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POSITION STATEMENT

Australian Atherosclerosis Society Position Statement on Lipoprotein(a): Clinical and Implementation Recommendations

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This position statement provides guidance to cardiologists and related specialists on the management of adult patients with elevated lipoprotein(a) [Lp(a)]. Elevated Lp(a) is an independent and causal risk factor for atherosclerotic cardiovascular disease (ASCVD) and calcific aortic valve disease (CAVD). While circulating Lp(a) levels are largely determined by ancestry, they are also influenced by ethnicity, hormones, renal function, and acute inflammatory events, such that measurement should be done after accounting for these factors. Further, circulating Lp(a) concentrations should be estimated using an apo(a)-isoform independent assay that employs appropriate calibrators and reports the results in molar units (nmol/L). Selective screening strategies of high-risk patients are recommended, but universal screening of the population is currently not advised. Testing for elevated Lp(a) is recommended in all patients with premature ASCVD and those considered to be at intermediate-to-high risk of ASCVD. Elevated Lp(a) should be employed to assess and stratify risk and to enable a decision on initiation or intensification of preventative treatments, such as cholesterol lowering therapy. In adult patients with elevated Lp(a) at intermediate-to-high risk of ASCVD, absolute risk should be reduced by addressing all modifiable behavioural, lifestyle, psychosocial and clinical risk factors, including maximising cholesterol-lowering with statin and ezetimibe and, where appropriate, PCSK9 inhibitors. Apheresis should be considered in patients with progressive ASCVD. New ribonucleic acid (RNA)-based therapies which directly lower Lp(a) are undergoing clinical trials.

Keywords Lipoprotein(a) • Atherosclerotic cardiovascular disease • Australian Atherosclerosis Society • Cardiovascular risk

Background

Elevated lipoprotein(a) [Lp(a)] is the most common inherited monogenic cause of premature coronary artery disease (CAD) [1,2]. A polymorphic particle that is structurally similar to, but larger than, low-density lipoprotein (LDL), Lp(a) is comprised of an LDL particle covalently linked via a disulfide bond to apolipoprotein(a) [apo(a)]. Within the apo(a), there are multiple repeated copies of sequences homologous to the plasminogen kringle 4 domain (KIV). The KIV domain exists as ten distinct types (KIV types 1–10), which differ in their amino acid sequence. KIV type 2 (KIV2) is present at varying copy numbers (ranging from 12 to 51), which influence apo(a) isoform size and plasma Lp(a) concentration [3–5].

Epidemiological and Mendelian randomisation studies have demonstrated that elevated Lp(a) is an independent and causative risk factor for atherosclerotic cardiovascular disease (ASCVD) and calcific aortic valve disease (CAVD) [1,6]. Elevated Lp(a) is strongly associated with an increased risk of myocardial infarction (MI), stroke, peripheral artery disease (PAD), heart failure and cardiovascular mortality [2,7–9]. The estimated prevalence of elevated Lp(a) above 100 nmol/L is 1 in 5 (20%) [10], with approximately 5.1 million Australians and 1 million New Zealanders affected, which may be further influenced by the multi-cultural make-up of both countries. The Australian and New Zealand Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) study demonstrated the prognostic value of an elevated Lp(a) in patients who survived an acute coronary syndrome, where an elevated level was an independent predictor of recurrent cardiovascular disease (CVD) over the 6-year follow up [11].

Clinical interest in Lp(a) has been hampered by issues with its measurement, reporting and treatment. Advances in analytical chemistry, in particular the development of isoform-independent assays and the standardisation of reference material, have improved measurement, however the method employed must comply with these requirements [12,13]. Currently, in Australia and New Zealand, measurement of Lp(a) involves an out-of-pocket expense of variable price. Molecular therapeutics have led to the development of ribonucleic acid (RNA)-based treatments that specifically and substantially lower elevated Lp(a), but these agents are not yet available in clinical practice [14,15]. Most major international guidelines now recognise Lp(a) as a risk enhancer, particularly in the presence of other conventional ASCVD risk factors [1,16–22]. A review of Lp(a) from an Australian perspective was published recently [5]. Beyond this, the Australian Atherosclerosis Society (AAS) recognises that it is now appropriate to review cumulative research and international guidelines on Lp(a) to provide a position statement; this foreshadows the imminent need to manage Lp(a) in the context of the Australian and New Zealand health care systems. The work presented was developed as a series of evidence-informed clinical and implementation recommendations to aid clinical and laboratory practice for the primary and secondary prevention of ASCVD in adults.

