Research Review™
EDUCATIONAL SERIES

Secondary events in cardiovascular disease – Triglycerides as a marker of residual risk

Making Education Easy 2024

Independent commentary by Associate Professor John Amerena

Associate Professor John Amerena trained in Melbourne before spending four years in the United States at the University of Michigan. Over that period of time he worked in the fields of hypertension and hyperlipidemia, before returning to Australia where he is now a Cardiologist at Barwon Health. He currently has a joint appointment in the Department of Clinical and Biomedical Sciences at the University of Melbourne and the Department of Epidemiology and Preventive Medicine at Monash University. He is the director of the Geelong Cardiology Research Unit, which is currently involved in many phase II-III clinical trials. While still actively researching in hypertension, his focus has changed to research in antithrombotic/antiplatelet therapies, particularly in the context of acute coronary syndromes and atrial fibrillation. Heart failure is also a major interest, and he is also the Director of the Heart Failure Programme at Barwon Health. He is well published in these areas, as well as in many other areas of cardiovascular medicine.

Abbreviations used in this review:

ACEIs = Angiotensin-Converting Enzyme Inhibitors
ACS = acute coronary syndromes
AF = atrial fibrillation
ASCVD = atherosclerotic cardiovascular disease
BP = blood pressure
CI = confidence interval
CV = cardiovascular
CVD = cardiovascular disease
dL = decilitre
EPA = eicosapentaenoic acid
HDL = high-density lipoproteins
HDL-C = high-density lipoproteins cholesterol
HR = hazard ratio
IVUS = intravascular ultrasound
L = litre
LDL = low-density lipoproteins
LDL-C = low-density lipoproteins cholesterol
LV = left ventricular
Mg = milligram
mmol = millimole
MTP = microsomal triglyceride transfer
NOACs = novel oral anticoagulants
PBS = Pharmaceutical Benefits Scheme
PCKS9 = proprotein convertase subtilisin/kexin type 9
TG = triglyceride
TGA = Therapeutic Goods Administration
TRL = triglyceride-rich lipoproteins
VLDL = very low-density lipoproteins

Claim CPD/CME points Click here for more info.

Research Review Australia is now on LinkedIn. Follow us to keep up to date.

This educational review provides an overview of the role of triglycerides in secondary cardiovascular events, with an emphasis on the importance of ensuring elevated triglycerides are managed to mitigate risk of cardiovascular events.

Cardiovascular Disease in Australia

Advancements in diagnostics, medications and clinical interventions have achieved declines in cardiovascular disease (CVD) related mortality over the past decade. Despite this, more than four million (or one in six) Australians are living with CVD. On average, every day 1,619 Australians are hospitalised and 118 will die from CVD.[1]

Secondary cardiovascular events

Cardiac function often deteriorates with recurrent cardiovascular events. Individuals who have experienced a primary cardiovascular event, such as a myocardial infarction or stroke, are at a substantially heightened risk of experiencing subsequent acute cardiovascular incidents. Interestingly, evidence suggests that the risk of a secondary event of the same kind as the first event is three to five-fold higher as compared to experiencing an event of a different kind in a different vascular territory.[2]

It is estimated that 20% of strokes are recurrent events, more specifically, around 10% of people who have a stroke will experience a second stroke within the seven days after the initial event. It is also estimated that one in every ten individuals who have experienced a myocardial infarction will experience recurrent events within one year.[2]

This increased risk highlights the critical importance for implementation of robust preventive strategies, including lifestyle modifications and appropriate pharmacotherapy, to mitigate elevated risk and enhance the long-term prognosis of patients who have survived a primary cardiovascular event.

Preventing secondary cardiovascular events

While exercise-based cardiac rehabilitation, lifestyle modifications and pharmacological interventions are recommended for all patients with symptomatic coronary artery disease to reduce the risk of cardiovascular mortality,[3] estimates suggest only 50% of patients receive complete, guideline directed treatment.[2]

Lifestyle modifications to stabilise blood sugar levels and to reduce cardiac inflammation, weight and blood pressure are known to significantly reduce risk of secondary cardiovascular events. These include smoking cessation, dietary modifications, limiting alcohol intake, weight control, and participating in regular exercise and physical activity.

