Jupiter or Aurora? Micro-inflammation and dyslipidaemia: twin targets for statin therapy in CKD

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Received: 17 August 2009 / Accepted: 9 September 2009 / Published online: 14 October 2009
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Dyslipidaemia is nearly ubiquitous in chronic kidney disease—although the nature and extent of the phenotypic abnormality profile vary as CKD severity increases, and with dialysis and transplantation [1]. In the non-CKD setting, dyslipidaemia is a key factor in the development and progression of atherosclerosis. Atherosclerosis is known to be an inflammatory process, and not just a lipid-storage problem and of course in CKD it is also well known that there is chronic elevation of CRP and IL-6 in many patients [2]. Interestingly, while elevation in CRP is strongly associated with adverse outcomes in CKD [3], there is a “reverse epidemiology” relationship between plasma cholesterol and outcome in advanced CKD (such that low cholesterol levels are strongly associated with increased mortality [4]). This apparently perverse/inverse relationship, in marked contrast to the general population, continues to puzzle nephrologists (as similar observations do for body weight and blood pressure [5]). Patients with low cholesterol in the context of advanced CKD tend to be those with the most atherosclerotic burden, the most “inflamed” and the least well nourished [2, 4]. Thus,

conventional reliance on a “threshold” value of say LDL-cholesterol level to trigger intervention may not be the recommended approach to target CV risk in this challenging group of patients. In fact, we feel there are just three theoretical potential explanations of what appears to be a completely different behaviour in ESRD patients. First—an anathema for the majority of nephrologists until very recently—a completely different vascular pathophysiology in CKD, with cholesterol—and therefore current cholesterol lowering strategies—playing a minimal role—the “different disease” theory. Second, the atherosclerotic end-point is usually reached after years, or decades, of exposure to a cardinal risk factor (such as elevated cholesterol or BP), but, for dialysis-specific reasons (malnutrition, heart failure) by the time the CV end-point is reached on dialysis, the risk factor is “under-represented”. In this, the “too late to intervene” theory, by the time patients are on dialysis, elevation of BP and cholesterol are no longer the dominant predictors of mortality outcomes [5], and BP or cholesterol interventions are thus futile. Finally, the uraemic milieu and permanent low grade inflammation may act as facilitators for any ongoing endothelial damage (e.g. from BP, dyslipidaemia)—the “permissive” theory. In this case it is evident that a response to say cholesterol manipulation (or BP lowering) may require a more sophisticated analytical approach fully to understand it.

The CKD patient cohort has one of the highest CV event rates of any recorded population, and yet no

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recognised medical intervention has been shown in an RCT to ameliorate this massive increase in risk [6]. This has bred a kind of “renalism” (or renal nihilism) where the utility of single-targeted interventions has been called into question (see [6] for a detailed review). Specifically, for the dyslipidaemia–atherosclerosis “saga”, Wanner et al.’s 4D study [7, 8] showed that atorvastatin therapy given to type II diabetic patients on haemodialysis, while successfully reducing as expected and predicted plasma cholesterol over many years, did not lead to any change in overall mortality, which remained very high. This unexpected and highly debated negative result has now been confirmed spectacularly by the Aurora study, just published [9]. Both of these studies, very similar in design, execution and outcome, are two of the very few where a significant reduction in plasma cholesterol as a result of statin use was not accompanied by an improvement in overall and CV mortality. Also different from the non-renal literature, important causes for death in both dialysis studies included sudden cardiac death, and sepsis, and relatively fewer deaths due to “conventional” ischaemic heart disease. Dropout rates from both studies were much higher than with similar interventions in non-CKD cohorts (e.g. death, events, and transplantation). This RCT-derived evidence-base stands in marked contrast to post hoc meta-analytic analyses where large cohorts of trial subjects have included significant numbers of patients with “mild-to-moderate” CKD (MDRD-derived). These meta-analyses tend to show CV benefit for the deployment of statins (not “so late” in the course of disease), in this very high-risk group of patients (many of whom have substantial CV disease burdens [10]). Potentially linking, and providing a narrative path between, these opening paragraphs is another recently published study, again involving rosuvastatin, but primarily not in a moderate-to-severe CKD setting—indeed in a notionally “healthy” population. Ridker et al. published the “Jupiter” study in which rosuvastatin therapy, administered to patients at vascular risk with both (modest) dyslipidaemia but concomitantly raised high-sensitivity CRP (>2 mg/L), was accompanied by a very significant reduction in adverse cardiovascular events [11]. This non-CKD outcome is in direct and stark contrast to the CKD one seen with 4D and Aurora.

