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For more quizzes, visit: **https://bpac.org.nz/Mybpac/quiz**

Clinical Audit: Reviewing type 2 diabetes management in patients at high risk of cardiovascular and renal complications

This audit helps health professionals in primary care identify patients with type 2 diabetes who are eligible for funded treatment with empagliflozin or dulaglutide*, new medicines available for those at high risk of cardiovascular disease or renal complications, including all Māori and Pacific peoples.

* Availability pending Medsafe approval

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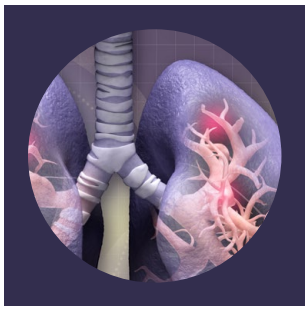

Peer group discussion: Early detection of lung cancer in primary care

Lung cancer is a leading cause of cancer in New Zealand and accounts for the most cancer-related deaths. Lung cancer mortality rates in New Zealand are high compared to other countries with similar healthcare systems, likely due to factors relating late presentation and diagnosis and lack of access to funded treatments. Lung cancer incidence and mortality rates in Māori and Pacific peoples are two to three times higher than in other ethnic groups. This summary includes questions that can be used as discussion points for clinical peer groups, study groups or self-reflection of practice.

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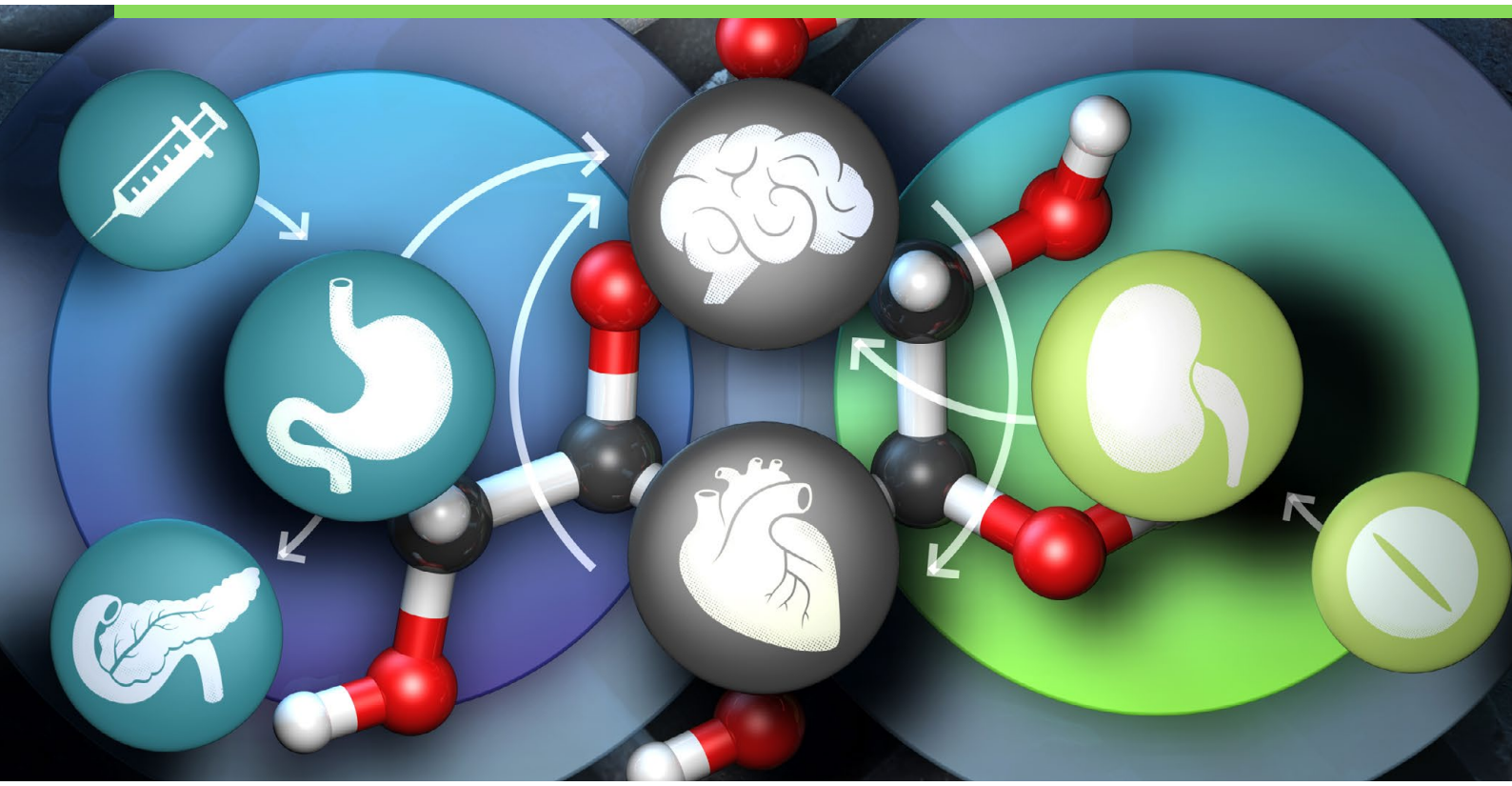

New diabetes medicines funded: **empagliflozin and dulaglutide**

Sodium-glucose co-transporter 2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists have been recommended for the treatment of type 2 diabetes for some time, but until now have not been funded in New Zealand. As of 1 February, 2021, empagliflozin, a SGLT-2 inhibitor, is available fully funded for the treatment of people with type 2 diabetes who are at high risk of cardiovascular disease or have renal complications, including all Māori and Pacific peoples; dulaglutide, a GLP-1 receptor agonist, will be available once it has Medsafe approval later this year.

KEY PRACTICE POINTS:

- Lifestyle interventions, i.e. diet and exercise to induce weight loss, and metformin remain the cornerstone of type 2 diabetes management
- Empagliflozin, an oral SGLT-2 inhibitor (with or without metformin) and dulaglutide, an injectable GLP-1 receptor agonist, are newly funded options for eligible people with type 2 diabetes to add to lifestyle interventions and metformin
- Empagliflozin and dulaglutide are funded for people with HbA_{1c} levels > 53 mmol/mol who are at high risk of, or with established, cardiovascular disease, diabetic kidney disease, heart failure or who are of Māori or Pacific ethnicity. Dual treatment with these medicines is not funded.
- Empagliflozin and dulaglutide reduce the risk of cardiovascular and renal complications in people with type 2 diabetes; empagliflozin in particular reduces hospital admission with heart failure. Both classes of medicine also promote weight loss, especially dulaglutide.
- Common adverse effects of SGLT-2 inhibitors such as empagliflozin include polyuria and urogenital infections. This medicine class also increases the risk of diabetic ketoacidosis; discuss this risk with patients when initiating treatment and inform them of the key symptoms and signs that should prompt them to seek medical advice.
- Common adverse effects of GLP-1 receptor agonists such as dulaglutide include gastrointestinal disturbance and injection site reactions

More tools for the diabetes management toolbox

Sodium-glucose co-transporter 2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists have been recommended internationally in type 2 diabetes management guidelines for some time, but, until now, have been inaccessible to most people in New Zealand due to cost. As of 1 February, 2021, **empagliflozin** (with and without metformin), an oral SGLT-2 inhibitor, is available fully funded with Special Authority approval (see: "Initiating funded treatment").[1] **Dulaglutide**, an injectable GLP-1 receptor agonist, will be available fully funded by Special Authority as soon as it is approved by Medsafe.[1] Both medicines will be the sole subsidised brands until at least 2024.[1]

SGLT-2 inhibitors lower blood glucose levels by inhibiting glucose reabsorption in the renal tubule. In contrast, GLP-1 receptor agonists lower blood glucose levels by stimulating insulin secretion after meals. When added to metformin, SGLT-2 inhibitors and GLP-1 receptor agonists may reduce HbA_{1c} levels by a further 7 to 15 mmol/mol.[2–4]

For further information on the decision to fund these medicines, see: **https://pharmac.govt.nz/news-and-resources/consultations-and-decisions/decision-to-fund-two-new-medicines-for-type-2-diabetes/**

People at high risk of cardiovascular and renal complications will benefit

Several large randomised controlled trials (RCTs) have shown that treatment with a SGLT-2 inhibitor or GLP-1 receptor agonist provides significant cardiovascular benefit to people with type 2 diabetes.[5] A recent meta-analysis of 764 RCTs including 421,346 people with type 2 diabetes found that both medicine classes reduced:[6]

- All-cause mortality
- Cardiovascular mortality
- Non-fatal myocardial infarction
- Kidney failure

The mechanism by which these medicines reduce adverse cardiovascular outcomes remains uncertain; trials are currently underway to explore the pathways involved, including investigating reductions in oxidative stress and cardiac pre-load.[7]

Table 1 describes the estimated absolute difference in outcomes with SGLT-2 inhibitors and GLP-1 receptor agonists compared with placebo per 1,000 people with type 2 diabetes with moderate or very high cardiovascular risk.[6]*

* Moderate risk defined as people with cardiovascular disease; very high risk defined as people with both cardiovascular disease and chronic kidney disease

Funding criteria is intended to help reduce inequities

For the first time, Māori and Pacific peoples have been specifically identified within Special Authority criteria for funding (see: "Initiating funded treatment" for the full criteria). The prevalence of type 2 diabetes is two to three times higher in these ethnic groups than others.[8] Māori and Pacific peoples with type 2 diabetes have worse health outcomes compared to Europeans.[9, 10] Improved access to medicines with established cardiovascular and renal benefits is hoped to reduce the inequities in diabetes health outcomes in these vulnerable populations.

Table 1. Estimated absolute differences in outcomes with SGLT-2 inhibitors and GLP-1 receptor agonists compared with placebo per 1,000 people with type 2 diabetes with moderate and very high cardiovascular risk, treated for five years. Adapted from Palmer et al. (2021).[6]

	CVD risk category*	All-cause mortality	Cardiovascular mortality	Non-fatal myocardial infarction	Non-fatal stroke	Kidney failure	Hospital admission for heart failure
SGLT-2 inhibitor	Moderate	25 fewer (32 fewer – 18 fewer)	12 fewer (18 fewer – 6 fewer)	13 fewer (21 fewer – 3 fewer)	1 more (11 fewer– 13 more)	6 fewer (9 fewer – 2 fewer)	23 fewer (28 fewer – 17 fewer)
	Very high	48 fewer (range 61 – 35 fewer)	24 fewer (range 36 – 12 fewer)	21 fewer (range 34 – 5 fewer)	2 more (range (17 fewer to 21 more)	38 fewer (range 58 – 14 fewer)	58 fewer (range 73 – 44 fewer)
GLP-1 receptor agonist	Moderate	13 fewer (18 fewer – 6 fewer)	9 fewer (15 fewer – 1 fewer)	8 fewer (15 fewer – 1 fewer)	16 fewer (24 fewer – 7 fewer)	4 fewer (7 fewer – 2 fewer)	4 fewer (11 fewer – 2 more)
	Very high	24 fewer (range 35 – 12 fewer)	18 fewer (range 30 – 6 fewer)	13 fewer (range 24 – 2 fewer)	25 fewer (range 39 – 11 fewer)	29 fewer (range 44 – 10 fewer)	11 fewer (range 28 – 5 fewer)

* Moderate risk defined as people with cardiovascular disease; very high risk defined as people with both cardiovascular disease (CVD) and chronic kidney disease

The place of empagliflozin and dulaglutide in type 2 diabetes management

Type 2 diabetes management follows a stepwise progression. Lifestyle interventions and metformin are the cornerstone of type 2 diabetes management (Step 1). If a sufficient reduction in HbA_{1c} levels is not achieved with metformin, treatment is typically escalated by reinforcing the importance of diet and exercise to induce weight loss, and adding a second non-insulin pharmacological treatment (Step 2a). If further intensification is required, a third non-insulin pharmacological treatment can be added (Step 2b) or insulin can be initiated (Step 3).

N.B. Consider starting at Step 2 at diagnosis for patients with HbA_{1c} levels > 64 mmol/mol, i.e. two pharmacological treatments (e.g. metformin and vildagliptin) and lifestyle management.[11] Consider initiating insulin at diagnosis if very high HbA_{1c} levels, e.g. >80 – 90 mmol/mol*, or significant symptoms of hyperglycaemia.[11] Insulin may be withdrawn once HbA_{1c} levels are controlled.

* This is a higher level than in previous guidance (75 mmol/mol) due to the availability of more medicines to manage hyperglycaemia[12]

Treatment options at Step 2 (typically added to metformin) include:

- **Empagliflozin** (oral, funded with Special Authority – see: "Initiating funded treatment" and "Prescribing empagliflozin"), taken either as separate metformin and empagliflozin tablets, or a combination empagliflozin + metformin formulation
- **Dulaglutide** (injectable, funded with Special Authority – see: "Initiating funded treatment" and "Prescribing dulaglutide")
- **Vildagliptin** (oral, funded), taken either as separate metformin and vildagliptin tablets, or a combination vildagliptin + metformin formulation
- A sulfonylurea (oral, funded), such as **gliclazide** or **glipizide**
- **Pioglitazone** (oral, funded)

The decision about which medicine to use should take into account any contraindications, cardiovascular co-morbidities, risk of hypoglycaemia, effects on weight, medicines interactions, adverse effects and eligibility for funding (Table 2 and "Initiating funded treatment").[5]

Empagliflozin or dulaglutide are preferred at Step 2 for people with or at high risk of cardiovascular disease (CVD), diabetic kidney disease or heart failure, regardless of their HbA_{1c} levels; currently only people with HbA_{1c} levels > 53 mmol/mol are eligible for funded treatment (see: "Initiating funded treatment").[11] Both medicine classes can be used together with likely additive benefits, however, dual treatment with empagliflozin and dulaglutide is not funded.[11] There is little risk of hypoglycaemia with these medicines without concomitant use of sulfonylureas or insulin.