In addition, pharmacological therapy (often a combination of therapies) is critical for reducing the risk of secondary cardiovascular events (**Table 1**).

Pharmacological therapy may include combinations of agents with varying modes of action. Anti-platelet agents such as aspirin and P2Y12 inhibitors prevent thrombus formation by preventing platelet aggregation. Anticoagulants like warfarin and non-vitamin K antagonist oral anticoagulants (NOACs) are crucial for preventing atrial fibrillation-related thromboembolic stroke. Lipid-lowering therapy with high-intensity statins like atorvastatin and rosuvastatin enable reductions in low-density lipoprotein (LDL). PCSK9 inhibitors reduce the degradation of LDL receptors, resulting in increased LDL-C clearance. Therapies targeting neurohormonal pathways, such as beta-blockers and renin-angiotensin antagonists reduce cardiac remodelling, and slow disease progression, especially in patients with impaired heart function.[4]

These evidence-based pharmacological therapies are integral components of secondary prevention, reducing the risk of recurrent cardiovascular events and improving quality of life.[4]

Table 1. Medications for prevention of secondary cardiovascular events[2,4]

Medication class	Mode of action	Recommended duration of treatment	Estimated risk-reduction
Aspirin[5]	Anti-platelet	Lifelong	25-30%
P2Y12 inhibitors[6]	Anti-platelet	12 months*	20-24%
Anticoagulants[7,8] In patients with AF and with thrombotic disorders	Clotting factor inhibition	Based on regular evaluation of thrombotic vs. bleeding risk	Varies with product
Lipid lowering therapy - Statins[9] PCSK9 Inhibitors (in appropriate pts)[10]	Cholesterol lowering	Lifelong[9]	20% per 1 mmol/L reduction in LDL[9] 50-60% LDL reduction[10]
Beta-blockers [11]	Neurohormonal antagonist, anti-anginal and anti-arrhythmic	At least 1-year†	23%
Renin-angiotensin antagonists[12]	Neurohormonal antagonist and anti-hypertensive	Lifelong	18%

Adapted from Baker Heart and Diabetes Institute No Second Chances report
*Shorter or longer treatment may be reasonable in select patients;
† Optimal treatment duration unknown; ‡ Not indicated in combination with dual anti-platelet therapy.

Expert comment

Once a patient has had a cardiovascular (CV) event, they are at increased risk of recurrent events, and it essential we use the proven secondary prevention strategies to reduce the risk of subsequent events. Antiplatelet therapy is primarily aspirin, but clopidogrel can be used in aspirin intolerant patients. Angiotensin-Converting Enzyme Inhibitors (ACEIs) have proven benefit in reducing secondary events and should be continued indefinitely if the blood pressure (BP) will tolerate. Beta-blockers are recommended post-acute coronary syndromes (ACS), and although many guidelines suggest indefinite treatment, there is a growing trend to discontinue them one to two years post ACS in patients who have undergone complete revascularisation and have normal left ventricular (LV) function. High dose atorvastatin post MI improved outcomes in the MIRACL study, as did high dose simvastatin/ezetimibe in the IMPROVE-IT study.[13] Now the PCSK9 inhibitors have demonstrated improvement in outcomes post event in patients whose LDL is > 1.8 mmol/L despite maximally tolerated dose of statin and ezetimibe, and are available in Australia for this patient cohort.[10] Australian guidelines for lipid management are not current, and at present suggest a one size fits all approach whether the patient is at low, intermediate or high risk of CV events. The European and US guidelines are much more contemporary, and based on the evidence from recent clinical trials, recommend a target LDL of < 1.4mmol/L in patients at high or very high risk (such as those who have already had an ACS). Advice regarding lifestyle modification is important in patient management, but is disappointingly seldom fully implemented. Despite the best available therapies for secondary prevention, there is still a treatment gap as recurrent events still occur.

