# Statins, Targets and Chronic Kidney Disease

Case Report

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## Introduction

Despite being recommended in high-risk patients, statins are often underprescribed, especially in patients with chronic kidney disease (CKD) [1] who are at increased risk of premature cardiovascular events [2,3], and would benefit of such therapy even in primary prevention [4]. A real-life clinical case is presented, and several issues are highlighted. In particular, specific indication to statins in the CKD patients are discussed, as well as whether consider the LDL-C targets recommended in the general population to identify CKD patients who should receive lipid lowering therapy (LLT) and judge the efficacy of this treatment in such patients.

## Clinical Case

A 66 year-old man, with hypertension, non-insulin dependent diabetes mellitus, a prior myocardial infarction (MI) in 1990, and family history for hypertension and nephropathy, was admitted to hospital with non-ST elevation MI (NSTEMI). He had been on hemodialysis (once-a-week) for 3 weeks due to end-stage membranous glomerulonephritis previously treated with Rituximab. Therapy at admission included ASA, bisoprolol, amlodipine, doxazosin, oral antidiabetics and medications for kidney failure. Ejection fraction (EF) was 50%. Coronary angiography showed a severe and diffuse calcific three-vessel disease (Figure 1), with eccentric critical stenosis of mid-distal left main (LM), proximal circumflex (Cx), proximal and mid left anterior descending (LAD), with involvement of the first diagonal branch (D1), which was occluded at its mid portion. The distal LAD was calcific and diffusely diseased, peri-apically occluded (thus preventing an effective surgical revascularization) and refilled by ipsilateral collaterals. The obtuse marginal branch was diffusely and severely diseased; a secondary marginal branch was occluded. The right coronary artery was hypoplasic and occluded at its proximal segment, refilled by weak contralateral collaterals. The culprit lesion was located on the dominant proximal Cx, and it was treated by a 3.5/18 mm drug-eluting stent (DES) implantation in the same session. After 3 days revascularization was completed with IVUS-guided percutaneous coronary intervention (PCI) on LM (4/28 mm DES) and LAD (3.5/38 mm DES), with kissing balloons at the LAD-D1 and the LM-LAD-Cx bifurcations. Blood tests showed that LDL-Cholesterol (LDL-C) was 125 mg/dL on admission; Troponin I peak reached 0.54 ng/mL. Therapy during hospitalization and at discharge included bisoprolol, ASA, ticagrelor bid and rosuvastatin 5 mg daily. The patient remained asymptomatic. Elective angiographic follow-up performed after 7 months showed patency of all implanted DES (Figure 2); the value of LDL-C 102 was mg/dL and rosuvastatin 5 mg was changed into atorvastatin 20 mg daily. Three months later the patient was switched to hemodialysis twice-a-week. After a few days, he was re-admitted to our department due to NSTEMI + atrial fibrillation (AF). Coronary angiography showed patency of all stents, but progression of disease at the mid portion of the Cx, which was treated by implantation of two DES (Figure 3). Despite LDL-C value was 43.4 mg/dL, atorvastatin 20 mg was replaced by rosuvastatin 10 mg. One month later the patients was admitted again due to angina during paroxysmal AF; Troponin I was slightly elevated (2.01 ng/mL); LDL-C was 35.4 mg/dL. The patient experienced a severe exfoliative dermatitis as a possible late reaction to contrast mean or to a non definite drug; no coronary angiography was performed. Rosuvastatin 10 mg was confirmed. A new hospitalization occurred after three months due to pulmonary edema related to fluids overload. The patient was switched to hemodialysis three times a week with benefit. The value of LDL-C was 40.8 mg/dL, nevertheless rosuvastatin 10 mg was changed with atorvastatin 20 mg. No further event occurred, and after 8 months from the last hospitalization, the patient is asymptomatic for angina and dyspnea and in good clinical status. The last value of LDL-C is 38 mg/dL and he has maintained the same therapy, including atorvastatin 20 mg daily.

