C-Reactive Protein in the Detection of Inflammation and It's Role in Coronary Artery Disease

Submitted by

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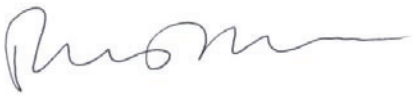
We hereby recommend that the research project prepared under our supervision by Lance Hein entitled C-Reactive Protein in the Detection of Inflammation and It's Role in Coronary Artery Disease will be accepted as partial fulfillment for the degree of Master of Physician Assistant.

Approved:



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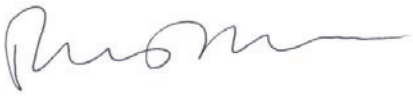

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Date

Abstract

Introduction: Heart failure is becoming more common and increasing annually with coronary artery disease (CAD) being the number one cause. Current research is focused on detecting more risk factors and markers for heart disease in order to develop interventions preventing its progression. C-Reactive Protein (CRP), the most widely studied inflammatory protein, plays a role in the atherosclerotic process of vessels, which subsequently can lead to infarct. However, the exact role of CRP in the acute coronary situations is not completely understood. Methodology: The purpose of this study was to perform a systematic evidence-based literature review addressing the issue of CAD and CRP. Medline was utilized to obtain adequate literature associated with certain, specific key terms. Articles were categorized into groups of evidence and separated into grades of evidence to answer the two main research questions: Is CRP a better marker for detection of inflammation? Is the presence of CRP associated with CAD? Results: Forty-eight articles matched the desired criteria and were reviewed using evidence-based methods. All forty-eight articles determined that CRP was a superior marker in the detection of inflammation. Twenty-four articles correlated CRP with CAD along with other mediated factors of vessel disease, with most being grade A evidence. Conclusion: CRP is a superior marker of inflammation and plays an important role in the development of CAD.

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Tables and Figures

Acknowledgements

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Introduction

C-Reactive Protein (CRP) was first discovered by William S. Tillett and Thomas Francis at the Rockefeller Institute for Medical Research in 1930 while studying serum in the immune response of pneumonia.[1] They tested "Fraction C" with a soluble extract known as C-polysaccharide, for a possible relationship response to *Streptococcus pneumonia*. A positive result occurred between "Fraction C" and C-polysaccharide while the patients were ill but immediately disappeared once the pneumonia had been resolved.[1,2] Further research from Tillett and Francis resulted in having positive results for "Fraction C", now known as CRP, in patients suffering from subacute bacterial endocarditis, acute rheumatic fever, lung abscess, and staphylococcal osteomyelitis. Once bacterial infections subsided in these medical patients, the levels of CRP returned to baseline measurements and only high levels of CRP remained in patients where illnesses were fatal. Patients with measles, chicken pox, and parasites tested negative for CRP,[1] and therefore no precipitation has ever been seen in viruses and certain parasites.[2]

According to Gotschlich in his approach to describe CRP, claims that CRP with the presence of Calcium (Ca^{2+}) binds to non-phosphorus lipid compounds. This protein rapidly accumulates in areas of injury, such as those in acute coronary conditions, and furthermore can serve as a marker for damaged tissues or membranes.[3] C-Reactive Protein is a pentameric protein consisting of five protomers in which each protomer has two binding sites for Ca^{2+}. This is important in understanding CRP binding and why it is elevated during inflammatory conditions; hence, in humans CRP is one of the few proteins detectable in acute situations.[2] Utilization of these techniques from past researchers has sparked an enormous amount of research regarding CRP and the

inflammatory state. Although CRP is not specific to any one inflammatory condition, it has gained increased recognition with diseases of the heart.

Concern

There are many risks associated with CAD such as high cholesterol, smoking, elevated body mass index (BMI), hypertension (HTN), and physical inactivity; many, if not all, of these risk factors can be prevented based on lifestyle changes.[4] The literature has already determined that these factors can lead to acute coronary events, and medical interventions have been developed to help minimize these risk factors. Further research is focusing on alternative markers for CAD in order to prevent acute coronary conditions from occurring, and CRP, a highly sensitive plasma protein indicating inflammation,[5] is a marker currently under investigation. The purpose of this study is to evaluate CPR and to determine if it is a valid marker for CAD. The study will attempt to answer the following research question: Is C-Reactive Protein (CRP) an effective marker in the detection of inflammation and associated with Coronary Artery Disease (CAD)?

Literature Review

Utilizing CRP as a marker for inflammation is not a new concept, with reports that date back to 1930 when CRP was discovered. In the Fragmin and Fast Revascularization during In Stability in Coronary artery disease (FRISC) study group, factors such as troponin T, CRP, and fibrinogen were evaluated in patients with unstable angina due to their relation with short-term risk of death. This prospective, randomized, multicentered trial evaluated 917 patients over 37 months and found that CRP and fibrinogen were significantly higher in patients that died of cardiac causes. There was no significant difference in CRP in patients with non-cardiac conditions. Patients at highest

risk of fatality from cardiac conditions showed the highest levels of CRP (>10 mg/L) compared to those individuals with <10 mg/L of CRP present in the body. This study claimed that there are no major changes in the relative risk of cardiac fatality and levels of CRP after adjustment for other risk factors like age, smoking, and gender; yet their findings support prior research that an active inflammatory condition is a reason of volatility in CAD.[6]

Delanghe et al compared serum amyloid A (SAA) with CRP in a healthy working class. They found that SAA concentrations were elevated in subjects with a history of Coronary Heart Disease (CHD) and correlated well with CRP, fibrinogen, and haptoglobin. Although SAA was elevated, it was not as significant of a predictor as CRP. The study stated that in order to obtain accurate values of CRP and SAA after an acute coronary event, adequate baseline plasma concentrations must be estimated prior to the event. They claimed that CRP should be the preferred method for determining inflammation in patients with CHD compared to any other inflammatory marker discovered to date.[4] Ridker and colleagues also compared CRP with another inflammatory marker, low-density lipoprotein cholesterol (LDL). They argued that CRP and LDL should be screened together in order to provide better prognostic information. In this study, CRP predicted risks associated with crude relative, age-adjusted relative, and risk factor-adjusted relative factors better than LDL.[5]

The 'Multiple Risk Factor Intervention Trial' (MRFIT) followed a group of men, who were at high risk of cardiovascular fatality, for 17 years. They found a direct, positive connection between the presence of CRP and the diagnosis of CHD.[7] A similar study conducted in the elderly, the Cardiovascular Health Study and the Rural Health

Promotion Project, found the same results as MRFIT. More individuals that presented with preclinical atherosclerosis also had higher levels of CRP, and therefore were at a greater risk for successive coronary events.[8]

The 'MONItoring of trends and determinants in CArdiovascular disease' (MONICA) trial provided clinical evidence from a study that lasted 10 years and incorporated 26 countries. The World Health Organization (WHO) initiated this study in order to monitor and fully understand changes in cardiovascular disease. Results indicated a 19 percent increase in the risks of fatal/non-fatal cardiac events and further clarified CRP as a marker for cardiac events, yet the results implied that the connection between CRP and cardiovascular risk is underestimated from only a CRP analysis.[9]

