



National Prescribing Service Limited

29 February 2008



000001 000
Dr Sam Sample
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Prescribing Practice Review

No. 40 Early use of insulin and oral antidiabetic agents

Dear Dr Sam Sample

This *Prescribing Practice Review* (PPR) examines intensive therapy to manage hyperglycaemia among patients with type 2 diabetes. Included are your prescribing data for oral antidiabetic agents, along with practice points for your review.

Early and continuing lifestyle interventions decrease disease progression

Encourage people to quit smoking, eat healthily and move more. Use structured assessment tools (such as Lifescrpts or SNAP) to reinforce the importance of lifestyle change.

Initiate insulin early by adding night-time basal insulin to oral antidiabetic agents

Insulin should be considered in any person who has had uncontrolled blood glucose for 3 months despite adhering to lifestyle changes and using metformin and a sulfonylurea.

A simple and safe way of starting insulin in general practice is to continue the metformin and sulfonylurea while adding a single bed-time dose of isophane insulin.

Ensure metformin is part of ongoing therapy and use of thiazolidinediones does not delay progression to insulin

Metformin is the most frequently prescribed oral antidiabetic reflecting prescriber knowledge of its favourable effects upon mortality and diabetes-related morbidity.

If metformin and a sulfonylurea no longer control blood glucose, start insulin promptly. Trialling a thiazolidinedione ('glitazone') as part of triple oral therapy may be an option but insulin should be started if hyperglycaemia is still uncontrolled after 3 months.

Review use of thiazolidinediones in heart failure and ischaemic heart disease

Both rosiglitazone and pioglitazone are associated with weight gain, oedema and fluid retention and should not be used in patients with moderate to severe heart failure. Rosiglitazone should not be used in people with a history of ischaemic heart disease.

The clinical audit *Optimising management of type 2 diabetes* is now available. See the enclosed enrolment form for more information.

Yours sincerely,

Dr Janette Randall
Chair, National Prescribing Service Limited

NPS is an independent, non-profit organisation for Quality Use of Medicines,
funded by the Australian Government Department of Health and Ageing.

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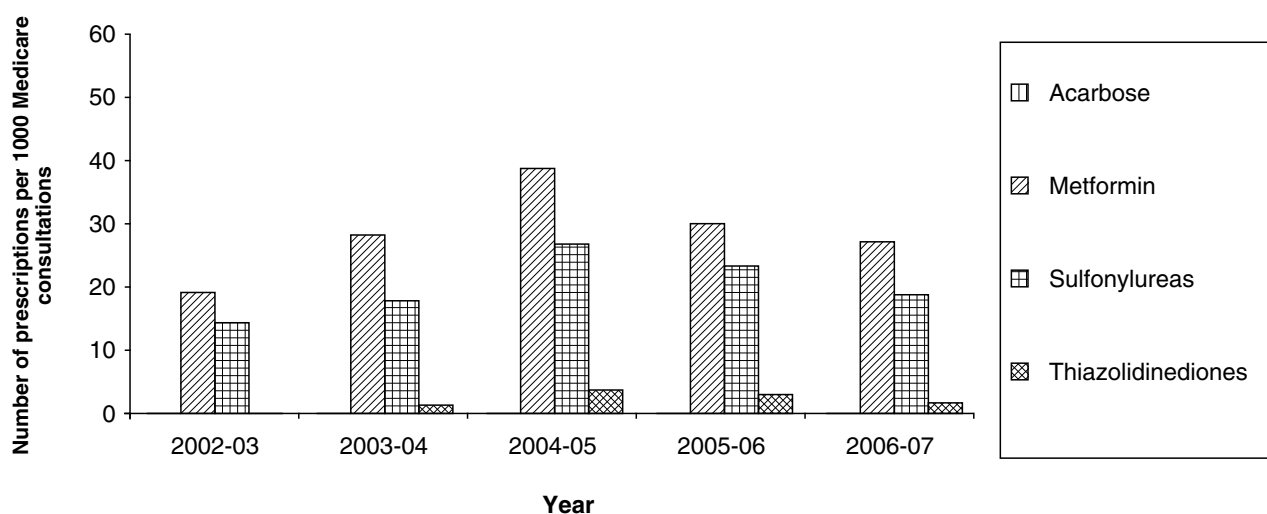
Your confidential prescribing data

