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REVIEW

A Narrative Review and Expert Panel Recommendations on Dyslipidaemia Management After Acute Coronary Syndrome in Countries Outside Western Europe and North America

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ABSTRACT

Patients who have experienced an acute coronary syndrome (ACS) are at very high risk of recurrent atherosclerotic cardiovascular disease (CVD) events. Dyslipidaemia, a major risk factor for CVD, is poorly controlled post ACS in countries outside Western Europe and North America, despite the availability of effective lipid-modifying therapies (LMTs) and guidelines governing their use. Recent guideline updates recommend that low-density lipoprotein cholesterol (LDL-C), the primary target for dyslipidaemia therapy, be reduced by $\geq$ 50% and to $<$ 1.4 mmol/L (55 mg/dL) in patients at very high risk of CVD, including those with ACS. The high prevalence of CVD risk factors in some regions outside Western Europe and North America confers a higher risk of CVD on patients in these countries. ACS onset is often earlier in these patients, and they may be more challenging to treat. Other barriers to effective dyslipidaemia control include low awareness of the value of intensive lipid lowering in patients with ACS, physician non-adherence to guideline recommendations, and lack of efficacy of currently used LMTs. Lack of appropriate pathways to guide follow-up of patients with ACS post discharge and poor access to intensive medications are important factors limiting

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dyslipidaemia therapy in many countries. Opportunities exist to improve attainment of LDL-C targets by the use of country-specific treatment algorithms to promote adherence to guideline recommendations, medical education and greater prioritisation by healthcare systems of dyslipidaemia management in very high risk patients.

Keywords: Atherosclerosis; Acute coronary syndrome; Dyslipidaemia; LDL-C; PCSK9 inhibitor; Statin

Key Summary Points
A systematic literature review of dyslipidaemia management after acute coronary syndrome (ACS) was conducted in patients outside Western Europe and North America
Dyslipidaemia control post ACS is suboptimal
Recent guidelines have lowered cholesterol targets for these patients
High-intensity dyslipidaemia therapy is available but is prescribed infrequently
Poor access to, and lack of reimbursement for, newer medications limits treatment

INTRODUCTION

Dyslipidaemia is a major risk factor for atherosclerotic cardiovascular disease (CVD) and reducing low-density lipoprotein cholesterol (LDL-C) is the primary target of lipid-modifying therapy (LMT) [1, 2]. CVD may manifest clinically as an acute coronary syndrome (ACS), including myocardial infarction (MI) and unstable angina (UA). The very high risk of recurrent events post ACS makes control of CVD risk factors a priority in these patients. It is important to determine whether patients with ACS are receiving optimal treatment in clinical practice, and to consider opportunities for improving goal achievement. Guidelines recommend LMT to achieve specified LDL-C targets for secondary prevention [1, 2]. Large observational studies of patients with dyslipidaemia, conducted predominantly in Western Europe and North America, indicate that achievement of LDL-C targets is generally poor, particularly among patients at higher CVD risk [3–6]. Studies of lipid management in countries outside of these regions show similar results [7, 8]. This article will examine the current state of dyslipidaemia management in patients with ACS in regions outside Western Europe and North America. Strategies for improving LDL-C control in this patient group will be examined, and the potential impact of recent clinical trial data and changes to treatment guidelines will be discussed.

KEY GUIDELINE RECOMMENDATIONS

The American Heart Association (AHA)/American College of Cardiology (ACC) guidelines state $\geq$ 50% reduction in LDL-C as the primary goal of therapy post ACS, but recommend intensification of LMT if LDL-C remains $\geq$ 1.8 mmol/L (approx. 70 mg/dL) [9]. The American Association of Clinical Endocrinologist and American College of Endocrinology guidelines propose a target LDL-C of $<$ 1.4 mmol/L (55 mg/dL) for patients at "extreme risk", which include patients post ACS with additional risk factors such as early onset of CVD (age $<$ 55 years in men; $<$ 65 years in women), diabetes, chronic kidney disease (CKD) or heterozygous familial hypercholesterolaemia (HeFH) [10]. The target of $<$ 1.4 mmol/L (55 mg/dL) is also recommended in guidelines in Taiwan for patients with ACS and diabetes [11]. Recently, the European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) lowered their recommended LDL-C goal for all patients post ACS from $<$ 1.8 mmol/L (70 mg/dL) to $<$ 1.4 mmol/L (55 mg/dL) and an LDL-C reduction of $\geq$ 50%, and to $<$ 1.0 mmol/L ($<$ 40 mg/dL) for patients with CVD on maximally tolerated statins who

experience a second vascular event within 2 years [2].

Most dyslipidaemia guidelines recommend high-intensity statin as first-line LMT post ACS; however, some local guidelines in Asia, e.g. China, recommend against the use of high-intensity statins, including post ACS and in patients with very high risk CVD [12]. Ezetimibe is recommended as second-line therapy when LDL-C goal is not achieved with maximal tolerated statin alone [1, 13], supported by the findings of the IMPROVE-IT trial [14]. Further intensification of LMT with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors is recommended post ACS in patients not at LDL-C goal with a statin–ezetimibe combination [1, 13]. The efficacy of PCSK9 inhibitors for reducing CVD events post ACS in patients treated with maximally tolerated statin therapy was established by the ODYSSEY OUTCOMES and FOURIER studies [15, 16].

