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

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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

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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 comorbidities1. 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 warranted2. 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...
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. 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. In EVOPACS, treatment with evolocumab during ACS admission and after 4 weeks was compared with placebo treatment (n=308). 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. 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 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. Krychtiuki was a member of the advisory boards at Novartis, Sanofi, and Amgen; and received speaker fees from Amgen. M. J. Claeyrs has no conflicts of interest to declare.
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.