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Testing for CVD, diabetes and renal disease in elderly people

As people age and their co-morbidities and medicine use increases, decisions about medical management change. There is limited evidence of benefit of some tests in older people, such as monitoring lipid levels for primary prevention of cardiovascular disease, and many tests become more difficult to interpret due to the effects of medicines and declining general health. Decisions about testing must be made on an individual patient basis, taking into consideration their "drugs, diseases and disabilities". In the following article we present some general concepts for consideration, along with some recommendations for testing (or not).

Does age affect laboratory testing?

Laboratory reference ranges are usually derived from populations of younger people, without significant illness or disability. As people get older, test results are less likely to lie within reference range values. This is due to the effect of co-morbidities and polypharmacy, which tend to increase in older people, as well as physiological changes associated with ageing.[1]

In the Sydney Older Person's Study, researchers measured a range of haematological and biochemical values in a sample of more than 300 people aged over 75 years living in the community. It was found that the distribution of test results fell outside of the established laboratory reference range in 31 of the 35 variables measured.[1] There were significant correlations between test results and number of medicines, total disability score and number of co-morbidities. Researchers concluded that rather than age alone, it is the presence of medical conditions, and the associated disability and need for medicines, which accounts for abnormal test results.[1]

These findings suggest that;

- Chronological age alone should not guide decisions on testing or interpretation of results
- A patient's "drugs, diseases and disabilities" should be taken into account when considering testing and interpreting results
- Decisions about testing will change with time – as life expectancy decreases and elderly people become frailer, their wishes may change, along with the management of their conditions

Cardiovascular risk assessment: is there an age when this should stop?

The incidence of cardiovascular disease increases with age and it is the leading cause of mortality in New Zealand, particularly among Māori and Pacific peoples.[2] There is clear guidance on when to begin regular CVD risk assessment, based on evidence that this can lead to a significant reduction in morbidity and mortality,[3] however, when to stop risk assessment is less clear.

At a population level, risk tables based on the Framingham equation are calculated to age 74 years and PHO Performance Programme incentives for CVD risk assessment include patients aged up to 74 years. At the individual patient level, risk can continue to be assessed beyond age 75 years, calculated using the risk associated with the age 65 – 74 years bracket.[3] However, some studies have cast doubt that Framingham risk factors can predict cardiovascular morbidity in an older population the same way as they do in younger adults,[4] and the evidence that interventions improve mortality in this age group is also less clear (see below).

This suggests that the decision when to stop CVD risk assessment should be made on an individual basis, after consideration of;

- The patient's "drugs, diseases and disabilities", e.g. CVD risk assessment may become less important in a patient with a terminal illness or advanced dementia
- A conversation with the patient about their own expectations and wishes (and for some patients, those of their family, caregiver or person with power of attorney)

Lipid testing becomes less useful with advancing age

Lipid levels naturally increase, until approximately age 65 years, when they begin to decline again in most people.[5] Repeated lipid testing in people aged over 65 years, with normal baseline lipid levels, is therefore considered to be of limited value.[6] As there is no clear optimal level of cholesterol in people aged over 80 years,[7] continued lipid testing at this age is less likely to be clinically relevant. A low lipid level in elderly people may actually be an indicator of poor nutritional status or occult disease and reflect an increased risk of underlying morbidity and mortality.[8]

The following points may help guide the use of lipid tests in elderly people;

- Continued lipid testing in older people with normal baseline lipid levels is generally unnecessary
- The clinical relevance of lipid levels in a very elderly person is unclear and generally a statin would not be initiated in this patient group
- There is a role for follow-up lipid testing in older people who are being treated with a statin for secondary prevention, but after goal lipid levels are reached, testing could be requested at a reduced frequency (e.g. every three years)[9,10]

The evidence for statin use in elderly people

The evidence of the effect of lipid levels on cardiovascular mortality in older people is uncertain and varies within this age group. There is evidence of benefit from lipid-lowering treatment in "young elderly people", however, the evidence of benefit for the "very elderly" group (age ≥ 80 years) tends to be sparse and contradictory and also varies depending on whether a statin is prescribed for primary or secondary prevention.