SUPPORTING DATA

Systematic Literature Review

A systematic literature search of Embase and PubMed databases was conducted. The search aimed to identify observational studies and systemic literature reviews (SLRs) reporting lipid management data in patients with ACS in 28 countries outside Western Europe and North America (Electronic Supplementary Appendix for included countries). The publication date range was restricted to 1 January 2009 to 13 February 2019 for the standard databases, and to the 2 years prior to the search date (13 February 2019) for conference abstracts (via Embase). Further details of the methods and strings used are provided in the Electronic Supplementary Methods and Tables S1 and S3 in the Electronic Supplementary Material. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

A total of 2946 articles were identified (Fig. S1 in the Electronic Supplementary Material). After full-text screening, 68 articles met the pre-determined search criteria and were included in the final database. The included studies account for 17 countries of interest. Of the 68 studies, 61 were reported as journal articles and seven as meeting abstracts. No SLRs or meta-analyses were identified. The included studies were 32 prospective cohort studies, 15 retrospective cohort studies, 17 non-comparative studies, three cross-sectional studies, and one case–control study.

Online Panel Discussion

In June 2019, a panel consisting of seven renowned experts (cardiologists) from Colombia, Egypt, Israel, Mexico, South Africa, Taiwan and the United Arab Emirates was convened via an online discussion platform (Within3; https://www.within3.com). All panel members were authors on previous publications on dyslipidaemia in patients with ACS and were identified via a literature search. Potential panel members were invited on the basis of their willingness and availability to participate in the online discussion. All are co-authors of this paper. Informed by the findings of the SLR conducted in February 2019 and other supportive data, including local published studies and their personal experience, the panel considered the current state of dyslipidaemia management post ACS in regions outside Western Europe and North America. The panel discussion took place during three online sessions: 3 June to 2 July 2019, 15 August to 3 September 2019 and October 1 to 14 2019, facilitated by open-ended questions (Electronic Supplementary Appendix) relating to the findings of the SLR, and on current dyslipidaemia management practices, barriers to treatment and opportunities for improved lipid control in each expert's country.

Limitations

The SLR included studies published in English only, and did not include those conducted in a wider patient population with dyslipidaemia that may have included patients with ACS. Consequently, the search may not have been fully representative of all studies reporting data

for dyslipidaemia management in patients with ACS. The patient populations and healthcare systems in these countries are heterogenous, with substantial historical, cultural, economic, genetic, lifestyle and religious differences. This heterogeneity contributes to the variability of the data and limits cross-country comparisons; however, it reflects the variation in dyslipidaemia management in patients with ACS in the real-world setting. The countries represented by the panel was a subset only (seven countries) of those examined in studies identified by the SLR; therefore, the panel's opinions and experience may not have fully reflected the state of dyslipidaemia management in all countries examined. Many of the studies identified by the SLR were performed before current guidelines were published and their findings may be based on previous recommendations for LMT and LDL-C targets. In particular, the ESC/EAS guidelines for dyslipidaemia management [2] were updated after the SLR was conducted.

CURRENT STATE OF DYSLIPIDAEMIA MANAGEMENT POST ACS IN COUNTRIES OUTSIDE WESTERN EUROPE AND NORTH AMERICA

Use of Guidelines

Information on the clinical guidelines followed, recommended LDL-C targets, LMTs commonly prescribed and details of the healthcare professional responsible for dyslipidaemia management post ACS was provided by members of the expert panel for their countries. These data were summarised and tabulated (Table 1).

The panel indicated that, in most countries represented, physicians follow recommendations of the ESC/EAS [13], AHA/ACC [9] and/or local consensus statements based on these recommendations. It should be noted that the panel discussion was initiated prior to publication of the 2019 update of the ESC/EAS guidelines [2]. In line with the AHA/ACC and previous ESC/EAS recommendations [13], an LDL-C target of < 1.8 mmol/L (70 mg/dL) was reported for most countries, although a lower target of < 1.3 mmol/L (50 mg/dL) had been adopted in Colombia [17], and the goal for patients post ACS with diabetes in Taiwan was < 1.4 mmol/L (55 mg/dL) [11]. The regional consensus statement on dyslipidaemia treatment in Mexico recommends a target of < 2.6 mmol/L (100 mg/dL); however, the panel member reported that following publication of the ODYSSEY-OUTCOMES study [15], current perception in Mexico is to treat to an LDL-C target of < 1.8 mmol/L (70 mg/dL) post ACS.

The panel noted that, in most countries, treatment algorithms based on the guidelines are employed to guide treatment decisions; the algorithm for Colombia has been published [17]. In some of the experts' countries, long-term management post discharge for ACS was the responsibility of a specialist (e.g. cardiologist, endocrinologist, internist); however, follow-up for dyslipidaemia management was most often conducted by the general practitioner or primary care physician, who may be less familiar with the treatment algorithms and may prescribe lower than recommended doses of statin therapy.

Achievement of LDL-C Goals

Of studies included in the SLR, 25 reported data on LDL-C parameters post ACS and these are summarised in Table 2. LDL-C goal achievement rate was reported in 20 of these studies, and generally indicated suboptimal control of dyslipidaemia in this patient population. Rates of LDL-C goal achievement reported 1 month after ACS ranged from 56.1% to 83.5% (three studies). Studies reporting LDL-C goal achievement 1 year post ACS (five studies) reported rates of between 19.8% and 64.6%.

Use of LMT

Rates of statin use are provided for each study included in the SLR in Table S3 in the Electronic Supplementary Material and are summarised by country/region in Table 3. The majority of patients were treated with a statin after ACS. In most studies reporting statin use in hospital or

Table 1 Guideline recommendations for dyslipidaemia management post ACS in countries represented by the expert panel

