lowering therapy (Table 11). A higher proportion of patients who were prescribed with combination statin and ezetimibe therapy (72%) and PCSK9 inhibitors (75%; albeit very few patients were prescribed this treatment, n=20) achieved the LDL-C treatment target, compared with 60% for statin monotherapy and 45% for ezetimibe alone. Of the patients on statin monotherapy (n=74,779), the proportion meeting the LDL-C target of <1.8 mmol/L progressively increased with

FIGURE 10: LDL-C LEVELS BY LIPID-LOWERING TREATMENT (A) AND STATIN MONOTHERAPY INTENSITY (B)

A



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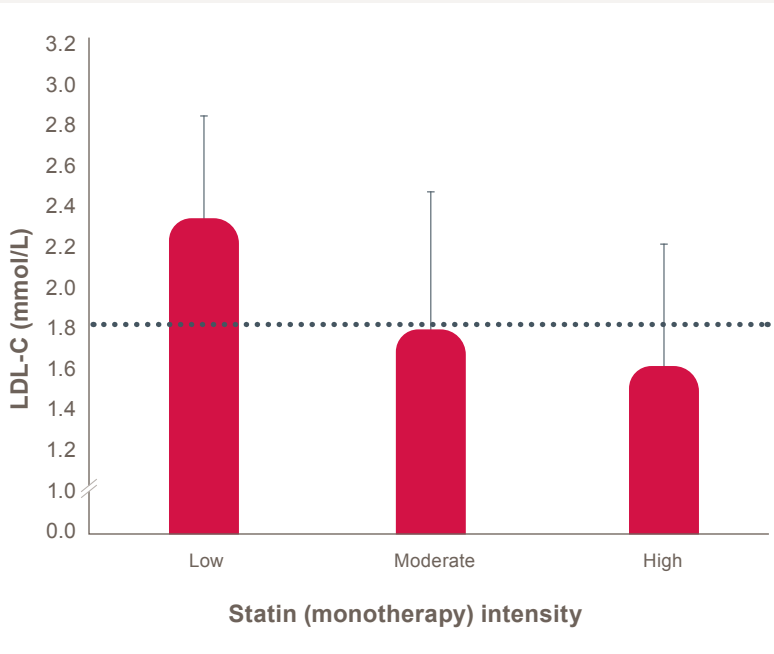
B



higher potency statin strength; with 26,550 of 40,198 (66%) patients on high intensity, 17,722 of 32,977 (54%) on moderate intensity and 522 of 1,530 patients (34%) on low intensity statins treated to target. There were 74 patients with missing strength information to determine statin intensity. In patients prescribed other forms of lipid-lowering treatment or not prescribed any lipid-lowering treatment, 53% and 10%, respectively, had an optimal LDL-C response.

Figure 11 highlights that average LDL-C levels were highest for cerebrovascular disease (2.05 mmol/L, SD 0.86 mmol/L) and PVD (1.95 mmol/L, SD 0.83 mmol/L) as their index CVD condition compared to 1.79 mmol/L (SD 0.76 mmol/L) for those classified with CAD. LDL-C levels were below target threshold (indicated by the horizontal line at 1.8 mmol/L) for patients with CAD only. Table 11 shows that less than half of patients with cerebrovascular disease (42%) and PVD (47%) achieved the LDL-C treatment target whilst a greater percentage of patients with CAD (57%) achieved the target of <1.8 mmol/L.

The representative LDL-C levels according to age group are shown in Figure 12 and highlight that they were above LDL-C target threshold (shown by the horizontal line at 1.8 mmol/L) for patients aged 18 to 65 years (1.90 mmol/L, SD 0.83 mmol/L) and above 65 years (1.84 mmol/L, SD 0.78 mmol/L). A similar number of patients of around 1 in 2 in each age group achieved the LDL-C treatment target (Table 11).

