Effect of angiotensin-converting enzyme inhibition on C-reactive protein levels: The Ramipril C-Reactive pRotein Randomized evaluation (4R) trial results

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BACKGROUND: 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.

METHODS: 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.

RESULTS: The mean ($\pm$ SD) age was 53 $\pm$ 9 years (60% men). Baseline demographics were similar between the volunteers allocated to receive either placebo or ramipril. The geometric mean CRP at baseline was 3.84 mg/L (95% CI 3.62 mg/L to 4.06 mg/L). The percentage change in geometric mean CRP values over 12 weeks was -13.2% (95% CI -22.3% to -3.2%) in the placebo group compared with -21.1% (95% CI -29.9% to -11.2%) in the ramipril group (P nonsignificant), indicating no significant reduction in the primary end point of the trial.

CONCLUSIONS: A 12-week ramipril treatment protocol for healthy middle-aged volunteers did not lower CRP levels compared with placebo. However, because of the inherent variability of CRP levels, a much larger study is required to exclude a small treatment effect.

Key Words: ACE inhibitors; CRP; Risk factors

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 (1-3). 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 (4). Accumulating evidence suggests that inflammation has a central role in the development and progression of atherothrombosis (5-7), and that biomarkers of inflammation, notably C-reactive protein (CRP), may be used to identify patients at increased cardiovascular risk (8). Recent evidence also suggests that high-risk patients who achieve low CRP levels (lower than 2 mg/L) in addition to low levels of low-density lipoprotein (LDL) cholesterol during statin treatment achieve greater cardiovascular benefits and atherosclerosis regression than those who achieve either low CRP or low LDL

L'effet de l'inhibition de l'enzyme de conversion de l'angiotensine sur les taux de protéine C réactive : Les résultats de l'essai sur l'évaluation randomisée de la protéine C réactive ramapril (4R)

HISTORIQUE : Les taux de plasma des biomarqueurs inflammatoires de protéine C réactive (PCR) permettent de prédire le risque cardiovasculaire et peuvent représenter une cible pour le traitement ou la surveillance des stratégies de réduction des risques. L'effet des inhibiteurs de l'enzyme de conversion de l'angiotensine sur les taux de PCR n'ont pas fait l'objet d'études pertinentes.

MÉTHODOLOGIE : Au total, 264 hommes et femmes, dont le taux de PCR était d'au moins 2 mg/L et qui n'avaient pas d'antécédents de maladie cardiovasculaire, ont participé à une étude à double insu, aléatoire et contrôlée contre placebo d'une durée de 12 semaines. Les participants ont été répartis au hasard entre l'administration de 10 mg/jour de ramipril (n=132) ou d'un placebo (n=132) pendant 12 semaines. La principale mesure d'issue était le changement de taux de PCR entre le début de l'étude et 12 semaines parmi les patients prenant du ramipril par rapport au placebo.

RÉSULTATS : Les patients avaient un âge moyen ($\pm$ ÉT) de 53 $\pm$ 9 ans (60 % d'hommes). Au départ, la démographie était similaire entre les volontaires répartis entre le placebo ou le ramipril. La PCR géométrique moyenne en début d'étude était de 3,84 mg/L (95 % IC 3,63 mg/L à 4,06 mg/L). Le changement de pourcentage des valeurs moyennes géométriques de PCR en 12 semaines était de -13,2 % (95 % IC -22,3 % à -3,2 %) dans le groupe prenant un placebo par rapport à -21,1 % (95 % IC -29,9 % à -11,2 %) dans celui prenant du ramipril (P non significatif), ce qui était indicateur d'une réduction non significative du principal paramètre ultime de l'étude.

