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EZETIMIBE REVIEW

REVIEW of CLINICAL GUIDELINES

Health Technology Assessment Team



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Glossary

ACC	American College of Cardiology
AHA	American Heart Association
AR	Absolute risk
ASCVD	Atherosclerotic Cardiovascular Disease
ATSI	Aboriginal and Torres Strait Islanders
AusDiab	Australian Diabetes, Obesity and Lifestyle Study
BP	Blood pressure
CCS	Canadian Cardiovascular Society
CHD	Coronary heart disease
CKD	Chronic kidney disease
CSANZ	Cardiac Society of Australia and New Zealand
CVD	cardiovascular disease
DM	Diabetes mellitus
EAS	European Atherosclerosis Society
ESC	European Society of Cardiology
FH	familial hypercholesterolaemia
FRS	Framingham Risk Score
GSLLD	General Statement for Lipid-Lowering Drugs
HDL-C	High Density Lipoprotein-Cholesterol
LDL-C	Low Density Lipoprotein-Cholesterol
NHF-2012	National Heart Foundation
NICE	National Institute for Health and Clinical Excellence (UK)
NLA	National Lipid Association (USA)
NVDPA	National vascular disease prevention alliance
PBS	Pharmaceutical Benefits Scheme
SCORE	Systematic COronary Risk Evaluation [assessment tool]
TC	Total cholesterol
TG	Triglycerides

Comparison of guidelines for cardiovascular disease risk assessment and management (cholesterol lowering therapy)

1. Summary

ToR 2: Review recent clinical guidelines for the treatment of hypercholesterolaemia and compare this to how ezetimibe is currently used on the Pharmaceutical Benefits Scheme (PBS);

The research questions in relation to the ToR 2 include:

Q1: Are the eligibility criteria for PBS subsidy of lipid-lowering therapies (as specified in the General Statement for Lipid-Lowering Drugs [GSLLD]) consistent with Australian guidelines for primary (NVDPA-2012) and secondary (NHF-2012) prevention of cardiovascular events? (Section 2).

Q2: Are the Australian NVDPA-12 guidelines consistent with international guidelines? (Sections 2-5).

These research questions are addressed by an analysis comparing and contrasting the definitions of cardiovascular disease (CVD) risk; tools used to quantify the degree of risk; criteria for initiating treatments; treatment targets for lipid reduction (if any); a recommended treatment pathway (i.e. primary and secondary lines of lipid-reducing therapy). *The research questions seek to clarify the differences between patient groups in whom treatment with ezetimibe and treatment with statins is recommended across the published guidelines.*

The most recent revisions of the major National and International guidelines for management of metabolic lipid disorders to prevent cardiovascular complications identified by the systematic literature search included:

- three Australian/NZ guidelines;
- three US guidelines/consensus statements;
- one Canadian guideline;
- two UK guidelines/technology appraisals;
- two International/European guidelines.

In addition, a number of publications on comparison of the International guidelines was identified and studied to inform the outcomes of this review (Anderson 2015; Morris 2014; McKenney 2015; Naylor 2016; Waite 2016).

Table 1.1 summarises characteristics of the published guidelines to provide a brief overview and highlight the differences **to inform Q2**. The full details for each of the guideline, health technology assessment or consensus statement are in Tables 2.1- 5.2 in the respective sections below. **Q1 is addressed in Section 2** (in particular, **Tables 2.1 to 2.3**).

Table 1.1 Comparative characteristics of the identified guidelines: Summary

Guidelines/country	Risk assessment tool/ end points	Risk categories/ cut-off criteria	Cholesterol treatment targets: primary/ secondary (by risk category)	Recommended lipid lowering therapy (first line treatment) by risk category	Recommended lipid lowering therapy (second line/ combination treatment)
National vascular disease prevention alliance (NVDPA-2012) Australia	Australian Absolute Cardiovascular Disease Risk Assessment tool, based on the Framingham Risk Equation (FRE), calculates the probability of End points: stroke, transient ischaemic attack, myocardial infarction, angina, peripheral arterial disease or heart failure occurring <i>within the next 5 years</i> .	Primary prevention high risk category: patients with DM and age ≥ 60 ; DM with micro-albuminuria; moderate or severe CKD; previous diagnosis of FH; hypertension ($\geq 180/110$ mmHg) and severe hypercholesterolaemia (TC >7.5 mmol/L) For patients aged ≥ 45 years, or ≥ 35 for ATSI risk is based on the estimates of the 5-year AR of CVD: high risk is $> 15\%$; moderate AR is 10%-15%; low risk is $<10\%$ Secondary prevention existing CHD=high risk	Recommended targets for lipid control in patients with high to moderate risk of CVD events TC <4.0 mmol/L; HDL-C ≥ 1.0 mmol/L; LDL-C <2.0 mmol/L; Non HDL-C <2.5 mmol/L; TG <2.0 mmol/L.	<u>High risk category</u> : both BP-lowering and lipid-lowering agents for all patients, unless contraindicated or clinically inappropriate; Both BP-lowering and lipid-lowering agents are recommended for <u>moderate risk</u> category, if the risk remains elevated after lifestyle interventions. Statins should be used as the first-line therapy; <i>no recommendations on the statin potency or dose are included in the guidelines, see GSLLD.</i>	If LDL-C levels are not sufficiently reduced on maximally tolerated dose of statin, one or more of the following may be added: • ezetimibe • bile acid binding resin • nicotinic acid
American College of Cardiology/American Heart Association (ACC/AHA-2013) USA The ACC Clinical Expert Consensus on the Role of Non-Statin Therapies (2016) USA	Pooled Cohort Equations to estimate 10-year ASCVD risk for patients 40-75 years of age. End points: probability of CHD death, nonfatal MI, fatal or nonfatal stroke	Identified 4 primary statin benefit groups: Secondary prevention 1) Individuals with clinical ASCVD Primary prevention 2) Individuals (adults ≥ 21 y.o) with primary elevations of LDL-C >190 mg/dL (4.9mmol/L) 3) Individuals with DM, without clinical ASCVD, aged 40-75 with LDL-C 70-189 mg/dL (1.8-4.9 mmol/L) 4) Individuals without clinical ASCVD or DM with LDL-C 70-189 mg/dL (1.8-4.9 mmol/L) and estimated 10-y ASCVD risk $\geq 7.5\%$	Not applicable; <i>fixed statin intensity approach is recommended instead.</i> The expected response to a moderate-potency statin is LDL-C reduction of 30-50%, while the expected response to a high-potency statin is LDL-C reduction of $\geq 50\%$. <i>The 2016 ACC Clinical Expert Consensus re-introduced lipid goals in the decision pathways.</i> Depending on the primary or secondary prevention status, comorbidities and the baseline LDL-C level, the lipid goals are set either at LDL-C <70 mg/dL (1.8 mmol/L) or LDL-C <100 mg/dL (2.6 mmol/L). For	Primary prevention Adults ≥ 21 years of age with LDL-C ≥ 4.9 mmol/L • High-intensity statin therapy (or maximum tolerated dose) unless contraindicated; Adults 40-75 y.o, without ASCVD or DM; LDL-C 1.8-4.9 mmol/L • If 10-y ASCVD risk $\geq 7.5\%$, consider moderate- to high intensity statin therapy Adults 40-75 y.o. with DM; LDL-C 1.8-4.9 mmol/L • Moderate-intensity statin therapy • High-intensity statin therapy if estimated 10-y ASCVD risk $\geq 7.5\%$, unless contraindicated	In high-risk individuals receiving maximum tolerated intensity of statin therapy who continue to have a less than- desired therapeutic response, addition of a nonstatin cholesterol-lowering drug(s) may be considered if the ASCVD risk-reduction benefits outweigh the potential for adverse effects.

			patients with diabetes the lipid goal is defined as non-HDL-C <130 mg/dL (3.4 mmol/L). Non-LDL-C targets are not discussed	Secondary prevention • High-intensity statin in patients ≤75 years of age; • Moderate-intensity statin in patients >75 years of age	
National Lipid Association recommendations (updates from 2014-2015) USA	<ul style="list-style-type: none"> • Framingham Risk Score to estimate 10-y or long-term and lifetime ASCVD risk End points: probability CHD death, nonfatal MI • Pooled Cohort Equations (ACC/AHA) to estimate 10-y ASCVD risk; End points: probability of CHD death, nonfatal MI, fatal or nonfatal stroke 	<p>Major risk factors for ASCVD:</p> <ul style="list-style-type: none"> • Age: Male ≥45 years; Female ≥55 years • Family history of early CHD: <55 years of age in a male first-degree relative, or <65 years of age in a female first-degree relative • Current cigarette smoking • High blood pressure (140/90 mmHg) • Low HDL-C: male <40 mg/dL; female <50 mg/dL <p>Identified 4 ASCVD risk groups (low, moderate, high and very high) the risk is assigned according to the number of major risk factors; AR scores; presence of DM, CKD, or severe hypercholesterolemia LDL-C ≥190 mg/dL (4.9 mmol/L).</p>	<p>Recommended targets for lipid control</p> <p>LDL-C <100 mg/dL (2.6 mmol/L) for low, medium and high risk categories and LDL-C <70 mg/dL (1.8 mmol/L) for very high risk category;</p> <p>non-HDL-C <130 mg/dL (3.4 mmol/L) for low, medium and high risk categories and non-HDL-C <100 mg/dL (2.6 mmol/L) for very high risk category</p> <p>ApoB (apolipoprotein) can be considered as an optional (secondary) target</p> <p>TGs become the primary target if ≥500 mg/dL.</p>	<p>Statin is recommended for primary prevention in patients without DM if LDL-C ≥190 mg/dL; ≥2 clinical risk factors and: High risk (10-y risk >20%) and LDL-C ≥100 mg/dL (≥70 mg/dL optional); Intermediate risk (10-y risk, 10%–20%) and LDL-C ≥130 mg/dL (≥100 mg/dL optional); statin may be considered in Low risk (10-y risk <10%) and LDL-C ≥160 mg/dL;</p> <p>Statin is recommended for primary prevention in patients with DM if LDL-C ≥100 mg/dL and optionally if LDL-C ≥70 mg/dL with high risk features; Statin is recommended for secondary prevention if LDL-C ≥100 mg/dL (2.6 mmol/L)</p>	Combination therapy with statins a second (or third) agent may be considered for patients in high- or very high-risk categories with recurrent or progressive ASCVD; patients with recent acute coronary syndromes, and patients with familial hypercholesterolemia (FH) who have not reached their treatment goals to maximally tolerated statin therapy. Drugs used in combination with statin are (in order of preference) ezetimibe , bile acid sequestrants, and extended release niacin.
Canadian Cardiovascular Society, the 2012 update of 2009 guidelines Canada	The 10-year risk of developing “total” cardiovascular events assessed with Framingham Risk Score (FRS), modified for a family history of premature coronary disease End points: CHD death, MI, coronary insufficiency, angina, ischemic or haemorrhagic stroke, transient ischemic attack, peripheral artery disease, heart failure	<p>High risk factors:</p> <ul style="list-style-type: none"> • Clinical vascular disease • Abdominal Aortic Aneurysm • Diabetes and age ≥ 40 yrs or >15 yrs duration and age ≥ 30 yrs or microvascular disease • Chronic kidney disease • High risk hypertension <p>Identified 3 ASCVD risk groups (low, intermediate and high risk) the risk is assigned according to the number of major risk factors; AR scores; presence of DM, CKD, or high risk hypertension</p>	No separate targets for primary and secondary prevention population. Recommended primary targets for lipid control for high and intermediate risk groups are LDL-C ≤2.0 mmol/L or ≥ 50% reduction of LDL-C from untreated baseline; Alternate targets include apo B ≤0.8 g/L or non-HDL-C ≤2.6mmol/L For the low risk group for whom treatment is recommended, the target is ≥ 50% reduction of LDL-C from untreated baseline;	<p>Statin is recommended for high risk patients with any of the high risk factors and: FRS ≥ 20%</p> <p>Statin is recommended for intermediate risk group of patients with no high risk factors; FRS 10%-19% and LDL-C ≥3.5 mmol/L</p> <p>Statin is recommended for low risk patients with FRS <10% and LDL-C ≥ 5 mmol/L or if there is evidence of genetic dyslipidaemia</p>	Combination therapy with statins: For subjects who do not tolerate statin therapy or only at low dose, favourable effects on LDL-C can be achieved with ezetimibe, bile acid resins, or niacin

<p>NICE clinical guideline CG181 for cardiovascular disease: risk assessment and reduction, including lipid modification, the 2014 replacement of CG67 United Kingdom</p>	<p>The 10-year risk assessment tool QRISK2 End points: CHD death, CHD (MI or angina), stroke, or transient ischemic attack</p>	<p>Guidelines differentiate between primary and secondary prevention populations; A 10 year threshold for the high risk of CVD is 10%</p>	<p>No lipid targets; However the primary outcome of therapy is assessed in non-HDL cholesterol, rather than in LDL-C reduction. Other lipid to measure are TC and HDL-C. High-intensity treatment with atorvastatin 80mg should aim for $\geq 40\%$ reduction in non-HDL cholesterol.</p>	<p>For the primary prevention subgroup of adults with type 1 diabetes; type 2 diabetes and CKD (if some specific conditions are met) attempt lifestyle first. If ineffective or inappropriate offer statin treatment</p> <ul style="list-style-type: none"> atorvastatin 20 mg; <p>For other categories of people with 10-year risk $\geq 10\%$ attempt lifestyle modification and management of other modifiable CVD risks; then start statin treatment with</p> <ul style="list-style-type: none"> atorvastatin 20 mg; <p>For the secondary prevention subgroup of adults with diagnosed CVD Start statin treatment with</p> <ul style="list-style-type: none"> atorvastatin 80 mg or a lower dose if potential drug interactions and/or high risk of adverse effects are likely 	<p>Combination therapy. Do not offer the combination of a bile acid sequestrant (anion exchange resin), fibrate, nicotinic acid or omega-3 fatty acid compound with a statin for the primary or secondary prevention of CVD. Ezetimibe treatment is initiated in line with ezetimibe for the treatment of primary hyper-cholesterolaemia guidelines (TA385), <i>which recommends ezetimibe if</i> a) <i>LDL-C is not appropriately controlled (according to CG181)</i> either after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance to the initial statin therapy. b) a change from initial statin therapy to an alternative statin is being considered</p>
<p>European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) task force, the 2016 update of the 2011 guidelines. European Union</p>	<p>The 10 year Systematic COronary Risk Evaluation assessment tool (SCORE), designed to assess the risk of a first fatal atherosclerotic event, whether heart attack, stroke, or other occlusive arterial disease, including sudden cardiac death</p>	<p>Identified 4 risk groups: Very high risk: • Diagnosed CVD; • Severe CKD • Type 2 DM or type 1 DM with target organ damage; • 10 year risk SCORE $\geq 10\%$. High risk: • Markedly elevated single risk factors e.g. in familial hypercholesterolaemia; cholesterol >8 mmol/L (>310 mg/dL) or severe hypertension (BP $\geq 180/110$ mmHg) • most patients with DM • moderate CKD • 10 year risk SCORE $\geq 5\%$ to $<10\%$ Moderate risk: • 10 year risk SCORE $\geq 1\%$ to $<5\%$; Low risk: • 10 year risk SCORE $<1\%$</p>	<p>Recommended primary targets for lipid control: Very high risk: <1.8 mmol/L (70 mg/dL) or at least 50% if the baseline LDL-C is between 1.8 and 3.5 mmol/L; High risk: <2.6 mmol/L (100 mg/dL) or at least 50% if the baseline LDL-C is between 2.6 and 5.2 mmol/L Low to Moderate risk: <3.0 mmol/L (115 mg/dL) SCORE requires TC value to be entered; and the AR charts are available for TC:HDL-C ratio; electronic version exists for HDL-C inputs.</p>	<p>Statin doses and the type of statin should reflect the degree of LDL-C reduction that is required to reach the target LDL-C (refer to Table A5.1 in Appendix)</p>	<p>Should the target value have not been met, statin combination with a cholesterol absorption inhibitor (ezetimibe) should be considered first followed by the statin combination with a bile acid sequestrant. In patients at very high-risk, with persistent high LDL-C despite treatment with maximal tolerated statin dose, in combination with ezetimibe or in patients with statin intolerance, a PCSK9 inhibitor may be considered.</p>

ASCVD= atherosclerotic cardiovascular disease; TC= total cholesterol; DM=diabetes mellitus; HDL-C high-density lipoprotein cholesterol; LDL-C low-density lipoprotein cholesterol; TG=triglycerides; ATSI= Aboriginal and Torres Strait Islanders; CKD=chronic kidney disease; GSLLD=General Statement for Lipid-Lowering Drugs;

Authors of all guidelines included in Table 1.1 share the view that management of hyperlipidaemia, as a modifiable risk factor, should be undertaken in the context of the absolute risk of cardiovascular disease (CVD) for each patient with their unique combination of inherited and behavioural risk factors. The Australian primary prevention NVDPA-2012 guidelines continue the trend of moving away from managing isolated risk factors, such as hypertension and dyslipidaemia, towards assessment and management of absolute CVD risk (Nelson 2013).