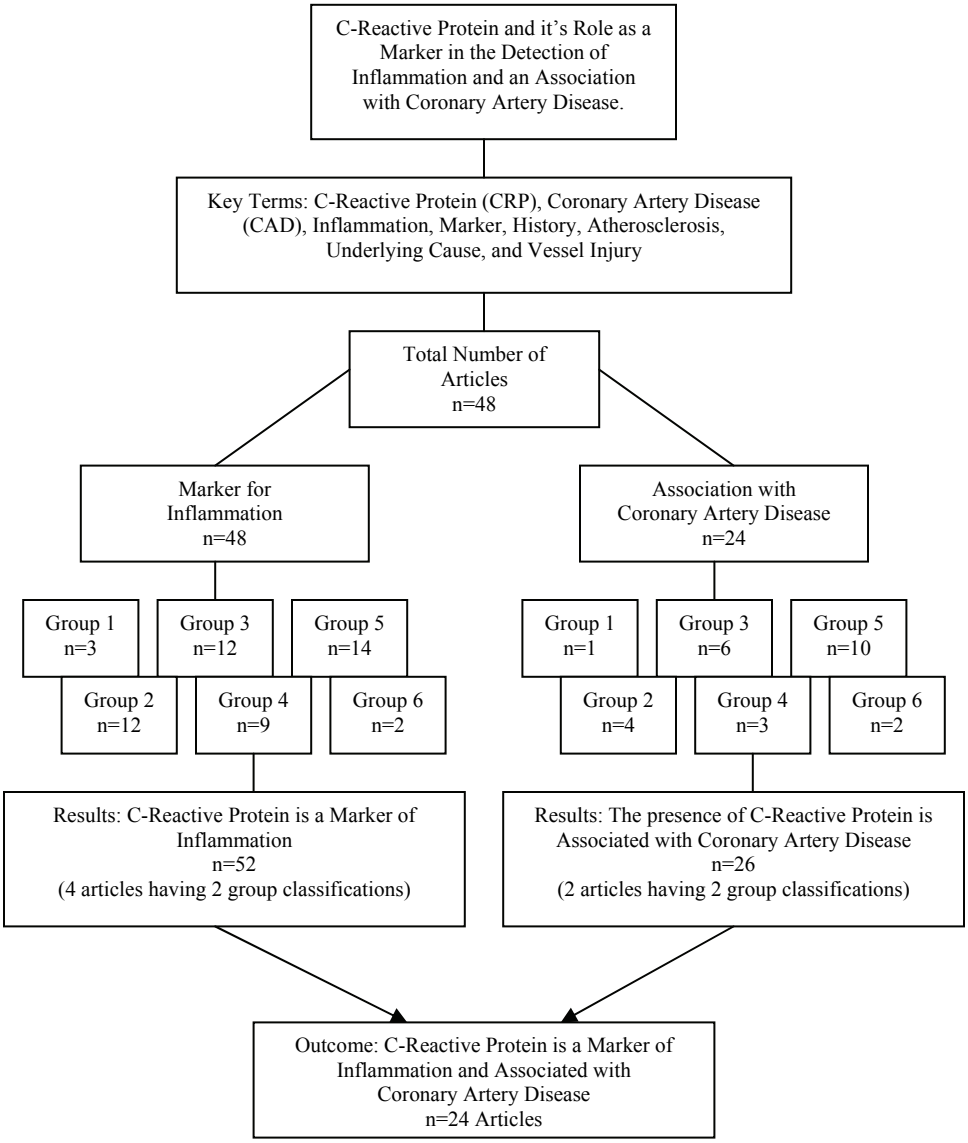
Methodology

The purpose of this study was to perform a systematic evidence-based literature review from peer-reviewed articles published in journals that addressed the issue of CAD and CRP. The literature review was performed using the search engine of peer-reviewed articles obtained from Medline, utilizing certain, specific key terms, including C-reactive protein, coronary artery disease, inflammation, atherosclerosis, vessel injury, marker, history, and underlying cause. Articles were selected based on their content associated with CRP and CAD; other articles used contained a variety of inflammatory markers and acute heart diseases in order to provide evidence that inflammatory markers are used to detect a variety of heart conditions such as stable and unstable angina. Articles were categorized into groups of evidence and separated into categories to answer the two main research questions: Is CRP a better marker for detection of inflammation? Is the presence of CRP associated with CAD?

Results

The overall analysis of forty-eight peer-reviewed journal articles, which met inclusion criteria based on key terms, is depicted in Figure 1. The study's research

Figure.1: Research Diagram



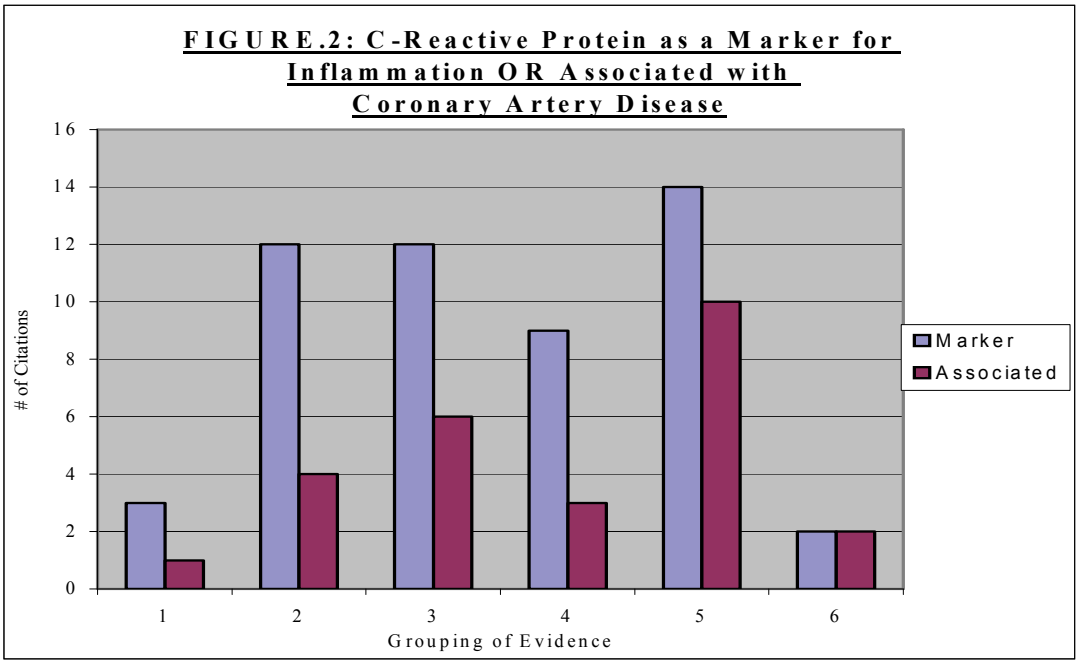
question contains two separate questions (Question one: Is CRP a marker in the detection of inflammation? Question two: Is the presence of CRP associated with CAD?). These questions were split up in order to determine how many articles answered each question.

