Targeted Literature Review of Unmet Need in the Hyperlipidaemia Population With High Risk of Cardiovascular Disease

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BACKGROUND

- Hyperlipidaemia patients not treated at goal have an increased risk for cardiovascular disease (CVD), which is the main cause of premature death and has been a major cause of disability and ill health in recent years (Yusuf et al., 2001; Schedlbauer et al., 2010; Perk et al., 2012).
- Guidelines published for Europe (Perk et al., 2012) and other countries before 2013 (Hata et al., 2002; Teramoto et al., 2013) recommend a treat-to-goal paradigm for LDL-C levels; the assumption is that there is a positive association between the LDL-C levels and the risk of cardiovascular (CV) events.

OBJECTIVES

- To perform a focused literature review of the unmet needs in high-risk patients with hyperlipidaemia:
  - To review treatment guidelines of various countries and to examine differences among recommended lipoprotein cholesterol (LDL-C) target levels for patients with hyperlipidaemia at high risk for CVD.
  - To review observational studies to determine the proportions of high-risk patients who do not achieve targeted LDL-C levels in a real-world setting.

METHODS

Study Identification

- A targeted literature search of the following databases was performed per a prespecified protocol: Medline, Medline In-Process, Embase, BIOSIS, and the Cochrane Library (1 January 2005 to 31 December 2013). Guideline searches were limited to publications in the last 5 years. There were no geographical or language restrictions.
- Internet sources searched to identify guidelines included the Agency for Healthcare Research and Quality's National Guideline Clearing House. Bibliographic lists of recent and relevant systematic literature reviews and health technology assessments were searched for further studies of interest.

Study Selection

- Screening criteria were as follows:
  - Population: adult hyperlipidaemia patients with high risk of CVD (i.e., two or more risk factors for coronary heart disease [CHD] or its risk equivalents)
  - Interventions: no limits
  - Study design: prospective observational studies
- One researcher reviewed studies for eligibility. A second researcher performed a quality check of a random selection of 10% of titles, abstracts, and full-text articles. Discrepancies were resolved; when a consensus was not reached, a third researcher was consulted.
- Exclusion criteria were as follows: sample size of less than 100; familial hypercholesterolaemia studies.

Outcomes

- Data of interest were as follows:
  - Guidelines: recommended target LDL-C levels in patients with hyperlipidaemia at high risk of CVD
  - Observational studies: number of patients with hyperlipidaemia at high risk of CVD who did not achieve target LDL-C levels

RESULTS

Search Results

- Searches for guidelines identified 545 records (databases = 533; Internet and hand searches = 12).
  - After the initial screening of titles and abstracts (level 1 screening), 82 publications (databases searches = 70; Internet and hand searches = 12) were progressed to level 2 screening.
  - From these, 17 guidelines were reviewed.
- Search results for observational studies are summarised in Figure 1.

Recommended LDL-C Target Levels for High-Risk Patients (Table 1)

- LDL-C target levels for high-risk patients varied based on risk and country. The most common target was < 100 mg/dL (< 2.6 mmol/L), recommended by eight different guidelines in Asia. Fourteen treatment guidelines (5 from Europe and 8 from Asia) set specific LDL-C targets for secondary prevention.
- The American College of Cardiology (ACC) and the American Heart Association (Stone et al., 2014) (AHA) did not set specific cholesterol targets, due to a lack of evidence. The Royal Australian College of General Practitioners (2012) did not make specific recommendations for high-risk patients. Guidelines from the National Collaborating Centre for Primary Care and Royal College of General Practitioners (Cooper et al., 2008) also did not set specific cholesterol targets, due to a lack of evidence.

Proportion of High-Risk Patients Not Achieving LDL-C Targets

- LDL-C targets used most commonly in studies were the NCEP-ATP guidelines (21), the Canadian Working Group (3), and the ESC (Third Joint European Task Force) (2); others used country-specific guidelines (4), one of which compared LDL-C level achievement by different targets.
- Most studies reported that between 68% and 96% of very high-risk patients did not achieve an LDL-C goal of < 70 mg/dL, as recommended by the NCEP-ATP guidelines (Figure 2), with the exception of one study conducted in China (16.9%).
- Most studies found that high-risk patients did not achieve a target (61.8%-93.8%) of < 100 mg/dL, as recommended by the NCEP-ATP guidelines (Figure 3); nine studies reported lower proportions (0.0%-47%).
- For patients at moderately high risk, in 10 out of the 16 studies 35.0% to 78.2% did not achieve the NCEP-ATP target goal of < 130 mg/dL; four studies conducted in the United States (US) reported lower proportions of between 6.6% and 24.0%. Similar results were observed in two other studies: Ilerigelen et al. 2007 (12.7%) and Punithavathi et al. 2009 (15.0%).
- Using the target of < 97 mg/dL (2.5 mmol/L) as recommended by the Canadian Working Group, three studies reported that between 38.0% and 42.3% of high-risk patients did not achieve this goal. Third Joint European Task Force guidelines, as well as guidelines from Brazil, Hungary, and South Africa, recommended < 2.5 mmol/L; and in five studies, 41.7% to 89.7% patients did not achieve this goal.
- Of all of the common comorbidities, patients with concomitant CVD and diabetes seemed the least likely to reach their target LDL-C goals (50%-91.4%). Three studies reported the likelihood of patients with diabetes, CHD, or the concomitant occurrence of both diseases reaching their LDL-C goals (Arafah et al., 2013; Wong et al., 2013; Dänschel et al., 2013).

