Major journals

CRP in atherosclerosis: Participant or bystander?

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There is a fierce debate currently raging as to whether or not C-reactive protein (CRP) is a participant or bystander in the process of atherosclerosis and cardiovascular events. Recent data presented by Paul Ridker (see right) and colleagues support the hypothesis that CRP is important in atherosclerosis, whereas data from Aroon Hingorani's group recently published in the journal *Circulation* (by Clapp et al; see below) support an alternative hypothesis that the relationship between CRP and atherosclerosis is one of reverse causality, whereby atherosclerotic arteries may actually produce CRP.

The article by Ridker et al is important outside this debate, as it also adds further fuel to the controversy regarding the pleiotropic effects of statins.

Ridker et al in PROVE IT-TIMI 22 explored the relationship between LDL cholesterol and CRP levels after treatment with 80 mg atorvastatin or 40 mg pravastatin. They explored the effect of these doses of statin on the risk of recurrent myocardial infarction or death from coronary causes among 3745 patients with acute coronary syndromes. Importantly they demonstrated that patients achieving an LDL cholesterol level of 1.8 mmol/l had substantially lower event rates than those with higher levels (2.7 versus 4.0 events per 100 person years). A similar difference was observed in patients with CRP levels <2 mg/l, and this effect was seen in patients with all levels of LDL cholesterol. Subsequent analysis demonstrated that what is important is not the agent but the levels of LDL cholesterol or CRP – these determine the outcome (patients with the lowest LDL cholesterol and CRP had the best outcome).

This important study illustrates that achieving very low LDL cholesterol levels after an acute coronary syndrome is an important goal. The study also supports the use of CRP as a way of monitoring response to therapy. Whether or not CRP is a target for therapy remains to be established and as yet it is not used as a routine test for risk stratification in the UK.

CIRCULATION

CRP's effect on nitric oxide and vascular reactivity

Readability	✓✓✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓✓✓

1 The fact that CRP is elevated during inflammation and sepsis – when modulation of vascular reactivity is possible – led the authors to investigate the direct effect of highly purified, well-characterised human CRP on vascular reactivity.

2 This effect was investigated *in vitro*, in vascular rings and cells; the effect on blood pressure was also studied, *in vivo* in rats.

3 A vaccine model of endothelial dysfunction was also used to explore the change in vascular effect of CRP over time.

4 In the rat model, there was no apparent effect of human CRP levels on blood pressure.

5 In the *in vitro* model, however, CRP was directly linked to vascular function, by inducing hyporeactivity to phenylephrine; this was supported by findings from the vaccine model.

6 Increased protein expression of the rate-limiting enzyme in synthesis of a nitric oxide synthase co-factor was highlighted as the mechanism.

Clapp BR, Hirschfield GM, Storry C, Gallimore JR, Stidwill RP, Singer M et al (2005) Inflammation and endothelial function: direct vascular effects of human C-reactive protein on nitric oxide bioavailability. *Circulation* **111**(12): 1530–6

NEW ENGLAND JOURNAL OF MEDICINE

CRP levels after statin therapy linked to clinical outcomes

Readability	✓✓✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! factor	✓✓✓✓✓

1 C-reactive protein (CRP) is known to be lowered by statin therapy, but the effect of this on clinical outcomes has not been previously established.

2 In this investigation, the effect on coronary risk of CRP levels achieved was examined in 3745 patients who were randomly assigned to either 80 mg atorvastatin or 40 mg pravastatin orally per day.

3 In patients with acute coronary syndromes treated with a statin, achieving a CRP level <2 mg/l was shown to relate to significant improvements in the rate of event-free survival.

4 This effect on event-free survival was shown to be independent of the level of LDL cholesterol that was achieved.

5 In terms of medical practice, support is provided for using statin treatment aggressively to get patients with acute coronary syndromes to CRP targets.

6 Monitoring of CRP levels in addition to cholesterol should thus form a part of strategies to reduce cardiovascular risk.

7 The data collected also provide evidence that a reduction of inflammation after acute coronary ischaemia might lead to an improvement in cardiovascular outcomes.

Ridker PM, Cannon CP, Morrow D, Rifai N, Rose LM, McCabe CH et al (2005) C-reactive protein levels and outcomes after statin therapy. New England Journal of Medicine **352**(1): 20–8

'This study aimed to establish the effect of high-dose GIK infusion (a simple, cheap and widely applicable treatment) on mortality in patients with acute ST-segment elevation myocardial infarction (STEMI).'

JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION

GIK infusion's effect on mortality in STEMI patients?

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! factor	✓✓✓✓

1 This study aimed to establish the effect of high-dose glucose–insulin–potassium (GIK) infusion (a simple, cheap and widely applicable treatment) on mortality in patients with acute ST-segment elevation myocardial infarction (STEMI).

2 A randomised controlled trial was carried out with 20 201 people with STEMI (from 470 centres) who presented within 12 hours of the onset of symptoms.

3 After 30 days, 9.7 % of control patients (who received only usual care) had died, compared with 10.0 % of patients on GIK intravenous infusion (hazard ratio, 1.03; 95 % confidence interval, 0.95–1.13; *P*=0.45).

4 There were also no significant differences in rates of reinfarction, cardiogenic shock or cardiac arrest between control and GIK infusion patients.

5 GIK infusion's lack of benefit remained when prespecified subgroups were analysed (based on diabetes diagnosis, presence of heart failure, time of symptom onset and whether patients were receiving reperfusion therapy).

6 The authors state that, with over 1900 deaths, the study was powered to detect even a moderate effect on mortality and other outcome measures; neutral effects suggest, then, that high-dose GIK infusion is unlikely to be valuable for patients with STEMI.

Mehta SR, Yusuf S, Diaz R, Zhu J, Pais P, Xavier D et al (2005) Effect of glucose-insulin-potassium infusion on mortality in patients with acute ST-segment elevation myocardial infarction: the CREATE-ECLA randomized controlled trial. *Journal of the American Medical Association* **293**(4): 437–46

'High-dose GIK infusion is unlikely to be valuable for patients with STEMI.'

ARCHIVES OF INTERNAL MEDICINE

CHD mortality sex differences vary over time

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓✓

1 It is known that diabetes has a greater effect on coronary heart disease (CHD) mortality in women than in men, but whether this intersexual difference varies over time has not been previously established.

2 CHD mortality was evaluated in 10 871 adults from the National Health and Nutrition Examination Survey Epidemiologic Follow-up Study, with diabetes split into recent (<10 years) and long-standing cases (≥10 years).

3 While diabetes duration had no major effect in men, women had a greater risk of CHD mortality with long-standing than with recent diabetes.

4 Refinement of current guidelines may thus be necessary, to take into account this additional risk.

Natarjan S, Liao Y, Sinha D, Cao G, McGee DL, Lipsitz SR (2005) Sex differences in the effect of diabetes duration on coronary heart disease mortality. *Archives of Internal Medicine* **165**(4): 430–5

NEW ENGLAND JOURNAL OF MEDICINE

Benefit of intensive statin therapy linked to CRP and LDL

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓✓

1 Better outcomes have recently been demonstrated with intensive statin therapy relative to moderate therapy, and the greater reductions seen in both LDL cholesterol and C-reactive protein (CRP) have been posited as a possible explanation.

2 Five hundred and two patients with coronary disease were randomised to intensive (80 mg atorvastatin daily) or moderate therapy (40 mg pravastatin daily).

3 Ultrasonography was performed and lipoprotein and CRP levels were measured at baseline and at 18 months' follow-up.

4 Reductions in LDL cholesterol and CRP levels were found to be independently related to the progression of atherosclerosis.

5 This finding has major implications for an understanding of both the mechanism of the benefit of statins and the pathogenesis of atherosclerosis.

Nissen SE, Tuzcu EM, Schoenhagen P, Crowe T, Sasiela WJ, Tsai J et al (2005) Statin therapy, LDL cholesterol, C-reactive protein and coronary artery disease. *New England Journal of Medicine* **352**(1): 29–38

AMERICAN JOURNAL OF MEDICINE

Cardiac risk after coronary stenting is greater in women

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓✓

1 Coronary stenting has been shown to be better than coronary balloon angioplasty in terms of associated restenosis rate among patients with diabetes, but sex differences have not previously been explored.

2 This study's population comprised 4460 consecutive patients (1084 of whom were women) who had coronary stenting for angina.

3 Diabetes had a greater negative effect on major adverse cardiac events 1 year after coronary stenting in women than in men (*P*=0.03, unadjusted; *P*=0.04, adjusted).

4 This finding may be clinically important in choosing suitable therapy; for instance, new, drug-eluting stents might be considered in women.

Ndrepepa G, Mehilli J, Bollwein H, Pache J, Schomig A, Kastrati A (2004) Sex-associated differences in clinical outcomes after coronary stenting in patients with diabetes mellitus. American Journal of Medicine **117**(11): 830–6