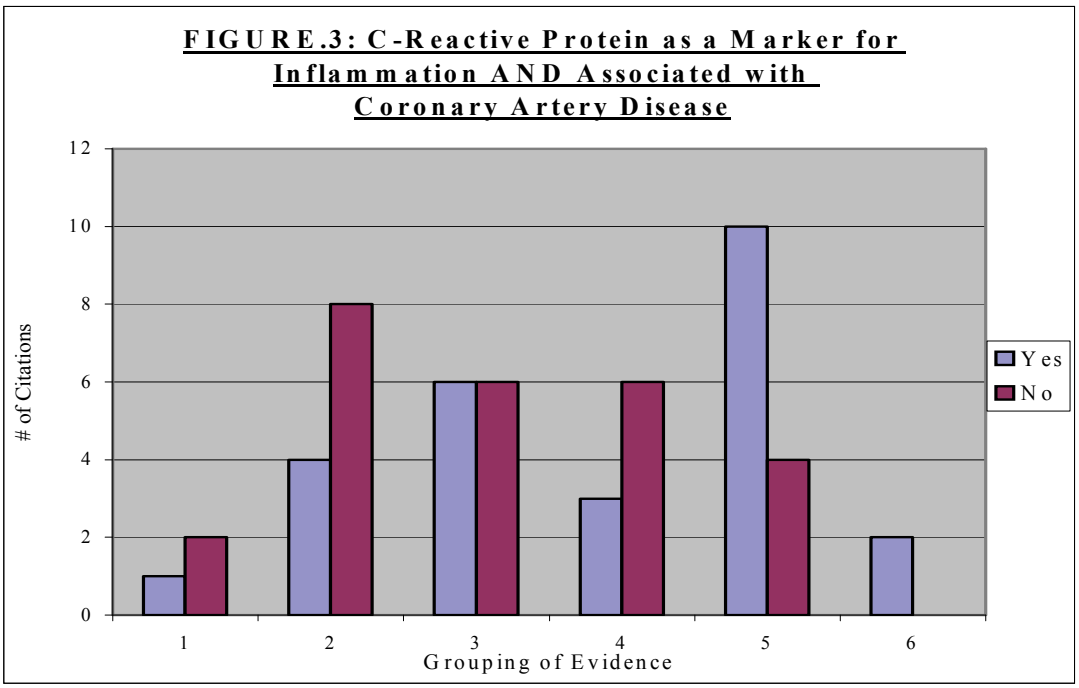
One-hundred percent of the articles (n=48) answered Question one and fifty percent of the articles (n=24) answered Question two. Question one and two were combined to determine which articles answered both questions (n=24). Of the articles searched, four articles did not meet the inclusion criteria and are listed in appendix A.[5,6,8,10] Group I evidence included articles with studies that were random and controlled.[5,6,9] Group II evidence consisted of retrospective and prospective cohorts.[5,6,8,10-18] Case control studies were labeled as Group III evidence.[4,7,8,10,19-26] Articles that contained cross sectional methods of research were classified as Group IV evidence.[27-35] Background information regarding key terms and meta-analysis of multiple studies involving Group I-IV evidence incorporated therein was given the title of Group V evidence.[2,36-48] All other articles that did not specify either of the above mentioned Group I-V but demonstrated a formal research study with proven results were termed Group VI evidence.[49-50] The articles that qualified as having met multiple groups of evidence classification criteria included two articles with Group I and Group II classifications.[5,6] The other two articles qualified as Group II and Group III classifications.[8,10]

The two separated research questions were evaluated and classified according to groups of evidence based medicine evidence[51] (Figure 2). Fifteen articles (30%) were classified as group one and two evidence. Twelve articles were classified as group three evidence. The remaining twenty-five articles were considered group three or four evidence. Overall, this translates into a grade of B in terms of evidence recommendation.

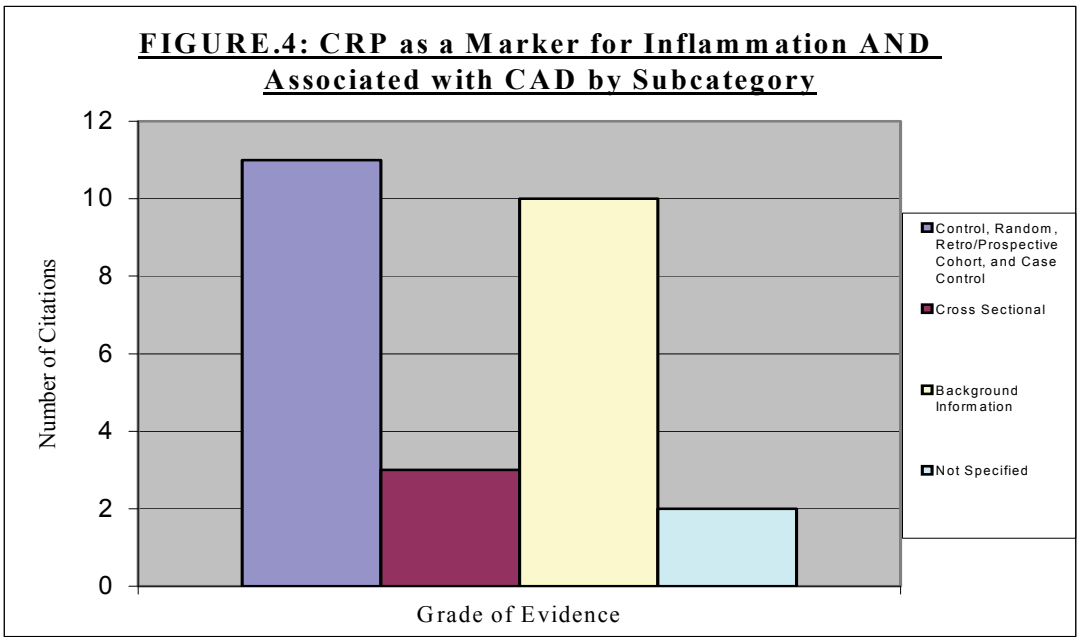
With the two research questions combined, the number of article citations per group of evidence was graphically demonstrated in Figure 3. Of these, one citation answered both questions and was classified as Group I evidence.[5,6,9] Four citations were

found in the retrospective and prospective cohorts' category.[5,6,8,10-18] Group III evidence hosted six citations answering the combined question.[4,7,8,10,19-26] Cross sectional evidence revealed three citations,[27-35] whereas ten citations were recorded with Group V evidence.[2,36-48] The outcome of Group VI evidence claimed two article citations.[49-50]





Overall, fifty percent of the articles that met inclusion criteria were found to prove that CRP is an effective marker in the detection of inflammation and is associated with coronary artery disease[2,8-10,13,18,20,23-25,27,28,35,39,40,42-50] (Figure 3). Due to the complexity of this topic and the plethora of articles circulating in peer-reviewed journals today, this finding further validates the effectiveness of CRP in the atherosclerotic process, which surrounds coronary artery disease.



Discussion

Evidence in Literature

The issue of CRP and CAD has been heavily debated over the years, and remarkable progression in the literature has been made regarding their involvement in acute coronary situations. However, CRP has been verified on many occasions to be elevated in other acute situations such as hypercholesterolemia,[5] myocardial infarction (MI),[5] muscle injury,[6] diabetes,[12] infection,[15] and hypertension.[33] It is apparent that CRP plays a role in acute coronary syndromes, yet its specificity is not significant like

troponin I, which is specific for acute MI.[49] Therefore, CRP analysis is not necessary for the diagnosis of CAD or MI; nevertheless, CRP has independently documented to be associated with an increased risk of cardiovascular disease.[52] Although there are no guidelines regarding the measurement of CRP in patients with CVD risk, the Centers for Disease Control and Prevention and the American Heart Association have considered using CRP measurement for evaluating risk of CVD.[53]

After evaluation of articles that met selection criterion, one-hundred percent of the articles found that CRP is the superior marker for inflammatory responses;[2,4-50] yet only fifty-percent found a correlation with CRP and the progression of CAD.[2,8-10,13,18,20,23-25,27,28,35,39,40,42-50] Although CRP is involved in the triggering mechanism associated with plaque vulnerability,[28] instability,[2,39,45] and rupture[25,27,50] including dramatic changes in arterial wall architecture[8,18,23,25,27,34,39,40,42,43,45-48,50] and clotting status,[8,38,40,42,43,50] CRP has not been determined to be the direct cause of CAD. Instead, CRP helps facilitate the cascade of mechanisms[2,18,27,39,43-45,47,48] that lead to the progression of CAD and ultimately the acute coronary situation.

CRP has also been found to be elevated in other situations including patients that smoke cigarettes,[7,9,31] hypercholesterolemia (elevated triglycerides, elevated LDL, decreased HDL),[5,21,22,26,40,41,43,45] hypertension (either elevations in systolic or diastolic blood pressures),[14,24,33] anemia,[15] obesity,[9,11,24] metabolic syndrome,[13,35] increasing age(male>45 y/o, females>55 y/o),[30] women not on hormone replacement therapy,[5] and diabetes mellitus.[12,26,41] It has been proven that CRP represents clinical inflammation[2,4-50] and these risk factors that show a relationship with the intensification of atherosclerosis present as inflammatory responses, making CRP a non-specific marker for inflammation.

