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Hazardous Drinking
Mercury Toxicity
INR Monitoring
Quiz Feedback: Men's and Women's Health

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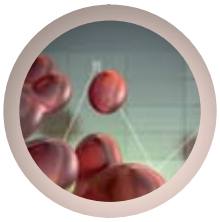

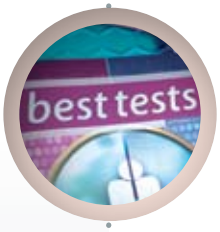

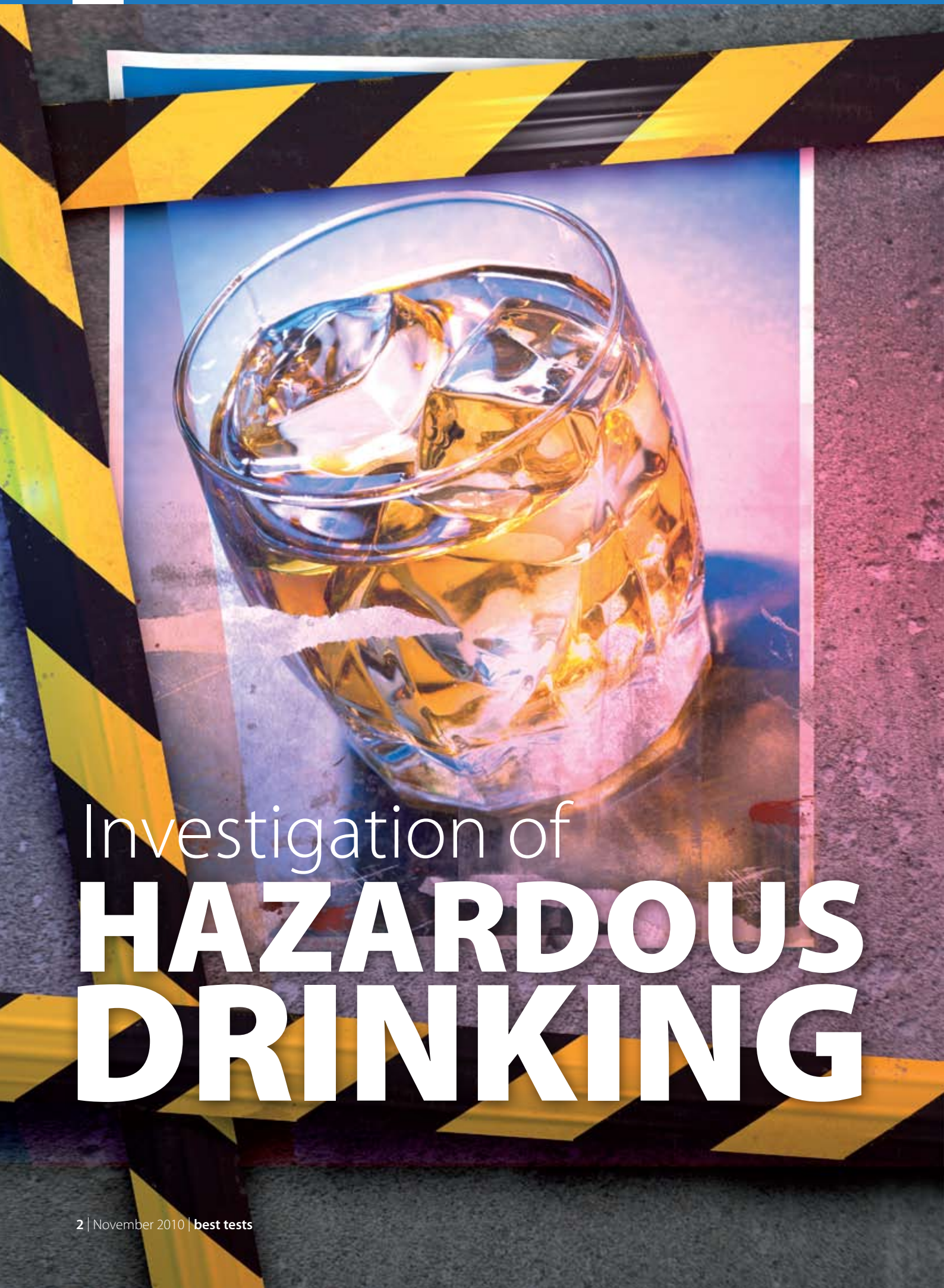

Investigation of HAZARDOUS DRINKING

Key concepts:

- Approximately 20–25% of New Zealanders consume alcohol at a harmful or hazardous level
- In approximately three-quarters of patients presenting to general practice with alcohol related problems, the problems are not detected
- A questionnaire, such as AUDIT, should be used when screening patients for hazardous drinking
- Laboratory tests are not recommended for the routine screening of hazardous drinking in primary care

Alcohol consumption is an established part of New Zealand culture, with 80% of all adults over the age of 18 years, identifying themselves as current drinkers.[1] It has been estimated that 20–25% of New Zealanders consume alcohol at a harmful or hazardous level.[2,3] However, the harms associated with alcohol are not just confined to the heaviest drinkers. Research from Finland identified that the majority of alcohol related problems in people who drank were seen in the 90% that consumed alcohol moderately, compared to the 10% that drank heavily.[4] It is likely that the majority of people seen in general practice in New Zealand, with alcohol-related problems, are non-dependent drinkers.

Binge drinking is frequently identified as a problem in New Zealand, but is difficult to quantify as the definitions of "heavy drinking" or "binge drinking" vary considerably.[5] While the official definition of binge drinking is six or more standard drinks in one session, research shows that most New Zealanders think binge drinking means having more than 14 standard drinks in a single session.[6]

There is also a lack of clarity surrounding the terminology used to describe unsafe drinking. Commonly used phrases include; risky drinking, hazardous drinking, alcohol-related risk, alcohol dependence, alcoholism and binge drinking. In addition, varying opinions exist about the quantity of alcohol required to satisfy these definitions.[7]

The terms recommended by the National Health Committee to best explain hazardous drinking are:[2]

- Alcohol misuse – repeated use despite recurrent adverse consequences
- Alcohol dependence – alcohol misuse combined with tolerance, withdrawal and an uncontrollable urge to drink

The definition of alcohol misuse and alcohol dependence

The American Psychiatric Association's classification system (DSM-IV) has set criteria for the syndromes of alcohol abuse and alcohol dependence.

Alcohol abuse (alcohol misuse)

The key features of the abuse syndrome are:

A maladaptive pattern of alcohol use causing clinically significant distress or impairment of social or occupational functioning.