Country/region	Guidelines followed	Recommended LDL-C target post ACS	LMT used post ACS	Healthcare professional responsible for dyslipidaemia management
UAE/Gulf	AHA/ACC [9]; ESC/EAS [13]; local consensus statements [56, 57]	< 1.8 mmol/L (< 70 mg/dL) and/or ≥ 50% reduction in LDL-C [9, 13, 56, 57]	High-dose statins	Cardiologist initially; then either cardiologist, internist or endocrinologist
Israel	ESC/EAS [13]; local health basket (Ministry of Health)	< 1.8 mmol/L (< 70 mg/dL) or a reduction of ≥ 50% [13]	Atorvastatin 80 mg or rosuvastatin 40 mg (if atorvastatin not tolerated) during hospitalisation or statin combined with ezetimibe	General practitioner after discharge
Egypt	ESC/EAS [13]; AHA/ACC [9]; local consensus statement [58]	< 1.8 mmol/dL (< 70 mg/dL) or 50% reduction [58]	High-intensity statin; varies according to physician decision	Principally cardiologist
South Africa	SA Heart/LASSA consensus statement [59]	< 1.8 mmol/L (< 70 mg/dL) and a reduction of ≥ 50% [59]	Recommended interventions strategies according to CVD risk score and LDL-C levels	Specialist; primary care physician after stabilisation for continued care
Taiwan	ESC/EAS [13]; AHA/ACC [9]; Taiwan guidelines [11]	< 1.8 mmol/L (< 70 mg/dL) and/or ≥ 50% reduction in LDL-C [9, 13] < 1.4 mmol/L (< 55 mg/dL) in patients with diabetes	Statin or statin/ezetimibe within the first few days of hospitalisation, and prior to PCI	Primary care physician
Colombia	AHA/ACC [9]; local consensus statement	≥ 50% reduction [9]; < 1.29 mmol/L (< 50 mg/dL) [17]	High-intensity statin therapy (80 mg of atorvastatin or 20–40 mg of rosuvastatin daily) as soon as possible if not at target. Intensify treatment with ezetimibe 10 mg daily then consider PCSK9 inhibitor if target not achieved	Cardiologist or primary care physician

Table 1 continued

Country/region	Guidelines followed	Recommended LDL-C target post ACS	LMT used post ACS	Healthcare professional responsible for dyslipidaemia management
Mexico	AHA/ACC [9]; regional consensus statement [60]	≥ 50% reduction; [9] 2.6 mmol/L (< 100 mg/dL) [60]	High-intensity statin (atorvastatin 80 mg or rosuvastatin in different doses). Reduce to atorvastatin 40 mg if at LDL-C target after 4 months	Cardiologist or primary care physician

ACC American College of Cardiology, *ACS* acute coronary syndrome, *AHA* American Heart Association, *CVD* cardiovascular disease, *EAS* European Atherosclerosis Society, *ESC* European Society of Cardiology, *LASSA* Lipid and Atherosclerosis Society of Southern Africa, *LDL-C* low-density lipoprotein cholesterol, *LMT* lipid-modifying therapy, *PCI* percutaneous coronary intervention, *SA Heart* South African Heart Association

at discharge, at least half of patients were taking statins (Table 3); 20/36 (56%) and 16/33 (48%) of studies reported rates of statin use of ≥ 90% in hospital and at discharge, respectively (Table S3 in the Electronic Supplementary Material). Of studies reporting statin use in hospital or at discharge, 11 reported rates of statin use at ≥ 1 subsequent time point; nine of these (82%) observed a reduction in rates of statin use over time (Table S3 in the Electronic Supplementary Material). Eight studies reported rate of statin use 1 year after ACS, with rates ranging from 59.4% to 87.0% (Table 3). A study of patients with ST-elevation MI (STEMI) in Turkey observed a lower mean LDL-C ± standard deviation in patients who continued taking statin medication after hospital discharge (2.69 ± 1.22 mmol/L, $n = 79$) compared with patients who discontinued statins (3.23 ± 0.99 mmol/L, $n = 29$) [18]. Studies reporting the rates of statin use according to type of ACS (STEMI, non-STEMI, UA) [19–27] generally reported similar rates for use in hospital and at discharge.

Use of High-Intensity LMT Statin Therapy

Few studies included in the SLR reported rates of high-intensity statin therapy post ACS; in those that did, rates varied widely between studies (Table 4). Low rates of ezetimibe use (≤ 11.3%) were reported (across six studies; Table 4), particularly after discharge from hospital.

Studies assessing LDL-C goal achievement demonstrate that, although patients on intensive LMT were more likely to achieve their LDL-C goal, target attainment rates were still suboptimal. For example, 57.3% of patients treated with high-potency statins in a study in Hong Kong ($n = 2850$) did not achieve LDL-C goal 12 months post ACS compared with 63.4% of patients treated with non-high-potency statins [28]. Consistent findings were noted in a study of 1026 patients with ACS in Turkey, in which patients treated with high-intensity statin therapy were more likely to achieve LDL-C targets compared with patients prescribed lower doses of statins; however, LDL-C goal achievement was still low (≤ 45.2%) [29]. A further study of 2034 Chinese patients with ACS receiving LMT but not at LDL-C goal reported that 71.5% of these patients were receiving intensive statin therapy [30]. A retrospective cohort study of 202 patients with ACS in China demonstrated that patients were more likely to achieve LDL-C goal if they were receiving ezetimibe plus statin (69.1%, $P = 0.007$) or intensive statin therapy (67.9%, $P = 0.047$) compared with moderate-intensity statin (46.9%) [31]. Consistent results were reported for a prospective cohort study in 84 Chinese patients with

Table 2 Rates of statin use and LDL-C parameters post ACS in articles identified in the systematic literature review that reported LDL-C parameters