In 2002 Verma and colleagues implemented a cross-sectional analysis of human saphenous veins where they found the effects of CRP on the architecture of the dissected vessels and how CRP was associated with interleukin-6 (IL-6), endothelin-1 (ET-1), intercellular adhesion molecule-1 (ICAM-1), vascular adhesion molecule-1 (VCAM-1), monocyte chemoattractant protein-1 (MCP-1), and low-density lipoprotein cholesterol (LDL). During the incubation of vessels with CRP, it was found that there was an increased secretion of ET-1, which is a very powerful endogenous vasoconstrictor, posing as a threat for endothelial dysfunction. When IL-6 is secreted in higher amounts, CRP levels increase suggesting plaque alteration in vessel architecture facilitating plaque rupture. CRP further initiates the up-regulation of cell adhesion molecules ICAM-1 and VCAM-1 leading to elevated secretion of MCP-1, a leukocyte chemo-attractant chemokine. With all these key molecular elevations, CRP promotes LDL uptake by macrophages, thus initiating inflammation and foam-cell formation leading to plaque instability and eventually plaque rupture.[27] Abrams et al and Kluft et al proved similar results in their literature review findings. With elevations of CRP, there were decreased levels of nitric oxide (NO) leading to the progression of cardiovascular disease (CVD) because NO encourages vasodilation and impedes smooth muscle proliferation, platelet adhesion and aggregation, and adhesion of monocytes to the arterial endothelium.[42,46] IL-6 was also found to be associated with obesity and colonized in adipose tissue.[11]

Koenig et al initially determined that CRP enhanced tissue factor (TF) production in its randomized MONICA trial.[9] Elevations in CRP have been found to stimulate the release and bioactivity of TF, which is a potent stimulus for thrombosis, thus further proved that Koenig et al were correct in their observation.[43,44] In a case-control analysis

of postmortem male and female patients suffering from acute coronary situations resulting in death, Burke and colleagues evaluated CRP levels in patients with a known history of atherosclerosis and no other inflammatory illness. In the evaluation of atherosclerotic arteries, it was noted that CRP was colonized in the necrotic core, the thin cap atheromas within the coronary tree, and in macrophages.[25] Soluble-thrombomodulin (s-TM) is derived from damaged endothelial cells within atherosclerotic coronary arteries, and CRP was elevated with s-TM present; during this inflammatory response CRP was synthesized in the intima of atherosclerotic vessels for an unknown amount of time before directly interacting with the diseased vessels during the acute coronary situation.[23]

Weaknesses in Literature

With all the hype concerning CRP and CAD, the suggestion of CRP initiating the development of CAD was never formulated. Instead, the literature only mentioned how CRP ended up being present during and after acute coronary situations. It has been hypothesized that statin medications[21] and anti-hypertensive medications[27] have, in part, helped lower CRP threshold by reducing inflammation; yet there has been very limited links with the development of medication especially designed to lower CRP levels.[54] Current studies are under investigation regarding roles of statin and thiazolidinediones in treatment of CVD inflammation.[55] There has also been a lack of randomized trials associated with CRP and CAD, and there needs to be more focus on how CRP can become an underling cause of CAD in order to initiate more effective interventions to prevent and further decrease the progression of CAD.

Gaps in Literature

According to Pearson et al, there needs to be heightened awareness to the consistence of inflammatory markers, such as CRP and SAA, when making an association to CVD. There was a significant amount of literature what focused on white North American or European populations as their study sample and held little evidence toward other ethnic groups or nationalities that are at risk for developing CAD. Although CRP has been linked to the atherosclerotic process, there have been poor correlations with diagnostic tests that evaluate the extent of atherosclerosis, which would further validate the importance of CRP in CAD.[53]

Validity of Literature

The article selection process was accomplished using the techniques mentioned in the methodology section. All articles were accessed utilizing Medline with the selected key terms. All articles chosen had to meet strict criteria before being initiated into this literature analysis. Once all data had been analyzed, it was organized into tables and evaluated based on the number of articles that answered the two main research questions. Calculations were determined based on number of articles meeting criteria divided by total number of articles. This procedure was performed with group I-VI evidence classification (I:random/control; II:retrospective/prospective cohorts; III:case control; IV:cross sectional; V:backgrouond information; VI:not specified in literature), grades of evidence (A:group I-III evidence; B:group IV evidence; C:group V evidence; D:groupVI evidence), research question one, and research question two.

Weaknesses in Review

This literature analysis poses some weaknesses that deters validity of the review. There was no methodology regarding the blinding of articles against specific authors, institutions, or journals of published articles; thus not protecting against bias. Although there were select, strict criteria associated with grouping of the literature, there was no mention of interval validity; thus leaving the reader to question strength of articles.

Conclusion

The purpose of this study was to determine the validity of CRP as a marker for inflammation and to determine its association with CAD. Based on the evidence reviewed, CRP is a superior marker for inflammation and plays a pivotal role in the atherosclerotic process; yet the exact role of CRP in the acute coronary situation in not completely understood.

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Appendix A: Raw Data Tables

Study (Year)	**Group of Evidence**	**Number and Characteristics**	**Pertinent Findings**	**Valid Marker**	**Associated With**
	1: random, control 2: retrospective/ prospective cohorts 3: case control 4: cross sectional 5: background 6: not specified			Yes: 2 No: 1	Yes: 2 No: 1
Tokac, M[49] 2003	6	Stable Angina Pectoris **(n=15)** 58.1 ± 8.9 y/o; 12 Male & 3 Female Unstable Angina Pectoris **(n=16)** 62.2 ± 5.5 y/o; 13 Male & 3 Female Percutaneous Transluminal Coronary Angioplasty **(n=16)** 57 ± 8.8 y/o; 12 Male & 4 Female	**Measured: Fibrinogen, CRP, & Troponin I** CRP is directly involved in the triggering stage of acute coronary events.	2	2
Verma, S[27] 2002	4	Saphenous vein endothelial cells were incubated with human recombinant CRP and the expression of vascular cell adhesion molecule (VCAM-1), intracellular adhesion molecule (ICAM-1), and monocyte chemoattractant chemokine-1 (MCP-1) were determined.	**Measured: CRP, IL-6, ET-1, ICAM-1, VCAM-1, MCP-1, and LDL** CRP speeds up the production of IL-6 and ET-1, one of the most potent endogenous vasoconstrictors, from endothelial cells. CRP increases ICAM-1 and VCAM-1 augmentation. CRP directly increases MCP-1 production leading to stimulation of ET-1 and IL-6. CRP facilitates macrophage LDL uptake developing foam cells. CRP and IL-6 participate in lesion formation by altering plaque architecture leading to rupture of vessels. CRP at dangerously high concentrations induces proinflammatory and proatherosclerotic phenotypes and colonizes in coronary plaques.	2	2

