

Laboratory Testing

For Cardiovascular Risk



bpac^{nz} Development Team: Rachael Clarke
Rebecca Didham
Dr Trevor Walker
Dr Sharyn Willis
David Woods

bpac^{nz} Clinical Advisory Group (laboratory programme):

Dr Dave Colquhoun
Michele Cray
Dr Chris Leathart
Dr Rosemary Ikram
Dr Cam Kyle
Dr Lynn McBain
Associate Professor Jim Reid
Dr David Reith
Professor Murray Tilyard

© October 2007

bpac^{nz}
10 George Street
PO Box 6032
Dunedin
phone 03 477 5418
free fax 0800 bpac nz

www.bpac.org.nz

All information is intended for use by competent health care professionals and should be utilised in conjunction with pertinent clinical data.

Introduction

Welcome to this document 'Laboratory Testing for Cardiovascular Risk'.

This is presented as a series of case scenarios in which a range of clinical situations are commented on. We hope you recognise some of your own patients within these.

This document has been developed with the assistance of our invited panel based on their clinical experience and knowledge of the literature. We are extremely appreciative of this input and we would like to acknowledge their help and expertise:

- Dr Michael Crooke, Chemical Pathologist, Wellington Hospital and Aotea Pathology, Wellington.
- Associate Professor Stewart Mann, Department of Medicine, University of Otago, Wellington.
- Professor Russell Scott, School of Medicine & Health Sciences, University of Otago, Christchurch.
- Dr Neil Whittaker, General Practitioner, Nelson.

Much of this document references the New Zealand Guidelines Group document 'The Assessment and Management of Cardiovascular Risk' which was produced in 2003. In the near future parts of this guideline are to be reviewed. Areas in which changes to the guideline will probably be considered are:

- How risk is expressed over time. Currently risk is expressed over five years. Many other countries express risk over ten years or even lifetime risk.
- Reduction of optimum LDL-cholesterol levels to below those currently in the guideline.
- Increased emphasis on family history in the assessment of risk.

We hope you enjoy this document

The bpac^{nz} team

Contents

The scenarios...

A fit 20-year-old...	6
1. A 20-year-old man has sprained his ankle. While a nurse is applying a compression bandage, he asks when he should start having “heart checkups”.	
A 29-year-old with abnormal lipids....	8
2. A 29-year-old very fit man attends for a check up because his father has just had an MI at age 62 years. He has normal blood pressure and does not smoke. His fasting glucose was normal. His fasting lipids are mildly elevated.	
Routine cardiovascular risk assessment....	10
3. A 45-year-old man is recalled for his tetanus booster. What cardiovascular risk assessment programme would you recommend at this time.	
Persistent adverse risk profile.....	12
4. A 55-year-old man's father died of an MI aged 46 years. He is taking an ACE inhibitor, beta-blocker, statins and aspirin. He is a smoker, overweight and his latest fasting lipids show marked elevations.	
The metabolic syndrome....	14
5. A 45-year-old woman with truncal obesity and the metabolic syndrome is determined to do something about it, as her mother has recently had significant eye problems related to type-2 diabetes.	
A recent MI....	17
6. A 52-year-old man has recently been discharged from hospital following acute MI. He is taking an ACE inhibitor, beta-blocker, statin and aspirin.	
Gout and cardiovascular risk....	18
7. A 35-year-old Māori male presents with acute gout.	
Troponin in atypical chest pain....	19
8. A 64-year-old man has atypical chest pain that you think might be angina.	

BNP in suspected heart failure... 21

9. You suspect a 60-year-old man with COPD is getting episodes of left heart failure at night.

Laboratory testing for newly diagnosed hypertension... 22

10. A 42-year-old man has been found to have a persistent significantly raised blood pressure. He considers himself a fit and healthy non-smoker and no other abnormalities were found during the examination.

Cardiovascular screening in the elderly... 24

11. A fit and healthy 78-year-old woman has recently moved to town. Her son brings her to you for a checkup.

Polycystic ovary syndrome... 25

12. A 30-year-old woman has just been diagnosed with PCOS.

Investigations which are currently not indicated in the routine assessment of cardiovascular risk 26

Homocysteine

HsCRP

Troponin

Lipoprotein (a)

Apolipoprotein A1 and Apolipoprotein B

BNP

Insulin

Creatine kinase and CK-MB

Uric acid

References and further reading 29

1.

A fit 20-year-old

A 20-year-old man has sprained his ankle. While a nurse is applying a compression bandage, he asks when he should start having “heart checkups”.



KEY POINTS:

- Here is an ideal opportunity to discuss important lifestyle issues
- Formal cardiovascular risk assessment is indicated at 45 years, or 35 years if he has risk factors

STARTING CARDIOVASCULAR RISK ASSESSMENT

Although there is no evidence to support cardiovascular risk assessment for this man at his current age, he has shown interest and it is worthwhile addressing his concerns.

Asking about a family history of premature cardiovascular disease and checking his blood pressure are an ideal opportunity to discuss important lifestyle issues, such as smoking, diet and exercise.

