VIA MEDICA

REVIEW ARTICLE

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Strategy of lipid-lowering treatment in patients with acute coronary syndrome. The ELECTRA-SIRIO 2 investigators' viewpoint

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Medical Research Journal 2024; Volume 9, Number 1, 90–95
DOI: 10.5603/mrj.98821

ISSN 2451-2591
e-ISSN 2451-4101

ABSTRACT

A linear reduction in cardiovascular adverse events has been shown even when LDL-C reduction surpassed recommended treatment goals, thus postulating 'the lower, the better for longer' as a therapeutic strategy in patients with acute coronary syndrome (ACS). It was linked with more and more data on dual lipid lowering therapy (LLT) with statin and ezetimibe that showed to be associated with additional reduction of inflammatory markers as compared with statin alone. Thus, we recommend dual LLT consisted of high dose of potent statin and ezetimibe to be applied from the very beginning of hospitalization in all ACS patients.

We recommended further increase the education of patients and improve the standards of care by physicians/cardiologists with the discharge letter recently suggested by the Polish Cardiac Society and Polish Lipid Association added to the standardized discharge letter. At the first follow-up study visit, achievement of the therapeutic LDL-C target should be assessed. Patients who did not achieve and are not expected to achieve this target, and those who have been diagnosed with statin intolerance should be referred to a lipidological consultation. Lipoprotein (a) [Lp(a)] has pro-inflammatory and pro-atherosclerotic properties. Concentration of Lp(a) is predominantly determined by genetics (> 90%), more than any other lipoprotein. Elevated concentration of Lp(a) is associated with increased risk of atherosclerotic cardiovascular disease, aortic stenosis, cardiovascular and all-cause mortality. Therefore, Lp(a) should be assessed once during hospitalization in patients with ASC. Patients with Lp(a) > 50 mg/dL (> 125 nmol/L) should be referred to a lipidological consultation. These recommendations regarding LLT apply to patients enrolled in to the ELECTRA-SIRIO 2 trial, however, we encourage to consider them for treatment of other patients with ACS.

Keywords: lipid-lowering treatment, acute coronary syndrome

Med Res J 2024; 9 (1): 90–95

Introduction

Patients with acute coronary syndrome (ACS) are at a high risk of recurrent ischaemic cardiovascular events, especially in the very early phase [1–4]. On the other hand, observational studies consistently show low rates of low-density lipoprotein cholesterol (LDL-C) target goal achievement (only 17% of patients in Poland based on Da Vinci study [5], leaving patients at residual risk, especially in this vulnerable period [6–10]. Therefore, the authors — the ELECTRA-SIRIO 2 investigators - decided to define and reinforce recommendations regarding lipid-lowering therapy (LLT) for patients enrolled on this trial. In brief, this is a randomized, multicentre study evaluating two novel ticagrelor-based de-escalation strategies after ACS.

Dual lipid-lowering strategy

The 2023 European Society of Cardiology (ESC) guidelines for the management of ACS recommend the LDL-C-guided, stepwise initiation and escalation of LLT [11]. The LLT with a high-intensity statin (e.g., atorvastatin or rosuvastatin) should be initiated as early as possible after hospital admission, preferably before planned PCI, and prescribed up to the highest tolerated dose in order to reach the LDL-C goals. Treatment with ezetimibe in addition to a statin may be considered during the ACS hospitalization [11]. The goals for secondary prevention were defined as reducing LDL-C to < 1.4 mmol/L (< 55 mg/dL) and achieving ≥ 50% LDL-C reduction from baseline. Moreover, for patients who experience a second CV event within 2 years (not necessarily of the same type as the first event), who are defined as those with extremely high CVD risk, an LDL-C goal of < 1.0 mmol/L (< 40 mg/dL) appears to confer additional benefit. Dual LLT with potent statin and ezetimibe should be started during the ACS hospitalization in patients who failed to reach the LDL-C therapeutic goal despite receiving a maximally tolerated statin dose prior to ACS. Triple LLT with statin, ezetimibe and the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor is recommended in patients who do not achieve LDL-C therapeutic goal on dual LLT. The increase of LLT intensity is recommended in patients who have not achieved the therapeutic goal 4–6 weeks after ACS [11]. However, it is also important to emphasize, that based on the International Lipid Expert Panel (ILEP) recommendations from April 2021, next confirmed in multiple RCTS subanalyses, and cohort studies, upfront (immediate) lipid-lowering combination therapy of statins and ezetimibe was also suggested for ACS patients with class IIB of recommendations [12, 13].