The majority of randomised controlled trials have found no evidence that lipid-lowering treatment using statins for primary prevention in people aged over 80 years reduces total mortality.[7] Some studies have shown that in elderly people all-cause mortality is highest when total cholesterol is lowest (<5.5 mmol/L).[7, 11]

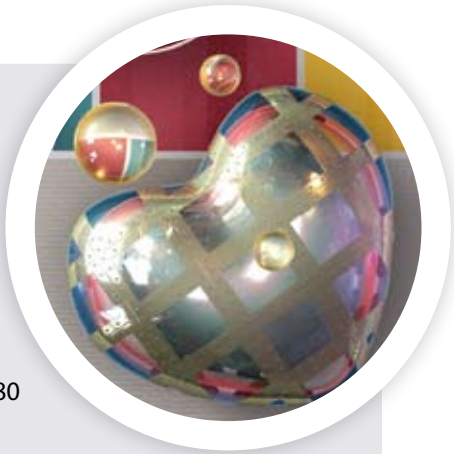
There is good evidence that lipid lowering treatment, when used for secondary prevention in people with established cardiovascular disease, reduces all-cause mortality and the incidence of cardiovascular events (including stroke). Although the majority of studies have specifically excluded older people, subgroup analyses of the trials that did include limited numbers of elderly participants, suggest similar benefits apply to people in older age groups.[12, 13]

In general the evidence from primary and secondary prevention trials suggests that;

- There is a role for the use of lipid-lowering treatment in elderly people for secondary prevention, particularly those at high cardiovascular risk
- The evidence for the use of lipid-lowering treatment in elderly people for primary prevention is more limited and should be based on individual clinical judgement. The age of the patient alone is not sufficient to determine whether or not a statin should be prescribed.

Testing for diabetes is beneficial at any age

The morbidity associated with type 2 diabetes is well-established, therefore testing for diabetes in a symptomatic person of any age is beneficial. There is strong evidence for beginning screening for type 2 diabetes in younger adults to reduce the long-term burden of micro- and macrovascular complications. However, whether the



Lipid testing in New Zealand

The rate of lipid testing in New Zealand is considerably higher in older people compared to younger age groups (Figure 1). The highest rate of lipid testing is in the age 70 to 74 year bracket, with 56% of all enrolled patients aged 70 to 74 receiving at least one lipid test in the year from September 2010 to September 2011. Testing volumes after this age remain high – almost half of all patients aged 80 to 84 years and one-third of those aged 85 to 90 years had a lipid test in this time period, with many patients receiving multiple tests. Repeated lipid testing in older people taking statins for primary prevention is not indicated and there is little evidence for the use of statins for primary prevention in people aged over 80 years.

The rate of lipid testing increases with age as more people are prescribed statins. However, it is important to review this rate of testing and consider whether this is still appropriate. Clinicians should justify why they are testing and whether it is beneficial to the patient.