Maladaptive use can include high daily consumption (e.g. seven drinks or more each day for men, five or more for women), regular heavy weekend drinking and binge drinking (staying drunk for days, often after periods of abstinence).

One or more of the following features must have occurred as a result of recurrent alcohol use within a 12 month period:

1. **Failure to fulfil major role obligations**, e.g. repeated absences or poor work performance related to alcohol use; suspensions, or expulsions from school; neglect of the children or household.
2. **Exposure to physical hazards**, e.g. driving an automobile or operating machinery when impaired by alcohol use.
3. **Legal problems**, e.g. arrests for alcohol related disorderly conduct.
4. **Social or interpersonal problems**, e.g. arguments with a partner about consequences of intoxication, physical fights whilst drunk.

N.B. A diagnosis of alcohol abuse syndrome is not made if the person is dependent on alcohol.

Adapted from: Guidelines for Recognising, Assessing and Treating Alcohol and Cannabis Abuse in Primary Care, National Health Committee, 1999.[2]

Alcohol dependence

The key features of alcohol dependence syndrome are:

A maladaptive pattern of alcohol use leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12 month period:

1. **Tolerance**, as defined by either:
   a) A need for markedly increased amounts of alcohol to achieve intoxication or the desired effect
   b) Continued use of the same amount of alcohol with markedly diminished effect
2. **Withdrawal**, as manifested by two or more of the following occurring after cessation or reduction of heavy prolonged alcohol use:
   a) Autonomic hyperactivity such as sweating or heart rate in excess of 100 beats per minute
   b) Hand tremor
   c) Nausea or vomiting
   d) Transient visual auditory or tactile
   e) Hallucinations
   f) Psychomotor agitation
   g) Anxiety
   h) Grand mal seizures
3. Alcohol is consumed in larger amounts or over a longer period than was intended
4. There is a persistent desire or unsuccessful efforts made to cut down or control alcohol use
5. A great deal of time is spent in activities necessary to obtain alcohol, consume it, or recover from its effects
6. Important social, occupational or recreational activities are given up or reduced because of alcohol use
7. Alcohol use is continued despite a physical or psychological problem that is likely to have been caused or exacerbated by the substance

The role of general practice in detecting and managing hazardous drinking

Approximately 80–90% of people visit a GP at least once a year,[8] placing general practice in an ideal position for identifying hazardous drinking. However, a high level of suspicion may be required to detect alcohol related issues as they can be easily missed or "disguised" by other health problems. It has been previously estimated that between 65% and 82% of patients who presented to general practice, with alcohol related problems, did not have these problems detected,[2] and only approximately 13% received any treatment for their drinking.[9]

Screening for alcohol consumption among patients in primary care has many potential benefits, including:[10]

- An opportunity to educate patients about low-risk consumption levels and the risks of excessive alcohol use
- May help with the diagnosis of the patient's presenting condition
- May alert clinicians to the need to advise patients whose alcohol consumption might adversely affect their use of medications and other aspects of current treatment
- An opportunity for practitioners to take preventative measures that have proven effectiveness in reducing alcohol-related risks

It is currently recommended that a useful approach for detecting hazardous drinking is to ask a simple screening question, followed by a more focused questionnaire if required. Studies have shown that validated questionnaires are the best way to screen for hazardous alcohol use. They are more sensitive, more specific and less expensive than blood tests, which are only indicated as an adjunct to screening.[11]

Simple screening for hazardous drinking

Integrating two to three simple questions about alcohol use into a primary care consultation can provide an opening for a more in-depth discussion.[12]

> Have you ever drunk more than you meant to in the last year?
>
> Have you felt that you wanted to cut down on your drinking in the past year?
>
> If yes, is this something you would like help with?

It is important the results are not over interpreted. If the answers to these questions raise concerns, this should be followed up with a more detailed questionnaire about alcohol use (see below).

Questionnaires for assessing hazardous drinking

There are a number of questionnaires available for the assessment of hazardous drinking, including CAGE, MAST AUDIT and AUDIT-C, which are relatively easy to understand and administer.

The **Alcohol Use Disorders Identification Test (AUDIT)** was developed by the World Health Organisation as a simple method of screening for excessive drinking and to assist in brief assessment. It has a key role in identifying people who would benefit from reducing or ceasing drinking. It is particularly designed for use by health care practitioners in a range of health settings, but it can also be self administered or used by non-health professionals. The AUDIT is a ten-item questionnaire that measures negative alcohol related consequences as well as total alcohol consumption. The benefit of the AUDIT in general practice is that it provides some discrimination between hazardous, harmful and dependent alcohol use. It has also been validated across a range of cultures (but not for Māori or Pacific peoples), making it mostly suitable for general practice. New Zealand data has shown the AUDIT tool to have a satisfactory detection rate for use in New Zealand general practice.[13]

The **AUDIT–C** is a shortened version of the AUDIT, including only three questions. It has similar validity to the full AUDIT test and is useful as a screening tool to identify patients

who are hazardous drinkers or have active alcohol use disorders (including alcohol misuse or dependence). The rapid use of this tool makes it very appealing for use in the general practice setting.

See **www.bpac.org.nz** keyword: addiction-tools for a copy of AUDIT (interview and self-report versions) and AUDIT-C. AUDIT can also be accessed within the *bestpractice* Decision Support depression module, with an electronic version of the results incorporated into the patient record.

The **CAGE** questionnaire screens for lifetime alcohol use problems, using four questions. It is recognised as having value as a screen for alcohol dependence, but has a limited role for the detection of hazardous or harmful alcohol use. For example, in young drinkers, it is less sensitive because it does not identify people who drink excessively, but are not concerned about their drinking.

The **Michigan Alcoholism Screening Test (MAST)** is one of the oldest alcohol screening tests available. It contains 22 "yes" or "no" questions, with six positive responses indicating a drinking problem. Although it is considered reasonably accurate, its disadvantage is the time required to complete and score the test. The MAST has a focus on alcoholism, and is most beneficial in people with established alcohol problems and self-acceptance of their alcohol use.

For further information about interpreting the results of alcohol screening tests and managing alcohol misuse, see: "Substance misuse and addiction in Maori", BPJ 28 (Jun, 2010)

Alcohol biomarkers

Although blood tests frequently show a number of changes in relation to alcohol use, they generally lack sufficient sensitivity and specificity for this purpose, so are not recommended for the routine screening of hazardous drinking in primary care.[14]

The biomarkers traditionally associated with hazardous drinking are gamma glutamyl transferase (GGT), mean cell volume (MCV), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and carbohydrate-deficient transferrin (CDT).[15] Elevation of these biomarkers may suggest heavy alcohol consumption by demonstrating the metabolic and toxic effects that alcohol may have had on an organ system or blood chemistry. However, it is important to remember that the incidental finding of elevated biomarkers should be interpreted cautiously, due to the relatively low specificity of the tests. Although elevated results may raise the suspicion of excessive alcohol intake, it is important that other causes for elevated results are considered.