CONCLUSIONS : Un protocole de traitement au ramipril de 12 semaines administré à des volontaires en santé d'âge mûr ne réduisait pas les taux de PCR par rapport à un placebo. Toutefois, en raison de la variabilité inhérente aux taux de PCR, il faudrait mener une étude beaucoup plus vaste pour exclure un léger effet du traitement.

cholesterol levels (9), suggesting that CRP levels may be useful in monitoring risk reduction with pharmacotherapeutic strategies. Although extensive data regarding the effects of statins on CRP levels and on cardiovascular events are available (10,11), prospective randomized evaluations of ACEIs on CRP levels have not been published. We hypothesized that inhibition of the renin-angiotensin system (RAS) would exert an anti-inflammatory effect, as evidenced by a reduction in CRP. To test this hypothesis, we performed a prospective randomized, double-blind trial to determine the effect of ramipril (10 mg) versus placebo on CRP levels in middle-aged healthy volunteers with baseline CRP levels of 2 mg/L or greater.

METHODS

Eligible subjects were recruited from one family practice group (Crowfoot Family Practice Group, Calgary, Alberta), one low-risk chest pain assessment group (C-Era Medical Clinic, Calgary) and a

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dedicated study clinic (McMaster University, Hamilton, Ontario). Coordination of the study occurred at the University of Calgary (Calgary) and McMaster University. The goal was to study relatively healthy subjects who would not otherwise be typical candidates for ACEI therapy, but who were believed to have an increase in inflammatory risk based on their CRP levels. Patients with established high-risk features had already been demonstrated to gain clinical benefit from ACEI therapy. To be eligible, patients were required to be 35 to 80 years of age, free of cardiovascular disease and have baseline CRP levels of 2.0 mg/L or greater. Exclusion criteria included structural heart disease or vascular disease, systolic blood pressure greater than 160 mmHg or less than 100 mmHg, renal or hepatic dysfunction, a white blood cell count of greater than $12 \times 10^9/L$, chronic inflammatory disease, recent or current infection, HIV, known sensitivity to ACEIs, steroid use and chronic (more than two weeks per year) use of nonsteroidal anti-inflammatory drugs, as well as treatment with ACEIs, angiotensin-receptor blockers, lipid-lowering agents, hormone replacement therapy, oral hypoglycemic agents, acetylsalicylic acid or antioxidants, and failure to give and maintain consent. The study was approved by the institutional ethics committees, participants gave written informed consent and the study was conducted according to Health Canada's good clinical practice guidelines. A clinical trials application was approved by the Therapeutic Products Directorate of Health Canada, and the trial was registered under International Standard Randomised Controlled Trial Number ISRCTN31129526.

Between March 2003 and September 2004, a total of 790 subjects consented to participate in the study and underwent screening bloodwork and CRP level measurements (Figure 1). The majority of exclusions occurred as a result of CRP levels below 2.0 mg/L ($n=464$) and refusal to continue in the study ($n=44$). The patient demographics of those excluded did not differ from those randomly assigned to therapy. A total of 264 subjects were randomly assigned (132 patients per group). The study was completed and the database closed April 2005.

Study protocol

The study was randomized, double blinded and placebo controlled. Subjects were randomly assigned to receive ramipril (sanofi-aventis Canada) or matching placebo for 12 weeks. Random assignment was performed by central research pharmacies at both universities using random-number generation in blocks of four. Random assignment was fully concealed with all study personnel unaware of the randomization procedure. Patients were seen in the clinic at baseline, and at two, six and 12 weeks. Participants were given the initial doses of study medication and, once safety laboratory data were obtained, patients were called at home and asked to begin taking the study medication. The baseline laboratory work included alanine aminotransferase (ALT), electrolytes, complete blood count, serum creatinine, fasting total cholesterol, high-density lipoprotein cholesterol, triglycerides (with calculated LDL cholesterol), fasting glucose and serum beta-human chorionic gonadotropin for women who were perimenopausal. Participants also received a blood pressure machine to assess their blood pressure before and after study drug administration during the titration phase, for safety reasons mandated by Health Canada. Titration occurred over the initial two weeks (2.5 mg in week 1, 5 mg in week 2). At two weeks, participants were titrated to 10 mg and safety bloodwork was repeated (creatinine and ALT). At six and 12 weeks, high-sensitivity CRP was obtained. Compliance was assessed at each visit by pill count. Compliance was excellent, with 96% of placebo and 98% of ramipril patients taking more than 80% of the study medication. Back titration of medications was performed for symptomatic hypotension or dizziness, persistent hyperkalemia (greater than 5.5 mmol/L) or a rise in creatinine to greater than 200 $\mu\text{mol/L}$. This occurred in seven participants (five ramipril and two placebo patients). Discontinuation of medications occurred in 30 participants (13 ramipril and 17 placebo patients) due to intolerable side effects. The only side effect that was increased in the ramipril group was cough