Methodology

The protocol outlining the development of this position statement, including selection of the working group, evidence review, document review and approval, and the classification of recommendations made is described in the Appendix at the end of this article.

Clinical Practice: Lp(a) in ASCVD Risk Assessment

Rationale

Measurement of Lp(a) has implications for both primary and secondary prevention of ASCVD. There is a continuous relationship between Lp(a) concentration and cardiovascular risk, with the 80th percentile in Caucasians (≥100 nmol/L) widely regarded as indicative of the threshold for high risk [23]. In primary prevention, focus should be directed toward appropriate multiple risk factor management, as evidenced by the European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk study [24], in which patients with elevated Lp(a) with other CVD risk factors had markedly increased absolute ASCVD risk compared with elevated Lp(a) alone. Recent analysis from the UK Biobank confirms that elevated Lp(a) positively predicts incident ASCVD risk in a manner that is directly dependent on the absolute risk of ASCVD at baseline; this accords with elevated Lp(a) as a risk enhancer [2]. In secondary prevention, Lp(a) is a significant independent contributor to residual risk, as evidenced by the JUPITER[1] study [25], AIM-HIGH[2] study [26] and a subsequent meta-analysis [27]. Furthermore, elevated Lp(a) is associated with increased risk of progression of coronary artery calcium (CAC) [28], with Lp(a) and CAC being independently predictive of ASCVD risk [9]. There are no clear cardiovascular outcomes data to guide therapeutic interventions specifically targeting Lp(a). Indicators of increased ASCVD risk, including multivessel disease, PAD, premature disease onset, familial hypercholesterolaemia (FH), diabetes, renal disease and recurrent acute coronary syndrome (ACS) may in the future be considered as indications for use of agents that specifically lower Lp(a) [9,27,29–31]. Within Australia and New Zealand, there are limited data on elevated Lp(a) in Aboriginal [32,33], Torres Strait Islander and Māori populations, as well as in children and adolescents; these populations require further investigation. Lp(a) measurement is not currently listed as a Medicare Benefits Schedule item, with testing currently incurring an out-of-pocket expense, and this is a significant barrier to its use in clinical practice.

Clinical Recommendations

1. Universal screening of the general population for elevated Lp(a) *is not* currently recommended.
2. Testing for elevated Lp(a) *should be considered* in adults:
   a. With established or at very high risk of ASCVD (CAD, PAD, cerebrovascular disease), especially when testing may lead to initiation or intensification of therapy (e.g.: ezetimibe, proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitor, apheresis, aspirin), increased adherence to medication, or when family cascade testing for elevated Lp(a) is indicated.
   b. To stratify ASCVD risk in adults with the following clinical features or conditions: a personal history of premature ASCVD (non-smoking men <55 years and women <60 years), family history of premature ASCVD, family history of elevated Lp(a), premature or rapidly progressive calcific aortic stenosis, very high or disproportionate coronary artery calcium score (CACS; >1000 Agatston Units or above 90th percentile), diabetes mellitus, familial hypercholesterolaemia, renal impairment, or chronic kidney disease.
   c. If low-density lipoprotein cholesterol (LDL-C) lowering is suboptimal despite good adherence to guideline recommended treatment
   d. With recurrent or rapidly progressive ASCVD or CAVD events despite optimally treated plasma LDL-C concentrations.
3. Lp(a) measurement *may be considered* in children and adolescents with familial hypercholesterolaemia, ischaemic stroke of unknown cause, a first-degree relative with elevated Lp(a), a family history of premature ASCVD, or as part of cascade testing for high Lp(a) in families.

Table 1 Atherosclerotic cardiovascular disease risk thresholds of Lp(a) concentration expressed in molar units, mass units and population percentiles [20].

