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In-hospital initiation of PCSK9 inhibitors in ACS: pros and cons

Konstantin A. Krychtiuk[1,2]*, MD, PhD; Marc J. Claeys[3], MD, PhD; Baris Gencer[4,5], MD, MPH; François Mach[4]**, MD

1. Division of Cardiology, Department of Internal Medicine II, Medical University of Vienna, Vienna, Austria; 2. Duke Clinical Research Institute, Durham, NC, USA; 3. Department of Cardiology, Antwerp University Hospital, Edegem, Belgium; 4. Department of Cardiology, Geneva University Hospital (HUG), University of Geneva, Geneva, Switzerland; 5. Institute of Primary Health Care (BIHAM), University of Bern, Bern, Switzerland

Introduction

PCSK9 inhibitors have emerged as an important treatment strategy to achieve secondary prevention targets of low-density lipoprotein cholesterol (LDL-C). This is particularly relevant among acute coronary syndrome patients who are at high risk of recurrent adverse events. Although in-hospital initiation of PCSK9 inhibitors has been advocated to induce a rapid and potent LDL-C reduction and to improve patient adherence and outcomes, limited data are available and the risk of overtreatment may be a concern for some patients; in addition, the cost-effectiveness of large-scale early PCSK9 inhibition should be also evaluated. Based on these considerations, whether in-hospital PCSK9 inhibitor initiation should become a standard of care for patients presenting acute coronary syndrome remains to be established.

Pros

Konstantin A. Krychtiuk, MD, PhD; Marc J. Claeys, MD, PhD

After an acute coronary syndrome (ACS), patients are at high risk of experiencing recurrent cardiovascular events, especially in the early phase. Current guidelines recommend a LDL-C goal of below 55 mg/dL and a reduction of at least 50% from baseline LDL-C levels in all ACS patients, irrespective of disease severity, or accompanying comorbidities[1]. To achieve these goals, the European Society of Cardiology Guidelines recommend initiation of a high-intensity statin and a step-wise approach to the addition of lipid-lowering therapies (ezetimibe and proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitors) based upon routine re-evaluation of LDL-C levels during follow-up. Unfortunately, observational studies have consistently shown low rates of treatment adjustment and a low rate of LDL-C target goal achievement in clinical practice, leaving vulnerable patients at unacceptable risk.

In light of the predictability of the magnitude of LDL-C response to lipid-lowering therapies, clear evidence for the benefits of a "the lower, the better" approach and trial evidence for beneficial effects of early and strong lipid-lowering after ACS, we believe a "strike early and strike strong" approach for lipid-lowering after ACS is strongly warranted[2]. While initiation of the combination of a high-dose statin and ezetimibe during index hospitalisation will increase the number of patients reaching target LDL-C levels, the expected reduction of about 65% will be insufficient for patients with untreated baseline LDL-C values >160 mg/dL. Other clinical scenarios requiring the addition of a PCSK9 inhibitor include patients with statin intolerance, as the newly approved combination of ezetimibe and bempedoic acid results in LDL-C lowering of only about 35%, and those with

*Corresponding author: Division of Cardiology, Department of Internal Medicine II, Medical University of Vienna, Vienna, Austria. E-mail: Konstantin.krychtiuk@meduniwien.ac.at

**Corresponding author: Department of Cardiology, Geneva University Hospital (HUG), University of Geneva, Geneva, Switzerland. E-mail: Francois.Mach@hcuge.ch

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recurrent ACS, for whom guidelines recommend more stringent LDL-C targets (<40 mg/dL).

In recent years, three smaller trials have assessed the concept of PCSK9-inhibitor initiation during hospitalisation for ACS and have demonstrated the safety, feasibility, and efficacy of such an approach[2]. In the small VCU-AlirocRT (n=20), administration of alirocumab within 24 hours of non-ST-elevation myocardial infarction (NSTEMI) presentation resulted in a nearly 70% reduction of LDL-C after just 14 days, with significant reductions evident as early as day 3. In the EVACS trial (n=57), two-thirds of patients receiving evolocumab within 24 hours after presentation for NSTEMI could be discharged with LDL-C levels reaching the target goal of <55 mg/dL[2]. In EVOPACS, treatment with evolocumab during ACS admission and after 4 weeks was compared with placebo treatment (n=308)[2]. Median LDL-C levels after 8 weeks were 80 mg/dL in the standard treatment group and around 30 mg/dL in the PCSK9-inhibitor group, with a vast majority of patients achieving the target LDL-C goal.

Two recently conducted, placebo-controlled, randomised clinical trials evaluated the effects of in-hospital PCSK9-inhibitor initiation on top of standard therapy on atherosclerotic plaques in non-infarct-related arteries in ACS patients[3,4]. Both trials, HUYGENS (n=161) and PACMAN-AMI (n=300), demonstrated improved plaque phenotype, assessed by intravascular imaging, after 1 year of treatment with PCSK9 inhibitors. Whether such an approach results in a reduction of cardiovascular events will be evaluated in the EVOLVE-MI trial (ClinicalTrials.gov: NCT05284747), including 4,000 patients hospitalised for acute myocardial infarction. The trial will test the effects of adding evolocumab on top of standard of care on major cardiovascular events, closing the evidence gap for PCSK9 treatment in the post-ACS phase.