Table 1. Recommended LDL-C Targets for High-Risk Patients From Treatment Guidelines

LDL-C Target Level	Patient Population / Risk Category as Described in Guidelines	Organisation and Reference	Country
Very high risk			
< 70 mg/dL (< 1.8 mmol/L)	Very high risk: acute coronary syndrome; stable CHD and T2DM; stable CHD and metabolic syndrome; peripheral arterial occlusive disease; progressive or recurrent CHD despite LDL-C < 100 mg/dL	Austrian Diabetes Association Wascher et al., 2012	Austria
< 70 mg/dL (< 1.8 mmol/L) and/or ≥ 50% reduction when target level not reached	Very high CV risk (established CVD, T2DM, T1DM with target organ damage, moderate to severe chronic kidney disease, or a SCORE level ≥ 10%)	ESC/EAS Reiner et al., 2011	Europe
< 70 mg/dL (< 1.8 mmol/L)	Very high risk	NCEP-ATP-III guidelines Grundy, 2004 (Hankey et al., 2010)	US, China (follows NCEP-ATP-III)
High risk			
< 120 mg/dL (3.1 mmol/L)	Category 3, high risk (10-year risk of death from CVD ≥ 2% derived from NIPPON DATA80)	Japanese Atherosclerosis Society Teramoto et al., 2013	Japan
< 100 mg/dL (2.6 mmol/L)	High risk: > 2 risk factors, SCORE 10-year risk ≥ 5%, Framingham 10-year risk > 20%, CHD, cerebrovascular disease, T2DM, T1DM and aged > 40 years, or nephropathy	Austrian Lipid Consensus (Lipidkonsensus) Austrian Lipid Consensus, 2010; Huber et al., 2011	Austria
	High risk: CHD or CHD risk equivalents or diabetes	Korean Stroke Society Hankey et al., 2010	Korea
		Malaysian Society of Neurosciences Hankey et al., 2010	Malaysia
		Swiss Atherosclerosis Association Rodondi et al., 2011	Switzerland
< 100 mg/dL (2.6 mmol/L)	High risk: CHD[a] or CHD risk equivalents[b] (10-year risk > 20%)	NCEP-ATP-III guidelines Grundy, 2004 (Hankey et al., 2010)	US, China (follows NCEP-ATP-III)
< 100 mg/dL (< 2.5 mmol/L)	High CV risk (markedly elevated single risk factors, a SCORE level ≥ 5% to < 10%)	ESC/EAS Reiner et al., 2011	Europe
	CVD, T2DM or T1DM with microalbuminuria, severe genetic lipid disorders (e.g., familial hypercholesterolaemia), or persistent asymptomatic CHD risk (> 20%) despite lifestyle change	South African Medical Association and Lipid and Atherosclerosis Society of Southern Africa Butler, 2010	South Africa
≤ 77 mg/dL (≤ 2.0 mmol/L) or ≥ 50% reduction	High risk (previous MI, clinical atherosclerosis, abdominal aortic aneurysm, diabetes of > 15 years' duration and age > 30 years, diabetes and age > 40 years, microvascular disease, high-risk kidney disease, high-risk hypertension, FRS ≥ 20%	Canadian Cardiovascular Society Anderson et al., 2013	Canada
< 70 mg/dL (< 1.8 mmol/L)	High risk: CHD or CHD risk equivalents (T2DM, T1DM with microalbuminuria, atherosclerosis, peripheral vascular disease), FRS 10-year risk of CHD event > 20%	Caribbean Cardiac Society Chung, 2008	Caribbean
Moderately high risk			
< 140 mg/dL (3.6 mmol/L)	Intermediate risk (10-year risk of death from CVD ≥ 0.5% to < 2%, with no additional risk factors or < 0.5% with presence of 1 or more risk factors[c])	Japanese Atherosclerosis Society Teramoto et al., 2013	Japan
< 130 mg/dL (3.4 mmol/L)	No CHD and ≥ 2 risk factors	Korean Stroke Society Hankey et al., 2010	Korea
		Indonesian Neurological Association Hankey et al., 2010	Indonesia
	Medium risk: 2 risk factors; SCORE 10-year risk 3%-4%, Framingham 10-year risk 10%-20%	Austrian Lipid Consensus (Lipidkonsensus) Austrian Lipid Consensus, 2010; Huber et al., 2011	Austria
	Moderate risk: ≥ 2 risk factors; FRS 10-year risk < 10%	Caribbean Cardiac Society Chung, 2008	Caribbean
		NCEP-ATP-III guidelines Grundy, 2004 (Hankey et al., 2010)	US, China (follows NCEP-ATP-III)
	Primary prevention: ≥ 1 risk factor	Malaysian Society of Neurosciences Hankey et al., 2010	Malaysia
	Medium risk	Swiss Atherosclerosis Association Rodondi et al., 2011	Switzerland
< 130 mg/dL (optional goal: < 100 mg/dL)	Moderately high risk: ≥ 2 risk factors[d] (FRS 10-year risk 10%-20%)	NCEP-ATP-III guidelines Grundy, 2004 (Hankey et al., 2010)	US, China (follows NCEP-ATP-III)
< 115 mg/dL (< 3.0 mmol/L)	Moderate risk (SCORE level > 1 to ≤ 5%)	ESC/EAS Reiner et al., 2011	Europe
	Asymptomatic individuals with initial 10-year CHD risk < 20%, or for initial 10-year CHD risk > 20% but reduced to < 20% with lifestyle changes	South African Medical Association and Lipid and Atherosclerosis Society of Southern Africa Butler, 2010	South Africa
< 100 mg/dL (< 2.6 mmol/L)	Moderately high risk: ≥ 2 risk factors; FRS 10-year risk 10%-20%	Caribbean Cardiac Society Chung, 2008	Caribbean
≤ 77 mg/dL (≤ 2.0 mmol/L) or ≥ 50% reduction	Intermediate risk identified through screening (adjusted FRS ≥ 10% and < 20%); treat if LDL-C ≥ 3.5 mmol/L	Canadian Cardiovascular Society Anderson et al., 2013	Canada