FIGURE 11: LDL-C LEVELS BY INDEX CVD CONDITION TYPE

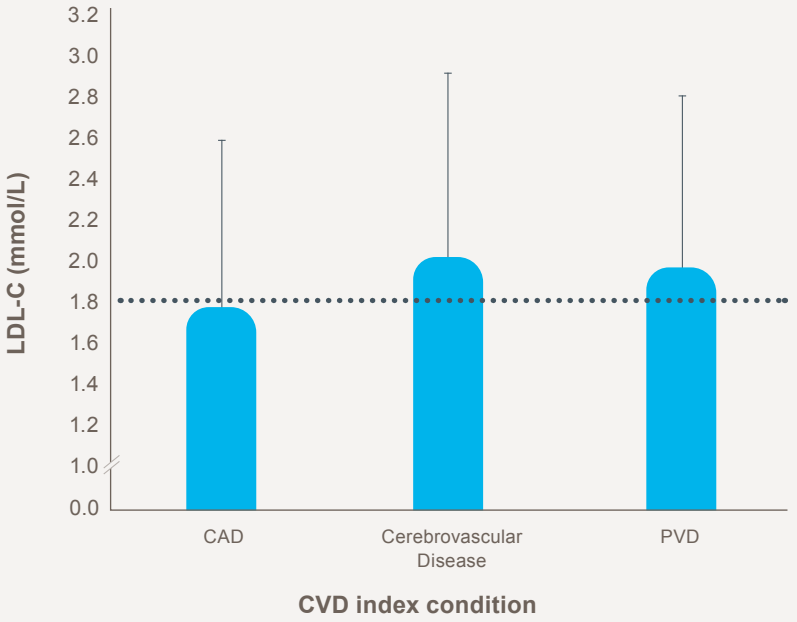


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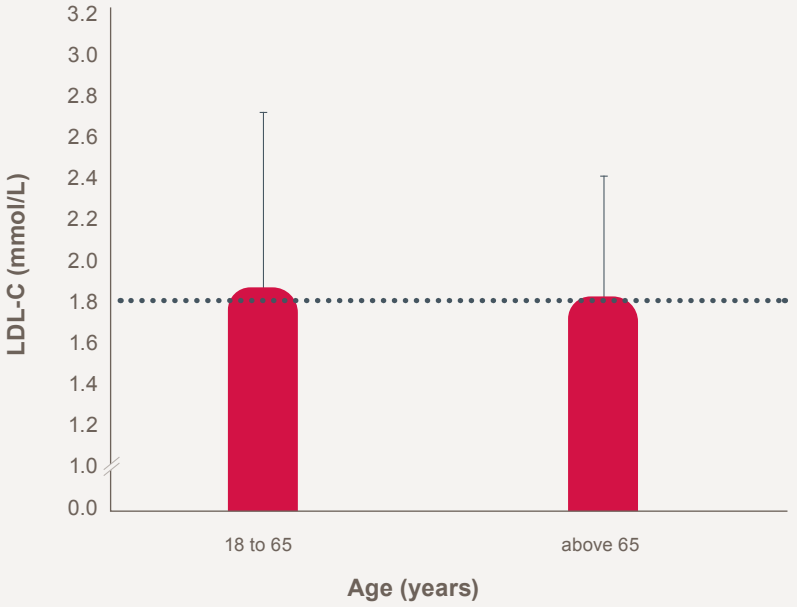
FIGURE 12: LDL-C LEVELS BY AGE GROUP



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DESPITE THE AVAILABILITY OF EFFECTIVE THERAPEUTICS AND CHOLESTEROL MANAGEMENT GUIDELINES, POTENTIAL TREATMENT GAPS HAVE BEEN IDENTIFIED IN INDIVIDUALS WITH PRIOR CVD.

FIGURE 13: LDL-C LEVELS BY GEOGRAPHICAL REGION

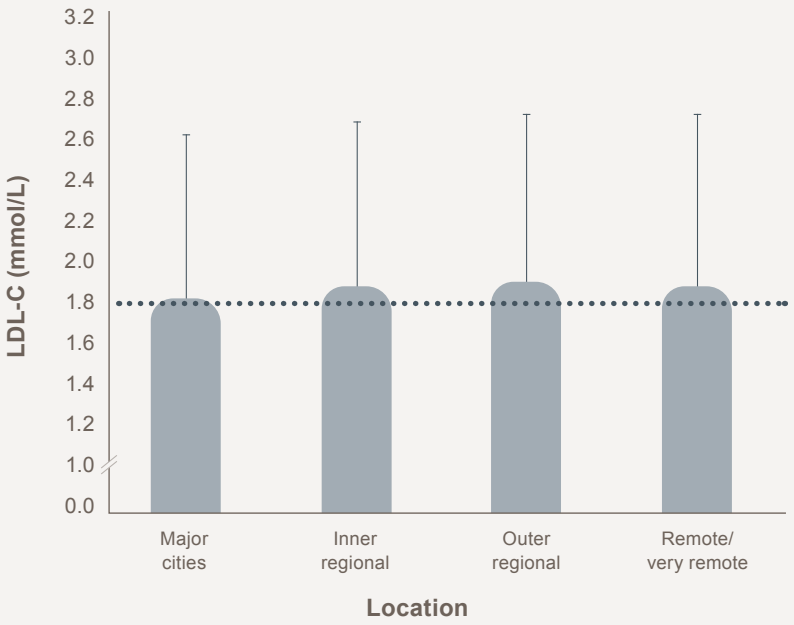

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Figure 13 shows the representative LDL-C levels according to geographical region. For all locations, the LDL-C measurements were above the LDL-C target threshold (shown by the horizontal line at 1.8 mmol/L). LDL-C levels were lowest for patients visiting a GP clinic in a major city (1.84 mmol/L (SD 0.79 mmol/L) but similar values of around 1.90 mmol/L were shown in all other locations. Table 11 shows that irrespective of location, a similar proportion of around half of patients achieved the LDL-C treatment target.

Table 12 summarises the representative LDL-C levels by state/territory and PHN in Australia. LDL-C levels were lowest in South Australia and highest in the Northern Territory. The range of LDL-C test results according to PHN was between 1.72 mmol/L and 2.00 mmol/L. Independent results for the representative values of LDL-C by PHN can be viewed in Table 12 below.

TABLE 12. LDL-C TEST RESULTS BY PRIMARY HEALTH NETWORKS WITHIN AUSTRALIAN STATES AND TERRITORIES

Primary Health Network	N	LDL-C (mean, SD)
New South Wales	**43,533**	**1.89 (0.79)**
Central and Eastern Sydney	4,505	1.87 (0.76)
Northern Sydney	2,173	1.90 (0.73)
Western Sydney	1,430	1.84 (0.76)
Nepean Blue Mountain	929	1.89 (0.82)
South Western Sydney	1,496	1.87 (0.81)
South Eastern NSW	4,582	1.79 (0.78)
Western NSW	1,686	1.77 (0.80)
Hunter New England And Central Coast	20,895	1.90 (0.80)
North Coast	5,209	1.95 (0.82)
Murrumbidgee	628	1.94 (0.87)
Victoria	**22,605**	**1.82 (0.78)**
North Western Melbourne	5,862	1.81 (0.77)
Eastern Melbourne	5,442	1.80 (0.76)
South Eastern Melbourne	2,648	1.88 (0.79)
Gippsland	1,963	2.00 (0.84)
Murray	4,012	1.85 (0.81)
Western Victoria	2,678	1.72 (0.76)
Queensland	**16,840**	**1.91 (0.84)**
Brisbane North	3,900	1.84 (0.81)
Brisbane South	4,474	1.92 (0.83)
Gold Coast	1,922	1.96 (0.86)
Darling Downs and West Moreton	1,931	1.89 (0.83)
Central Queensland and Sunshine Coast	3,153	1.94 (0.88)
Northern Queensland	1,460	2.00 (0.85)
South Australia	**3,304**	**1.73 (0.74)**
Adelaide	2,467	1.72 (0.74)
Country SA	837	1.78 (0.76)
Western Australia	**10,035**	**1.81 (0.79)**
Perth North	4,218	1.80 (0.78)
Perth South	4,488	1.78 (0.77)
Country WA	1,329	1.96 (0.86)
Tasmania	**8,681**	**1.93 (0.86)**
Northern Territory	**1,141**	**1.95 (0.89)**
Australian Capital Territory	**1,525**	**1.81 (0.80)**

