Should high sensitive C-reactive protein measurement be included in health screening packages?

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ABSTRACT

Introduction: The Centers for Disease Control and Prevention (CDC) and the American Heart Association (AHA) have endorsed the optional use of high sensitive C-reactive protein (hsCRP) to identify patients without known coronary heart disease but who may be at higher absolute risk than estimated by major risk factors. This study assessed the potential value of hsCRP measurement in addition to routine lipid and risk factor assessment on patient management for individuals undergoing multiphasic health screening.

Methods: hsCRP was measured on fasting lipid samples on patients attending the Health Enrichment Clinic at Tan Tock Seng Hospital between January and April 2004. These results were then compared with the outcome of individual patient risk assessment (using the 2001 Singapore Ministry of Heath Clinical Practice Guidelines on Lipids), the patient's lipid results and whether the patient was already on anti-lipid treatment.

Results: 212 samples were analysed for hsCRP. Seven patients were already on anti-lipid drugs. Using the AHA/CDC guidelines, hsCRP measurement would be of value in deciding management in 12.7 percent of all patients. Of this group, 11 percent had hsCRP concentrations in the high risk category. Restricting hsCRP measurement to only those patients with two or more cardiac risk factors and not on anti-lipid drugs would increase the proportion of patients where hsCRP could be useful in deciding management, to 81.8 percent.

Conclusion: For clinicians prepared to consider treatment in patients with elevated hsCRP levels, hsCRP measurement should be included as part of health screening packages to selected patients based on individual cardiac risk assessment.

Keywords: atherosclerosis, C-reactive protein, coronary heart disease, evidence-based medicine, health screening

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INTRODUCTION

Coronary heart disease (CHD) is second only to cancer as a cause of death in Singapore, accounting for 19.3% of deaths in 2002[1]. Hypercholesterolaemia is a major risk factor for CHD and the current Ministry of Health Clinical Practice Guidelines on Health Screening[2] recommends screening all individuals aged 40 years and above with a full lipid panel, including low-density lipoprotein cholesterol (LDL-C), fasting triglyceride (TG) and high-density lipoprotein cholesterol (HDL-C) at three-yearly intervals. Screening of selected patient groups, such as those with diabetes mellitus, cerebrovascular or peripheral artery disease, and of younger at-risk individuals, such as Indians, are also recommended. The Clinical Practice Guidelines on Lipids[3] advocate global risk assessment for the individual patient to allow sorting into one of three risk categories (0-1 risk factors, ≥2 risk factors and CHD/CHD equivalent), each with its own cut-offs for commencement of anti-lipid treatment. Although it is useful, international studies show that it fails to identify almost half of the individuals who suffer from myocardial infarction who have either normal or only mildly-raised cholesterol concentrations[4].

In recent years, markers of inflammation have been studied for their association with CHD. Until recently, assays for C-reactive protein (CRP) were unable to reliably measure concentrations in healthy persons and could only detect CRP during significant inflammation in most individuals. However, highly sensitive assays for CRP (hsCRP) have now become available, allowing studies to be performed on the CRP concentrations of individuals who are apparently healthy. There is particular interest in the ability of increased concentrations of CRP to predict increased risk of coronary heart disease in people without

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overt hyperlipidaemia. In 2003, the American Heart Association (AHA) and Centers for Disease Control and Prevention (CDC) published guidelines on the use of hsCRP in cardiovascular disease[5]. They concluded that measurement of hsCRP is an independent marker of risk, and in those judged at intermediate risk by global risk assessment (10-20% risk of CHD per ten years), hsCRP measurement may help further evaluation and therapy in the primary prevention of cardiovascular disease. This patient group is equivalent to the ≥2 risk factor group identified by the Singapore clinical practice guidelines. This study was designed to assess the potential value of hsCRP measurement in addition to routine lipid and risk factor assessment on patient management for individuals undergoing health screening.

METHODS

This study was part of a quality improvement project between the Health Enrichment Centre and the Department of Pathology and Laboratory Medicine to improve the utilisation of laboratory tests used in health screening. hsCRP was measured on anonymised fasting lipid samples on patients attending the Health Enrichment Clinic at Tan Tock Seng Hospital between January 1, and April 30, 2004. hsCRP measurement was performed on the Roche Modular PP clinical chemistry analyser (Roche Singapore) using the Roche CRP (Latex) HS assay (functional sensitivity 0.11 mg/L). hsCRP results were classified using the AHA/CDC guidelines into one of three relative risk categories: low <1 mg/L, average 1.0-3.0 mg/L and high >3 mg/L. CRP results were then compared with the outcome of individual patient risk assessment (using the 2001 Ministry of Heath Clinical Practice Guidelines on Lipids), the patient's lipid results and whether the patient was already on anti-lipid treatment.

RESULTS

212 samples were analysed for hsCRP. There were 120 men and 92 women with an average age of 42 (range 21-78, median 41) years. The average lipid concentrations (and ranges), all in mmol/L, were: cholesterol: 5.32 (3.25-8.54); HDL-cholesterol: 1.6 (0.65-3.05); LDL-cholesterol: 3.12 (1.43-6.28); TG: 1.32 (0.41-7.34). The risk factor details are given in Table I. In summary, 170 patients had 0-1 risk factors, 37 had ≥2 risk factors and 5 had CHD or CHD equivalent. There were seven patients already on anti-lipid treatment, and these patients were excluded from further analysis.

Each risk category has specific lipid cut-offs for commencement of anti-lipid treatment. Based on the individual lipid results, the need to commence anti-lipid drug treatment together with the CRP classification is shown in Table II. hsCRP measurement is of potential value in management in patients with risk factors ≥2 (i.e. at 10-20% risk of coronary events in the next ten years) whose lipid

Table I. CHD risk factors of health screening population.