Country/region	Study	Patient population	Number	Use of statins (%)				LDL-C management			
				In hospital	At discharge	3–6 months[a]	1 year	Time point	LDL-C goal	Patients at goal (%)	Additional LDL-C parameters
Brazil	Carvalho et al. [61]	STEMI	22	100				5 days			Mean LDL-C (change from BL): low HDL-C group, 2.30 (− 0.83) mmol/L; high HDL-C group, 2.09 (− 1.09) mmol/L
China	Atkins et al. [62]	ACS	15,140		92	79.9	74.8	1 year	< 2 mmol/L	22	
	Auckle et al. [33]	STEMI	498		97.9	98.2		1 year	< 1.8 mmol/L or 50% reduction	36.6	
	Dai et al. [31]	ACS	202					1 month	< 1.8 mmol/L or 50% reduction	56.1	Mean LDL-C: 1.78 mmol/L
	Jiang et al. [30]	ACS	2034					4–40 weeks	< 1.8 mmol/L	36.2	Mean LDL-C: 3.09 mmol/L
	Li et al. [32]	ACS DM2	84					1 month	< 1.8 mmol/L	61.9	
Egypt	DYSIS II [63]	ACS	199			54.2[b]		4 months	< 1.8 mmol/L	5.6	
Gulf[c]	GULF COAST[d] [34]	ACS	3224		89.9		80.5	1 year	< 1.8 mmol/L	19.8	
	DYSIS II[e] [64]	ACS	150					4 months	< 1.8 mmol/L	8.7	
	DYSIS II[f] [64]	ACS	166					4 months	< 1.8 mmol/L	44.8	

Table 2 continued

Country/region	Study	Patient population	Number	Use of statins (%)				LDL-C management			
				In hospital	At discharge	3–6 months[a]	1 year	Time point	LDL-C goal	Patients at goal (%)	Additional LDL-C parameters
Hong Kong	Prince of Wales Hospital [65]	ACS	402	73.1	74.1			At discharge	≤ 1.8 mmol/L	9.7	
	Yan et al. [66]	ACS	2588		87.7		85.5	1 year			Mean (SD) change in LDL-C from BL (% change): Low BL LDL-C group, 1.76 (0.6) mmol/L (+ 26.5%); moderate BL LDL-C group, 2.1 (0.7) mmol/L (− 19.2%); high BL LDL-C group, 2.4 (0.8) mmol/L (− 43.9%)
	Lee et al. [67]	PCI + statin	1684					1 year	≤ 1.8 mmol/L	39.1	
	Yan et al. [28]	ACS	2850					1 year	< 1.8 mmol/L	64.6	
	DYSIS II [64]	ACS	136			87.6[bg] [68]		4 months	< 1.8 mmol/L	48.1 [64]	
India	REMAINS [69]	ACS	635	75.6		81.7[h]		12 weeks	< 1.8 mmol/L < 2.6 mmol/L	45.8 77.1	Change in LDL-C from BL: − 0.85 mmol/L
	Patel et al. [70]	ACS	133		97.7			1 month	≤ 1.8 mmol/L	83.5	
	DYSIS II [64]	ACS	513					4 months	< 1.8 mmol/L	57.5	

Table 2 continued

Country/region	Study	Patient population	Number	Use of statins (%)				LDL-C management			
				In hospital	At discharge	3–6 months[a]	1 year	Time point	LDL-C goal	Patients at goal (%)	Additional LDL-C parameters
Israel	ACSIS [71]		3063					In hospital			Mean (SD) LDL-C: statin alone group, 2.68 (0.99) mmol/L; statin plus fibrate group, 2.63 (1.14) mmol/L
Philippines	DYSIS II [64]	ACS	21					4 months	< 1.8 mmol/L	50.0	
Taiwan	DYSIS II [64]	ACS	123			87.6[bg] [68]		4 months	< 1.8 mmol/L	36.6 [64]	
Turkey	Guntekin et al. [29]	ACS	1026			100		6 months	< 1.8 mmol/L ≥ 50% reduction	41.3 17.5	
	Ozaydın et al. [72]	ACS	1000					In hospital			Mean (SD) LDL-C: statin-naïve group, 2.87 (1.27) mmol/L; history of statin group, 2.43 (1.06) mmol/L
	Yamaç and Kiliç [18]	STEMI	108								Mean (SD) LDL-C: statin continued after discharge group, 2.69 (1.22) mmol/L; statin discontinued after discharge group, 3.23 (0.99) mmol/L

Table 2 continued

Country/region	Study	Patient population	Number	Use of statins (%)				LDL-C management			
				In hospital	At discharge	3–6 months[a]	1 year	Time point	LDL-C goal	Patients at goal (%)	Additional LDL-C parameters
Vietnam	DYSIS II [64]	ACS	191					4 months	< 1.8 mmol/L	26.9	

To convert LDL-C values to milligrams per decilitre (mg/dL), multiply by 38.67

ACS acute coronary syndrome, *ACSIS* Acute Coronary Syndrome Israeli Surveys, *BL* baseline, *DM2* type 2 diabetes mellitus, *DYSIS II* Dyslipidemia International Study II, *LDL-C* low-density lipoprotein cholesterol, *PCI* percutaneous coronary intervention, *REMAINS* The dyslipidemia REsidual and Mixed Abnormalities IN spite of Statin therapy, *SD* standard deviation, *SPACE* Saudi Project for Assessment of Coronary Events, *STEMI* ST-elevation myocardial infarction

[a] Measured at 6 months unless otherwise stated

[b] Measured at 4 months

[c] Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates

[d] Conducted in Bahrain, Kuwait, Oman and the United Arab Emirates

[e] Conducted in Saudi Arabia

[f] Conducted in the United Arab Emirates

[g] Included both Taiwan and Hong Kong data (n = 270)

[h] Measured at 3 months

Table 3 Rates of statin use post ACS in articles identified in the systematic literature review