Health economic analyses for the estimation of burden of disease

In 2017-2018, some 1,150,200 Australian adults reported having had at least one CVD event (heart, stroke or vascular disease) (4). In the Medicine Insight sample of 107,664 persons who had at least one LDL-C cholesterol test after an initial CVD occurrence between 2010 and 2019, 51,452 (or 48%) exceeded the recommended LDL-C levels (i.e. 1.8 mmol/L) based on their representative LDL-C measurement. This proportion was then applied to the 2017-18 Australian population with prior CVD to determine the population who would benefit (1,150,200 x 0.4779 = 549,681) if optimal cholesterol management were achieved.

If no action were taken with the sub-optimal treatment group (i.e. a 'do nothing' scenario), some 158,968 cardiovascular events (including 32,266 fatal events) would occur over the next five years. This number would rise to more than half a million cardiovascular events at the 20 year time horizon (111,255 fatal). The associated cost burden would rise from $15.7 billion in 5 years to $47.08 billion at 20 years.

Costs: Based on a 5 year time horizon and 70% rate of medication adherence, there would be a savings of $121.07 per additional patient (549,681 patients) whose cholesterol was optimally managed. Whilst mean management costs (the costs of outpatient consultations and cholesterol tests) increased by $101.21 per patient and the cost of statins by $47.42, these increases would be more than offset by reductions in the cost of hospitalisations (-$269.70). Intervention to bring the cholesterol level of all persons eligible at the national level to within the recommended target range would result in a savings of $66.6 million in the total cost burden over the 5 year period (Table 13).

The modelling indicates the substantial and growing cost burden arising from poor treatment of high cholesterol over the 20 year time horizon, and the significant cost savings which would be gained from optimal treatment at the 5 and 10 year timeframes. However, at 20 years, the intervention no longer results in cost savings. This is because patients with optimal LDL-C management are living longer, and the savings in CVD hospitalisations are insufficient to offset the LDL-C management costs.

TABLE 13. COSTS OF OPTIMAL CHOLESTEROL MANAGEMENT WITH 70% MEDICATION ADHERENCE: 5, 10 AND 20 YEAR TIME HORIZONS

	Time horizon		
	5 years	**10 years**	**20 years**
Total current cost burden of sub-optimal treatment group	$15.70 billion	$28.38 billion	$47.08 billion
Total cost saving of optimal treatment	-$66.55 million*	-$70.41 million*	$61.32 million#
Costs savings per patient			
Hospital costs	-$269.70	-$469.87	-$547.77
LDL-C management (outpatients and cholesterol testing)	$101.21	$249.27	$522.99
Medications	$47.42	$92.51	$136.34
Total cost saving per patient	-$121.07	-$128.08	$111.56

* this represents a reduction in the cost burden arising from optimal management

this represents an increase in the cost burden arising from optimal management

Benefits: Over the 5 year timeframe, optimal cholesterol management would result in savings of 0.0068 fatal and 0.0182 non-fatal CVD events and QALY gains of 0.0426 per person. For the national eligible population, this would equate to a reduction of 3,738 fatal and 10,004 non-fatal CVD events over the 5 year period. This will equate to gains of 23,444 QALYs (Table 14).

With optimal management, the benefits in terms of QALY gained and CVD events averted would rise over time.

Cost-effectiveness: At 5 and 10 years with 70% medication adherence, the intervention of optimal cholesterol treatment was found to be dominant (resulting in both health gains and cost savings) measured against the usual Australian threshold of $50,000 per QALY. However, at the 20 year timeframe, the intervention is no longer cost saving, but remains highly cost-effective at a cost of $492 per QALY gained.

Sensitivity analyses: Table 15 shows the key results if compliance to statin treatment is varied to either a lower (60%) or higher (80%) level.

TABLE 14. BENEFITS ARISING FROM OPTIMAL CHOLESTEROL MANAGEMENT WITH 70% MEDICATION ADHERENCE: 5, 10 AND 20 YEAR TIME HORIZONS

	Time horizon		
	5 year	**10 year**	**20 year**
QALY gains per person	0.0426	0.1152	0.2269
Total QALY gains	23,444	63,306	124,715
Fatal CVD events averted	3,738	3,298	5,552
Non-fatal CVD events averted	10,004	22,152	25,890
Cost per QALY gained	dominant	dominant	$492

Dominant means that the intervention would result in both health gains and cost-savings.