Elevated plasma triglyceride[14]

Epidemiological and genetic studies have established a strong and causal relationship between plasma triglyceride (TG) levels and atherosclerotic cardiovascular disease (ASCVD).[14]

Elevated TG levels indicate an increased presence of triglyceride-rich lipoproteins (TRLs) and their cholesterol-enriched remnants in the bloodstream, a result of lipolysis. Plasma TG and cholesterol are water-insoluble molecules, which are transported in the aqueous medium of plasma within lipoproteins. Lipoproteins consist of a lipid-filled core surrounded by phospholipids and specific proteins. Lipoproteins, including chylomicrons, very low-density lipoproteins (VLDL), LDL, lipoprotein (a), and high-density lipoproteins (HDL), play crucial roles in directing lipid metabolism. They do this by interacting with lipolytic enzymes and cell membrane receptors. Elevated levels of plasma TG and cholesterol which exceed the bodies physiological requirements increase the risk of developing ASCVD, promoting atherosclerotic plaque formation in arteries. In addition, genetic variants influencing plasma TG levels are associated with an altered risk of ASCVD events. It's believed that the cholesterol-enriched "remnants" of chylomicron and VLDL metabolism, rather than triglycerides themselves, contribute to atherogenesis.

An independent factor for early atherosclerosis

Dyslipidaemia, a term representing a range of lipid disorders, leads to atherosclerosis and subsequent cardiovascular events. While LDL-C is a major factor in atherosclerosis, other lipids, including high TG levels, may also contribute, even in the absence of high LDL-C.[15]

An observational study of 3,754 individuals with low to moderate cardiovascular risk by Raposeiras-Roubin, *et al.* was the first study to establish an association between plasma TG levels and subclinical atherosclerosis. This association held regardless of LDL-C levels, and as plasma TG levels increased, so too did the number of affected vascular territories. Additionally, the study explored the link between TG and vascular inflammation and identified that higher plasma TG levels were associated with increased arterial inflammation. Individuals with plasma TG ≥ 150 mg/dL (1.69 mmol/L) had a two-fold higher risk of arterial inflammation compared to those with plasma TG < 100 mg/dl (1.13 mmol/L).[15]

Expert comment

Atherogenic dyslipidaemia is common in patients with ASCVD, especially in patients with type two diabetes and the metabolic syndrome, and is characterised by elevated triglycerides and low HDL. These underlying comorbidities markedly increase risk of developing CVD, and recurrent events after the index event, despite optimal guideline-based therapy. Current strategies to reduce triglycerides and increase HDL (through lifestyle and fibrates) have not been shown to improve outcomes in primary or secondary prevention, and receive weak recommendations in guidelines, as although the numbers look better there is no demonstrable effect on outcomes.

A marker of residual risk

It is widely accepted that elevated LDL-C is a cardiovascular risk factor which can be mitigated quite effectively using statin therapy. However, as highlighted in the review by Yani *et al.*, despite effective treatment of LDL-C, for some patients elevated plasma TG may persist leading to a residual risk of subsequent cardiovascular events.[16]

In order to understand the residual risk in individuals treated with statins to reduce LDL-C, Yani *et al.* conducted a review of eight randomised, double blind, placebo-controlled trials which studied the effects of statin therapy. The review included the WOSCOPS[17], ASCOT-LLA[18], AFCAPS/TexCAPS[19], CARDS[20], and JUPITER[21] studies where individuals received statins for primary prevention of CVD, and the 4S[22], LIPID[23] and CARE[24] studies where individuals received statin therapy for secondary prevention.

