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Should we measure PCSK9 levels in patients with acute coronary syndromes?

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Summary

Background: Several studies have shown that inhibitors of proprotein convertase kexin 9 (PCSK9) efficiently lowered levels of low-density lipoprotein cholesterol (LDL-C), especially in patients with familial hypercholesterolaemia, intolerant of statins or with poorly controlled LDL-C on maximally tolerated statin treatment. However, circulating PCSK9 levels have been little studied in the acute phase of acucte coronary syndromes (ACS), especially their evolution over time and association with clinical outcomes.

Methods and results: We observed that higher PCSK9 levels at initial presentation of 2030 patients with ACS were associated with the presence of familial hypercholesterolaemia, the use of lipid-lowering therapy, the duration of chest pain and inflammation (C-reactive protein). To confirm this hypothesis, we found that PCSK9 levels increased 12–24 hours after ACS, probably with the inflammatory process during ACS. Then we assessed the increment value of adding PCSK9 to recommended risk stratification scores, such as the GRACE score, and found that PCSK9 did not predict mortality at 30 days and at 1 year. However, patients with high initial PCSK9 levels less frequently reached target LDL-cholesterol levels (<1.8 mmol/l) at 1 year.

Conclusions: The measurement of PCSK9 is currently poorly implemented in clinical practice. Our findings suggest that PCSK9 might be useful for clinicians to identify patients who might need more intensive lipid-lowering therapy (e.g. PCSK9 inhibitors) to lower LDL-C.

Key words: cardiovascular prevention; lipids; risk factors; pharmacological therapies

The 2016 Swiss Society of Cardiology meeting was a very exciting event in my career. With the publication of the article entitled "Prognostic values of PCSK9 in acute coronary syndrome" in the *European Heart Journal*, I was honoured to receive the 2016 Swiss Amgen Research Award from the Scientific Committee of the Swiss Society of Cardiology [1]. I had the opportunity to present this work during my lecture entitled "Should we measure PCSK9 levels in patients with acute coronary syndromes?". This award provides not only strong support for young clinicians involved in clinical research, but also a recognition of the scientific activities in Swiss Universities. The project was the fruit of an extensive collaboration between universities and various experts in different fields (preventive medicine specialist, interventional cardiologist, statistician, fundamental and clinical researcher, study nurses). I would like to thank to all my valuable colleagues and mentors, in particular Professor François Mach for his support in this project and the Swiss National Science Foundation (SPUM SPUM 33CM30-124112 and SPUM 33CM30-140 336). The current article refers to the lecture given during the annual meeting, following a longstanding tradition, of the Swiss Society of Cardiology. In addition to main findings reported in the *European Heart Journal*, this article extends and deepens the discussion and perspectives of a potential new biomarker.

Dyslipidaemia and atherosclerosis

Cardiovascular congresses and meetings have shown increasing interest in presenting scientific activities in the field of cardiovascular prevention and dyslipidaemia. Cardiovascular prevention remains the most cost effective intervention to minimise the morbidity related to cardiovascular disease [2]. The recent guidelines for cardiovascular prevention from the European Society of Cardiology (ESC) underlined both population-based and individualised approaches [2]. Lifestyles measures are recommended for everyone to keep a low global level of risk, while more intensive treatments are needed for subjects at high risk. Dyslipidaemias, especially of low-density lipoprotein cholesterol (LDL-C), are well-documented and established risk factors for atherosclerosis and cardiovascular disease (CVD). Treatments lowering LDL-C, such as statins, are associated with a reduction in CVD risk, and guidelines recommend specific targets according to the global

CVD risk [2]. Non-statin agents, such as proprotein convertase kexin 9 (PCSK9) inhibitors and ezetimibe, are now considered to be additional options for reaching recommended LDL-C targets, .