Inclisiran, a novel small interfering RNA (siRNA) targeting PCSK9, may represent another interesting approach in the acute phase, as one injection results in a 50% reduction in LDL-C for 3 months, potentially bridging the highest risk phase post-ACS.

Given the low rates of LDL-C goal attainment in clinical practice and the demonstrated safety, feasibility, and efficacy of early initiation of PCSK9 inhibitors, resulting in high rates of LDL-C control within days after the event and subsequent plaque stabilisation, initiation of PCSK9 inhibitors in the very early phase after ACS seems attractive.

Conflict of interest statement

K. Krychtiuk was a member of the advisory boards at Novartis, Sanofi, and Amgen; and received speaker fees from Amgen. M. J. Claeys has no conflicts of interest to declare.

Cons

François Mach, MD; Baris Gencer, MD, MPH

Lipid-lowering therapies are effective to prevent major adverse cardiovascular events (MACE) after an ACS[1]. The 2019 European Society of Cardiology (ESC) Guidelines recommend the addition of PCSK9 inhibitors on top of high-intensity statin and ezetimibe, if the LDL-C targets of <1.4 mmol/L are not achieved after 6-12 weeks[5]. We drafted a review paper some years ago, "Lipid management in ACS: Should we go lower faster?", highlighting the importance of optimal process of care for improving quality of care and controlling for cardiovascular risk after ACS[6]. We also acknowledged that the addition of PCSK9 inhibitors at the time of hospitalisation was not supported by evidence, since no trial had tested this hypothesis.

Indeed, nothing has really changed since then, except that two trials have tested the use of PCSK9 inhibitors at the time of ACS hospitalisation but were not powered for clinical outcomes. The EVOPACS trial showed that evolocumab was effective in reducing LDL-C levels, and the PACMAN-AMI trial showed that alirocumab was able to slow plaque regression[7,3]. The guidelines give a recommendation for the initiation of PCSK9 inhibitors during the acute phase of ACS if LDL-C levels are above the targets despite maximal therapy (class of recommendation IIa)[5]. Of note, the Level of Evidence is low (C) because no outcome data have been available so far. In the ODYSSEY Outcomes trial, ACS patients were included but not in the acute phase[8]. ODYSSEY was designed to allow for a period of 6-12 weeks of titration before considering alirocumab. In the FOURIER trial, high-risk patients were included but not ACS patients[9]. In a secondary analysis of FOURIER, patients with a recent myocardial infarction (MI) (within 12 months) had a reduction of MACE by 19% compared to 8% for patients with a remote MI[10]. Since patients with a recent MI were at higher risk, they were more likely to benefit from evolocumab with an absolute risk reduction of MACE by 3.7%, corresponding to a number needed to treat (NNT) of 27 in comparison to patients with a remote MI who had an absolute risk reduction of 1.1% and a NNT of 91 over a median follow-up of 2.2 years. However, the survival curves started to diverge only after 12 months, and no effect was observed on outcomes measured at discharge or 6 months.

The period of titration of therapies of 4-6 weeks after ACS is a major step that requires particular attention. Referral to cardiac rehabilitation is also strongly advised to improve the control of cardiovascular risks factors, including a healthier lifestyle and adherence to therapies[1]. Most patients can reach the LDL-C target if the combination of high-intensity statin and ezetimibe are implemented appropriately (85% of ACS patients)[11]. Indeed, titration of therapies can motivate ACS patients to reach the targets without escalating therapies, given that most patients are reluctant to take several therapies, especially if there is no clear benefit.

Besides that, there is no strong clinical evidence to initiate PCSK9 inhibitors at the time of hospitalisation; however, there are other valid reasons supporting the prescription of PCSK9 inhibitors after hospital discharge. First, most countries implemented

the diagnosis-related group (DRG) system to improve efficiency and control costs at the hospital level. PCSK9 inhibitors are expensive drugs, and with the DRG system, the injection of PCSK9 cannot be reimbursed as a separate intervention. Second, the use of a PCSK9 inhibitor improves outcomes when it is used for long-term management. Unless treatment continuation can be guaranteed post-discharge, a one-off PCSK9 injection in hospital has no proven benefit and results in unnecessary and /or unjustified costs. Reimbursement criteria are defined by strict rules, which are far more restrictive than the guidelines. For instance, in Switzerland, the reimbursement for PCSK9 inhibitors was limited in ACS patients to those with an LDL-C level >2.6 mmol/L under maximal statin-tolerated therapy.

In conclusion, PCSK9 inhibitors have their place in the management of ACS, but given their mechanisms of action and their lagging effect, their utilisation should be considered as a preventive therapy after discharge and not as an acute therapy for emergency medicine.

Conflict of interest statement

The authors have no conflicts of interest to declare related to the manuscript.

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