N.B. A SGLT-2 inhibitor or GLP-1 receptor agonist are also preferred in some international guidelines if there is a need to minimise weight gain or promote weight loss, however, they are not funded for these indications in New Zealand.[5,13]

Table 2. Effects of diabetes medicines (excluding insulin) on HbA_{1c}, cardiovascular co-morbidities, progression of kidney disease, weight and risk of hypoglycaemia and diabetic ketoacidosis. Adapted from the American Diabetes Association (2021).[5, 11]

Medicine	Efficacy for lowering HbA_{1c}	Cardiovascular effects		Renal effects: progression of DKD	Effects on weight	Risk of hypoglycaemia	Risk of DKA
		CVD	HF				
Metformin	High	Potential benefit	Neutral	Neutral	Neutral with potential for modest loss	Low	Low
Empagliflozin	Intermediate	Benefit	Benefit	Benefit	Loss	Low	High
Dulaglutide	High	Benefit	Neutral	Benefit	Loss	Low	Low
Vildagliptin	Intermediate	Neutral	Neutral	Neutral	Neutral	Low	Low
Sulfonylureas	High	Neutral	Neutral	Neutral	Gain	High	Low
Pioglitazone	High	Potential benefit	Increased risk	Neutral	Gain	Low	Low

CVD = cardiovascular disease HF = heart failure DKD = diabetic kidney disease DKA = diabetic ketoacidosis

Clinical scenarios where empagliflozin or dulaglutide are recommended, but not funded

The recently released type 2 diabetes management guidelines developed by the New Zealand Society for the Study of Diabetes (NZSSD), and supported by the Ministry of Health, states that while the Special Authority criteria for empagliflozin and dulaglutide ensure access for those at high risk of cardiovascular and renal disease, the funding restriction is not fully consistent with best practice.[11]

Patients likely to benefit from these medicines who do not meet the criteria for funded treatment are those:[11]

- With cardiovascular disease (or five-year CVD risk ≥15%), renal disease or heart failure with an HbA_{1c} < 53 mmol/mol or eGFR 60 – 90 mL/min without albuminuria
- With cardiovascular disease (or five-year CVD risk ≥15%), renal disease or heart failure who are already taking funded empagliflozin or dulaglutide (i.e. dual treatment with these medicines is recommended, but only one can be funded at a time)
- Who are overweight or obese and have HbA_{1c} levels above target despite regular use of or inability to tolerate metformin, but who do not have cardiovascular or renal disease and are not of Māori or Pacific ethnicity
- With an HbA_{1c} above target despite regular use of or inability to tolerate metformin and vildagliptin, but who do not have cardiovascular or renal disease and are not of Māori or Pacific ethnicity
- With an HbA_{1c} within the target range but where an SGLT-2 inhibitor is preferred to reduce adverse effects, e.g. weight gain or hypoglycaemia with a thiazolidinedione or sulfonylurea, respectively

Discuss the recommendation with patients and the option to self-fund treatment, unless there are contraindications or significant cautions. This may be a challenging conversation to negotiate as there will be patients who are unable to meet the financial burden of self-funding treatment and may find this distressing.

Vildagliptin is recommended at Step 2 for people type 2 diabetes who are not eligible for funded SGLT-2 inhibitor or GLP-1 receptor agonist treatment (also see: "Clinical scenarios where where empagliflozin or dulaglutide are recommended, but not funded").[11] Vildagliptin is particularly useful in older patients, either combined with metformin or alone if metformin is contraindicated or not tolerated.

A new type 2 diabetes management guideline published by the New Zealand Society for the Study of Diabetes and the Ministry of Health is available here: **https://t2dm.nzssd.org.nz/**

Initiating funded treatment

To initiate funded empagliflozin or dulaglutide treatment, patients must have type 2 diabetes and meet **all** of the following criteria:[1]

1. Have at **least one** of the following characteristics:
   a) Māori or any Pacific ethnicity; or
   b) Pre-existing CVD or risk equivalent*; or
   c) An absolute five-year CVD risk of ≥ 15% according to a validated cardiovascular risk assessment calculator; or
   d) A high lifetime cardiovascular risk due to being diagnosed with type 2 diabetes during childhood or as a young adult; or
   e) Diabetic kidney disease†; and
2. HbA_{1c} level > 53 mmol/mol despite the regular use of at least one blood-glucose lowering agent (e.g. metformin, vildagliptin or insulin) for at least three months; and
3. Treatment will not be used in combination with a funded GLP-1 receptor agonist/SGLT-2 inhibitor (as appropriate)

* Defined as: prior cardiovascular disease event (i.e. angina, myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, transient ischaemic attack, ischaemic stroke, peripheral vascular disease), congestive heart failure or familial hypercholesterolaemia

† Defined as: persistent albuminuria (albumin:creatinine ratio greater than or equal to 3 mg/mmol, in at least two out of three samples over a 3 – 6-month period) and/or eGFR less than 60 mL/min/1.73m^2 in the presence of diabetes, without alternative cause

Applications can be made by any relevant practitioner and are valid without further renewal (unless notified) for eligible patients.

A calculator to assess cardiovascular disease risk in people with type 2 diabetes is available here: **https://www.nzssd.org.nz/cvd/**

Choosing between empagliflozin and dulaglutide

The decision to initiate a SGLT-2 inhibitor versus a GLP-1 receptor agonist* is based primarily on the predominant co-morbidity, i.e. CVD, heart failure or diabetic kidney disease, and patient preference, particularly regarding the route of administration (Figure 1).[11] If heart failure or diabetic kidney disease predominates, a SGLT-2 inhibitor (i.e. empagliflozin) is preferred. Otherwise either a SGLT-2 inhibitor or a GLP-1 receptor agonist is recommended; a GLP-1 receptor agonist treatment will likely lead to greater improvements in glycaemic control and weight loss than SGLT-2 inhibitor treatment.[11]

An interactive decision support tool is available here: **https://magicevidence.org/match-it/200820dist/#!/**

* Availability pending Medsafe approval

Dulaglutide is administered as a once weekly injection

Patients may be reluctant to take dulaglutide as it is an injectable treatment rather than an oral medicine. However, unlike insulin, which requires one or more daily injections, dulaglutide is administered once weekly. Furthermore, self-monitoring blood glucose is not necessary for patients taking dulaglutide, unless their regimen also includes a sulfonylurea or insulin. Providing patients who are hesitant about initiating an injectable treatment with this information may help them to feel more confident with this treatment option. A treatment trial of dulaglutide may be very useful before initiating insulin.

Prescribing empagliflozin

When initiating empagliflozin, reinforce lifestyle advice, i.e. dietary and exercise interventions, and offer support as required. Metformin should be continued unless it is contraindicated or not tolerated; combination empagliflozin + metformin formulations are available (Table 3).[11] Other glucose-lowering treatments (e.g. vildagliptin, a sulfonylurea, dulaglutide,* or insulin) should be continued if needed for glycaemic control or cardiovascular or renal protection.[11] If the patient is taking insulin or a sulfonylurea, the dose may need to be reduced; a reduction of 15 – 20% of the daily total insulin or 50% of the sulfonylurea dose is recommended as a starting point.[11] People with an HbA_{1c} > 75 mmol/mol do not usually require a reduction in insulin or sulfonylurea, unless they have a history of hypoglycaemia.[11] Patients taking SGLT-2 inhibitors must discontinue treatment during an acute illness or two days before an elective medical procedure.[11]

* Availability pending Medsafe approval; dual empagliflozin and dulaglutide treatment is not currently funded under the Special Authority criteria

For further information on sick-day management, see: **https://t2dm.nzssd.org.nz/Section-95-Sick-day-management-in-patients-with-diabetes**

Table 3. Key empagliflozin prescribing information.[11, 14, 15]

	Formulation	Dose information	Notes
Empagliflozin	10 mg and 25 mg, tablet	▪ Initiate at 10 mg daily ▪ Increase to maximum of 25 mg daily after several weeks if no adverse effects AND as required for glycaemic control	▪ Contraindicated for people with eGFR < 30 mL/min as it is ineffective in reducing glucose levels* ▪ No dose adjustment required for people with mild renal impairment
Empagliflozin with metformin hydrochloride	5 mg empagliflozin with 500 mg or 1000 mg metformin, tablet	▪ Initiate at 5 mg empagliflozin twice daily (10 mg total daily dose); choose the dose of metformin similar to the dose already being taken	▪ Contraindicated for people with eGFR < 30 mL/min due to metformin component and the ineffectiveness of the empagliflozin component
	12.5 mg empagliflozin with 500 mg or 1000 mg metformin, tablet	▪ Maximum recommended daily dose is 25 mg empagliflozin and 2000 mg metformin	▪ Reduce metformin dose for people with renal impairment; no empagliflozin dose adjustment is required for people with mild renal impairment

* It may assist kidney function, but this has not been definitively proven

At diagnosis:

Discuss non-pharmacological treatment:

- Lifestyle changes are the cornerstone of management; emphasise the importance of diet and exercise approaches regardless of which medicines are used
- Support and encourage patients to make lifestyle changes throughout follow-up
- Refer patients to support services, e.g. Green prescription or dietitian, to assist with lifestyle changes

Determine an appropriate HbA_{1c} target:

Prescribe an appropriate medicine regimen based on the extent of hyperglycaemia:

- Initiate metformin at, or soon after diagnosis, unless contraindicated
- Consider initiating two pharmacological treatments at diagnosis (e.g. metformin and vildagliptin) if HbA_{1c} > 64 mmol/mol
- Consider initiating insulin at diagnosis if patients have high HbA_{1c} levels at diagnosis, e.g. > 90 mmol/mol

Escalating treatment:

DKD* or HF or known CVD or five-year CVD risk ≥ 15%?

* DKD = urinary albumin:creatinine ratio > 3 mg/mmol and/or reduced eGFR

Yes

HF or DKD predominates?

Yes

SGL T-2 inhibitor preferred†

No

GLP-1 receptor agonist†
or
SGL T-2 inhibitor†

Treatment not tolerated or HbA_{1c} above target

Add another pharmacological treatment:

- GLP-1 receptor agonist preferred treatment to add to SGLT-2 inhibitor
- SGLT-2 inhibitor preferred treatment to add to GLP-1 receptor agonist

N.B. Dual SGLT-2 inhibitor/GLP-1 receptor agonist treatment not currently funded

Alternatives:

- Vildagliptin, if not on GLP-1 receptor agonist
- Pioglitazone (unless heart failure)
- A sulfonylurea
- Insulin

No

Add another pharmacological treatment:

- SGLT-2 inhibitor†
- GLP-1 receptor agonist†
- Vildagliptin

Alternatives:

- Pioglitazone
- A sulfonylurea
- Insulin

† Special Authority criteria apply
DKD = diabetic kidney disease
HF= heart failure
CVD = cardiovascular disease

Figure 1. An overview of management of patients with type 2 diabetes. Adapted from the New Zealand Society for the Study of Diabetes type 2 diabetes guideline (2021).[11]

Contraindications and cautions to empagliflozin treatment

Empagliflozin is currently contraindicated in people with severe renal impairment; it is ineffective at lowering glucose if eGFR < 30 mL/minute/1.73 m^2. Empagliflozin is not recommended for use in people who:[11]

- Are aged < 18 years
- Are pregnant or breastfeeding
- Have a history of severe genitourinary infections
- With nephrolithiasis/recurrent renal calculi
- Are on a ketogenic diet (due to the increased risk of diabetic ketoacidosis – see below)

For further information, refer to the New Zealand Formulary: **https://www.nzf.org.nz/nzf_70809**

Discuss potential adverse effects before initiating treatment

Adverse effects of SGLT-2 inhibitors such as empagliflozin include:[11]

- Polyuria – consider reducing diuretics before initiating treatment
- Genitourinary infections, e.g. urinary tract infection, vaginal thrush, balantitis – this is thought to be due to the increased urinary excretion of glucose. Ensure patients are given information on hygiene measures and the rare risk of necrotising fasciitis of the perineum (Fournier's gangrene).
- Hypotension – consider reducing antihypertensive medicines before initiating treatment or before a dose increase
- Diabetic ketoacidosis (DKA) – increased risk (see below)

SGLT-2 inhibitor use is associated with an increased risk of severe DKA

People taking SGLT-2 inhibitors are at increased risk of DKA, particularly in the first few months of treatment or peri-operatively.[11] This can occur with normal blood glucose levels (euglycaemia).[11] While this is a rare adverse effect (ranging from one in 1,000 to one in 3,000 people), this should be discussed with patients before initiating treatment, with advice provided on the symptoms and signs of DKA and when to seek medical attention to get their blood ketones checked (i.e. if they experience nausea, vomiting or abdominal pain).[11] In general, it is advisable to temporarily stop empagliflozin if patients are unwell and febrile, especially if they are not eating or vomiting.

N.B. Patients with type 2 diabetes taking a SGLT-2 inhibitor do not currently qualify for a funded CareSens Dual glucometer (measures both blood glucose and blood ketone levels).

For further information on SGLT-2 inhibitors and DKA, see: **https://diabetessociety.com.au/documents/ADS_DKA_SGLT2i_Alert_update_2020.pdf**

Prescribing dulaglutide

Dulaglutide, a GLP-1 receptor agonist, is awaiting approval by Medsafe. Once it has been approved, dulaglutide will be funded (with Special Authority) and the monograph will be available in the NZF.

When initiating dulaglutide, reinforce lifestyle advice and offer support as required, and provide information on how to administer treatment (see below). Metformin should be continued unless it is contraindicated or not tolerated.[11] Dipeptidyl peptidase-4 (DPP-4) inhibitors (i.e. vildagliptin) must be stopped before initiating a GLP-1 receptor agonist as they have similar mechanisms of action.[11] Other glucose-lowering treatments can be continued if needed for glycaemic control or cardiovascular or renal protection, with the dose of insulin or a sulfonylurea reduced to prevent hypoglycaemia, if required (see: "Prescribing empagliflozin" for guidance on dose reduction).[11] Advise patients to stop treatment if they have an acute gastrointestinal illness (and resume treatment once they have recovered).[11]

Table 4. Key dulaglutide prescribing information.[11, 16]

Funded GLP-1 receptor agonist*	Formulation	Dose information
Dulaglutide	1.5 mg per 0.5 ml prefilled pen, injectable	■ Administered subcutaneously, once weekly; each pen contains one dose of dulaglutide and should only be used once

* Other non-funded GLP-1 receptor agonists approved in New Zealand include liraglutide, exenatide and exenatide extended release (soon to be withdrawn from the local market)

Dulaglutide administration guide:[16]

- Dulaglutide is administered once weekly, at any time of day, with or without food
- Patients can inject dulaglutide in the abdomen, thigh or upper arm
- Injection sites should be rotated with each dose
- If a dose is missed, it should be administered as soon as possible if there are ≥ 3 days until the next scheduled dose; if < 3 three days until the next dose, the missed dose should not be taken, and the next dose taken at the normal time

- If the regimen includes insulin, these should be administered as separate injections, i.e. not mixed. If injected in the same body region, ensure the injections are not next to each other
- The single-use pen should be disposed of in a specified sharps container or a closable puncture-resistant container, i.e. not in the household rubbish*

* Community pharmacies and some Diabetes NZ branches offer sharps disposal services; patients can return their sharps in a specified sharps container (available to purchase) or other suitable container.