The age for starting formal cardiovascular risk assessment was carefully considered by the New Zealand Guidelines Group (NZGG) committee. There is little data available on interpretation of risk factors at an early age. On the basis of expert opinion NZGG produced the recommendations in Table 1.

Table 1: NZGG recommendation for cardiovascular risk assessment (NZGG, 2003)

Population group	Age to commence testing	
	Men	Women
Asymptomatic people without known risk factors	45 years	55 years
Māori, Pacific peoples and people from the Indian subcontinent	35 years	45 years
People with cardiovascular risk factors (see below*) or at high risk of developing diabetes	35 years	45 years

***These people will have one or more of the following risk factors:**

- family history of premature cardiovascular disease in a first degree male relative (parent or sibling) under 55 years or female relative under 65 years
- family history of diabetes in a first-degree relative (parent or sibling)
- personal history of gestational diabetes
- personal history of polycystic ovary syndrome
- personal history of current or recent smoking
- prior blood pressure of more than 160/95 mmHg
- prior TC:HDL ratio of more than 7
- known impaired glucose tolerance (IGT) or impaired fasting glycaemia (IFG)
- obesity (BMI ≥ 30) or truncal obesity (waist circumference ≥ 100 cm in men or ≥ 90 cm in women)

INDICATIONS FOR TESTING EARLIER THAN NZGG RECOMMENDATIONS

Assessment of cardiovascular risk may be indicated at a younger age especially when family history of premature cardiovascular disease is suggestive of familial dyslipidaemia. Even if the family history does not quite reach the stated criteria for premature cardiovascular disease, clinicians will want to adopt a pragmatic approach to testing.

Assessment may also be indicated for those with obesity or features of the metabolic syndrome. Young men are infrequent attenders in primary care and it can be useful to take any opportunity to promote and reinforce the improvement of lifestyle factors associated with increased cardiovascular risk.

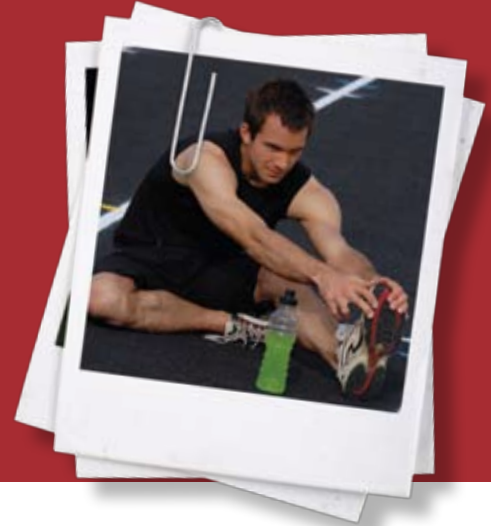
2.

A 29-year-old with abnormal lipids

A 29-year-old very fit man attends for a check up because his father has just had an MI at age 62 years. He has normal blood pressure and does not smoke. His fasting glucose was normal, his fasting lipids are:

Lipids Master Panel

Fasting status:	Fasting
Total cholesterol:	6.9 mmol/L (<4.0) H
Triglyceride:	1.1 mmol/L (<1.7)
HDL Cholesterol:	1.0 mmol/L (>1)
LDL Cholesterol:	5.4 mmol/L (<2.5) H
Total Chol/HDL Ratio:	6.9 (<4.5) H



KEY POINTS:

- This man's absolute risk of a cardiovascular event in the next ten years is very low despite his elevated lipids
- Lifestyle management is usually the best initial intervention for young people with elevated lipids

THIS IS A SIGNIFICANT ELEVATION OF LIPIDS

Confirmed total cholesterol of 6.9 mmol/L and LDL cholesterol of 5.4 mmol/L is a significant elevation for a man of this age, and the HDL is on the low side (especially for someone as fit as he is). Despite this, his absolute risk of a cardiovascular event in the next ten years is very low.

Although there is lack of evidence of benefit for cardiovascular risk assessment at this age the panel acknowledged that in this situation, when the patient requests the test, it would be difficult not to comply. Once the results are known, there is an obligation to follow up.

The MI in this man's father at the age 62 years, does not constitute premature cardiovascular disease according to Framingham, but it is certainly rather young and it would be appropriate to find out more about the young man's family history, especially any evidence of a lipid disorder. They are probably unlikely, but the cholesterol of 6.9 mmol/L, at age 29, would fit within the lower end of the range seen in heterozygous familial hypercholesterolaemia. Specialist assessment may be indicated, especially if the family history is suspicious.

Currently the best option is probably aggressive management of lifestyle issues such as diet, smoking and fitness. Focusing on lifestyle measures is more important at this age than drug therapy, the risks and costs of which are likely to outweigh the intangible benefits.

Lipids should be followed up 3–6 monthly until acceptable and thereafter annually.

STATINS WILL PROBABLY BE NEEDED IN THE FUTURE

For this patient, who is already very fit (presumably eats well and does not smoke) lifestyle advice may not make a significant difference to his lipid profile. It is probably worthwhile to let the patient know, that in view of his family history, medication will probably be required in the future.