To complicate this further, a key feature for many people who have alcohol dependence is denial or minimisation of reported alcohol use. This can result in a mismatch between the observation of abnormal blood results, which may suggest excessive alcohol consumption, and what the patient is self reporting in the screening questionnaires. Elevated results of biomarkers can be useful in offering a further opportunity to discuss reduction of alcohol use.

A summary of the commonly used biomarkers is presented in Table 1.

GGT

Gamma glutamyl transferase (GGT) is the most commonly recognised alcohol biomarker despite its relatively low sensitivity for detecting increased alcohol intake in the general population. Overall, GGT sensitivity for screening heavy drinking is moderate, ranging from low to high values, depending on the population and setting where it is used. Despite this, it is the hepatic biomarker most strongly associated with alcohol intake.[16]

GGT has a long window of assessment. Values remain elevated for two to three weeks after cessation of heavy drinking and increase within approximately two weeks after a relapse to heavy drinking. Elevation occurs due to alcohol related enzyme induction and also, over time, structural injury to the liver/hepatobiliary system.

Chronic drinking of four or more drinks a day, for four to eight weeks, raises the GGT level, making this test more sensitive in chronic drinkers.[17] Elevations of GGT are usually detected less often in adolescents and young adults who drink heavily. This may be because a certain number of years of exposure to alcohol is needed to cause GGT elevation.[15] The most significant association is that average GGT levels are higher in both current and former drinkers compared to lifetime abstainers, although there is genetic variation in baseline GGT levels. GGT is less sensitive in people aged less than 30 years or greater than 70 years.[18]

Table 1: Characteristics of commonly used alcohol biomarkers (Adapted from Center for Substance Abuse Treatment, 2006)[19]

Biomarker	Type of drinking characterised	Sensitivity/Specificity	Examples of possible sources of false positives	General comments
Gamma Glutamyl Transferase (GGT)	Probably at least five drinks/day for several weeks	Moderate/Moderate (as a screen for alcohol dependence)	Liver and biliary disease, smoking, obesity, and medications inducing microsomal enzymes	Traditionally the most commonly used biomarker. Primarily reflects liver damage that is often related to alcohol consumption. Performs best in adults aged 30 to 70 years.
Aspartate Amino Transferase (AST) **Alanine Amino Transferase (ALT)**	Unknown, but heavy and lasting for several weeks	Moderate/Moderate (somewhat lower than GGT as screen for alcohol dependence)	As above for GGT Excessive coffee consumption can lower values	Primarily reflects liver damage that is often related to alcohol. ALT seems less sensitive than AST. Ratios of AST to ALT >2 may suggest liver damage that is alcohol related. Performs best in adults aged 30 to 70 years.
Mean Corpuscular Volume (MCV)	Unknown, but heavy and lasting at least a few months	Low/Moderate-High (sensitivity somewhat below GGT as screen for dependence)	Liver disease, haemolysis, bleeding disorders, anaemia, folate deficiency and medications reducing folate	Poor biomarker for relapse because of slow response to drinking.
Carbohydrate-Deficient Transferrin (CDT)	Probably at least five drinks/day for around two weeks	Moderate/High (as a screen for alcohol dependence)	Iron deficiency, hormonal status in women, carbohydrate-deficient glycoprotein syndrome, fulminant hepatitis C and severe alcohol disease	Equal to, or possibly slightly superior than, GGT but much more specific. Very good biomarker of relapse to drinking following a period of abstinence. Likely less sensitive for women and younger people.

It is very important to note that GGT may be elevated in isolation by a number of conditions not related to alcohol intake, including non-alcohol-related liver diseases, obesity, diabetes, smoking and medications such as anticonvulsants, anticoagulants and barbiturates.[15]

ALT and AST

Although AST and ALT may be used as markers of heavy alcohol consumption, they are not recommended as they have a lower sensitivity than GGT.[18]

MCV

A raised mean cell volume (MCV) is frequently used as an alcohol biomarker, as chronic heavy drinking increases the size of red blood cells. MCV appears to have lower sensitivity in males and higher sensitivity in females than GGT and is more specific than GGT. However, there are also numerous sources of potential false positive results including folate and B_{12} deficiencies, non-alcohol-related liver diseases, haemolysis, bleeding disorders, hypothyroidism, medications that can induce marrow toxicity and bone marrow disorders.

MCV is most useful for adults aged from 30 to 60 years. MCV values can remain elevated for up to several months after cessation of drinking, due to the long half-life (13 to 27 weeks) of red blood cells.[15]

CDT

The most recently introduced biomarker for increased alcohol intake is carbohydrate-deficient transferrin (CDT). High alcohol intake reduces the number of carbohydrate (sialic acid) residues attached to this transferrin, thereby increasing the number of carbohydrate deficient sites.

CDT is a more specific biomarker of hazardous alcohol intake than standard markers, although there is some individual genetic variation in CDT levels and several identified sources of false positive results (Table 1). CDT is influenced by factors such as smoking, body weight and female gender.[15]

Regular drinking is required to increase the CDT, and it is usually not affected by binge drinking. Heavy drinking (50 to 80 g alcohol/day) for seven to ten days decreases the carbohydrate content of transferrin, thus increasing the CDT level. Because the baseline value of CDT tends to be fairly specific to an individual patient, CDT is sometimes used to monitor abstinence, as following cessation of drinking, CDT values will usually return to normal within two to three weeks.

Biomarker combinations

Because all biomarkers have some limitations, one approach to improve accuracy has been to use these tests in combination. The highest sensitivities are obtained with the combination of CDT and GGT, ranging from 65% to 73%. Combinations with AST, ALT and MCV have lower sensitivities of 50%, 35%, and 52%, respectively. The positive predictive value of an isolated raised result in an otherwise low risk patient is likely to be even lower.

ACKNOWLEDGEMENT: Thank you to **Vanessa Caldwell** (Ngāi Tahu), National Project Manager, Matua Raki (National Addictions Workforce Development Centre), Wellington for providing expert guidance in developing this article.

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Investigating Mercury TOXICITY

Occasionally patients may present to primary care expressing concern about mercury toxicity, or requesting testing following their own research. Although there are many potential sources of exposure to mercury and its compounds, most patients can be reassured that they are at low risk of mercury toxicity. The exception to this is the exposure of the developing foetal brain to organic mercury.