Patient instructions for use of dulaglutide (with images) are available from: **https://uspl.lilly.com/trulicity/trulicity.html#ug**

Contraindications and cautions to dulaglutide treatment

Dulaglutide is contraindicated in people with personal or family history of medullary thyroid carcinoma or a personal history of multiple endocrine neoplasia syndrome type 2.[11, 16] Rodent studies have shown an increased incidence of thyroid C-cell adenomas and carcinomas with GLP-1 receptor agonist treatment.[17] While a causal relationship has not been established and there is no evidence of increased prevalence of any form of thyroid cancer in humans with long-term use, dulaglutide is not recommended for use in people at increased risk of thyroid cancer, e.g. due to family history, radiation exposure.[11] Advise patients prescribed dulaglutide to seek medical advice if they develop any symptoms that could indicate thyroid cancer, e.g. a mass in the neck, dysphagia, dyspnoea, persistent hoarseness.[16]

Dulaglutide is not recommended for people:[11]

- Aged < 18 years
- Who are pregnant or breastfeeding
- With severe gastrointestinal disease, including gastroparesis
- With previous pancreatitis

Mild adverse effects with dulaglutide are usually transient

Common adverse effects of GLP-1 receptor agonists include gastrointestinal disturbance (nausea [most common], vomiting, anorexia and diarrhoea) and injection site reactions (e.g. nodules, pruritus, bruising, erythema).[11, 18] These are usually transient and improve with continued treatment.[11] Rare adverse effects include pancreatitis, myalgias and muscle weakness, Stevens-Johnson's syndrome and thrombocytopenia.[11]

Reviewing treatment and ongoing monitoring

Regular review of treatment is necessary for all patients with type 2 diabetes to optimise individual goals and ensure medicine regimens remain appropriate. Nutrition, physical activity and body weight monitoring should be discussed with patients at all stages of management. HbA_{1c} levels should be checked every three months if they are above target and the treatment regimen has changed.[11] Once target HbA_{1c} levels have been achieved, repeat measurement every six months and complete a diabetes review annually.[11] Renal function should be assessed at least annually in patients taking empagliflozin (with or without metformin) and prior to initiating any medicines that may reduce renal function.[14] No additional monitoring is required for patients taking dulaglutide.

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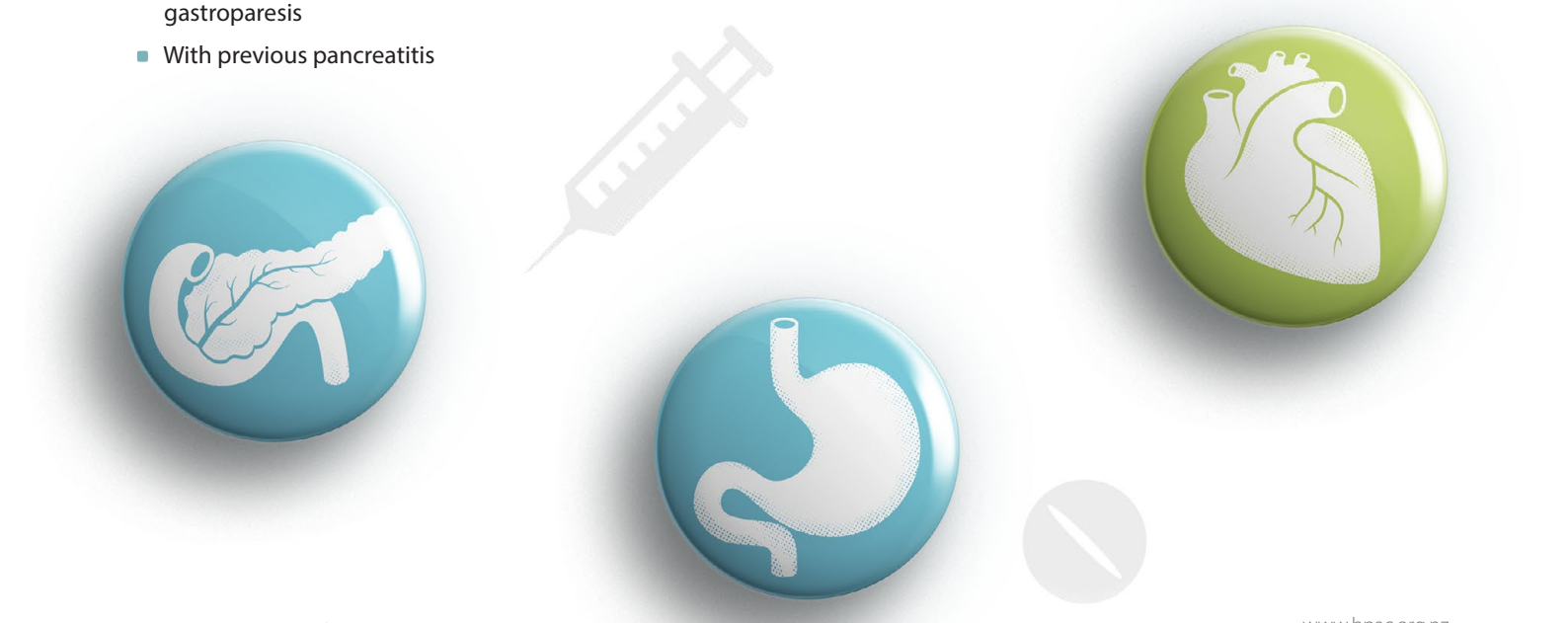
N.B. Expert reviewers do not write the articles and are not responsible for the final content. bpac^{nz} retains editorial oversight of all content.



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Prescribing statins to reduce cardiovascular risk

Lowering lipid levels should be viewed as one aspect of reducing a patient's overall cardiovascular disease risk, and treatment decisions are based on this. Statins remain the medicine of choice for lowering lipids and should be prescribed at an appropriate potency and dose; atorvastatin is the first-line choice of statin.

KEY PRACTICE POINTS:

- Statins are the recommended first-line lipid-lowering medicine in New Zealand and international guidelines
- The decision to initiate a statin should be based on individual cardiovascular disease (CVD) risk, the likely benefit of treatment and the risk of adverse effects
- Five-year CVD risk >15% or TC/HDL-C ratio ≥8: lipid-lowering treatment recommended with LDL-C target ≤1.8 mmol/L
- Five-year CVD risk 5 to 15%: consider benefits and risks of statin treatment. Aim for LDL-C target reduction of ≥40% if statin treatment is commenced.
- Five-year CVD risk <5%: recommend lifestyle interventions only
- Atorvastatin is the first line choice of statin treatment
- There is some evidence of benefit of adding ezetimibe for secondary prevention of CVD in selected groups of people
- Fibrates are no longer routinely used in New Zealand

Treat overall cardiovascular disease risk: a summary

There has recently been a shift in focus from treating hyperlipidaemia in isolation to an approach that aims to reduce a patient's overall cardiovascular disease (CVD) risk.[1] Risk calculators based on New Zealand PREDICT equations are now incorporated into decision support software for clinicians to begin discussions with patients. In addition, an interactive tool is available on the Heart Foundation website to aid patients' awareness and understanding of their CVD risk. New Zealand Primary Prevention Equations are designed for men and women aged 30–74 years; separate equations are used for people with or without diabetes.

Lifestyle modifications to reduce CVD risk are appropriate for everyone; this includes a healthy diet, regular exercise, weight management, limiting alcohol consumption and smoking cessation. Substituting saturated dietary fat with mono and polyunsaturated fats is most effective in reducing LDL-C whilst improving HDL-C from a dietary standpoint, based on current recommendations.[1]

For patients with a five-year CVD risk ≥15%, lipid-lowering and blood pressure-lowering medicines are recommended, as their risk is equivalent to the risk for people with prior CVD. Aspirin should also be considered in some groups (see: **https://www.health.govt.nz/publication/cardiovascular-disease-risk-assessment-and-management-primary-care**).[1]

There is a large body of evidence that supports the use of statins for both primary and secondary prevention of CVD.[2–4] However, there is still debate in the medical literature on the place of statins for primary prevention in people aged over 75 years, mainly due to a lack of quality evidence.[5–9]

A CVD risk assessment tool is available via bestpractice Decision Support on your patient management system. If your practice does not have access to this, contact BPAC Clinical Solutions: **https://bpacsolutions.co.nz/contact/**; alternatively, an online CVD risk calculator, with the option of using the Predict data, is available from: **http://chd.bestsciencemedicine.com/calc2.html**

The Heart Foundation interactive tool for patients is available here: **www.heartfoundation.org.nz/your-heart/my-heart-check**

Discussing cardiovascular risk with patients

Discussions about CVD risk reduction should begin with consideration of the patient's point of view, including their:[11]

- Current knowledge about their CVD risk and what this means to them
- Thoughts and beliefs regarding their health in the future
- Readiness to make (and sustain) lifestyle changes
- Feelings about taking long-term medicines to reduce risk

Sometimes a clinician will have to guide a patient to a more realistic view of their risk and help them to understand the implications of having an event, such as a stroke. An individualised plan for future management can be developed, based on current evidence and practice; check that the patient agrees with the plan and understands what has been discussed. Actively engaging the patient in decisions about their health means they are more likely to take responsibility and assist with attaining and sustaining lifestyle changes and may improve adherence to medicines if required.

For further information on communicating cardiovascular risk with patients, see: **www.bpac.org.nz/BPJ/2014/September/cvrisk.aspx**

When should a statin be considered?

Current New Zealand recommendations on lipid management are primarily determined by the patient's level of cardiovascular risk with some exceptions, e.g. those with a TC/HDL-C ratio ≥8:[1]

Pharmacological treatment is not recommended for people at low risk (<5%)

Lipid-lowering medicines are generally not recommended for patients with a five-year CVD risk less than 5%; lifestyle interventions should be encouraged.

Discuss the use of medicines for people with a 5–15% five-year intermediate risk

The benefits and harms of lipid-lowering medicines should be clearly presented and discussed with all patients with a five-year CVD risk of 5–15% to allow an individualised decision about the initiation of pharmacological treatment. However, the benefit of lipid-lowering treatment is likely to outweigh harm for most people in this risk category.

Lipid-lowering medicines are recommended for patients with existing CVD or a ≥15% five-year risk

All patients with known CVD or with a five-year risk ≥15% should be prescribed lipid-lowering treatment along with advice on lifestyle interventions.

Lipid-lowering medicines are recommended for patients with TC/HDL-C ratio ≥8 regardless of CVD risk

If a patient has a TC/HDL-C ratio of ≥8 despite lifestyle interventions, lipid-lowering medicines are recommended, regardless of their calculated CVD risk.

Key practice points from the Cardiovascular Disease Risk Assessment and Management for Primary Care: 2018 consensus – a reminder

In 2018 a consensus statement on CVD was published by the Ministry of Health and the Heart Foundation. Important changes from the previous New Zealand Primary Care Handbook: 2013 update included:[10]

- New Zealand Primary Prevention Equations were developed from the New Zealand PREDICT study rather than using Framingham equations which did not consider unique aspects of the New Zealand population
- Māori, Pacific and South Asian population screening now starts earlier at age 30 and 40 years for men and women, respectively
- Screening from age 25 years is recommended for those with severe mental illness due to high-risk categorisation
- New classification of clinical high-risk groups (heart failure, eGFR <30 mL/min/1.73 m^2 and diagnosis of asymptomatic carotid or coronary disease)
- >15% CVD risk or TC/HDL-C ratio ≥8, classified as high-risk, lipid-lowering treatment recommended
- 5–15% CVD risk classified as intermediate risk, benefits/harms to be discussed about whether to initiate treatment
- <5% CVD risk, no pharmacotherapy, lifestyle improvement recommended
- Introduction of 'targets' for lipid management. High-risk individuals are recommended to aim for an LDL-C target of 1.8 mmol/L or lower. Intermediate-risk individuals taking statin treatment, are recommended to aim for an LDL-C target reduction of 40% or greater.

For further information, see: "2018 Cardiovascular Disease Risk Assessment and Management Series" available at **https://bpac.org.nz/** or for information on specific subgroups, see: CVD Consensus Statement Updates – Heart Foundation, available from: **www.heartfoundation.org.nz/professionals/health-professionals/cvd-consensus-summary**

People with very high triglycerides need special consideration

Patients with very high triglyceride levels (>11 mmol/L) may benefit from lipid-lowering medicines, independent of their estimated CVD risk as they are at increased risk of pancreatitis. Advice on lifestyle interventions and appropriate management of co-morbidities, e.g. diabetes, is strongly recommended and may successfully reduce triglyceride levels. If triglyceride levels remain high in these patients despite lipid-lowering treatment, consider discussion with a cardiologist.

For full details of the CVD risk assessment and management for primary care, see: "Cardiovascular Disease Risk Assessment and Management for Primary Care", available from: **www.health.govt.nz/publication/cardiovascular-disease-risk-assessment-and-management-primary-care**

Discuss risks and benefits before prescribing a statin

If a patient's CVD risk indicates that a statin may be appropriate, consider the following discussion points:[1, 11]

- How successful lifestyle changes have been
- Patient preference
- Co-morbidities
- Other medicines currently being prescribed
- General frailty
- Life expectancy

There is satisfactory evidence that statin treatment results in beneficial effects for CVD risk reduction, such as:[21]

- Statins through each mmol/L reduction in LDL-C, reduce relative CVD risk by 25% over five years
- Statins can reduce LDL cholesterol by >50 % in people who have a pre-treatment LDL-C level of ≥4 mmol/L
- Every 1 mmol/L decrease in LDL-C produces a reduction in major vascular events of approximately 25% and reduction in coronary mortality of at least 20% in patients at differing levels of CVD risk
- If 10,000 patients took an effective dose of a statin for primary prevention for five years which resulted in an LDL-C reduction of 2 mmol/L, major vascular events would be prevented in approximately 500 (5%)
- If 10,000 patients took an effective dose of a statin for secondary prevention for five years which resulted in an LDL-C reduction of 2 mmol/L, major vascular events would be prevented in approximately 1,000 (10%)

The risks of statin treatment include potential adverse effects (see: "The debate about adverse effects of statins"), medicine interactions, polypharmacy and "pill burden".

The balance of benefit and risk will differ for each patient. For example, people at the highest CVD risk will benefit the most from taking a statin, with larger reductions in absolute risk, and any potential harms from statin treatment likely to be perceived as a lower risk. In contrast, people at a lower level of CVD risk receive less benefit from taking a statin but have the same risk of harms, therefore may feel that the risk of taking a statin outweighs the benefit.[1] An informed discussion about potential adverse effects of statins and how these can be managed (see below), and reassurance about any "myths" about statins, may help in this decision process.