Country/region	Number of studies	Use of statins (%), range[a]				
		In hospital	At discharge	30 days	3–6 months	1 year
Algeria	1 [23]	90 [23]	94 [23]			
Brazil	11 [22, 61, 73–81]	64.7–100 [22, 61, 73, 74, 76–81]	82.7–93 [22, 75, 77]		76.8–85.4 [22, 75]	79.5 [75]
Chile	1 [82]	96.0 [82]	89.9 [82]			87 [82]
China	9 [33, 62, 83–89]	71.2–96.7 [84–87]	80.4–97.9 [33, 62, 83, 84]	56.3–83.2 [86, 88]	65.8–99.2 [33, 62, 83, 86, 89]	59.4–74.8 [62, 83, 86]
Egypt	2 [63, 90]		99.0 [90]		54.2 [63]	
Gulf region	11 [19, 24, 27, 34, 91–97]	83.0–95.6 [19, 91–93, 96]	83.0–97.7 [19, 24, 34, 94, 95, 97]			80.5 [34]
Hong Kong	3 [65, 66, 68]	73.1 [65]	74.1–87.7 [65, 66]		87.6 [68]	85.5 [66]
India	10 [20, 21, 69, 70, 89, 98–102]	69–99.2 [20, 21, 69, 98–101]	70.1–99.0 [21, 70, 98, 100–102]		81.7–100 [69, 89]	
Israel	2 [103, 104]		87.0–92.1 [103, 104]			
Mexico	1 [48]	14.0 [48]				
Philippines	1 [89]				100 [89]	
Russia	1 [105]		90.9 [105]			
South Africa	1 [106]	95.7 [106]				85.6 [106]
Taiwan	5 [25, 26, 68, 107, 108]	48.4–76.3 [26, 107]	48.8–77.0 [25, 26, 108]		87.6 [68]	
Turkey	1 [29]				100 [29]	
Vietnam	3 [89, 109, 110]	93.1–94.1 [109, 110]	90.7 [110]		100 [89]	

ACS acute coronary syndrome

[a] For studies that recorded percentage statin use over more than 1 time period, the data for the most recent time period are presented

Table 4 Rates of high-intensity statin use post ACS in articles identified in the systematic literature review

Country/region	Study	Time period of study	Patient population	Number	LMT	Time point	Rate of use (%)
China	Auckle et al. [33]	2013–2015	STEMI	498	High-potency LMT	Discharge	5.6
						1 year	2.9
					Ezetimibe	Discharge	1.5
						1 year	1.3
	DYSIS II [89]	2013–2014	ACS	306	Statin + ezetimibe	4 months	1.2
Egypt	DYSIS II [63]	2013–2014	ACS	199	Ezetimibe	4 months	0
Gulf–Qatar	Heart Hospital [95]	2011–2014	ACS	1064	High-potency statin	Discharge	0.09
					High-dose statin	Discharge	80.4
Gulf–UAE	UAE-ACS [19]	2003–2006	ACS	1842	Ezetimibe	In hospital	1.7
						Discharge	1.8
Hong Kong	Yan et al. [66]	2010–2014	ACS	2588	High-potency statin	12 months	8.0
	DYSIS II[a] [68]	2013–2014	ACS	270	Statin + ezetimibe	4 months	1.3
India	REMAINS [69]	2010–2012	ACS	474	High-potency statin	In hospital	84.8
						12 weeks	83.5
	Patel et al. [70]	2007–2008	ACS	133	Statin 40 mg	Discharge	26.3
					Statin 80 mg	Discharge	68.4
					Statin + ezetimibe	Discharge	11.3
	DYSIS II [89]	2013–2014	ACS	532	Statin + ezetimibe	4 months	0
Philippines	DYSIS II [89]	2013–2014	ACS	48	Statin + ezetimibe	4 months	0
Taiwan	DYSIS II[a] [68]	2013–2014	ACS	270	Statin + ezetimibe	4 months	1.3
Turkey	Guntekin et al. [29]	2014–2016	ACS	1026	High-potency statin	BL to 6 months	60.2
Vietnam	DYSIS II [89]	2013–2014	ACS	205	Statin + ezetimibe	4 months	0.5

ACS acute coronary syndrome, *DYSIS II* Dyslipidemia International Study II, *LMT* lipid-modifying therapy, *REMAINS* The dyslipidemia REsidual and Mixed Abnormalities IN spite of Statin therapy, *STEMI* ST-elevation myocardial infarction, *UAE-ACS* United Arab Emirates Acute Coronary Syndromes

[a] Included both Taiwan and Hong Kong data, and was counted in both countries

type 2 diabetes, which noted greater LDL-C goal achievement with statins plus ezetimibe (77%) compared with statins alone (45%) at 1 month post ACS [32].

Gaps in the Evidence

No studies included in the SLR reported rates of PCSK9 inhibitor use. Few studies examined patient subgroups that may be at increased risk of CVD compared with the post-ACS population as a whole. Two studies indicated that LDL-C goal achievement rates may be lower among patients with familial hypercholesterolaemia (FH). Auckle et al. [33] reported poorer LDL-C goal achievement (< 1.8 mmol/L or $> 50\%$ reduction) with moderate potency LMT at 1 year post STEMI in patients with possible FH compared with those without FH (18.7% vs. 51.4%) in China. In a separate study, patients ($n = 3224$) from the GULF COAST registry (2012–2013) were stratified by FH status (probable, possible or unlikely) [34]. Rates of statin use were similar in the three groups at discharge (96–98%) and at 1 year post ACS (93–96%); however, goal attainment rates differed between the groups ($P < 0.001$); 23% of patients in whom FH was unlikely achieved their LDL-C goal, compared with 13% and 12% of patients with probable and possible FH, respectively.

