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White blood cell count testing to predict coronary artery disease in the general population.

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PRIORITISING SUMMARY

REGISTER ID: **000169**

NAME OF TECHNOLOGY: **WHITE BLOOD CELL COUNT TESTING TO PREDICT CORONARY ARTERY DISEASE**

PURPOSE AND TARGET GROUP: **FOR EARLY DETECTION OF CORONARY HEART DISEASE IN THE GENERAL POPULATION**

STAGE OF DEVELOPMENT (IN AUSTRALIA):

- ☒ Yet to emerge
- ☐ Experimental
- ☐ Investigational
- ☐ Nearly established
- ☐ Established
- ☐ Established *but* changed indication or modification of technique
- ☐ Should be taken out of use

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

- ☐ Yes
- ☐ No
- ARTG number
- ☒ Not applicable

INTERNATIONAL UTILISATION:

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
United States	✓		

IMPACT SUMMARY:

This Prioritising Summary reports on current research regarding the association between leukocytes or white blood cells as important biomarkers in predicting coronary heart disease mortality, with a particular focus on the diagnosis of cardiovascular disease in women.

BACKGROUND

The Australian Government Department of Health and Ageing recognises cardiovascular health as a national health priority area for focusing on strategies in reducing the burden of disease and associated economic costs in Australian population (Australian Government Department of Health and Ageing, 2005).

A major contributor to cardiovascular disease is coronary heart disease (CHD), which may result in acute myocardial infarction and unstable angina in patients. CHD is caused by atherosclerotic lesions composed of lipoprotein particles, macrophages, leukocytes and smooth muscle cells narrow the coronary artery walls. Recognised risk factors for CHD include cigarette smoking, high blood cholesterol, physical inactivity, obesity, high blood pressure and diabetes (AIHW 2005). Higher white blood cell counts have been associated with several of these risk factors including cigarette smoking and high blood cholesterol, and there is considerable interest in research aimed at identifying inflammatory markers which may indicate a risk factor for future cardiovascular events (Brown et al 2001; Madjid et al 2004).

One of the avenues for preventing CHD is to accurately identify and monitor persons at risk of developing CHD. In particular, signs and symptoms of CHD in women may differ from those of men and may lead to delays in treatment and diagnosis (Sclavo 2001 and Legrys 1999).

There is increasing evidence that initiation, growth and complications of atherosclerotic plaques in coronary arteries are due to inflammatory responses to vascular injury. Elevated levels of white blood cells may indicate coronary artery inflammation and its use in predicting coronary heart disease is currently being examined.

CLINICAL NEED AND BURDEN OF DISEASE

Cardiovascular disease includes coronary heart disease, stroke, heart failure and peripheral vascular disease. Cardiovascular disease contributes to the major burden of disease in Australia, accounting for 38 per cent of all deaths and 22 per cent of the burden of disease through premature mortality, ill health, impairment and disability (National Heart, Stroke and Vascular Health Strategies Group 2004). Coronary or ischemic heart disease (ICD-9 codes 410--414 and ICD-10 codes I20--I25) is the most common form of heart disease in Australia. In 2002 there were 124 per 100, 000 deaths (for all ages) due to CHD in females and 142 per 100, 000 in males (AIHW 2005).

Cardiovascular disease is a major illness encountered in general practice in Australia. In 2002-03, 16 per cent of visits to a general practitioner were for the treatment of heart, stroke or vascular disease or its risk factors (AIHW 2003).

In 2001, an estimated 90 per cent of the adult Australian population had at least one of the following risk factors for heart, stroke and vascular disease: tobacco smoking, physical inactivity, overweight or obesity, high blood cholesterol, high blood pressure, heavy alcohol consumption and diabetes. In addition, 24 per cent of the adult Australian population had three or more risk factors (AIHW 2003).

DIFFUSION

Given that that leukocyte testing is a simple and inexpensive pathology test, its use for coronary heart disease would be likely to be incorporated into clinical practice.

COMPARATORS

WBC count as a prognostic biomarker for CHD would be used in addition to other methods of detecting CHD in patients. The standard testing in a general practice setting for the assessment of coronary heart disease includes testing for LDL and HDL cholesterol levels, monitoring blood pressure and examining lifestyle factors.

Several inflammatory markers for identifying persons at risk of CHD can also be used, including high-sensitivity C-reactive protein (hs-CRP) and serum amyloid and fibrinogen (Pearson et al 2003). The most reliable and accessible for clinical use is currently high-sensitivity C-reactive protein (Willerson and Ridker 2004, Pearson et al 2003).