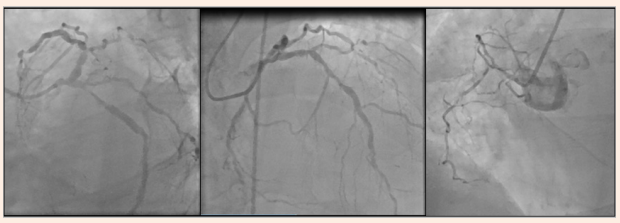

**Figure 1**: Severe and diffuse three-vessel disease at coronary angiography.

## Discussion

This clinical case highlights several issues regarding statins use in routine clinical practice in CKD patients:

### Underprescription

As it often happen in CKD patients, no statin was ongoing at first hospital admission, despite the evidence-based indication

to such therapy [1]. First, statins in CKD patients may be useful in primary prevention. The SHARP study randomized 9270 patients aged ≥ 40 years old with CKD of any stage (32.6% on hemodialysis) and no history of myocardial infarction or coronary revascularization to simvastatin 20/ezetimibe 10 mg daily or placebo, and clearly showed this benefit [4]. At a median follow-up of 4.9 years a statistically significant reduction of 17% (RR 0.83, p=0.0021) in major atherosclerotic events (cardiac death from coronary disease, MI, ischemic stroke, revascularisation) was observed in the simvastatin/ ezetimibe arm as compared to placebo. The largest contribution to the primary endpoint was reduction in coronary revascularization. Disappointingly, no survival benefit or evidence of a renal protective effect were observed, and more than 2000 dialysis-independent patients progressed to end-stage CKD during the trial. No difference in cancer and myopathy were detected confirming the safety of LLT in such population. The clear message of this trial was that LLT prevents atherosclerotic events in CKD patients. Several studies examining the cardiovascular risk associated with different clinical conditions have demonstrated that the presence of CKD confers a risk of myocardial infarction and mortality higher than that associated with diabetes. The association of both conditions raises even more the risk [5]. Therefore, CKD should be then regarded as a coronary heart disease risk equivalent, that is a condition which entails a risk of coronary death or MI at 10 years which is equivalent to that associated with a previous MI (generally a risk > 20% ) [6], and with a prognostic importance higher than diabetes. The concept of primary prevention in the CKD patients has been acknowledged by the KDIGO (Kidney Disease Improving Global Outcomes) guidelines [7], but not yet by the cardiologic guidelines. Also, most cardiovascular risk score calculators do not consider the presence of CKD. However, statins were not prescribed in this patient despite the history of prior MI and the established indication in secondary prevention, with no caveat regarding CKD [8,9]. It has to be noted that no cardiological evaluation was done in our patient at the beginning of hemodyalisis, as it often happens in such patients.

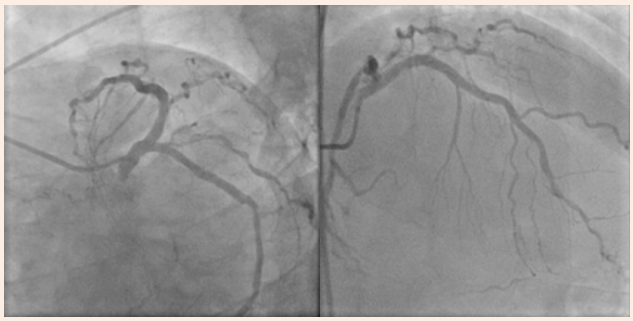

**Figure 2**: Elective angiographic follow-up performed at 7 months showing patency of drug-eluting stents implanted on left main, left anterior descending artery and circumflex artery.

Reasons for underprescription of statins in CKD patients [10,11] lay on the perceived uncertain benefits and higher risk of drug-related adverse effects, especially in dialysis patients, who are often already taking several medications. Even in the SHARP trial the adherence rates were only 2/3. Indeed, a significant interaction between statin prescription and the stage of nephropathy has been seen: the more the stage of the nephropathy is advanced, the less LLT is prescribed; i.e. statin prescription in secondary prevention after MI ranges from 81% in eGFR G1 stage to 1-31 % in eGFR G5 stage (GFR < 15 ml/min or dialysis) [1]. Similarly, statins are often the first medications to be withdrawn in CKD patients in case of side effects like itch, dermatitis, myalgia, etc. Luckily, rosuvastatin was confirmed after the severe exfoliative dermatitis experienced by our patient, but this is not the rule.

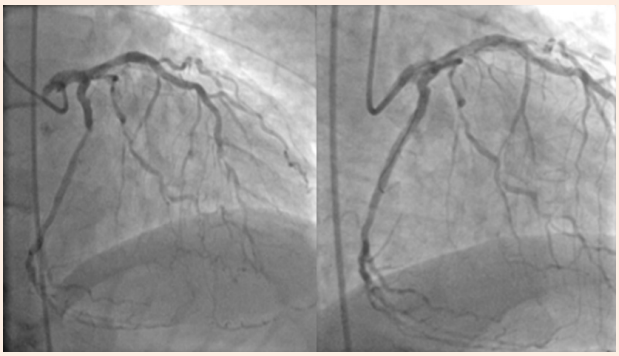

**Figure 3**: Progression of disease at the mid segment of the circumflex artery (left panel) 10 months after index hospitalization and its treatment (right panel) by drug-eluting stent implantation.