Age alone is not a reason to decline a statin

There is increasing evidence that statins benefit older people for both primary and secondary prevention, therefore age alone is not a reason to decide against or to stop a statin (see: "The benefits of using statins among older people").[5] The decision to initiate a statin in an older patient for primary prevention should take into account factors such as frailty, co-morbidities, life-expectancy, polypharmacy, the potential for adverse effects and interactions as well as the patient's view on taking preventative medicines.[5, 11, 22, 23]

Providing a definite age cut-off at which a statin should not be prescribed is difficult due to the physical heterogeneity of older people, and also because risks and benefits do not "change overnight" when a person reaches a certain age, e.g. 75 years.[11, 23] Current New Zealand Primary Prevention Equations have not been validated for people aged 75 years and older and such are estimates only; equation estimates can still be a useful indicator or starting point in CVD management.[1]

Whether a statin should be de-prescribed in an older person also depends on individual factors. A study recently found from 18 international guidelines that discontinuation among older adults was primarily due to health status and statin intolerance.[24] The decision may be straightforward in a patient with limited life expectancy or a poor functional status, but is likely to be more complicated in those who are well and independent, or those at very high risk of recurrent cardiovascular events where there is evidence of continued benefit.[25, 26]

For further information, see: "A guide to deprescribing - general information" and "A guide to deprescribing – statins", available from: **http://www.cpsedu.com.au/resources**

International guidelines on lipid-lowering

There have been a number of new or updated international guidelines on dyslipidaemia and CVD risk reduction over the last few years.[3, 11–17] Changes were made due to evidence indicating that better outcomes could be achieved, especially in primary prevention, by the management of absolute CVD risk rather than management of single risk factors.[3,18,19] There has been some criticism of this risk-based approach because it widens the number of people who would "qualify" for treatment with a statin, yet other authors feel that statins are underused.[5]

The majority of international guidelines now follow a similar approach, including that:[1, 3, 9, 12–16, 18, 19]

- Lipid management should be viewed as one aspect of reducing CVD risk rather than in isolation
- There remains an emphasis on intensifying lifestyle modifications to reduce CVD risk for all patients, particularly smoking cessation, weight optimisation, exercise and healthy diet
- There is shared decision making and comprehensive discussions with patients
- There is a focus on prescribing a statin of appropriate intensity and titrating to the maximum tolerated dose for each patient to reflect risk level
- LDL-C is used as a tool for monitoring effectiveness and change
- Sub-optimal LDL-C despite maximum tolerated dose of statin and lifestyle, allows for non-statin treatments to be considered in high-risk adults
- Ezetimibe may be considered for secondary prevention in certain circumstances such as people with statin intolerance and/or familial hypercholesterolaemia
- Fibrates are not generally recommended

Variations between the major guidelines, include:[9, 16, 19, 20]

- The way in which CVD risk is determined (which tool is used) and how it is expressed, e.g. five versus ten years
- Definition of high-risk populations and their subsequent management
- Risk modifiers such as blood pressure or diabetes
- The CVD risk threshold at which treatment with a statin is recommended
- Whether or not a specific reduction in lipid levels is recommended
- The use of fasting or non-fasting lipid levels

Choice and dose of statin

Atorvastatin is the first-line choice of statin for most patients. If it is not tolerated, consider lowering the dose or changing to another statin (see "An approach to managing statin-associated symptoms").

The recommended dose is:[30]

- Five-year CVD risk 5–15%: 10–20 mg atorvastatin (max 80 mg daily)
- Five-year CVD risk >15% (including those with known CVD): 10–40 mg atorvastatin (max 80 mg daily)

It is recommended to monitor non-fasting lipids every six-to-twelve months until the desired target is reached. Once achieved, annual monitoring is appropriate.[1]

Statin intensity

Statins can be classified by the percentage that they can reduce LDL-C levels, referred to as the intensity, which may help in determining equivalent doses if switching between statins due to intolerance (Table 1).[14] Rosuvastatin (not funded) is the most potent statin available in New Zealand, followed by atorvastatin, simvastatin then pravastatin.[30]

N.B. The maximum recommended dose for simvastatin is 80 mg, however, doses of simvastatin above 40 mg should be used with caution due to the increased risk of myopathy and in most cases patients should be prescribed atorvastatin if higher doses are required.[4, 30]

Timing of administration

Cholesterol biosynthesis peaks overnight, therefore statins with a short half-life, such as simvastatin and pravastatin, should be taken in the evening.[31] Statins with a longer half-life, such as atorvastatin and rosuvastatin, can be taken in the morning or at night with equivalent efficacy.[31] Being able to take a statin at their preferred time of the day is likely to improve a patient's adherence to treatment and reduce discontinuation.

The benefits of using statins among older people

Data from JUPITER and HOPE-3 trials began discussions on statin use among older people; use of statins for primary prevention in those aged 70 years and older was supported based on evidence of benefit for non-fatal stroke, myocardial infarction and cardiovascular death, but there was a non-significant reduction in all-cause mortality.[22] However, it should be noted that the proportion of older participants in these trials were small, and that both had initial support from the pharmaceutical industry.

Since then further benefits in older people have been reported such as:

- In patients aged 75 years and older, lipid-lowering treatments were found to be as effective in reducing CVD events as in those aged less than 75 years[27]
- Statin treatment for primary prevention of CVD in people aged 50 to 75 years with a life expectancy of at least 2.5 years was found to reduce CVD events[28]
- A systematic review and meta-analysis found no additional prevalence of muscle-related symptoms, adverse effects or treatment cessations attributable to statin treatment among older adults without CVD[29]

A systematic review comparing international guidelines supported the use of statins for primary prevention in this population.[7]

Table 1: Statin potency table: approximate equivalence.[1]

Treatment Intensity	Pravastatin	Rosuvastatin	Atorvastatin	Simvastatin	%↓LDL-C
Low	20 mg			10 mg	30%
Medium	40 mg		10 mg	20 mg	38%
Medium	80 mg	5 mg	20 mg	40 mg	41%
High		10 mg	40 mg	80 mg†	47%
High		20 mg	80 mg		55%
Very High		40 mg			63%

† Simvastatin 80 mg, daily, may be associated with an increased risk of muscle-related adverse effects [5]

Managing adverse effects of statins

Most patients tolerate statin treatment well. Serious adverse effects are rare and most emerge in the first three months of use.[32] A recent systematic review of evidence from randomised controlled trials reported that the only adverse effects that have been reliably proven to be caused by statins were myopathy (muscle pain or weakness with a rise in creatinine kinase), an increased risk of the development of type 2 diabetes (see "Statin use and diabetes") and an increase in haemorrhagic stroke (although this is outweighed by the decreased risk of ischaemic stroke).[21] Depending on the concentration of the statin (influenced by co-morbidities), rhabdomyolysis can occur; although rare, this can lead to significant kidney problems.[33]

Adverse effects with long-term statin treatment:[1]

- For every 10,000 people treated for five years, five cases of myopathy would result
- For every 10,000 people treated per year, additional muscle related problems would occur in every 10–20 cases. Of those, only one case would be expected to have significantly elevated creatine kinase levels.
- For every 10,000 people treated for five years, 50–100 new cases of diabetes would result

"Statin-associated symptoms"

Observational studies report a wider range of adverse effects and appear to be more in step with "real world" experiences of people taking statins. The lack of consensus on whether

Statin use and type 2 diabetes

Statins as a class can increase the risk of developing hyperglycaemia and insulin resistance which eventually can lead to the development of type 2 diabetes, possibly due to the raised activity of LDL receptors allowing more cholesterol to enter pancreatic cells.[21] People most at risk of developing diabetes while taking a statin are those who already have risk factors such as impaired fasting glucose, elevated HbA_{1c}, increased BMI or advanced age.[21] Meta-analyses from randomised controlled trials report that the risk of developing diabetes ranges from approximately 4–12%, but if observational studies are included, much higher figures are quoted, e.g. 44% increase in risk.[38–40] More recently, a study reported a 38% increased risk of type 2 diabetes associated with statin use.[41] Preventative strategies such as weight management and dietary control can be used to minimise type 2 diabetes risk prior to statin treatment.

Pravastatin (lowest potency statin) is associated with the lowest risk of developing new onset diabetes mellitus, atorvastatin has moderate risk and rosuvastatin (highest potency) has the highest risk.[33] As well as the dose-dependent risk, there is also a time-dependent risk of developing type 2 diabetes.[42] The evidence also suggests that statin treatment should not be withheld in people at risk of diabetes or if diabetes develops, as the expected decrease in major vascular events when taking a statin is greater than the increased CVD risk with statin-induced diabetes.[21]

The possibility of this adverse effect should be discussed with patients prior to prescribing a statin, especially those with pre-existing risk factors for diabetes.

statins are actually causative has led to the use of the term statin-associated symptoms.[16, 18, 34, 35] It is estimated that statin-associated muscle symptoms (e.g. muscle aches and weakness, not necessarily accompanied by a rise in creatinine kinase) affect 10–15% of people taking statins.[18] Other reported statin-associated symptoms include effects on cognitive function primarily memory loss and confusion, but also effects on sleep and mood, and changes in hepatic* and renal function. While there is a lack of evidence that these symptoms are actually caused by statins, they are clinically important as they contribute to the way people feel about taking statins and can result in poor adherence and cessation.

The nocebo effect (the opposite of the placebo effect) can also influence a patient's decision to start, or continue, a statin.[35] This is when patients expect to experience adverse effects based on information from the media, other people or even from their clinician.[35, 36] Whether statin-associated muscle symptoms are caused by a pharmacological effect or nocebo effect remains controversial.[32]

* Statins can cause usually asymptomatic elevations in liver function tests particularly early in treatment, however, hepatotoxicity is very rare.[21]

For further information, see: "The nocebo effect: what is it, why is it important and how can it be reduced?", available from: **https://bpac.org.nz/2019/nocebo.aspx**

An approach to managing statin-associated symptoms

When a patient taking a statin reports symptoms, a suggested approach is to:[1, 34, 35]

- Review the patient's other medicines to check for interactions and evaluate risk factors
- Check creatine kinase (CK) levels only in those with symptomatic muscle pain, tenderness or weakness. Request liver function tests only if hepatotoxicity is suspected.
- Reduce dose or discontinue the statin for muscle pain without a rise in CK. Reconsider statin once symptoms have subsided.
- Monitor symptoms and CK weekly along with dose reduction or discontinuation with a CK rise three to ten times above normal
- Discontinue statin immediately with a rise in CK of more than ten times above normal with symptoms

Current expert advice and limited trial evidence supports the view that any statin is better than no statin, and patients should be encouraged to persist with treatment at whatever dose and frequency they can tolerate.[35] If symptoms recur when the statin is recommenced consider options such as dose reduction, alternate day dosing, or switching to another lipid-lowering treatment.[35] Alternative day dosing has been found to be better tolerated than every day dosing for myalgia, however the CVD benefit has not yet been demonstrated.[35] Some patients may tolerate low dose pravastatin (the least potent statin), others may prefer to take atorvastatin intermittently, e.g. twice a week. If the symptoms recur gradually but are initially tolerable some patients may find "pulse dosing" a useful strategy. This is where the statin is taken for a specified time followed by a break and then repeating on a continuing cycle (e.g. statin for three months, stop for one month and then restart pattern).[36]

It is important to identify those who are truly statin intolerant to avoid unnecessary discontinuation of the beneficial treatment.

Be aware of medicine interactions with statins

Statins can have serious interactions with some other medicines; in particular, be aware of the interaction between simvastatin and potent CYP3A4 inhibitors such as erythromycin, clarithromycin, azole antifungals (e.g. itraconazole, ketoconazole) and ciclosporin, which can result in rhabdomyolysis.

For further information, see: Simvastatin and atorvastatin: beware of potential CYP3A4 interactions when prescribing other medicines, available from: **http://www.bpac.org.nz/BPJ/2014/April/news.aspx**

Check for medicine interactions prior to prescribing a statin to reduce the risk of adverse effects: **www.nzf.org.nz**

Should other lipid-lowering medicines be considered?

Some international guidelines recommend the use of non-statin medicines for the primary or secondary prevention of CVD, such as ezetimibe and alirocumab, both of which are available in New Zealand (only ezetimibe is funded).[3, 14–16, 18] A non-statin medicine, e.g. ezetimibe may be considered in high risk patients such as those who have had a CVD event in addition to a statin, if lifestyle measures and optimal statin treatment (maximally tolerated dose and potency of statin) has not produced a sufficient response, or as monotherapy if a statin is intolerable or contraindicated.[14]

Ezetimibe

Ezetimibe inhibits the absorption of dietary cholesterol in the small intestine resulting in LDL-C reductions.[30] Most guidelines now recommend that ezetimibe be considered in patients with familial hypercholesterolaemia as a monotherapy if statins are intolerable or contraindicated, or added to a statin if the patient's lipid levels are not adequately controlled despite optimal statin treatment.[3, 15–18]

Evidence from IMPROVE-IT show ezetimibe when added to simvastatin reduces cardiovascular events in patients with previous acute coronary syndrome. When stratified by diabetes, the benefit of the combination treatment was enhanced in patients with diabetes and those high-risk patients without diabetes.[43] A meta-analysis found ezetimibe reduces the risk of myocardial infarction and stroke by 13.5% and 16% respectively and its use has since been recommended in combination with a PCSK9 inhibitor, should the maximum tolerated dose of a statin not achieve LDL-C goals.[18, 44] A 2020 study found ezetimibe plus a statin to be more effective in reducing LDL-C than doubling the dose of the statin; in accordance with those results, a meta-analysis and systematic review found treatment with ezetimibe and a statin produced a modest LDL-C reduction compared to a statin alone. Furthermore, atorvastatin and ezetimibe together have been found to have the best therapeutic effect.[45]

Other non-statin medicines

Alirocumab: This is a PCSK9 inhibitor which enhances LDL-C uptake by increasing the number of LDL-receptors.[30] Although an approved medicine in New Zealand, it is not subsidised on the community pharmaceutical schedule and given it is a monoclonal antibody-based treatment, is expensive. Since 2019, alirocumab has been included in the ESC/EAS guidelines for dyslipidaemia due to efficacy advancements in this class.[18] PCSK9 inhibitors in addition to statins or ezetimibe, are effective for people intolerant of other treatments or for those who are unable to meet their LDL-C goals despite optimal use of other medicines.[18] Recent results demonstrate alirocumab taken every other week significantly reduces ischaemic events, with the majority of patients on a high potency and high dose statin.[46] However, there is minimal evidence on safety or use in place of a statin, so it is first recommended to try other lipid-lowering treatments.[46]

Fibrates

Fibrates primarily lower triglycerides and increase HDL-C. They are no longer routinely recommended for reducing CVD risk for either primary or secondary prevention due to a lack of strong evidence in the reduction of cardiovascular morbidity, mortality and LDL-C.[9, 36] Gemfibrozil has now been discontinued leaving bezafibrate as the only fully funded fibrate available in New Zealand.

Bezafibrate, although not routinely recommended and advised against in some guidelines, may be used in conjunction with statin treatment in patients with a high CVD risk where lifestyle changes and a maximally tolerated dose of statin have not produced reasonable reductions in lipid levels.[11] This combination increases the risk of myopathy; to minimise this risk it is suggested that the fibrate is taken in the morning and the statin in the evening.

N.B. Nicotinic acid is no longer recommended as a lipid-lowering treatment, either as monotherapy or in combination with a statin.[11]

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Early detection of lung cancer in primary care

Lung cancer is one of the most common cancers in New Zealand and the leading cause of cancer death. By the time of diagnosis, most people already have advanced disease, when there is little or no chance of cure. Increasing the early detection of lung cancer in high-risk symptomatic people is therefore key to improving survival outcomes.