TABLE 15: BENEFITS ARISING FROM OPTIMAL CHOLESTEROL MANAGEMENT WITH 60% AND 80% MEDICATION ADHERENCE: 5, 10 AND 20 YEAR TIME HORIZONS

	Time horizon (60% compliance)		
	5 year	**10 year**	**20 year**
Total cost savings	-$55.62 million	-59.32 million	$64.41 million
Total QALY gains	22,916	62,046	113,696
Fatal CVD events averted	3,518	2,803	4,233
Non-fatal CVD events averted	8,795	20,558	20,668
Cost per QALY gained	dominant	dominant	$567
	Time horizon (80% compliance)		
	5 year	**10 year**	**20 year**
Total cost savings	-$80.21 million	-$89.66 million	$45.96 million
Total QALY gains	24,101	65,537	139,447
Fatal CVD events averted	4,068	3,738	7,366
Non-fatal CVD events averted	11,488	24,846	32,596
Cost per QALY gained	dominant	dominant	$330

Dominant means that the intervention would result in both health gains and cost-savings.

Strengths & limitations

The strengths of this analysis include the size and national coverage of the MedicineInsight data.

Use of clinical records reduces subjective biases often found in self-reported health surveys. MedicineInsight data comprise GP-identified diagnoses, pathology test results and medicines prescribed to patients including both PBS and Repatriation Schedule of PBS subsidised and private (non-subsidised) medicines.

There are a number of limitations that require comment in this large and contemporary snapshot of patient electronic medical records in primary care in Australia. These mainly arise from the naturalistic type of data collected as part of routine clinical practice and not in a systematic manner for research purposes. MedicineInsight data are dependent on the accuracy and completeness of data recorded in, and available for extraction from, the general practice clinical systems. Incomplete or missing information for the care of patients provided outside of a participating MedicineInsight practice or in another health care setting (e.g. specialist or hospital) could have occurred. Within the Australian health care system, patients are free to visit different practices and receive care from different clinicians but their data would only be available to MedicineInsight if the information were forwarded to their "usual" MedicineInsight participating GP and depending on the recording procedures of that general practice. Further, linkage between general practices within MedicineInsight is not possible and individuals could conceivably consult another GP who is participating in MedicineInsight and they could be included more than once in the data set. We have no way of determining these instances.

Including patients with only one LDL-C result could provide less reassurance that the study cohort was being managed at the MedicineInsight general practice and were not representative of regularly attending patients. However, the majority of the study cohort had repeat LDL-C testing (84%) and we ensured to review lipid-lowering prescription medication within 12 months prior to the LDL-C pathology test date to provide greater certainty that patients were receiving medical care at the practice. Patients with limited data may have less follow-up and reduced opportunity for improvement in LDL-C levels which were not adjusted for in analyses. Accounting for these factors and other confounding variables in the overall study cohort will be embedded in future analyses of these data.

Selection of high risk patients with prior CVD were identified using derived variables produced by criteria established by NPS MedicineWise. Since these data are used for quality improvement activities and regular reporting to providers and funding bodies, it is assumed that inconsistencies or discrepancies would be identified and rectified, however formal validation studies are soon to be published. Identification of conditions is dependent on GPs recording these items in their clinical software systems. Conditions may be underreported in MedicineInsight data depending on GPs' recording practices. Treatment was based on therapies prescribed and not dispensed and did not include medicines prescribed outside the MedicineInsight practice (e.g. by specialists or GPs not participating in the MedicineInsight program). Thus, determinations about lipid management should carefully be reviewed in the context of either one or both reasons of medication non-adherence and ineffective treatment.

The retrospective data analysis also did not enable us to differentiate between incident CVD events and subsequent CVD events using the existing data fields in MedicineInsight and recording of CVD-related events, hospitalisation or death was not always well defined. To do so would require linkage to other administrative datasets which was outside the scope of this report.

Lastly, these data describe a select patient population of participating general practices and caution should be applied when making extrapolations (i.e. beyond within cohort comparisons) to the broader primary care setting in Australia and, indeed, the wider population. However, characteristics of the MedicineInsight patient data is broadly comparable to patients who visited their GP in 2016-2017 (37).

The patient perspective

Alistair Blake: A family history of heart attack requires extra care

Father of three and accountant, Alistair Blake suffered a heart attack at the age of 41 on the tennis court. Nine years later, history repeated itself with a second heart attack on the tennis court, with a 100% blockage this time requiring a stent. Then last January, he had a cardiac arrest and required another stent. Since then, a 60% blockage in another artery has resulted in an additional stent.

For Alistair, who also enjoys regular walking and cycling, he knows genetics are working against him. He has a strong family history of heart disease, with his father dying of a heart attack on the badminton court in 1975. Since his mid-20s, Alistair has been having regular cholesterol checks and whilst it has been slightly elevated at times, he knows he is now in a high-risk category having suffered multiple cardiac events and that it is critical he keeps his cholesterol in check. Running an accounting practice, he has cut his working hours to a more manageable 40 hours and prioritises exercise every day. Alistair is part of a group called Cardiac Athletes, a global group dedicated to beating heart disease.

I'M LUCKY TO BE ALIVE. I'M IN A MAJOR FIGHT AGAINST HEART DISEASE.

Her cardiac arrest is never far from her mind

When 46-year-old mother of five, Kathryn Di Paolo set out for a trip to her cousin's house last October, she had no idea how her day would be turned upside down. By the time she arrived at the house, she was suffering severe chest pains. An ambulance was called, and she suffered a cardiac arrest from ischaemic heart disease, with 30 minutes of CPR and resuscitation required on the side of the highway. Kathryn spent two days in a coma and six nights in hospital and required two stents.

She doesn't have a family history of heart disease and her cholesterol had been fairly well maintained. However, as she continues her road to recovery, Kathryn knows that maintaining her risk factors like cholesterol will now be especially critical to ensure that she doesn't suffer another severe cardiac event. It is something that plays on her mind and is a source of significant stress. Her kids are young adults and teenagers now but they all live at home and depend on her.

I DON'T WANT TO HAVE ANOTHER HEART ATTACK. MAINTAINING MY CHOLESTEROL IS A TOP PRIORITY.

