European Heart Journal Supplements (2017) **19** (Supplement D), D64–D69
The Heart of the Matter
doi:10.1093/eurheartj/sux018

ANMCO Scientific Statement: clinical management of hypercholesterolaemia in patients with acute coronary syndromes

Furio Colivicchi, FACC, FESC (Coordinator)[1]*, Michele Massimo Gulizia, FACC, FESC (Coordinator)[2], Marcello Arca[3], Maurizio Giuseppe Abrignani[4], Gian Piero Perna[5], Gian Francesco Mureddu[6], Federico Nardi, FACC, FESC[7], and Carmine Riccio[8]; on behalf of the Italian Association of Hospital Cardiologists (ANMCO)

[1]*Cardiology Department, Ospedale S. Filippo Neri, ASL Roma 1, Via Giovanni Martinotti, 20 - 00135, Rome, Italy*
[2]*Cardiology Department, Ospedale Garibaldi-Nesima, Azienda di Rilievo Nazionale e Alta Specializzazione "Garibaldi", Catania, Italy*
[3]*Atherosclerosis Center, Policlinico Umberto I, Sapienza Università di Roma, Rome, Italy*
[4]*Cardiology Department, Ospedale Civile Sant'Antonio Abate, Erice, Trapani, Italy*
[5]*Cardiology Department, Ospedali Riuniti di Ancona, Italy*
[6]*Cardiology Department, Ospedale S. Giovanni, Rome, Italy*
[7]*Cardiology Department, Ospedale Castelli, Verbania, Italy*
[8]*Cardiology Department, S. Sebastiano, Caserta, Italy*

Revised by Pasquale Caldarola, Giacomo Chiarandà, Mario Chiatto, Mauro Mennuni, Marino Scherillo, Massimo Uguccioni

Consensus Document Approval Faculty in Appendix

KEYWORDS
Acute coronary syndromes;
Hypercholesterolaemia;
Statins

LDL cholesterol (LDL-C) reduction after Acute Coronary Syndromes (ACS) is associated with a significant decrease in subsequent atherosclerotic cardiovascular events. Accordingly, international guidelines recommend a reduction of LDL-C below 70 mg/dL in ACS patients. Such a result can be effectively accomplished in most cases by using high intensity statins. In selected cases, the association with ezetimibe may be necessary in order to achieve recommended LDL-C targets. This document outlines management strategies that can be consistently implemented in clinical practice in order to achieve and maintain guidelines recommended therapeutic goals.

Introduction

Patients affected by acute coronary syndromes (ACS) are at high risk of further ischaemic cardiovascular events both in the short and medium term after discharge.[1,2] Effective reduction of LDL cholesterol (LDL-C) levels obtained with statin treatment after an ACS has been associated with a substantial decrease in cardiovascular morbidity.[3,4] In fact, there is undisputed evidence that every statin-induced reduction of LDL-C of about 35–40 mg/dL correlates with a 20–25% decrease in the relative risk of subsequent ischaemic cardiovascular events.[3,4]

*Corresponding author. Tel: +39.06.3306.2294, Fax: +39.06.3306.2489, Email: furio.colivichi@aslroma1.it

Table 1 Comparative effects of different statins in terms of reduction in LDL-cholesterol (LDL-C) with respect to the initial values[10]

Atorvastatin	Simvastatin	Pravastatin	Fluvastatin	Rosuvastatin	LDL-C reduction
	10 mg	20 mg	40 mg		25–30%
10 mg	20 mg	40 mg	80 mg		31–35%
20 mg	40 mg			5 mg	36–40%
40 mg				10 mg	41–50%
80 mg				20 mg	51–55%
				40 mg	56–60%