Nomoto, K[19] 2003	3	Acute Coronary Syndrome **(n=56)** Acute Myocardial Infarction **(n=48)** Unstable Angina **(n=8)** 64.9 ± 9.5 y/o; Male **(n=44)** Chronic CAD **(n=104)** Old Myocardial Infarction **(n=46)** Stable Angina Pectoris **(n=58)** 60.1 ± 10.2 y/o; Male **(n=81)** Control - no disease **(n=38)** No Ischemic Heart Disease **(n=38)** 59.6 ± 9.7 y/o; Male **(n=28)**	**Measured: hs-CRP, MMP-9, & interferon-ϧ** hs-CRP (44.5mg/l) in ACS > SAP (2.1 mg/l) > Control (0.6 mg/l) MMP-9 (333.8 ng/ml) in ACS > SAP (110.8ng/ml) > Control (72.0 ng/ml) Interferon-ϧ not significant Acute Coronary Syndrome is associated with significantly increased levels of hs-CRP.	2	1
Luc, G[11] 2003 PRIME	2	Initially - Subjects free of Coronary Heart Disease **(n=9758)**; 1991-1994 Individuals developing CHD **(n=317)** 55.3 ± 2.9 y/o; Male **(n=317)** Control **(n=609)** 55.2 ± 2.7 y/o; Male **(n=609)**	**Measured: Interleukin-6, CRP, & Fibrinogen** MI Coronary Death: CRP - 2.00 mg/l, IL-6 - 1.65 ng/l, Fibrinogen - 353 mg/dl Angina: CRP - 1.92 mg/l, IL-6 - 1.29 ng/l, & Fibrinogen - 329 mg/dl All associated with future MI-coronary death events. Increases in all markers are associated with increase in coronary event risk. IL-6 deemed the most discriminating risk marker. IL-6 is associated with adipose tissue.	2	1
Leu, H[12] 2004	2	All subjects were non-diabetic patients with stable coronary artery disease. Coronary Revascularization **(n=75)** PCI **(n=48)**, CABG **(n=27)** Male **(n=66)**, 67.9 ± 9.3 y/o Medical Treatment Group based on age, gender, history, cardiovascular risk factors, and disease entities. **(n=75)** Male **(n=66)**, 68.1 ± 10.1 y/o	**Measured: hsCRP, Homocysteine, LDL-C, and TC/HDL-C** In the revascularization group, patients with future adverse events had more severe CAD and higher hsCRP values than with no revascularization. In the medidal group, patients with future cardiovascular events had higher baseline hsCRP levels compared to non-cardiovascular events. hsCRP and TC/HDL-C are the strongest predictors of future cardiovascular events, especially when hsCRP is > 0.1 mg/dL and TC/HDL-C ratios are >4.8. Baseline hsCRP levels are elevated in non-diabetic patients with stable CAD.	2	1

Abbate, A[37] 2003	5	N/A	CRP an "almost perfect marker for inflammation." Recommends use of CRP as a progressive marker in patients with ACS in addition to the progressive factors including troponin levels. AHA and the European Society of Cardiology recommend hs-CRP in ACS as an independent marker for recurrent events.	2	1
Ferroni, P[20] 2003	3	Previous History of MI **(n=66)** 65.7 ± 10.1 y/o; Male **(n=42)**, Female **(n=24)**	**Measured: Fibrinogen, CRP, IL-6, MMP-2, and MMP-9** MMP-9, IL-6, CRP, and fibrinogen levels increased and correlated with each other Increases in MMP-9 importantly represents a sensitive marker of inflammation in patients with previous MI.	2	2
Arroyo-Espliguero, R[28] 2004	4	Acute Coronary Syndrome (ACS) **(n=125)** Male **(n=86)**; 63 ± 11 y/o Chronic Stable Angina (CSA) **(n=700)** Male **(n=523)**; 63 ± 10 y/o	**Measured: CRP** Elevated hs-CRP increases the chances of having an acute event. hs-CRP not associated with CAD severity or extend. hs-CRP was higher in the ACS patients hs-CRP showed a significant correlation with the number of coronary artery lesions. CRP predicts future cardiovascular events in CSA patients; CRP predicts cardiovascular risk in ACS patients. CRP is much more elevated in patients with NYHA functional class III and IV. CRP is not merely a marker of angiographic atherosclerosis burden but a marker of CAD activity. Elevated CRP levels in CSA patients indicates plaque vulnerability and progression to unstable syndromes. CRP is a major risk factor for the development of Clinical manifestations of CAD. All findings are likely the result of diffuse inflammation Leading to plaque instability.	2	2

Latkovskis,G[29] 2004	4	Caucasian patients with CHD confirmed by coronary angiography with no evidence of an inflammatory condition **(n=160).** Male ≤ 60 y/o and Female ≤ 70 y/o	**Measured: IL-1 alleles in conjunction with CRP.** IL-1B is strongly associated with eleveated CRP levels leading to a greater degree of systemic inflammation.	2	1
Ridker, P[13] 2003 WHS ext.	2	American women 45 y/o and older with no prior history of cardiovascular disease or cancer. 54.7 ± 7.6 y/o **(n=14,719)**; 1992-1995.	**Measured: CRP** CRP levels were significantly higher among women who had each component (triglycerides ≥ 150 mg/dL, HDL < 50 mg/dL, blood pressure ≥ 135/85 mm Hg, obesity BMI ≥ 30 kg/m², fasting glucose ≥ 110 mg/dL) of the metabolic syndrome. CRP can be predicted if there are 3 or more of the components associated with metabolic syndrome present. CRP is a marker for future cardiovascular risk. CRP has direct effects at the level of the vessel wall.	2	2
Ford, E[30] 2003 NHANES ext.	4	Caucasian men, African American men, Mexican American men, and other men ≥ 20 y/o **(n=1940)**.	**Measured: CRP** CRP concentrations: Caucasian (1.6 mg/dL), African American (1.7 mg/dL), Mexican American (1.5 mg/dL, other (1.8 mg/dL) CRP increased steadily with age. No major racial or ethnic differences exist with CRP concentrations. Describes CRP as a representative sample of the US male population. CRP is a very non-specific marker for inflammation.	2	1
Fröhlich, M[31] 2003 3rd MONICA	4	All patients were current smokers participating in the MONICA Ausburg survey in 1994/1995. Male **(n=2305)**; 49.9 ± 14.2 y/o Female **(n=2211)**; 49.0 ± 13.8 y/o	**Measured: CRP, fibrinogen, plasma viscosity, Albumin, WBC count** Smoking is associted with acute phase markers such as CRP and fibrinogen. When compared to never-smoking individuals, smokers' serum CRP concentrations are nearly doubled. Smoking is a major risk factor for developing CAD, and CRP levels are significantly elevated in smokers.	2	1

Blake, G[14] 2003 WHS ext.	2	American women 45 y/o and older with no prior history of cardiovascular disease. 54.1 ± 7.76 y/o **(n=15,215)**	**Measured: CRP** As CRP levels increase, there are increases in the systolic/diastolic blood pressures. There was an 8-fold increase in the risk for future cardiovascular events in women with a blood pressure ≥ 160/95 mm Hg and CRP levels ≥ 3 mg/dL.	2	1
Fine, A[15] 2002	2	All patients were on peritoneal dialysis. **(n=170)** Female **(n=94)**; 53 ± 15 y/o	**Measured: CRP, erythropoietin, ferritin, and parathyroid hormone.** High ferritin correlates with elevated CRP levels. Erythropoietin resistance was higher with elevated CRP levels. CRP is a poor predictor of CAD and PVD in peritoneal dialysis (PD) patients because not all PD patients have CAD or PVD, otherwise CRP would suffice as a marker for CAD CRP levels were elevated in the presence of an inflammatory infection. The spontaneous fluctuations in CRP levels strongly suggests inflammation associated with atherosclerosis.	2	1
Kuller, L[7] 1996 MRFIT	3	The trial enrolled 12,866 men aged 35-57 who were randomized at 22 centers between Dec. 1973 and Feb. 1976. Nonfatal Myocardial Infarction **(n=98)** Coronary Heart Disease **(n=148)** Control **(n=491)** Matched to MI and CHD cases ± 5 y/o. Two controls were selected for each case.	**Measured: CRP and α1 acid glycoprotein (AAG)** There was a statistically significant association between CRP and CHD mortality. Nearly two-thirds of CHD cases of smokers and non-smokers had elevated CRP levels in the upper two quartiles (>2 mg/L) For patients that died from CHD, levels of CRP among smoking categories are always higher than for non-smokers. Smoking causes inflammation of the coronary arteries leading to elevated CRP levels; thus establishing a direct association between smoking and CRP. CRP is a marker of an acute phase protein and inflammation.	2	1