Conclusions

THE 'CODE RED' REPORT HIGHLIGHTS THE CRITICAL AND TIMELY OPPORTUNITY TO INVEST IN GREATER AWARENESS AND SUPPORT FOR CHOLESTEROL MANAGEMENT IN HIGH-RISK PATIENTS.

This report provides contemporary real-world evidence of cholesterol management and attainment of goal LDL-C levels in secondary CVD prevention observed in general practices in Australia.

The majority of patients had repeated testing for LDL-C (84%). Our findings showed an average LDL-C level of 1.87 mmol/L and 48% of patients who did not achieve an optimal LDL-C response <1.8 mmol/L.

Women recorded higher LDL-C values than men and 56% had a sub-optimal LDL-C level compared to 42% of men. The proportion of patients with a sub-optimal LDL-C response was greatest for cerebrovascular disease (58%) and for patients who had a diagnosis of CVD more recently in the past 5 years (58%). The majority of patients (79%) were receiving recommended lipid-lowering therapy for secondary prevention of CVD. Of those who were prescribed recommended medication, 40% did not achieve an optimal LDL-C response. The proportion of patients who achieved the LDL-C target was higher for those who were prescribed more intensive lipid-lowering therapies.

We found 4 in 5 high risk patients with secondary CVD attending primary care being prescribed with recommended lipid-lowering medication. The rate of 79% that we reported is higher than the CONCORDANCE hospital registry of 55%, which defined appropriate therapy more stringently as "intensive" lipid lowering therapy (22), and is in accord with data from the REACH general practice registry study which limited the assessment of prescribing rates to statin therapy only (25). It is unknown from these data the timing of prescribing and whether it was at the stage of discharge following a hospitalisation for a CVD event, which is a positive predictor of longer term maintenance of therapy (44, 45). Our finding of reported lipid-lowering prescription medication is below rates reported in the EUROASPIRE (European Action Secondary and Primary Prevention) IV study undertaken at 78 centres from 24 European countries among patients with coronary disease, which found 86% of participants on statin therapy (46).

Despite a reasonable number of patients (but not all) being prescribed lipid-lowering medications, LDL-C risk factor control remained inadequate. At best using primarily the lowest LDL-C levels achieved in this high risk patient cohort, 2 out of 5 patients who were receiving recommended lipid-lowering therapy had a recorded LDL-C result above the target levels advocated in clinical guidelines. Our present findings of the remaining 60% who achieved the LDL-C target of <1.8 mmol/L are not consistent with a larger primary care data audit of 130,926 patients with CAD

between 2014 and 2018, whereby less than a third of patients (37.5% of men and 22.7% of women) achieved recommended treatment targets (24). They are also incongruous with the multi-national EUROASPIRE IV survey which showed 19.5% (22% of men and 17% of women) had LDL-C <1.8 mmol/L (46). One explanation for our findings being almost double and more favorable may be explained by the LDL-C indicator used – we mainly chose the minimum LDL-C result achieved.

Women were less likely to achieve LDL-C <1.8 mmol/L and this gender difference is in accordance with other national and international survey findings (24, 46).

The more widespread treatment gap in women may be explained by commonly held misperceptions about these individuals being a lower risk group for which more intensive lipid lowering may not be a key consideration and treatment adherence more problematic. Likewise, patients who had a more recent CVD occurrence were also less likely to achieve target LDL-C levels. This could imply that treatment combined with healthy eating and lifestyle advice has had less time to have an impact or that patients are not managed actively and soon enough to achieve an optimal LDL-C response. Our findings also indicate the potential impact of improving treatment targets in the context of cerebrovascular disease in particular. Leading factors influencing lipid-lowering prescribing behaviours in stroke is the presence of dyslipidaemia and the perception that lipid-lowering therapeutics are usually considered for the prevention of CAD (47).

At the very least, these data provide an important indicator of LDL-C levels in secondary prevention patients being managed in primary care in Australia. These LDL-C test results represent the levels that GPs would contemplate in making pharmacological treatment decisions to achieve LDL-C targets. GPs are heavily relied upon to provide health care; Medicare statistics from the 2018/19 financial year indicate that 88% of the Australian population visited their GP at least once (48) and many patients (84%) self reported making multiple visits per year (49). Patients tend to visit their GP more than any other (non-GP) specialist (84.3% for GPs and 37.4% for medical specialists) and older individuals, women, and people from lower socioeconomic positions visit their GP more frequently (49). As such, GPs are a pivotal player in supporting the management of secondary CVD prevention.

Therefore, there remains scope to improve lipid levels in these patients who would highly benefit from more proactive management by increasing the intensity of treatment. A meta-analysis showed that more potent statin therapy has greater efficacy compared to less intensive regimens and is associated with added improvements in CVD event rates (7). Further, the IMPROVE-IT trial highlighted that combination therapy with a statin plus ezetimibe resulted in reduced risk of major cardiovascular events compared to statin therapy alone in CAD patients (9). Thus, the application of greater intensity and or combination lipid-lowering therapeutics increases the likelihood of achieving LDL-C control (earlier) and the ramifications of not reaching target include the risk of a recurrent CVD event, which could prove to be more fatal in the future.

The cost of elevated lipid levels in Australia takes a significant toll and could be improved with better management. Our study showed that with intervention of lipid-lowering treatment to achieve optimal LDL-C targets, savings of $66.6 million in the total cost burden, 13,742 fatal and non-fatal CVD related events would be averted and health gains of 23,444 in quality survival would ensure over a 5 year period. Greater benefits were estimated over longer 10 and 20 year time periods, by which time the cost saving is lost but still representing a health benefit for CVD. Given the enormous investment in managing cholesterol we are not gaining the full potential from subsidised lipid-lowering therapies.