In the primary prevention studies, the residual risk of CVD ranged from 56% to 79% and in the secondary prevention studies 65% to 76%. It was also observed that after the trials, average serum TG ranges from 99 mg/dL (1.12 mmol/L) to 143 mg/dL (1.62 mmol/L).[16]

The results of this review were validated in the real world analysis by Toth *et al.* which included 23,181 patients aged > 45 years of age with diabetes and/or ASCVD who were prescribed statins. The analysis stratified patients by plasma TG; 150 mg/dL (i.e., ≥ 1.8 mmol/L) or < 150 mg/dL (i.e., < 1.8 mmol/L and HDL-C > 40 mg/dL (i.e., 1 mmol/L).[25]

The multivariate analysis revealed that statin treated patients with elevated TG ≥ 1.8 mmol/L experienced worse clinical outcomes than those with well managed TG and HDL-C.[23] Patients with elevated TG demonstrated a significantly greater risk of composite major cardiovascular events as compared to those with TG < 1.8 mmol/L (HR, 1.26; 95% CI, 1.19-1.34; P < 0.001). This increase in risk was maintained when non-HDL-C was included in the multivariate model, and in the high and low HDL-C subgroup analyses.[25] Specifically, patients with elevated TG were at a greater risk of:

- nonfatal myocardial infarction (HR, 1.32; 95% CI, 1.20-1.45; P < 0.001),
- nonfatal stroke (HR, 1.14; 95% CI, 1.04-1.24; P = 0.004), and
- need for coronary revascularisation (HR, 1.46; 95% CI, 1.33-1.61; P < 0.001).[25]

Expert comment

Elevated triglycerides are a marker of increased risk of ASCVD in both primary and secondary prevention and are associated with an increased risk of future events in patients with ASCVD despite optimal guideline-based treatment regimens. This residual risk is significant, and until recently we have had no specific therapy to reduce risk in these high-risk individuals.

Clinical advances in the management of residual risk

PCSK9 inhibitors[26]

In recent times, Australia has gained access to alirocumab and evolocumab. These monoclonal antibodies, administered subcutaneously at two- to four-weekly intervals, inhibit the PCSK9 enzyme, thereby reducing degradation of LDL receptors and lowering LDL-C levels. Data demonstrated that administration of PCSK9 inhibitors leads to reduction in LDL-C levels of around 50%. They may also reduce lipoprotein (a) by 25-30%, with maximum reduction levels observed when used in combination with statin therapy. While these two treatments will support better LDL-C control, the challenges with managing TG remains.

Icosapent ethyl (Vazkepa®)[27, 28, 29, 30]

Comprised of eicosapentaenoic acid (EPA), an omega-3 fatty acid, icosapent ethyl improves the lipoprotein profile by suppressing cholesterol-, fatty acid- and TG synthesising enzymes, increasing fatty acid β-oxidation, and reducing microsomal triglyceride transfer (MTP) protein, resulting in decreased hepatic TG and VLDL synthesis and release.

Icosapent ethyl increases expression of lipoprotein lipase leading to increased TG removal from circulating VLDL and chylomicron particles. In patients with elevated TG levels, it lowers TG, VLDL, remnant lipoprotein cholesterol, and levels of inflammatory markers such as C-reactive protein. Interestingly, the observed TG reduction appears to provide only a minor contribution to the overall significant reduction in risk of cardiovascular events.

The observed risk reduction with icosapent ethyl is beyond what can be explained by the degree of triglyceride changes alone, and so it is thought that another mechanism is driving benefit. Presently, the exact mechanism remains unclear, however potential mechanisms include; reduction of circulating triglyceride levels, antiplatelet aggregation effect, anti-inflammatory and anti-oxidant effect, reduction of circulating levels of remnant, stabilising effect on atherosclerotic plaque, reduction of hepatic production of VLDL, inhibition of hepatic triglyceride synthesis, increased mechanisms of hepatic beta-oxidation, and reduction of blood pressure.

Further to these benefits, imaging studies of coronary arteries with intravascular ultrasound (IVUS) and optical coherence tomography (OCT) have shown that icosapent ethyl has favourable effects on plaque morphology, by enabling a reduction in plaque volume and an increase in the fibrous cap, indicating a decrease in the vulnerability of the plaque.