Regular monitoring of his lipids is indicated to assess the effectiveness of lifestyle changes and the need for statins. However, it is difficult to know when to introduce statins as there is a lack of evidence about the benefits of statin use in younger age groups. The panel advises introducing a statin should the cholesterol reach 8 mmol/L, with corresponding increase in LDL. However, even at these high lipid levels, there is no evidence of benefit when absolute risk is low.

At levels lower than this, a decision will need to be made on a case-by-case basis. The panel would probably start this man on a statin at around 40 years old.

3.

Routine cardiovascular risk assessment

A 45-year-old man is recalled for his tetanus booster.

What cardiovascular risk assessment programme would you recommend at this time?



KEY POINTS:

- Attendance for tetanus booster at this age provides the ideal opportunity for cardiovascular risk assessment
- Risk assessment includes at least, diet, smoking status, family history, fasting lipids and glucose, blood pressure, weight and waist circumference

All men should have full cardiovascular risk assessment by the age of 45 years and women by the age of 55 years. This should include at the minimum, dietary patterns, smoking status, family history, fasting routine lipid profile and glucose, blood pressure, weight and waist circumference, with calculation of absolute risk. Any recommendation for additional laboratory tests would depend on the findings at the initial assessment.

The frequency of further CVD assessments recommended by NZGG is shown in Table 2.

Table 2. Frequency of further cardiovascular risk assessments (NZGG, 2003)

People with a 5-year cardiovascular risk under 5% should have a further cardiovascular risk assessment in 10 years.

People with a 5-year cardiovascular risk between 5 and 15% should have a further cardiovascular risk assessment in 5 years.

Annual cardiovascular risk assessments are recommended in people with:

- a 5-year cardiovascular risk greater than 15%
- diabetes
- people receiving treatment with lipid-modifying or blood pressure lowering medication.

People with diabetes or receiving medication or intensive lifestyle advice may need individual risk factor measurements taken more frequently, e.g. monitored 3 monthly until controlled, then every 6 months.

OTHER FACTORS ASSOCIATED WITH AN INCREASED CARDIOVASCULAR RISK

Alcohol consumption increases mortality across all ranges of consumption

Alcohol consumption is worth discussing as a lifestyle issue. It is often perceived that moderate alcohol use is protective, however studies have demonstrated an overall increase in total mortality as alcohol consumption increases across all ranges of intake. It is unwise to advise any patient to increase their alcohol consumption. To minimise the risks associated with alcohol, the following safe drinking guidelines have been developed by ALAC, Table 3.

Table 3: Safe alcohol guidelines (ALAC, 2002)

Drinking Occasion	Men	Women
If drinking every day, drink no more than:	3 standard drinks	2 standard drinks
On any one drinking occasion: drink no more than:	6 standard drinks	4 standard drinks
In any one week, drink no more than:	21 standard drinks	14 standard drinks

OTHER LABORATORY TESTS

Impaired renal function best indicated by decreased eGFR and is associated with increased cardiovascular risk. It will be considered by the NZGG for introduction into routine assessment.

Other laboratory tests (page 26) are under investigation internationally but there is no indication for their use in routine cardiovascular risk assessment in primary care

4.

Persistent adverse risk profile

A 55-year-old man's father died of an MI aged 46 years. He is taking an ACE inhibitor, beta-blocker, statins and aspirin. He is a smoker, overweight and his latest fasting lipids show:

Lipids Master Panel

Fasting status:	Fasting
Total cholesterol:	8.4 mmol/L (<4.0) H
Triglyceride:	3.6 mmol/L (<1.7) H
HDL Cholesterol:	0.87 mmol/L (>1) L
LDL Cholesterol:	5.9 mmol/L (<2.5) H
Total Chol/HDL Ratio:	9.7 (<4.5) H



KEY POINTS:

- This man is at extremely high risk of a cardiovascular event
- This lipid pattern in a patient on statins raises the suspicion of non adherence to therapy
- Aggressive management of lifestyle factors and adherence to medication are the priorities for this man
- Additional lipid lowering agents may be considered if these issues have been addressed and the lipid profile does not show a satisfactory response

EMPHASISE THE NEED FOR AGGRESSIVE LIFESTYLE MANAGEMENT AND ADHERENCE TO MEDICATION

This man is at extremely high risk of a cardiovascular event. His lipid profile suggests he is not taking his medication or following lifestyle advice. He needs to:

- stop smoking
- lose weight
- take his medications regularly

The challenge is to motivate him and support him to make these changes. Even if a 'stalemate' has been reached, regular visits with messages repeatedly given will influence some patients who are initially resistant. Referral to dietary services may help to reinforce some changes.

The high triglycerides combined with a low HDL may be quite refractory to drug intervention. Intensification of lipid modifying medication alone is seldom the answer and practitioners should resist simply adding more medication. However, if there is reasonable adherence to drug therapy, this may need intensification and consideration given to familial dyslipidaemia. Specialist referral may be useful.

There is no normal or ideal lipid level. When lipid levels are chosen as targets they should be individualised to each patient and the calculated risk.

LDL-C should be used as the primary indicator of optimum lipid management and used to monitor lipid-lowering treatment. HDL-C is a secondary indicator of optimum lipid management.