Risk assessment tools

Recently there has been a proliferation of the country-specific absolute risk assessment tools. Some of the tools (e.g. Australian Absolute Cardiovascular Disease Risk Assessment tool; European “SCORE”) are based on the Framingham Risk Equation (FRE), while other were newly developed (e.g. “Pooled Cohort Equations” in US and QRISK2 in UK). The tools also vary with respect to the time horizon for the risk estimate. Both the NICE approach and the ACC/AHA guideline offer statin therapy on the basis of an estimated 10-year risk of ASCVD. In comparison, the Australian NVDPA-2012 guidelines are based on 5 year risk assessment. There are substantial differences in the CVD risks that can be assessed; these may include only the first fatal atherosclerotic event (European “SCORE”), or a selected number of fatal and non-fatal CV events (QRISK2; Canadian version of FRE; “Pooled Cohort Equations”, Australian Risk Assessment tool) that vary in degree of comprehensiveness and result in the vastly different populations assumed to be at risk of an CV event. The risk threshold of $\geq 10\%$ for treatment initiation is set by Australian, Canadian and NICE guidelines, in contrast to the $\geq 7.5\%$ threshold set by ACC/AHA, which is the lowest threshold in all other leading international guidelines.

Categories of risk

All guidelines use a combination of an absolute risk score and other risk factors (e.g. diabetes mellitus (DM); chronic kidney disease (CKD); familial hypercholesterolaemia (FH); or hypertension) to assign a risk category to patients. The number of risk subgroups varied from three in Australian and Canadian guidelines (high, medium and low) to four in the US National Lipid Association (NLA) recommendations and the European ESC/EAS guidelines (very high, high, moderate and low). The UK NICE guidelines differentiated population only into the primary and secondary prevention subgroups, although a 10 year threshold of 10% was used to identify high risk of CVD in primary prevention population. The guidelines that separated primary from secondary prevention population (all but the European ESC/EAS and Canadian guidelines) assigned the latter into the high risk subgroup. Most of the guidelines included at least one baseline lipid value as a criterion for assigning the degree of risk (the lipids included TC in Australian and European guidelines, LDL-C in both American (NLA and ACC/AHA) guidelines; Canadian guidelines favoured blood pressure (BP) over lipids and NICE did not elaborate on risk categories).

Cholesterol treatment targets

Most of the guidelines included lipid targets at least for high and moderate risk categories. Low Density Lipoprotein-Cholesterol (LDL-C) was a primary target in NLA recommendations, European and Canadian guidelines, however secondary targets in terms of non-High Density Lipoprotein-Cholesterol (non-HDL-C) were also suggested in NLA recommendations and Canadian guidelines. The Australian Guidelines included cholesterol treatment targets for each lipid metric (TC, HDL-C; LDL-C; non-HDL-C) and triglycerides (TG).

However, even if the target LDL-C levels are recommended, they are not necessarily consistent across the guidelines.

- European: very high risk (< 1.8 mmol/L); high risk (< 2.6 mmol/L); moderate risk (< 3.0 mmol/L)
- NLA: very high risk (< 1.8 mmol/L); high, intermediate and low risk (< 2.6 mmol/L);

- Canadian guidelines: high to intermediate risk (< 2.0 mmol/L);
- Australian guidelines: high to moderate risk (< 2.0 mmol/L);

The 2013 ACC/AHA guidelines endorses a paradigm shift in strategies for reducing atherosclerotic cardiovascular disease (ASCVD) events by lowering blood cholesterol. Contrary to all previous (both US and international) guidelines that primarily focused on decreasing low-density lipoprotein to specific target levels, the new guidelines proposes instead implementation of cholesterol-lowering treatment using evidenced-based intensity of statin therapy without such targets (Smith 2014). The expected response to a moderate-potency statin is LDL-C reduction of 30-50%, while the expected response to a high-potency statin is LDL-C reduction of $\geq 50\%$. Consistent with the 2013 ACC/AHA guidelines, the 2014 NICE guidelines did not suggest any lipid targets either but stated that high-intensity treatment with atorvastatin 80mg should aim for $\geq 40\%$ reduction in non-HDL cholesterol, therefore completely eschewing the LDL-C metric.

It was argued that the absence of cholesterol goals leaves the physician in the dark for setting an individualized statin dose, deciding on appropriateness of combination therapy and evaluating the adequacy of the risk reduction from therapy (Smith 2014). Responding to these concerns, the 2016 ACC Clinical Expert Consensus on the role of non-statin therapies re-introduced LDL-cholesterol goals in the decision pathways. Depending on the primary or secondary prevention status, comorbidities and the baseline LDL-C level, the lipid goals are set either at LDL-C <1.8 mmol/L or LDL-C <2.6 mmol/L. For patients with diabetes the lipid goal is defined as non-HDL-C <3.4 mmol/L.

Recommended lipid lowering therapy

All guidelines recommend lifestyle and dietary modification in primary prevention population to establish eligibility for pharmaceutical treatment. Patients from the high risk subgroups may be offered lipid-lowering drugs on the first presentation. Statins are universally suggested as the first line therapy, unless poorly tolerated or contraindicated. There are differences in the suggested strategies of managing statin intolerance, ranging from prescribing a non-statin alternative to the repeated attempts to reintroduce patients to statins by reducing the dose, taking drug-free periods and altering a statin. The 2013 ACC/AHA are the most specific in their recommendations towards the choice of a statin of particular potency for each of the four “statin benefit” groups of patients. This approach influenced the 2014 NICE guidelines that are even more specific in recommending atorvastatin 20 mg or 80 mg for the primary and secondary prevention populations respectively. The most conflicting recommendations across the guidelines relates to non-statin cholesterol lowering medications. Consistent with the General Statement for Lipid-Lowering Drugs (GSLLD), if LDL-C levels are not sufficiently reduced on maximally tolerated dose of statin, the Australian guidelines recommend a combination of statin with one or more of alternative drugs: ezetimibe, bile acid binding resin, or nicotinic acid. The Canadian guidelines and the 2014 NLA recommendations are essentially the same, except the latter limits a combination therapy to high- and very-high risk categories.

The 2013 ACC/AHA guideline takes a similar position with respect to high-risk individuals, if they continue to have a less than desired therapeutic response, after receiving maximum tolerated intensity of statin. In such instances addition of a non-statin cholesterol-lowering drug(s) may be considered. The guidelines did not elaborate on the possible non-statin options but, by referring to the “desired therapeutic response”, revealed the lack of a substitute to the recommended lipid goal and the associated uncertainty in clinical decision making. The purpose of the 2016 ACC Clinical Expert Consensus statement was to address this problem by including an optional non-statin medication for the patients who did not achieved a 50% LDL-C reduction (or, alternatively, a lipid goal).

Ezetimibe was suggested as either the first choice of the non-statin second line medications or the only option in four out of six pathways outlined in the 2016 ACC Clinical Expert Consensus statement. However, bile acid sequestrants can be used instead as the second line therapy if a patient is ezetimibe intolerant and with TG<300 mg/dL. Across the subgroups, the statement is inconsistent in introducing the requirement for the patients to be on the maximum tolerated dose of statin to be considered for ezetimibe treatment. The Expert Panel also included a PCSK9 inhibitor, which is consistently recommended only in combination with maximally tolerated statin. Depending on the subgroup, the second line therapy with PCSK9 inhibitors can be a first choice (i.e. rather than ezetimibe), the second choice (i.e. after ezetimibe) or an equal option. The 2016 ESC/EAS guidelines are the only other current guideline that included a PCSK9 inhibitor as a third line treatment limited to the very high risk category or to patients with statin intolerance. The guideline conventionally suggested that ezetimibe in combination with statin should be considered first followed by the statin combination with a bile acid sequestrant.

The 2014 NICE guidelines stand in sharp contrast to the above as they do not offer the combination of a bile acid sequestrant, fibrates, nicotinic acid or omega-3 fatty acid compound with a statin for the primary or secondary prevention of CVD. Ezetimibe treatment is initiated according to the recommendations of the independently conducted technology assessment (TA385). Inconsistently with the NICE guidelines that used non-HDL-C as a primary treatment outcome, the TA385 maintained LDL-C levels as a primary target. Ezetimibe is recommended if LDL-C target could not be achieved after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance. *It can also be prescribed if a change from initial statin therapy to an alternative statin is being considered.*

In summary,

The Australian guidelines, along with every other identified guideline, approach cholesterol management in the context of the absolute CVD risk reduction. Absolute risk assessment is based on the variation of the FRE, which is frequently used in other assessment tools across the world. However the time horizon for risk assessment of 5 years is the shortest among the identified guidelines. The 10% cut-off point for a 10-year risk of CVD is also recommended in every other guideline, but the 2013 ACC/AHA guideline that used 7.5% threshold. The Australian guidelines adhere to the treatment targets that are defined for each cholesterol metric not just for LDL-cholesterol levels, as became customary in other countries. The recommended LDL-C levels are the same as in Canadian guidelines and in the ballpark of other guidelines that maintain treatment targets in LDL-C levels. If LDL-C levels are not sufficiently reduced on maximally tolerated dose of statin, the Australian guidelines recommend a combination of statin with one or more of alternative drugs: ezetimibe, bile acid binding resin, or nicotinic acid. This recommendation is replicated in other guidelines, however may be limited to high- or very high risk categories of patients. The Australian guidelines do not recommend a PCSK9 inhibitor as the second or third line of therapy as the most recent the 2016 ESC/EAS guidelines or the 2016 ACC Clinical Expert Consensus statement. The latter suggests that, depending on the characteristics of the subgroup, a PCSK9 inhibitor can be a first choice in the second line therapy (i.e. rather than ezetimibe), the second choice (i.e. after ezetimibe) or an equal option.

2. Australian guidelines

Lipid management guidelines have consistently recommended absolute cardiovascular disease (CVD) risk assessment (based on the Framingham Risk Equation) as the basis for lipid management and as criteria for prescribing lipid-modifying drugs such as statins (NHF-2001; NHF-2005). Ezetimibe was first mentioned in 2005 Position Statement on Lipid Management as an optional prescription choice as monotherapy or in combination with statins that potentially reduces the concentration of LDL-C by 15–20% (NHF-2005). The approach to the CVD risk assessment, lipid targets and management recommendations of the updated lipid management guidelines have contributed to the following documents that currently offer guidance in risk assessment and management for the primary and secondary prevention of CVD events.

Primary prevention: National vascular disease prevention alliance (NVDPA) guidelines for the management of absolute cardiovascular disease risk for primary preventions (NVDPA-2012) used in connection with the Australian Absolute Cardiovascular Disease Risk Assessment that can be done with a web calculator and/or cardiovascular risk charts (NVDPA-2009).

Secondary prevention: The National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand. Reducing risk in heart disease: an expert guide to clinical practice for secondary prevention of coronary heart disease. Melbourne: National Heart Foundation of Australia, 2012. (NHF-2012).

Familial hypercholesterolaemia (FH): Separate Australian guidelines for identification and management of familial hypercholesterolaemia were produced by the Cardiac Society of Australia and New Zealand (CSANZ) in 2013 (Table A2.1 in Appendix).

Unlike the earlier lipid management guidelines (NHF-2001; NHF-2005), the current guidelines separate the population with existing coronary heart disease (CHD) from the population without a CHD diagnosis. While patients from the first subgroup are automatically assigned to the high risk category, the latter subgroup is assessed for the high, moderate or low level of the absolute risk of CVD event based on the algorithm described in Figure 1.1 (reproduced from p.7 of the NVDPA guidelines for the management of absolute cardiovascular disease risk for primary preventions, NVDPA-2012).

The NHF-2012 guidelines for secondary prevention recommend statin therapy for all patients with CHD (apart from in exceptional circumstances). It also states that ezetimibe reduces the concentration of LDL-C by 15–20% as monotherapy, or when added to a statin and that long-term safety data is satisfactory. **The NHF-2012 guidelines did not explicitly position ezetimibe as a second line therapy.**

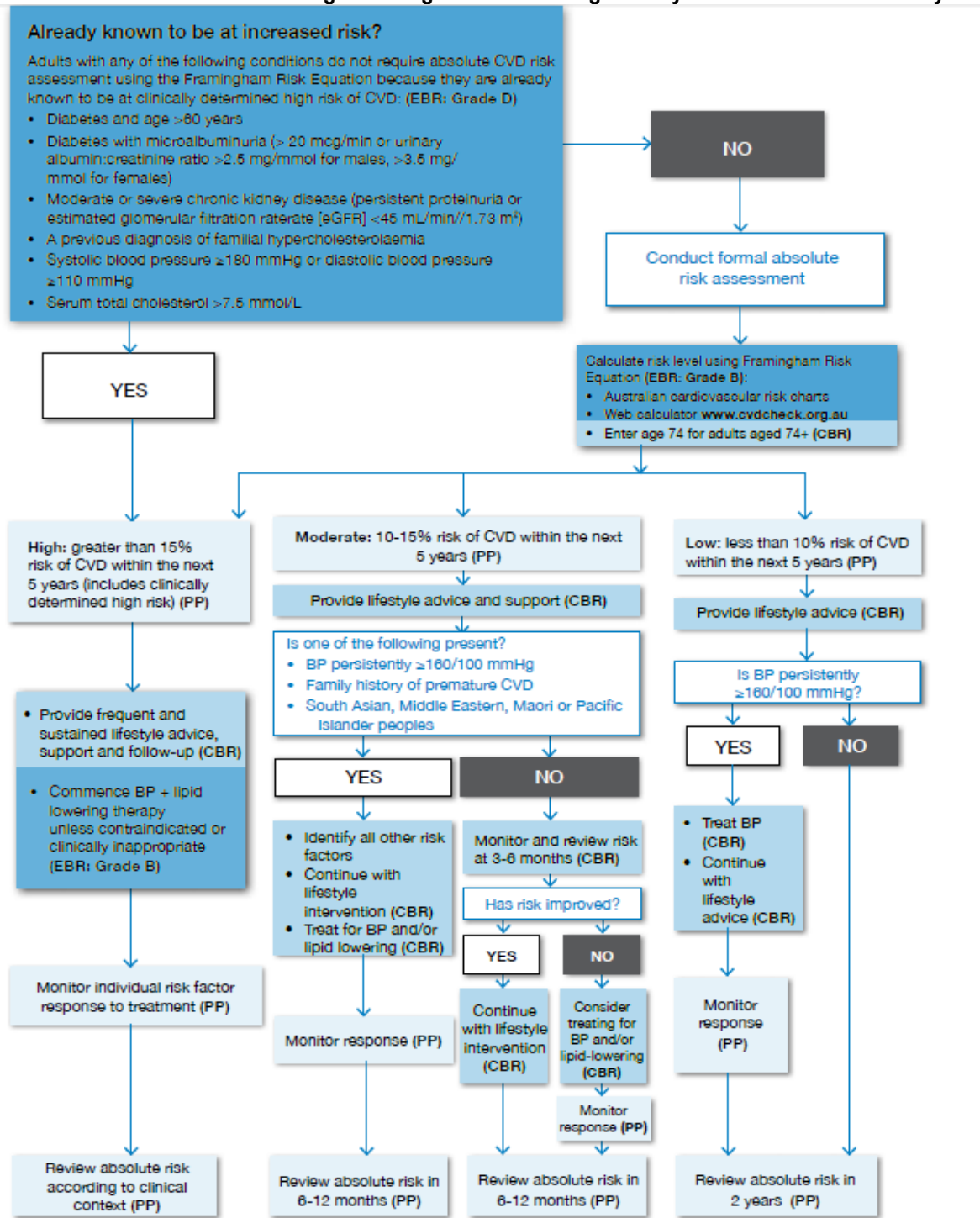
The NVDPA-2012 guidelines for primary prevention also recommend simultaneous treatment with lipid lowering and BP lowering drugs in patients assessed at high risk for CVD event unless contraindicated or clinically inappropriate. For the moderate risk patients BP lowering and/or lipid lowering drugs are recommended in addition to lifestyle advice if 3-6 months of lifestyle intervention does not reduce risk or one or more of the following is present:

- BP is persistently $\geq 160/100$ mmHg
- Family history of premature CVD
- Specific population where the Framingham Risk Equation systematically underestimates risk e.g. in Aboriginal or Torres Strait Islander [A&TSI] people, South Asian, Maori and Pacific Islander, or Middle

Eastern origin.