The prescribing data from Medicare Australia includes dispensed prescriptions for the following oral agents:

- **acarbose**;
- **metformin** – prescriptions for concessional card holders only as the cost is below the general patient co-payment;
- **sulfonylureas** (glibenclamide, gliclazide, glimepiride, glipizide) – prescriptions for concessional card holders only as the cost is below the general patient co-payment; and
- **thiazolidinediones** (pioglitazone and rosiglitazone) – PBS listed November 2003 onwards, both above co-payment.

Data is not included on insulin prescriptions because we cannot distinguish between people with type 1 or type 2 diabetes. It is difficult to interpret individual prescribing data of insulin since the injectable regimens are so diverse.

Your oral antidiabetic drug prescribing 2002-03 to 2006-07

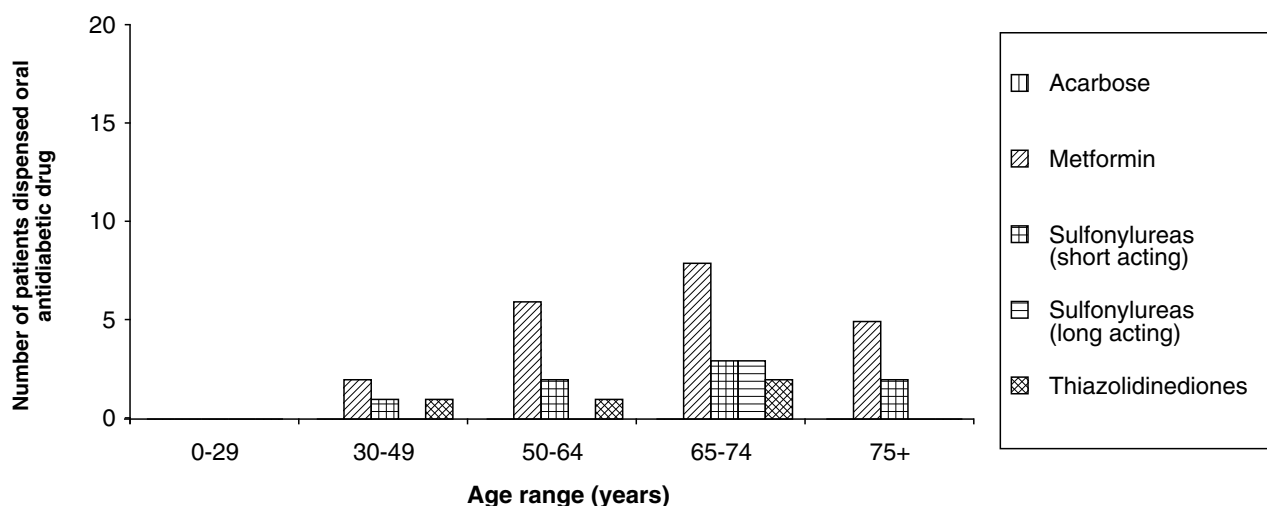


Practice points

- Increased use of oral antidiabetic drugs may be seen if more patients are diagnosed, newly diagnosed patients are treated earlier or more intensive drug therapy is used to gain tighter blood glucose control.
- Metformin use should be higher than all other agents as it is first-line therapy for overweight diabetic patients and probably all patients with type 2 diabetes (unless contraindicated), where drug therapy is required. Metformin is also used for polycystic ovary syndrome.