TC:HDL ratios are an artificial construct designed to simplify the calculation of cardiovascular risk by combining several results into a single number. Once they have been used to calculate the risk, they have no role in the monitoring of treatment.

NZGG recommend the optimum levels at Table 4. It may be impossible for some people to reach these optimal levels, and for them the simultaneous improvement of several risk factors, represents a better approach than the aggressive pursuit of further small reductions of LDL. However, the lower the LDL the better and it is likely that the NZGG will reduce the recommended levels, especially for secondary prevention.

Table 4: Optimal lipid levels (NZGG, 2003)

Lipid Fraction	Value
Total Cholesterol	<4 mmol/L
LDL Cholesterol	<2.5 mmol/L
HDL Cholesterol	>1 mmol/L
TC:HDL Ratio	<4.5
Triglycerides	<1.7 mmol/L

5.

The metabolic syndrome

A 45-year-old woman with truncal obesity and the metabolic syndrome is determined to do something about it, as her mother has recently had significant eye problems related to type-2 diabetes. The following results are available.

Glucose Tolerance Test: Dose: 75 g
 Fasting Glucose: 5.4 mmol/L (3.5–5.5 g)
 Glucose 2 hours: 9.5 mmol/L (3.0–7.7) **HH**

Lipids Master Panel
 Fasting status: FASTING
 Total Cholesterol: 6.5 mmol/L (<4.0) **H**
 Triglyceride: 2.6 mmol/L (<1.7) **H**
 HDL Cholesterol: 1.11 mmol/L (>1)
 LDL Cholesterol: 4.1 mmol/L (<2.5) **H**
 Total Chol/HDL ratio: 5.8 (<4.5) **H**



KEY POINTS:

- Best treatment for the metabolic syndrome is “weight loss, weight loss, weight loss”.

THE METABOLIC SYNDROME IS A CONFUSING DIAGNOSIS

The metabolic syndrome is a confusing entity because individuals can cluster different components and still be labelled the metabolic syndrome. See Table 5.

The hierarchy of importance in regards to risk of the variable components of the metabolic syndrome is likely to be the blood pressure being most important followed by the HDL. Waist measurement is a weak cardiovascular risk factor.

Table 5: A definition of metabolic syndrome (3 or more out of 5)

Risk Factor	Sex	Defining level
<i>Abdominal Obesity</i>	Men Women	≥100 cm waist circumference ≥90 cm waist circumference
<i>Triglycerides</i>		≥1.7 mmol/L
<i>HDL Cholesterol</i>	Men Women	<1.0 mmol/L <1.3 mmol/L
<i>Blood pressure</i>		SBP ≥130 or DBP ≥85
<i>Fasting glucose</i>		≥6.1 mmol/L

The Diabetes Prevention Programme (DPP) Trial determined the progression from IGT to type-2 diabetes. Aggressive lifestyle intervention reduced the incidence of progression by 58% and metformin combined with lifestyle advice reduced the incidence by 31% compared to a placebo group.

Aggressive lifestyle intervention included a 16 lesson curriculum encouraging patients to adopt a low-calorie, low-fat diet to achieve a 7% reduction in body weight and 150 minutes of moderate exercise per week.

(Knowler, 2002)

IMPAIRED GLUCOSE TOLERANCE

This 45-year-old woman does not have diabetes but is at high risk of developing it. The oral glucose tolerance test (OGTT) indicates impaired glucose tolerance, and this by itself confers an increased risk of macrovascular disease, that is almost as high as that of diabetes.

For this woman, cardiovascular risk should be determined on the basis of classical risk factors. Her calculated absolute risk at age 45 will probably still be under 10%, even after adjustment for the metabolic syndrome (around 2–3 fold relative increase) However, this is the type of patient in whom this may be an underestimate and her risk projected to age 60 is definitely high. Therefore, early intervention is essential, especially in this apparently motivated patient.

WEIGHT LOSS IS THE BEST MANAGEMENT FOR METABOLIC SYNDROME

The panel emphasised the most effective management for this patient is – “weight loss, weight loss, weight loss”.

There is strong evidence that weight loss significantly reduces the risk of progression to diabetes, although this may be difficult to achieve in routine clinical practice. Patients needs to understand that diet and lifestyle changes are the most effective way to prevent progression to diabetes, medication should not be viewed as an alternative pathway. The long term benefits of metformin use are not known.

Lipid intervention drugs should be a lower priority here and would not typically be used until the primary management of the metabolic syndrome (i.e. lifestyle) has reached the point of frustration.

FOLLOW UP TESTS

An annual OGTT is currently recommended for patients with this profile. There is no reason to recommend self monitoring of blood glucose or routine HbA1c.

There are no defined targets for lipids and blood pressure in IGT/metabolic syndrome but it is generally agreed that blood pressure targets should be the same as those for uncomplicated diabetes, Table 6 below.

There is no role for measurement of insulin.

For lipids the optimal levels (Table 4, page 12) recommended for primary prevention could be regarded as an actual target. At this stage, the panel would probably not recommend aspirin, although there is some non-evidence-based opinion that this would be a reasonable option, perhaps from age 50 as absolute risk is increasing.