The link with CRP elevation and adverse outcome, which is strongly bolstered by the Jupiter study [11],

may also explain the negative findings in the two renal dialysis interventional studies 4D and Aurora—as unlike other statin intervention studies, CRP values in the presence of atorvastatin (4D) and rosuvastatin (Aurora) remained stubbornly high (i.e. did not fall significantly), while the non-statin placebo group in both studies showed a sustained further progressive rise in CRP values as the trial continued [7–9]. Of note, in both the 4D and Aurora studies the overall CRP values, in both treated and placebo groups, were the highest seen in any published lipid-lowering therapy trial population (See Table 1).

Table 1 lists several studies, using potent statins [7–9, 12–14], in which CRP values fell dramatically with statin treatment—the two obvious exceptions being the 4D and Aurora studies [10, 11]. The concept of dual control (e.g. achieving LDL-C <2.0 mmol/L and also CRP <2 mg/L), which post-Jupiter is gaining ground as a goal for cardiovascularly “at high risk” populations, may be of special importance in advanced CKD too, where it might be a necessary “permissive” pre-condition for a successful reduction in mortality. Now, while it might be possible, using higher doses of the most powerful statins, in order to attempt further to target CRP, and not just cholesterol alone (as in Jupiter), and by so doing to induce a significant fall in CRP at the same time as a significant fall in plasma cholesterol, the marked “disconnect” between the equivalent ease of cholesterol reduction comparing CKD and non-CKD studies, with the disappointing CRP reductions seen in CKD patients exposed to statins, must make us pause and wonder if this is telling us something important about inflammation in CKD. In other non-CKD trials, the dominant reason for CRP elevation is active “hot” atherosclerotic lesions (i.e. a vascular origin for plasma CRP elevation), which is of course likely to be suppressible by the action of statins on unstable inflamed vascular plaques [15]. While there is little doubt that in CKD and dialysis patients there is a contribution from vascular atherosclerotic lesions to the generally very high chronic inflammatory state seen in CKD, this may not be the dominant reason, as CRP elevation can also of course arise from dialysis, water, access, chronic infection, bacterial translocation across leaky gut wall, chronic gingival infection and many other causes [16]. It would therefore be optimistic to assume that these non-vascular plaque-related aetiologies would be statin-responsive, hence

Table 1

Author	Year	Population	Intervention number	Prestatin CRP/mg/L LDL-C mmol/L	Post-statin CRP (Rx, not) mg/L	% Change in primary outcome
Heldstrom	2009	Prevalent haemodialysis, aged 50–80 Rosuvastatin 10 mg versus placebo	2,776	~5 (LDL 2.6)	4.3 versus 5.9 (LDL fell 43%)	Survival $P = NS$
Wanner	2005/2008	Prevalent haemodialysis, type II diabetes Atorvastatin 20 mg vs Placebo	1,255	5 (LDL > 3.0)	4.4 versus 6.0 (LDL fell 42%)	Survival $P = NS$
Ridker	2008	Healthy men and women Rosuvastatin versus Placebo	17,802	4.2 (all > 2) LDL < 3.4	8 versus 3.0	Survival RR 0.56 < .00001
Yu	2007	CAD patients Atorvastatin 80 mg vs 10 mg	110	3.92 (80 mg only)	1.18 (80 MG ANLY)	Carotid IMT 1.21 to 1.1 mm $P 0.01-0.02$
Betteridge	2007	Type II diabetes; dyslipidaemia Atorva or Rosuvastatin	509	2.1	1.3 Rosuvastatin 40% reduction in CRP levels	Reduction in LDL-C and CRP < 0.0001
Pearson	2007	Primary hypercholesterolaemia Pooled factorial simvastatin trials Atorvastatin factorial trials	2,514 and 1,832	2	4 to 38% reduction in CRP levels (and up to 60% reduction in LDL-C)	Reduction in LDL-C and CRP < 0.001

the relative lack of impact on CRP of statin deployment.

In our view, we urgently, therefore, need to apply both cholesterol reduction, and simultaneous successful chronic inflammation reduction (using most likely several approaches), to address this duple highly interlinked cardiovascular risk profile. It would be interesting, in a post hoc analysis of Aurora, to examine the outcome for patients who experienced sustained significant LDL-C and CRP reductions to see if this group did show benefit (but this group may be small in number so a negative finding on post hoc analysis does not in our view invalidate this hypothesis). In the end, we now have to wait for UK HARP-2 in dialysis and chronic kidney disease patients [17], involving around 9,000 subjects using simvastatin and ezetimibe in a two-by-two factorial design. This may finally answer some of these important questions, though was not of course designed to address inflammation alongside elevated plasma cholesterol. If “men are from Mars, and women from Venus”, it may be that non-CKD patients are from Jupiter, while advanced CKD patients are from Aurora (a fictional planet in a novel by Asimov).

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