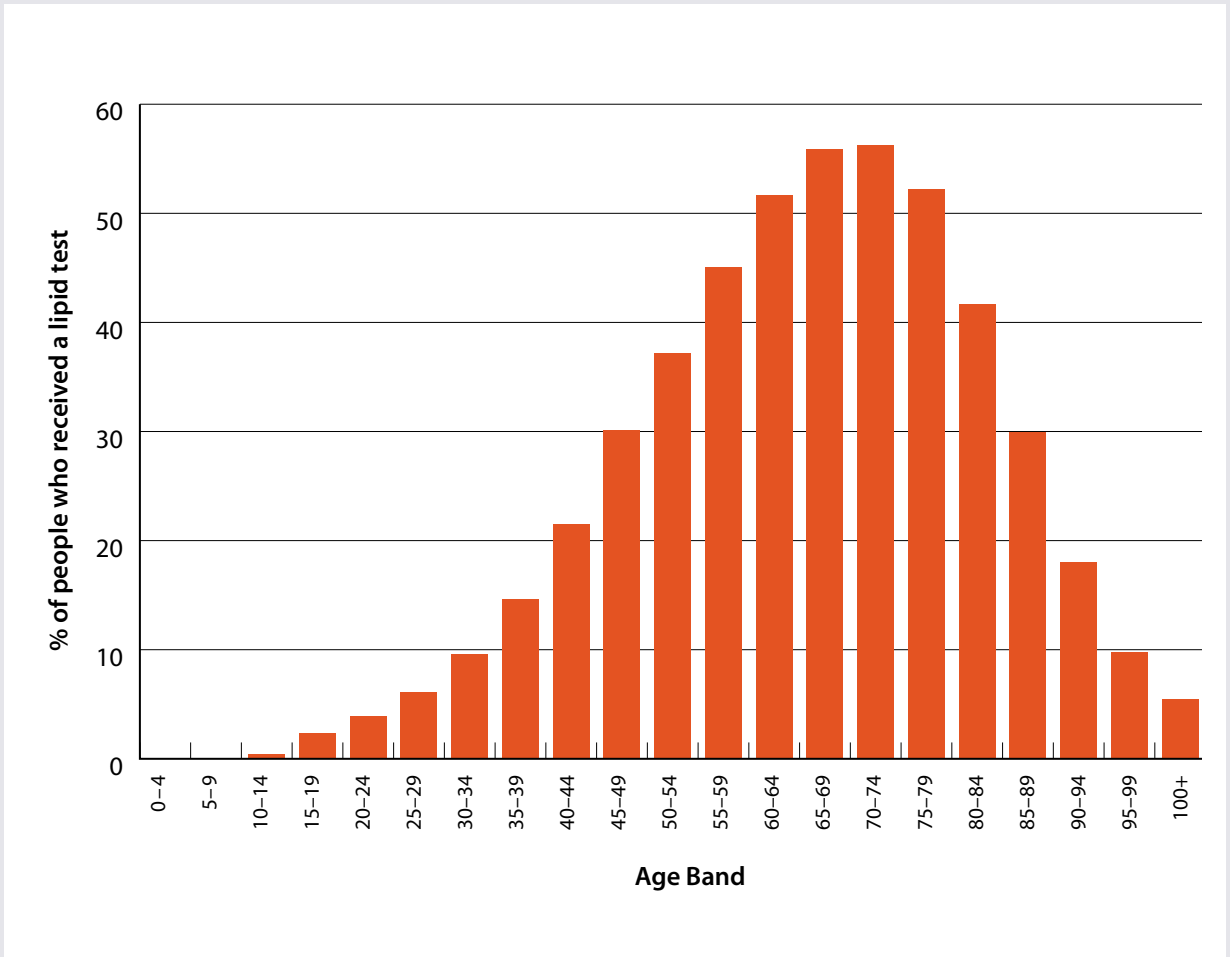


Figure 1. Percentage of people who received a lipid test from September, 2010, to September 2011, by age of enrolled population (Laboratory Data Warehouse)

detection of asymptomatic diabetes in very elderly people is beneficial in reducing morbidity and mortality is less clear.

The preferred test for diagnosing diabetes in New Zealand is HbA_{1c}. This is a useful test in elderly people as it provides a convenient (non-fasting) means of identifying clinically significant chronic glucose elevation, as well as guiding the need for intervention. Fasting may be difficult in frail elderly people and a random glucose result, unless clearly high, is often unhelpful.

The HbA_{1c} reference interval is not age adjusted, although there is some evidence from population studies that HbA_{1c} levels increase slightly with age, even in elderly people with normal glucose tolerance.[14, 15] Insulin sensitivity also slowly declines with age in many patients. While the same threshold for diagnosis of diabetes ($HbA_{1c} \geq 50$ mmol/mol) is currently applied to all patients, the benefits versus risks of intervening in elderly people, especially if they have a modest degree of glucose intolerance, are less well established.[16] It is recommended that borderline HbA_{1c} results are followed-up by a second HbA_{1c} test after several months of lifestyle modification.[16]

HbA_{1c} is also used for monitoring glycaemic control and predicting risk of future complications in people with diabetes.

In summary;

- The best test for the detection of diabetes in people of all ages is HbA_{1c}
- In elderly people with borderline HbA_{1c} results, repeat HbA_{1c} several months after giving advice on lifestyle modifications
- In elderly people with modest glucose intolerance, consider the risks and benefits of treatment interventions
- In elderly people with diabetes, HbA_{1c} should be checked at least annually, however, testing should not be requested more frequently in people with stable, well-controlled diabetes
- Glycaemic control targets should be individualised, with the aim of deciding on a realistic goal that reduces long-term risk. In most adults, the target HbA_{1c} is 50 – 55 mmol/mol.[17] This target may be less stringent in older adults, as "drugs, diseases and disability" are taken into account. Older people also have an increased risk of hypoglycaemia and adverse effects from diabetes medicines, therefore maintaining strict control may not be the best management option.[15]

Testing renal function in elderly people

Renal function often deteriorates in older people due to co-morbidities, especially hypertension and diabetes, and medicine use. Renal function is most commonly measured by estimated glomerular filtration rate (eGFR), calculated with the Modification of Diet in Renal Disease (MDRD) equation, which is automatically reported by New Zealand laboratories when a serum creatinine is requested. However, eGFR becomes more difficult to estimate and interpret in elderly people. The MDRD calculation is based on a standard adult BMI, therefore is less accurate in frail, elderly people with a BMI < 18.5 kg/m^2 (or those with a BMI > 30 kg/m^2). In addition, the formula was derived in people aged under 75 years and has not been validated for all ethnic groups. It is also thought that co-morbidities, particularly inflammation, have a confounding affect on eGFR.[18]

An alternative method for estimating GFR is to calculate creatinine clearance, using the Cockcroft-Gault equation, which includes serum creatinine, age and also weight. Although the equation does incorporate body weight, it does not account specifically for muscle mass, and is therefore also potentially inaccurate in people who are very frail or oedematous. Calculated creatinine clearance is preferable when titrating medicine doses in elderly people, using standard drug dosing charts.