LDL-C in patients with ACS

The systemic inflammatory response that constantly accompanies an ACS induces major modifications in LDL-C levels, even in the absence of any specific treatment. Clinical studies performed in ACS patients before the dissemination of revascularization procedures have shown the occurrence of a spontaneous 30% reduction of LDL-C during the initial clinical course.[5] Subsequent investigations in ACS patients undergoing pharmacological or mechanical reperfusion have detected less relevant variations, with an average LDL-C reduction of about 10%.[6,7] Generally, LDL-C levels drop significantly within the first 24 h from admission and reach their minimum in about 7 days from clinical onset.[6,7] It is therefore appropriate to measure LDL-C as soon as possible in the course of the hospitalization. Such initial values should be considered as a reference point and used to support the choice of pharmacological therapy. In general, average LDL-C values during hospitalisation in 'statin-naive' ACS patients may vary between 120 and 130 mg/dL.[8,9] Lower values (90–110 mg/dL) are usually detected in patients experiencing an ACS despite an ongoing statin treatment.[8,9]

Recommendations from international guidelines and new evidence from clinical studies

The ESC/EAS joint guidelines on clinical management of dyslipidaemias[10] contain the following indications:

(1) LDL-C is recommended to be used as the primary lipid analysis for screening, risk estimation, diagnosis, and management (recommendation of level I, class of evidence A); besides, LDL-C is recommended as the primary target for treatment (recommendation of level I, class of evidence A).
(2) In patients at very high cardiovascular risk, including those with ACS, an LDL-C goal of < 70 mg/dL is recommended; if the baseline LDL-C is between 70 and 135 mg/dL a 50% reduction is recommended (recommendation of level I, class of evidence A).
(3) If the goal is not reached, statin combination with a cholesterol absorption inhibitor (ezetimibe) should be considered (recommendation of level IIa, class of evidence B).

The most recent ESC guidelines on the management of ACS[11] confirm the need for an early treatment with high efficacy statins, which should be effective in reducing LDL-C of at least 50%.[11] The only available statin agents that may possibly achieve such effects are atorvastatin (dosage of 40–80 mg/day) and rosuvastatin (dosage of 20–40 mg/day)[10] (*Table 1*). In the same guidelines on the management of ACS the goal of reducing LDL-C below 70 mg/dL is also confirmed.[11] In those cases where, despite treatment with the maximum tolerated statin dose, it is not possible to reach the recommended LDL-C target, the addition of ezetimibe to cholesterol lowering therapy should be considered (recommendation of level IIa, class of evidence B).

Ezetimibe is a selective inhibitor of the intestinal absorption of cholesterol, belonging to the class of 2-azetidinones. This drug blocks a critical mediator of cholesterol absorption, the Niemann-Pick C1-like 1 (NPC1L1) protein in brush border of the intestine.[12] In response to reduced cholesterol delivery, the liver reacts by upregulating LDL receptor expression, which in turn leads to an increased clearance of LDL-C from the blood. In clinical studies, ezetimibe in monotherapy has proven effective in reducing LDL-C by 15–22%. The combination of ezetimibe with a statin, which inhibits the hepatic synthesis of cholesterol, determines an interesting therapeutic synergy and provides greater reductions in LDL-C through a dual inhibition of both cholesterol production and absorption.[12] Overall, when added to a statin, ezetimibe provides an incremental reduction in LDL-C levels of 15–20%.[13] In fact, the addition of a standard dose of 10 mg of ezetimibe to a treatment with only 10 mg of atorvastatin produces an overall reduction of LDL-C of about 50%.[13]

The recommendations supporting the use of ezetimbe in patients with ACS, which have been recently included in the ESC guidelines,[10,11] follow the results of the study IMProved Reduction of outcomes: Vytorin Efficacy International Trial (IMPROVE-IT).[14] In fact, this is the first randomized clinical trial evaluating the efficacy of the combination of ezetimibe (10 mg) and simvastatin (40 mg) in patients with ACS. This combination therapy was compared, in a double-blind fashion, with simvastatin alone (40 mg). The study enrolled 18 144 ACS patients in more than 1000 hospitals in 39 different countries. The patients were included in the study within 10 days from admission and had LDL-C levels below 125 mg/dL. The study had a follow-up lasting on average more than 6 years. The