EAS = European Atherosclerosis Society; ESC = European Society of Cardiology; FRS = Framingham Risk Score; HDL-C = high-density lipoprotein cholesterol; MI = myocardial infarction; NCEP-ATP-III = National Cholesterol Education Program-Adult Treatment Panel III; SCORE = Systematic Coronary Risk Evaluation; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

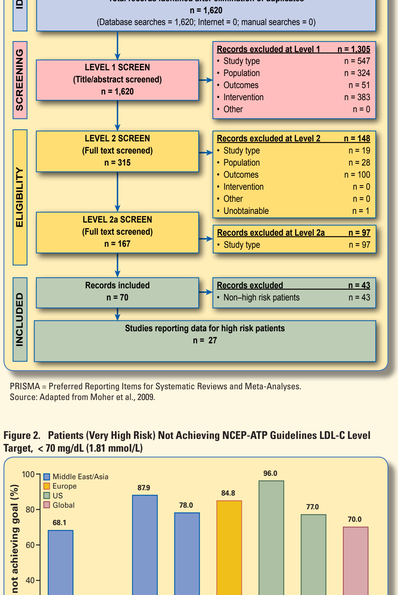
[a] CHD includes history of MI, unstable angina, stable angina, coronary artery procedures (angioplasty or bypass surgery), or evidence of clinically significant myocardial ischaemia.

[b] CHD risk equivalents include clinical manifestations of noncoronary forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease [transient ischaemic attacks or stroke of carotid origin or > 50% obstruction of a carotid artery]), diabetes, and 2 or more risk factors with 10-year risk for hard CHD > 20%.

[c] Risk factors include hypo-HDL-C < 40 mg/dL, family history of premature coronary artery disease in first-degree relatives (a man aged < 55 years or a woman < 65 years), and impaired glucose tolerance.

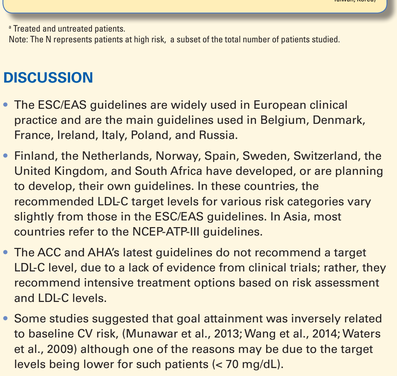
[d] Risk factors include cigarette smoking, hypertension (blood pressure ≥ 140/90 mm Hg or on antihypertensive medication), low HDL-C (< 40 mg/dL), family history of premature CHD (CHD in male first-degree relative < 55 years of age; CHD in female first-degree relative < 65 years of age), and age (men ≥ 45 years; women ≥ 55 years).