KEY PRACTICE POINTS:

- Lung cancer accounts for the most cancer-related deaths in New Zealand; mortality rates are high compared to countries with similar healthcare systems
- Lung cancer incidence and mortality rates in Māori and Pacific peoples are two to three times higher than in Europeans/Others
- Early detection of lung cancer increases the chance of survival, however, many people present late when the disease is already at an advanced stage. Contributing factors include the subtlety of symptoms, difficulties accessing care because of cost, location or other systemic barriers, and psychological factors such as denial or fear.
- Clinical barriers to early detection include the lack of specific symptoms, attributing symptoms to another respiratory condition or cause (e.g. smoking), and discontinuities in care
- People at high risk of lung cancer include those with a current or previous history of smoking, asbestos exposure, pre-existing lung disease, personal history of any cancer or family history of lung cancer. All people at high risk should undergo a respiratory assessment annually to determine if symptoms are present (see below). Most lung cancers are diagnosed in people aged > 40 years.
- Key symptoms and signs that may be suggestive of early stage lung cancer, particularly in those with known risk factors, include unexplained persistent (> 3 weeks) cough (new or changed), haemoptysis, chest or shoulder pain, unresolved or recurrent chest infection, breathlessness, hoarseness and weight loss
- Refer people aged 40 years and over with symptoms or signs of lung cancer for urgent chest x-ray (preferably same day, if available); x-ray should be completed, reviewed and reported within one week of referral

Lung cancer is the leading cause of cancer death in New Zealand

Lung cancer is one of the most common cancers in New Zealand and accounts for the most cancer-related deaths.[1] In 2017, there were 2,232 lung cancer* registrations and 1,779 lung cancer deaths, equating to nearly 20% of all cancer deaths.[2,3] Lung cancer mortality rates in New Zealand are high compared to other countries with similar healthcare systems. A comparison of five-year survival rates (2010–2014) between seven high-income countries† found that New Zealand had the second lowest lung cancer survival rate (16%), ahead of only the United Kingdom (15%); the highest survival rates were in Canada (22%) and Australia (21%).[4] Various factors are likely to explain this finding, including late presentation and diagnosis and lack of access to funded treatments.

* Includes malignancy of the trachea, bronchus and lung (ICD-10 codes C33–C34)

† Australia, Canada, Denmark, Ireland, New Zealand, Norway and the United Kingdom

Early detection is key to increasing lung cancer survival rates

The stage at diagnosis is a major determinant of lung cancer prognosis, i.e. the earlier the stage the greater the chance of curative treatment. A study of people in the New Zealand Midland Cancer Network region who were diagnosed with early-stage lung cancer (stage I and II – see "Types and stages of lung cancer" for definitions) between 2011–2018 found a five-year survival rate of 70% in those who underwent curative-intent treatment – mainly surgery, but increasingly with stereotactic ablative body radiotherapy.[5] However, most people have advanced disease at diagnosis (see: "Factors contributing to the late presentation and detection of lung cancer"). Another study in the Midland Cancer Network region found that only 17% of people were diagnosed with early-stage lung cancer; 61% were diagnosed with advanced-stage (stage IV) cancer.[6] The one-year survival rate in people diagnosed with advanced lung cancer is typically < 20%.[7]

Types and stages of lung cancer

There are two main classifications of lung cancer: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC is the most common type of lung cancer; 89% of people in New Zealand diagnosed with lung cancer between 2008 and 2012 had NSCLC.[1] SCLC tends to metastasise earlier, is more aggressive and harder to treat than NSCLC.[6] SCLC is more common in Māori than non-Māori, even after controlling for smoking status;[6] the reason for this is not known, but may involve genetic factors.

Lung cancer, as with many other cancers, is typically staged using the TNM system, which describes the primary tumour (T), spread to nearby lymph nodes (N) and metastasis (M). The overall stage is then determined based on the TMN characteristics.

The stages of NSCLC are:[8]

- **Stage 0:** The cancer is small in size and has not spread into deeper lung tissues or outside the lungs (also known as carcinoma in situ).
- **Stage I:** Cancer may be present in the surrounding lung tissues, but the lymph nodes remain unaffected.
- **Stage II:** Cancer may have spread to nearby lymph nodes or into the chest wall.
- **Stage III:** Cancer has spread from the lungs to the lymph nodes or to nearby structures and organs, such as the heart, trachea and oesophagus.
- **Stage IV:** Cancer has metastasised to distant lymph nodes, structures or organs not near the lung.

The stages of SCLC are:[9]

- **Limited (equivalent to stages 0–III):** Cancer is only on one side of the chest.
- **Extensive (equivalent to stage IV):** Cancer has spread widely throughout the lung, to the other lung, to lymph nodes on the other side of the chest, or to other parts of the body.

Factors contributing to the late presentation and detection of lung cancer

Illness presentation

Early stage lung cancer can easily be missed as people are often asymptomatic and when symptoms do develop they are typically non-specific, commonly encountered in primary care, e.g. cough, chest pain, breathlessness, and usually have a non-malignant cause.[12]

N.B. SCLC can present differently to NSCLC (see "Types and stages of lung cancer"); the duration of symptoms is often shorter as SCLC is more aggressive.

Concurrent chronic respiratory symptoms

People with lung cancer often have a history of chronic respiratory symptoms or disease, particularly those who smoke[12] Patients and clinicians may have difficulty identifying changes in chronic symptoms and may be more likely to attribute changes to their co-existing respiratory condition and/or to smoking, rather than potential lung cancer.[12] However, chronic respiratory disease is a risk factor for lung cancer, even after controlling for smoking history.[13] Clinicians should therefore have a low threshold for investigating lung cancer in patients who have persistent symptoms, including those with COPD (see: "Assessing people with symptoms and signs of lung cancer").

Psychological factors

Denial, fear, shame and nihilism (belief that if lung cancer is diagnosed it cannot be treated) are common psychological factors that may contribute to people delaying their presentation to primary care or other healthcare service.[12] Public awareness of the causal link between smoking and lung cancer may lead some people to feel embarrassed, ashamed, or think that they are undeserving of or unable to access treatment. Incorporating positive messaging about the benefits of early detection, rather than focusing on blame due to smoking, may help to encourage people who have risk factors for lung cancer to present earlier.

What can primary care do to improve early detection rates?

Increasing early detection is critical to improving lung cancer survival rates, and primary care has an essential role in achieving this outcome by:

- Encouraging people not to start smoking and supporting smoking cessation
- Considering lung cancer as part of the differential diagnosis in patients with symptoms that could be indicative of cancer
- Identifying and assessing people with symptoms and signs of lung cancer and ensuring prompt referral and follow up for chest x-ray and secondary care assessment, as appropriate
- Identifying and assessing people at high risk of lung cancer, and providing advice about when to seek medical attention if they become symptomatic in a non-judgemental way that focuses on the benefits of early detection (see: "Factors contributing to the late presentation and detection of lung cancer")

N.B. A lung cancer screening pilot study including high-risk Māori patients from up to 50 general practices across the Auckland and Waitematā DHBs has been planned.[10] A recent study showed that biennial lung cancer screening with low-dose CT is likely to be cost-effective, improve total population health and reduce health inequities in New Zealand.[11]

Lifestyle, environmental, occupational and personal factors contributing to lung cancer risk

There are a range of factors that increase a person's risk of developing lung cancer (Table 1); those considered at highest risk are people with:[14]

- A current or previous history of smoking
- A history of exposure to asbestos
- Pre-existing lung disease, particularly chronic obstructive pulmonary disease (COPD) or interstitial lung disease
- A personal history of any cancer
- A family history of lung cancer

The incidence of non-smoking-related lung cancer is increasing

The incidence of lung cancer among people who have never smoked is increasing worldwide, particularly in females and people of East Asian ethnicity.[14] The cause of non-smoking-related lung cancer is not always known; genetic susceptibility and/or current or past exposure to environmental or occupational pollutants may explain this trend.[23] People with non-smoking-related lung cancer tend to be significantly younger, have a better prognosis and respond to treatment better than people with smoking-related lung cancer.[23]

Table 1. Risk factors for developing lung cancer[14]

Category	Risk factor	Comments
Lifestyle	Current or previous history of smoking	The major modifiable risk factor for lung cancer; approximately 90% of cases in males and 65% of cases in females are attributed to smoking[15]
Environmental or occupational	Passive smoking	Exposure to passive smoke is estimated to increase the risk of lung cancer by approximately 25%[16]
	Occupational exposure to known carcinogens, e.g. asbestos, diesel exhaust, silica, radon	Asbestos exposure can cause mesothelioma, a peripheral tumour that can be easily missed on chest x-ray if at an early stage. Radon exposure in New Zealand is low as soils only contain trace amounts of uranium and radium (the sources of radon).[17] A 2016 survey of indoor radon concentrations in New Zealand buildings (mainly private dwellings/houses in the main centres) identified no radon affected areas that warrant specific monitoring.[18] Underground miners may be exposed to higher concentrations of radon; WorkSafe has guidance outlining ventilation requirements and mine operators are responsible for ensuring monitoring arrangements are in place for detecting radon.[19]
	Air pollution	In general, New Zealand has good air quality in most places at most times of the year.[20] During autumn and winter, emissions from home heating can raise particulate matter to levels above recommended limits, especially when environmental and geographical conditions contribute to build up.[20] However, the extent to which this contributes to lung cancer incidence is not known. A cohort study of people living in urban centres in New Zealand investigating the association between air pollution and mortality found a positive association between estimated long-term exposure to air pollution and lung cancer mortality, i.e. the risk of mortality in people with lung cancer was higher in those exposed to air pollution.[21]
Personal	Increasing age	Lung cancer is rare in people aged < 40 years and is most commonly diagnosed in people aged ≥ 60 years.[6] East Asian ethnicity, female sex and family history are risk factors for a lung cancer diagnosis in people aged < 40 years.
	Family or personal history of lung cancer; personal history of other cancer, e.g. head and neck, bladder	Lung cancer is a common second cancer among people who have survived a first cancer[22]
	Pre-existing lung disease, e.g. COPD, interstitial lung disease, tuberculosis	Cancer risk is likely related to the increased lung inflammation associated with these conditions[13]
	Māori or Pacific ethnicity	Lung cancer incidence rates are two to three times higher in Māori and Pacific peoples than other ethnic groups (see: "Lung cancer incidence and mortality rates are higher in Māori and Pacific peoples")

Lung cancer incidence and mortality rates are higher in Māori and Pacific peoples

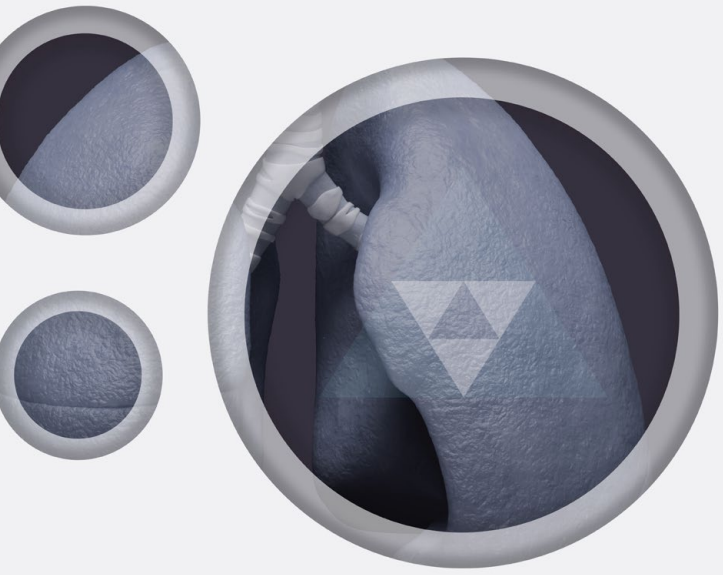
Māori have higher rates of lung cancer at an earlier age than non-Māori.[1] In 2017, the incidence and mortality rates were 3.7 and 3.4 times higher, respectively, in Māori than non-Māori.[2, 3] Lung cancer incidence is higher in Māori females than males, however, the mortality rate is similar between the sexes.[2, 3]

Pacific males are also disproportionately affected by lung cancer. The incidence rate between 2006 and 2011 was nearly two times higher in Pacific males than European/Others and mortality rate was nearly 2.5 times higher.[24] Neither the incidence nor mortality rates for lung cancer were significantly different between Pacific females and European/Others.[24]

High rates of smoking among Māori and Pacific peoples is an important contributing factor to the increased incidence of lung cancer in these groups (see: "Continue to encourage and support smoking cessation"). The 2019/20 New Zealand Health Survey* found that 31% of Māori aged 15 years and older reported current† tobacco smoking, with higher rates in females (35%) than males (27%).[25] Among Pacific peoples, 22% reported current tobacco smoking, with higher rates in males (27%) than females (19%).[25] Smoking rates in Europeans were nearly three-fold lower than Māori and two-fold lower than Pacific peoples.[25] Other contributing factors include higher rates of COPD and reduced healthcare access and continuity of care in these ethnic groups.[26]

* Due to the COVID-19 pandemic, data were collected for three-quarters of the survey year only

† Defined as people who smoke at least monthly and have smoked more than 100 cigarettes in their lifetime



Assessing people with symptoms and signs of lung cancer

The symptoms or signs of lung cancer can be variable and non-specific; they may include:[14, 15, 27]

- Haemoptysis
- Cough (new or changed; may be dry or productive)
- Shortness of breath
- Chest or shoulder pain
- Hoarse voice – due to laryngeal nerve compression
- Fatigue
- Weight loss > 10%
- Abnormal chest signs
- Unresolved chest infection
- Pleural effusion
- Thrombocytosis
- Venous thromboembolism
- Finger clubbing
- Symptoms or signs of metastatic lung cancer, such as in brain, bone, liver or skin (e.g. subcutaneous nodules)
- Cervical or persistent supraclavicular lymphadenopathy
- Superior vena cava syndrome
- Horner syndrome
- Paraneoplastic syndromes

Many of these symptoms or signs will have a cause other than lung cancer. However, due to the benefits of early detection, lung cancer should always be considered in patients who have any of the above symptoms or signs that are unexplained and/or persistent (lasting > 3 weeks*).[14] Even if there is a likely explanation for the patient's symptoms, e.g. recent upper respiratory tract infection, consider whether investigation with chest x-ray is indicated based on risk factors for lung cancer. If immediate chest x-ray is not necessary, arrange a follow-up appointment within an appropriate timeframe to check for symptom resolution; cough in particular can persist for longer than three weeks following a viral respiratory tract infection.