The NVDPA-2012 guidelines explicitly positioned ezetimibe as a second line therapy when LDL-C levels are not sufficiently reduced on maximally tolerated dose of statin (p.12).

Figure 2.1 Risk Assessment and Management Algorithm: Adults aged ≥ 45 years without known history of CVD



EBR: Evidence-based recommendation (Graded A-D) CBR: Consensus-based recommendation PP: Practice point

To summarise, **the approach to clinical management corresponds to the hierarchy in risk assessment**: for example, decision to prescribe BP-lowering and lipid lowering agents would depend

on a) whether the patient is in a high risk category, and if negative, b) on the combination of other risk factors, such as ethnicity, hypertension, and family history of CVD. Table 1.1 outlines NVDPA-2012 and NHF-2012 in terms of the setting, population, risk factors and suggested lipid lowering management

Table 2.1 Australian guidelines for assessment and management of absolute cardiovascular disease risk (NVDPA-2012)

Guidelines	Setting/Population/ scope	Risk factors included	Absolute risk assessment tool	Suggested lipid lowering management
<p>National Vascular Disease Prevention Alliance. <i>Guidelines for the management of absolute cardiovascular disease risk.</i> Australia, 2012 +</p> <p>the Australian <i>Absolute Cardiovascular Disease Risk Assessment</i></p>	<p>Primary prevention setting in all adults over 45 years of age (35 years for people of Aboriginal or Torres Strait Islander [A&TSI] decent) without known history of CVD*;</p>	<p><i>The following conditions are identified with high risk of a cardiovascular event without resorting to risk assessment chart or a calculator:</i></p> <ul style="list-style-type: none"> •Diabetes and age >60 years •Diabetes with microalbuminuria (> 20 mcg/min or urinary albumin:creatinine ratio >2.5 mg/mmol for males, >3.5 mg/mmol for females) •Moderate or severe chronic kidney disease (persistent proteinuria or estimated glomerular filtration rate [eGFR] <45 mL/min/1.73 m²) •A previous diagnosis of familial hypercholesterolaemia •Systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg •Serum total cholesterol >7.5 mmol/L •Aboriginal and Torres Strait Islander adults aged over 74 <p><i>For patients aged ≥ 45 years, or ≥ 35 for Aboriginal and Torres Strait Islander people without any of the above high risk conditions use an absolute risk calculator</i> (Framingham Risk Equation) to assess an absolute risk of CHD event</p>	<p>Framingham Risk Equation http://www.cvdcheck.org.au/ assesses CVD risk = likelihood of a person experiencing a cardiovascular event within the next five years;</p> <p>Absolute risk (AR) is calculated as the probability of a stroke, transient ischaemic attack, myocardial infarction, angina, peripheral arterial disease or heart failure occurring within the next 5 years.</p> <p>Cut-off threshold for high risk is >15%; moderate AR is 10%-15%; low risk is <10%</p>	<p>Patients at high absolute risk of CVD (>15% over 5 years) should be treated with both BP-lowering and lipid lowering agents;</p> <p>For patients at moderate absolute risk of CVD (10%–15%) treatment with a BP-lowering and/or a lipid-lowering agent should be considered if the risk remains elevated after lifestyle interventions, BP is >160/100mmHg, there is a family history of premature CVD, or an ethnicity factor; statins should be used as the first-line therapy. If LDL-C levels are not sufficiently reduced on maximally tolerated dose of statin, one or more of the following may be added:</p> <ul style="list-style-type: none"> • ezetimibe • bile acid binding resin • nicotinic acid <p>Recommended targets for lipid control in patients with high to moderate risk of CVD events</p> <p>TC <4.0 mmol/L; HDL-C ≥1.0 mmol/L; LDL-C <2.0 mmol/L; Non HDL-C <2.5 mmol/L; TG <2.0 mmol/L.</p>
National Heart	Secondary	By definition, patients diagnosed with	Not applicable	Use of lifestyle modification. statins

<p>Foundation of Australia and the Cardiac Society of Australia and New Zealand. <i>Reducing risk in heart disease: an expert guide to clinical practice for secondary prevention of coronary heart disease.</i> Australia, 2012</p>	<p>prevention Patients with existing coronary heart disease (CHD). This guide can be used by health professionals across the continuum of CHD care, including in acute settings, general practice, including for Chronic Disease Management (CDM) Medicare items, primary care, cardiac rehabilitation, and community and allied health services</p>	<p>existing coronary heart disease are at high risk of CVD event. In addition, the guidance stated that</p> <ul style="list-style-type: none"> • diabetes, • renal impairment and • non-CHD manifestations of atherosclerosis, such as cerebrovascular or peripheral vascular disease, <p>indicate high risk for coronary events and suggests that patients with CHD should be screened for these conditions regularly.</p>		<p>and BP-lowering medication for the secondary prevention of CVD event in high risk population</p> <ul style="list-style-type: none"> • Statin therapy is recommended for all patients with CHD (unless exceptional circumstances apply) • Statins are an added benefit to improve health that do not replace lifestyle changes • Muscle aches and pains are a common side effect, but rhabdomyolysis is rare. If creatine kinase is three times the upper limit of normal, monitor the patient closely and consider stopping statin therapy. • Fibrates effectively reduce cardiovascular risk in patients with type 2 diabetes, high TG or low HDL-C, and in patients who are overweight. • A combination of statins and a fibrate, can be prescribed but with caution. To reduce risk of myopathy with concomitant therapy, use fenofibrate instead of gemfibrozil. • Ezetimibe reduces the concentration of LDL-C by 15–20% as monotherapy, or when added to a statin. Long-term safety data of ezetimibe is satisfactory.
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*CVD refers collectively to coronary heart disease, stroke and other vascular disease, including peripheral arterial disease and renovascular disease.

In 2006, the Pharmaceutical Benefits Advisory Committee (PBAC) revised the Pharmaceutical Benefits Scheme (PBS) General Statement for Lipid-Lowering Drugs (GSLLD) prescribed as pharmaceutical benefits. This revision aimed to bring the PBS prescribing criteria for lipid-lowering drugs more in line with the absolute risk approach, while recognising that, at the time, a lack of widespread access to a CVD risk calculator was a barrier to using absolute risk as a prescribing criterion (Nelson, 2013).

The GSLLD covers both subgroups with and without a diagnosis of cardiovascular disease (CVD), where coronary heart disease (CHD) is just one condition in the broader category of CVD. Consistent with the NVDPA guidelines, the GSLLD assigns a high risk category to patients with a symptomatic CVD (CHD; cerebrovascular disease and peripheral vascular disease). Also consistent with NVDPA guidelines, patients with diabetes mellitus (DM) are assigned a high risk category if they are ≥ 60 years of age, Aboriginal or Torres Strait Islander patients or diagnosed with DM with microalbuminuria. Other criteria for high risk are defined differently in the GSLLD and the NVDPA guidelines (Table 2.2.)

Table 2.2. Discrepancies in risk factors corresponding to the high risk of a CVD event

Risk factor	Included in GSLLD	Included in NVDPA-2012
moderate or severe chronic kidney disease (CKD)	no	yes
family history of CHD which has become symptomatic before the age of 55 years in two or more 1 st degree relatives	yes	Not explicitly, but carries additional weight in the calculation of a cardiovascular risk with a web calculator or a chart
family history of CHD which has become symptomatic before the age of 45 years in one or more 1 st degree relatives	yes	Not explicitly, but carries additional weight in the calculation of a cardiovascular risk with a web calculator or a chart
A previous diagnosis of familial hypercholesterolaemia	Yes, conditional on the specified threshold in cholesterol level as in Table 2.4.	Yes, unconditionally [^]
Systolic blood pressure ≥ 180 mmHg or diastolic blood pressure ≥ 110 mmHg	Patients with hypertension (without specified thresholds) need to meet the specified cholesterol level thresholds as in Table 2.4.	Yes, unconditionally
Serum total cholesterol >7.5 mmol/L	No, except for males aged 35-75 years and post-menopausal women Table 2.4.	Yes, unconditionally

[^]consistent with guidelines identification and management of familial hypercholesterolaemia (Table A2.1 in appendix)

According to the GSLLD eligibility criteria, patients from the high risk categories are eligible for statins/other lipid lowering drugs at any level of fasting cholesterol. Patients who do not meet the criteria for high risk listed in Table 2.3 may still be eligible for the subsidised prescription of lipid-lowering drugs if they meet specified threshold in cholesterol level (Table 2.4)

Comparison of the GSLLD eligibility criteria with NVDPA/NHF guidelines is not straightforward as the documents differ in their objectives and scope. The GSLLD objective needs to be interpreted within the framework of the universal Australian health care system. One way of maximising the overall health of Australians is by restricting the PBS subsidised medications to the patients who are most

likely to achieve the expected health gains at a given budget. The objective of the NVDPA/NHF guidelines should be interpreted within the specific professional context of providing the evidence-based care to the population at risk of CVD. On the other hand, while any PBS restriction is necessarily focused on the specific medication (or a group, as in the case of statins), the focus of NVDPA/NHF guidelines is in helping the clinicians to develop an optimal clinical pathway, where any specific medication is only one of many inputs to consider.

Although the GSLLD eligibility criteria are broadly consistent with NVDPA/NHF guidelines the outlined differences are manifested in the definition of the target population and details of treatment recommendations. The NVDPA-2012, but not NHF guidelines include the lipid control targets (by TC; LDL-C; HDL-C, non HDL-C and TG) equally for all the patients with high to moderate risk of CVD events (Table 2.1). In comparison, the GSLLD sets the differential lipid eligibility thresholds for various combinations of risk factors in the population who are not in the high risk category.

With respect to the high risk population, the most obvious discrepancy is the absence of CKD from the list of the high risk factors in the GSLLD. Also, the NVDPA guidelines include a TC threshold of 7.5 mmol/L as a separate high risk criteria and not in combination with other risk factors (i.e. being a male aged 35-75 years or a post-menopausal woman) as in the GSLLD. The GSLLD elaborates on the family history of CHD by specifying 4 separate risk categories depending on the age, ethnicity, degree of relations and number of relatives. Depending on the combination of these factors the patients could be categorised as a high or low risk, where the low risk outcome would attract additional restrictions on the lipid levels. In contrast, the NVDPA guidelines include an unspecified family history of premature CVD as one of the risk categories. The same applies to a single risk factor of systolic blood pressure ≥ 180 mmHg or diastolic blood pressure ≥ 110 mmHg, a factor that, according to the NVDPA guidelines, would identify a patient as a high risk and in need of blood pressure (BP) and lipid lowering medications. According to the GSLLD, a patient with hypertension is required to try dietary therapy for at least 6 weeks and, if lipids are still above the specified levels, a patient would qualify for a subsidised treatment. There are some apparent inconsistencies in the NVDPA guidelines and the GSLLD in assigning the degree of risk to some patients that result in differences between the recommendations of the professional body of Australian cardiologists and patients' eligibility for the subsidised lipid-lowering medications (Doust 2012, Nelson 2013).

Table 2.3. General Statement For Lipid-Lowering Drugs prescribed as pharmaceutical benefits

Guidelines	Setting/Population/ scope	Risk factors included	Evidence base	Suggested lipid lowering management
<p>GENERAL STATEMENT FOR LIPID-LOWERING DRUGS PRESCRIBED AS PHARMACEUTICAL BENEFITS Australia, effective 1 October 2006.</p>	<p>Implicitly, both primary and secondary prevention in high and low risk patients to determine patient eligibility for subsidised prescription of PBS-listed lipid-lowering drugs atorvastatin calcium fluvastatin sodium pravastatin sodium rosuvastatin calcium simvastatin fenofibrate gemfibrozil</p>	<p>High risk population (can start statins or other lipid-lowering drugs at any level of cholesterol)</p> <ul style="list-style-type: none"> •coronary heart disease which has become symptomatic •cerebrovascular disease which has become symptomatic •peripheral vascular disease which has become symptomatic •diabetes mellitus with microalbuminuria (defined as urinary albumin excretion rate of >20mcg/min or urinary albumin to creatinine ratio of > 2.5 for males, > 3.5 for females) •diabetes mellitus in Aboriginal or Torres Strait Islander patients •diabetes mellitus in patients aged 60 years or more •family history of coronary heart disease which has become symptomatic before the age of 55 years in two or more first degree relatives •family history of coronary heart disease which has become symptomatic before the age of 45 years in one or more first degree relatives <p>Low risk population with elevated cholesterol level should first be provided with dietary therapy for at least 6 weeks. If unsuccessful, eligibility for PBS subsidised statins and other lipid-lowering drugs is determined by Table 2.4 below</p>	<p>included the Heart Protection Study (HPS), the United Kingdom Prospective Diabetes Study (UKPDS), Australian data audits and input from experts**</p>	<p><i>High risk population starts statins/other lipid lowering drugs at any level of fasting cholesterol.</i> <i>Low risk population with elevated fasting cholesterol level should first be provided with dietary therapy for at least 6 weeks. If unsuccessful, refer to other combination of a specified lipid levels and other risk factors (Table 1.4) to establish eligibility for PBS subsidised statins and other lipid-lowering drugs</i></p>

**Schilling et al, 2014.

Table 2.4. Post-dietary qualifying criteria for PBS subsidised cholesterol-lowering drugs

PATIENT CATEGORY	LIPID LEVELS FOR PBS SUBSIDY
Patients with diabetes mellitus not otherwise included	total cholesterol > 5.5 mmol/L
Aboriginal or Torres Strait Islander patients Patients with hypertension	total cholesterol > 6.5 mmol/L or total cholesterol > 5.5 mmol/L and HDL cholesterol < 1 mmol/L
Patients with HDL cholesterol < 1 mmol/L	total cholesterol > 6.5 mmol/L
Patients with familial hypercholesterolaemia identified by: DNA mutation; or tendon xanthomas in the patient or their first or second degree relative Patients with: family history of coronary heart disease which has become symptomatic before the age of 60 years in one or more first degree relatives; or family history of coronary heart disease which has become symptomatic before the age of 50 years in one or more second degree relatives	If aged 18 years or less at treatment initiation: LDL cholesterol > 4 mmol/L If aged more than 18 years at treatment initiation: LDL cholesterol > 5 mmol/L or total cholesterol > 6.5 mmol/L or total cholesterol > 5.5 mmol/L and HDL cholesterol < 1 mmol/L
Patients not eligible under the above: men aged 35 to 75 years post-menopausal women aged up to 75 years	total cholesterol > 7.5 mmol/L or triglyceride > 4 mmol/L
Patients not otherwise included	total cholesterol > 9 mmol/L or triglyceride > 8 mmol/L

3. Northern America (USA and Canada)

Issued in 2001, the guidelines by the US National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) set up a gold standard in cholesterol blood treatment. The ATP III provided guidelines on both when to initiate lipid-lowering therapy based on LDL-C level and CHD risk factors and recommended LDL-C targets for optimal CHD risk reduction (NCEP-ATP III, 2002). Following the publication of new evidence, the targets were updated in 2004 (NCEP-ATP III, 2004). According to the guidelines, clinicians could use statin monotherapy or combination therapy with statin and another lipid-lowering agent to achieve the specified LDL-C goals as the primary target followed by non-high-density lipoprotein cholesterol (non-HDL-C) as the secondary target in patients with triglycerides ≥ 200 mg/dL. It was suggested that there are potential benefits to treat with multiple agents, as the different mechanisms of action may produce other benefits unlikely to be achieved with statin alone. However, a combination of agents could result in an increase in side effects, as patients may experience the side effects common to both drugs (AHRQ 2014).