Figure 1. PRISMA Diagram for Observational Studies



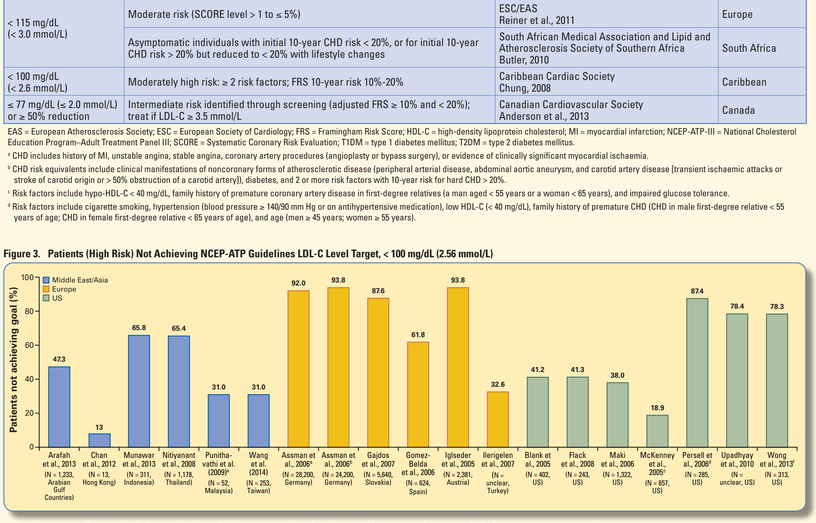
PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
Source: Adapted from Moher et al., 2009.

Figure 2. Patients (Very High Risk) Not Achieving NCEP-ATP Guidelines LDL-C Level Target, < 70 mg/dL (1.81 mmol/L)



[a] Treated and untreated patients.
Note: The N represents patients at high risk, a subset of the total number of patients studied.

Figure 3. Patients (High Risk) Not Achieving NCEP-ATP Guidelines LDL-C Level Target, < 100 mg/dL (2.56 mmol/L)



[a] Primary prevention, 9 months, men; [b] Primary prevention, 9 months, women. [c] Week 8; [d] Based on 2004 guidelines; [e] Population in 2003; [f] Treated and untreated patients.
Note: The N represents patients at high risk, a subset of the total number of patients studied.

DISCUSSION

- The ESC/EAS guidelines are widely used in European clinical practice and are the main guidelines used in Belgium, Denmark, France, Ireland, Italy, Poland, and Russia.
- Finland, the Netherlands, Norway, Spain, Sweden, Switzerland, the United Kingdom, and South Africa have developed, or are planning to develop, their own guidelines. In these countries, the recommended LDL-C target levels for various risk categories vary slightly from those in the ESC/EAS guidelines. In Asia, most countries refer to the NCEP-ATP-III guidelines.
- The ACC and AHA's latest guidelines do not recommend a target LDL-C level, due to a lack of evidence from clinical trials; rather, they recommend intensive treatment options based on risk assessment and LDL-C levels.
- Some studies suggested that goal attainment was inversely related to baseline CV risk, (Munawar et al., 2013; Wang et al., 2014; Waters et al., 2009) although one of the reasons may be due to the target levels being lower for such patients (< 70 mg/dL).
- Patient nonadherence is cited as an issue in patients not achieving LDL-C goals in various countries (Bourgault et al., 2005; Munawar et al., 2013; Michel et al., 2008; Vacanti et al., 2005). Nonadherence could be due to scarce financial resources (Vacanti et al., 2005) or improper communication between the health care professional and the patient, particularly among elderly patients and those with poor literacy.

CONCLUSIONS

- In patients in high-risk or very high-risk categories, attainment of LDL-C goals is lower, highlighting suboptimal hyperlipidaemia management worldwide.
- Patients in higher CV-risk categories tend to have more stringent LDL-C target levels, which may contribute to failure to achieve target levels.
- Limited evidence suggests that the reasons for not achieving the target LDL-C could be gender, age, comorbidities (e.g., diabetes and CV risk), hypertension, baseline LDL-C and total cholesterol levels, and choice of treatments and their doses. There is still a need to rigorously explore the causes for this failure through primary studies.
- These conclusions suggest several unmet needs: the failure of large numbers of patients to achieve LDL-C targets, reduction of the patients' risk for CVD, and consequent reduction of the occurrence of CV events.

REFERENCES

Please see the handout for a complete reference list.

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