* A shorter timeframe may be appropriate for people with known risk factors or those presenting with multiple symptoms or signs[15]

Immediate referral to the emergency department is indicated for people with:[14, 15]

- Massive haemoptysis
- Signs of airway obstruction, e.g. stridor or respiratory distress
- Signs of superior vena cava obstruction, e.g. dilated veins in neck or over chest, swollen face or head, redness of face
- Symptoms or signs of spinal cord compression

Clinical assessment of patients with suspected lung cancer

The assessment of patients with symptoms or signs suggestive of lung cancer should include:

- A comprehensive history of the symptoms, i.e. onset, duration, frequency, changes from any concurrent respiratory symptoms, change in appetite or weight loss
- Documentation of the patient's personal history of smoking, environmental or occupational exposures to known carcinogens, personal or family history of lung or other cancer
- Physical examination that includes:
  - General appearance and basic observations, e.g. weight, breathlessness at rest or with mild exertion, heart rate, blood pressure, oxygen saturation
  - Respiratory assessment that includes:
    - Inspection – respiratory rate, pattern, effort of breathing, tracheal deviation, peripheral features, e.g. finger clubbing, evidence of superior vena cava obstruction
    - Palpation – chest expansion, chest wall tenderness, tactile fremitus, lymphadenopathy
    - Percussion – including assessment of the diaphragm, presence of localised dullness or effusion
    - Auscultation
  - Abdominal palpation, including assessment of liver size
  - Neurological examination if history suggests spinal cord compression or brain metastases
- Request for laboratory tests:
  - Full blood count
  - Electrolytes and creatinine
  - Calcium – hypercalcaemia is associated with advanced lung cancer
  - Liver function tests
  - Coagulation studies – lung (and other) cancer is associated with hypercoagulation; cancer cells may release substances that directly activate the coagulation cascade, activate endothelial cells and platelets to enhance clotting activation[28]
- Referral for investigations:
  - Urgent chest x-ray – see below
  - Sputum cytology, particularly if haemoptysis is present
  - Spirometry, if available – to detect a restrictive rather than obstructive respiratory pattern

Follow up for patients referred for chest x-ray

Chest x-ray is the first line investigation for people with suspected lung cancer. Same day access is preferable, but service availability varies by DHB. Some regions have providers that offer "walk in" clinics where patients can access same-day x-ray services following referral, without a prior appointment. This allows greater flexibility and reduces barriers to timely investigation. If same day access is unavailable, chest x-ray should ideally be completed, reported and reviewed within one week of the referral.[15] Ensure that it is clearly documented and communicated who is taking responsibility for following up the results and informing the patient of the outcome, e.g. if the patient has presented at an after-hours clinic.

A repeat chest x-ray after six weeks may be indicated for some patients

If consolidation is found on chest x-ray, repeat after six weeks to confirm that this has resolved.[14] Pneumonia and episodes of atelectasis can occur due to airway blockage by a tumour, which may then not be immediately detected due to the associated inflammatory processes.[29] Ensure that patients who require a repeat chest x-ray are followed up, and that the results are communicated to them. Slowly resolving or unresolved consolidation can be suggestive of lung cancer and patients should be referred for assessment by a respiratory physician.[14]

Consider a repeat chest x-ray or referral for high risk patients who have persistent symptoms or signs for more than six weeks even if the initial chest x-ray was normal, as this may not exclude lung cancer.[14] Some analyses indicate that up to 25% of lung cancers may be not be identified on chest x-ray.[15]

When to refer patients with suspected lung cancer

Urgent referral for assessment by a respiratory physician is indicated for:[14, 15]

- People with chest x-ray or other imaging* suggestive or suspicious of lung cancer, including new pleural effusion, pleural mass, mass elsewhere in the lung fields/ mediastinum, or slowly resolving consolidation
- Persistent or unexplained haemoptysis in high-risk individuals aged over 40 years
- People with a high clinical suspicion of cancer (i.e. symptoms and signs of lung cancer and in a high-risk group), despite normal chest x-ray

* In some DHBs, general practitioners may be able to refer directly for chest CT, with or without advice from a respiratory physician or radiologist

Flag the referral as 'high suspicion of lung cancer'.

Managing people at high risk of lung cancer

Identifying patients who are at high risk* of lung cancer and ensuring that they are asked regularly about their respiratory health and undergo an annual respiratory assessment increases the likelihood of detecting potential lung cancer early. This assessment should include referral for chest x-ray† if they have any symptoms suggestive of lung cancer and:[30]

- The patient has not had a chest x-ray in the previous 12 months

OR

- The patient presents with new symptoms

N.B. There may be clinical scenarios where chest x-ray is indicated even though the patient has had one in the previous 12 months.

* Defined as current or previous history of smoking, history of exposure to asbestos, pre-existing lung disease, personal history of any cancer or family history of lung cancer[14]

† While it is acknowledged that this approach is likely to increase demand on health system resources, investigating and treating advanced cancer is also associated with significant burden, both in terms of health system resource utilisation and the socioeconomic costs to the community. Furthermore, expert opinion is that community-referred chest x-ray is currently underutilised in many DHBs.

Discuss the symptoms and signs of lung cancer with people who are at high risk and encourage them to seek medical advice if they develop these or become worried about their health. Emphasise that when detected early, lung cancer can be cured.

Continue to encourage and support smoking cessation

Prevention is ultimately the best strategy to reduce lung cancer rates. Tobacco smoking increases the risk of lung cancer by 20– to 50–fold, with duration of smoking being the strongest determinant of lung cancer risk.[31] The risk decreases within five years of stopping smoking, but is never completely reversed.[31, 32] After 25 years since stopping smoking, the risk of lung cancer is still three times higher than people who have never smoked.[31, 32] Exposure to passive smoke is also associated with an increased risk of lung cancer, with the excess risk estimated to be 20–30% for a non-smoking partner of someone who smokes.[31] The long-term health effects of using electronic cigarettes/vapes in terms of lung cancer risk is not yet known. Data from mice shows the development of lung adenocarcinoma in those exposed to electronic cigarette smoke.[33]

Cannabis smoke also contains carcinogens, however, the association between cannabis smoking and lung cancer incidence is less well understood – the available data are of poor quality and inconclusive.[34] Tobacco smoking among people who smoke cannabis is a major confounding factor, as is the small number of heavy, chronic cannabis users who have been studied.[34]

Ensure that smoking status is regularly updated in the clinical notes of all adolescent and adult patients, and encourage and support smoking cessation in those who currently smoke. The ABC model can be used as a guide:

- **Ask** about and document the smoking status of every patient, including use of e-cigarettes and exposure to passive smoking
- Give **Brief advice** to stop to every patient who smokes
- Strongly encourage every person who smokes to use **Cessation support** and offer help accessing this. A combination of behavioural support and smoking cessation medicine works best.

 For further information on smoking cessation, see: **www.bpac.org.nz/BPJ/2015/October/smoking.aspx**

 A smoking cessation clinical audit is available here: **www.bpac.org.nz/Audits/encouraging-smoking-cessation-2019.aspx**

 For further information on vaping, see: **https://bpac.org.nz/2018/vaping.aspx**

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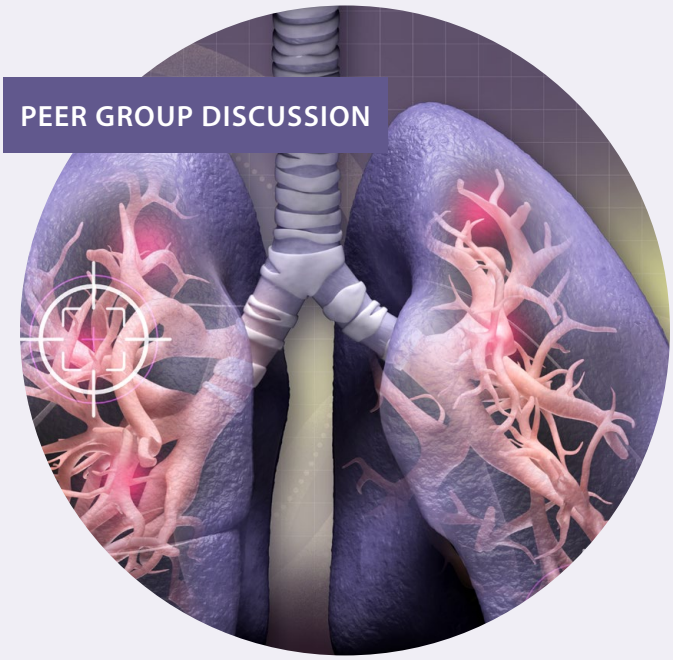
PEER GROUP DISCUSSION



Early detection of lung cancer in primary care

The following questions can be used as discussion points for peer groups or self-reflection of practice.

It is strongly recommended that the following article is read before considering the questions. "**Early detection of lung cancer in primary care**"

Lung cancer is a leading cause of cancer in New Zealand and accounts for the most cancer-related deaths. Lung cancer mortality rates in New Zealand are high compared to other countries with similar healthcare systems, likely due to factors relating late presentation and diagnosis and lack of access to funded treatments. Lung cancer incidence and mortality rates in Māori and Pacific peoples are two to three times higher than in other ethnic groups.

The stage at diagnosis is a major determinant of lung cancer prognosis. The earlier the stage the greater the chance of curative treatment, yet by the time most people are diagnosed the disease is already at an advanced stage. Patient-related factors that may contribute to the late presentation and diagnosis of lung cancer include the subtlety of symptoms, difficulties accessing care because of cost, location or other systemic barriers, and psychological factors such as denial or fear. Clinical barriers to early detection include the lack of specific symptoms, attributing symptoms to another respiratory condition or cause (e.g. smoking), and discontinuities in care.

There are a range of lifestyle, environmental, occupational and personal factors contributing to lung cancer risk. People considered at highest risk are those with:

- A current of previous history of smoking
- A history of asbestos exposure
- Pre-existing lung disease, such as chronic obstructive pulmonary disease or interstitial lung disease
- A personal history of any cancer
- A family history of lung cancer

As smoking is the major modifiable risk factor for lung cancer, smoking prevention and cessation should be encouraged and supported. The incidence of non-smoking-related lung cancer is also increasing, particularly in females and people of East Asian ethnicity. Genetic susceptibility and/or current or past exposure to environmental or occupational pollutants may explain this trend.

The symptoms and signs of lung cancer can be variable and non-specific, which can lead to delays in early detection. Key symptoms and signs that may be suggestive of early stage lung cancer, particularly in those with known risk factors, include unexplained persistent (> 3 weeks) cough (new or changed), haemoptysis, chest or shoulder pain, unresolved or recurrent chest infection, breathlessness, hoarse voice and weight loss. Red flag symptoms and signs that should prompt immediate referral to the emergency department include massive haemoptysis, signs of airway or superior vena cava obstruction or symptoms of signs of spinal cord compression.

Clinical assessment of patients with suspected lung cancer should include a comprehensive history of the symptoms, documentation of the patient's personal history of smoking, environmental or occupational exposures to known carcinogens, personal or family history of lung or other cancer, physical examination including basic observations (e.g. weight, heart rate, blood pressure, oxygen saturation) and a respiratory assessment. Recommended laboratory tests include full blood count, electrolytes and creatinine, calcium, liver function tests and coagulation screen. Chest x-ray is the first line investigation for people with suspected lung cancer, although this may not exclude a cancer diagnosis. Same day access is preferable, if available, but x-ray should ideally be completed, reported and reviewed within one week of the referral. If consolidation

is found on chest x-ray, repeat after six weeks to confirm resolution; slowly resolving or unresolved consolidation can be suggestive of lung cancer. Urgent referral to a respiratory physician is indicated for patients with imaging suggestive of lung cancer, persistent or unexplained haemoptysis in those aged > 40 years in a high-risk group or if there is a high clinical suspicion of cancer based on sympto**ms, signs and risk factors, despite normal chest x-ray.**

All people at high risk of lung cancer should undergo a respiratory assessment annually to determine if symptoms are present, therefore increasing the likelihood of early detection. If symptomatic, refer the patient for chest x-ray (if one has not been done in the previous 12 months) or new symptoms have developed since the last chest x-ray. There may be clinical scenarios where chest x-ray is indicated even though the patient has had one in the previous 12 months.

Questions to consider:

1. Many people with lung cancer are not diagnosed until their disease is advanced. What do you think are some of the main patient-related factors and clinical barriers that contribute to late diagnosis? Are there any solutions that could be implemented in your practice (or that you have implemented) to address these factors or barriers?
2. People of Māori or Pacific ethnicity have higher rates of lung cancer and worse outcomes following lung cancer diagnosis. Various factors may explain this, including high rates of smoking, socioeconomic barriers to accessing care, and a higher incidence of small cell carcinoma, the more aggressive type of lung cancer. Can you identify any strategies that might help to address some of these factors?
3. The symptoms and signs of early lung cancer are non-specific and commonly encountered in primary care, such as cough. How do you differentiate the cause of cough and what is your threshold for considering or suspecting lung cancer, e.g. risk factors, new or worsening symptoms, symptoms without a likely explanation?
4. Chest x-ray is the first-line investigation for people with suspected lung cancer. Guidelines recommend prompt turnaround, i.e. no more than one week, and ideally same day, if available. How achievable is this goal in your region of practice? In your experience, what is the typical timeframe from chest x-ray referral to completion, report and review? Does this discourage you from attempting to access same day chest x-ray? After reading this article, will this change the way you refer for x-ray?
5. Ideally, all people at high risk of lung cancer should be reviewed periodically, e.g. annually, to assess for suggestive symptoms or signs. Do you think this is feasible in your practice? Have you found (or do you anticipate) difficulty accessing chest x-ray as part of reviewing symptomatic high-risk patients?
6. Public awareness of the link between smoking and lung cancer can contribute to delays in presentation to primary care, e.g. due to embarrassment or shame. How do you balance educating patients about the risks of smoking and encouraging cessation with positive messaging that focuses on the benefits of early detection of lung cancer? How frequently do you talk to patients at high risk of lung cancer about the important symptoms and signs to be aware of?