Summary about discovery and clinical importance of PCSK9

PCSK9 became, in a few years, a major target for the management of hypercholesterolaemia and also a biomarker studied in various association analyses (table 1) [3]. Development from the discovery of the loss-of-function mutations to the approval of therapeutic agents (PCSK9 inhibitors) was especially fast and impressive, taking place within a timeframe of 10–15 years [4]. There were several reasons for this success:

(1.) LDL-C is a well-established causal risk factor for CVD. PCSK9 plays a key role in the regulation of LDL-C levels and is a potential target to control LDL-C [5].

(2.) The concept of lower is better for LDL-C is supported by several studies, mainly with statin therapy. The reduction of CVD events by statin therapy depends on the absolute risk of the subjects and the reduction of the LDL-C levels by the treatment [6]. A huge decrease in LDL-C levels is associated with a lower risk of CVD events. PCSK9 inhibitors effectively reduce LDL-C by 50% compared with placebo, in combination with a statin [7]. *Post-hoc* analysis of the impact on CVD events is also very promising [7].

(3.) Familial hypercholesterolaemia (FH) gained a major focus in term of definition, diagnosis and risk stratification [8, 9]. FH is the most prevalent genetic disease and the Dutch clinical classification is a practical tool for identifying those patients. We have reported that 20% of patients at very high risk, such as those hospitalised with acute coronary syndrome (ACS), had diagnostic criteria for FH [10]. The prevalence of FH was even higher (up to 50%) in subjects with a premature ACS event.[10] Recognising FH patients at an early stage is a major step for the use of PCSK9 inhibitors, especially in the presence of high-risk factors [11]. The following question remains open: Will the diagnosis of now FH increase, given the availability of additional effective treatments?

(4.) Real-life data suggest that the achievement of recommended LDL-C targets is suboptimal. About 40% of contemporary ACS patients reached LDL-C targets of less than 1.8 mmol/l or had a decrease in LDL-C levels by 50% [12]. Although LDL-C control can be improved by the prescription of high-intensity statins or the recommended addition of ezetimibe, there is a room for improvement in the control of LDL-C levels and a need for alternate therapy on in addition to statins.

(5.) The residual risk of CVD events despite statin therapy with excessively high LDL-C levels is an argument for the development of additional therapy [5]. Ongoing large clinical trials with PCSK9 inhibitors are assessing their impact on clinical outcomes. In addition to LDL-C levels, PCSK9 inhibitors can decrease lipoprotein(a) [Lp(a)] by 30%. Several reports suggest that Lp(a) is a causal risk factor for CVD and will become an additional factor in the selection of intensive lipid-lowering therapy (e.g. Lp(a) ≥50 mg/dl) [13]. In contrast, the impact of statin therapy on Lp(a) levels remained controversial.

(6.) Intolerance to statin therapy is currently a strong argument for the use of a non-statin agent. Recently, the ESC published a consensus paper on the definition of statin-associated muscular symptoms (SAMS) and their management [14]. At least a switch between three different statin is needed before considering the use of an alternate non-statin agent. Further data are needed to evaluate the possible increase in diagnosis of statin intolerance following increased awareness of this and the approval of non-statin agents as alternative.

(7.) Statins are among the most prescribed drugs and remain a large market for pharmaceutical companies. The benefit of statins in secondary prevention is strong and growing evidence suggests a benefit in primary prevention also for selected patients (e.g. HOPE-3) [15]. Statins have been a target of negative reports in terms of safety. This negative image (or "conviction") of statins by patients and also by physicians, and partially re-enforced by the media, is an issue for optimal adherence to the therapy in practice [16]. Administration of a PCSK9 inhibitor every 2 or 4 weeks subcutaneously might be a good alternativee to optimise adherence to treatment. The role of clinician scientist in assessing the available evidence and informing the patient ac-

Table 1: Factors associated with high PCSK9 levels.