A linear reduction in cardiovascular adverse events has been described even when LDL-C reduction surpassed current guideline-recommended treatment goals, thus postulating 'the lower, the better for longer' as a therapeutic strategy in patients with ACS [14–21]. The recent data also support the approach of "the earlier on LDL-C goal, the better" [22]. It was linked with more and more data on dual LLT with statin and ezetimibe that showed to be associated with additional reduction of inflammatory markers as compared with statin alone [21–24]. According to the clinical consensus statement of the Association for Acute CardioVascular Care (ACVC), in collaboration with the European Association of Preventive Cardiology (EAPC) and the ESC Working Group on Cardiovascular Pharmacotherapy, the systematic addition of ezetimibe to high-intensity statins early after ACS irrespectively of the LDL-C appears reasonable [17]. Faced with difficulties with reaching the therapeutic target with the stepwise approach, and in an attempt to simplify the prescription, the French experts, following the ILEP recommendations, proposed a new "fire to target" strategy, namely combination therapy (statin plus ezetimibe) for all, immediately, and without conditions [25]. This easily applicable in routine practice approach is based on the higher efficacy of dual LLT demonstrated in the IMPROVE-IT Trial [14]. It comprises an initial prescription of high-intensity statin and ezetimibe, preferably in the single-pill form [25], which was first suggested in the Polish Lipid Association (and 5 other scientific associations) guidelines 2021 [26]. As the LDL-C lowering *per se* is the main driver of cardiovascular risk reduction, therefore, such a strategy seems to be a wise therapeutic option for all ACS patients, unless known and confirmed statin intolerance is present [12, 27]. This approach together with the education of patients before discharge should enhance adherence to the therapeutic plan to combat therapeutic inertia [28–36].

Thus, the authors recommend dual LLT consisting of a high dose of potent statin (atorvastatin ≥ 40 mg, or rosuvastatin ≥ 20 mg) and ezetimibe (10 mg) to be applied from the very beginning of hospitalization in all ACS patients. Patients should be informed about the purposefulness of the treatment and therapeutic goals.

Lipid-lowering treatment at follow-up

The Multilevel Educational and Motivational Intervention in Patients After Myocardial Infarction (MEDMOTION) project has been adopted to support adherence to the study treatment in the ELECTRA-SIRIO 2 trial [37–39]. The MEDMOTION project

contains educational interventions aimed at improving the knowledge and practical skills of both patients after ACS and their cohabitating family members. The individualized education initiated during hospitalization and continued after discharge explains the pathophysiology, symptoms and prevention of coronary artery disease, elucidating goals and potential benefits of treatment [40–49]. Patients' education is supported by motivational interviews conducted by healthcare staff [50–52]. The MEDMOTION Project includes a questionnaire-based comprehensive, multistage assessment of patients including the Readiness for Hospital Discharge after Myocardial Infarction Scale (RHD-MIS), the Adherence in Chronic Diseases Scale — ACDS) and the Functioning in Chronic Illness Scale (FCIS) [53-61].

The authors recommended further increasing the education of patients and improving the standards of care by physicians/cardiologists with the discharge letter recently suggested by the Polish Cardiac Society and Polish Lipid Association added to the standardized discharge letter in all ELECTRA-SIRIO 2 patients [62].

At the first follow-up study visit (31+/–5 days from hospital admission), achievement of the therapeutic LDL-C target should be assessed. Patients who did not achieve and are not expected to achieve this target and those who have been diagnosed with statin intolerance should be referred to a lipidological consultation at a centre that participates in a drug program allowing the use of a PCSK-9 inhibitor or inclisiran [63].