IMPACT OF RECENT DEVELOPMENTS IN DYSLIPIDAEMIA MANAGEMENT

Recent guidelines for the treatment of dyslipidaemia specify lower LDL-C targets for patients at very high risk of CVD than previous recommendations. Treating patients with ACS to an LDL-C target of < 1.4 mmol/L (55 mg/dL) is supported by the findings of the IMPROVE-IT [14], ODYSSEY-OUTCOMES [15] and FOURIER [16] studies. In IMPROVE-IT, addition of ezetimibe to high-dose simvastatin in patients with ACS lowered LDL-C to a mean of 1.4 mmol/L (53.2 mg/dL) and reduced CVD event rate compared with placebo without evidence of harm [14]. The benefit of ezetimibe on CVD event rate appeared to emerge after 1 year of treatment, was statistically significant at 7-year follow-up, and was particularly pronounced in elderly patients and in those with diabetes mellitus. The ODYSSEY-OUTCOMES trial is the only study to investigate the effects of a PCSK9 inhibitor in patients with ACS. It examined the effect of alirocumab in patients with ACS and LDL-C ≥ 1.8 mmol/L (70 mg/dL), non-high-density lipoprotein cholesterol ≥ 2.6 mmol/L (100 mg/dL) or apolipoprotein B ≥ 80 mg/dL despite statin therapy [15]. Addition of alirocumab lowered mean LDL-C to 1.24 mmol/L (48 mg/dL) at 12 months and reduced major CVD events and total mortality by 15% compared with placebo after a 2.8-year follow-up. FOURIER was conducted in statin-treated patients with stable coronary heart disease, peripheral artery disease or prior stroke and LDL-C ≥ 1.8 mmol/L (70 mg/dL) [16]. Patients treated with the PCSK9 inhibitor evolocumab had a mean LDL-C of 0.78 mmol/L (30 mg/dL) after 48 weeks of treatment. At follow-up (median 2.2 years), the risk of CVD events was reduced by 15% with evolocumab compared with placebo. On the basis of the findings of these studies, lowering the LDL-C goal for patients with ACS to < 1.4 mmol/L (55 mg/dL) would be expected to reduce the risk of recurrent events. Given the low attainment of higher LDL-C goals reported post ACS in the studies included in the SLR, these more stringent targets are unlikely to be met with current clinical practice, and greater use of intensive LMTs will be required.

The low rates of high-potency statin and ezetimibe use in the studies included in the SLR suggest that LMT is often not intensified in clinical practice. Despite recommendations of previous guidelines for LMT to achieve specified LDL-C targets, lipid testing and high-intensity statin use are often infrequent after ACS [35]. Current guidelines include clearer recommendations for the measurement of LDL-C during the course of ACS and for intensification of LMT [2, 9], which may encourage optimal dyslipidaemia management.

Lipoprotein(a) (Lp[a]) is an indicator of increased CVD risk and may identify patients at premature risk of ACS. The ESC/EAS guidelines

recommend that measurement of Lp(a) should be considered at least once during an adult's lifetime to identify those with very high inherited levels (> 180 mg/dL) [2]. These patients have a lifetime risk of CVD equivalent to that of patients with HeFH [36], and may therefore be candidates for aggressive LMT. An analysis of data from the FOURIER study demonstrated the potential benefit of PCSK9 inhibitors for reducing CVD risk in patients with elevated Lp(a) [37]. Evolocumab produced a significant reduction in Lp(a) levels (median 26.9% reduction at 48 weeks), and patients with higher baseline Lp(a) levels derived greater absolute CVD risk reductions from evolocumab treatment compared with those with lower baseline Lp(a).

KNOWLEDGE GAPS AND RESEARCH NEEDS

Whether the LDL-C target for patients with ACS and other very high risk patients should be lowered further, e.g. < 1.3 mmol/L (50 mg/dL) is the subject of ongoing debate. The ESC/EAS guidelines state that an LDL-C goal of < 1.0 mmol/L (< 40 mg/dL) may be considered for patients with CVD who experience a second vascular event within 2 years while taking maximally tolerated statin-based therapy [2]. However, the panel reported that many physicians may be reluctant to treat to such low LDL-C levels because of long-term safety concerns, and further evidence of the safety of treating to very low LDL-C targets is needed.

Guidelines recommend the addition of ezetimibe in patients not at LDL-C goal with maximally tolerated statins, followed by further intensification with a PCSK9 inhibitor if needed to achieve LDL-C goal [2, 9]. The current recommendation of reserving treatment with PCSK9 inhibitors for patients not at LDL-C goals on a statin–ezetimibe combination is based on the wider availability and lower cost of ezetimibe, rather than on clinical evidence. The ODYSSEY-OUTCOMES and FOURIER trials allowed enrolment of patients treated with a statin–ezetimibe combination at baseline; however, most patients included were not treated with ezetimibe [15, 16]. These studies established the clinical efficacy of PCSK9 inhibitors in statin-treated patients; however, the efficacy of ezetimibe first followed by PCSK9 inhibitors for intensification of LMT post ACS has not been examined in randomised controlled trials, and further studies are needed. Newer LMTs, such as bempedoic acid and inclisiran, are currently in clinical development; however, their efficacy for reducing CVD risk has yet to be established in clinical trials [38].

The role of PCSK9 in the initial phase after ACS is poorly understood. Studies have shown a positive association between PCSK9 levels and severity of coronary artery lesions in patients with ACS [39–41], highlighting the potential importance of PCSK9 inhibitors immediately after ACS for neutralising these increased levels. The ESC/EAS guidelines state that PCSK9 inhibitors may be considered early upon admission for ACS in patients with LDL-C not at goal despite already taking a statin at the maximally tolerated dose [2]. The EVOPACS study (n = 308) examined the efficacy of evolocumab initiated on top of atorvastatin 40 mg during the in-hospital phase of ACS in patients with elevated LDL-C (≥ 1.8 mmol/L on high-intensity statin for at least 4 weeks; ≥ 2.3 mmol/L on low- or moderate-intensity statin; or ≥ 3.2 mmol/L on no stable dose of statin) [42]. Most patients (78.2%) were statin-naïve on admission. After 8 weeks, 95.7% of patients achieved an LDL-C goal of < 1.8 mmol/L with evolocumab compared with 37.6% with placebo. More data are required to confirm the findings that PCSK9 levels rise during the acute phase of ACS, to determine the influence of early high-dose statin use on PCSK9 levels during this period and to establish the clinical efficacy for reducing CVD risk of immediate treatment with PCSK9 inhibitors. The possibility of negative pleiotropic effects of early blockade of PCSK9 activity, and the long-term safety and efficacy of early initiation of PCSK9 inhibitors on top of statin–ezetimibe, needs to be established.