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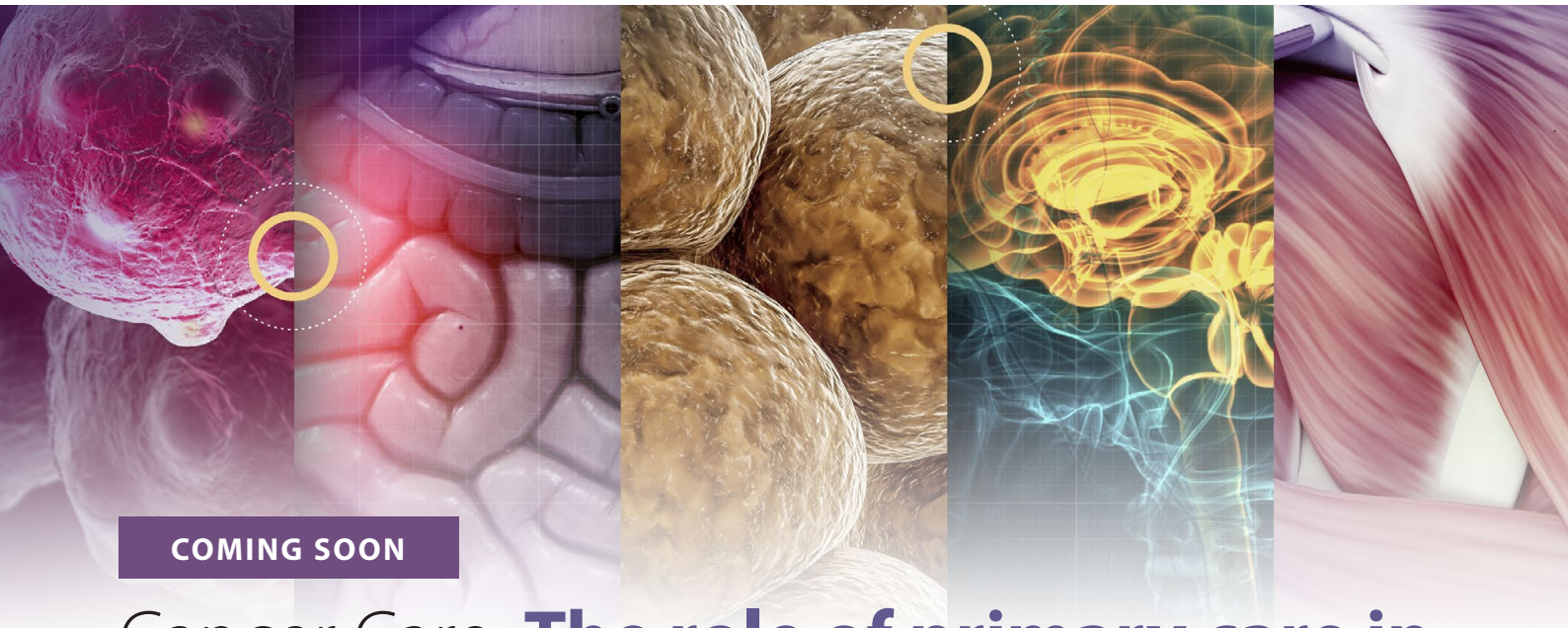

COMING SOON

Cancer Care: **The role of primary care in identifying and managing cachexia**

Through improvements in diagnosis and treatment, one in three people in New Zealand with cancer now achieve sustained remission or live with it as a long-term condition. As the demand for oncology services increases, primary care health professionals have an increasingly important role in the management of people with cancer.

Primary care health professionals can be involved in providing:

- Continuous care throughout a patient's cancer journey, including cancer prevention, early detection and diagnosis, shared follow-up, long-term surveillance and end-of-life care
- More conveniently located care, with oncology and palliative care services often only in major cities
- A single point of care, where the patient can feel reassured that someone who knows them and their history is aware of the treatments they are undergoing, the medicines they are taking, the adverse effects or other complications they are experiencing, and how their cancer management fits into their overall health and wellbeing
- Education and psychosocial support for patients and their families/whānau, which may include referral to community support agencies, counselling services, other health providers and hospice care
- Monitoring haematological and biochemical status during chemotherapy or other treatments
- Management of adverse effects caused by chemotherapy, immunotherapy, radiotherapy and other medicines, e.g. nausea/vomiting, constipation, skin conditions

As an example of where primary care, through greater awareness and proactive management, can improve patient outcomes and quality of life, we take a closer look at cachexia, a co-morbidity of cancer, that is often not diagnosed until advanced stage disease.

Cachexia is a complex, multifactorial metabolic syndrome characterised by weight loss and muscle wasting. It can result from adverse effects of cancer treatment, in particular chemotherapy, or from the malignancy itself.

Cachexia is often under-recognised. Early detection and management by primary care can make significant differences, not only relating to patient prognosis and quality of life, but also by improving adherence to chemotherapy or other cancer treatments.

A multi-modal approach to cachexia management that combines nutritional, physical, psychosocial and pharmacological interventions is recommended.

This article is due to be published on our website in April. Make sure you are signed up to our mailing list to receive notifications when new resources are available.

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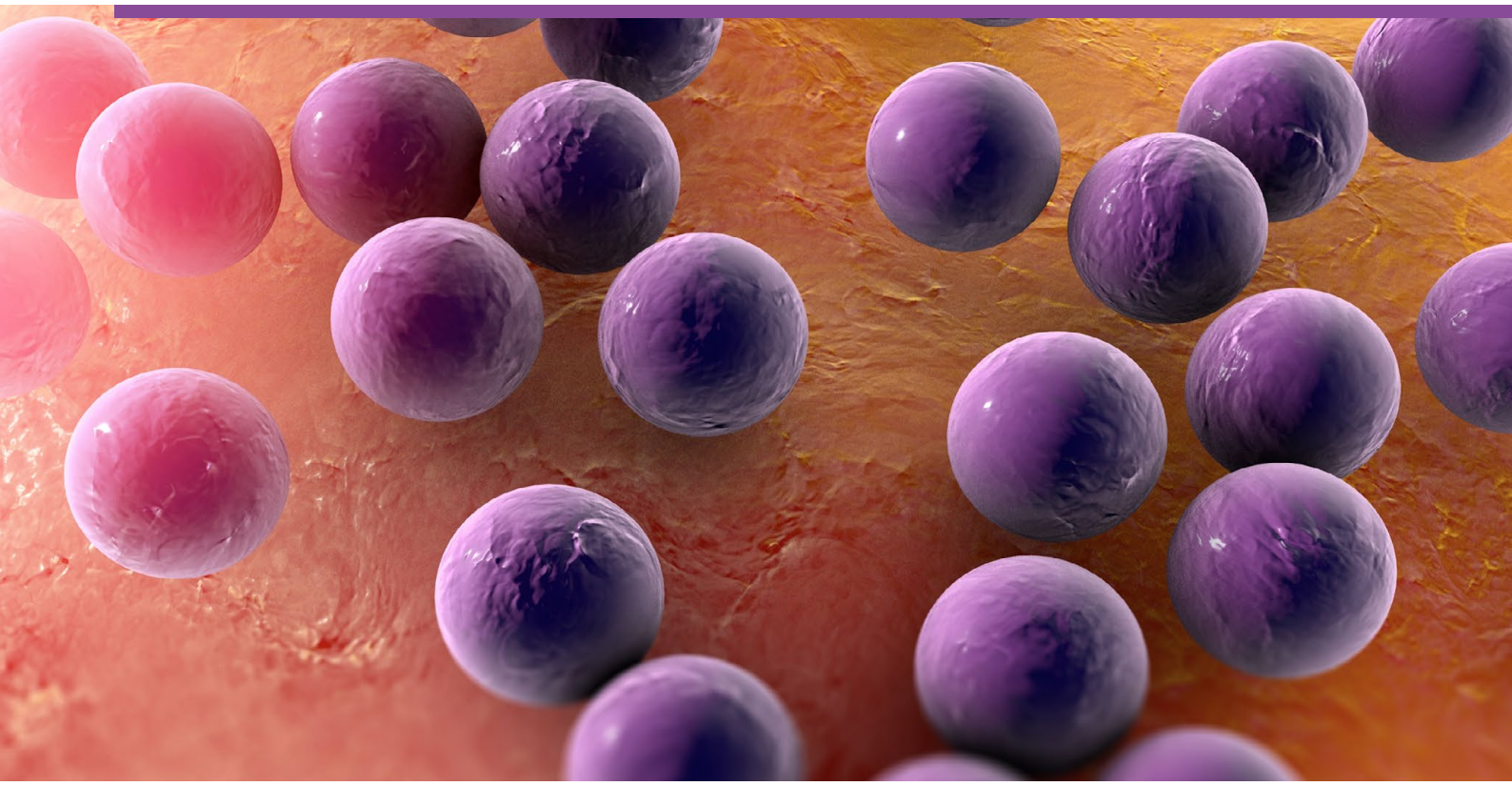

Management of impetigo

Impetigo is a highly contagious, bacterial infection of the skin, most commonly seen in children. It is typically diagnosed clinically, and the aim of treatment is to clear the eruption and prevent the spread of infection to others. Good skin hygiene measures and topical antiseptic treatment is usually adequate. Antibiotics should only be used in specific circumstances, and if required, oral is almost always preferable to topical unless the infection is very localised.

KEY PRACTICE POINTS:

- Impetigo, also known as "school sores", is a common, highly contagious bacterial infection of the skin
- Impetigo is usually diagnosed clinically. Swabs may be required for recurrent infections, treatment failure with oral antibiotics, or where there is a community outbreak.
- First-line treatment of localised non-bullous impetigo should focus on good skin hygiene measures and use of a topical antiseptic
- Use of a topical antibiotic is discouraged, but it may be considered for a small area of localised infection if topical antiseptics have been trialled and were unsuccessful or were not appropriate due to location of infection (e.g. around the eye)
- Oral antibiotics are recommended for people with more extensive infection (i.e. more than three lesions/clusters), bullous impetigo, systemic symptoms or when topical treatment is ineffective

Impetigo is a common, highly contagious bacterial infection of the skin

Impetigo can affect people of any age, but it most commonly occurs in young children (i.e. aged two to six years).[1] *Staphylococcus aureus* and *Streptococcus pyogenes*, either alone or together, are the most common causes of impetigo.[1] Impetigo can occur in an area of previously healthy skin or at the site of minor trauma that disrupts the skin barrier, such as a graze, scratch or eczema.[2]

Impetigo is highly contagious and can be transmitted by direct contact, often spreading rapidly through families, day-care or schools.[1]

Impetigo is more common in:[1,3–6]

- Hot humid weather
- Conditions of poor hygiene, e.g. overcrowding, or close physical contact, e.g. contact sports

- People who have skin conditions or experience trauma that impairs the normal skin barrier, e.g. eczema, scabies, fungal skin infections, abrasion, insect bites
- People with diabetes mellitus
- People who are immunocompromised
- People who use intravenous drugs

There are two types of impetigo: bullous and non-bullous

Non-bullous impetigo (Figure 1) is the most common variant, and is usually caused by *S. aureus* but in some cases may be caused by *S. pyogenes*.[1] Lesions begin as a vesicle that ruptures and the contents dry to form a gold-coloured plaque on the skin.[1] These lesions are often 1–2 cm in diameter and most frequently affect the face (especially around the mouth and nose) and limbs.[3] Systemic signs are not usually present, however, with more extensive impetigo, fever and regional lymphadenopathy may occur.[2, 7]

Bullous impetigo (Figure 2) is only caused by *S. aureus* and accounts for approximately 10% of cases, most often seen in infants.[1, 2] It is characterised by larger fluid-filled blisters that rupture less easily than blisters from non-bullous impetigo, leaving a yellow-brown crust.[1] Systemic signs of infection such as fever and lymphadenopathy are more likely to occur and the trunk is more likely to be affected.[2]

N.B Ecthyma is a deep tissue form of impetigo. It is characterised by crusted sores beneath which ulcers form with a "punched out" appearance.[8] It is more common in children, older people and immunocompromised people or in conditions of poor hygiene and hot humid weather.[8] Treatment follows the same guidelines as impetigo, but oral antibiotics are usually required.[9]

Impetigo is usually diagnosed clinically

Impetigo can be diagnosed on clinical examination and initial treatment decisions are rarely based on the results of skin swabs.[3] Swabs may be required for people with recurrent infections, treatment failure with oral antibiotics, or where there is a community outbreak and the cause needs to be identified.[5] For people with recurrent impetigo, nasal swabs can identify staphylococcal nasal carriage requiring specific management.[5]

Treatment of impetigo

Key points:

- The aims of treatment are to clear the eruption and prevent the spread of the infection to others
- Good skin hygiene measures and a topical antiseptic are first-line for children with mild to moderate impetigo
- Due to increasing resistance, infectious disease experts recommend that topical antibiotics should have a very limited role in clinical practice[10, 11]
- Oral antibiotics are suitable for people with more extensive or recurrent infection[5]
- Combination treatment with a topical and oral antibiotic should not be offered[5]
- Underlying conditions e.g. eczema need to be treated as well to reduce the risk of recurrent impetigo[4]

For further information, see:

"Topical antibiotics: keep reducing use", available from: **https://bpac.org.nz/2018/topical-antibiotics.aspx**

"Childhood eczema: improving adherence to treatment basics", available from: **https://bpac.org.nz/2016/childhood-eczema.aspx**

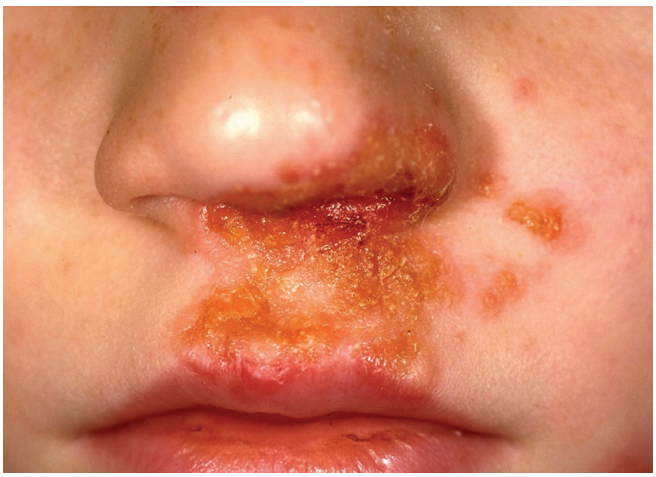

Figure 1. Non-bullous impetigo. Image provided by DermnetNZ

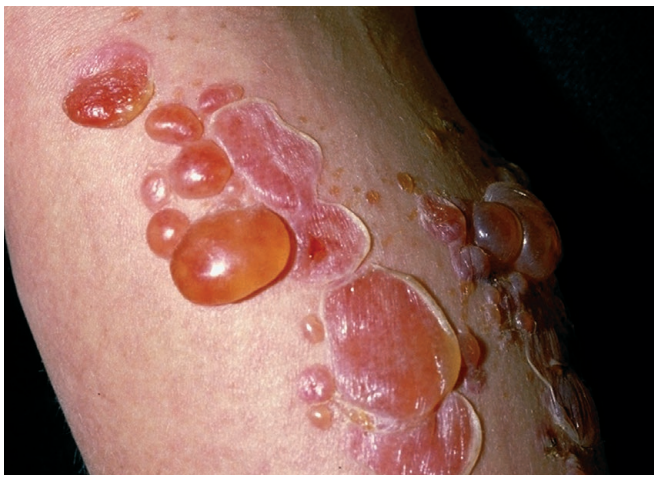

Figure 2. Bullous impetigo. Image provided by DermnetNZ

Topical antiseptic is the initial treatment for localised patches of impetigo

A topical antiseptic, e.g. hydrogen peroxide 1% or povidone-iodine 10%, applied two to three times daily, is the first-line treatment for localised, uncomplicated non-bullous impetigo (e.g. three or less lesions/clusters).[4, 5] The crusts on the lesions should be removed with warm water before any topical preparation is applied (see: "Advice for patients with impetigo").[2] Remind parents/caregivers to wash their hands before and after application.