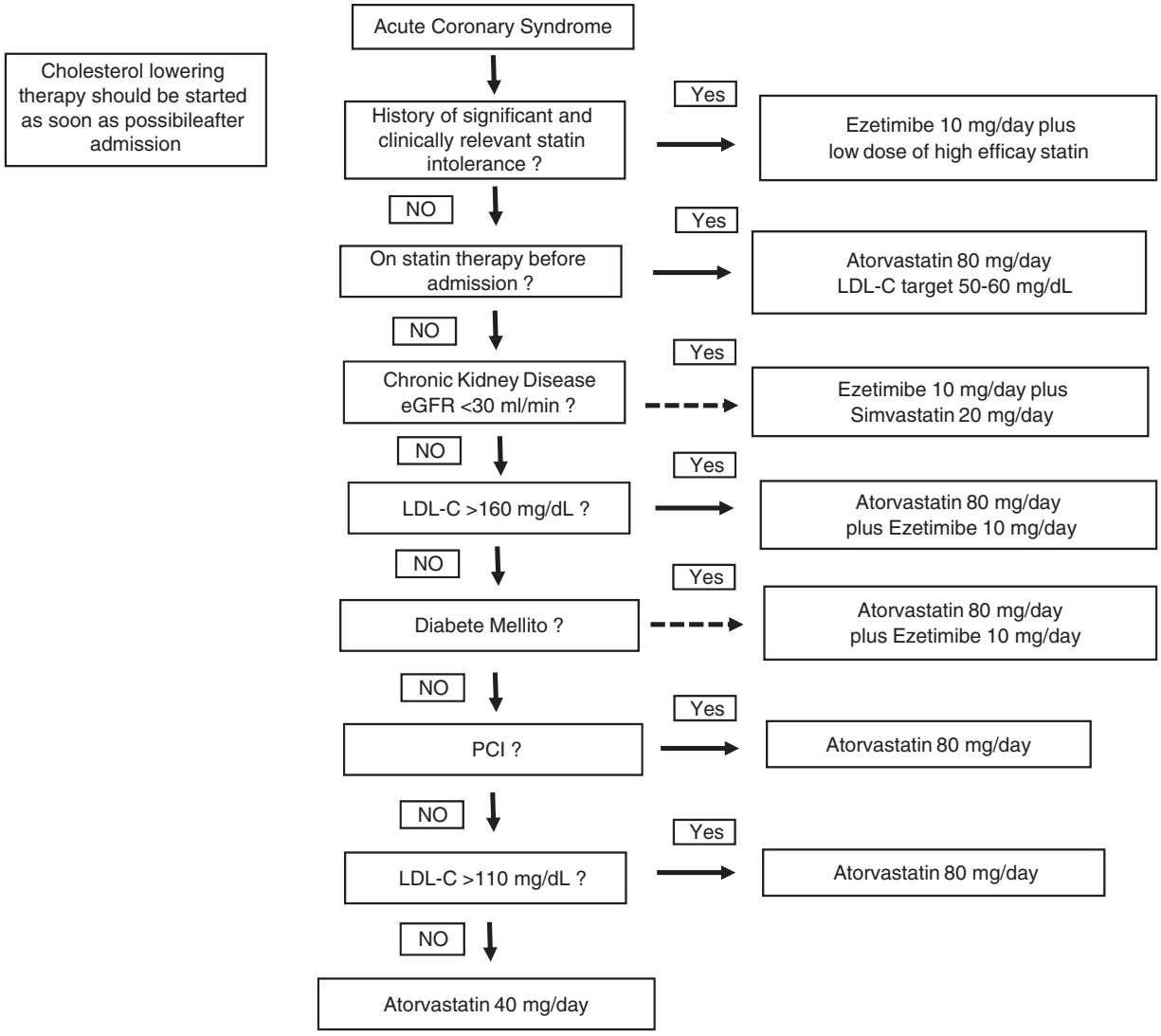

Figure 1 Cholesterol lowering therapy during admission in patients with acute coronary syndrome. LDL-C, LDL cholesterol, PCI, percutaneous coronary intervention. Solid lines represent recommendations, dotted lines represent suggestions to be considered in the clinical context.