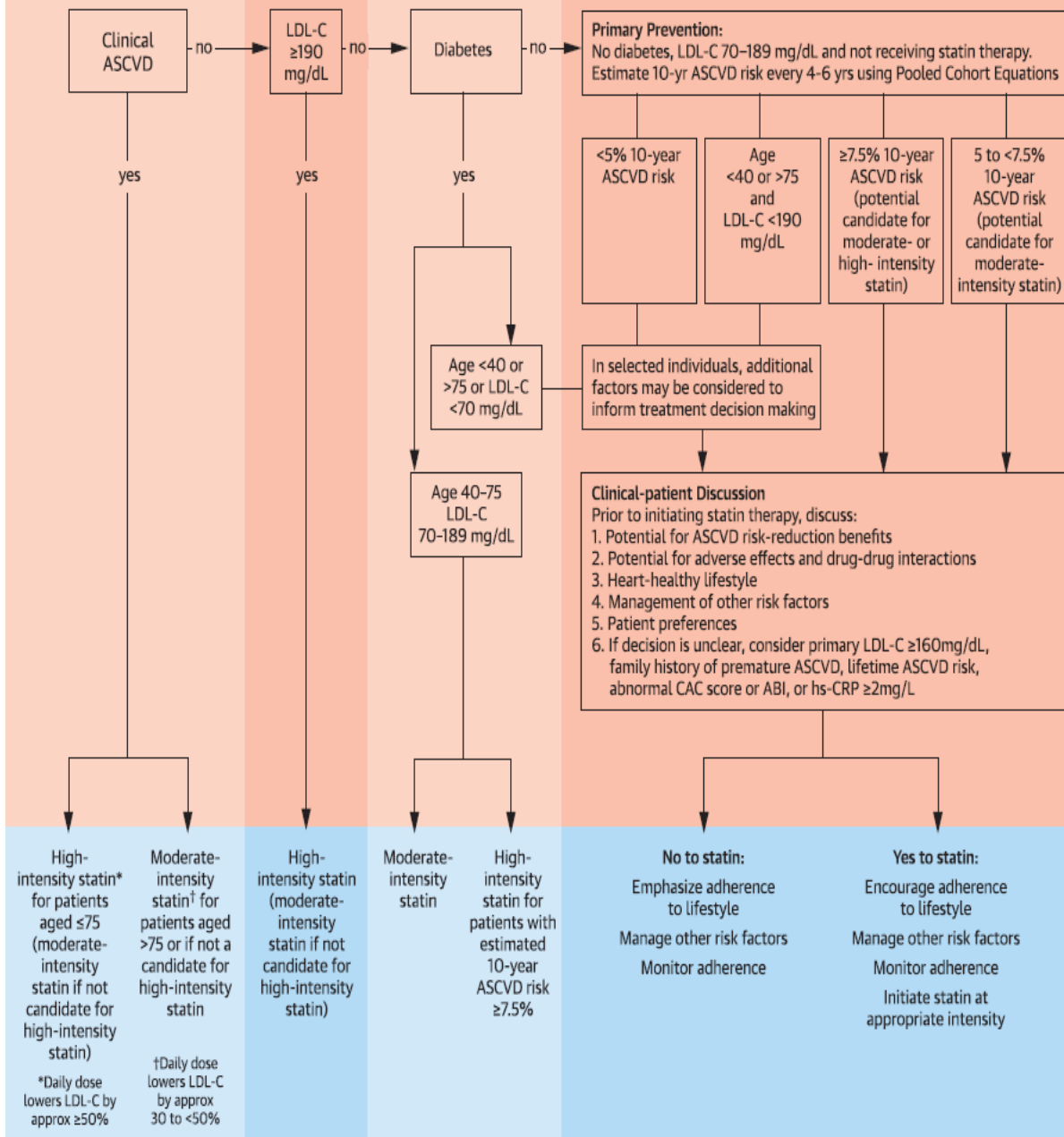
In 2008 the National Heart, Lung, and Blood Institute (NHLBI) convened a panel to review the evolving evidence base from RCTs regarding treatment of blood cholesterol. The resulting American College of Cardiology (ACC)/American Heart Association (AHA) Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults was released in November 2013 (ACCF/AHA-2013, Fihn 2012). The guideline is strongly focused on the recent large RCTs of fixed-dose statins versus placebo, or higher-intensity versus lower-intensity statin. The guideline advocates not only a new perspective on treatment strategies, but also a new paradigm focusing on proven therapy, rather than arbitrary low-density lipoprotein cholesterol and/or non-high-density lipoprotein cholesterol targets. It recommends prescribing at least a moderate dose statin to all patients with atherosclerotic cardiovascular disease (ASCVD) regardless of LDL-C values. No specific LDL-C targets (e.g. LDL-C ≤ 70 mg/dL (1.8 mmol/L) for high risk patients) were presented in the new guidelines given the lack of RCT evidence supporting specific targets. Rather, four “statin benefit groups” were identified: one secondary prevention group included patients with clinical atherosclerotic CVD; three primary prevention groups were: patients with LDL-C ≥ 190 mg/dL (4.91 mmol/L), diabetics aged 40-75 who have LDL-C levels 70 to 189 mg/dl (1.8 -4.9 mmol/L), and patients aged 40-75 who have LDL-C levels 70 to 189 mg/dl (1.8 -4.9 mmol/L) without diabetes but with a $\geq 7.5\%$ 10-year atherosclerotic CVD risk. A new risk assessment calculator, the Pooled Cohort Equations (PCE) with 10-year ASCVD risk projections for adults aged 40 to 75 years in the primary prevention setting was developed in parallel with the guidelines. In contrast to the Framingham Risk Score (FRS), which only predicts risk of “hard” coronary heart disease (clinical evidence of MI and coronary death), the PCE is more comprehensive. It predicts risk of ASCVD, including coronary heart disease, stroke and symptomatic carotid artery disease (Goff 2014, Naylor 2016).

Patients in one of the “statin benefit groups” are recommended for treatment with moderate- or high-potency statin monotherapy. A reference table where all FDA-approved statin doses are allocated into high-, moderate-, and low-intensity statin therapy is provided (and reproduced in Table A3.1 in Appendix). The expected response to a moderate-potency statin is LDL-C reduction of 30-50%, while the expected response to a high-potency statin is LDL-C reduction of $\geq 50\%$. Although low-intensity statin regimens are identified, they include doses that are lower than standard recommended starting doses. On average, low-intensity statin regimens are expected to reduce LDL-C less than 30%. Nonstatin therapies (i.e. ezetimibe, bile acid sequestrants, fibrates, niacin, and omega-3 fatty acids) are not recommended for routine use within these guidelines. For patients who do not have an expected response, once adherence has been assessed, the guidelines recommend considering intensification of statin therapy if the patient is not at maximum dose or the addition

of a non-statin agent with proven efficacy in reducing CVD events. Combination therapy can be considered in patients who cannot tolerate a high or moderate potency statin. Figure 3.1 illustrates the decision making algorithm for statin initiation.

Figure 3.1. ACCF/AHA-2013 guidelines on statin initiation in treatment of blood cholesterol

HEALTH STATUS OF ADULT CANDIDATE FOR STATIN THERAPY



For all patients, heart healthy lifestyle habits are recommended as the foundation of Atherosclerotic Cardiovascular Disease (ASCVD) prevention

Source: Smith, 2014

These guideline represents a significant change from the ATP III approach, which generated considerable discussion around the calculation of CVD risk, lack of cholesterol treatment targets, and reliance on RCT data only (McKenney 2015). For example, it was argued that the goal of assisting physicians in management of patients at risk was not achieved as the guidelines effectively apply a public health strategy rather than a clinical strategy by recommending standard doses of statins using evidence derived from RCTs (Smith 2014). The expected benefits would only be observed in practice if each patient's risk happen to be similar to the average risk of participants in the RCTs.

The National Lipid Association (NLA) has also produced recommendations for management of lipids that, unlike the treatment approach in ACC/AHA, endorsed a traditional lipoprotein target approach, similar to the NCEP ATP III (Jacobson 2014a, 2015). The NLA recommends specific non-HDL-C and LDL-C targets based on a patient's individual risk for CV disease, which is determined by the presence of major atherosclerotic cardiovascular disease (ASCVD) risk factors and the results of Framingham Risk Score estimations. Specific targets of therapy recommended by NLA for very high risk patients are non-HDL-C <100 mg/dL (2.6 mmol/L), LDL-C <70 mg/dL (1.8 mmol/L), and Apo B <80 mg/dL (2.1 mmol/L). In patients considered low, moderate, or high risk, these target values are slightly higher: non-HDL-C <130 mg/dL (3.4 mmol/L), LDL-C <100 mg/dL (2.6 mmol/L), and Apo B < 90 mg/dL (2.3 mmol/L). For patients considered high risk, the NLA recommends drug therapy when patients are above their individual targets. For moderate risk patient, the NLA recommends drug therapy when patients are ≥ 30 mg/dL (0.8 mmol/L) above their non-HDL-C and/or LDL-C targets. However, for low risk patients, they recommend considering drug therapy when lipoprotein values are considerably higher (≥ 60 mg/dL (1.55 mmol/L)) than the identified targets. Similar to ACC/AHA, the NLA strongly endorses use of moderate- to high-intensity statin therapy, but there is a greater endorsement for nonstatin drug combinations including (in order of preference) ezetimibe, bile acid sequestrants, and extended release niacin, for further lowering of atherogenic cholesterol in patients with a less than desirable response to maximally tolerated statin therapy: high- or very high-risk patients with recurrent or progressive ASCVD, patients with recent acute coronary syndromes, and patients with familial hypercholesterolemia (FH) (Jacobson 2015).

The fundamental differences between the ACC/AHA guidelines and the NLA recommendations relate to the fixed statin intensity approach recommended by ACC/AHA vs a treat to target approach, similar to the treatment management that many clinicians have used for decades in several other chronic diseases (e.g. diabetes and hypertension). Advocacy for treating to achieve a certain lipoprotein target is based on a rationale that achieving greater reductions in LDL-C (or non-HDL-C) is associated with greater reductions in risk of CVD event. However, only few RCTs allowed titration of the statin dose and the trials that allowed titration only allowed for 1 dose adjustment and targeted the certain total cholesterol or LDL-C concentration that have never been recommended as treatment targets. It was argued that without prospective clinical trials comparing a fixed dose approach versus a treat to target approach, it will never be definitively known which approach is superior (Phillips, 2016).

Both ACC/AHA guidelines and the NLA recommendations nominate statin therapy as first-line drug therapy for either primary or secondary prevention patients. Both ACC/AHA guidelines and NLA recommendations agree that statin intolerant patients are candidates for nonstatin medications. The NLA defines statin intolerance as a clinical syndrome characterized by the inability to tolerate at least 2 statins, one statin at the lowest starting daily dose and

another statin at any daily dose. The ACC/AHA guidelines do not provide any definition. In general, “statin intolerance” has not been systematically defined and estimates of statin intolerance within the statin treated population vary between the studies but could be up to 10% (Jacobson, 2014b). The NLA recommendations advocate for initiation of statin therapy based on risk category. Initiation of statin therapy typically starts at a moderate intensity dose with titration of the statin to a targeted non- HDL-C and LDL-C goal as tolerated. Therefore by default, the NLA recommendations advocate combination therapy as needed to achieve targets if not met while receiving the maximum tolerated high potency statin dose. The ACC/AHA guidelines advocate for a use of a specific statin dose based on the intensity that is matched to the patient’s statin benefit group. **The ACC/AHA guidelines do not advocate for specific lipoprotein targets and as a result the role of combination therapy is not as clear** (Phillips, 2016).

Table 3.1 presents the ACC/AHA guidelines and presents Table 3.2 NLA recommendations (reproduced from Table 1 in Waite, 2016)

Table 3.1 North American Guidelines (USA): the 2013 ACC/AHA guidelines

Guidelines/country/ year	Population/scope /setting	Risk factors and categories	Absolute risk assessment tool	Suggested lipid lowering management
<p>The American College of Cardiology/American Heart Association (ACC/AHA) guidelines USA 2013</p> <p>N.J. Stone, J.G. Robinson, A.H. Lichtenstein, et al., 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic</p>	<p>Treatment differentiates between primary and secondary preventions and uses strength of clinical evidence for justification of intensity of statin therapy (see Table A3.1 in Appendix)</p> <p>Intended to guide general practitioners’ clinical decisions in managing blood cholesterol</p>	<p>Identified 4 primary statin benefit groups:</p> <p>1) Individuals with clinical ASCVD (acute coronary syndromes, or a history of myocardial infarction, stable angina, coronary or other arterial revascularization, stroke, TIA, or peripheral arterial disease of atherosclerotic origin)</p> <p>2) Individuals with primary elevations of LDL-C >190 mg/dL (adults ≥21 y.o)</p> <p>3) Individuals with diabetes mellitus, without clinical ASCVD, aged 40-75 with LDL-C 70-189 mg/dL</p> <p>4) Individuals without clinical ASCVD or diabetes mellitus with LDL-C 70-189 mg/dL</p>	<p>Pooled Cohort Equations to estimate 10-year ASCVD risk (and lifetime risk for patients 20-59 years of age)</p>	<p>No evidence to recommend for or against lipid goals (specific LDL-C and non-HDL-C treatment goals); LDL-C levels and percent LDL-C reduction from baseline are used to assess adherence and response to therapy.</p> <p>Moderate- or high-intensity statin as first-line drug therapy in those groups shown to benefit.</p> <p>Primary prevention: LDL-C ≥190 mg/dL (adults ≥21 years of age)</p> <ul style="list-style-type: none"> • High-intensity statin therapy (or maximum tolerated dose) unless contraindicated; • Consider non-statin drug after maximum statin dose achieved if further LDL-C lowering needed <p>LDL-C 70-189 mg/dL (adults 40-75 years of age, without clinical ASCVD or diabetes mellitus)</p> <ul style="list-style-type: none"> • If 10-y ASCVD risk ≥7.5%, consider moderate- to high intensity statin therapy • If 10-y ASCVD risk of 5% to 7.5%, consider risks