Estimated ASCVD Risk*	Lp(a) level (nmol/L)	Lp(a) level (mg/dL)	Percentile of population
Low	<100	<40	80th
Moderate	100–200	40–90	80–95th
High	200–400	90–180	95–99th
Very high	>400	>180	99th

*Australian Absolute Risk Score where low <10% risk, moderate is a 10–15% risk and high is a >15% risk of CVD within the next 5 years.
Abbreviations: ASCVD, atherosclerotic cardiovascular disease; Lp(a), lipoprotein (a); CVD, cardiovascular disease.

Atherosclerotic cardiovascular disease risk thresholds of Lp(a) concentration are summarised in Table 1. Implementation recommendations for Lp(a) in ASCVD risk assessment are presented in Box A.

Management of Patients With Elevated Lp(a)

Rationale

Although dietary and lifestyle interventions do not appear to have any direct effect on an individual's Lp(a) levels, management of modifiable behavioural, lifestyle, psychosocial and clinical ASCVD risk factors, especially elevated LDL-C, should still be addressed in all patients with elevated Lp(a)

[1] Justification for the Use of Statin in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER).
[2] The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial.

Box A. Lp(a) in ASCVD Risk Assessment: *implementation recommendations.*

- A Medicare Benefits Schedule (MBS) item for testing Lp(a) should be approved to enable incorporation of Lp(a) into clinical practice.
- An ICD-10 code for elevated Lp(a) should be established and utilised in primary and tertiary care, and in clinical registries.
- Calculators for ASCVD risk stratification in both primary and secondary prevention should be developed and validated to include Lp(a) as a predictor variable.
- Patients with elevated Lp(a) and multiple ASCVD risk factors or established ASCVD should be referred to or discussed with a specialist with expertise in lipidology.
- Consumer-friendly resources and education should be made available to support communication of risk to individuals with elevated Lp(a).

Abbreviations: Lp(a), lipoprotein(a); ICD-10, International Classification of Diseases-10; ASCVD, atherosclerotic cardiovascular disease.

[5,19,20]. This initial approach to therapy in both primary and secondary prevention is supported by recent analysis of the UK Biobank data in which the predicted benefit from multiple risk factor reduction was considered to be greatest in people with both high Lp(a) and high ASCVD risk [2]. Mendelian randomisation studies suggest that the clinical benefit of lowering Lp(a) is proportional to the absolute reduction in Lp(a) concentration [34]. Theoretically, in secondary prevention, lowering of Lp(a) by 105 nmol/L in the short-term (<5 years) may reduce cardiovascular risk by 20% [35]. There are currently no specific and effective treatments to lower Lp(a). Niacin is a moderately effective Lp(a) lowering agent, but there are no clinical outcome trial data demonstrating benefit. Apheresis is Food and Drug Administration (US FDA) approved and can be considered in patients with elevated Lp(a) at very high risk of ASCVD, but it is expensive, inconvenient, and not widely available. Statin therapy does not reliably lower Lp(a) and may even slightly raise levels [36,37]. Recent analysis from the ASPirin in Reducing Events in the Elderly (ASPREE) study suggests aspirin may benefit older individuals with elevated Lp(a) genotypes in primary prevention of major adverse cardiovascular events (MACE) [38], however the role of other antiplatelet therapies remains to be established [39]. Monoclonal PCSK9 antibodies, as well as RNA-based inhibitors of PCSK9, which lower LDL-C, can also reduce Lp(a) by up to 30%, resulting in reduced cardiovascular outcomes [40–42]. Emerging RNA technologies [14,43–45] promise specific and more substantial Lp(a) reductions and clinical outcome trials are about to start or are currently underway (HORIZON[3], National Clinical Trial number [NCT]04023552; OCEAN(a)-DOSE[4]; NCT04270760). While treating Lp(a) with PCSK9 inhibitors is not currently reimbursable through the Pharmaceutical Benefits Scheme, elevated Lp(a) can be treated coincidentally in patients with FH or clinical ASCVD whose LDL-C remains above 2.6 mmol/L despite maximal statin and ezetimibe therapy. Subanalysis of the major outcomes trials for PCSK9 inhibitors have shown greater relative and absolute risk reduction was achieved in patients with elevated Lp(a) [41,42].