Vazkepa® (icosapent ethyl) was approved by the Therapeutic Goods Administration (TGA) in November 2022 and by MedSafe New Zealand in January 2023. With a recommended daily dose of 4g, delivered as two capsules, twice daily. It is indicated to reduce the risk of cardiovascular events in adult statin-treated patients at high cardiovascular risk with elevated TG (≥ 1.7- 5.6 mmol/L) and either;

- established cardiovascular disease, or
- diabetes, and at least one other cardiovascular risk factor.

Evidence for registration of Vazkepa® was gathered in the multicentre, randomised, double-blind, placebo-controlled study, REDUCE-IT (NCT01492361). The study enrolled 8,179 statin-treated patients with established CVD or diabetes and other CVD risk factors. 70.7% were accessing treatment for secondary prevention of cardiovascular events. Patients in the trial were followed for a median of 4.9 years.

Key outcomes of this study included;

- Compared to 22% in the placebo group, 17.2% of individuals receiving icosapent ethyl experienced a primary end-point event, defined as cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularisation, or unstable angina. (HR 0.75; 95% CI: 0.68 to 0.83; P < 0.001).
- Similarly, compared to 14.8% in the placebo group, 11.2% of individuals receiving icosapent ethyl experienced a key secondary endpoint, defined as cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. (HR 0.74; 95% CI: 0.65 to 0.83; P < 0.001).
- Despite achieving modest reductions in TG (1 mmol/L), icosapent ethyl achieved cardiovascular disease benefits irrespective of baseline TG. As compared to placebo, patients taking icosapent ethyl demonstrated a significantly lower risk of major adverse cardiovascular disease events irrespective of their TG level at one year. These observed benefits suggest icosapent ethyl likely induces metabolic effects which are independent of TG lowering.[28]

Expert comment

Despite the best therapies available, many patients with ASCVD/ACS have recurrent events. The use of PCSK9 inhibitors has been liberalised recently by the Pharmaceutical Benefits Scheme (PBS) so that many patients who cannot achieve target LDL levels despite high intensity statins and ezetimibe are now eligible for treatment with these agents (evolocumab, alirocumab and soon incliseran). Although these agents lower LDL extremely well they have little impact on triglycerides, which are a marker of residual risk. Icosapent ethyl addresses this and improves outcomes in patients with ASCVD and triglycerides between 1.7 and 5.6 mmol/L, probably by affecting plaque characteristics rather than by just lowering triglycerides. It has been approved by the TGA and hopefully will be reimbursed by the PBS in the near future and will be a valuable new therapy to improve outcomes in this high-risk population where there is currently no alternative treatment.

Take-home messages

- Elevated TG levels indicate an increased presence of triglyceride-rich lipoproteins and their cholesterol-enriched remnants in the bloodstream, a result of lipolysis.
- A strong and causal relationship exists between TG levels and atherosclerotic cardiovascular disease.
- Clinical trials and registry data have shown that elevated TG levels significantly contribute to the residual risk in individuals treated with statins, highlighting the unmet need to address this risk in preventing cardiovascular disease.
- Vazkepa® (icosapent ethyl) is a new oral treatment approved by the TGA to reduce the risk of cardiovascular events in adult patients with a high risk of cardiovascular events who are receiving statin therapy with TG > 1.7mmol/L.
- The reduction in risk observed with Vazkepa® (icosapent ethyl) use is beyond what can be explained by the degree of triglyceride changes, which may be owing in part to it's anti-inflammatory and anti-platelet effects, in addition to a stabilising effect on atherosclerotic plaque.