Several comorbidities increase CVD risk and may impact on dyslipidaemia management, including diabetes, peripheral artery disease, CKD, heart failure, non-alcoholic fatty liver

disease, atrial fibrillation and premature CVD [1, 2]. Few data are available on dyslipidaemia management post ACS in patients with these conditions. In addition, more data are needed on the effects of other factors that may increase CVD risk or make the patient more challenging to treat, including age (elderly and young patients with premature atherosclerosis), menopausal status in women (i.e. pre vs. post menopause), chronic inflammatory disease, rheumatoid arthritis, systemic lupus erythematosus, psoriasis and HIV infection. Given that genetic mutations that impact dyslipidaemia vary between ethnic groups, ethnicity is another important factor, and its effect on LDL-C goal achievement should be studied further. In addition to real-life observational studies in these subgroups, studies are also required to establish the efficacy of intensive LMT in these patient populations.

BARRIERS TO OPTIMAL DYSLIPIDAEMIA MANAGEMENT POST ACS

The findings of the SLR demonstrate that, although statins are widely prescribed after ACS, the intensity of therapy is suboptimal and the proportion of patients achieving target LDL-C levels is low. These findings suggest that dyslipidaemia management is often not conducted in line with guideline recommendations, especially in patients at high risk.

Not all patients with ACS are discharged from hospital on a statin. These patients may be less likely to receive subsequent statin therapy from their primary care physician or have their LDL-C level monitored regularly. Frequent monitoring of LDL-C, starting 6–8 weeks after discharge to assess response to therapy [2], is recommended, with intensification of LMT if not at goal [2, 9]. In many countries this may not be possible, and the panel report that monitoring of LDL-C is often not performed, either because physicians follow outdated guidelines, the ACS pathway for follow-up post discharge is not properly organised, follow-up is not arranged or the patient fails to attend. For patients who are followed up, a certain inertia regarding LDL-C control is quite prevalent among physicians intervening post discharge. They may either fail to set LDL-C goals or not monitor progress towards these goals. They may underestimate poor disease control and be uncertain about the need to intervene, accepting higher than recommended LDL-C targets [43, 44]. Primary care physicians may be reluctant to intensify treatment to comply with stringent LDL-C targets because of the perceived lower risk of CVD with time since ACS and the potential for adverse events with LMT. This may be particularly true for patients they perceive as being at higher risk of adverse events, such as the elderly and those with comorbidities in multiple concomitant medications. In addition, physicians often underestimate CVD risk [7], which may result in setting less aggressive LDL-C targets than those recommended for patients post ACS. The TRANSLATE-ACS study conducted in the USA reported that one-third of patients with MI discontinued at least one medication by 6 months post MI, although high rates of statin use (90% vs. 95% at discharge) were noted [45]. Of patients who discontinued statin therapy, 23.3% did so on the physician's instruction (9.5% because the physician felt it was no longer needed). Advanced age and the presence of comorbidities were associated with reduced persistence with medications.

Poor patient compliance with long-term medication is also a likely factor in reducing the rate of LMT use over time. Poor patient understanding of the importance of dyslipidaemia as a CVD risk factor, lack of acknowledgement of disease severity and reluctance to have treatments intensified may contribute to non-compliance. In the TRANSLATE-ACS study, 26.0% of patients who discontinued statin therapy did so because of side effects, 9.5% did so because of cost and 6.4% did so for other patient-related reasons [45]. Private insurance and cost assistance were associated with higher persistence with medication.

A lack of effective pathways exists in patients with ACS post discharge. No active outreach to patients and no team approach to care post discharge for cardiovascular secondary prevention and LDL-C control are healthcare system

factors that may contribute to undertreatment. The lack of a discharge letter with treatment-decision support for primary care physicians is another barrier to effective dyslipidaemia management in primary care. Limited availability and restrictive reimbursement practices are also key healthcare system barriers to intensification of LMT with newer medications. The findings of the SLR indicated a low rate of use of high-intensity statins and ezetimibe. PCSK9 inhibitors were not available in some countries at the time the studies were performed; however, the addition of PCSK9 inhibitors to statin therapy in patients not at goal with statins alone is predicted to improve LDL-C goal achievement rates and clinical outcomes [46]. Generic forms are not available for all LMTs and sometimes health insurance does not cover high-intensity statins or PCSK9 inhibitors.

The high prevalence of CVD risk factors [47–49] in certain countries outside Western Europe and North America contributes to premature atherosclerosis and an earlier onset of ACS and higher age-standardised mortality rates from ischaemic heart disease [50] in these regions. This includes the higher prevalence of FH in some regions as a result of founder effects (e.g. Afrikaners in South Africa) or traditional family marriages (e.g. Middle East) [51, 52]. Observational studies have demonstrated the early onset of ACS in these regions. For example, at 51.2 ± 10.3 years, the mean age for first presentation of acute MI in Middle Eastern countries is around 10 years younger than that reported in other regions of the world [49, 53]. The Egyptian CardioRisk project reported that premature ACS was common: of 1681 patients admitted to hospital with ACS, 43% of men were aged < 55 years, and 67% of women were aged < 65 years [47]. A study of South African Asian Indian patients with ACS reported mean ± standard deviation age at presentation as 54.6 ± 10.9 years [52]. Of patients presenting with ACS, 21.9% were aged ≤ 45 years and 54% had a family history of premature MI. Premature CVD comprises a subgroup of patients with ACS who are at extreme risk and deserve a more aggressive lipid-lowering strategy than those of other high-risk subgroups, but which may be challenging to treat.