primary endpoint was a composite of cardiovascular mortality, non-fatal myocardial infarction, hospitalization for unstable angina, myocardial revascularization, and non-fatal stroke. As expected, during follow-up, patients treated with the combination of ezetimibe and statin showed a greater reduction in the LDL-C levels as compared with those treated with simvastatin alone. In the simvastatin–ezetimibe group the median LDL-C level during the study was 53.7 mg/dL, as compared with 69.5 mg/dL in the simvastatin-monotherapy group. This significant reduction in LDL-C was associated with a lower incidence of cardiovascular adverse events during follow-up. In fact, patients treated with the association simvastatin-ezetimibe showed a significant 6.4% reduction in the risk of major adverse cardiovascular events. In terms of individual components of the primary end-point, the event reduction was mainly driven by a statistically significant reduction in the risk of non-fatal myocardial infarction (13% reduction), and non-fatal ischaemic stroke (21% reduction). Overall, there was a significant 10% reduction in the combined risk of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. Finally, in pre-specified subgroup analyses, the benefit of the combination treatment appeared to be particularly pronounced in patients with diabetes mellitus and in elderly patients ($\geq$75 years).

Management strategies in clinical practice

Patients with ACS require a tailored therapeutic intervention aimed at achieving recommended LDL-C targets.[10,11] However, it should be emphasized that the results of the IMPROVE IT trial support the idea that more ambitious targets could be considered, especially in patients with higher ischaemic risk (e.g. diabetics). However, in clinical practice, physicians must also take into account all factors possibly favouring the occurrence of side effects and adverse reactions of lipid lowering therapies, bearing in mind that adverse events usually occur when higher doses of statins are used.[15]