Sources and risks of mercury exposure

Mercury exists in three different forms:[1]

- **Elemental mercury** (also known as quicksilver) – a silvery, shiny, volatile liquid, which emits a colourless, odourless vapour at room temperature
- **Inorganic mercury** – compounds formed when elemental mercury combines with other elements such as sulphur, chlorine or oxygen to create mercury salts
- **Organic mercury** – compounds that are formed when elemental mercury combines with carbon, such as methyl mercury

The adverse health effects of mercury exposure depend on its chemical form (elemental, inorganic or organic), the route of exposure (inhalation, ingestion or skin absorption), and the level of exposure. Vapour from liquid elemental mercury and methyl mercury are both more easily absorbed than inorganic mercury salts and are therefore more toxic.

Potential sources of exposure to mercury[2]

Elemental mercury:

- Inhalation and skin absorption when handling liquid mercury, e.g. broken thermometers, sphygmomanometers, fluorescent light bulbs
- Amalgam dental fillings
- Environmental exposure, e.g. air contamination from burning coal and industrial waste
- Release from soil in geothermally active areas (low levels in New Zealand)

Inorganic mercury salts:

- Non-prescription calcium supplements
- Some complementary medicines
- Topical agents such as bleaching creams to remove freckles
- Some fungicides
- Red colouring in some tattoos

Organic mercury salts:

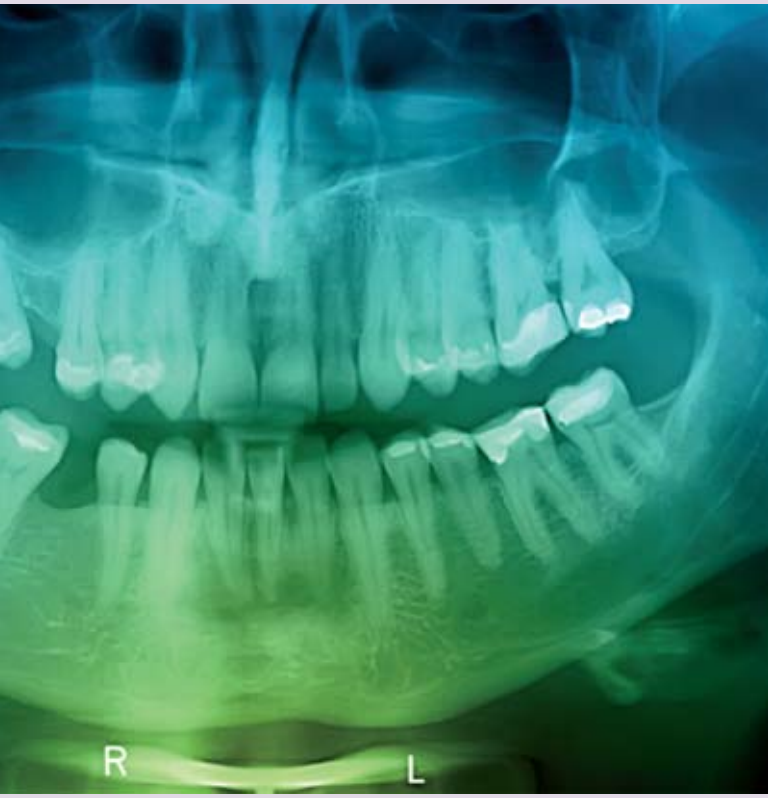
- Fish (methyl mercury)

Amalgam dental fillings

Dental amalgam fillings contribute only a minor amount to the total mercury levels in the body, and do not cause a significant increase in blood mercury level. There is no good evidence that amalgam fillings cause mercury toxicity.[4]

The American Dental Association (ADA) states that amalgam is a safe material with no sound scientific evidence supporting a link between amalgam fillings and systemic diseases or chronic illness. The U.S Food and Drug administration group (FDA) concludes that amalgam fillings do not significantly contribute to mercury-related toxicity. The FDA found that in adults and children aged six years and over, who have fifteen or more amalgam surfaces, mercury exposure was far below the lowest levels associated with harm.[5] In addition the FDA does not recommend that amalgam fillings are removed or replaced. Removing sound amalgam fillings results in unnecessary loss of healthy tooth structure, and results in exposure to mercury vapour released during the removal process.

Although amalgam fillings are considered safe, research to develop new filling materials is ongoing.



Mercury in fish

Fish is by far the biggest source of exposure to organic mercury, in the form of methyl mercury. Organic mercury is passed along the food chain from smaller fish to larger predator fish, e.g. swordfish, shark, tuna, which contain the highest levels of accumulated mercury. Mercury levels can also be high in trout caught from geothermal lakes. Cooking does not reduce mercury content in fish. All canned fish (including tuna, herring and mackerel) sold in New Zealand contain acceptably low levels of mercury.[2]

The developing foetus, infants and young children are most susceptible to mercury-related neurotoxicity that may result from consuming large amounts of fish. The New Zealand Food Safety Authority advises that pregnant women should choose fish varieties with lower mercury concentrations.[3] Fish that are likely to contain the lowest levels of mercury include: farmed salmon, skipjack tuna, tarakihi, blue cod, hoki, john dory, monkfish, warehou, whitebait and flat fish (e.g. flounder), as well as mussels and pacific oysters. Small, canned fish such as sardines and mixed fish (e.g. fish portions and fish fingers) can also be eaten without restriction.

Symptoms of mercury toxicity

Low grade continuous exposure to mercury can lead to:[6]

- Inflammation of the mouth, soft gums, loose teeth, excessive salivation, metallic taste and foul breath
- Tremor (hatter's shakes), particularly when the person is being observed or is in an unfamiliar environment or job
- Mental and nervous symptoms including behavioural changes, stammering, anxiety, insomnia and loss of energy and drive

Laboratory testing of mercury

Appropriate indications for testing blood or urine mercury:[4]

- History of mercury ingestion (other than normal consumption of fish) or other exposure
- Occupational health monitoring
- Neurological symptoms suggesting occult mercury poisoning

Inappropriate reasons for requesting blood or urine mercury:[4]

- Non-specific symptoms such as memory loss, cognitive decline, depression or chronic fatigue syndrome
- The presence of amalgam fillings
- Autism spectrum disorder or Alzheimer's disease (there is no convincing evidence that mercury is linked to either of these conditions)
- Routine "screening" or an "annual check"

Blood mercury is the recommended test to diagnose mercury poisoning as most mercury is present in red blood cells. Levels are raised by recent exposure, e.g. a large seafood meal may raise blood mercury, which then declines over subsequent weeks. The half-life of organic mercury in blood after exposure is approximately seven to ten weeks and three to 15 days after vapour exposure. After inorganic mercury exposure, the half-life is three to four weeks.[2]

Urine testing is used to assess chronic exposure to inorganic and elemental mercury. Organic mercury exposure (i.e. through seafood ingestion) usually only has a minimal effect on urine mercury levels.