EFFECTIVENESS AND SAFETY ISSUES

The Women's Health Initiative Observational (WHI-OS) study is a multi-centre, six year, cohort study (level II prospective cohort study) of 72, 242 postmenopausal women from different racial and socioeconomic groups in the United States (Margolis et al 2005). Baseline white blood cell counts were taken and association with future cardiovascular events was examined. Association was examined independent from other known CVD risk factors and biomarkers (lipids and CRP).

All women enrolled into the study were free from cardiovascular disease and cancer. WBC categories and observed cardiovascular events are described in Table 1 below. Each of the

cardiovascular events had a strong and graded association with WBC count quartile in the age and race adjusted models. Women in the fourth WBC quartile had twice the risk for CHD death and a 40% to 50% higher risk (p<.001) for non-fatal myocardial infarction compared to women with WBC counts in the first quartile.

Table 1. Association between WBC Quartile and Incident Cardiovascular Events

WBC Count Quartile#	CVD Events, No. (%)*
CHD death	
Q1	28 (0.2)
Q2	24 (0.1)
Q3	44 (0.3)
Q4	91 (0.6)
Total	187 (0.3)
Nonfatal MI	
Q1	118 (0.7)
Q2	140 (0.8)
Q3	193 (1.2)
Q4	250 (1.6)
Total	701 (1.1)
Stroke	
Q1	137 (0.8)
Q2	167 (1.0)
Q3	168 (1.0)
Q4	166 (1.7)
Total	738 (1.1)
Total CVD	
Q1	265 (1.6)
Q2	319 (1.9)
Q3	381 (2.3)
Q4	545 (3.5)
Total	1510 (2.3)

Percentage is total percentage over 403, 572 person-years of follow-up
Quartiles: Q1 = 2.50-4.70 x 10^9 cells/L, Q2 = 4.71-5.60 x 10^9 cells/L, Q3 = 5.61-6.70 x 10^9 cells/L, Q4 = 6.71-15.00 x 10^9 cells/L

The association between WBC count and CHD mortality independent of smoking was studied (level II prospective cohort study) in 8,914 men and women enrolled in the NHANES II Mortality Study (1976 – 1992) (Brown et al 2000). There were three categories of WBC count: < 6.1, 6.1-7.6 and >7.6 x 10^9 cells/L. Baseline counts varied from 2.2 to 18.4 x 10^9 cells/L. During a maximum of 16.8 follow-up years, there were 548/2,053 (26.7%) deaths due to CHD. The mortality CHD rate among persons with a WBC count <7.6 x 10^9 cells/L was nearly double that of persons with a WBC count of <6.1. After adjusting for CVD risk factors, individuals with a WBC count >7.6 remained at increased risk of death from CHD (RR = 1.4, 95% CI [1.1-1.8]). Rates for CHD in both genders are described in Table 2. Both men and women with WBC counts >7.6 per 10^9 were at higher risk of CHD mortality: the risk of death for women with a WBC count >7.6 was 1.7 times (95% CI [1.1-2.6]) that for women with a WBC count <6.1 x 10^9 cells/L.

Table 2. Association between white blood cell count and Coronary heart disease mortality

WBC count (1×10^9 cells/L)	Mortality rate per 10,000	Age-adj RR (95% CI)	Multi-adj RR (95% CI)
2-6.0	18.8	1.0 (referent)	1.0 (referent)
6.1-7.6	31.8	1.7 (1.3 2.2)	1.4 (1.3-2.2)
7.7-18.4	34.0	2.2 (1.8-2.8)	1.4 (1.1-1.8)

Madjid et al (2004) reviewed numerous studies that have shown WBC count as an independent risk factor for future cardiovascular events in patients without CHD and a prognostic marker of future events in patients with already diagnosed CHD (Madjid et al 2004). The relationship was observed in prospective and retrospective cohort studies and case-control studies. This review is not a systematic review of all available evidence, thus it is likely that there are more studies that examine the relationship between WBC and CHD.

COST IMPACT

CHD accounts for the largest proportion of Australian health system costs, comprising $3.7 billion (12 per cent) of total costs in 1993–94 (AIHW2002). In 2002-2003, an estimated $1.4 billion was spent through the Pharmaceutical Benefits Scheme (PBS) on heart, stroke and vascular drugs, representing around 30 per cent of total PBS expenditure in that year National Heart, Stroke and Vascular Health Strategies Group, 2004).