Familial hypercholesterolaemia (e.g. PCSK9 gene mutations)
High levels of low-density and small dense lipoprotein cholesterol
High triglycerides
Physical inactivity
Inflammation (e.g. C-Reactive Protein)
Acute phase of acute coronary syndromes
Long chest pain duration
Use of statins or fibrates
Insulin resistance
Women and postmenopause
HIV-infected patients
Peripheral arterial disease

HIV = human immunodeficieny virus; PCSK9 = proprotein convertase subtilisin kexin 9

cordingly concerning preferences and values is becoming more and more important [17].

(8.) PCSK9 inhibitors were among of the first monoclonal antibodies in cardiology; the others are abciximab and an antibody against digoxin [18]. Other fields of medicine, such as oncology, rheumatology, immunology, gastroenterology have widely used biological therapies. In this sense, it is rather a positive development for cardiology, but also a source of additional concerns about the costs. More data will be needed to assess the cost-effectiveness of a preventive treatment. For instance, it is estimated the number needed to treat to save one CVD event over 5 years would be 28, with an average treatment cost expected between 7000–8000 €/year [19]. As with some expensive emergent agents in the field of oncology, physicians would not only need to justify the use of PCSK9 inhibitors according to LDL-C levels of their high-risk patients, but also document either well-conducted statin therapy of high-intensity (e.g., rosuvastatin 20–40 mg or atorvastatin 40–80 mg), or the impossibility of prescribing recommended statin therapy due to side effects, especially for SAMS [20].

The effect of PCSK9 inhibitors in patients with coronary artery disease and ACS

The prognosis of ACS has considerably improved with the implementation of recommended therapies, but the risk of recurrent adverse events is persists [21]. The evidence for the efficacy of statins in the reduction of LDL-C levels and subsequently in the incidence of CVD events is strong and based on several randomised controlled trials and meta-analyses [22, 23]. The European Society of Cardiology (ESC) and American Heart Association (AHA) guidelines make strong recommendations for the use of statins, especially high-intensity statin therapy after ACS (table 2) [21, 24]. According to the ESC guidelines, the recommended target LDL-C level is less than 1.8 mmol/l (70 mg/dl) in patients with very high CVD risk, such as those with ACS [21]. However, data from real life suggest that only one third of ACS patients and only 10% of patients who fulfilled the criteria of FH can reach such stringent targets [10, 12]. Several reasons could lead to such poor outcomes, such as (1) poor adherence to therapy and life-style recommendations, (2) side effects of statin treatment (e.g. SAMS), (3) inertia in statin therapy intensification by physicians, and (4) severe lipid disorders as observed in patients with FH [12, 16, 25].

The last 2015 ESC guidelines for the management of ACS recommended for the first time the use of non-statin agent in patients who need additional lipid-lowering (table 2) [21]. Currently, the evidence is available for ezetimibe. An additional relative decrease of 20% in LDL-C levels was associated with a significant reduction in the occurrence of major adverse cardiovascular events in the IMPROVE-IT trial [26]. However, the clinical significance of these results is still controversial, given the modest absolute effect, expressed as a high number needed to treat for 5 years. There is a need for the development of new lipid-lowering strategies in very high-risk patients [3, 8]. Several studies have shown that monoclonal antibodies inhibiting PCSK9 decrease LDL-C levels by 50% in comparison with placebo [5]. These promising results were also reported for combination therapy with a statin in patients with poorly controlled LDL-C or with statin intolerance [7]. Two ongoing trials are investigating the impact of PCKS9 inhibitors on clinical outcomes after ACS; observational studies have reported controversial results on the association with CVD events.