In a primary care setting, testing for mercury in other samples, e.g. hair, nails or cerebrospinal fluid, is difficult and expensive, and is not recommended.

ACKNOWLEDGEMENT: Thank you to **Associate Professor James Davidson**, Labplus, Auckland City Hospital for providing expert guidance in developing this article.

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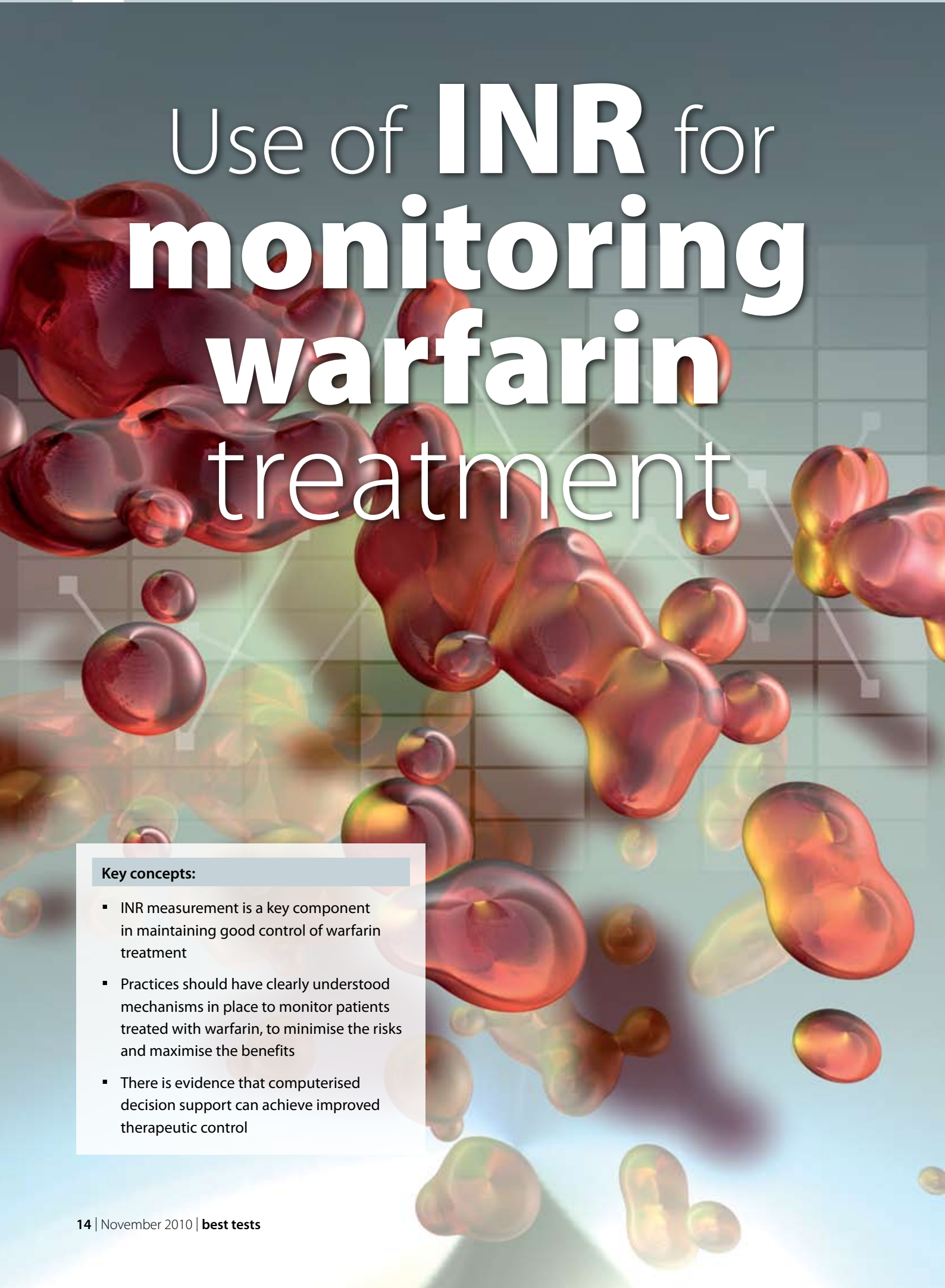
Use of **INR** for **monitoring warfarin** treatment



Key concepts:

- INR measurement is a key component in maintaining good control of warfarin treatment
- Practices should have clearly understood mechanisms in place to monitor patients treated with warfarin, to minimise the risks and maximise the benefits
- There is evidence that computerised decision support can achieve improved therapeutic control

INR monitoring is essential for all patients treated with warfarin

International Normalised Ratio (INR) testing is well established as an integral part of warfarin treatment. INR has a critical role in maintaining the warfarin response within a therapeutic range, to provide the benefits of anticoagulation, while avoiding the risks of haemorrhage (Figure 1).

Therapeutic monitoring of warfarin treatment requires two key elements to be undertaken if it is to be successful: the measurement of the INR and an interpretation of the result in order to advise on dosage of warfarin and when the next test should be performed.

INR levels can be difficult to control

Although regular testing of INR levels is essential for all people taking warfarin to maintain control of the INR, in practice, INR levels show considerable intra-patient variability. A study has demonstrated that a group of stable patients, on long-term warfarin treatment achieved the therapeutic range for INR approximately 55% of the time.[2]

Maintaining good systems is important

It is important that practices develop a standardised management protocol for all patients treated with warfarin, in order to optimise health outcomes, by achieving tighter control.

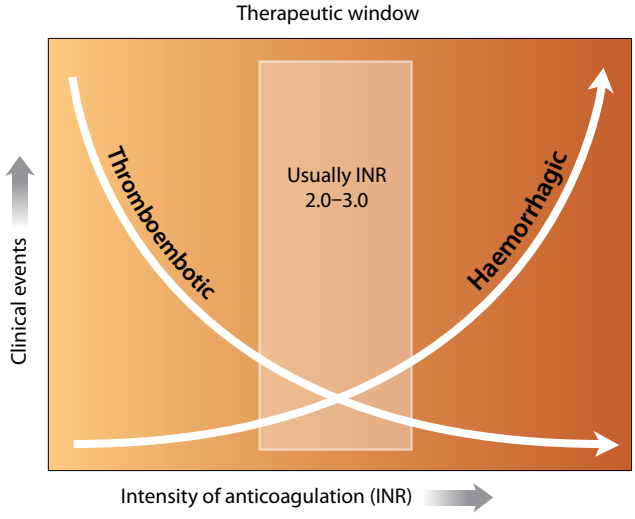


Figure 1: Balancing the risk of anticoagulation treatment (adapted from Blann, 2003)[1]

The plan for anticoagulation therapy should be detailed in the patient's clinical notes, using a standardised method, to minimise misunderstandings. The method chosen will depend on how clinical records are managed within the practice but there should at least be a standard location within the patient notes for the following information:

- A note that the patient is on warfarin
- Condition for which warfarin has been prescribed
- Target INR range
- Planned duration of treatment
- Brand of warfarin

The information that a patient is on warfarin must be immediately obvious to any clinician who accesses the patient's clinical record.