References

1. Heart Foundation. Key Statistics: Cardiovascular Disease, Statistics and Information on Cardiovascular Disease in Australia. Available at: www.heartfoundation.org.au [Accessed 27-Oct-2023].
2. Baker Heart & Diabetes Institute. No Second Chances, Controlling Risk in Cardiovascular Disease. Available at: https://baker.edu.au/impact/advocacy/no-second-chances [Accessed 27-Oct-2023]
3. Anderson L, et al. Exercise-based cardiac rehabilitation for coronary heart disease. Cochrane Database Syst Rev. 2016:CD001800.
4. Chew DP, et al. National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand: Australian Clinical Guidelines for the management of acute coronary syndromes 2016. Med J Aust. 2016;205:128-33
5. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ. 2002;324: 71-86.
6. Aradi D, et al. Impact of clopidogrel and potent P2Y 12 -inhibitors on mortality and stroke in patients with acute coronary syndrome or undergoing percutaneous coronary intervention: a systematic review and meta-analysis. Thrombosis and haemostasis. 2013;109:93-101.
7. Lip GYH, et al. 2018 Joint European consensus document on the management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous cardiovascular interventions: a joint consensus document of the European Heart Rhythm Association (EHRA), European Society of Cardiology Working Group on Thrombosis, European Association of Percutaneous Cardiovascular Interventions (EAPCI), and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS), Latin America Heart Rhythm Society (LAHRS), and Cardiac Arrhythmia Society of Southern Africa (CASSA). Europace. 2018.
8. Eikelboom JW, et al. Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. N Engl J Med. 2017;377:1319-1330.
9. Baigent C, 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: 1670-81.
10. Shapiro MD, et al. Relationship between low-density lipoprotein cholesterol and lipoprotein(a) lowering in response to PCSK9 inhibition with evolocumab. 2019. JAHA 8(4):1-14
11. de Peuter OR, et al. A systematic review of selective and non-selective beta blockers for prevention of vascular events in patients with acute coronary syndrome or heart failure. The Netherlands journal of medicine. 2009;67:284-94.
12. Dagenais GR, et al. Angiotensin-converting enzyme inhibitors in stable vascular disease without left ventricular systolic dysfunction or heart failure: a combined analysis of three trials. The Lancet. 2006;368:581-588.
13. Cannon CP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med. 2015; 372:2387-2397
14. Packard CJ. Triglyceride-rich Lipoproteins and Their Role in Cardiovascular Disease. 2023. Br J Cardiol 2023;30(Suppl 2):S4-S9
15. Raposeiras-Roubin et al. Triglycerides and residual atherosclerosis risk. J. American College Cardiology. 22 Jun 2021. 77(24):3031-3041
16. Yani H, et al. Molecular biological and clinical understanding of the statin residual cardiovascular disease risk and peroxisome proliferator-activated receptor alpha agonists and exetimibe for its treatment. Int. J. Mol. Sco. 2022. 23:3418
17. Shepherd J, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N. Engl. J. Med. 1995, 333, 1301–1307.
18. Sever P.S, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA): A multicentre randomised controlled trial. Lancet 2003, 361, 1149–1158.
19. Downs, J.R, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: Results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. JAMA 1998, 279, 1615–1622.
20. Colhoun, H.M, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): Multicentre randomised placebo-controlled trial. Lancet 2004, 364, 685–696
21. Ridker, P.M, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N. Engl. J. Med. 2008, 359, 2195–2207
22. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). Lancet 1994, 344, 1383–1389.
23. Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N. Engl. J. Med. 1998, 339, 1349–1357.
24. Sacks, F.M, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. N. Engl. J. Med. 1996, 335, 1001–1009.
25. Toth PT, et al. Association of Elevated Triglycerides with Increased Cardiovascular Risk and Direct Costs in Statin-Treated Patients. Mayo Clin Proc. 2019. 94(9):1670-1680
26. Simons LA. Lipid management, what counts what is new? Medicine Today, Cardiology Today. October 2021. 11(2).
27. Australian Government Department of Health and Aged Care, Therapeutic Goods Administration. Vazkepa. Available at: www.tga.gov.au [Accessed 28-Oct-2023]
28. Bhatt DL, et al. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. 2019. N Engl J Med. 380:11-22
29. Szarek M, et al. Eicosapentaenoic acid, arachidonic acid, and triglyceride levels mediate most of the benefit of icosapent ethyl in REDUCE-IT. European Heart Journal. 2023. 44(2).
30. Borghi C and Bragagni A. Clinical results and mechanisms of action of icosapent ethyl. European Heart Journal Supplements. 2023. 25(Supplement B):B37-B40.