Risk factor	Prevalence
Smoker	26%
Hypertension	15%
Low HDL-C	5%
High HDL-C*	48%
Family history of premature CHD	10%
Age ≥45 years (male), ≥55 years (female)	28%
Known diabetes mellitus	2%
CHD	0%

* Note that high HDL-C is a negative risk factor for CHD.

Table II. Categorisation of hsCRP concentrations of health screening patients based on risk category and lipid results.

Risk factors	Lipids justify drug treatment	Total no. of patients	hsCRP <1 mg/L	hsCRP 1-3 mg/L	hsCRP 3-10 mg/L	hsCRP >10 mg/L
0-1	No	158	93	48	14	3
0-1	Yes	9	8	1	0	0
≥2	No	27	13	10	3	1
≥2	Yes	6	1	4	1	0
CHD/CHD equivalent	No	3	1	2	0	0
CHD/CHD equivalent	Yes	2	0	2	0	0

results do not warrant anti-lipid treatment at present. As can be seen from Table II, 27 patients fell into this category.

Using the AHA/CDC guidelines, hsCRP measurement would be of value in deciding management in 27 patients, of which three had raised hsCRP concentrations. The potential value of hsCRP measurements varies with the population tested. Using a stepwise approach to define an increasingly smaller population in which the test is used, there is potential value for hsCRP measurement in 12.7% of patients (27/212) if all patients are tested, in 13.2% of patients (27/205) if those on anti-lipid treatment are excluded, in 81.8% of patients (27/33) if those with 0-1 risk factors, CHD/CHD equivalent or already on anti-lipid treatment are excluded and in 100% of patients (27/27) if those whose lipid measurements justify drug treatment, have 0-1 risk factors or CHD/CHD equivalent or are already on anti-lipid treatment are excluded.

DISCUSSION

In 2003, the CDC and the AHA published a detailed scientific statement on markers of inflammation, and cardiovascular disease and their application, to clinical and public health practices[5]. They concluded that hsCRP had an independent association with incident coronary events after adjusting for smoking, total cholesterol, HDL-cholesterol, smoking, body mass index, diabetes mellitus, history of hypertension, exercise level and family history of coronary disease. They endorsed the optional use of hsCRP to identify patients without known CHD who may be at higher absolute risk than estimated by major risk factors, specifically patients at intermediate risk (10-20% risk of CHD over ten years). They note that those with a ten-year risk >20% are designated as CHD risk equivalents and already qualify for intensive medical interventions. The report discourages the use of CRP as an alternative to major risk factor assessment. Measurements of hsCRP should be done twice (averaging results), optimally two weeks apart, fasting or non-fasting in metabolically stable patients. If the hsCRP level is >10 mg/L, the test should be repeated and the patient examined for sources of infection or inflammation. The hsCRP result can be used to classify patients into one of three relative risk categories: low <1 mg/L, average 1.0-3.0 mg/L and high >3 mg/L. However they note that that data is limited on non-Caucasian populations and more work is needed. Although a positive relationship between hsCRP and cardiac risk is seen across populations, the specific cut-offs may require modification for different ethnic groups[6].

Since the guideline publication in 2002, data has continued to accumulate, supporting the role of hsCRP as an independent risk factor. Over 20 large-scale prospective studies have shown baseline levels of hsCRP to independently predict future myocardial infarction, stroke, cardiovascular death, and incident peripheral arterial disease[7, 8]. Statins are now recognised to lower hsCRP concentrations in a manner largely independent of LDL-C reduction [9-11] with evidence from the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22 (PROVE IT–TIMI 22) trial[12] that the level of hsCRP achieved after initiation of statin therapy is of equal importance for subsequent vascular events as was the achieved level of LDL-C. The best overall survival in this study was observed among those who not only lowered LDL-C below 70 mg/dL, but who also lowered hsCRP below 2 mg/L, regardless of the statin regimen used. However, it is important to recognise that there is presently no firm data that lowering CRP levels alone will reduce cardiovascular risk[13] and there is no universal acceptance of the value of hsCRP measurement in cardiovascular disease[14]. The upcoming Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) study, which investigates the effects of statins in the primary prevention of cardiovascular events in individuals with low levels of HDL-C but elevated hsCRP levels, should provide an evidence base for the use of hsCRP to guide treatment in primary prevention[15].

For those clinicians prepared to consider treatment of patients based on elevated hsCRP levels, this study suggests that hsCRP measurement would be useful in a significant percentage of individuals presenting for health screening. Its value increases markedly if its use is restricted to those with intermediate risk of coronary events. A two-step approach would be even more effective, when hsCRP is requested only on patients with ≥2 CHD risk factors and after evaluation of serum lipids. However, such a strategy may be difficult logistically given the desire for a single follow-up appointment by health screening patients.

One compromise would be to decide on the need for hsCRP measurement at the end of the first consultation after initial cardiac risk assessment is completed (note that full risk factor assessment cannot be completed without HDL-C measurement). The result of this initial assessment can be used to rule out the need for hsCRP measurement in those with CHD/CHD equivalent, those already on anti-lipid treatment and those with a risk factor total of 0

(such patients will remain in the lowest risk category irrespective of the HDL-C result). In this study, this would exclude 111 patients (7+5+99 respectively) or 52% of all individuals from hsCRP measurement. Using this approach would mean that 27.6% of those tested patients would potentially benefit from hsCRP measurement – a doubling of efficiency over indiscriminate use.

We conclude that for clinicians prepared to consider treatment in patients with elevated hsCRP levels, hsCRP measurement should be included as part of health screening packages to selected patients based on individual cardiac risk assessment. Such a strategy is a cost-effective approach and ensures that hsCRP measurements are available to aid in management decisions for the appropriate subset of health screening patients.

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