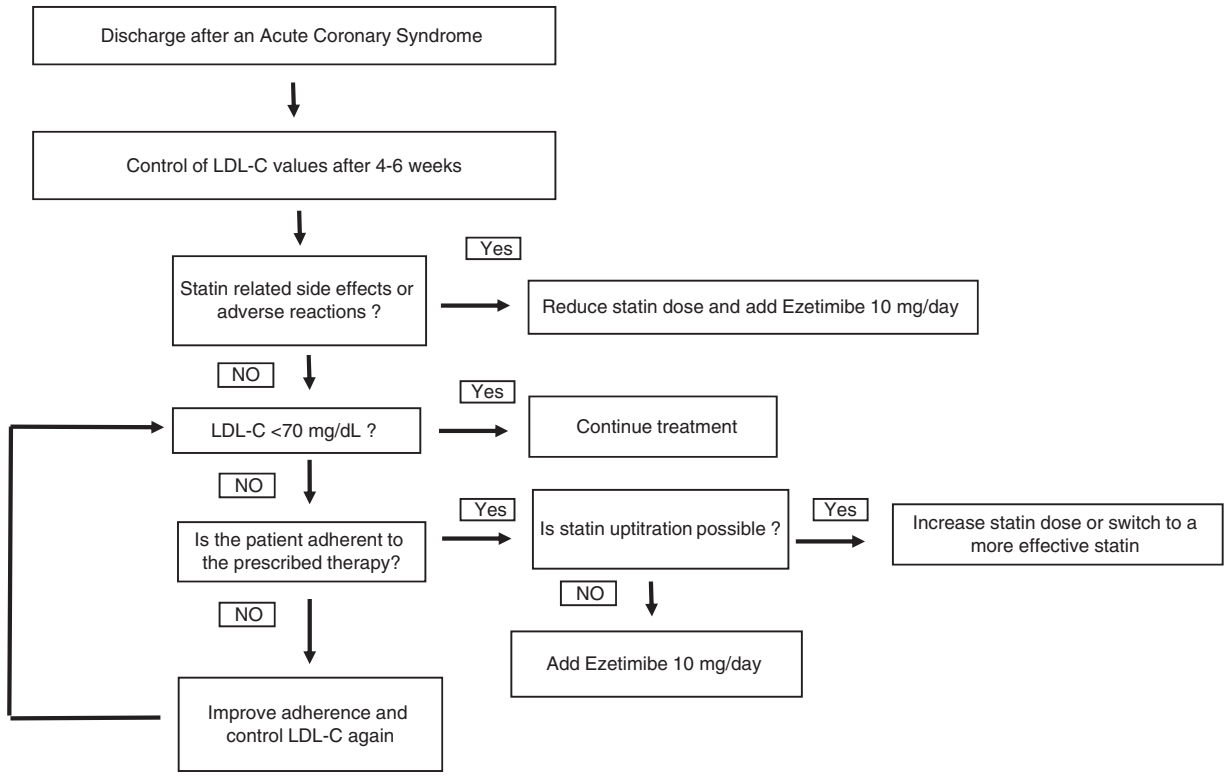

Figure 2 Management of cholesterol lowering treatment after discharge.

Initiation of treatment during hospitalization for ACS

(1) High efficacy statin therapy should be initiated as soon as possible after admission in 'statin-naïve' ACS patients. The initial statin treatment of choice is represented by atorvastatin with a target does of 80 mg/day.[8,9] In particular, all patients undergoing percutaneous coronary procedures (PCI) should receive full-dose atorvastatin treatment (80 mg) before the procedure.[16] In medically managed ACS patients, the decision on atorvastatin dosage could take into account initial LDL-C levels, age, and comorbidities. However, when LDL-C exceeds 110 mg/dL, atorvastatin 80 mg/day should always be prescribed.

(2) In patients experiencing an ACS during statin therapy, the drug, and dosage in use prior to the event should be considered. In general, atorvastatin at the full dose of 80 mg/day is recommended. Whenever available, on treatment LDL-C levels before admission should be considered for further appropriate statin prescription. Besides, given the high ischaemic risk of these particular patients, it may be necessary to pursue lower LDL-C levels (50-60 mg/dL).

(3) In ACS patients with a clinical history of proven statin intolerance, ezetimibe 10 mg/day can be prescribed. This drug may be possibly associated with a limited dose of a high efficacy statin high (e.g. atorvastatin 10 mg/die or rosuvastatin 5–10 mg).

(4) In ACS patients with a clinical history of chronic kidney disease (eGFR $<$30 mL/min), given the SHARP trial results,[17] the fixed combination of ezetimibe 10 mg and simvastatin 20 mg could be considered. This therapeutic choice could reduce the risk of subsequent side effects or adverse reactions.

(5) In ACS patients with very high LDL-C values ($>$160 mg/dL) it is appropriate to associate ezetimibe 10 mg/die with atorvastatin 80 mg/die, from the beginning of the treatment. This prescription would increase the likelihood of reaching the recommended LDL-C target of 70 mg/dL. In patients with familial hypercholesterolaemia, which generally have very high values of LDL-C ($>$200 mg/dL), rosuvastatin 40 mg/day should be prescribed (*Figure 1*).

(6) In diabetic ACS patients, given the IMPROVE IT trial results, the association of ezetimibe 10 mg/die with atorvastatin 80 mg/die could be prescribed from the beginning of the treatment during hospitalization.

Medium- and long-term treatment after discharge

(1) Lipid lowering therapy must continue indefinitely after discharge. Achievement and maintenance of recommended lipid targets (LDL-C $<$70 mg/dL) is recommended. A first control of LDL-C values should be carried out after 4–6 weeks from discharge, while subsequent assessments could be performed according to clinical needs. Patient

adherence to prescribed treatments, as well as occurrence of any adverse reaction to lipid lowering therapy, should be verified during all follow-up visits.

(2) In patients who, despite treatment with the maximum tolerated statin dose, do not reach the recommended LDL-C values ezetimibe 10 mg/day should be added.

(3) In patients developing mild side effects or adverse reactions during statin treatment, a dose reduction (for example from 80 to 40–20 mg/day of atorvastatin) and the simultaneous addition of ezetimibe 10 mg/day can be implemented. This measure ensures a lower risk of side effects and a higher probability of reaching lipid targets (*Figure 2*).