The current cost of pathology testing for WBC (leukocyte) count, haemotology (MBS item number 65070) is $17.20. There are no studies that examine the cost impact of incorporating the use of WBC testing for diagnostic or prognostic purposes.

A cost impact might examine the impact on acute treatment and for the management of chronic coronary artery disease. Firstly, if the use of WBC testing resulted in less episodes of myocardial infarction, it is likely that there would be a reduction in hospital and treatment costs. Second, if WBC testing resulted in a greater number of patients detected with coronary heart disease such as angina, there would be an increase in costs associated with prescription medication use.

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

No issues were identified/raised in the sources examined.

OTHER ISSUES

No issues were identified/raised in the sources examined.

CONCLUSION:

Coronary heart disease contributes to a great burden of disease and economic cost to the Australian population. A number of studies reported a correlation between WBC and coronary artery inflammation, however there are many markers currently available and in use for the prediction of coronary artery disease.

HEALTH PACT ACTION:

Archive

LIST OF STUDIES INCLUDED

Total number of studies

Level II prognostic evidence 2

SOURCES OF FURTHER INFORMATION:

AIHW (2002*) Australia's Health 2002.* Australian Institute of Health and Welfare, Canberra.

AIHW (2003) *General practice activity in Australia 2002–03.* AIHW Cat. No. GEP 14. Canberra: Australian Institute of Health and Welfare (General Practice Series No. 14).

AIHW (2005) *Death rates for cardiovascular disease by state and territory* [Internet]. Australian Institute of Health and Welfare. Available from: http://www.aihw.gov.au/cvd/statistics/deathratetableAge.cfm [Accessed 12th April, 2005].

Australian Department Health and Ageing (2005) *National Health Priority Areas initiative* [Internet] Available from: http://www.health.gov.au/internet/wcms/publishing.nsf/Content/health-pq-nhpa-index.htm#overview [Accessed 12th April, 2005].

Brown, D. W., Giles, W. H. & Croft, J. B. (2001). 'White blood cell count: an independent predictor of coronary heart disease mortality among a national cohort', *J Clin Epidemiol,* 54 (3), 316-322.

Grzybowski, M., Welch, R. D. et al (2004). 'The association between white blood cell count and acute myocardial infarction in-hospital mortality: findings from the National Registry of Myocardial Infarction', *Acad Emerg Med,* 11 (10), 1049-1060.

Lee, C. D., Folsom, A. R. et al (2001). 'White blood cell count and incidence of coronary heart disease and ischemic stroke and mortality from cardiovascular disease in African-American and White men and women: atherosclerosis risk in communities study', *Am J Epidemiol,* 154 (8), 758-764.

Legrys, V. A. (1999). 'Coronary heart disease in women and the role of the laboratory', *Clin Lab Sci,* 12 (4), 246-251.

Margolis, K. L., Manson, J. E. et al (2005). 'Leukocyte count as a predictor of cardiovascular events and mortality in postmenopausal women: the Women's Health Initiative Observational Study', *Arch Intern Med,* 165 (5), 500-508.

National Heart, Stroke and Vascular Health Strategies Group (2004) *National strategy for heart, stroke and vascular health in Australia.* Australian Government Department of Health and Ageing

Pearson, T. A., Mensah, G. A. et al (2003). 'Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association', *Circulation,* 107 (3), 499-511.

Sabatine, M. S., Morrow, D. A. et al (2002). 'Relationship between baseline white blood cell count and degree of coronary artery disease and mortality in patients with acute coronary syndromes: a TACTICS-TIMI 18 (Treat Angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy- Thrombolysis in Myocardial Infarction 18 trial)substudy', *J Am Coll Cardiol,* 40 (10), 1761-1768.

Sclavo, M. (2001). '[Cardiovascular risk factors and prevention in women: similarities and differences]', *Ital Heart J Suppl,* 2 (2), 125-141.

Willerson, J. T. & Ridker, P. M. (2004). 'Inflammation as a cardiovascular risk factor', *Circulation,* 109 (21 Suppl 1), II2-10.

SEARCH CRITERIA TO BE USED:

Arteriosclerosis/ immunology
Biological Markers/blood
C-Reactive Protein/analysis
Cardiovascular Diseases/ blood/diagnosis/ mortality
Cardiovascular Diseases/ diagnosis/prevention & control
Inflammation/complications/diagnosis
Leukocyte Count
Leukocytosis/complications/epidemiology