Lipoprotein (a) — an underestimated risk factor

Lipoprotein (a) [Lp(a)] has pro-inflammatory and pro-atherosclerotic properties. The concentration of Lp(a) is predominantly determined by genetics (> 90%), more than any other lipoprotein. Elevated concentration of Lp(a) is associated with an increased risk of atherosclerotic cardiovascular disease, aortic stenosis, and cardiovascular and all-cause mortality in the primary prevention setting. In secondary prevention patients, elevated Lp(a) is associated with an increased risk of major adverse cardiovascular events [64–67]. According to the current recommendations Lp(a) should be measured at least once in adults to identify those with high cardiovascular risk [64]. Screening is also recommended in youth with a history of ischaemic stroke or a family history of premature atherosclerotic cardiovascular disease or high Lp(a) and no other identifiable risk factors. Moreover, cascade testing for high Lp(a) is recommended in the settings of familial hypercholesterolemia, family history of (very) high Lp(a), and personal or family history of atherosclerotic cardiovascular disease [64]. Patients with Lp(a) > 50 mg/dL (> 125 nmol/L) are considered to be at high risk of serious adverse cardiovascular events. Standard dual LLT based on statin and ezetimibe is ineffective in lowering Lp(a). The complete lipid panel assessment in patients with ACS should include measurement of Lp(a). It is recommended to assess Lp(a) in patients with ASC during hospitalization. Patients with Lp(a) > 50 mg/dL (> 125 nmol/L) should be referred to a lipidological consultation.

In summary, the authors recommend:

- Dual LLT consisting of a high dose of potent statin (atorvastatin $\geq$ 40 mg or rosuvastatin $\geq$ 20 mg) and ezetimibe (10 mg) to be applied from the very beginning of hospitalization in all ACS patients. Patients should be informed about the purposefulness of the treatment and therapeutic goals.
- Information regarding optimal lipid-lowering therapy after ACS should be added to the standardized discharge letter in all ELECTRA-SIRIO 2 patients.
- At the first follow-up study visit, the achievement of the therapeutic LDL-C target should be assessed. Patients who did not achieve and are not expected to achieve this target and those who have been diagnosed with statin intolerance should be referred to a lipidological consultation.
- Lp(a) should be assessed in patients with ASC during hospitalization (enrolment blood sampling). Patients with Lp(a) > 50 mg/dL(> 125 nmol/L) should be referred to a lipidological consultation.

These recommendations regarding LLT apply to patients enrolled on the ELECTRA-SIRIO 2 trial, however, the authors encourage to consider them for the treatment of other patients with ACS.

Article information

Author contribution: *JC and MB — conceptualisation; JC, MB, AB, PB and UT — draft preparation; PA, SDS, RG, RG, AKO, JK, PM, PN, MO, MP, UR, JMU, AK, EPN and PAG — review and editing; AK, EPN and PAG — supervision.*

Founding: *The ELECTRA-SIRIO 2 study received financial support from the Medical Research Agency, Poland, Project no. 2019/ABM/01/00009.*

Acknowledgements: *None.*

Conflict of interests: *Jacek Kubica: PI investigator of the ELECTRA-SIRIO 2 trial Maciej Banach: fees from Amgen, Daichii Sankyo, KRKA, Polpharma, Novartis, Sanofi-Aventis, Teva, Zentiva; Piotr Adamski: none Andrzej Budaj: Prof. Budaj reports personal fees and nonfinancial support from Sanofi Aventis, Bristol-Myers Squibb/Pfizer, Bayer, and AstraZeneca, as well*

as personal fees from Novartis, Amgen, and Novo Nordisk. Piotr Buszman: none Salvatore Di Somma: none Rahima Gabulova: none Robert Gajda: none Paul A. Gurbel: Dr. Gurbel has received consulting fees and/or honoraria from Bayer, Otitopic/Vectura, Janssen, UpToDate, Cleveland Clinic, Wolters Kluwer Pharma, WebMD Medscape, Baron and Budd, North American Thrombosis Forum, Innovative Sciences; institutional research grants from the Haemonetics, Janssen, Bayer, Instrumentation Laboratories, Idorsia, Otitopic, Hikari Dx, Novartis, and R-Pharma International; in addition, Dr. Gurbel has two patents, Detection of restenosis risk in patients issued and Assessment of cardiac health and thrombotic risk in a patient. Dr. Gurbel was an expert witness in a lawsuit associated with Plavix. Other authors report no conflict of interest. Agata Kosobucka-Ozdoba: none Jacek Konarski: none Aldona Kubica: none Przemysław Magielski: none Piotr Niezgoda: none Małgorzata Ostrowska: none Maciej Piasecki: none Uzeyir Rahimov: none Udaya Tantry: Dr. Tantry has received honoraria from Wolters Kluwer Pharma Julia M. Umińska: none Eliano P. Navarese: Co-PI investigator of the ELECTRA-SIRIO 2 trial.

Supplementary material: *None.*

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