Five days of topical antiseptic treatment is usually sufficient for treating impetigo.[5] This can be increased to seven days depending on the severity and number of lesions.[5]

Use of topical antibiotics is discouraged

Topical antibiotics are rarely indicated for use in skin infections due to bacterial resistance and the potential for contact dermatitis.[4] However, there may be some instances where a topical antibiotic is considered for treating a small, localised area of impetigo, such as if a topical antiseptic is unsuitable (e.g. impetigo around the eyes) or has been ineffective.[5] Fusidic acid should be prescribed unless antibiotic sensitivities (if known) indicate that resistance is present. Mupirocin (partly funded) is reserved for treating MRSA (see: "Impetigo caused by MRSA").[10]

Oral antibiotics should be used for multiple lesions or if topical treatment is ineffective

Oral antibiotics are recommended to treat patients with more than three to five lesions/clusters, bullous impetigo, systemic symptoms or when topical treatment is ineffective.[5] Flucloxacillin is the first-line choice as it is effective against *S. aureus* and Group A *streptococci*.[4, 5]

Trimethoprim + sulfamethoxazole or erythromycin can be used if MRSA is present or the patient is allergic or intolerant to flucloxacillin. Cefalexin is another option if flucloxacillin is not tolerated.[4, 5]

A five day course of oral antibiotics is generally sufficient, but can be increased to seven days depending on the severity and number of lesions.[5] If treatment is unsuccessful after this time, medicine adherence should be checked and swabs can be taken to detect sensitivities.[5]

Refer to "Antibiotics: choices for common infections" for dose and regimen information. Available from: **https://bpac.org.nz/antibiotics/guide.aspx**

Impetigo caused by MRSA

The prevalence of impetigo caused by methicillin-resistant *S. aureus* (MRSA) is unknown, but is likely to be increasing.[12] In August 2017*, 956 MRSA laboratory isolates were reported in New Zealand, equating to a period-prevalence rate of 19.9 patients with MRSA per 100,000 population.[13] This is double that of isolates from 2009, but rates have remained relatively stable over the last four years.[13] Some community strains of MRSA show increasing resistance to fusidic acid, while resistance rates of mupirocin are decreasing concurrently with declining dispensing rates.[11,14] Oral trimethoprim + sulfamethoxazole, tetracyclines or clindamycin are usually effective against MRSA.[15]

* 2017 is the latest data as this survey has not been conducted since.

Prevention of recurrent impetigo infections

Recurrent infection may result from the nasal carriage of causative microorganisms, close contact with others or from fomite colonisation e.g. bed sheets, towels and clothing that may be shared.[4, 16] If nasal carriage is suspected, a nasal swab is required to confirm this and to establish antibiotic susceptibility. A topical antibiotic should be applied inside each nostril, three times daily for seven days. The choice of antibiotic will be guided by sensitivities (from swab result). All household members and close contacts should also be treated.[4]

For further information on decolonisation, see: **https://bpac.org.nz/2017/topical-antibiotics-2.aspx**

Advice for patients with impetigo or their caregivers [4, 20]

To remove crusted areas:

- Use a clean cloth soaked in warm water to gently remove crusts from lesions. Wash the cloth after use.

To prevent the spread of infection:

- Children should stay away from day-care or school until the lesions have crusted over or they have received at least 24 hours of antiseptic or antibiotic treatment*. This may not be necessary for older children (e.g. secondary school) who are able to minimise risk of transmission by avoiding physical contact with others.
- Avoid close contact with other people, e.g. siblings and other family members, contact play with other children
- Use separate towels, face cloths, clothing and bathwater until the infection has cleared. Disinfect linen and clothing by hot wash, hot dry or ironing.
- Follow the "clean, cut (nails) and cover" message, which also can apply to people with other skin infections or injuries:
  - Use hand sanitiser and/or careful washing with household soap and water, several times daily
  - Keep children's fingernails cut short to prevent bacteria spreading from one part of the body to another through scratching
  - Cover the affected areas with a breathable dressing and wash hands after touching patches of impetigo or applying topical treatments

* As days off school equate to increasing educational disparity and parental time off work (often without pay), families should be educated and supported in strategies to prevent skin infections.

For further information, see: **https://www.kidshealth.org.nz/how-stop-skin-infections**

Complications of impetigo

Post-streptococcal glomerulonephritis, which can lead to renal failure, is a rare complication of streptococcal impetigo.[4] Treatment of impetigo may not prevent susceptible people developing this complication.[15] Prevalence of post-streptococcal glomerulonephritis is highest in primary school aged children, particularly males and people of Māori and Pacific descent.[17]

Scarring may occur in people with more severe impetigo, when lesions extend deeper into the dermis.[8] N.B. In milder cases of impetigo, healed lesions may result in changes in skin pigmentation, however, this should resolve over time.[2, 3]

Soft tissue infection such as cellulitis may occur.[4]

Staphylococcal scalded skin syndrome is characterised by red blistering skin which leaves an area that looks like a burn once the lesions have ruptured. Children aged under five years, particularly neonates, immunocompromised people or those with renal failure are most at risk of this complication.[18]

Streptococcal toxic shock syndrome is a rare complication of impetigo. It is more commonly seen in healthy people aged 20 to 50 years, despite children, immunocompromised and elderly people being more susceptible to impetigo. Symptoms include fever, rash, hypotension and erythematous rash.[19]

Rheumatic fever is rarely linked to skin infections however it can occur when group A streptococci found on the skin moves to the throat.[4]

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N.B. Expert reviewers do not write the articles and are not responsible for the final content. bpac^{nz} retains editorial oversight of all content.

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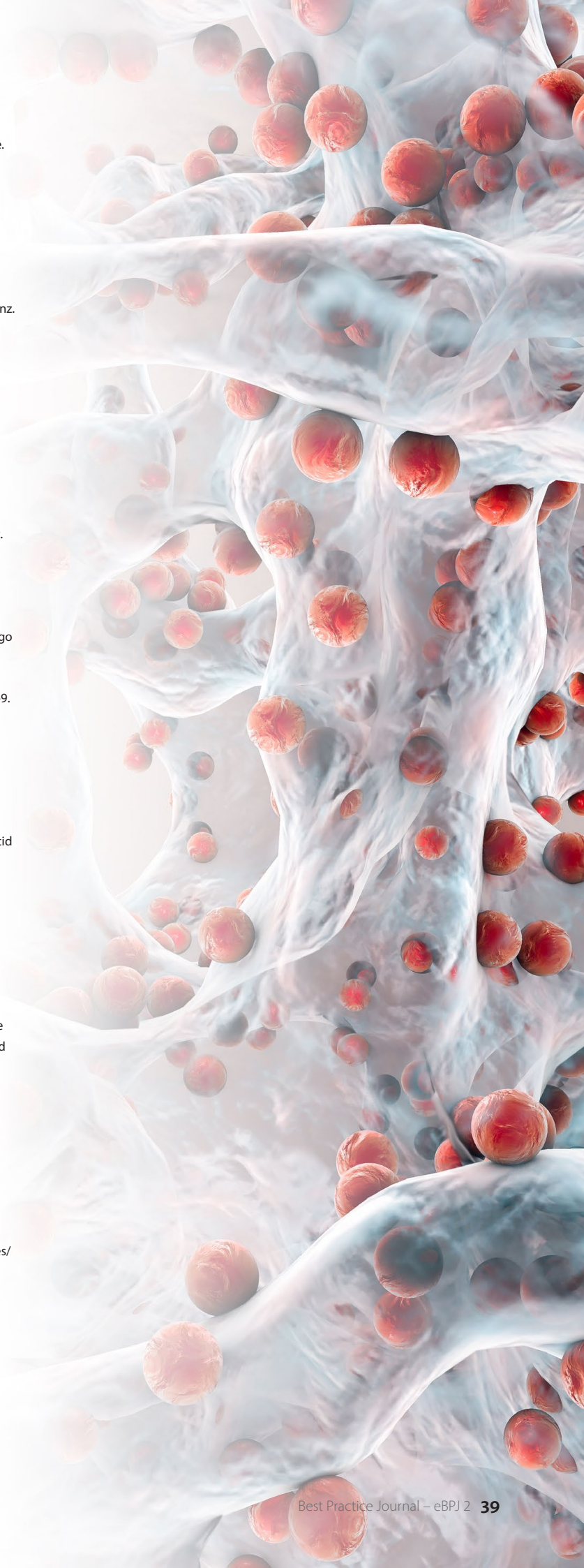

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Question 1: Diabetes

Which of the following patients with type 2 diabetes are eligible for funded treatment with empagliflozin or dulaglutide?

- ☐ All patients with HbA_{1c} > 53 mmol/mol despite the regular use of at least one blood-glucose lowering medicine for at least six months
- ☐ Māori or Pacific patients with HbA_{1c} > 53 mmol/mol despite the regular use of at least one blood-glucose lowering medicine for at least three months
- ☐ Patients with cardiovascular or renal disease or heart failure with an HbA_{1c} < 53 mmol/mol or eGFR 60 – 90 mL/min without albuminuria
- ☐ Patients with HbA_{1c} > 53 mmol/mol and five-year cardiovascular disease risk ≥ 15%
- ☐ Patients with cardiovascular or renal disease or heart failure who are already taking funded empagliflozin or dulaglutide (i.e. dual treatment)

Question 2: Diabetes

Which of the following statements about prescribing empagliflozin for the treatment of type 2 diabetes are true?

- ☐ Metformin should be continued unless it is contraindicated or not tolerated
- ☐ All glucose-lowering treatments aside from metformin must be discontinued when initiating empagliflozin
- ☐ Dose adjustment is required for people with mild renal impairment
- ☐ People taking empagliflozin are at increased risk of diabetic ketoacidosis, even if they have normal blood glucose levels
- ☐ People taking empagliflozin are at increased risk of genitourinary infection

Question 3: Diabetes

Which of the following statements about prescribing dulaglutide are true?

- ☐ Dulaglutide is administered as a once daily subcutaneous injection
- ☐ Vildagliptin must be stopped before initiating a GLP-1 receptor agonist
- ☐ All patients taking dulaglutide must monitor their blood glucose levels
- ☐ Dulaglutide must be administered in the morning, with food
- ☐ Gastrointestinal upset and injection site reactions are the most common adverse effects

Question 4: Impetigo

Which of the following statements about impetigo are true?

- ☐ Impetigo can affect people of any age, however, young adults are the age group most at risk
- ☐ Ecthyma occurs more commonly in conditions of poor hygiene and hot humid weather
- ☐ Treatment decisions for impetigo should be based on skin swab results
- ☐ Recurrent impetigo infection occurs only when there is direct skin contact with a person already infected with impetigo
- ☐ Impetigo can occur in an area of previously healthy skin

Question 5: Impetigo

Which of the following statements about treating impetigo in New Zealand are true?

- ☐ Underlying conditions such as eczema increase the risk of recurrent impetigo
- ☐ Topical antibiotics and good skin hygiene are the first-line treatment for children with mild to moderate impetigo
- ☐ The crusts topping the lesions should not be removed before topical treatment
- ☐ Oral antibiotics are recommended for treating patients with localised, uncomplicated non-bullous impetigo (i.e. three or less lesions/clusters)
- ☐ If oral antibiotic treatment is unsuccessful after five to seven days, medicine adherence and sensitivities should be checked

Question 6: Impetigo

Which of the following statements about the complications of impetigo are true?

- ☐ Rheumatic fever can occur when group A streptococci, found on the skin, moves to the throat
- ☐ Post-streptococcal glomerulonephritis is most prevalent in older adolescents and young adults, particularly females of European descent
- ☐ Streptococcal toxic shock syndrome is more commonly seen in children, older people and people who are immunocompromised
- ☐ Children aged under five years, particularly neonates, are one of the population groups most at risk of developing staphylococcal scalded skin syndrome
- ☐ Scarring may occur in more severe cases of impetigo however any skin pigmentation changes in milder cases should resolve over time

Question 7: Lung cancer

Which of the following statements about lung cancer are true?

- ☐ Lung cancer is the most common cause of cancer death in New Zealand
- ☐ Most people have advanced stage disease at diagnosis
- ☐ Most lung cancers are diagnosed in people aged > 40 years
- ☐ Small cell lung cancer is less common in Māori
- ☐ The incidence of lung cancer among people who have never smoked is decreasing

Question 8: Lung cancer

Which of the following are risk factors for lung cancer?

- ☐ Current or previous history of smoking
- ☐ Occupational exposure to silica or diesel exhaust
- ☐ Personal history of any cancer
- ☐ Pre-existing lung disease, but only if they also have a history of smoking
- ☐ Māori or Pacific ethnicity

Question 9: Lung cancer

Which of the following are symptoms or signs of lung cancer?

- ☐ Haemoptysis
- ☐ Unexplained and/or persistent cough
- ☐ Inferior vena cava syndrome
- ☐ Thrombocytosis
- ☐ Hoarse voice

Question 10: Statins

Which of the following statements about cardiovascular disease (CVD) risk are true?

- ☐ Patients with a five-year CVD risk >15% should only take a lipid-lowering medicine to control their CVD risk
- ☐ Atorvastatin is the first-line choice of statin for reducing CVD risk
- ☐ Lifestyle modifications are only appropriate for people considered to be at a low five-year CVD risk
- ☐ Patients at intermediate-risk of CVD should aim for an LDL-C target of 1.8 mmol/L or lower following treatment
- ☐ A lipid-lowering medicine is always recommended in patients with a TC/HDL-C ratio ≥8

Question 11: Statins

Which of the following statements are correct about the association between statins and diabetes?

- ☐ Statins should be withheld in people at risk of developing diabetes
- ☐ Pravastatin is associated with the lowest risk of developing new onset diabetes mellitus
- ☐ A healthy diet can be an effective method to minimise the risk of developing type 2 diabetes when taking a statin
- ☐ Younger people with normal HbA_{1c} and BMI are at a higher risk of developing type 2 diabetes when taking a statin
- ☐ Statins may increase the risk of developing hyperglycaemia

Question 12: Non-statin medicines

Which of the following statements regarding the use of non-statin medicines are true?

- ☐ Fibrates are the second-line treatment if a statin is ineffective
- ☐ Ezetimibe may be considered for use in high risk patients
- ☐ Alirocumab can be used in combination with a statin for people who cannot achieve an adequate LDL-C reduction
- ☐ A statin must be discontinued before initiating a non-statin medicine
- ☐ Nicotinic acid is recommended as monotherapy if a statin is unable to be tolerated

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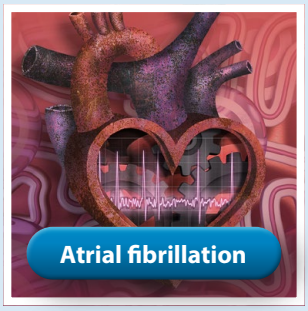

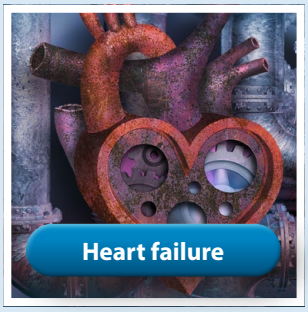

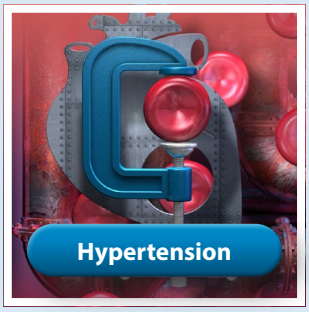

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