Managing warfarin treatment

INR testing schedule

Regular testing of the INR is essential for all people taking warfarin. The risk of bleeding while on warfarin is greatest in patients who have not previously received warfarin, and in the first three months of treatment.[3]

Any patient on warfarin should be aware of the risks and early warning signs of bleeding, and they should be followed closely, during the first three months in particular, to ensure that the INR does not exceed 3.0.

After this time period, the frequency of INR testing can be reduced. For most people once the INR is stable, the rate of INR testing can be extended to two weekly and then four to six weekly. In some stable patients the frequency may be extended out to eight weeks.[4] However, people with higher levels of risk, e.g. cormorbidities, may need more frequent testing.

Target INR range and duration of treatment

In most situations the INR target is 2.5 (target range 2.0 – 3.0). This range is appropriate for the prophylaxis or treatment of venous thromboembolism and reduction of the risk of systemic embolism for people with atrial fibrillation and valvular heart disease.[5] In some situations higher ranges are more appropriate. The target INR may vary depending on individual clinical situations. The target

INR for mechanical prosthetic valves is dependent on the type of valve replacement used.[6]

The duration of warfarin therapy for a provoked DVT or PE is 13 weeks. For unprovoked DVT or PE the duration again is 13 weeks, but for individual patients within their clinical context, the indefinite use of warfarin may be appropriate.[5] For atrial fibrillation, cardiomyopathy and valvular heart disease (selected cases) an indefinite period of warfarin treatment is recommended.[6]

Managing alterations in the INR

Some fluctuations in INR level can be expected, and for minor variations, changes in weekly doses are usually not required. For more significant fluctuations, use of a standard guide is important to reduce the risk of incorrect dosing. The use of dosing calendars for more complicated dosage sequencing may be of benefit.

Changes in warfarin dosage may take several days to affect INR level, therefore it is important that doses are not adjusted more frequently than every four to five days.

Changes in the INR level in a usually stable patient may be due to a number of reasons, including:[7, 8]

- Major changes in diet or alcohol intake
- Drug interactions (pharmaceutical or complementary)
- Systemic or concurrent illness
- Non-adherence to dosage regimen
- Unknown causes

Diet or alcohol

Patients on warfarin are usually advised to consume a reasonably consistent proportion of vitamin K rich foods such as broccoli, spinach and cabbage. This is probably most relevant in patients who have had markedly reduced food intake because of illness, hospitalisation, travel and fad diets.[9] A recent study suggests that the role of excessive dietary vitamin K may have been overstated, with the exception of natto (Japanese fermented soybean) which causes a marked and prolonged inhibition of warfarin.[10]

Increased consumption of alcohol (particularly binge drinking) can affect warfarin control although moderate, regular alcohol consumption has little effect.

Drug interactions

Many medicines and herbal products can interact with warfarin. An interaction can occur when the interacting agent is started or stopped or when the dose is altered. Whilst most interactions involve a change in the INR, it is important to recognise that some interactions cause an increase in bleeding without alteration of the INR, e.g. NSAIDs, aspirin and SSRIs (Table 1).

Table 1 shows some of the important interactions with warfarin. It is not all-inclusive and practitioners should always check if there is a clinically significant interaction if they are prescribing a medicine for a person taking warfarin. Patients should also be advised not to take any other prescribed medicines, over-the-counter medicines or food supplements/herbal products without consulting their doctor or pharmacist.

For a complete list of interactions and advice on managing interactions such as when to check the INR, refer to appropriate information resources such as a formulary or your PMS system.

Systemic or concurrent disease

Many systemic diseases can influence INR results:

- Congestive heart failure – may cause hepatic congestion of blood flow and inhibit warfarin metabolism, this may be particularly troublesome during exacerbations of heart failure.
- Hypothyroidism – decreased catabolism of vitamin K clotting factors may decrease INR values.
- Hyperthyroidism – conversely, hyperthyroidism may increase catabolism of vitamin K clotting factors and increase INR values.
- Liver failure – may cause elevation of INR due to reduced production of clotting factors.
- Other illnesses – other intermittent conditions such as fever, vomiting and diarrhoea may affect the INR; ill patients may also reduce their usual dietary intake.

Table 1: Some of the main medicines, medicine classes and other agents that can interact with warfarin (adapted from Juurlink, 2007)[11]

	Risk of Bleeding	Mechanism
Antibiotics		
Most antibiotics but especially macrolides, metronidazole, quinolones and cotrimoxazole	↑	Inhibition of vitamin K synthesis by intestinal flora, inhibition of warfarin metabolism or both
Rifampicin*	↓	Induction of hepatic metabolism
Antifungals		
Fluconazole, miconazole (including gel and vaginal preparations)	↑	Inhibition of warfarin metabolism
Antidepressants		
Serotonergic agents (SSRIs and venlafaxine)	↑	Inhibition with platelet function – increased bleeding risk without alteration of INR. Some, e.g. fluoxetine, paroxetine, can also inhibit warfarin metabolism
Antiplatelet agents		
Aspirin, clopidogrel, dipyridamole	↑	Interference with primary haemostasis – increased bleeding risk without alteration of INR
Amiodarone	↑	Inhibition of warfarin metabolism
Anti-inflammatory agents		
NSAIDS, Cox-2 inhibitors	↑	Direct mucosal injury, antiplatelet effects may also have a role. Increased bleeding risk without alteration of INR. Inhibition of warfarin metabolism and an increase in INR rarely reported with some NSAIDs
Analgesics		
Tramadol	↑	Inhibition of warfarin metabolism
Paracetamol	↑	Direct interference with vitamin K cycle Interaction possible with chronic, regular use of paracetamol, short-term (a few days) unlikely to interact
Alternative remedies/foods		
Ginkgo, fenugreek, chamomile, dong quai, cranberry products	↑	Unclear, multiple mechanisms
St John's wort*	↓	Unclear, possible effects on warfarin metabolism
Foods with high vitamin K content, e.g. leafy greens, broccoli*	↓	Increased vitamin K synthesis antagonises anticoagulant effect of warfarin