Verdaet, D[32] 2004 BELSTRESS sub-sample	4 with controls	Coronary Heart Disease **(n=804)** Patients were apparently healthy, working in the same environment, and free from an clinical CHD or ECG Abnormalitits. Male **(n=804)**; 49.5 ± 5.4 y/o	**Measured: CRP, serum amyloid A, and fibrinogen** Negative relationship between leisure time physical activity (LTPA) and levels of CRP and fibrinogen. LTPA is not associated with CRP, fibrinogen, and serum amyloid A.	2	1
Danesh, J[16] 2004 Reykjavik follow-up	2	Major Coronary Event Group Patients of the Reykjavik study that had major coronary events between the beginning of follow-up (1991) to December 31, 1995. **(n=2459)** Male **(n=1774)**; 55.8 ± 9.3 y/o Control Group Subjects from the Reykjavik study that survived to the end of the syudy period without having a MI. **(n=3969)** Male **(n=2743)**; 55.7 ± 9.1 y/o Updated Meta-Analysis **(n=7068)** 22 prospective studies comprising 7068 patients with mean age of 57 y/o.	**Measured: CRP, ESR, von Willebrand factor** All markers provided little evidence over established risk factors. Associations between CRP concentration and the risk of coronary heart disease did not vary significantly according to established risk factors, such as smoking, elevated lipid profiles, blood pressure, or BMI. All markers are sufficient for stable, long-term prediction of CHD. CRP is a relatively moderate predictor of CHD.	2	1
Koenig, W[9] 1999 MONICA	1	Initial collection: 282,279 male patients from urban/rural communities of Augsburg Germany from 1984-1985. These patients did not have a history of CHD or any other illness. Random Criterion Group: **(n=936)** Male: 45-64 y/o	**Measured: CRP** There was a strong relationship CRP, future risk of fatal/nonfatal coronary events, and middle-aged males. Current smokers and obese patients had CRP concentrations that were twice as high as those patients that did not have these risk factors. Elevated CRP levels could be caused by an inflammatory process localized somewhere else in the body, other than the heart, that could be protherogenic and procoagulant. CRP enhances tissue factor production, which suggests a causative link between CRP and coronary events. Modest rises in CRP predict future coronary syndromes.	2	2

Ogasawara, K[17] 2004	2	Patients who underwent diagnostic coronary angiography (CAG) and who had at least 1 coronary artery stenosis more than 50% in diameter. **(n=140)** Patients free of end-point at 18 months **(n=119)** Patients with an end-point at 18 months **(n=21)**	**Measured: SAA, SAA/LDL complex, and CRP** SAA/LDL complex is associated with future cardiac events in patients associated with stable CAD, as well as CRP and SAA. All markers for inflammation indicate plaque activity; yet SAA/LDL complexes could be a better predictor of plaque activity in patients with stable CAD.	2	1
Tracy, R[8] 1997 CHS-RHPP	2, 3	Incidence of CVD including angina, MI, and death **(n=146)** Male **(n=90)**; 72.9 ± 5.3 y/o Control **(n=146)** Male **(n=90)**; 72.89 ± 5.7 y/o	**Measured: CRP and fibrinogen** In women, CRP levels were significantly higher for CVD group, even at baseline. Firbrnogen levels were only slightly higher in the CVD group compared with controls. Patients with elevated CRP and fibrinogen (in the upper quartile) had a 2 - 5 fold increase of having an MI later in life. CRP value represents clinical "inflammation". Elevated CRP is associated with the short-term process leading to a clinical event, including changes in the arterial wall and/or clotting status.	2	2
Wang, C[50] 2003	6	Human saphenous vein vascular smooth muscle cells were grown in IMDM and incubated with human recombinant CRP for 24 hours.	**Measured: CRP, AT1-R, AT2-R, Ang. II, ROS, [^{3}H]-thymidine incorporation** CRP significantly increases AT1-R mRNA expression in VSM cells. CRP did not alter AT2-R or Ang II release from VSM. CRP significantly increases [^{3}H]-thymidine production elevating VSM cell proliferation. CRP augmented ROS production. CRP increases neointimal thickness reflecting greater matrix formation, collagen, and elastin content. CRP is a mediator of CAD because it contributes to lesion formation, plaque rupture, and coronary thrombosis by interacting with endothelial cell phenotypes.	2	2

Delanghe, J[4] 2002	3	Case: Patients with AMI, CABG, and prominent Q:Qs waves in resting EKG Male: 35-59 y/o **(n=446)** Control: **(n=892)**	**Measured: CRP and SAA** CRP and SAA levels were higher in the case group. CRP proved to be an independent discriminator of CHD and SAA failed to prove this. CRP is a stronger discriminator for CHD compared to all other markers, such as SAA. CRP is the preferred serum marker for inflammation in the detection of CHD.	2	1
Lindahl, B[6] 2000 FRISC	1, 2	Delteparin Group: Patients with unstable coronary artery disease **(n=173)** Mean age: 70 y/o Placebo Group **(n=173)** Mean age: 70 y/o	**Measured: troponin T, CRP, and fibrinogen** CRP and fibrinogen were both significantly elevated in individuals that died of cardiac causes. Increased levels of troponin T in patients with unstable coronary artery disease have an elevated risk for an ACS for up to 4 years. If CRP is elevated, troponin T is elevated. CRP (inflammation) and troponin T (MI damage) together help to predict death from cardiac causes. Active inflammation is the cause of instability in coronary arteries.	2	1
De Backer, J[21] 2002 BELSTRESS Extension	3	Case: Prevalence of hospitalizations for AMI, coronary angioplasty, bypass surgery, and any ECG abnormalities suggestive of myocardial scar in men at work. Male **(n=446)**; 49.8 ± 5.3 y/o Control: Twice the number of men free of clinical CHD, working in the same environment. Male **(n=892)**; 49.7 ± 5.4 y/o	**Measured: Fibrinogen, CRP, and SAA** CRP and fibrinogen were both significantly elevated in the case group; SAA was borderline significant and elevated in the case group. With individuals taking lipid lowering drugs, the CRP level was, on average, higher than patients not taking these medications. CRP was a better discriminator with more clinical significance in the detection of ACS compared to fibrinogen and SAA.	2	1
Moreno, P[38] 2004	5	N/A	Arterial injury in CRPtg mice results in elevated thrombotic occlusion. CRP is a relatively moderate predictor of CHD. Class I, IIa, IIb, and III developed to determine when to measure hsCRP.	2	1

Ridker, P[5] 2002 WHS ext.	1, 2	American women 45 y/o and older with no prior history of cardiovascular disease. Mean age: 54.7 y/o **(n=27,939)**	**Measured: CRP and LDL** CRP was a better discriminator than LDL cholesterol in prediciting CVD. CRP is a strong, independent predictor of future cardiovascular events among women not taking hormone replacement therapy According to the Framingham risk score, CRP remained a strong predictor of future cardiac events. Women with high CRP and low LDL levels were at higher absolute risk for cardiac events than women with low CRP and high LDL levels.	2	1
Lowe, G[22] 2004 West of Scotland Coronary Prevention Study	3	Case: Patients with non-fatal MI, death from coronary heart disease, and revascularization that received 40mg pravastatin daily. Male **(n=485)**; 56.8 ± 5.1 y/o Control: Patients received a placebo. Male **(n=934)**; 56.7 ± 5.1 y/o	**Measured: CRP, D-Dimer, IL-6, Fibrinogen, Factor VII, and Factor XIIa** All markers correlated with CRP except Factor VII. D-dimer, CRP, and IL-6 have strong relationships With each other. IL-6 and, thus, CRP were predictors of coronary risk in middle-aged men with hypercholesterolemia. Factor VII and Factor XIIa antigens were not associated with coronary risk. D-Dimer was an independent predictor of coronary risk.	2	1
Du Clos, T[39] 2000	5	N/A	CRP was the phosphatidylcholine present on damaged cell membranes, binds to chromatin when exposed or denatured during apoptosis and necrosis. CRP binds to C1q, the 1st component in the phagocytic cascade. Activation by CRP induces phagocytic ativity through deposition of C3b and iC3b leading to damage of membranes. CRP stimulates IL-1, TNF, IL-1α, IL-1β, and TNF-α. CRP plays a pivotal role in the removal of Fc receptors on phagocytic cells.	2	2