Higher PCSK9 levels were associated with more severe anatomical vascular disease as measured with angiography. Mechanistic studies reported that PCSK9 levels were associated with inflammation, an increased necrotic component of the plaque and an enhanced thrombotic substrate (fig. 1) [27]. Animal and human data suggest that the plasma PCSK9 concentration is increased in the acute phase of ACS, as is the expression of PCSK9 messenger RNA, reaching a peak at 48 hours. The administration of PCSK9 inhibitors subcutaneously is followed by a maximal effect on PSK9 within 3 days and might represent a very interesting therapeutic option for early plaque stabilisation of culprit and non-culprit lesions in ACS patients [27]. Several studies suggest that the inhibition of PCSK9 has specific effects beyond LDL-C reduction on the atheroscle-

Table 2: Evaluation of PCSK9 as a novel marker for CVD risk assessment. (Reprinted from Hlatky MA, Greenland P, Arnett DK, et al. Criteria for evaluation of novel markers of cardiovascular risk: a scientific statement from the American Heart Association. Circulation. 2009;119:2408–16, with permission.)

1. Proof of concept – do novel marker levels differ between subjects with and without outcome?	Probable
2. Prospective validation – does the novel marker predict development of future outcomes in a prospective cohort or nested case-cohort/ case-cohort study?	Possible, still controversial
3. Incremental value – does the novel marker add predictive information to established, standard risk markers?	Improbable
4. Clinical utility – does the novel risk marker change predicted risk sufficiently to change recommended therapy?	No data
5. Clinical outcomes – does use of the novel risk marker improve clinical outcomes, especially when tested in a randomized clinical trial?	No data
6. Cost-effectiveness – does use of the marker improve clinical outcomes sufficiently to justify the additional costs of testing and treatment?	No data

CVD = cardiovasular disease; PCSK9 = proprotein convertase subtilisin kexin

rosis mechanism, such as reduction of the inflammatory process and necrotic core of the plaque, and inhibition of the effects of oxidised LDL-C and Lp(a) levels. Third, the reductions in myocardial infarction reported in the *post-hoc* analyses of the ODYSSEY LONG TERM and OSLER studies are the strongest available evidence for the potential benefit of PCSK9 inhibitors in the early management of ACS [28, 29]. However, more data are needed to confirm the potential role of PCSK9 inhibitors beyond reduction of LDL-C levels in the ACS population. Moreover, therapy with evolocumab and alirocumab did not reduce C-reactive protein in the available clinical studies. Further studies should assess the impact of early administration of PCSK9 inhibitors prior to percutaneous conronary intervention on reducing ischaemia and plaque stabilisation, with subsequent measurement of inflammatory and thrombotic markers, plaque composition (e.g. with intravascular ultrasound as planned in the GLAGOV study, NCT01813422) and finally clinical outcomes in an adequately powered randomised clinical trial.

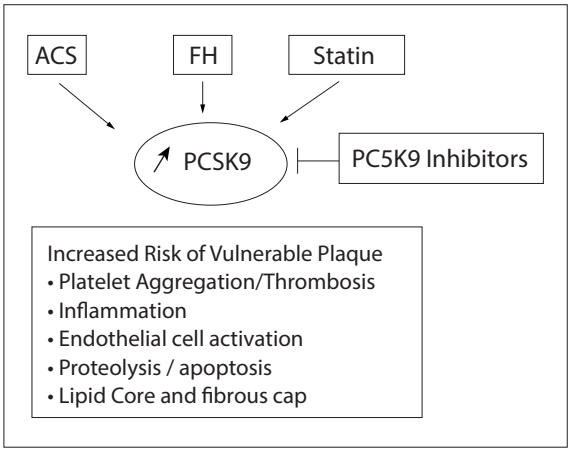

Figure 1: Potential role of PCSK9 in recurrent ischaemia in ACS. Mechanistic studies suggest that PCSK9 has adverse effects on coronary plaque through several pathways, including pro-inflammatory low-density lipoprotein oxidation and modification of plaque composition [27]. Levels of PCSK9 are increased during ACS, suggesting that PCSK9 inhibitors could be a beneficial treatment in the acute phase of ACS patients through effects on plaque stabilisation. This hypothesis needs to be explored in further trials.
ACS = acute coronary syndrome; FH = familial hypercholesterolaemia; CSK9 = proprotein convertase kexin 9

Key messages from our research published in the *European Heart Journal*

Why do this research?