These findings highlight that secondary CVD patients warrant more attention. More patients need to be managed more actively for reducing LDL-C levels.

The World Heart Federation Cholesterol Roadmap provides guidance to achieve this goal (3). Known effective strategies include increasing the intensity of statin doses and/or considering combination therapy when goal levels aren't achieved. The provision of subsidised medicines via the PBS and the removal of patents and use of generic drugs have made lipid-lowering medications more affordable. A systematic and stepped care approach to the management of cholesterol in secondary CVD prevention patients is recommended, similar to what has been achieved in

hypertension management (50). However, it is acknowledged that medication adherence can be poor and getting patients to take their medications regularly requires a greater understanding about cholesterol and the impact that elevated LDL-C can have for existing CVD sufferers. This is particularly important for lipid management in recognition of the detrimental media exposure on the adverse effects of statin therapy (51), that could negatively influence patient attitudes and perceptions towards statin therapy (52). Cardiac rehabilitation programs can enhance patient knowledge, understanding and self-care abilities and provide scope for patients to receive (nurse-led) clinical and lifestyle advice, treatment and continuity of care.

Elevated cholesterol represents an important heath issue and is a CODE RED signal to combat the future burden of secondary CVD within our ageing population. Despite the availability of effective lipid-lowering therapies, LDL-C levels remain above recommended Australian targets in secondary CVD prevention observed in general practice. This mandates a more proactive and intensive approach to reduce elevated cholesterol in order to avert a recurrent CVD event in patients already at high risk. Ongoing protection from this key contributor to CVD would require the impact of elevated cholesterol to be more fully recognised by government, the health care workforce and consumers, and the factors influencing the treatment gap to be better understood so that successful strategies could be implemented.

Call to action

Education

Australia needs greater awareness and education campaigns to **improve knowledge about treatment to target and the importance of intense treatment of secondary prevention of CVD** for both clinicians and patients. A cholesterol level that is continually above recommended targets is not okay. We need to treat people to target to improve health outcomes.

Wider access to PCSK9 inhibitors

in Australia these have been extended from familial homozygous hypercholesterolaemia or familial heterozygous hypercholesterolaemia, to include individuals with atherosclerotic CVD and additional risk factors. We are in support of a wider and more quantitative approach to access PCSK9 inhibitors, taking into account both the high cost of these therapeutics and potential health benefits.

Health system reform

Australia needs a re-design of hospital involvement with secondary CVD prevention. The hospital focus on performing procedures can compromise a holistic approach to effectively treat patients. **Patients admitted to hospital should have a follow-up lipid profile** which could be routinely conducted by nurses. This should be considered part of hospital treatment guidelines to improve the current system, with financial incentives attached to those hospitals that can demonstrate implementation of this.

Effective lipid lowering medications

Australia should consider **revision of the PBS criteria for lipid-modifying drugs**. Easier access to ezetimibe in patients who are prescribed statin therapy would enable more patients to reach target. The Baker Heart and Diabetes Institute will raise this issue with the Cardiac Society of Australia and New Zealand, the Heart Foundation and other cardiovascular health and research organisations to seek support for a submission to the Pharmaceutical Benefits Advisory Committee (PBAC).

Identification of higher risk patients

Australian cholesterol management guidelines need to reflect **acceptance of risk stratification in secondary CVD prevention** in order to identify who may benefit most from more intensive treatment. Historically, all secondary prevention patients are deemed “at risk”, but there is a broad spectrum of risk. If we are to consider expensive lipid-lowering therapy in secondary prevention, such as PCSK9 inhibitors, we need to target them at those with the greatest risk. Risk scores need to be integrated into current guideline recommendations.

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References

1. Feingold KR, Grunfeld C. Introduction to Lipids and Lipoproteins. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, Dungan K, Grossman A, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000.
2. Pang J, Sullivan DR, Brett T, Kostner KM, Hare DL, Watts GF. Familial Hypercholesterolaemia in 2020: A Leading Tier 1 Genomic Application. Heart Lung Circ 2020;29(4):619-633.
3. Murphy A, Faria-Neto JR, Al-Rasadi K, Blom D, Catapano A, Cuevas A, et al. World Heart Federation Cholesterol Roadmap. Glob Heart 2017;12(3):179-197 e5.
4. Australian Bureau of Statistics. National Health Survey: First Results, 2017-18. Canberra, ACT, Australia: ABS cat. no. 4364.0.55.001.
5. Rossouw JE, Lewis B, Rifkind BM. The value of lowering cholesterol after myocardial infarction. N Engl J Med 1990;323(16):1112-9.
6. Aung PP, Maxwell HG, Jepson RG, Price JF, Leng GC. Lipid-lowering for peripheral arterial disease of the lower limb. Cochrane Database Syst Rev 2007(4):CD000123.
7. Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 2010;376(9753):1670-81.
8. Collins R, Reith C, Emberson J, Armitage J, Baigent C, Blackwell L, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. Lancet 2016;388(10059):2532-2561.
9. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. N Engl J Med 2015;372(25):2387-97.
10. Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J 2017;38(32):2459-2472.
11. National Vascular Disease Prevention Alliance. Guidelines for the assessment of absolute cardiovascular disease risk: National Heart Foundation of Australia, 2009.
12. Royal Australian College of General Practitioners. Guidelines for preventive activites in general practice. 9th ed. East Melbourne, Vic: RACGP, 2018.
13. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2019;139(25):e1082-e1143.
14. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J 2019.
15. Stroke Foundation (2019). Clinical Guidelines for Stroke Management. Melbourne, Australia.
16. Sabatine MS, Giugliano RP, Wiviott SD, Raal FJ, Blom DJ, Robinson J, et al. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. N Engl J Med 2015;372(16):1500-9.
17. Robinson JG, Farnier M, Krempf M, Bergeron J, Luc G, Averna M, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. N Engl J Med 2015;372(16):1489-99.
18. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. N Engl J Med 2017;376(18):1713-1722.
19. Cannon CP, Khan I, Klimchak AC, Reynolds MR, Sanchez RJ, Sasiela WJ. Simulation of Lipid-Lowering Therapy Intensification in a Population With Atherosclerotic Cardiovascular Disease. JAMA Cardiol 2017;2(9):959-966.