Mezaki, T[23] 2003	3	Pt. that went through diagnostic coronary arteriography **(n=55)** Severe Organic Stenosis **(n=11)** Male **(n=10)** Female **(n=1)** Mean Age: 65.2 ± 3.1 y/o Mild Organic Stenosis **(n=29)** Male **(n=23)** Female **(n=6)** Mean Age: 62.8 ± 1.9 y/o Control: No Organic Stenosis **(n=15)** Male **(n=9)** Female **(n=6)** Mean Age: 61.5 ± 3.0 y/o	**Measured: CRP, SAA and soluble-thrombomodulin (s-TM)** Plasma CRP and SAA levels are elevated according to disease severity. s-TM is derived from damaged endothelial cells, thus sparking an inflammatory state produced by atherosclerotic coronary arteries. CRP and SAA levels are more sensitive in detecting the degree of inflammation compared to blood alone. CRP could be synthesized in the intima of diseased atherosclerotic coronary arteries for a certain period of time before interacting directly with these vessels in the ACS state.	2	2
Danesh, J[10] 2000	2, 3	7735 men aged 40-59 y/o were randomly selected from 24 british towns. 5661 men in 18 towns had venous blood samples taken from 1978-80. Case: History of CHD events Male **(n=506)**; 52.2 ± 5.3 y/o Control: No history of MI Male **(n=1025)**; 52.2 ± 5.3 y/o	**Measured: CRP, SAA, leucocyte count, and Albumin** All markers were associated with each other and with future risk of CHD. These factors were not associated with chronic infective processes. This study suggests that low grade inflammation activity is relevant to CHD.	2	2
Haidari, M[24] 2001	3	Targeted population: Tehran, Iran patients Patients with angiographically documented Coronary Artery Disease if one or more coronary arteries had stenosis ≥ 50% **(n=284)** Male **(n=185)** Female **(n=99)** Mean Age: 57 ± 10 y/o Control Group: **(n=166)** Male **(n=82)** Female **(n=84)** Mean Age: 52 ± 8 y/o	**Measured: CRP** Patients that were hypertensive or obese had higher levels of CRP compared to their counterparts. Three-vessel disease individuals had markedly higher levels of CRP compared to another group. The more elevated the level of CRP, the more severe the CAD is. There is a link between CRP and coronary artery narowing.	2	2

Choi, H[33] 2004	4	Hypertensive Group (diastolic BP ≥ 95 mm Hg on 2 separate occasions) Male **(n=43)** Female **(n=79)** Mean Age: 47.7 ± 8.2 y/o **(n=122)** Normotensive Group (BP<140/90mm Hg) Male **(n=25)** Female **(n=39)** Mean Age: 47.7 ± 8.1 y/o **(n=64)**	**Measured: hs-CRP, WBC, ESR, albumin, IL-6, and fibrinogen** HTN group had higher levels of albumin, WBC, and hs-CRP levels. hs-CRP, IL-6, and WBC were significantly associated with the 10-year risk of CHD based on the Framingham criteria. hs-CRP is a useful marker for the prediction of future cardiovascular diseases in the HTN patient.	2	1
Hirschfield, G[40] 2003	5	N/A	CRP accurately reflects on-going inflammation better than plasma viscosity and erythrocyte sedimentation rate. CRP binds to apoptotic cells enhancing opsonization and phagocytosis by macrophages. CRP is induced by IL-6 with IL-1 and TNF-α contributing. CRP selectively binds to LDL, is deposited in plaque, and contributes to the progression of atherosclerosis. CRP levels reflect tissue damage and significantly contribute to the severity of ischemic myocardial injury. CRP production and endothelial dysfunction, a marker of atherosclerosis in coronary arteries, are directly related. Foam cells become stimulated in atherosclerotic plaques with the addition of CRP to LDL.	2	2
Mendall, M[41] 1998	5	N/A	Raised CRP levels are associated with raised fibrinogen, plasminogen, factor VIII, white blood cell count, fasting insulin, serum triglyceride, fasting blood sugar concentrations, and decreased high density lipoprotein-cholesterol. IL-6 and TFN play a pivotal role in regulating acute phase responses from the liver, linking CRP to CAD.	2	1

Vermeire, S[2] 2004	5	N/A	CRP-ligand complex activates the complement cascade (C1-C9), resulting in opsonization and phagocytosis localized in macrophages and neutrophils.	2	2
Burke, A[25] 2002	3	Postmortem patients without inflammation other than atherosclerosis **(n=302)** Group 1 - atherosclerosis pt. **(n=302)** Control: No evidence of CAD **(n=158)** Male **(n=122)** Female **(n=36)** Mean Age: 46 ± 10 y/o Stable Coronary Atherosclerosis: **(n=71)** Male **(n=56)** Female **(n=15)** Mean Age: 56 ± 14 y/o Acute Coronary Thrombosis: **(n=53)** Male **(n=50)** Female **(n=3)** Mean Age: 48 ± 10 y/o Coronary Plaque Erosion: **(n=20)** Male **(n=14)** Female **(n=6)** Mean Age: 48 ± 10 y/o Group 2 - Non-atherosclerosis pt. **(n=172)** Inflammatory Conditions **(n=61)** Congestive Heart Failure **(n=40)** AMI with CAD **(n=33)** Miscellaneous Conditions **(n=38)** Random Selection of major epicardial arteries (LAD, left circ., and right Coronary arteries) **(n=30)** Arteries from plaque erosion **(n=10)** Arteries from plaque rupture **(n=10)** Arteries without coronary thrombi **(n=10)**	**Measured: hsCRP** hsCRP was higher in the acute thrombi group including plaque erosion and rupture when compared with stable plaque. There was immunocolonization of CRP in tissue sections with a necrotic core and in macrophages. There was marked elevations in hsCRP in patients suffering from acute myocardial necrosis and other inflammatory conditions. The greater the value of CRP in fatal lesions correlates well with death of tissue. A strong correlation exists with hsCRP and elevated numbers of thin cap atheromas in the coronary tree, resulting in the numbers of atherosclerotic plaques with superficial foam cells and large necrotic cores leading to accumulation of CRP in coronary lesions. Elevated CRP levels were found more commonly in hearts harboring acute rupture and erosion. There is a significant association of hsCRP and the risk of dying from stable coronary artery plaque.	2	2