Figure 1) Patient participant flow diagram. CRP C-reactive protein; ITT Intention to treat

($n=15$ versus $n=5$, $P<0.05$), which was the most common cause of study drug discontinuation. No patients were lost to follow-up during the study period and an intention-to-treat design was used.

Blood tests

Blood count, electrolytes, creatinine, ALT, glucose, total cholesterol, high-density lipoprotein and triglycerides were determined at the two recruiting institutions, using standardized techniques. LDL cholesterol was calculated according to the Friedewald formula. CRP concentrations were measured by a particle-enhanced immunoturbidometric method using a Hitachi 912 analyzer (Roche Diagnostics, Canada) and reagents of Tina-quant CRP (latex) ultra-sensitive assay (Roche Diagnostics). This measurement was standardized against the International Federation of Clinical Chemistry Certified Reference Material Standard (IFCC CRM 470). The lower detection limit reported for the assay was 0.21 mg/L and the coefficient of variation at 0.21 mg/L was acceptable at 7.2%.

Statistical analysis

Results presented are from the intention-to-treat population, which includes all subjects randomly assigned to a study drug with available outcomes. In those subjects who had to discontinue medication ($n=30$), a 12-week CRP level was still obtained in the majority of subjects ($n=256$). The remaining subjects had their six-week values brought forward ($n=8$). The primary efficacy analysis was the change in CRP in the ramipril group compared with placebo from baseline to 12 weeks. The study was initially powered to detect a change in CRP of 15%, assuming an SD of 50% in the placebo group, which yielded a total sample size of 400 subjects (allowing for a 10% dropout rate). Due to emerging evidence about the variability of CRP levels during the study, an interim analysis was performed by the study statistician (RB) when 150 subjects were completely tested, to recalculate variance and sample size and to look for futility. The statistician who conducted the interim analysis at 150 patients was blinded to the actual treatment groups. The estimated relative percentage difference in 12-week geometric mean CRP levels (ramipril versus placebo) was -7.6% (95% CI -24.8% to 13.6%). The SD for percentage reduction was 80%, indicating that an overall sample size of 1800 would be required to provide 80% power for a 10% difference and a sample size of 900 would be required for a 15% difference. A futility analysis indicated that the power for the original sample size of 400, conditional on results already obtained, was only 18%. Recruitment timelines and study budget also factored into the decision to terminate the study.

Symmetrically distributed continuous variables are summarized as mean $\pm$ SD, while skewed variables are presented as median (interquartile range). Inferential results are reported using 95% CIs. Statistical significance at the 5% level (two-sided) is implied by

TABLE 1
Baseline characteristics of the Ramipril C-Reactive protein Randomized evaluation (4R) study participants

Characteristics	Placebo (n=132)	Ramipril (n=132)
Age, years	54.3±8.5	52.8±8.8
Male sex, n (%)	76 (58)	83 (63)
Body mass index, kg/m ²	30.2±4.6	30.7±5.4
Glucose, mmol/L, median (IQR)	5.3 (5.0 to 5.3)	5.3 (4.9 to 5.5)
Total cholesterol, mmol/L	5.8±0.9	5.8±1.0
LDL cholesterol, mmol/L	3.6±0.8	3.6±0.9
HDL cholesterol, mmol/L	1.39±0.3	1.32±0.3
Triglycerides, mmol/L, median (IQR)	1.5 (1.1 to 1.8)	1.7 (1.2 to 2.0)
Cigarette smoking, n (%)	21 (16)	22 (17)
Hypertension, n (%)	19 (14)	17 (13)
Diabetes mellitus, n (%)	2 (1.5)	3 (2)
Framingham risk score	5.7±3.2	5.4±3.3