20. Kumar R, Tonkin A, Liew D, Zomer E. The cost-effectiveness of PCSK9 inhibitors - The Australian healthcare perspective. Int J Cardiol 2018;267:183-187.

21. Aliprandi-Costa B, Ranasinghe I, Turnbull F, Brown A, Kritharides L, Patel A, et al. The design and rationale of the Australian Cooperative National Registry of Acute Coronary care, Guideline Adherence and Clinical Events (CONCORDANCE). Heart Lung Circ 2013;22(7):533-41.

22. Brieger D, D'Souza M, Hyun K, Weaver JC, Kritharides L. Intensive lipid-lowering therapy in the 12 months after an acute coronary syndrome in Australia: an observational analysis. Med J Aust 2019;210(2):80-85.

23. Stroke Foundation. National Stroke Audit – Rehabilitation Services Report 2016. Melbourne, Australia.

24. Lee CMY, Mnatzaganian G, Woodward M, Chow CK, Sitas F, Robinson S, et al. Sex disparities in the management of coronary heart disease in general practices in Australia. Heart 2019;105(24):1898-1904.

25. Reid C, Nelson MR, Shiel L, Chew D, Connor G, DeLooze F. Australians at risk: management of cardiovascular risk factors in the REACH Registry. Heart Lung Circ 2008;17(2):114-8.

26. Banks E, Crouch SR, Korda RJ, Stavreski B, Page K, Thurber KA, et al. Absolute risk of cardiovascular disease events, and blood pressure- and lipid-lowering therapy in Australia. Med J Aust 2016;204(8):320.

27. Atkins ER, Geelhoed EA, Knuiman M, Briffa TG. One third of hospital costs for atherothrombotic disease are attributable to readmissions: a linked data analysis. BMC Health Serv Res 2014;14:338.

28. Institute for Health Metrics and Evaluation. Global Health Data Exchange. http://ghdx.healthdata.org/gbd-results-tool. Accessed 6 December 2019.

29. National Heart Foundation of Australia. The economic burden of hypercholesterolaemia. National Heart Foundation of Australia, November 2018.

30. Department of Human Services. Expenditure and prescriptions twelve months to 30 June 2019. Canberra: Department of Human Services.

31. Department of Health. Medicare Benefits Scheme Online. http://www9.health.gov.au/mbs/search.cfm. Accessed 6 December 2019.

32. Independent Hospital Pricing Authority. National Hospital Cost Data Collection, AR-DRG Cost Weight tables V8.0x, Round 21 (Financial year 2016-17). https://www.ihpa.gov.au/publications/national-hospital-cost-data-collection-ar-drg-cost-weight-tables-v80x-round-21. Accessed 6 December 2019.

33. Australian Bureau of Statistics. Gender Indicators, Australia, Sep 2018. https://www.abs.gov.au/AUSSTATS/abs@.nsf/allprimarymainfeatures/CB1290DF0D3F4D5DCA2584A4001711D6?opendocument. Accessed 6 December 2019.

34. Australian Bureau of Statistics. Employee Earnings and Hours, Australia, May 2018. https://www.abs.gov.au/ausstats/abs@.nsf/latestProducts/6306.0Media%20Release1May%202018. Accessed 6 December 2019.

35. George B, Harris A, Mitchell A. Cost-effectiveness analysis and the consistency of decision making: evidence from pharmaceutical reimbursement in australia (1991 to 1996). Pharmacoeconomics 2001;19(11):1103-9.

36. NPS MedicineWise. MedicineInsight. https://www.nps.org.au/medicine-insight. Accessed 6 December 2019.

37. Busingye D, Gianacas C, Pollack A, Chidwick K, Merrifield A, Norman S, et al. Data Resource Profile: MedicineInsight, an Australian national primary health care database. Int J Epidemiol 2019.

38. Colantonio LD, Rosenson RS, Deng L, Monda KL, Dai Y, Farkouh ME, et al. Adherence to Statin Therapy Among US Adults Between 2007 and 2014. J Am Heart Assoc 2019;8(1):e010376.

39. Romanelli RJ, Segal JB. Predictors of statin compliance after switching from branded to generic agents among managed-care beneficiaries. J Gen Intern Med 2014;29(10):1372-8.

40. Cholesterol Treatment Trialists Collaboration, Fulcher J, O'Connell R, Voysey M, Emberson J, Blackwell L, et al. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. Lancet 2015;385(9976):1397-405.

41. Australian Bureau of Statistics. Causes of Death, Australia 2017. https://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/3303.0~2017~Main%20Features~Australia's%20leading%20causes%20of%20death,%202017~2. Accessed 6 December 2019.

42. Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, et al. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. N Engl J Med 2019;380(1):11-22.

43. Australian Institute of Health and Welfare. Cardiovascular disease 2019. Cat. no: CVD 83. Canberra: AIHW, 2019.

44. Rosenson RS, Kent ST, Brown TM, Farkouh ME, Levitan EB, Yun H, et al. Underutilization of high-intensity statin therapy after hospitalization for coronary heart disease. J Am Coll Cardiol 2015;65(3):270-7.

45. Thrift AG, Kim J, Douzmanian V, Gall SL, Arabshahi S, Loh M, et al. Discharge is a critical time to influence 10-year use of secondary prevention therapies for stroke. Stroke 2014;45(2):539-44.

