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Effect of ACE Inhibitors on C Reactive Protein in Patients with Ischemic Heart Disease



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ABSTRACT

Inflammatory processes are increasingly recognized as important participants in the pathophysiology of hypertension and cardiovascular disease. Anti-inflammatory properties may contribute to the pharmacological effects of angiotensin II receptor blockers (ARBs), a leading therapeutic class in the management of hypertension and related cardiovascular and renal diseases. That possibility, supported by consistent evidence from *in-vitro* and animal studies showing pro-inflammatory properties of angiotensin II, has been evaluated clinically by measuring the effect of ACE inhibitors on CRP and other circulating indices of inflammation (e-selectin, adhesion molecules, interleukin-6, tissue necrosis factor-alpha, monocyte chemoattractant protein-1) of potential clinical relevance.



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INTRODUCTION

C-reactive protein (CRP), the prototypical acute-phase reactant, is one of the most widely known biomarkers of cardiovascular disease. Circulating levels of CRP are clinically used to predict the occurrence of cardiovascular events and to aid in the selection of therapies based on more accurate risk assessment of individuals who are at intermediate risk. This paper reviews the role of CRP in hypertension. In hypertensive individuals, CRP levels associate with vascular stiffness, atherosclerosis and the development of end-organ damage and cardiovascular events. Data suggest that some anti-hypertensive medications may lower CRP levels in a manner independent of their effect on blood pressure. In individuals who are normotensive at baseline, CRP levels have been shown in multiple cohorts to foretell the development of hypertension on follow-up. Whether genetic variability that influences circulating levels of CRP independent of environmental and behavioral factors can also be used in a similar manner to predict the change in blood pressure and development of hypertension is controversial. In addition to its role as a biomarker, experimental studies have unraveled an active direct participation of CRP in the development of endothelial dysfunction, vascular stiffness and elevated blood pressure. CRP has also been implicated as a mediator of vascular remodeling in response to injury and cardiac remodeling in response to pressure overload. Emerging data may reveal novel vascular inflammatory pathways and identify new targets for treatment of vascular pathology.

Angiotensin-converting enzyme inhibitors (ACEIs) have been demonstrated to reduce cardiovascular events and mortality in diverse patient populations, including patients with atherosclerosis and preserved left ventricular function. A variety of direct anti-atherosclerotic, antithrombotic and anti-inflammatory effects of ACEIs on vascular structure and function have been reported and are believed to contribute to the risk reduction associated with the use of this class of medications. Accumulating evidence suggests that inflammation has a central role in the development and progression of atherothrombosis and that biomarkers of inflammation, notably C-reactive protein (CRP), may be used to identify patients at increased cardiovascular risk.

LITERATURE REVIEW

Blake and Ridker 2001; Sesso et al 2003

Patients with CVD present increased expression and plasma concentrations of inflammatory markers and mediators. Among them, C-reactive protein (CRP) has been demonstrated as an independent risk factor for the development of hypertension and has been associated with increased risk of diabetes and CVD. Numerous epidemiological studies have shown that plasma levels of high-sensitivity CRP (hsCRP) are a powerful predictor of ischemic cardiovascular events in patients with stable or unstable angina. They appear to correlate with softer plaques that are more prone to rupture, and may even predict cardiovascular events among apparently healthy subjects. Furthermore, hsCRP levels have been shown to correlate with systolic blood pressure (BP), pulse pressure, and incident hypertension. Thus, CRP and high BP in combination has additional predictive value for cardiovascular outcomes, as they contribute as independent determinants of cardiovascular risk.

Del Fiorentino A, Cianchetti S, Celi A, Dell'Omo G, Pedrinelli R2009;

The effect of angiotensin receptor blockers on C-reactive protein and other circulating inflammatory indices in man. Anti-inflammatory properties may contribute to the pharmacological effects of angiotensin II receptor blockers (ARBs), a leading therapeutic class in the management of hypertension and related cardiovascular and renal diseases. That possibility, supported by consistent evidence from *in-vitro* and animal studies showing pro-inflammatory properties of angiotensin II, has been evaluated clinically by measuring the effect of ARBs on C-reactive protein and other circulating indices of inflammation (e-selectin, adhesion molecules, interleukin-6, tissue necrosis factor-alpha, monocyte chemoattractant protein-1) of potential clinical relevance, a body of evidence that this paper aims to review.

Can J Cardiol. 2009 Jul; 25

Effect of angiotensin-converting enzyme inhibition on C-reactive protein levels: Ramipril C-Reactive pRotein Randomized evaluation (4R) trial results. Plasma levels of the inflammatory biomarker C-reactive protein (CRP) predict cardiovascular risk and may represent a target for treating and/or monitoring risk-reduction strategies. The effect of angiotensin-converting enzyme

inhibitors on CRP levels has not been adequately studied. A total of 264 men and women, with CRP levels of 2 mg/L or greater and no history of cardiovascular disease, were enrolled in a 12-week randomized, double-blind, placebo-controlled study. Participants were randomly assigned to receive 10 mg/day of ramipril (n=132) or placebo (n=132) for 12 weeks. The main outcome measure was the change in CRP levels from baseline to 12 weeks in the ramipril- versus placebo-treated patients.

King DE¹, Egan BM, Mainous AG 3rd, Geesey ME 2006 Apr;8

The effect of extended-release metoprolol succinate on C-reactive protein levels in persons with hypertension.

The objective of this study was to determine whether 3 months of treatment with extended-release metoprolol succinate would reduce C-reactive protein (CRP) levels. Seventy-five patients aged 30-65 years with uncontrolled hypertension were treated with extended-release metoprolol at 25-50mg, titrated up to 100-200mg daily.

CRP was evaluated at baseline and at 1 and 3 months. In the 61 hypertensive patients who completed the study, CRP decreased from 6.2±7.5 mg/L at baseline to 5.4±7.0 mg/L (p=0.03) at 1 month and showed no further change at 3 months (5.6±6.5 mg/L; p=0.13). The 13 patients who received 200mg of extended-release metoprolol had a 32% decline in CRP from 7.0±9.0 mg/L to 4.8±6.6 mg/L (-2.2 mg/L) (p=0.005) over the 3-months period, whereas lower doses did not reduce CRP (p>0.05). Age, race, sex, and change in blood pressure were not related to the reduction in CRP in multivariate analysis. If CRP evolves into a confirmed modifiable risk factor, a beta blocker such as metoprolol may be used as addition to pharmacotherapy options.

CONCLUSION

Hypertension may be considered a disease associated with low-grade inflammation that contributes to cardiovascular disease. Non pharmacological and pharmacological approaches to control high BP may decrease vascular inflammation independently of BP reduction in patients with hypertension, resulting in reduced cardiovascular events in randomized clinical trials. Among other antihypertensive agents, ARBs have shown more potent anti-inflammatory properties unrelated to BP-lowering effect of this class of drugs, but more probably the result of

a direct antagonism of the pro-inflammatory effects induced by angiotensin II. Thus, although reducing BP is the primary goal in order to decrease cardiovascular events in hypertensive patients, reduction of low-grade inflammation in hypertension may be an interesting and important target in order to reduce the cardiovascular morbidity and mortality associated with hypertension. C-reactive protein (CRP) predict cardiovascular risk and may represent a target for treating and/or monitoring risk reduction strategies.

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