Current KDIGO guidelines recommend statins in all adults with CKD aged > 50 years old, in those aged 18-49 years old at high risk (diabetes, prior stroke, risk of MI or cardiac death > 10%) or in secondary prevention, and in all patients with kidney transplant [7].

## Type and dosages

The repeated switch from rosuvastatin to atorvastatin and viceversa, even with LDL-C values within recommended targets, highlights the presence in common clinical practice of doubts regarding type and dosages of statins to employ in CKD patients. Actually, recommendations on the basis of ALERT [12], 4D, [13] AURORA [14] and SHARP [4] trials data suggest in eGFR G1-G2 stages similar statin type and dosages as in the general population, with the exception of rosuvastatin 40 mg, which is not recommended due to the increased risk of possible renal adverse events.

Reduced statin dosages are recommended in G3a - G5 stages (GFR ≤59 ml/min/1.73 m2), as well as in patients on dyalisis or with a kidney transplant [7]. In the latter population, it is important to tailor type and dosage of statins irrespectively of eGFR recovery. However, if a reduction of LDL-C more pronounced than that achieved with the higher dose of statin recommended for the CKD population is desired, ezetimibe could be added [4].

For our patient, in particular, both atorvastatin up to 20 mg daily or rosuvastatin up to 10 mg daily are allowed, therefore the repeated crossover from the one to the other was not justified.

### Whether consider LDL-C targets to identify CKD patients who should receive LLT and follow therapy efficacy

Current ESC [15] and AHA [16] guidelines recommend in high-risk patients intensive LLT with targets of LDL-C below 70 mg/dL or at least 50% of the initial LDL-C values, respectively. According to KDIGO guidelines no specific LDL-C targets are defined in the CKD population: a "fire and forget" is preferred as compared to a "treat-to-target" strategy, and follow-up measurement of lipid levels is not required [7]. Definitively, a correct evaluation of the patients' profile risk helps in judging the best treatment strategy. In CKD patients, moreover, a linear relation between LDL-C and coronary artery disease (CAD) exists only in the early stages of the nephropathy (which is why LLT should be started early); in the advanced phases of CKD sudden cardiac death (related to arrhythmias or heart failure) may prevail over non-fatal MI. Moreover, extensive comorbidities increase the risk of non-cardiac mortality [1,7]. The absolute benefit from statin treatment in CKD patients is proportional to the cardiovascular risk profile rather than baseline LDL-C values.

In particular, observational data indicate that in the subset of dialysis patients there is a paradoxical association between LDL-C and outcome: the highest and lowest LDL-C levels confer the highest risk of adverse events, that is all-cause and cardiovascular mortality [7]. The lowest LDL-C levels may be the effect of protein energy wasting, inflammation and malnutrition, which are all common in CKD patients. In such population the best attitude is to consider the absolute risk of coronary events and the evidence of benefit from LLT, rather than only biochemical targets [18].

In our patient LDL-C was 102 mg/dL after seven months from the first admission, not reaching either the ESC (<70 mg/dL) or the AHA (50% of the baseline value, that is 62.5 mg/dL) targets, which were later reached with atorvastatin 20 mg and maintained with rosuvastatin 10 mg. Despite this, as showed in the SHARP trial, no nephroprotective effect was seen. In our case, rather, a correlation between worsening of the renal function (and increase of the number of hemodyalisis sessions per week) and hospitalization for cardiac causes was seen.

## Conclusion

The issue of statins in CKD is provocative: on the one hand it arises the need to start LLT as soon as possible in CKD patients at any stage, on the other hand, patients on dialysis are the ones for whom the evidence for this treatment is not definite [4,13,14], although this does not mean that they would not benefit from it [19,20]. The matter is that LLT acts on different backgrounds according to the nephropathy stage: in early stages of kidney disease the physiopathology of cardiovascular events is cholesterol-dependent; in advanced stages, cardiovascular events are more represented by cardiac deaths than CAD. For this reason, it remains unclear whether statin therapy should be started when the patient is already on dialysis and cardiovascular damage has been mostly occurred already. In such patients implementation and targets of LLT should be tailored on an individual basis.

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