Table 6: Target Blood pressure levels (NZGG, 2003)

	Systolic Blood Pressure	Diastolic Blood Pressure
People without clinical cardiovascular disease	<140 mm Hg*	<85 mm Hg*
People with diabetes or cardiovascular disease	<130 mm Hg*	<80 mm Hg*
People with diabetes and overt nephropathy, diabetes and microalbuminuria or diabetes with other renal disease	Aggressive blood pressure control is recommended	
*Where risk factor thresholds are given these should be interpreted as approximate guides to clinical practice only.		

A recent MI

A 52-year-old man has recently been discharged from hospital following acute MI. He is taking an ACE inhibitor, beta-blocker, statin and aspirin.

Lipids Master Panel

Fasting Status:	FASTING
Total Cholesterol:	8.4 mmol/L (<4.0) H
Triglyceride:	3.6 mmol/L (<1.7) H
HDL Cholesterol:	0.87 mmol/L (>1) L
LDL Cholesterol:	5.9 mmol/L (<2.5) H
Total Chol/HDL Ratio:	9.7 (<4.5) H

KEY POINTS:

- Lower this man's LDL as much as possible while maintaining his quality of life

CURRENT CVD RISK

This man has at least a 20% risk of a recurrent cardiovascular event over the next five years. Follow-up is essential to assess progress, reinforce messages and titrate medication as necessary.

Relative risk reductions that might be expected are about 50% from smoking cessation, 30% from optimal lipid reduction and 10–20% each with the use of beta-blocker and ACE inhibitor. Although medications will have been introduced prior to discharge from hospital, diet, lifestyle changes and exercise remain essential.

It is unnecessary to re-assess lipid levels more frequently than three-monthly, especially just after myocardial infarction when levels may be depressed anyway. Ongoing review of fasting lipids is recommended every three months until levels are controlled, then six monthly.

LIPID TARGETS

The targets for LDL cholesterol levels have been an area of debate, and are likely to be reconsidered by the NZGG. Many specialists would recommend LDL levels of <2.0 mmol/L for this man. However achieving very low LDL levels often requires high dose combination therapies.

Our panel supports the principle of lowering the LDL cholesterol as much as possible using multifactorial interventions, but cautioned against the addition of multiple drugs at detriment to the patient's quality of life. The largest benefit of statins is in the introduction of the drug. Increasing doses and adding other drugs produces incrementally smaller benefits. Once low levels have been achieved, more aggressive pharmacotherapy results in only small improvements in absolute risk, while increasing the likelihood of adverse effects.

Therapy needs to be individualised for each patient's unique circumstances. It may be better to focus on achieving a significant reduction rather than setting the patient's target at an unachievable low level.

7.

Gout and cardiovascular risk

A 35-year-old Māori male presents with acute gout.



KEY POINTS:

- See gout and think about cardiovascular risk
- Uric acid levels do not provide additional information in cardiovascular risk assessment

USE THE PRESENTATION FOR GOUT AS AN OPPORTUNITY FOR CARDIOVASCULAR RISK ASSESSMENT

Gout and hyperuricaemia are both associated with increased cardiovascular risk. This man should therefore have full cardiovascular risk assessment.

Cardiovascular risk assessment would be advocated anyway at the age of 35 years, based on ethnicity. His current presentation with gout has provided the opportunity.

URIC ACID NOT USEFUL IN ROUTINE CARDIOVASCULAR RISK ASSESSMENT

Although uric acid appears to be a weak risk marker for CVD, it is not strong enough to provide information additional to conventional risk factors in formal risk calculation.

Troponin in atypical chest pain



A 64-year-old man has atypical chest pain you think might be angina.

KEY POINTS:

- Troponin is not indicated for an acute presentation of possible MI in primary care
- The best use of troponin in primary care is to exclude MI in someone who presents a day or two after atypical chest pain

NO ROLE FOR TROPONIN TESTING IN SUSPECTED ACUTE MI PRIMARY CARE

There is almost no use for troponin in an acute presentation of possible MI in primary care. Measurements of troponin are likely to be negative immediately after acute MI and a repeat test is needed after 8–10 hours. A single early negative test is therefore, not particularly useful. If an acute MI is suspected the patient should be in hospital.

TROPONIN USEFUL FOR DELAYED PRESENTATION OF ATYPICAL CHEST PAIN

The best use of troponin in primary care is for the patient who presents a day or two after atypical chest pain (e.g. the Monday morning consult) when acute treatment may not be so much of an issue. If there has been MI, troponin is likely to remain elevated, unlike other more transient markers, for up to ten days. Therefore it is useful for both rule in and rule out of MI in this context.

Even when presentation is delayed but there has been prolonged chest pain raising suspicion of MI, referral for admission should not be delayed by waiting for a result.

Survey of admitted patients

A member of the panel had been involved in a survey of admitted patients with diagnosed MI. The survey revealed some patients had delayed admission to hospital because their GP (sometimes on the advice of a medical registrar) had awaited troponin results. However, a survey and audit showed that GPs do have to triage a large number of patients with chest pains who do not have coronary disease, so there are matters that call for fine judgement.

Overall GPs demonstrated a good knowledge of the use of troponin. They were generally aware of false negatives, (especially due to the test being done too early) but nevertheless a number of tests were done within ten hours of the onset of pain, that were not repeated.