Consensus Approval Faculty

Alunni Gianfranco, Amico Antonio Francesco, Amodeo Vincenzo, Angeli Fabio, Aspromonte Nadia, Audo Andrea, Azzarito Michele, Battistoni Ilaria, Bianca Innocenzo, Bisceglia Irma, Bongarzoni Amedeo, Bonvicini Marco, Cacciavillani Luisa, Calculli Giacinto, Capecchi Alessandro, Caporale Roberto, Caretta Giorgio, Carmina Maria Gabriella, Casazza Franco, Casolo Giancarlo, Cassin Matteo, Casu Gavino, Cemin Roberto, Chiarella Francesco, Cibinel Gian Alfonso, Ciccone Marco Matteo, Cicini Maria Paola, Clerico Aldo, D'Agostino Carlo, De Luca Giovanni, De Maria Renata, Del Sindaco Donatella, Di Fusco Stefania Angela, Di Lenarda Andrea, Di Tano Giuseppe, Egidy Assenza Gabriele, Egman Sabrina, Enea Iolanda, Fattirolli Francesco, Favilli Silvia, Ferraiuolo Giuseppe, Francese Giuseppina Maura, Gabrielli Domenico, Geraci Giovanna, Giardina Achille, Greco Cesare, Gregorio Giovanni, Iacoviello Massimo, Khoury Georgette, Ledda Antonietta, Luca Fabiana, Lukic Vjerica, Macera Francesca, Marini Marco, Masson Serge, Maurea Nicola, Mazzanti Marco, Menotti Alberto, Menozzi Alberto, Mininni Nicola, Moreo Antonella, Moretti Luciano, Mortara Andrea, Mureddu Gian Francesco, Murrone Adriano, Musumeci Giuseppe, Navazio Alessandro, Nicolosi Pier Luigi, Oliva Fabrizio, Parato Vito Maurizio, Parrini Iris, Patane Leonardo, Pini Daniela, Pino Paolo Giuseppe, Pirelli Salvatore, Procaccini Vincenza, Pugliese Francesco Rocco, Pulignano Giovanni, Radini Donatella, Rao Carmelo Massimiliano, Roncon Loris, Rossini Roberta, Ruggieri Maria Pia, Rugolotto Matteo, Sanna Fabiola, Sauro Rosario, Severi Silva, Sicuro Marco, Silvestri Paolo, Sisto Francesco, Tarantini Luigi, Urbinati Stefano, Valente Serafina, Vatrano Marco, Vianello Gabriele, Vinci Eugenio, Zuin Guerrino.