Clinical Recommendations

1. In adults with elevated Lp(a) (>100 nmol/L), absolute risk of ASCVD *should be lowered* by addressing all modifiable behavioural, lifestyle, psychosocial and clinical risk factors, including obesity, unhealthy diet, smoking, hypertension, renal impairment and macroproteinuria, diabetes and especially elevated LDL-C.
2. In adults at intermediate absolute ASCVD risk, elevated Lp(a) (>100 nmol/L) *should be considered* as a risk modifying factor with a view to offering initiation of lipid-lowering therapy to lower LDL-C.
3. In adults at high or very high absolute risk of ASCVD, elevated Lp(a) (>100 nmol/L) *should be considered* as a rationale for more intensively lowering LDL-C below guideline recommended goals by offering addition of ezetimibe to a maximally tolerated dose of a statin.
4. In adults at high, or very high, absolute risk of ASCVD and on maximal statin and ezetimibe therapy, elevated Lp(a) (>100 nmol/L) *may be considered* to initiate use of PCSK9 inhibitors, noting current restrictions and cost associated with their use.
5. Lipoprotein apheresis *should be considered* as Lp(a) lowering therapy in adults with elevated Lp(a) (>200 nmol/L) and recurrent ASCVD events who are already receiving a maximally tolerated dose of a statin, ezetimibe and a PCSK9 inhibitor.
6. Niacin and hormone replacement therapy *should not* be used to specifically lower elevated Lp(a) concentrations.
7. The use of aspirin *may be considered* in primary prevention in adults with elevated Lp(a) (>100 nmol/L) and multiple

[3] Assessing the Impact of Lipoprotein (a) Lowering With Pelacarsen (TQJ230) on Major Cardiovascular Events in Patients with Cardiovascular Disease (HORIZON).
[4] Olpasiran trials of Cardiovascular Events And LipoproteiN(a) reduction-DOSE Finding Study (OCEAN(a)-DOSE).

Box B. Management of patients with elevated Lp(a): *implementation recommendations.*

- Evidence-informed interventions should be incorporated into personalised care plans for patients with elevated Lp(a), with the specific aim of improving adherence to management of behavioural risk factors and to medications for lowering cardiovascular risk.
- Shared decision making should be employed at the point of prescribing new medicines or interventions to lower Lp(a).
- Digital health technologies and decision support systems should be employed to enhance the management of patients with elevated Lp(a); telehealth services should be utilised for patients in rural and remote areas.
- All patients identified as having elevated Lp(a) should be offered participation in a clinical quality registry.
- An advocacy group of patients, family members and relevant stakeholders should be established to support improvements in the care of patients and families with elevated Lp(a).

ASCVD risk factors or subclinical evidence of ASCVD, provided there are no bleeding contraindications.

Implementation recommendations for management of patients with elevated Lp(a) are presented in Box B.

Lp(a) Testing and Reporting

Rationale

Plasma Lp(a) concentrations within populations can vary by up to 1,000-fold. In Caucasian populations, the distribution of Lp(a) is positively skewed, the median concentration being ~20 nmol/L (10 mg/dL) [5]. Unit conversion varies with the assay used, the Lp(a) concentration, and storage. Given that mass units (mg/dL) reflect all constituent components of the Lp(a) particle, they are considered more variable than measures of particle concentration expressed in nmol/L. In addition, there are large variations among ancestry groups [46]. Lp(a) concentration is strongly genetically determined, with minimal influence from diet or lifestyle modification. Variation in KIV2 copy number repeats are inversely associated with apo(a) size, which can impact measurement of Lp(a) concentration when using assays that are not isoform independent [5]. Higher Lp(a) concentrations may occur with impaired renal function, menopause, hypothyroidism, and acute and chronic inflammation. Severe acute illnesses may lower Lp(a). Furthermore, plasma Lp(a) levels are not stable during childhood, with considerable intra-individual variation, and concentrations appear to plateau at 15 years [47]. There is a continuous relationship between Lp(a) concentration and cardiovascular risk, with the 80th percentile in Caucasians (≥100 nmol/L) widely regarded as the threshold above which risk increases [23], which is further enhanced by the presence of other ASCVD risk factors [2]. Elevated Lp(a) may also be clinically associated with venous thromboembolism, particularly with inherited thrombophilias, but a causal link is not supported by Mendelian randomisation studies or current guidelines [2,48]. As inheritance is autosomal co-dominant, cascade testing of relatives of individuals with high Lp(a) appears justified. Genetic testing for Lp(a) isoforms and polygenic risk scores do not appear to provide additional predictive value beyond measurement of Lp(a) mass or molar concentration [49].