Values presented as mean ± SD unless specified otherwise. HDL High-density lipoprotein; IQR Interquartile range; LDL Low-density lipoprotein

TABLE 2
Blood pressure during study period

	Blood pressure, mmHg	
	Placebo (n=132)	Ramipril (n=132)
Baseline	127±16/81±10	128±17/82±10
6 weeks	131±14/81±10	124±15/77±9
12 weeks	131±13/81±10	126±15/80±9*

Data presented as mean ± SD. *P<0.01 for change in systolic blood pressure at 12 weeks compared with baseline for the ramipril group versus placebo

intervals that do not cross zero. Intervals associated with unpaired *t* tests were applied to treatment comparisons; paired *t* test intervals were applied to assess within-group differences. Due to the skewed distribution of CRP, analysis was based on logarithmically transformed values. For ease of interpretation, differences on the logarithmic scale were antilogged, yielding estimates of ratios of geometric means that, in turn, were converted to relative (per cent) differences by subtracting 1 and multiplying by 100. Additional analyses included analysis of covariance with effects for treatment, baseline values and recruitment centre, as well as the application of linear mixed effects models to assess longitudinal trends (12). Analysis of the primary end point was also assessed after excluding patients who had CRP values of greater than 10 mg/L during the study and subjects who reported any illness during the 12-week period. This analysis yielded results similar to those presented below.

RESULTS

The intention-to-treat population consisted of 264 subjects (n=132 per group). Subjects were free from vascular disease and at low to medium Framingham risk (Framingham risk score 5.5±3.3). The random assignment process resulted in well-matched groups with no difference in any of the baseline demographics between the two groups (Table 1). There was a small, yet statistically significant reduction in systolic blood pressure (Table 2) in the ramipril group (placebo +4.2±15 mmHg versus ramipril -2.0±16 mmHg, P=0.002), with a trend toward a reduction in diastolic blood pressure (placebo +0.5±12 mmHg versus ramipril -1.9±11 mmHg, P=0.093).

Beginning from comparable distributions, the two groups experienced similar patterns of decrease in CRP from baseline to 12 weeks. In the placebo group, the relative decrease in geometric mean CRP was -13.9% (95% CI -22.8% to -3.9%) at six weeks and -13.2% (95% CI -22.3% to -3.2%) at 12 weeks. Corresponding values for the ramipril group were -13.3% (95% CI -23.9% to -1.2%) and -21.1% (95% CI -29.9% to -11.2%) (Figure 2). Thus, there was a significant decrease in CRP in both the placebo (P=0.012) and ramipril

Figure 2 Boxplots of percentage change (relative to baseline) in C-reactive protein (CRP), plotted on a logarithmic scale. Simple percentage change is defined as $100 \times (CRP_{12 \text{ weeks}} - CRP_{\text{baseline}}) / CRP_{\text{baseline}}$

TABLE 3
C-reactive protein (CRP) during the study period

Characteristic	Placebo (n=132)	Ramipril (n=132)
Baseline CRP, mg/L	4.00 (3.69 to 4.34)	3.68 (3.40 to 4.00)
6-week CRP, mg/L	3.37 (2.96 to 3.85)	3.17 (2.75 to 3.63)
12-week CRP, mg/L	3.48 (3.07 to 3.94)	2.89 (2.55 to 3.27)
Change in geometric mean CRP from baseline to 12 weeks, %	-13.2 (-22.3 to -3.2)	-21.1 (-29.9 to -11.2)
P for within-group change in CRP	0.012	0.0001
P for between-group change in CRP		0.26

CRP data presented as geometric mean (95% CI)

(P=0.001) groups at 12 weeks, but the difference between the two groups was not significant (Table 3).