<p>cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, Circulation 129 (2014) S1-S45</p>		<p>and estimated 10-y ASCVD risk $\geq 7.5\%$</p> <p>The expected response to a moderate-potency statin is LDL-C reduction of 30-50%, while the expected response to a high-potency statin is LDL-C reduction of $\geq 50\%$.</p>	<p>vs. benefits with moderate-intensity statin therapy</p> <p>Diabetes mellitus: (adults 40-75 years of age with diabetes mellitus)</p> <ul style="list-style-type: none"> • Moderate-intensity statin therapy • High-intensity statin therapy should be considered if estimated 10-y ASCVD risk $\geq 7.5\%$, unless contraindicated <p>Secondary prevention:</p> <ul style="list-style-type: none"> • High-intensity statin therapy should be initiated or continued in patients ≤ 75 years of age, unless contraindicated. If high-intensity statin therapy is not tolerable, use the maximum tolerated dose. • Moderate-intensity statin therapy should be initiated in individuals > 75 years of age, unless candidate for high-intensity statin therapy; evaluate ASCVD risk-reduction benefits vs. adverse effects, drug-drug interactions, and assess patient preferences prior to initiating moderate-intensity statin therapy <p>Nonstatin therapy</p> <ul style="list-style-type: none"> • For statin-intolerant patients due to adverse effects, once adverse effects resolve may consider re-starting statin at a low dose of the same statin or different statin and gradually increase the dose as tolerated • In patients who are unable to tolerate a less than recommended statin regimen (either moderate or high intensity) or who are statin-intolerant, may consider nonstatin monotherapy or the addition of a nonstatin cholesterol lowering agent <p>Combination therapy with statins</p> <p>In high-risk individuals receiving maximum tolerated</p>
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				<p>intensity of statin therapy who continue to have a less than- desired therapeutic response, addition of a nonstatin cholesterol-lowering drug(s) may be considered if the ASCVD risk-reduction benefits outweigh the potential for adverse effects. Higher-risk individuals include:</p> <ul style="list-style-type: none"> • Individuals with clinical ASCVD <75 years of age • Individuals with baseline LDL-C \geq190 mg/dL • Individuals 40-75 years of age with diabetes mellitus
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Table 3.2 North American Guidelines (USA): the 2014 NLA recommendations

Guidelines/country/ year	Population/scope /setting	Risk factors and categories	Absolute risk assessment tool	Suggested lipid lowering management
<p>NLA recommendations Jacobson TA, et al. National Lipid Association recommendations for patient-centered management of dyslipidemia: part 1-executive summary. J Clin Lipidol. 2014; 8(5):473-488.</p> <p>Jacobson TA, et al. National Lipid Association recommendations for patient-centered</p>	<p>Treatment differentiates between the categories of risk for ASCVD events rather than between primary and secondary preventions. Both Part 1 and 2 of NLA recommendations required more complex risk assessment and incorporated several specific populations that might be managed by both generalists and Specialists.</p>	<p>Major risk factors for ASCVD:</p> <ul style="list-style-type: none"> • Age: Male \geq45 years; Female \geq55 years • Family history of early CHD: <55 years of age in a male first-degree relative, or <65 years of age in a female first-degree relative • Current cigarette smoking • High blood pressure (\geq140/\geq90 mm Hg, or receiving blood pressure medication) • Low HDL-C: male <40 mg/dL; female <50 mg/dL <p>Risk indicators, other than major ASCVD risk factors, that can be considered for optional risk refinement:</p> <ul style="list-style-type: none"> • Strong smoking history (e.g., multiple packs per day) • Strong family history of ASCVD • Indicators of subclinical disease (e.g., coronary artery calcium \geq300 Agatston units) • LDL-C \geq160 mg/dL and 	<ul style="list-style-type: none"> • Framingham Risk Score (ATP III) to estimate 10-year or long-term and lifetime ASCVD risk • Pooled Cohort Equations (ACC/AHA) to estimate 10-year ASCVD risk 	<p>Moderate- or high-intensity statin should be first-line drug therapy for treatment of elevated levels of atherogenic cholesterol (non-HDL-C and LDL-C), unless contraindicated. Intensity of statin therapy should be individualized and based on patient-specific risk factors as well as baseline levels of atherogenic cholesterol.</p> <p>Levels of atherogenic cholesterol (non-HDL-C and LDL-C) should be the primary targets of therapy. (LDL-C <100 mg/dL for low, medium and high risk categories and <70 mg/dL for very high risk category); (non-HDL-C <130 mg/dL for low, medium and high risk categories and <100 mg/dL for very high risk category) ApoB (apolipoprotein) can be considered as an optional (secondary) target TGs become the primary target if \geq500 mg/dL. Goal levels are typically achieved in approximately 6 months. If LDL-C falls to <40 mg/dL, therapy may be continued in absence of intolerance.</p>

<p>management of dyslipidemia: part 2. J Clin Lipidol. 2015; 9(6 suppl): S1-S122</p>		<p>non-HDL-C \geq190 mg/dL</p> <ul style="list-style-type: none"> • hsCRP \geq2 mg/dL • Lp(a) \geq50 mg/dL • Urine albumin:creatinine ratio \geq30mg/g 		<p>For patients with TGs \geq500 mg/dL, target is a level of <500 mg/dL to prevent pancreatitis.</p> <p>If TGs \geq1000 mg/dL, then consider fibric acids, high-dose (2-4 g/d) long-chain omega-3 fatty acids, or nicotinic acid. If TGs 500-999 mg/dL and no history of pancreatitis, then consider fibric acids, long chain omega-3 fatty acids, or statin.</p>								
		<table border="1"> <tr> <td data-bbox="692 378 837 485">Low</td> <td data-bbox="837 378 1225 485"> <ul style="list-style-type: none"> •0-1 major ASCVD risk factors •Consider other risk indicators, if known </td> </tr> <tr> <td data-bbox="692 485 837 628">Moderate</td> <td data-bbox="837 485 1225 628"> <ul style="list-style-type: none"> •2 major ASCVD risk factors •Consider quantitative risk scoring •Consider other risk indicators </td> </tr> <tr> <td data-bbox="692 628 837 1278">High</td> <td data-bbox="837 628 1225 1278"> <ul style="list-style-type: none"> •3 major ASCVD risk factors •Diabetes mellitus (type 1 or 2) with 0-1 other major ASCVD risk factors and no evidence of end organ damage •Chronic kidney disease, stage \geq3B •LDL-C \geq190 mg/dL (severe hypercholesterolemia) •Quantitative risk scoring reaching the high risk threshold (defined as \geq10% 10-year risk using Framingham Risk Score; \geq15% 10-year risk using 2013 Pooled Cohort Equations; or \geq45% lifetime risk using the Framingham long-term risk calculation) </td> </tr> <tr> <td data-bbox="692 1278 837 1383">Very high</td> <td data-bbox="837 1278 1225 1383"> <ul style="list-style-type: none"> •ASCVD •Diabetes mellitus (type 1 or 2) and either 2 other major </td> </tr> </table>	Low	<ul style="list-style-type: none"> •0-1 major ASCVD risk factors •Consider other risk indicators, if known 	Moderate	<ul style="list-style-type: none"> •2 major ASCVD risk factors •Consider quantitative risk scoring •Consider other risk indicators 	High	<ul style="list-style-type: none"> •3 major ASCVD risk factors •Diabetes mellitus (type 1 or 2) with 0-1 other major ASCVD risk factors and no evidence of end organ damage •Chronic kidney disease, stage \geq3B •LDL-C \geq190 mg/dL (severe hypercholesterolemia) •Quantitative risk scoring reaching the high risk threshold (defined as \geq10% 10-year risk using Framingham Risk Score; \geq15% 10-year risk using 2013 Pooled Cohort Equations; or \geq45% lifetime risk using the Framingham long-term risk calculation) 	Very high	<ul style="list-style-type: none"> •ASCVD •Diabetes mellitus (type 1 or 2) and either 2 other major 		<p>Nonstatin therapy: For statin-intolerant patients consider switching statins; alternate-day or lower-dose statins; nonstatin monotherapy or in combination with other cholesterol-lowering agents.</p> <p>Combination therapy with statins a second (or third) agent may be considered for patients in high- or very high-risk categories with recurrent or progressive ASCVD; patients with recent acute coronary syndromes, and patients with familial hypercholesterolemia (FH) who have not reached their treatment goals to maximally tolerated statin therapy. Drugs used in combination with statin are (in order of preference) ezetimibe, bile acid sequestrants, and extended release niacin.</p>
Low	<ul style="list-style-type: none"> •0-1 major ASCVD risk factors •Consider other risk indicators, if known 											
Moderate	<ul style="list-style-type: none"> •2 major ASCVD risk factors •Consider quantitative risk scoring •Consider other risk indicators 											
High	<ul style="list-style-type: none"> •3 major ASCVD risk factors •Diabetes mellitus (type 1 or 2) with 0-1 other major ASCVD risk factors and no evidence of end organ damage •Chronic kidney disease, stage \geq3B •LDL-C \geq190 mg/dL (severe hypercholesterolemia) •Quantitative risk scoring reaching the high risk threshold (defined as \geq10% 10-year risk using Framingham Risk Score; \geq15% 10-year risk using 2013 Pooled Cohort Equations; or \geq45% lifetime risk using the Framingham long-term risk calculation) 											
Very high	<ul style="list-style-type: none"> •ASCVD •Diabetes mellitus (type 1 or 2) and either 2 other major 											

			ASCVD risk factors or Evidence of end-organ damage		
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Abbreviations used: ACC/AHA, American College of Cardiology/American Heart Association; NLA, National Lipid Association; RCT, randomized controlled trial; ASCVD, atherosclerotic cardiovascular disease; ATP III, National Cholesterol Education Program Adult Treatment Panel III; PCOS, polycystic ovary syndrome; ART, antiretroviral therapy; TIA, transient ischemic attack; LDL-C, low density lipoprotein cholesterol; non-HDL-C, non-high density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; CHD, coronary heart disease; hsCRP, high-sensitivity C-reactive protein; Lp(a), lipoprotein (a); Apo, apolipoprotein; TG, triglycerides; HIV, human immunodeficiency virus; FH, familial hypercholesterolemia.

The 2016 report of the Task Force on “ACC Clinical Expert Consensus Decision Pathway on the Role of Non-Statin Therapies”.

In January 2016 the American College of Cardiology released a report of the Task Force on “2016 ACC Clinical Expert Consensus Decision Pathway on the Role of Non-Statin Therapies in the Management of Atherosclerotic Cardiovascular Disease Risk”. The document was endorsed by the National Lipid Association (Lloyd-Jones 2016).

The recent position of the ACC as described in the Consensus Report supported the major evidence-based recommendations of the 2013 ACC/AHA Guideline. In particular, it is emphasised that the amount of the atherosclerotic cardiovascular disease (ASCVD) risk reduction observed with statins was directly related to the amount of LDL-C lowering achieved as a percentage of baseline. In agreement with the 2013 ACC/AHA cholesterol guideline, for all patient groups, the current consensus emphasizes that lifestyle modification (i.e., adherence to a heart-healthy diet, regular exercise habits, avoidance of tobacco products, and maintenance of a healthy weight) remains a critical component of ASCVD risk reduction, both before and in concert with the use of cholesterol-lowering drug therapies. The approach to statin intolerance adopted in the 2013 ACC/AHA Guideline was repeated and should include discontinuation of statin therapy and subsequent rechallenge to verify recurrence of muscle related symptoms. The rechallenge should involve at least 2 to 3 statins, preferably ones that use different metabolic pathways and have different lipophilicity of which is prescribed at the lowest approved dose. Non-statin therapies are not considered to be an alternative to evidence-based statin therapy unless statin intolerance has been systematically and rigorously evaluated and documented.

The Expert Panel has also explained the absence of the particular lipid lowering targets in the Guideline by stating that “Because no large RCTs have evaluated the outcome of drug titration to specific LDL-C targets, the 2013 ACC/AHA cholesterol guideline panel did not make specific recommendations regarding lipoprotein goals of therapy”. The Expert Panel also recognised the existing “lack of firmer and more specific guidance on the adequacy of statin therapy and whether or when to use non-statin therapies if response to statins is deemed inadequate,” and set out to address the gap by answer the following questions:

1. In what patient populations, should non-statin therapies be considered? *The patients are assumed to be currently taking or has attempted to take a statin.*
2. In what situations should non-statin therapies be considered, that is, when is the amount of LDL-C lowering (percent LDL-C reduction or LDL-C range achieved on therapy) less than anticipated, less than desired, or inadequate, and which treatment options should be considered in patients who are truly statin intolerant? *Answering this question in the absence of lipid targets presents a considerable challenge.*
3. If non-statin therapies are to be added, which agents or therapies should be considered and in what order?

The Expert Consensus produced treatment algorithms for a patient in each of the 4 evidence-based statin benefit groups identified in the 2013 ACC/AHA cholesterol guideline. However, the Expert Panel further subdivided the four original “statin benefit” patient groups. For example, the secondary prevention patient group with clinically diagnosed ASCVD was split into three depending on whether the ASCVD was stable; the presence of comorbidities (including diabetes, recent (<3 months) ASCVD event, ASCVD event while already taking a statin, poorly controlled other major

ASCVD risk factors, elevated lipoprotein, or CKD not on haemodialysis); and whether the baseline LDL-C was below or above the 190 mg/dL (4.91 mmol/L) threshold. For the patients who do not fall in one of these four groups who may be at elevated risk for ASCVD events (special populations), the Expert Panel recommended individualized care in the context of shared decision making between the clinician and patient.

The expert consensus endorsed the evidence-based findings from the 2013 ACC/AHA cholesterol guideline regarding the use of appropriate intensity statin therapy and the indicators of efficacy (e.g., >50% LDL-C reduction for high-intensity statin doses and 30% to <50% reduction for moderate intensity doses). At the same time, the Expert Panel acknowledged that patients in the RCTs that formed the evidential basis for the 2013 ACC/AHA guideline tended to achieve absolute LDL-C levels within a given range. Therefore, assuming adherence to therapy, patients with LDL-C levels above that range may not achieve maximal benefit and might be considered for additional therapy. Backing out somewhat from the 2013 ACC/AHA position in the guideline, **the Expert Panel therefore, judged that it was appropriate to provide levels of LDL-C, or “thresholds,” in terms of both percentage LDL-C reduction from baseline and absolute on-treatment LDL-C measurement**, which, if not achieved by adherent patients, would serve as factors to consider in decision making regarding further therapy. Therefore each of the Consensus Decision Pathways (algorithms) included an optional non-statin medication to consider on the basis of the indicative lipid goal.

In each algorithm, the lipid goals are expressed both in terms of %reduction, in accordance with the statin intensity (Table A3.1 in the Appendix) and in terms of absolute LDL-C level. Depending on the primary or secondary prevention status, comorbidities and the baseline LDL-C level, the lipid goals are set either at LDL-C <70mg/dL (1.8 mmol/L) or LDL-C <100mg/dL (2.6 mmol/L). For patients with diabetes the lipid goal is defined as non-HDL-C <130 mg/dL (3.4 mmol/L). However, the Expert Panel emphasised that these goals are not firm triggers for adding medication, but they are factors that may be considered within the broader context of an individual patient’s clinical situation. As an example, Figures A3.1 – A3.2 in the Appendix show two (out of the total 6 algorithms included in the Consensus statement) decision pathways.

For the patients who did not achieve a 50% LDL-C reduction (or, alternatively, a lipid goal), each decision making pathway includes an optional non-statin medication to consider. Ezetimibe is suggested as either the first choice of the non-statin second line medications or the only option in four out of 6 pathways. However, bile acid sequestrants can be used instead as the second line therapy if a patient is ezetimibe intolerant and with TG<300 mg/dL. **There is no clearly stated requirement for the patients to be on the maximum tolerated dose of statin to be considered for ezetimibe treatment.** If the lipid goal still not achieved in the secondary prevention subgroups with the baseline LDL-C <190 mg/dL (2.6 mmol/L), a PCSK9 inhibitor then can be prescribed either in addition or as a replacement of ezetimibe. For the secondary prevention subgroup with the baseline LDL-C ≥190 mg/dL (2.6 mmol/L), the Expert Panel considered to be reasonable to prescribe a PCSK9 inhibitor as a first choice of the second line therapy rather than ezetimibe. Interestingly, that **if a PCSK9 inhibitor is prescribed clinicians should continue maximally tolerated statin and monitoring for adherence to medications** and lifestyle, side effects, and ongoing LDL-C response to therapy. The subgroup of patients without the ASCVD diagnosis but with the baseline LDL-C ≥190 mg/dL (2.6 mmol/L), are recommended to be given **either ezetimibe or a PCSK9 inhibitor in combination with maximally tolerated statin therapy.** Due to tolerability, convenience, and single-tablet daily dose **ezetimibe is the preferred initial non-statin therapy in patients with diabetes** (regardless of the predicted 10-year ASCVD risk) **on maximally tolerated statin therapy.** PCSK9 inhibitors do not have an established role in primary prevention of ASCVD in patients with diabetes.