Clinical Recommendations

1. Lp(a) *should be* measured by a method (e.g.: immunoassay or mass spectroscopy) that is apo(a) isoform independent, uses appropriate calibrators, and is ideally estimated and reported in molar rather than mass units.
2. If measurement of Lp(a) in molar units is not available, units for the assay based on its calibration *should be* reported.
3. A single standard conversion factor from mass units (mg/dL) to molar units (nmol/L) *should not* be routinely employed.
4. All laboratories that measure Lp(a) *should participate* in an external quality assurance program which adheres to these recommendations.
5. Measurement of Lp(a) does not require fasting and *should be* carried out in freshly separated plasma or serum.
6. Measurement of the cholesterol or oxidised phospholipid components of Lp(a), *should not* at present be considered for clinically assessing patients.
7. With the exception of acute coronary syndrome, Lp(a) *should not* be measured in the presence of concurrent illness or inflammatory conditions.
8. Measurement of Lp(a) concentration *should be repeated* after correction of secondary causes and when assessing the response to Lp(a) lowering.

Implementation recommendations for Lp(a) testing and reporting are presented in Box C.

Box C. Lp(a) testing and reporting: *implementation recommendations.*

- Alerts and interpretive comments on laboratory reports on Lp(a) should emphasise the potential need for assessment of ASCVD risk and cascade testing.
- All health care professionals involved in screening for elevated Lp(a) should have skills in the interpretation of laboratory results and family counselling.
- Cascade testing for elevated Lp(a) in relatives of index cases should employ careful risk communication and shared decision-making strategies.
- All patients with elevated Lp(a) should be offered participation in a clinical quality registry.

Conclusions

This position statement provides a series of evidence-informed clinical recommendations for the screening, testing and management of adult patients with elevated Lp(a). It extends other recently published international guidelines [2,17,19–22] and provides the basis for more comprehensive use of Lp(a) in clinical practice. The gradual incorporation of Lp(a) into routine clinical practice for the prevention of ASCVD will involve multiple iterative processes. With the development of therapies that specifically lower Lp(a), inclusion of this lipoprotein in risk-prediction calculators and guidelines should be implemented. Future research should explore the value of detecting elevated Lp(a) in specific populations, including Indigenous Australians and New Zealanders, as well as in children and adolescents. An expanding evidence base will enable more integrated, multi-level strategies for the detection and treatment of Lp(a) in the context of primary and secondary prevention of ASCVD. Universally testing the population for elevated Lp(a) has been proposed by other expert groups [17,22]. However, in the absence of clearly defined risk-reduction pathways and a realistic assessment of cost-effectiveness, we do not at present support such proposals. As the value of treating elevated Lp(a) with specific molecular therapies becomes established, the case that every adult be tested once in a lifetime for Lp(a) may be more defensible. The detection of high Lp(a) in an index case should be coupled with cascade testing of their close relatives. Models of care for elevated Lp(a) may be based on those developed for FH [50–53] and are likely to result in a paradigm shift in the prevention of ASCVD. However, the added value and cost-effectiveness of such models will need to be clearly demonstrated.

Declarations of Perceived Conflicts of Interest

Warrick Bishop—Honorarium from AstraZeneca, Novartis, Sanofi, Boehringer Ingelheim, Novo Nordisk and Bayer. Sells books and online material in relation to Heart Health.

David Colquhoun—Amgen, Pfizer, AstraZeneca, Novartis, Sanofi, Bayer, Novo Nordisk.

Christian Hamilton-Craig—Honoraria from Amgen, Novartis, Sanofi.

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Nadarajah Kangaharan—none.

Karam M. Kostner—Honoraria for lectures and advisory boards from Amgen, Novartis.

Leonard Kritharides—Novartis, Amgen, Seqirus.

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Natalie Raffoul—Amgen and Novartis. Views are representative of her own and do not imply endorsement by the National Heart Foundation.

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Boards for Genentech, Inc. (an affiliate of F. Hoffmann-La Roche Ltd) and for Boehringer Ingelheim.