TROPONIN HAS NO ROLE IN ASYMPTOMATIC PATIENTS

There was strong agreement among the panel that there is no indication for undertaking troponin testing in asymptomatic patients. Troponin testing should be confined to individuals in whom a cardiac event is suspected. The panel have noticed the increasing frequency of troponin use for screening. This is inappropriate outside of research projects.

INTERPRETATION OF TROPONIN

A positive result for troponin, whether with the laboratory test or the point-of-care test, is always significant indicating myocardial damage and, in the appropriate clinical setting, is strongly predictive of MI even if there are no ECG changes.

A negative result for troponin is an appropriate rule out test for MI, if the initial symptoms were more than nine hours ago. A laboratory method is best used, because some point-of-care methods for troponin testing, are not sufficiently sensitive to rule out MI.

OTHER CAUSES OF RAISED TROPONIN LEVEL

Occasionally troponin is raised by pathological processes other than myocardial ischaemia leading to MI. These include severe heart failure, pulmonary embolism, myocarditis, pericarditis, cardiomyopathy and any other cause of damage to cardiac muscle. Troponin elevations are also common in people with end-stage renal disease, but the clinical interpretation of these results remains unclear.

According to the current definitions, troponin is not raised by angina, even unstable angina. Any elevation of troponin, in the clinical setting of a definite acute coronary syndrome, indicates MI.

BNP in suspected heart failure



You suspect a 60-year-old man with COPD is getting episodes of left heart failure at night.

KEY POINTS:

- Heart failure is unlikely with a normal ECG
- BNP is useful if the ECG shows abnormalities

This clinical scenario is relatively common and often difficult to sort out, because for some people, respiratory and cardiac causes of their breathlessness can be very difficult to distinguish clinically. A chest X-ray done once the symptoms have resolved is often not helpful. Although it is still an important investigation at some point for this patient.

An ECG is unlikely to be normal in the presence of heart failure but abnormalities do not confirm the diagnosis. When the ECG is abnormal, BNP testing offers a potentially useful way of excluding heart failure.

It is recommended that either BNP or ECG be used as part of the diagnostic workup of individuals with suspected chronic heart failure. In most cases the choice will be made based on the relative availability of each test.

Completely normal BNP values are a good rule out test of heart failure. High levels, above a certain cut off points, strongly indicate heart failure, although mixed aetiologies are common. Results between the high and low cut off points are not diagnostically useful.

Measurement of BNP could play a useful role in the patient described but is not yet uniformly available throughout the country.

10.

Laboratory testing for newly diagnosed hypertension

A 42-year-old man has just been found to have a persistent significantly raised blood pressure. He considers himself a fit and healthy non-smoker and no other abnormalities were found during the examination.



KEY POINTS:

- Recommendations for routine testing are made
- Secondary hypertension should be considered in those with severe hypertension resistant to treatment

Cardiovascular risk increases with elevation in blood pressure. Lowering the blood pressure reduces the risk. However, blood pressure is not managed in isolation and other cardiovascular risk factors also need to be addressed.

History, examination and initial laboratory investigations (Table 7) aim to assess overall cardiovascular risk, determine if there is already end-organ damage and alert the clinician to the possibility that this may be a secondary hypertension.

“Tip: always check leg pulses – it’s very embarrassing for an aortic coarctation to be diagnosed after months of frustratingly ineffective treatment.” (Mann, 2007)

Table 7: Recommended laboratory investigations for high blood pressure (Mann, 2007)

Fasting glucose Fasting lipids	Directed at establishing overall cardiovascular risk
Creatinine and derived eGFR urinalysis, possibly including microalbuminuria	Helps determine if there has been renal target organ damage requiring a more aggressive approach to therapy
Potassium	A low potassium level should trigger a search for some causes of secondary hypertension (e.g. hyperaldosteronism, Cushing's Syndrome, some renal pathologies) and it is also important to establish the baseline level of potassium before administering diuretics
Blood count	A blood count may be useful in identifying any co-morbidities

Blood pressure should be treated with lifestyle and drugs in order to achieve systolic values under 140 mm Hg and lower if possible. When cardiovascular risk is high due to other factors such as diabetes or smoking, the blood pressure will need to be managed more aggressively. See Table 8.

Table 8: Target blood pressure levels (NZGG, 2003)

	Systolic Blood Pressure	Diastolic Blood Pressure
People without clinical cardiovascular disease	<140 mm Hg*	<85 mm Hg*
People with diabetes or cardiovascular disease	<130 mm Hg*	<80 mm Hg*
People with diabetes and overt nephropathy, diabetes and microalbuminuria or diabetes with other renal disease	Aggressive blood pressure control is recommended	
*Where risk factor thresholds are given these should be interpreted as approximate guides to clinical practice only.		

SECONDARY CAUSES

For the younger patient (<45 years) with severe hypertension or the patient highly resistant to simple therapy, further tests for a cause of secondary hypertension can be considered, even if potassium levels are normal. These include blood levels of renin, aldosterone and cortisol, 24-hour urine collection for catecholamines, renal/adrenal ultrasound and computed tomography or magnetic resonance angiography of the renal arteries to look for stenosis.