Table 3.3 North American Guidelines (Canadian Cardiovascular Society)

Guidelines/country/ year	Population/scope /setting	Risk factors and categories	Absolute risk assessment tool	Suggested lipid lowering management
<p>Canadian Cardiovascular Society T.J. Anderson 2012 update of the CCS guidelines for the diagnosis and treatment of dyslipidaemia for the prevention of cardiovascular disease in the adult, Can. J. Cardiol.29 (2013) 151-167</p> <p>Update of the 2009 CCS guidelines</p>	<p>Primary prevention population</p> <p>The CCS guideline goal is to increase the appropriate use of evidence-based CVD event risk assessment in the management of dyslipidaemia.</p>	<p>Factors moderating High risk assessment for ASCVD:</p> <ul style="list-style-type: none"> • Age: Male ≥40 years; Female ≥50 years or postmenopausal • Ethnicity (Native population or South Asia origin) • Current cigarette smoking; • Diabetes • Arterial hypertension • Obesity (body mass index > 27) • Family history of premature CVD • Family history of hyperlipidaemia • Erectile dysfunction • Chronic kidney disease • Inflammatory disease • HIV infection • Chronic obstructive pulmonary disease • Clinical evidence of atherosclerosis or abdominal aneurysm • Clinical manifestation of hyperlipidaemia <p>Proceed with history and examination, LDL, HDL, TG, non-HDL, glucose, estimated glomerular filtration rate (eGFR) and optionally apoB (instead of standard lipid panel), urine albumin:creatinine ratio (if eGFR < 60, hypertension, diabetes)</p>	<p>The 10-year risk of developing “total” cardiovascular events assessed with Framingham Risk Score (FRS), modified for a family history of premature coronary disease, is recommended for risk assessment. Threshold for low risk is <5%. FRS also estimates an individual patient “Cardiovascular Age”</p>	<p>The panel has retained the concept of lipid thresholds and targets for treatment. However, it is important to recognize that overall cardiovascular risk is dependent on the phenotype of the patient with LDL-C being only one of those factors. Also, targets for treatment are somewhat arbitrary because none of the intervention studies have aimed for specific lipid targets. In this update of the 2009 guidelines defined CKD as a significant cardiovascular risk factor.</p> <p>Nonstatin therapy: despite concerns about a variety of other possible adverse effects, all purported statin-associated symptoms should be evaluated systematically, incorporating observation during cessation, reinitiation (same or different statin, same or lower potency, same or decreased frequency of dosing) to identify a tolerated, statin-based therapy for chronic use. For subjects who do not tolerate statin therapy or only at a low dose, favourable effects on LDL-C can be achieved with ezetimibe, bile acid resins, or niacin. Niacin therapy alone has been shown to decrease CVD events. Fibrates have a favourable effect on triglyceride levels with minimal change on LDL-C, and gemfibrozil decreased CVD events in subjects with established coronary artery disease.</p> <p>Combination therapy with statins: none</p>

		Low risk	<ul style="list-style-type: none"> • No high risk features • FRS < 10% <p>≥50% reduction of LDL-C in LR individuals for whom treatment is initiated is recommended</p>	<p>If LDL-C <5 mmol/L and FRS< 5% - health behaviour modification; If LDL-C < 5 mmol/L and FRS 5%-9% proceed with optional secondary testing before prescribing statin therapy in addition to health behaviour modification If LDL-C ≥ 5 mmol/L or there is evidence of genetic dyslipidaemia (such as familial hypercholesterolemia) prescribe statin therapy in addition to health behaviour modification</p>
		Intermediate risk	<ul style="list-style-type: none"> • No high risk features • FRS 10%-19% <p>the primary target remains LDL-C ≤2.0 mmol/L or ≥ 50% reduction of LDL-C from untreated baseline. Alternate targets include apo B ≤0.8 g/L (unchanged) or non-HDL-C ≤2.6mmol/L (new).</p>	<p>If LDL-C <3.5 mmol/L proceed with optional additional risk stratification based on alternative targets (apolipoprotein [Apo] B ≥1.2 g/L or non-HDL-C ≥4.3 mmol/L) or secondary testing before prescribing statin therapy in addition to health behaviour modification; If LDL-C ≥ 3.5 mmol/L prescribe statin therapy in addition to health behaviour modification; Prescribe statin therapy to patients who met JUPITER trial selection criteria men >50 years and women > 60 years of age and C-reactive protein (CRP) ≥2 mg/L and LDL < 3.5 mmol/L</p>
		High risk	<ul style="list-style-type: none"> • FRS ≥ 20% • Clinical vascular disease • Abdominal Aortic Aneurysm • Diabetes and age ≥ 40 yrs or >15 yrs duration and age ≥ 30 yrs or microvascular disease • Chronic kidney disease • High risk hypertension <p>The primary target remains LDL-C ≤2.0 mmol/L or ≥ 50% reduction of LDL-C from untreated baseline.</p>	<p>Prescribe statin therapy in addition to health behaviour modification</p>

The 2012 CCS guidelines recommended risk stratification using the total cardiovascular disease Framingham Risk Score (FRS), advocated the use of LDL-C thresholds for the initiation of treatment in low- and intermediate-risk subjects and expanded the phenotype of high-risk subjects to include subjects with atherosclerosis, most patients with diabetes, high-risk hypertension and pre-dialysis CKD. LDL-C continues to be used as the atherogenic metric, but now non-HDL-C and apolipoprotein B (apo B) could be measured as alternatives. When treatment is initiated, LDL-C (< 2.0 mmol/L or 50% reduction) continues to be the primary target of therapy. Figure 3.2. Illustrates a statin treatment decision pathway.

Figure 3.2. 2012 CCS guidelines on statin initiation according to risk stratification by FRS and phenotype

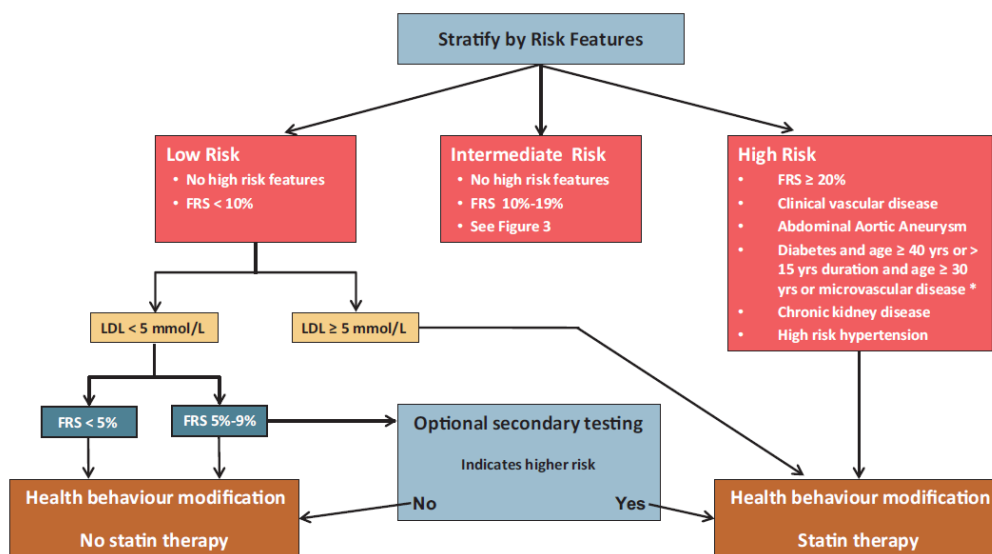


Figure 2. Risk stratification by Framingham Risk Score (FRS) and phenotype. *Not all subjects with diabetes are at high 10-year risk; included for treatment based on randomized studies and high long-term risk.

The 2012 CCS guidelines were compared with the ACC/AHA guidelines that were the latest to be released and created the most controversy. A major novel aspect of these guidelines was the recommendation to calculate risk using the newly developed Pooled Cohort Equation. This approach represents a departure from the use of the FRS, used for decades. It was suggested that of the 4 “statin-benefit” groups, 3 were the same as the CCS guidelines. These include subjects with: (1) clinical evidence of atherosclerosis; (2) most subjects with diabetes; and (3) individuals with LDL-C ≥5.0 mmol/L. The fourth group includes subjects with a 10-year risk of total atherosclerotic events calculated using the Pooled Cohort Equation of ≥7.5%. There was no specific recommendation for CKD and other populations such as genetic dyslipidemia or high-risk hypertension. An additional novel aspect of the ACC/AHA guidelines was the lack of specific targets of therapy. Although these guidelines recommend the use of high- or moderate intensity statin regimens based on level of risk and anticipate a 50% LDL-C decrease with high-intensity statin therapy, there is no recommendation for treating to any specific target. Therefore, lipid measurements after initiation of statin therapy are recommended, primarily to ensure adherence (Anderson, 2015). Although the 2012 CCS guidelines retained lipid goals as an instrument for clinical decision making, it has also kept the 50% LDL-C reduction as an alternative criteria, as in the 2013 ACC/AHA. Another common characteristic is in identifying the target population in terms of the selection criteria of the published RCTs, although in the 2012 CCS it applies only to CKD population.

4. National Institute for Health and Care Excellence (NICE) guidelines (UK)

The 2014 NICE recommendations “Cardiovascular disease: risk assessment and reduction, including lipid modification” (2014 NICE guidance/cg181) are the update of the 2008 NICE clinical guideline for cardiovascular disease: risk assessment and reduction, including lipid modification (2008 NICE guidance/cg67) and the 2006 technology appraisal guidance (2006 NICE TA94). The 2014 NICE update are based on systematic reviews of best available evidence and explicit consideration of cost effectiveness. When minimal evidence is available, recommendations are based on the guideline development group's experience and opinion of what constitutes good practice. The update makes a clear recommendation for the use of QRISK2 as the preferred cardiovascular disease (CVD) risk assessment tool, including people with type 2 diabetes. The threshold for consideration of statin treatment has dropped from 20% CVD risk to 10% CVD 10-year risk. The guideline recommends the use of non-HDL-cholesterol rather than LDL-C because non-HDL-cholesterol does not require a fasting sample. For the purpose of the 2014 guidelines, statins are grouped into 3 different intensity categories according to the percentage reduction in low-density lipoprotein cholesterol (see Table A4.1 in Appendix). The assigned intensity categories are generally consistent with the categories assigned by the ACC/AHA experts (Table A3.1 in Appendix).

Both the NICE approach and the ACC/AHA guideline offer statin therapy on the basis of an estimated 10-year risk of ASCVD (Table 4.1). *In comparison, the Australian NVDPA-2012 guidelines are based on 5-year risk assessment. The risk threshold of $\geq 10\%$ for treatment initiation is set by both Australian and NICE guidelines, in contrast to the $\geq 7.5\%$ threshold set by ACC/AHA, which is the lowest threshold in all other leading international guidelines.* Neither the 2013 ACC/AHA nor the 2014 NICE guidance (cg181) endorse a treat-to-target strategy but specify instead the appropriate intensity of statin for each risk category. However, the separate recent technology appraisal “Ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia” (2016 NICE TA385) departed from the 2014 NICE guidelines by **ruling that despite the recommendations in NICE's guideline on lipid modification, based on 10-year cardiovascular risk assessment, meeting target cholesterol levels to prevent CV disease remained an important part of clinical practice in England.** This is the same dilemma that brought about the 2016 ACC/AHA Consensus statement, namely that without the defined lipid targets it is not clear for the clinicians when initiation of non-statin second line treatment is warranted. Therefore both the recent ACC/AHA Consensus statement on the role of non-statin therapies and the 2016 NICE TA385 clearly identify the position of ezetimibe in the treatment algorithm in the context of failure to achieve lipid targets. The TA385 also concluded that no treatments apart from ezetimibe monotherapy are established NHS practice in England for treating familial and non-familial hypercholesterolaemia in adults who are unable to take a statin (Table 4.2).

Table 4.1 the 2014 National Institute for Health and Care Excellence (NICE) guidelines

Guidelines/country/ year	Setting/Population/ scope	Risk factors included	Absolute risk assessment tool	Suggested lipid lowering management
<p>Cardiovascular disease: risk assessment and reduction, including lipid modification. <i>Clinical guideline CG181</i> July 2014 nice.org.uk/guidance/cg181 Replacement of clinical guidelines CG67 and NICE technology appraisal guidance 94</p>	<p>People at risk of cardiovascular disease (except people on renal replacement therapy). Guidelines differentiate between primary and secondary prevention populations</p>	<p>None of the risk factors were explicitly identified, the emphasis is paid to the factors that can result in the underestimation of the QRISK2 risk assessment score: People being treated for HIV</p> <ul style="list-style-type: none"> -People with serious mental health problems -People taking drugs that can cause dyslipidaemia such as antipsychotic drugs, corticosteroids, or immunosuppressants -People with systemic inflammatory disorders such as systemic lupus erythematosus 	<p>The 10 year QRISK2 risk assessment tool is used to assess CVD risk for the primary prevention of CVD in people ≤ 84 years, based on their risk profile in medical records. QRISK2 risk assessment tool is not suitable for people with familial hypercholesterolaemia; type 1 diabetes or in people with (eGFR) ≤ 60 ml/min/1.73m² and/or albuminuria and pre-existing CVD</p> <p>Threshold for the high risk of CVD is 10% over 10 years</p>	<p>Before starting lipid modification therapy for the primary prevention of CVD, measure a full lipid profile including measurement of TC, HDL-C, non-HDL cholesterol, and triglyceride concentrations. A fasting sample is not needed.</p> <p>For the primary prevention of CVD Discuss the benefits of lifestyle modification and offer statins after the patients have tried to change their lifestyle. Offer statin treatment after [a repeated] risk assessment to adults with type 1 diabetes; type 2 diabetes and CKD (<i>if some specific conditions are met</i>) Start statin treatment with</p> <ul style="list-style-type: none"> • atorvastatin 20 mg <p>for other categories of people with $\geq 10\%$ 10-year risk of developing CVD discuss the benefits of lifestyle modification and optimise the management of all other modifiable CVD risk factors if possible; If lifestyle modification is ineffective or inappropriate start statin treatment with</p> <ul style="list-style-type: none"> • atorvastatin 20 mg <p>For people with CVD (secondary prevention) Do not delay statin treatment in secondary prevention to manage modifiable risk factors; Do not delay statin treatment if a person has acute coronary syndrome. Start statin treatment with</p> <ul style="list-style-type: none"> • atorvastatin 80 mg or • a lower dose if potential drug interactions and/or high risk of adverse effects are likely <p>Measure TC, HDL-C and non-HDL cholesterol at 3 months of high-intensity treatment and aim for $\geq 40\%$ reduction in non-HDL</p>

		<p>-People who are already taking antihypertensive or lipid modifying drugs</p> <p>-People who have recently stopped smoking</p> <p>-Severely obese people (body mass index greater than 40).</p>		<p>cholesterol. If $\geq 40\%$ reduction in non-HDL cholesterol is not achieved: discuss adherence and timing of dose; optimise adherence to diet and lifestyle measures; consider increasing the dose if started on less than atorvastatin 80 mg and the person is judged to be at higher risk because of comorbidities, risk score or using clinical judgement.</p> <p>When people who are stable on a low- or middle-intensity statin, discuss the likely benefits and potential risks of changing to a high-intensity statin when they have an annual medication review and agree with the person whether a change is needed.</p> <p>Statin intolerance</p> <ul style="list-style-type: none"> • Stop the statin and try again when the symptoms have resolved to check if the symptoms are related to the statin • Reducing the dose within the same intensity group • Changing the statin to a lower intensity group. <p>Combination therapy for preventing CVD</p> <p>Do not offer the combination of a bile acid sequestrant (anion exchange resin), fibrate, nicotinic acid or omega-3 fatty acid compound with a statin for the primary or secondary prevention of CVD</p> <p>Ezetimibe treatment</p> <p>Ezetimibe treatment is initiated in line with ezetimibe for the treatment of primary hyper-cholesterolaemia guidelines (<i>TA385, replacing TA132</i>).</p>
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Table 4.2 the 2016 National Institute for Health and Care Excellence (NICE) ezetimibe technology appraisal guidance [TA385].