IMPROVING THE MANAGEMENT OF DYSLIPIDAEMIA AFTER ACS IN COUNTRIES OUTSIDE WESTERN EUROPE AND NORTH AMERICA: EXPERT PANEL RECOMMENDATIONS

The promotion of best practice in the management of dyslipidaemia post ACS requires several elements, including the development and use of county-specific consensus statements and treatment algorithms, medical and patient education, and changes in health practices.

LDL-C Goal Post ACS

The panel supports the recommendations of recent guideline updates that recommend lowering LDL-C to < 1.4 mmol/L (55 mg/dL) post ACS.

The ESC/EAS recommendations for FH screening are also supported as well as the use of Lp(a) to identify patients at higher risk of CVD, particularly for patients with premature atherosclerosis and those with a positive family history for CVD.

Combination LMT

All patients with ACS should receive a high-intensity statin therapy, unless contraindicated, regardless of the baseline LDL-C level. The IMPROVE-IT trial showed that in high-risk patients post ACS, ezetimibe 10 mg/simvastatin 40 mg was superior to simvastatin 40 mg alone in reducing long-term CVD events [14]. The 2019 ESC/EAS dyslipidaemia guidelines recommended follow-up of lipid profile within 4–6 weeks with the addition of a PCSK9 inhibitor if LDL-C goal is not achieved despite maximally tolerated statin dose and ezetimibe combination. It may also be reasonable to add a PCSK9 inhibitor during hospitalisation for patients admitted with ACS, who are not at LDL-C goal despite adherence to maximally tolerated LMT.

Use of Country-Specific Treatment Algorithms

Treatment algorithms are beneficial to guide treatment decisions and promote best practice. They define strategies to improve the management of dyslipidaemia and provide clear guidance on how (including dosage) and when patients should be initiated on statins, and when to intensify LMT with ezetimibe and PCSK9 inhibitors. A large study of patients with ACS in China (n = 29,346) supports their use, noting that initiation of a clinical pathway-based, multifaceted quality of care initiative in hospitals improved the use of appropriate therapies for secondary prevention at discharge [54]. Given the differences in healthcare systems and availability of newer LMTs between countries, and between hospitals within countries, treatment algorithms should be developed for the country in which they are to be used and should be tailored at a hospital level. These should be updated as newer therapies become available and guidelines are updated. An example of a country-specific clinical pathway for guiding the use of PCSK9 inhibitors is the one that has been developed for use in Colombia [17].

Improving Outpatient Follow-Up

Follow-up after discharge from hospital is vital to ensure monitoring of LDL-C levels and intensification of LMT for patients not at LDL-C goal. Initiating the appropriate secondary prevention management at discharge and providing a strategy or prescription for intensification of LMT when transferring the patient into primary care will result in a better outcome for the patient. Outpatient follow-up should be arranged prior to discharge, as this practice is associated with higher persistence with medication after ACS [45]. The patient's lipid profile should be assessed 6–8 weeks post discharge and treatment intensified if LDL-C levels are not at target. Every effort should be made for all patients to be at target LDL-C goals within 6 months post index event. Lipid levels should be monitored at least annually in all patients to ensure that LDL-C levels remain at goal, which also indirectly enables clinicians to evaluate treatment compliance.

Medical Education

Medical education is important to raise awareness among physicians of the short- and long-term benefits of significant lipid lowering in the acute setting. The first medical contact should be trained to routinely measure LDL-C levels and initiate high-dose statin therapy or intensify current LMT with ezetimibe and PCSK9 inhibitors if appropriate. Physician education programmes and scientific symposia are encouraged for medical education, and the increasing use of online resources and social media to facilitate wider access to medical education is supported. Providing feedback to physicians on quality indices of dyslipidaemia management, e.g. annual reporting of statistics on uncontrolled dyslipidaemia from patient registries, is beneficial to encourage greater adherence to guideline recommendations.

Educating the patient in the importance of dyslipidaemia as a CVD risk factor and the benefit of LMT post ACS is a vital aspect of treatment. A study in Taiwan demonstrated that an electronic-based patient and family education system during hospitalisation resulted in higher prescription rates of guideline-recommended therapies including statins, and contributed significantly to adherence to these medications [55].

Prioritising Dyslipidaemia Management Within Healthcare Policy

It is essential that health policymakers recognise the importance of adequate dyslipidaemia management for reducing the risk of CVD in high risk patients. Effective LMTs are available, and reducing LDL-C to below recommended targets has proven clinical benefit for reducing major CVD events. Despite this, many patients remain at elevated risk because of undertreatment. With limited availability and reimbursement of newer medications, physician education is not enough to ensure patients are

treated according to best practice recommendations. A global commitment is required to adopt effective LMT as a critical target of healthcare systems to improve prevention of CVD and reduce associated mortality and morbidity.

CONCLUSION

Recent guidelines have lowered their recommended LDL-C targets for patients with ACS. The new LDL-C goals are based on LDL-C levels achieved in clinical trials with intensive LMT that were associated with a reduced risk of CVD events. Studies reporting attainment of the previously recommended LDL-C goals in countries outside of Western Europe and North America have indicated that dyslipidaemia management is suboptimal in patients with ACS despite the availability of effective LMTs. Undertreatment is common, with few patients treated with high-intensity statins and/or ezetimibe. Greater intensification of LMT after ACS will be needed to achieve the more stringent targets now recommended.

While there is a need for improved medical education in the treatment of dyslipidaemia, a lack of availability and reimbursement of intensive LMTs is a key factor limiting dyslipidaemia management. CVD remains a leading cause of death worldwide, and effective LDL-C control improves clinical outcomes in patients with dyslipidaemia. The gap between guideline recommendations and clinical practice will not be addressed without greater prioritisation of adequate dyslipidaemia therapy by healthcare systems to enable wider access and greater use of intensive LMT.

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