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Appendix. Protocol for the Development of the Position Statement on Lp(a)

Selection of Committees and Contributors

The Working Group was selected from members of the Australian Atherosclerosis Society Clinical Council for having expertise in lipidology, cardiology and chemical pathology, with equitable representation from all Australian States and Territories as well as New Zealand.

Evidence Review

Guidelines on the management of Lp(a), published between 2018 and 2022 [16,17,19–22,52] were independently assessed using the Appraisal of Guidelines for Research & Evaluation Instrument (AGREE-II) [53] assessment criteria by four members (NCW, TAM, GFW, DS) of the Working Group. The top-ranking guidelines (see Appendix Table) were employed in the development of this position statement.

The evidence in support of the clinical recommendations in the position statement was based on the aforementioned guidelines, a peer-assessed review of Lp(a) [5] that was co-authored by core members of the Working Group, as well as on additional published works. For the review paper, a literature search of the English language was undertaken between January 2014 and September 2022. The search employed the PubMed database with search string (all fields) "Lipoprotein(a)" and/or "Lp(a)" in combination with diagnosis, treatment, pathogenesis and guidelines with additional key references identified by the Working Group. Additional published works were searched for using the above search terms in 2021 and 2022 to generate relevant publications, which were also provided *ad hoc* by the Working Group and by individual contributors up to September 2022.

To develop the position statement, the Working Group employed these publications, as well as clinical experience and expert opinion. The first draft of the position statement outline was produced by NCW, DS and GFW. Workshops chaired by DS and NCW were held by video conference between August 2021 and May 2022. The agenda focussed on discussion of the evidence and subsequent development and consolidation of the statements for recommendation, which were designated a Class of Recommendation. The totality of evidence (epidemiology, basic science, clinical observations, clinical trials, evidence opinion) was assessed to inform the recommendations.

Document Review and Approval

The majority view (80%) was employed to reach a consensus on the class of recommendation on earlier drafts of the guidance. The statements were reviewed and edited by smaller working groups. These discussions were arranged by the chair via telephone or email communication. All revised statements were subsequently circulated to all contributors

Appendix Table International lipid guidelines and consensus statements assessed by four members of the Working Group according to AGREE II.

Guidelines	Year	Organisation Responsible	Country/ Region	Conflicts of Interest	AGREE II assessments [53]*
Tsimikas et al. [52]	2018	National Heart, Lung, Blood Institute Working Group	USA	Declared	5
Grundy et al. [21]	2018	American College of Cardiology/ American Heart Association	USA	Declared	4.5
Wilson et al. [19]	2019	National Lipid Association	USA	Declared	6
Mach et al. [22]	2019	European Society of Cardiology/ European Atherosclerosis Society	Europe	Declared	4.5
Cegla et al. [20]	2019	HEART UK	UK	Declared	5
Pearson et al. [17]	2021	Canadian Cardiovascular Society	Canada	Declared	4.5
Durlach et al. [16]	2021	Nouvelle Societe Francophone d'Atherosclerose	France	Declared	5
Reyes-Soffer et al. [1]	2022	American Heart Association	USA	Declared	4.5
Kronenberg et al. [2]	2022	European Atherosclerosis Society	Europe	Declared	5.5

Abbreviations: AGREE, Appraisal of Guidelines, Research and Evaluation.

*Based on assessment of 6 domains: (i) scope and purpose, (ii) stakeholder involvement, (iii) rigour of development, (iv) clarity of presentation, (v) applicability, and (vi) editorial independence. Each domain is given a rating of 1 (strongly disagree, where no information that is relevant to the item is presented or met) through to 7 (strongly agree, where quality of reporting for that item is exceptional and all criteria have been met).

for comment. Specific queries and disagreements with statements were resolved via telephone or email discussion arranged by NCW, with full agreement subsequently reached via email and/or videoconference. The Working Group examined the pre-final draft of the position statement and reached full consensus on the recommendations and wording of statements. All contributors reviewed and commented on evolving drafts of the document and approved the final version before submission.

Classes of Recommendation

The clinical recommendations were classed as 'strong', 'moderate' and 'weak', the modality of the grammar employed to reflect these classes were *'should be done'*, *'should be considered'*, and *'may be considered'*, respectively. The class of recommendation for implementation practice employed was by consensus agreed to be strong, and accordingly, the wording used was *'should be done'*.