Guidelines/Technical appraisal /year	Population/scope	Risk factors included	Absolute risk assessment tool	Suggested lipid lowering management
<p>Ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia</p> <p><i>NICE technology appraisal guidance [TA385]</i></p> <p>February 2016</p> <p>nice.org.uk/guidance/ta385</p>	<p>Adults with primary heterozygous-familial and non-familial hypercholesterolaemia.</p>	<p>Appropriate control of cholesterol concentrations should be based on individual risk assessment according to national guidance on managing cardiovascular disease (CG181).</p>	<p>Cardiovascular disease risk calculator QRISK2 for assessing 10-year cardiovascular risk may be used in clinical decision making</p> <p><i>Although meeting a lipid target is acknowledged as a legitimate therapy goal, no specific targets are recommended</i></p>	<p><i>Consistent with clinical practice in the NHS, treating hypercholesterolaemia to prevent cardiovascular disease starts <u>either</u> because of a person's 10-year risk of developing cardiovascular disease <u>or</u> to meet a specific target cholesterol level.</i></p> <p><i>The Committee concluded that statins are the main option for treating primary hypercholesterolaemia (when a statin is considered appropriate), and that no treatments apart from ezetimibe monotherapy are established NHS practice in adults who are unable to take a statin</i></p> <p>Ezetimibe monotherapy is recommended as an option in adults</p> <ul style="list-style-type: none"> a) in whom initial statin therapy is contraindicated; b) who cannot tolerate statin therapy (i.e. in presence of clinically significant adverse effects that represent an unacceptable risk to the patient or that may reduce compliance with therapy); <p>Ezetimibe, co-administered with initial statin therapy, is recommended in adults when</p> <ul style="list-style-type: none"> a) serum total or low-density lipoprotein (LDL) cholesterol concentration is not appropriately controlled (<i>according to the national guidance on managing cardiovascular disease CG181</i>) either after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance to the initial statin therapy and b) a change from initial statin therapy to an alternative statin is being considered

5. European guidelines

The literature search identified the 2012 European Guidelines on cardiovascular disease prevention in clinical practice by the Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (Perk 2012). The lifetime approach to cardiovascular (CV) risk advocated in the 2012 European Guidelines was adopted in the 2016 “Guidelines for the Management of Dyslipidaemias” by the European Society of Cardiology/ European Atherosclerosis Society (Catapano 2016), which updated the 2011 version of the ESC/EAS guidelines (Reiner 2011). As in the previous version, the 2016 guidelines makes a comprehensive document addressing cardiovascular risk assessment, laboratory examinations, lifestyle modifications, drug treatment, and the approach to treatment of specific clinical subgroups such as patients with familial dyslipidemias or diabetes. The ESC/EAS task force based its findings on a comprehensive review of the literature in which greater confidence was placed in the results of randomized, controlled trials but was inclusive of all study designs.

A CV risk in the context of these guidelines means the likelihood of a person developing a fatal or non-fatal atherosclerotic CV event over a defined period of time. For the primary prevention population, both the ESC/EAS and the European guidelines recommend the Systematic Coronary Risk Evaluation (SCORE) risk assessment tool because it is based on large, representative European cohort datasets. Of note, the SCORE risk assessment is also based on the Framingham risk equation (Anderson Mitchell 2015) and is not used for patients with diagnosed CVD, diabetes, chronic kidney disease (CKD), familial hypercholesterolaemia or very high levels of individual risk factors because such people are already defined as at high-risk (see below). SCORE charts (and electronic version, HeartScore) are available for both total cholesterol (TC), HDL-C and the TC:HDL-C ratio. The SCORE system estimates the 10-year cumulative risk of a first fatal atherosclerotic event, whether heart attack, stroke or other occlusive arterial disease, including sudden cardiac death. The reasons for retaining a system that estimates fatal as opposed to total fatal + non-fatal events are that non-fatal events are dependent on the definition, developments in diagnostic tests and methods of ascertainment, all of which can vary. The total cardiovascular mortality can be easier re-calibrated to obtain the risk estimates as charts for high- and low-risk regions in Europe. To convert the risk of fatal CVD to the risk of total (fatal + nonfatal) CVD, the former is multiplied by 3 in men and 4 in women, and slightly less in old people (Catapano 2016).

The European guidelines are consistent with the 2004 and 2014 NCEP ATP III recommendations (Grundy 2004, Jacobson 2014 a,b) in dividing cardiovascular risk into four categories (low, moderate, high, very high). Very high risk is assigned to patients with documented CVD, type 2 diabetes mellitus, type 1 diabetes mellitus with target organ damage or with a major risk factor such as smoking, hypertension or dyslipidaemia, severe CKD (glomerular filtration rate (GFR) <30 mL/min/1.73 m²), or estimated 10-year absolute risk of fatal CVD $\geq 10\%$. High-risk individuals are those with markedly elevated single risk factors (e.g. in familial hypercholesterolaemia) or severe hypertension; most patients with DM (unless in the high risk category); patients with moderate CKD (GFR 30–59 mL/min/1.73 m²); or with a 10-year risk of fatal CVD of 5% to 9.9%. Moderate risk is defined as a 10-year risk of fatal CVD of 1% to 4.9%, and low risk is defined as an estimated 10-year risk of fatal CVD event $<1\%$ (Table 5.1).

Extrapolating from clinical trials, the task force recommended LDL-C goals of approximately <70 mg/dL (1.8 mmol/L) for very high risk, <100 mg/dL (2.6 mmol/L) for high risk, <115 mg/dL (3.0 mmol/L) for low to moderate risk subgroups (Table 5.1)

Table 5.1 the 2016 ESC/EAS European guidelines

Guidelines/country/year	Population/scope/setting	Risk factors and categories	Absolute risk assessment tool	Suggested lipid lowering management **
<p>European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) task force A.L. Catapano, et al., 2016 ESC/EAS guidelines for the management of dyslipidaemias. The task force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) Eur Heart J, 27 August, 2016 (http://eurheartj.oxfordjournals.org/content/early/2016/08/26/eurheartj.ewh272)</p> <p>Is an update of the 2011 ESC/EAS guidelines Z. Reiner, A.L. Catapano, ESC/EAS guidelines for the management of dyslipidaemias: the task force for the management of dyslipidaemias of the ESC and EAS. Eur Heart J, 32 (2011), pp. 1769–1818</p>	<p>The aim is to assist physicians [e.g. general practitioners and cardiologists] interested in CVD prevention, and also specialists from lipid clinics or metabolic units in selecting the best management strategies for an individual patient, with a given condition, taking into account the impact on outcome, as well as the risk–benefit ratio of particular diagnostic or therapeutic means</p>	<p>Very high risk:</p> <ul style="list-style-type: none"> • Diagnosed CVD • Severe CKD [GFR <30 mL/min/1.73 m²] • Type 2 diabetes or type 1 diabetes with target organ damage; • 10 year risk SCORE ≥10%. <p>High risk:</p> <ul style="list-style-type: none"> • Markedly elevated single risk factors e.g. in familial hypercholesterolaemia; cholesterol >8 mmol/L (>310 mg/dL) or severe hypertension (BP ≥180/110 mmHg) • most patients with DM • moderate CKD (GFR 30–59 mL/min/1.73 m²). • 10 year risk SCORE ≥5% to <10% <p>Moderate risk:</p> <ul style="list-style-type: none"> • 10 year risk SCORE ≥1% to <5%; <p>Low risk:</p> <ul style="list-style-type: none"> • 10 year risk SCORE <1% 	<p>The Systematic COronary Risk Evaluation (SCORE) risk assessment tool, designed to assess the risk of a first fatal atherosclerotic event, whether heart attack, stroke, or other occlusive arterial disease, including sudden cardiac death, calculated for 10 years or until age 60. Requires TC value to be entered; and the charts are also available for TC:HDL-C ratio; electronic version exists for HDL-C inputs.</p>	<p>After exploiting lifestyle and dietary modifications start with a statin; statin doses and the type of statin should reflect the degree of LDL-C reduction that is required to reach the target LDL-C (Table A5.1 in Appendix). Prescribe statin up to the highest recommended dose or highest tolerable dose to reach the goal. In the case of statin intolerance, ezetimibe or bile acid sequestrants, or these combined, should be considered. Should the target value have not been met, statin combination with a cholesterol absorption inhibitor (ezetimibe) should be considered first followed by the statin combination with a bile acid sequestrant. In patients at very high-risk, with persistent high LDL-C despite treatment with maximal tolerated statin dose, in combination with ezetimibe or in patients with statin intolerance, a PCSK9 inhibitor may be considered.</p>

*Source: Table 5, p.16 & Table 10, p.21 (Catapano, 2016) ** Source: Table 16, p.32 (Catapano, 2016)

TC and LDL-C remain the primary targets recommended in the ESC/EAS guidelines since virtually all drug trials are based on TC and LDL-C, and that clinical benefit from using other measures, including apoB, non-HDL-C and various ratios, has largely been based on post hoc analyses. LDL-C levels continue to constitute the primary targets of therapy. However, with TG values beyond > 200 mg/dL (5.2 mmol/L), treatment decisions should be made on the basis of non-HDL-C.

In the 2016 update of the ESC/EAS guidelines the definitions of treatment targets for LDL-C was expanded by including the percentage reduction from the baseline LDL-C for the very high and high risk groups. The secondary targets expressed in non-HDL-C were introduced for some patient subgroups. Table 5.2 summarises the treatment targets.

Table 5.2 Primary and secondary treatment targets

Subgroup	LDL-C target	% reduction from the baseline LDL-C	Other lipids (secondary targets)
Very high-risk	<1.8 mmol/L (70 mg/dL)	at least 50% if the baseline is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL).	Non-HDL-C <2.6 mmol/L (100 mg/dL)
High-risk	<2.6 mmol/L (100 mg/dL)	at least 50% if the baseline is between 2.6 and 5.2 mmol/L (100 and 200 mg/dL).	Non-HDL-C <3.4 mmol/L (130 mg/dL)
Low to moderate risk:	<3.0 mmol/L (115 mg/dL)	Not defined	Non-HDL-C <3.8 mmol/L (145 mg/dL)

Source: Table 10, p.21 (Catapano, 2016)

Variations in the treatment targets introduced in the 2016 update of the ESC/EAS guidelines reflect the ACC/AHA preference to fixed-dose strategies instead of targeted goals to lower blood cholesterol by introducing percentage reduction from the LDL-C baseline. The secondary target expressed in non-HDL-C lipid measure is consistent with the recent NICE guidelines that utilise non-HDL-C in the QRISK2 risk calculator.

The ESC/EAS guidelines also summarised the current evidence of clinical effectiveness of ezetimibe (p.31):

- As a monotherapy ezetimibe reduce LDL-C by 15–22%.
- Combined therapy with ezetimibe and a statin provides an incremental reduction in LDL-C of 15–20%.
- The efficacy of PCSK9 inhibitor at reducing LDL-C is in the range of 50–70%, independent of the presence of a background therapy (statins, ezetimibe, etc).

Conclusion

ToR 2: Review recent clinical guidelines for the treatment of hypercholesterolaemia and compare this to how ezetimibe is currently used on the Pharmaceutical Benefits Scheme (PBS);

The research questions in relation to the ToR 2 include:

Q1: Are the eligibility criteria for PBS subsidy of lipid-lowering therapies (as specified in the General Statement for Lipid-Lowering Drugs [GSLLD]) consistent with Australian guidelines for primary (NVDPA-2012) and secondary (NHF-2012) prevention of cardiovascular events?

The GSLLD covers both subgroups with and without a diagnosis of cardiovascular disease (CVD), where coronary heart disease (CHD) is just one condition in the broader category of CVD. Consistent with the NVDPA guidelines, the GSLLD assigns a high risk category to patients with a symptomatic CVD (CHD; cerebrovascular disease and peripheral vascular disease). Also consistent with NVDPA guidelines, patients with diabetes mellitus (DM) are assigned a high risk category if they are ≥ 60 years of age, Aboriginal or Torres Strait Islander patients or diagnosed with DM with microalbuminuria. Other criteria for high risk are defined differently in the GSLLD and the NVDPA guidelines. The Table below, reproduced from Section 2 lists discrepancies in risk factors corresponding to the high risk of a CVD event.

Risk factor	Included in GSLLD	Included in NVDPA-2012
moderate or severe chronic kidney disease (CKD)	no	yes
family history of CHD which has become symptomatic before the age of 55 years in two or more 1 st degree relatives	yes	Not explicitly, but carries additional weight in the calculation of a cardiovascular risk with a web calculator or a chart
family history of CHD which has become symptomatic before the age of 45 years in one or more 1 st degree relatives	yes	Not explicitly, but carries additional weight in the calculation of a cardiovascular risk with a web calculator or a chart
A previous diagnosis of familial hypercholesterolaemia	Yes, conditional on the specified threshold in cholesterol level as in Table 2.4.	Yes, unconditionally [^]
Systolic blood pressure ≥ 180 mmHg or diastolic blood pressure ≥ 110 mmHg	Yes, conditional on the specified threshold in cholesterol level as in Table 2.4.	Yes, unconditionally
Serum total cholesterol >7.5 mmol/L	No, except for males aged 35-75 years and post-menopausal women Table 2.4.	Yes, unconditionally

[^]consistent with guidelines identification and management of familial hypercholesterolaemia (Table A2.1 in appendix)

According to the GSLLD eligibility criteria, patients from the high risk categories are eligible for statins/other lipid lowering drugs at any level of fasting cholesterol. Patients who do not meet the criteria for high risk listed may still be eligible for the subsidised prescription of lipid-lowering drugs if they meet specified threshold in cholesterol level.

Comparison of the GSLLD eligibility criteria with NVDPA/NHF guidelines is not straightforward as the documents differ in their objectives and scope. The GSLLD objective needs to be interpreted within the framework of the universal Australian health care system. One way of maximising the overall health of Australians is by restricting the PBS subsidised medications to the patients who are most likely to achieve the expected health gains at a given budget. The objective of the NVDPA/NHF guidelines should be interpreted within the specific professional context of providing the evidence-based care to the population at risk of CVD. On the other hand, while any PBS restriction is necessarily focused on the specific medication (or a group, as in case of statins), the focus of NVDPA/NHF guidelines is in helping the clinicians to develop an optimal clinical pathway, where any specific medication is only one of many inputs to consider.

Although the GSLLD eligibility criteria are broadly consistent with NVDPA/NHF guidelines the outlined differences are manifested in the definition of the target population and details of treatment recommendations. The NVDPA-2012, but not NHF guidelines include the lipid control targets (by TC; LDL-C; HDL-C, non HDL-C and TG) equally for all the patients with high to moderate risk of CVD events (Table 2.1). In comparison, the GSLLD sets the differential lipid eligibility thresholds for various combinations of risk factors in the population who are not in the high risk category.

With respect to the high risk population, the most obvious discrepancy is the absence of CKD from the list of the high risk factors in the GSLLD. Also, the NVDPA guidelines include a TC threshold of >7.5 mmol/L as a separate high risk criteria and not in combination with other risk factors (i.e. being a male aged 35-75 years or a post-menopausal woman) as in the GSLLD. The GSLLD elaborates on the family history of CHD by specifying 4 separate risk categories depending on the age, ethnicity, degree of relations and number of relatives. Depending on the combination of these factors the patients could be categorised as a high or low risk, where the low risk outcome would attract additional restrictions on the lipid levels. In contrast, the NVDPA guidelines include an unspecified family history of premature CVD as one of the risk categories. The same applies to a single risk factor of systolic blood pressure ≥ 180 mmHg or diastolic blood pressure ≥ 110 mmHg, a factor that, according to the NVDPA guidelines, would identify a patient as a high risk and in need of blood pressure (BP) and lipid lowering medications. According to the GSLLD, a patient with hypertension is required to try dietary therapy for at least 6 weeks and, if lipids are still above the specified levels, a patient would qualify for a subsidised treatment. There are some apparent inconsistencies in the NVDPA guidelines and the GSLLD in assigning the degree of risk to some patients that result in differences between the recommendations of the professional body of Australian cardiologists and the patients' eligibility for the subsidised lipid-lowering medications.