The estimated relative percentage difference in geometric mean CRP from baseline (ramipril minus placebo) was 0.7% (95% CI -15.1% to 19.4%) at six weeks and -9.1% (95% CI -22.6% to 6.8%, P=0.26) at 12 weeks. Longitudinal analysis revealed no significant trend beyond six weeks.

DISCUSSION

The present report describes the first prospective randomized controlled trial evaluating the effects of ACEIs on CRP levels in otherwise healthy middle-aged volunteers with elevated baseline CRP levels of 2 mg/L or greater. For the primary outcome measure, we found that ramipril treatment, at a dose of 10 mg/day over 12 weeks, did not result in a significant reduction in CRP levels compared with placebo. However, we cannot exclude a modest treatment effect that could only be uncovered in a much larger trial.

Accumulating evidence suggests that inflammation may play a critical role in the development and progression of atherothrombosis (5-7) and that markers of inflammation, notably CRP (8-11,13-15), may be valuable to identify and/or follow patients at risk for cardiovascular events. Numerous studies have demonstrated that CRP is an independent predictor of future vascular events, and that it may offer prognostic information beyond conventional risk assessment algorithms and measurement of LDL cholesterol. Additionally, it has been suggested that CRP participates in the development of

endothelial dysfunction and atherothrombosis (8), although whether CRP is simply a marker or partaker of vascular disease is still debated. Statins have been demonstrated to reduce CRP levels (10) and this effect, believed to be independent of LDL cholesterol lowering, has been suggested to contribute to the observed risk reduction during statin therapy in low-, medium- and high-risk populations. Although definitive trial evidence linking a lowering CRP level to a reduction in vascular events is anticipated (16), recent analysis of the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) (13) and Pravastatin or Atorvastatin Evaluation and Infection Therapy – Thrombolysis in Myocardial Infarction 22 (PROVE-IT TIMI 22) (9) trials indicates that in patients with coronary artery disease, the reduced rate of progression of atherosclerosis associated with statin treatment is significantly related to a reduction of CRP and that patients who have low CRP levels after statin therapy have better clinical outcomes than those with higher CRP levels, regardless of the resultant level of LDL cholesterol. In these studies and others, the magnitude of CRP lowering with high-dose potent statins is in the range of 30% to 40%. These data point toward a role for CRP as a target for monitoring risk reduction approaches.

Inhibition of the RAS has emerged as a cornerstone of treatment in patients with heart failure, diabetes, hypertension and atherosclerosis. Large-scale studies have demonstrated that ACEIs reduce cardiovascular morbidity and mortality in patients with atherosclerosis and preserved left ventricular function (2,3), and that part of this effect may be secondary to pleiotropic effects of ACEIs on endothelial and vascular smooth muscle cell function, which may serve to stabilize vulnerable plaques and limit atherothrombotic events (4,17,18). This has led to the widespread belief that ACEIs, similar to statins, may be anti-inflammatory and that their benefit may be linked to reductions in inflammatory biomarkers such as CRP. In a small study by Kovacs et al (19), it was reported that the effects of ACEI in improving endothelial function in postmyocardial infarction patients may be related to a reduction in inflammatory biomarkers, including CRP. Mitrovic et al (20) reported results of an uncontrolled, open-label study of 10 mg/day of ramipril in 24 subjects with documented atherosclerosis. CRP levels decreased from 3.99 ± 1.61 mg/L to 2.72 ± 1.19 mg/L (–32%) after three months, and this effect was greater in patients not treated with statins. Di Napoli and Papa (21) conducted a prospective observational study of 507 patients with first-ever ischemic stroke to analyze the effect of ACEI treatment at the time of stroke onset on CRP levels within the first 24 h and the relationship to outcome. The authors reported that ACEI treatment was associated with lower (2.6-fold; $P < 0.0001$) median CRP levels and a reduced two-year cardiovascular risk (hazard ratio 0.39; 95% CI 0.29 to 0.53; $P < 0.0001$) compared with a different blood pressure-lowering regimen, an effect that remained significant following multivariate adjustment.