References

1. Erdem G, Bakhai A, Taneja AK, Collinson J, Banya W, Flather MD. Rates and causes of death from non-ST elevation acute coronary syndromes: ten year follow-up of the PRAIS-UK registry. *Int J Cardiol* 2012;**168**:490–494.
2. Vagnarelli F, Taglieri N, Ortolani P, Norscini G, Cinti L, Bacchi Reggiani ML, Marino M, Lorenzini M, Bugani G, Corsini A, Semprini F, Nanni S, Tricoci P, De Palma R, Rapezzi C, Melandri G. Long-term outcomes and causes of death after acute coronary syndrome in patients in the Bologna, Italy, area. *Am J Cardiol* 2015;**115**:171–177.
3. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, Kirby A, Sourjina T, Peto R, Collins R, Simes R Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005;**366**:1267–1278.
4. Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, Peto R, Barnes EH, Keech A, Simes J, Collins R Cholesterol Treatment Trialists' (CTT). Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 2010;**376**:1670–1681.
5. Fyfe T, Baxter RH, Cochran KM, Booth EM. Plasma-lipid changes after myocardial infarction. *Lancet* 1971;**2**:997–1001.
6. Fresh C, Maggioni AP, Signorini S, Merlini PA, Mocarelli P, Fabbri G, Lucci D, Tubaro M, Gattone M, Schweiger C LATIN Investigators. Variations in lipoprotein levels after myocardial infarction and unstable angina: the Latin trial. *Ital Heart J* 2002;**3**:587–592.
7. Pitt B, Loscalzo J, Ycas J, Raichlen JS. Lipid levels after acute coronary syndromes. *J Am Coll Cardiol* 2008;**51**:1440–1445.
8. Briel M, Schwartz GG, Thompson PL, de Lemos JA, Blazing MA, van Es GA, Kayikçioglu M, Arntz HR, den Hartog FR, Veeger NJ, Colivicchi F, Dupuis J, Okazaki S, Wright RS, Bucher HC, Nordmann AJ. Effects of early treatment with statins on short-term clinical outcomes in acute coronary syndromes: a meta-analysis of randomized controlled trials. *jama* 2006;**295**:2046–2056.
9. Cannon CP, Braunwald McCabe CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pfeffer MA, Skene AM. Pravastatin or atorvastatin evaluation and infection therapy-thrombolysis in myocardial infarction investigators 22. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004; **350**:1495–1504.
10. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, Hoes AW, Jennings CS, Landmesser U, Pedersen TR, Reiner Ž, Riccardi G, Taskinen MR, Tokgozoglu L, Verschuren WM, Vlachopoulos C, Wood DA, Zamorano JL. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias: The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). *Eur Heart J* 2016;**37**:2999–3058.
11. Roffi M, Patron C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S, Baumgartner H, Gaemperli O, Achenbach S, Agewall S, Badimon L, Baigent C, Bueno H, Bugiardini R, Carerj S, Casselman F, Cuisset T, Erol Ç, Fitzsimons D, Halle M, Hamm C, Hildick-Smith D, Huber K, Iliodromitis E, James S, Lewis BS, Lip GY, Piepoli MF, Richter D, Rosemann T, Sechtem U, Steg PG, Vrints C, Luis Zamorano J. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the management of acute coronary syndromes in patients presenting without persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2016;**37**:267–315.
12. Daskalopoulou SS, Mikhailidis DP. Reaching goals in hypercholesterolaemia: dual inhibition of cholesterol synthesis and absorption with simvastatin plus ezetimibe. *Curr Med Res Opin* 2006;**22**:511–528.
13. The Ballantyne CM, Houri J, Notarbartolo A, Melani L, Lipka LJ, Suresh R, Sun S, LeBeaut AP, Sager PT, Veltri EP. Effect of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial. *Circulation* 2003;**107**:2409–2415.
14. Cannon CP, Blazing BUT, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, De Ferrari GM, Ruzyllo W, De Lucca P, Im K, Bohula EA, Reist C, Wiviott SD, Tershakovec AM, Musliner TA, Braunwald E, Califf RM. Ezetimibe added to statin therapy after Acute Coronary Syndromes. *N Engl J Med* 2015 Jun 18;**372**:2387–2397.
15. Pasternak RC, Smith SC, Jr, Bairey-Merz CN, Grundy SM, Cleeman JI, Lenfant C. ACC/AHA/NHLBI Clinical Advisory on the use and safety of statins. *Stroke* 2002;**33**:2337–2341.
16. Liu Y, Su Q, Li L. Efficacy of short-term high-dose atorvastatin pretreatment in patients with acute coronary syndrome undergoing

percutaneous coronary intervention: a meta-analysis of nine randomized controlled trials. *Clin Cardiol* 2013;**36**:E41–E48.
17. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, Wanner C, Krane V, Cass A, Craig J, Neal B, Jiang L, Hooi LS, Levin A, Agodoa L, Gaziano M, Kasiske B, Walker R, Massy ZA, Feldt-Rasmussen B, Krairittichai U, Ophascharoensuk V, Fellström B, Holdaas H, Tesar V, Wiecek A, Grobbee D, de Zeeuw D, Grönhagen-Riska C, Dasgupta T, Lewis D, Herrington W, Mafham M, Majoni W, Wallendszus K, Grimm R, Pedersen T, Tobert J, Armitage J, Baxter A, Bray C, Chen Y, Chen Z, Hill M, Knott C, Parish C, Parish S, Simpson D, Sleight P, Young A, Collins R. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet* 2011;**377**:2181–2192.