11.

Cardiovascular screening in the elderly

A fit and healthy 78-year-old woman has recently moved to town. Her son brings her to you for a checkup.



KEY POINTS:

- Preventative treatments may alter the causes of morbidity or mortality but not reduce them
- Identify factors which may affect quality or quantity of life

There are limited data from clinical trials about lipid modification in older subjects and our experts had mixed opinions of how to best manage this woman. On the one hand a woman of this age has increased short-medium term cardiovascular risk, and therefore greater capacity to benefit. On the other hand she has a shorter life expectancy and therefore a reduced long-term capacity to benefit.

Using evidence from younger populations and extrapolating them to the elderly has resulted in the use of statins for risk reduction in the elderly population. The PROSPER trial, however, looked at the use of statins by elderly people and followed 5000 participants aged

between 70–82 years for an average of 3.2 years. There was a clear, but small effect on the absolute risk of cardiovascular disease, but no change in the mortality or morbidity from all causes. Statin use merely shifted the cause of morbidity and mortality. The matter is still not resolved.

Our panel's approach to the woman in our scenario would be to identify any significant co-morbidities that would limit quality or likely quantity of life. This would include: detecting and treating undiagnosed diabetes, managing hypertension if present, looking for occult malignancies, anaemia and a wide range of other conditions. Other important issues would be looking at mobility and risk of falls.

Investigation would generally be targeted at risk areas identified from the history and examination.

“Single disease models should not be applied to preventive treatments in elderly people. Preventive use of statins shows no overall benefit in elderly people as cardiovascular mortality and morbidity are replaced by cancer. Preventive treatments in elderly people may select cause of death without the patient's informed consent.”
(Mangin 2007)

Polycystic ovary syndrome (PCOS)

A 30-year-old woman has just been diagnosed with PCOS



KEY POINTS:

- This woman has increased risk of metabolic syndrome, IFG, IGT and type-2 diabetes
- It is reasonable to check fasting glucose and lipids

It would be interesting to know on what basis PCOS was diagnosed, as this, by itself, is a controversial area.

For this discussion the panel assumed the diagnosis of PCOS was correct and addressed the question of whether there is increased cardiovascular risk. Issues related to fertility were not discussed except where they overlapped with risk assessment. The patient may be more concerned about her body weight and hirsutism than anything else and these concerns need careful management.

The phenotypic expression of PCOS is variable but there is no doubt that most subjects have insulin resistance. Although about half of all women with PCOS are obese, there is evidence that some degree of insulin resistance is present independent of obesity. Routine assessment of insulin resistance in PCOS is however, not recommended, as the magnitude does not predict clinical response (Samaras, 2006).

PCOS AND CARDIOVASCULAR RISK

Women with PCOS have increased risk of metabolic syndrome, IFG, IGT and type 2 diabetes. It is therefore reasonable to check fasting glucose and to follow up with an OGTT if this falls in the range of 5.5–6.9 mmol/l. Some recommend that fasting glucose be repeated on an annual basis.

It is not clear if there is a characteristic dyslipidaemia associated with PCOS, but some women do have low HDL cholesterol and raised triglycerides and increases in LDL cholesterol are also common. It is reasonable to measure a lipid profile.

Despite the high prevalence of obesity, insulin resistance, IFG, IGT and dyslipidaemia together with possibly raised androgens and overall high frequency of metabolic syndrome, all of which might predispose to increased cardiovascular risk, the actual data on increased risk are not convincing.

Whatever the case, some of the treatments relevant to improving the endocrinopathy of PCOS and improving fertility, are relevant to reducing risk of type 2 diabetes and cardiovascular risk. These include weight loss, exercise and possibly the use of metformin. For those who are found to have type 2 diabetes or IGT the management is the same as for non-PCOS patients with these disorders.

Appendix

Investigations which are currently not indicated in the routine assessment of cardiovascular risk

Homocysteine

The panel agreed there are no routine indications for measurement of homocysteine as part of a cardiovascular risk assessment.

There has been an epidemiological association of raised homocysteine with increased risk of cardiovascular event, but this is not as strong as was first thought. Although interpretation of data is complex and controversial, intervention trials of folate have not shown significant benefit, and in fact there was some evidence of harm. At the present state of knowledge, measurement of homocysteine should be abandoned.

HsCRP

The panel felt there is no indication to measure HsCRP as part of routine clinical practice. While it was noted there have been some epidemiological associations of raised HsCRP with cardiovascular risk, these studies have proved to be problematic when applied to individual patients.

There are issues relating to biological variation, to such an extent that it is not possible to accurately classify an individual into the risk groups shown in the epidemiology.

The American Heart Association (AHA) has stated the evidence and opinion on the use of HsCRP is conflicting. They state the general use of HsCRP is not recommended, the test may have a role as a 'tiebreaker' in patients with intermediate ten year risk, and may, at the discretion of the physician, help direct further evaluation.

At the current state of the art, HsCRP has no use in routine primary care.

Troponin

Troponin has no role as a risk marker for general CVD risk assessment in primary care. It is purely a useful tool for identifying myocardial infarction in a patient with suspicious symptoms.