*These agents will reduce the bleeding risk but the INR may be become sub-therapeutic and warfarin dose may need to be increased

Notes:

- Interactions do not occur, or are not significant, in everyone. There are many variables including genetic factors.
- This table does not include all possible interactions with warfarin. Please check before prescribing or recommending any medicine, herbal product or food supplement

Non-adherence to dosage regimen

An erratic INR may reflect non-adherence to the medicine regimen, often due to misunderstandings of dosage requirements. A missed dose of warfarin is usually reflected in the INR result two to five days after the missed dose,[12] although a response may be seen within 16 hours.[13]

Unknown causes

In many cases, no explanation may be found for unstable INR values. It may be worthwhile discussing aspects of the dosing regimen. Changes in the INR may also be the result of occult causes, such as undisclosed drug use, lifestyle and medical causes.

Computerised decision support

Computerised decision support is a very useful tool for maintaining therapeutic INR levels in patients receiving anticoagulant treatment. There is evidence that computerised decision support can achieve improved therapeutic control in terms of INR, when compared with human performance.[14]

A meta-analysis of randomised controlled trials compared computerised decision support methods of determining warfarin dosage with traditional manual methods in 3416 patients.[15] The computerised decision support groups did better in terms of percentage of INR tests within target (65% computer group, 59% manual group, NNT 17) and showed a significant reduction in the incidence of bleeding (2% computer group, 4.4% manual group).

A randomised controlled trial compared the INR control (by the percentage of time within-target) of two groups of patients attending an anticoagulation clinic in Italy.[16] One group were managed using computerised decision support and the other group were dosed using manual methods by experienced haematologists. The INR control in the computerised decision support group was significantly better (71% of time within range for the computer group, 68% for manual group) and fewer tests were needed to achieve this control.[15]

One of the advantages of computerised decision support tools is that information can be easily retrieved, providing many opportunities for clinical practice audit, including indentifying patients who are on anticoagulant treatment but are not receiving INR monitoring.

The bpac^{nz} clinical audit "Safe and effective anticoagulation with warfarin" has been recently updated and is available to download or order at: **www.bpac.org.nz**

best practice Decision Support INR module

A best practice Decision Support module has been developed for managing warfarin treatment, based on data from the Coventry system,[17] which has been widely accepted internationally.

This module is available free to General Practices in New Zealand. It enables clinicians to more easily adjust oral anticoagulant doses and schedule follow-up consultations. INR results can be tracked and monitored over time and a dose calendar can be printed for the patient.

Guide for over anti-coagulation[18]

Current INR is 5–9

1. Stop warfarin
2. Test INR daily until it has returned to the therapeutic range
3. Restart warfarin with a reduced dose when INR < 5
4. Give vitamin K 1.0 – 2.5 mg, orally if INR fails to reduce, or if there is high risk of serious bleeding (N.B. subcutaneous administration is not effective)

Current INR is > 9, without bleeding

Where there is a low risk of bleeding from other causes

1. Stop warfarin therapy
2. Give vitamin K 2.5 – 5 mg, orally
3. Measure INR in 24 hours
4. Restart warfarin with a reduced dose when INR < 5

Where there is a high risk of bleeding from other causes

1. Stop warfarin
2. Seek specialist advice

Current INR is ≥ 9, with minor bleeding

1. Stop warfarin
2. Consider referral to secondary care if clinically appropriate
3. Give vitamin K 1 – 5 mg, orally
4. Test INR daily until stable
5. Restart warfarin with a reduced dose when INR < 5

Major bleeding occurs

If at any time major bleeding occurs:

1. Stop warfarin
2. Give vitamin K 10 mg, slow IV
3. Refer to secondary care immediately for factor replacement

Transfer of care across the primary – secondary interface is associated with a high risk

Transfer of the care of a patient on warfarin treatment from secondary to primary care is associated with a high risk for several reasons:

- Poor communication on discharge may leave the primary care clinician with inadequate information to make safe testing and dose adjustment decisions
- Patients may be discharged from hospital with tablet strengths, which were used for loading doses but are inappropriate for maintenance therapy. Warfarin has a very long half-life, so accumulates, leading to over-anticoagulation
- Patients often leave hospital with other medicines, e.g. antibiotics, which can interact with warfarin

Some New Zealand hospitals have developed protocols for the timely transfer of information about warfarin therapy to primary care on patient discharge. Essential details have been found to be:

- Condition for which warfarin has been prescribed
- Target INR range
- Planned duration of treatment
- Brand and strength of warfarin tablets given
- Last three doses
- Last three INR levels
- Date next INR test is due

It is useful to also record this information in the patient's anticoagulation record ("The Red Book").

New Zealand hospitals use a variety of warfarin initiation protocols and there is little evidence that one is any better than another. It is recommended to follow on with the protocol initiated in secondary care for patients who start warfarin in this environment. It would be helpful for primary care clinicians to become familiar with local hospital protocols.

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QUIZ FEEDBACK

Men's & Women's health

Introduction

This quiz feedback provides an opportunity to revisit the September 2010 "Best Tests" document and accompanying quiz which focused on appropriate use of laboratory tests in the primary care setting, for men's and women's health. All general practitioners who responded to this quiz will receive personalised online feedback and CME points.

1.	When investigating erectile dysfunction in a patient, which of the following tests are recommended?		
		Your peers	Preferred
☐	Lipid profile	94%	✓
☐	Fasting glucose	99%	✓
☐	Testosterone	24%	
☐	Prolactin	6%	

Comment:
Evidence suggests that up to 80% of erectile dysfunction (ED) cases have an organic cause. Organic causes include vasculogenic, neurogenic and hormonal aetiologies, of which vasculogenic aetiologies represent the largest group. Hormonal aetiologies are by contrast a rare cause.

There is a lack of consensus regarding the best choice of laboratory tests for the evaluation of patients with ED. However given the association of ED with vascular disease and diabetes, it is recommended that a cardiovascular risk assessment is performed and screening for diabetes is undertaken. In terms of hormonal tests, the American College of Physicians has been unable to recommend either for or against routine use of hormonal blood tests or hormonal treatment in the management of patients with ED.

2.	When investigating a patient with gynaecomastia, when is laboratory testing most useful?		
		Your peers	Preferred
☐	Long standing gynaecomastia	6%	
☐	Pseudogynaecomastia	<1%	
☐	Bilateral or tender gynaecomastia	71%	✓
☐	Acute onset gynaecomastia	95%	✓

Comment:
Gynaecomastia (GM), a benign enlargement of male breast tissue, is a common condition which indicates an imbalance between free oestrogen and androgen action in the breast tissue.