46. Kotseva K, Wood D, De Bacquer D, De Backer G, Ryden L, Jennings C, et al. EUROASPIRE IV: A European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries. Eur J Prev Cardiol 2016;23(6):636-48.

47. Canavero I, Cavallini A, Perrone P, Magoni M, Sacchi L, Quaglini S, et al. Clinical factors associated with statins prescription in acute ischemic stroke patients: findings from the Lombardia Stroke Registry. BMC Neurol 2014;14:53.

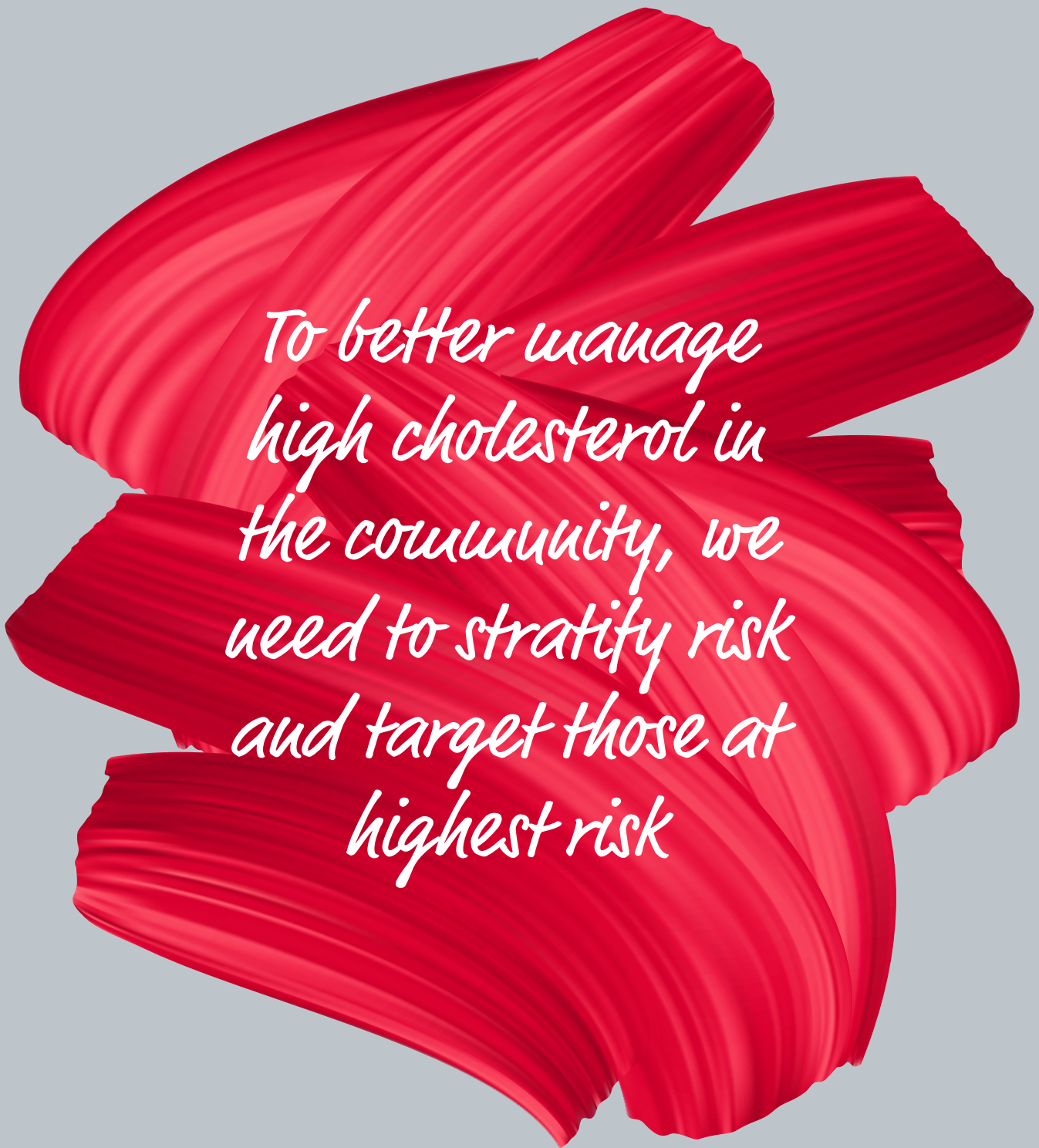
48. Department of Health. Annual Medicare statistics: Financial year 1984–85 to 2018–19. https://www1.health.gov.au/internet/main/publishing.nsf/Content/Annual-Medicare-Statistics. Accessed 23 March 2020.

49. Australian Institute of Health and Welfare. Patient experiences in Australia by small geographic areas in 2017–18. Cat. no: HFP 52. Canberra: AIHW, 2020.

50. Stewart S, Carrington MJ, Swemmer CH, Anderson C, Kurstjens NP, Amerena J, et al. Effect of intensive structured care on individual blood pressure targets in primary care: multicentre randomised controlled trial. BMJ 2012;345:e7156.

51. Mach F, Ray KK, Wiklund O, Corsini A, Catapano AL, Bruckert E, et al. Adverse effects of statin therapy: perception vs. the evidence - focus on glucose homeostasis, cognitive, renal and hepatic function, haemorrhagic stroke and cataract. Eur Heart J 2018;39(27):2526-2539.

52. Nielsen SF, Nordestgaard BG. Negative statin-related news stories decrease statin persistence and increase myocardial infarction and cardiovascular mortality: a nationwide prospective cohort study. Eur Heart J 2016;37(11):908-916.


To better manage
high cholesterol in
the community, we
need to stratify risk
and target those at
highest risk

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