The panel expressed concern at the growing use in primary care of troponin as a 'screening' test. They have noted in their own practices that some GPs are requesting troponin checks several weeks or even several months in advance. There is no rationale or logic for this and the practice should be strongly discouraged. There is some obvious confusion around this point. While troponin does have prognostic value but this is only in the context of an acute event.

Lipoprotein (a)

Lipoprotein (a) should not be used in routine assessment of cardiovascular risk.

There is inconsistent clinical evidence regarding the interpretation of lipoprotein (a) and furthermore there are no useful interventions once the level is measured. The panel felt in many cases measurement of lipoprotein (a) in a person with a vascular event, but no other risk factors is done, only to satisfy curiosity.

Lipoprotein (a) should remain as a specialist test.

Apolipoprotein A1 and Apolipoprotein B

There is evidence that the ratio of ApoB/ApoA1 is a risk factor for cardiovascular disease that may eventually be a more suitable target for lipid lowering therapy than LDL cholesterol, although all studies do not agree. Currently there is no risk equation which allows these apolipoproteins to be included in the calculation of absolute risk, and the cut off values that have been published differ from study to study. Additionally the tests are not widely available through community laboratories in New Zealand.

At this stage, the measurements cannot be recommended for routine use in primary care.

BNP

The best established use for BNP is as a **rule out** test for heart failure in patients with difficult to diagnose shortness of breath. Despite the relatively high cost of the test this is regarded as a cost effective use, especially as it may aid in the decision as to whether to refer for cardiological assessment or echocardiography.

In routine practice BNP should not be used in 'screening' for early heart failure in asymptomatic patients, nor is it recommended for titrating therapy in primary care for established heart failure. It may occasionally be helpful in some difficult to manage patients.

The use of the test to **rule in** heart failure is problematic. There are a wide range of results which are indeterminate and results lack sensitivity. In the elderly and in those with impaired renal function, the cut off points may be higher than those usually reported as indicating definite heart failure.

Insulin

The panel agree there is no place for routine use of insulin measurement in cardiovascular risk assessment.

There appears to be some interest in measurement of insulin levels for measurement of sensitivity or resistance but this does not add significantly to risk assessment or management in any evidence-based way.

Measurements of insulin or the insulin glucose ratio are poor markers for insulin resistance. Assays are poorly standardised internationally and the cut off points that might indicate insulin resistance are not established for routine practice.

The relevant information is best obtained through conventional assessment of the presence of the metabolic syndrome with clinical markers, fasting glucose and lipid profile. If fasting glucose falls in the range 5.5-6.9 then an OGTT is indicated.

Creatine Kinase (CK) and CK-MB

These are obsolete as markers of cardiac damage. All international guidelines recommend troponin, either T or I, as the preferred test. Both CK and CK-MB are of limited value in diagnosing myocardial damage.

CK or CK-MB may infrequently be used to register possible recurrent damage as levels drop rapidly after the initial cardiac event (unlike troponin).

CK is useful to identify serious muscle inflammation which occurs rarely with statin therapy. If people using statins express muscle discomfort, CK should be measured. Studies have shown routine surveillance of CK (or LFTs) for people on statins to be of no benefit.

Uric acid

While uric acid appears to be a weak risk marker for CVD it is not strong enough to feature in a formal risk calculation. Uric acid may be worth noting but is not recommended as part of a routine cardiovascular assessment. Whether or not uric acid becomes an independent marker of risk of cardiovascular disease remains controversial.

References and further reading

NZGG, *The Assessment and Management of Cardiovascular Risk*, December 2003
Available from: <http://snipurl.com/1qzct> (accessed 19 October 2007).

Policy: *Upper Limits for Responsible Drinking*. Last Updated 7 August 2002 Alcohol Advisory Council of New Zealand Policy Statement 6. Available from: <http://snipurl.com/1qzcx> (accessed 19 October 2007).

Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the Incidence of Type-2 Diabetes with Lifestyle Intervention or Metformin. *N Engl J Med* 2002;346(6):393-403.

Khan NA, Hemmelgarn BR, Tonelli M, et al. Prognostic Value of Troponin T and I Among Asymptomatic Patients With End-Stage Renal Disease. *Circulation*. 2005;112:3088-3096.

Mann S. Hypertension update. Recommended Investigations for Investigating High Blood Pressure. *NZ Fam Physician* 2007;34:270-273.

Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in Elderly Individuals at Risk of Vascular Disease (PROSPER): a randomised controlled trial. *Lancet* 2002;360:1623-30.

Samaras K, McElduff A, Twigg SM, et al. Insulin Levels in Insulin Resistance: Phantom of the Metabolic Opera? — *Med J Aust* 2006;185(3):159-161.

Lloyd-Jones DM, Liu K, Tian L, et al. *Ann Intern Med*. 2006;145:35-42. Narrative Review: Assessment of C-Reactive Protein in Risk Prediction for Cardiovascular Disease.

Mangin D, Sweeney K, Heath I. Preventive Health Care in Elderly People Needs Rethinking. *BMJ* 2007;335(7614):285-7.



www.bpac.org.nz