In 2009, thanks to the Swiss National Science Foundation, we established in Switzerland a cohort of patients hospitalised for ACS (SPUM-ACS, www.spum-acs.ch) in order to identify new strategies for diagnosis and treatment of ACS. Recruitment is currently ongoing and rhas eached more than 4000 patients. The assessment of new biomarkers was one of the major aims of the SPUM-ACS project. PCSK9 has gained a lot of attention in the last decade as an emergent target for the treatment of hypercholesterolaemia, with the recent approval of PCSK9 inhibitors [3]. Several studies have shown that PCSK9 inhibitors efficiently lowered LDL-C levels, especially in patients with FH, intolerant to statins or with poorly controlled LDL-C on maximally tolerated statin treatment [7]. Large ongoing clinical trials are assessing the impact of PCSK9 inhibitors on clinical prognosis after ACS. However, PCSK9 has been little studied in the acute phase of ACS, especially its evolution over time and the association with clinical outcomes. In Geneva, we are working on clinical projects measuring PCSK9. Recently, one of them showed that an increase in physical activity might lower PCSK9 levels in healthy adults [30]. Therefore, we decided to measure PCSK9 in the SPUM-SCS during angiography for ACS, 12–24 hours and 1 year after the index ACS event.

What are the most significant findings?

We observed that higher PCSK9 levels at the initial presentation of ACS were associated with the presence of FH, the use of lipid-lowering therapy, the duration of chest pain and inflammation (C-reactive protein) [1]. To confirm this, we found that PCSK9 levels increased 12–24 hours after ACS, probably with the inflammatory process during ACS, in accordance with previous *in vivo* models suggesting that PCSK9 expression was enhanced in the context of ACS and inflammation [31, 32]. Then we assessed the incremental value of adding PCSK9 to recommended risk stratification scores, such as the GRACE score, and found that PCSK9 did not predict mortality at 30 days and at 1 year. However, we cannot exclude the possibility that blood sampling in the acute clinical setting could have biased the prognostic value of PCSK9. Patients who had usual statin therapy prior to the ACS index event had significantly higher PCSK9 levels than patients untreated with a statin. In addition, 1 year after ACS, PCSK9 levels were higher than at baseline, probably associated with a greater use of statins (94% vs 30%). This was in line with experimental studies in humans showing the increase of PCSK9 levels with the use of statins [33–35]. Similarly, patients with higher PCSK9 levels tend to be less likely to reach the recommended LDL-C level <1.8 mmol/l 1 year after ACS, suggesting that PCSK9 is involved in the phenomena of statin resistance.

What are the implications for future research and for patient care?

The measurement of PCSK9 is currently poorly implemented in clinical practice. Our findings suggest that PCSK9 might be useful to clinicians for identifying patients who might need more intensive lipid-lowering therapy (e.g. PCSK9 inhibitors) to lower LDL-C. In addition, our findings suggest that PCSK9 is up-regulated in the acute phase of ACS (fig. 1) [27]. However, the clinical utility of measuring PCSK9 for risk prediction in ACS patients is poor and no recommendations can be formulated for this purpose.

The following steps summarize the evaluation of the clinical implications of PCSK9 (table 3) [36]:

1. Proof of concept – do novel marker levels differ between subjects with and without outcome?

Yes, PCSK9 is a key target for hypercholesterolaemia and also higher in patients at high risk of cardiovascular disease (table 1) [3]. Mechanistic studies suggest that PCSK9 is involved in the acute phase of inflammation in ACS [27]. We have shown that PCSK9 was higher with inflammation, indicated by increased C-reactive protein, and FH according to the Dutch clinical classification.