Kluft, C[42] 2004	5	N/A	CRP is found to be the the best predictor of the probability and severity of future coronary events. CRP participates in CVD by increasing expression and bioactivity of TF, prodominately in monocytes and macrophages. This leads to an increase of procoagulant activity, contributing to development of intravascular coagulation and thrombosis. CRP increases ICAM-1 and VCAM-1, enhancing vascular disease progression by promoting leukocyte adhesion in the intima. High levels of CRP suppress the production of NO mRNA expression, protein levels, and enzyme activity leading to progression of CVD b/c NO promotes vasodilation and inhibits smooth muscle cell proliferation, LSL-oxidation, platlet adhesion and aggragation, and adhesion of monocytes to the arterial endothelium. CRP levels correlate with the presence of active vulnerable plaques; thus enhancing and exacerbating the natural response of atherosclerosis.	2	2
Fichtlscherer, S[34] 2000	4	All patients had documented Coronary Artery Disease with identification of culprit lesion on coronary angiography. **(n=60)** Endothelium-dependent and endothelium-independent forearm blood flow responses were measured using venous occlusion plethysmography. Stable Angina ≥ 3 months **(n=26)** Angina at rest with ST-segment alterations **(n=34)** Male **(n=34)**; 55.8 ± 10.3 y/o	**Measured: CRP, Troponin T, serum lipid, TNF-α, and sICAM-1** Acute coronary syndromes revealed significant rises in CRP levels. Elevated CRP levels were associated with a reduction in forarm vasodilatory response and blunted endothelium-mediated systemic vasodilator capacity in patients with CAD regardless of an episode of unstable angina. is associated with elevated CRP levels. CRP is an independent predictor of endothelial dysfunction and is a way to monitor atherosclerotic disease progression.	2	1

Mueller, C[18] 2002	2	Consecutive patients admitted for non-ST Segment elevation acute coronary syndromes (NSTACS) from 01/1996 - 12/1999 were treated with coronary angiography and coronary stenting of the culprit lesion within 24 hours. **(n=1042)** CRP < 3 mg/L: **(n=412)** Male **(n=296)** Female **(n=116)** Mean Age: 64 ± 2 y/o CRP = 3-10 mg/L: **(n=362)** Male **(n=249)** Female **(n=113)** Mean Age: 65 ± 2 y/o CRP > 10 mg/L: **(n=268)** Male **(n=195)** Female **(n=73)** Mean Age: 66 ± 2 y/o	**Measured: CRP** In-hospital mortality was significantly higher in patients with CRP > 10 mg/L. CRP was higher in patients that died while in study. CRP mirrors inflammatory processes participating in complement activation, tissue damage, and expression of adhesion molecules and chemokines in human endothelial cells.	2	2
Rowley, K[35] 2003	4	Aboriginal people from Western Australia because individuals from this area suffer very high mortality from coronary heart disease. Male **(n=76)**; 38 ± 4 y/o Female **(n=95)**; 37 ± 3 y/o	**Measured : CRP, E-Selectin** Mean CRP concentration was significantly elevated in the presence of metabolic syndrome. The higher the value of CRP, the lower the levels of lycopene, β-carotene, cryptoxanthin, and retinol. With elevated E-Selectin levels, there was a decline in concentrations of lycopene, β-carotene, cryptoxanthin, and lutein + zeaxanthin. Insulin resistance decreases with eleveated CRP and E-Selectin levels. CRP has possible negative effects on vascular tissues, leading to insulin resistance and inflammation Protection of oxidative stress from carotenoids and other dietary supplements is beneficial to vascular tissues and preventing CHD.	2	2

Heilbronn, L[43] 2002	5	N/A	CRP serves as a marker of enhanced thrombotic risk. CRP binds to LDL and promotes its uptake by macrophages, mediating tissue damage through activation of the complement system. Activated complement, modified LDL, and CRP can be found in close proximity to each other in the deep intima of early atherosclerotic coronary lesions. CRP stimulates peripheral monocytes to produce tissue factor, a potent stimulus for thrombosis. Approximately 25-30% of IL-6, activator of CRP, is located in adipose tissue and subcutaneous fat; yet omental fat cells secretes approximately 2-3 times more IL-6 than subcutaneous adipocytes. Elevated IL-6 is located in atherosclerotic lesions, suggesting that IL-6 via CRP has a role in lesion development. CRP enhances thrombosis by stimulating tissue factor production.	2	2
Shah, S[44] 2003	5	N/A	CRP is directly involved in the pro-inflammatory state stimulating monocyte release of inflammatory cytokines and tissue factor, inducing expression of intracellular adhesion molecules by endothelial cells, and is associated with the upregulated messenger RNAs in atherosclerotic plaques. CRP is found in infarcted myocardium where it promotes activation of compliment. CRP is involved in the inflammatory pathway of initiation/progression of atherosclerotic CVD. CRP is associated with the size of infarct and attenuated by early reperfusion. Elevated baseline CRP levels predict risk of MI, stroke, peripheral vascular disease, and death. CRP is integrally invovled in the etiologic mechanisms of cardiovascular disease.	2	2

Zampelas, A[45] 2003	5	N/A	CRP predicts coronary events in the primary and secondary prevention of CAD. CRP is found in atherosclerotic lesions and CRP-opsonised native LDL-cholesterol by macrophages contribute to foam cell formation. CRP can activate complement in atherosclerotic plaques leading to plaque instability, initiating tissue factor production by macrophages, promoting coagulation, and induces expression of cellular adhesion molecules. Increased intake of Alpha-Linolenic Acid decreases the risk of CAD in secondary prevention.	2	2
Lundman, P[26] 2003	3	Case Group: **(n=15)** Healthy men < 40 y/o that were employees of private companies in the Stockholm metropolitan area with a fasting plasma triglyceride conc. b/w 265 mg/dl - 885 mg/dl on 2 occasions Male **(n=15)**; 34 ± 5 y/o Control Group: **(n=15)** Matched with age, gender, and BMI with a fasting plasma concentration of < 142 mg/dl among hosp. staff/volunteers. Male **(n=15)**; 34.3 ± 4.5 y/o	**Measured: hs-CRP, interleukin-6, sICAM-1, sVCAM-1, soulble E-selectin, endothelin-1, & von Willebrand factor antigen.** Elevated cholesterol levels related to elevated CRP, sICAM-1, soluble E-selectin, von Willebrand factor antigen, and IL-6, leading to risks of developing CAD. Hypertriglyceridemia is associated with endothelial dysfunction. Elevated CRP, IL-6, and tumor necrosis factor-α are related to insulin resistance syndrome and for developing CAD.	2	1
Abrams, J[46] 2003	5	N/A	Normal levels of CRP indicate an absence of ACS. CRP is a better marker for subsequent cardiovascular events when compared to LDL-cholesterol. CRP stimulates monocyte adherence, induces endothelial cell damage and dysfunction, and is associated with increases in cell surface adhesion molecules (ICAM-1, VCAM-1, e-selectin, MCP). CRP is associated with decreased levels of NO and fibrinolytic capacity; yet CRP increases white blood cells and vascular endothelial cells. CRP is associated with plaque rupture.	2	2

Lagrand, W[47] 1999	5	Studies analyzing links between CRP and Cardiovascular disease. Number of Studies **(n=17)** Prospective **(n=12)** Retrospective **(n=1)** Cross-Sectional **(n=1)** Nested, Case-Controlled **(n=3)** Overall Citations **(n=70)**	High-normal CRP levels can still predict coronary events in stable and unstable angina pectoris, including healthy people. CRP may increase CVD in response to infectious agents inducing inflammatory reactions in coronary vessels. CRP is a marker for severity and progression of disease in coronary vessels. CRP localizes in ischemic myocardium and atherosclerotic lesions. Ligand-bound CRP activates the classic pathway of complementation, which enhances inflammation and contributes to myocardial tissue damage or dysfunction.	2	2
Libby, P[36] 2003	5	N/A	CRP is the "Champion Marker".	2	1
Yeh, E[48] 2001	5	N/A	CRP binds to damaged tissues, nuclear antigens, lipoproteins, and apoptotic cells. CRP participates/complements activation and tissue damage. CRP induces the expression of adhesion molecules and chemokines in endothelial cells. CRP is an amplifer of inflammation.	2	2

Appendix B: Discarded Articles

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17. Taubes G. Does inflammation cut to the heart of the matter? *Science.* 2002 Apr; 296(5566):242-5.

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