In a recent small randomized study, Schieffer et al (22) assessed whether RAS inhibition elicits anti-inflammatory and antiaggregatory effects in patients with coronary artery disease and arterial hypertension six to eight weeks after coronary angioplasty. Patients were randomly assigned to either 20 mg enalapril ($n=27$) or 300 mg irbesartan ($n=21$) for three months. Both treatment regimens enhanced serum interleukin-10 levels and reduced serum matrix metalloproteinase-9 protein; however, only irbesartan reduced serum interleukin-6 and CRP levels. Although this represents a small study, it suggests that RAS inhibition may exert anti-inflammatory effects on a variety of biomarkers independent of changes in CRP. Recently, Ridker et al (23) reported no change in CRP in hypertensive subjects receiving six weeks of therapy with valsartan and a thiazide diuretic. However, subjects treated with valsartan alone had a small (0.12 mg/L) but significant decrease in CRP levels. Finally, CRP was measured in the Prevention of Events with Angiotensin-Converting Enzyme Inhibition (PEACE) trial (24) in subjects with stable coronary disease. While CRP was predictive of events, treatment with trandolapril did not reduce CRP levels.

Our data, derived from a prospective randomized study, indicates that in healthy middle-aged volunteers who are free of known cardiovascular disease with CRP levels of 2 mg/L or greater, 10 mg/day of ramipril did not lower CRP levels from baseline to 12 weeks compared with placebo. One explanation for the negative finding may be related to the population studied. In those without significant activation of the RAS, this therapy may have limited anti-inflammatory effect. A second reason may be due to the considerable variability in CRP values in the placebo group, with a significant 13.2% reduction in CRP from baseline to 12 weeks. While some of this represents regression to the mean, these observations point to the variability in CRP values, a question that has resulted in recent discussions and debates. Although considered an extremely stable and reproducible biomarker by many (1), others have found that CRP values fluctuate considerably over time, particularly in the short to medium term. For example, Bogaty et al (25) examined serial serum CRP values in 159 patients with atherosclerosis. The authors reported that CRP values in individual patients fluctuated considerably when examined in the following ranges: less than 1 mg/L, 1 mg/L to 3 mg/L, and greater than 3 mg/L (proposed to indicate low, average and high risk, respectively). Sixty-four patients (40.3%) changed risk category between the first and the second measurement. The variability in CRP in our study occurred despite careful exclusion of patients with acute, subacute or chronic inflammation and infection, or those taking other medications that may affect CRP levels.

Limitations

While ramipril treatment was associated with a small reduction in CRP compared with placebo, the reduction was not statistically significant and we cannot exclude a small treatment effect due to the relatively small sample size. Based on our interim analysis and final data, a study would require approximately 1800 subjects to detect a change of 10% between the active group and placebo. Based on the CIs of the difference between the ramipril and placebo groups, we cannot exclude a lowering of CRP up to 22.6% with active treatment. Due to the study design of including subjects with a single CRP value of 2 mg/L or greater and the recently recognized variance in this measurement, a significant decrease was observed in the placebo group, due in part to regression to the mean. However, the placebo-controlled nature of the study and the use of the change in CRP as the primary efficacy analysis decreases the concern of this observation. Duplicate measures of CRP at baseline and follow-up should be considered for future trials. Finally, our study was conducted in healthy individuals without known vascular disease, and hence, it is unknown whether these data will apply to higher-risk secondary prevention cohorts.

CONCLUSIONS

The present study, a randomized placebo-controlled trial, demonstrated that 12-week ramipril treatment was not associated with a significant reduction in CRP levels. A much larger trial may uncover a small treatment effect in this or a higher risk population.

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