Q2: Are the Australian NVDPA-12 guidelines consistent with international guidelines?

The Australian guidelines, along with every other identified guideline, approach cholesterol management in the context of the absolute CVD risk reduction. Absolute risk assessment is based on the variation of the FRE, which is frequently used in other assessment tools across the world. However the time horizon for risk assessment of 5 years is the shortest among the identified guidelines. The 10% cut-off point for a 10-year risk of CVD is also recommended in every other guideline, but the 2013 ACC/AHA guideline, that used 7.5% threshold. The Australian guidelines adhere to the treatment targets that are defined for each cholesterol metric, rather than only in LDL-cholesterol levels, as became customary in other countries. The recommended LDL-C levels are the same as in Canadian guidelines and in the ballpark as other guidelines that maintain treatment targets in LDL-C levels. If LDL-C levels are not sufficiently reduced on maximally tolerated dose of

statin, the Australian guidelines recommend a combination of statin with one or more of alternative drugs: ezetimibe, bile acid binding resin, or nicotinic acid. This recommendation is replicated in other guidelines, however may be limited to high- or very high risk categories of patients. The Australian guidelines do not recommend a PCSK9 inhibitor as the second or third line of therapy as the most recent the 2016 ESC/EAS guidelines or the 2016 ACC Clinical Expert Consensus statement. The latter suggests that, depending on the characteristics of the subgroup, a PCSK9 inhibitor can be a first choice in the second line therapy (i.e. rather than ezetimibe), the second choice (i.e. after ezetimibe) or an equal option.

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Appendix

Table A2.1 Australian guidelines for identification and management of familial hypercholesterolaemia (FH)

Guidelines	Diagnosis		Management
	<i>Dutch Lipid Clinic criteria:</i>		
The Cardiac Society of Australia and New Zealand (CSANZ). Guidelines for the Diagnosis and Management of Familial Hypercholesterolaemia. November 2013. http://www.csanz.edu.au/wp-content/uploads/2013/12/Familial_Hypercholesterolemia_2013.pdf	8 points 6 points 5 points 4 points 3 points 2 points 1 point	DNA Mutation, or LDL-C > 8.5 mmol/L Tendon xanthomas LDL-C 6.5 – 8.4 mmol/L Arcus senilis < 45 yrs LDL 5.0 – 6.4 mmol/L Xanthomas or premature arcus in 1st degree relative, childhood LDL > 95 th percentile, or premature CHD 1st degree relative with premature CVD or LDL > 95th percentile, personal history of LDL 4.0 – 4.9 mmol/L or premature CVD	Diet, exercise and avoidance of smoking are mandatory, and all cardiovascular risk factors should be evaluated and treated. Consideration should be given to general measures to protect against vascular events including the use of aspirin. First line treatment is with statins. The effect of statins can be enhanced by bile acid sequestrants or cholesterol absorption inhibitors such as plant sterols or ezetimibe .
	Definite FH: > 8 points Probable FH: 6 – 8 points Possible FH: 3-5 points		
	<i>Modified UK (Simon Broome) criteria</i>		
<i>The Australian guidelines are compatible, but more detailed than the UK NICE and other European guidelines for FH.</i>	1. 2. 3. 4. 5. 6.	DNA Mutation Tendon xanthomas in patient or 1st /2nd degree relative Family history MI<60 in 1st or MI<50 in 2nd degree relative Family history Cholesterol >7.5 mmol/L in 1st /2nd degree relative Cholesterol >7.5 mmol/L (adult) or >6.7 mmol/L (age<16) LDL-C >4.9 mmol/L (adult) or >4.0 mmol/L (age<16)	target plasma levels for low risk FH = LDL-C <4 mmol/L intermediate = LDL-C <3 mmol/L high risk FH = LDL-C < 2 mmol/L,
	Definite FH: (5 or 6) + 1 Probable FH: (5 or 6) + 2 Possible FH: (5 or 6) + (3 or 4)		

Table A3.1 High-, Moderate-, and Low-Intensity Statin Therapy as classified in the 2013 ACC/AHA Guideline

Intensity of statin therapy* [#]	Drug and dose [~]
High-intensity daily dose (reduces LDL-C, on average, by $\geq 50\%$)	Atorvastatin, 40-80 [†] mg Rosuvastatin, 20-40 mg
Moderate-intensity daily dose (reduces LDL-C, on average, by 30% to <50%)	Atorvastatin, 10-20 mg Rosuvastatin, 5-10 mg Simvastatin, 20-40 mg Pravastatin, 40-80 mg Fluvastatin, 40 mg BID Fluvastatin XL, 80 mg Lovastatin, 40 mg Pitavastatin, 2-4 mg
Low-intensity daily dose (reduces LDL-C, on average, by <30%)	Simvastatin, 10 mg Pravastatin, 10-20 mg Fluvastatin 20-40 mg Lovastatin, 20 mg Pitavastatin, 1 mg

*Moderate- or high-intensity statin therapy is defined similarly in both the 2013 ACC/AHA Guidelines and the NLA Recommendations

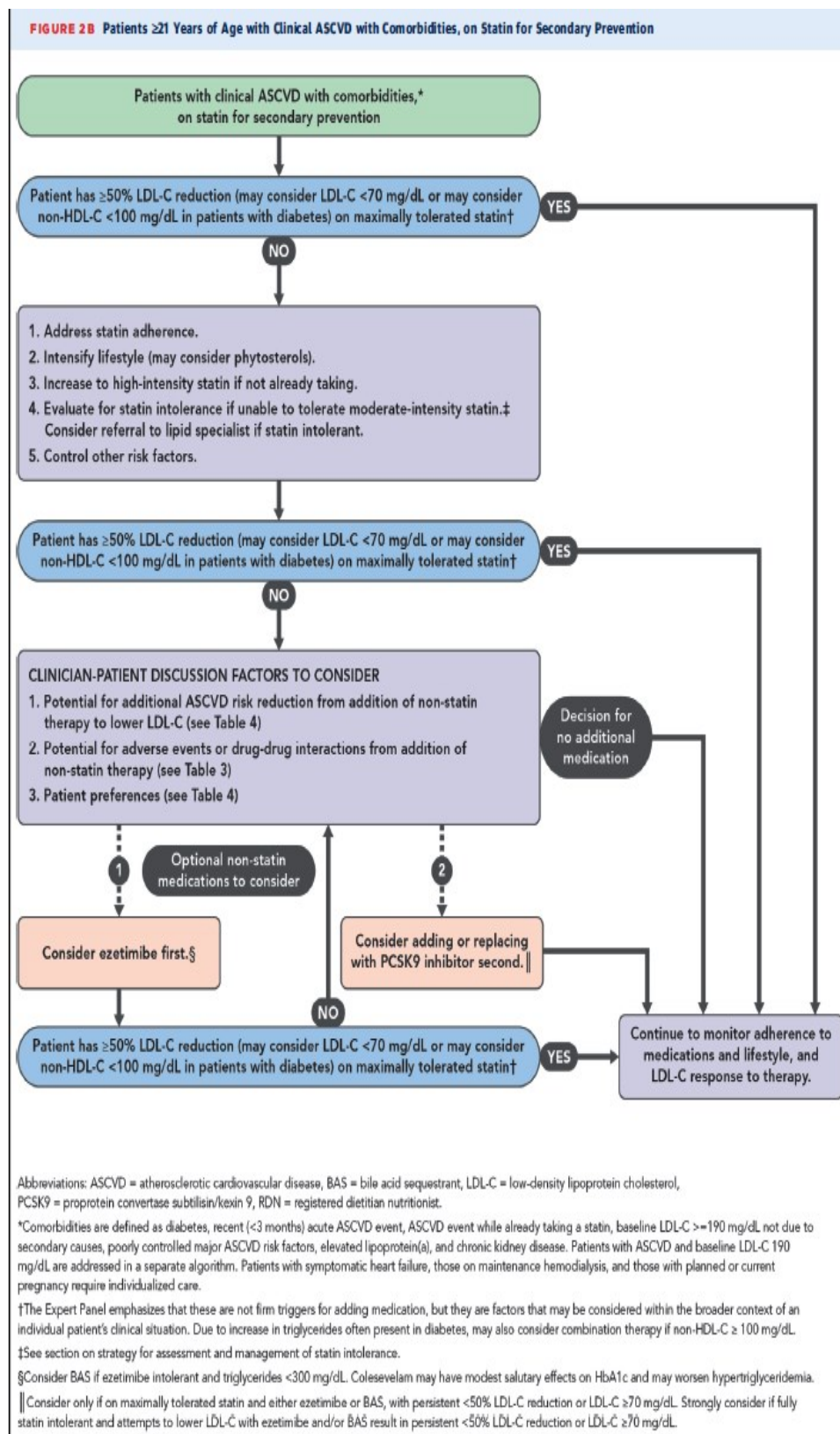
[#]The therapies were used in the RCTs reviewed by the expert panel.

[~]Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice. There might be a biological basis for a less-than-average response.

[†]Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA because of the increased risk of myopathy, including rhabdomyolysis.

Source: Table 5 from Stone et al 2014.

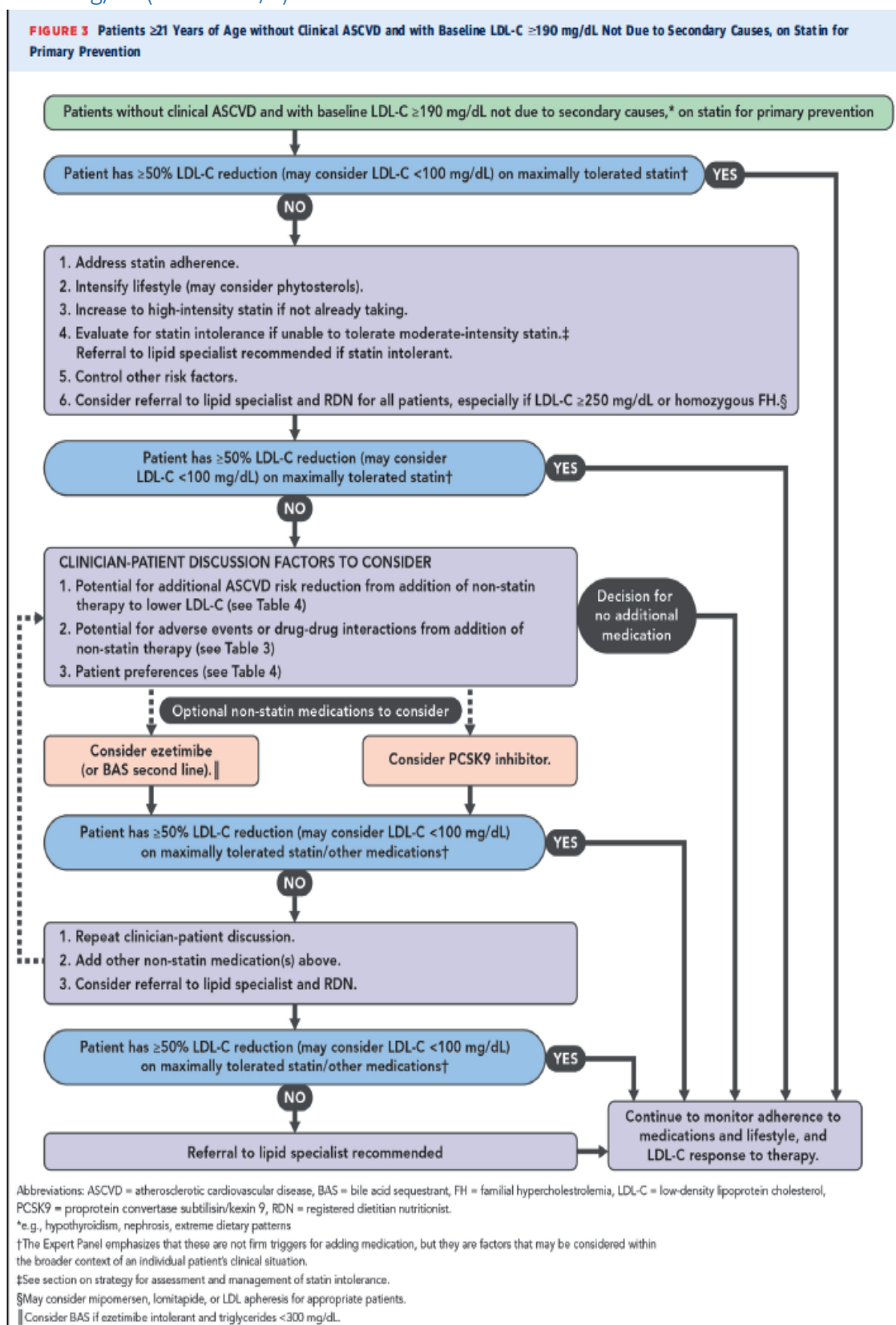
Figure A3.1 Clinical decision pathway for secondary prevention population with ASCVD



diagnosis and comorbidities

Source: Figure 2B, Lloyd-Jones 2016

Figure A3.2 Clinical decision pathway for primary prevention population with baseline LDL-C ≥ 190 mg/dL (2.6 mmol/L)



Source: Figure 3, Lloyd-Jones 2016

Table A4.1 Grouping of statins by intensity category used in the 2014 NICE guidance

Table 1 Grouping of statins used in this guideline

Dose (mg/day)	Reduction in low-density lipoprotein cholesterol				
	5	10	20	40	80
Fluvastatin	–	–	21% ¹	27% ¹	33% ²
Pravastatin	–	20% ¹	24% ¹	29% ¹	–
Simvastatin	–	27% ¹	32% ²	37% ²	42% ^{3,4}
Atorvastatin	–	37% ²	43% ³	49% ³	55% ³
Rosuvastatin	38% ²	43% ³	48% ³	53% ³	–

¹ 20%–30%: low intensity.
² 31%–40%: medium intensity.
³ Above 40%: high intensity.
⁴ Advice from the MHRA: there is an increased risk of myopathy associated with high-dose (80 mg) simvastatin. The 80 mg dose should be considered only in patients with severe hypercholesterolaemia and high risk of cardiovascular complications who have not achieved their treatment goals on lower doses, when the benefits are expected to outweigh the potential risks.

Source: Table 1, Appendix A; 2014 NICE guidance/cg181.

Note to Table A4.1: For the purpose of this guideline, statins are grouped into 3 different intensity categories according to the percentage reduction in low-density lipoprotein cholesterol. This grouping was agreed by the 2014 NICE Guidance Development Group consensus, informed by analyses in the literature.

Table A5.1 Percentage reduction of low-density lipoprotein cholesterol (LDL-C) requested to achieve goals as a function of the starting value

Starting LDL-C		Reduction to reach LDL-C goal, %		
mmol/L	~mg/dL	<1.8 mmol/L (~70 mg/dL)	<2.6 mmol/L (~100 mg/dL)	<3 mmol/L (~115 mg/dL)
>6.2	>240	>70	>60	>55
5.2–6.2	200–240	65–70	50–60	40–55
4.4–5.2	170–200	60–65	40–50	30–45
3.9–4.4	150–170	55–60	35–40	25–30
3.4–3.9	130–150	45–55	25–35	10–25
2.9–3.4	110–130	35–45	10–25	<10
2.3–2.9	90–110	22–35	<10	–
1.8–2.3	70–90	<22	–	–

Source: Supplementary Table A, p.28 (Catapano 2016)