Although laboratory evaluation may be appropriate, abnormalities are not detected in the majority of patients with GM. Endocrine evaluation in adolescent patients, and in adult patients with longstanding fibrotic GM, is contentious.

If an adult male presents with unilateral or bilateral GM that is of acute onset, particularly if tender, and if the patient's history and physical examination do not reveal the cause, then serum testosterone, LH, oestradiol and hCG are usually sufficient.

3.	Why is the role of testosterone testing limited?		
		Your peers	Preferred
☐	Lack of clarity around reference ranges	60%	✓
☐	Levels drop as people age	74%	✓
☐	Lack of clear recommendations around appropriate use of the test	78%	✓
☐	It is not widely available	11%	

Comment:
The association between ageing-related testosterone reduction and late-onset hypogonadism in men remains a controversial concept due to the high prevalence of hypogonadal symptoms in the aging male population and the non-specific nature of these symptoms.

The issue is further complicated by the impact of a variety of medical conditions on the male gonadal axis, the diurnal variation in testosterone levels (more than one pre-9 am sample is essential) and the limitations of available total and free testosterone assays.

As healthy men age, the serum concentration of testosterone, particularly free testosterone but also total testosterone, declines by 0.4 – 2.6% per year after the age of 40 years. This results in a total testosterone level that is below the normal laboratory range in approximately 25% of men aged over 70 years and 50% aged over 80 years.

4.	What is the most common cause of delayed puberty in boys?		
		Your peers	Preferred
☐	Constitutional delay in growth and puberty	99%	✓
☐	Tumour	5%	
☐	Genetic causes	8%	
☐	Stress	3%	

Comment:
Delayed puberty in males is defined by the absence or incomplete development of secondary sexual characteristics by age 14 years, i.e. the age at which 95% of males have initiated sexual maturation.

The most common cause of delayed puberty is constitutional delay in growth and puberty. These patients will eventually spontaneously progress through puberty. For boys aged under 16 years, watchful waiting should reliably distinguish those with constitutional delay from those with other causes of delayed puberty. A positive family history for constitutional delay of puberty, especially in the father, can be useful for helping to confirm this. Reassessment of the patient may be considered after six months.

5.	Which of the following define primary amenorrhoea?		
		Your peers	Preferred
☐	Absence of menses by age 16 years with development of secondary sexual characteristics	97%	✓
☐	Absence of menses by age 13 years with no development of secondary sexual characteristics	81%	✓
☐	Absence of menses by age 16 years with no development of secondary sexual characteristics	5%	✓
☐	Absence of menses by age 13 years with development of secondary sexual characteristics	2%	

Comment:
Amenorrhoea is the absence of menstruation flow. It can be classified as either primary or secondary, relative to menarche. Primary amenorrhoea is the absence of menses by age 16 years in a female with appropriate development of secondary sexual characteristics or absence of menses by age 13 years and no other pubertal maturation.

Although only a small number of respondents correctly selected this option, absence of menses in a 16 year old girl with no secondary sexual characteristics is also considered as primary amenorrhoea.

6.	What is the most common cause of secondary amenorrhoea?		
		Your peers	Preferred
☐	PCOS	15%	
☐	Premature menopause	9%	
☐	Pregnancy	90%	✓
☐	Breastfeeding	6%	

Comment:
Secondary amenorrhoea is the lack of menses in a previously menstruating, non-pregnant female, for greater than six months. Pregnancy is the most common cause of secondary amenorrhoea, followed by:

- Ovarian disease (40%) – ovarian failure due to normal or early menopause, hyperandrogenism, e.g. PCOS, testosterone supplementation
- Functional hypothalamic anovulation (35%) – due to excessive exercise, eating disorders, stress or some medicines, e.g. oral contraceptives, depot medroxyprogesterone
- Pituitary disease (19%) – has a similar presentation to functional hypothalamic amenorrhoea except for the occasional additional finding of galactorrhoea in some women. Rare causes are sellar masses, other diseases of the pituitary and primary hypothyroidism.
- Uterine disease (5%) – Asherman's syndrome is the only uterine cause of secondary amenorrhoea

7.	Which of the following tests is usually helpful when investigating loss of libido in a woman?		
		Your peers	Preferred
☐	Testosterone	3%	
☐	Prolactin	2%	
☐	FSH	2%	
☐	None of the above	96%	✓

Comment:
A full history and clinical examination, including sexual history and relationship factors is important. A key requirement for the evaluation of female sexual dysfunction is to determine whether sexual issues are associated with personal stress. Laboratory testing should be performed only if indicated by history or examination. The correlation between androgen levels and sexual dysfunction is considered weak, apart from a few well defined situations such as proven pituitary or adrenal insufficiency or past bilateral oophorectomy. Similarly, testing oestradiol or other hormones e.g. FSH and prolactin, has limited utility in evaluating sexual dysfunction.

8.	Which of the following is true for a women presenting with secondary amenorrhoea?		
		Your peers	Preferred
☐	It is important to exclude pregnancy	99%	✓
☐	The history will seldom be helpful	2%	
☐	Laboratory results can be difficult to interpret	59%	✓
☐	FSH, LH and prolactin levels may be helpful	78%	✓

Comment:
Pregnancy should be first excluded by testing rather than relying solely on history. The history, physical examination and measurement of FSH, TSH and prolactin will often be helpful to identify the most common causes of amenorrhoea. In addition, for women with evidence of hyperandrogenism, the measurement of testosterone would also be indicated.

9.	Which of the following is true for a women presenting with dysfunctional uterine bleeding?		
		Your peers	Preferred
☐	It is important to exclude pregnancy	93%	✓
☐	Coagulation tests should always be requested	2%	
☐	Trauma will frequently be the cause	1%	
☐	It is important to exclude cervical and uterine cancer	98%	✓

Comment:
A pregnancy test is indicated for women of reproductive age with dysfunctional uterine bleeding, to exclude intrauterine or ectopic pregnancy, or gestational trophoblastic disease (hydatiform mole).

Any malignancy of the genital tract can cause dysfunctional bleeding. It can be difficult to determine whether bleeding is from an endocervical or endometrial source, so cervical cancer must be excluded. Any visible cervical lesion should be biopsied, even if cervical cytology is negative for malignancy.

Depending upon the history, clinical examination and initial evaluations, a second tier of laboratory testing may be appropriate. Coagulation tests are only useful in women with a history suggestive of haemostatic defect, e.g. frequent nosebleeds, easy bruising.

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