2. Prospective validation – does the novel marker predict development of future outcome in a prospective cohort?

PCSK9 levels at time of angiography for ACS are not associated with the occurrence of major adverse cardiovascular events at 1 year [1]. Conflicting results have been reported in primary prevention, with one positive study suggesting an association with the occurrence of CVD events, and another study not [37, 38]. However, in ACS patients who had higher PCKS9 values less frequently reached the recommended target for LDL-C [1].

3. Incremental value – does the novel marker add predictive information to established, standard risk markers?

The addition of PCSK9 to the recommended GRACE score in ACS patients did not add significant incremental values (C-index, reclassification, integrated discrimination index) [1]. In primary prevention, the addition of PCSK9 did not improve the risk prediction and reclassification of the Framingham score [37, 38].

4. Clinical utility – does the novel risk marker change predicted risk sufficiently to change recommended therapy?

No data are available to support the clinical utility of PCSK9 for risk stratification. However, ACS patients who had higher PCKS9 values less frequently reached the recommended target for LDL-C [1]. In addition, PCSK9 levels were significantly higher in subjects with FH and might be used to identify subjects who could benefit most from PCSK9 inhibitors [11].

5. Clinical outcomes – does use of the novel risk marker improve clinical outcomes, especially when tested in a randomised clinical trial?

No randomised controlled trial has analysed PCSK9 as a marker for medical decision making and for identifying patients at high risk. Meta-analysis from *post-hoc* analysis of randomised controlled trials suggests that the use of PCSK9 inhibitors is associated with a reduction of CVD events [7]. The estimated risk reduction is about 50%. Large ongoing clinical trials will clarify the impact of PCSK9 inhibitors in combination with the maximum tolerated doses of a statin.

6. Cost-effectiveness – does use of the marker improve clinical outcomes sufficiently to justify the additional costs of testing and treatment?

Currently, measurement of PCSK9 is considered expensive and is not implemented as routine. Concerns regarding the costs of PCSK9 inhibitors will be a source of controversy and debate among clinicians, decision-makers and key stakeholders in the healthcare system [19].

Table 3: Recommendations from guidelines on the use of PCSK9 inhibitors.

2015 ESC guidelines on NSTE-ACS [21]
In patients with LDL-C ≥70 mg/dl (≥1.8 mmol/l) despite a maximum tolerated statin dose, further reduction in LDL-C with a non-statin agent are recommended (IIa, B).
NLA Dyslipidemia Recommendations [39]
Until cardiovascular outcome trials with PCSK9 inhibitors are completed, these drugs should be considered primarily in: (1) patients with ASCVD who have LDL-C ≥100 mg/dL while on maximally-tolerated statin (±ezetimibe) (strength B, quality moderate); (2) heterozygous FH patients without ASCVD who have LDL-C ≥130 mg/dL (non-HDL-C ≥160 mg/dL) while on maximally-tolerated statin (±ezetimibe) (strength B, quality moderate).
In addition, PCSK9 inhibitor use may be considered for selected high risk patients with ASCVD (e.g., recurrent ASCVD events) who have atherogenic cholesterol levels below the specified values, but above their treatment goals (i.e., LDL-C ≥70 mg/dL [non-HDL-C ≥100 mg/dL]). Strength C, quality low)
PCSK9 inhibitor use may be considered in selected high or very high risk patients who meet the definition of statin intoleranceand who require substantial additional atherogenic cholesterol lowering, despite the use of other lipid lowering therapies. (Strength C, quality low)

Conclusion

Guidelines do not make any recommendations regarding the clinical effectiveness of the measurement of PCSK9 in patients with ACS. The data in a large Swiss cohort of ACS patients did not support the clinical utility

of PCKS9 for risk stratification, but PCKS9 measurement could help to identify patients with FH. However, PCSK9 is an emergent target for monoclonal antibodies in the treatment of primary hypercholesterolaemia and, potentially, for secondary prevention in ACS patient, depending on the results of ongoing large clinical trials.

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