Serum creatinine alone is not a useful marker of renal dysfunction as levels can remain in the normal range until there is a significant decrease in kidney function, especially in elderly people.[19]

Chronic kidney disease

Age-associated diseases, such as cardiovascular disease and diabetes, are significant risk factors for chronic kidney disease (CKD). The prevalence of CKD in people aged over 64 years is estimated to be between 23% to 36%.[19] CKD is increasingly prevalent in older females, compared to males, although the reason for this is not completely understood.[20] CKD is also more prevalent in people of Māori, Pacific or Asian ethnicity.[21, 22]

Risk factors for CKD include:[20]

- Diabetes
- Hypertension
- Cardiovascular disease
- Other renal disease or abnormality, including persistent proteinuria or haematuria
- Family history of CKD or other renal disease
- Long-term use of potentially nephrotoxic medicines, e.g. NSAIDs, ACE inhibitors, diuretics, aminoglycosides, lithium

People with any of the above risk factors should be considered for annual assessment and testing for CKD.[20]

The risk of CKD is assessed by investigating the **eGFR** level.

- CKD guidelines state that if eGFR is < 60 mL/min/1.73m^2 or there is a strong suspicion of CKD despite a value greater than this, further assessment for signs of kidney damage should be performed.[20]

The threshold for further investigations for CKD must be determined by clinical judgement in older people, taking into consideration their co-morbidities and medicine use.

- In people aged > 70 years, eGFR values between 45 and 59 mL/min/1.73m^2 should be interpreted with caution. If there are no other signs of kidney damage and eGFR levels are stable over time, then CKD is less likely.[23]

The **rate of decline of eGFR** may be more useful than the actual value in older people, e.g. a decline of >15% in eGFR over three months, regardless of baseline value, would prompt investigation for CKD or other causes.[23]

- An initial result of a decreased eGFR level should be repeated within two weeks to assess the rate of change:[24]
  - If stable, test should be repeated after 90 days
  - If decreasing, two further repeat tests should be requested within 90 days

If eGFR results indicate the possibility of CKD, assess for proteinuria and haematuria. Studies suggest, however, that many older people with CKD will have negative urinalysis or low-grade proteinuria only.[25]

Proteinuria can be assessed by quantifying the urinary albumin:creatinine ratio (ACR). Protein:creatinine ratio (PCR) may also be used, but the ACR is superior for detecting low levels of proteinuria,[20] which is especially important in patients with diabetes.[20] Abnormal ACR results should be repeated with an early morning urine sample, if not previously obtained.[20]

- In people with diabetes, ACR > 2.5 mg/mmol in males and > 3.5 mg/mmol in females indicates microalbuminuria
- In people without diabetes, ACR ≥ 30 mg/mmol indicates clinically significant proteinuria

Urine protein excretion has significant biological variation and persistence should be verified with at least two abnormal results from three separate specimens.[24]

Haematuria can be assessed using a urine "dipstick".[20] If assessing for haematuria in relation to CKD only, no laboratory confirmation is required.[20] However, further investigation for the cause of persistent haematuria is required in elderly people, e.g. to investigate urinary tract malignancy.

There is no specific recommendation on when to stop testing for CKD. Interventions that slow the progression of CKD, such as blood pressure management, are just as beneficial in older people as in younger people.[26]

Resources are available online and via electronic decision support tools such as *bestpractice* to aid in the assessment of eGFR and its decline.

Diabetic nephropathy

Diabetes is associated with an increased risk of renal complications and disease,[17] and this risk increases with the duration of diabetes. Diabetic nephropathy is one of the most common forms of chronic kidney failure in the developed world and occurs in more than 30% of people with diabetes.[27] Diabetic nephropathy generally takes six to 15 years to develop, therefore it is more prevalent in

older people that have a long history of diabetes, however, 5 – 10% of people will have clinical nephropathy at the time of diabetes diagnosis.[27]

Microalbuminuria is the first clinical sign of nephropathy, but not all people with microalbuminuria will progress to full nephropathy. If detected early, microalbuminuria can be reversible with good glycaemic control and management of blood pressure.

The recommended test for microalbuminuria is an albumin:creatinine ratio (ACR), using an early morning urine sample (or a random sample if this is not possible).

- ACR should be tested at least once per year in people with diabetes without previous microalbuminuria.[17]
- An elevated ratio (i.e. > 2.5 mg/mmol in males or > 3.5 mg/mmol in females) should be confirmed with two repeat tests within three to six months, with a diagnosis of microalbuminuria made if at least two of the three samples are elevated.

The specificity of ACR decreases with age, so the likelihood of predicting nephropathy in older people becomes less robust.[28] However, regular monitoring of ACR is important in people with diabetes, regardless of their age.

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