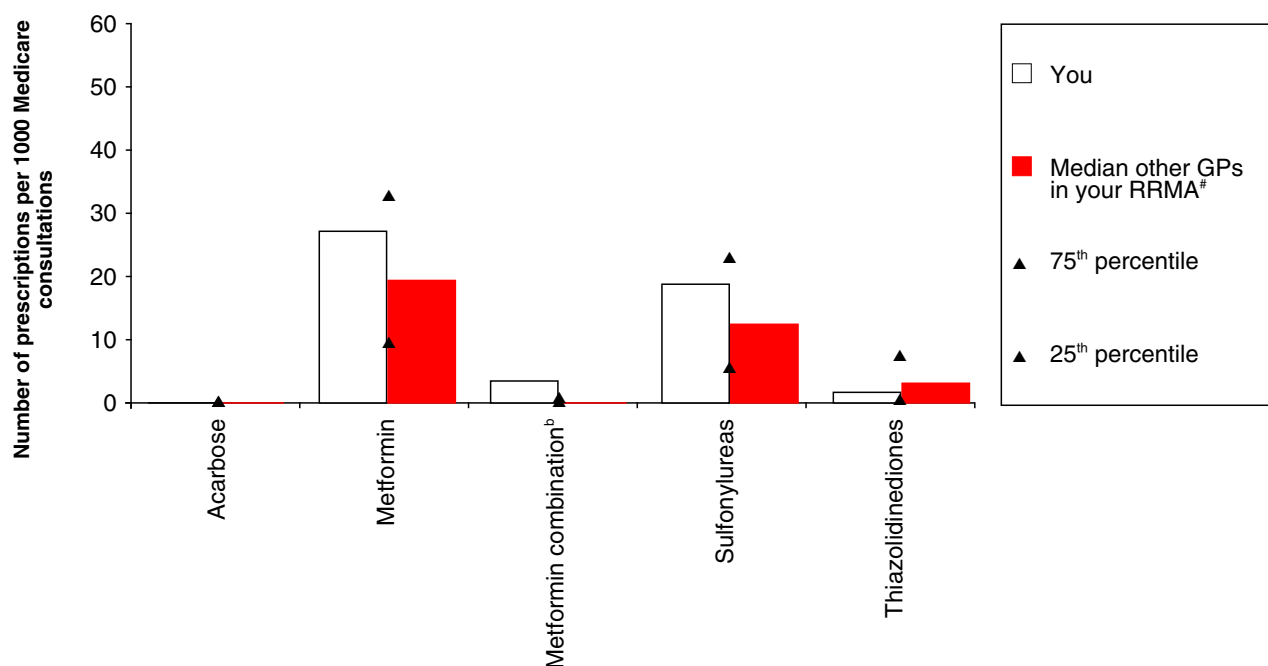
In 2006-07, 27 patients were dispensed PBS subsidised oral antidiabetic drugs from prescriptions written by you. Some patients may be taking more than one type of oral antidiabetic drug. Some patients may not be represented because their oral antidiabetic drugs are under general patient co-payment and hence not captured in the chart below.

Your oral antidiabetic drug prescribing by patient age 2006-07^a



^aPatients on more than one drug will be counted in each drug category.

Oral antidiabetic drug use 2006-07



^bMetformin fixed dose combination includes metformin with rosiglitazone (PBS listed in Dec 06) and metformin with glibenclamide. The former combination is above general patient co-payment the latter is not.

Practice points

- Longer-acting sulfonylureas (glibenclamide and gliclazide) are more likely to cause profound hypoglycaemia, particularly in the elderly. Consider your selection in older persons.
- Recent guidelines recommend the initiation and intensification of insulin therapy in preference to triple oral therapy as many patients will already have failing pancreatic beta-cell function and the non-responder rate to thiazolidinediones is 25 – 30%.¹
- Compared with newer agents (acarbose and thiazolidinediones), older agents (metformin and sulfonylureas) have similar or superior effects on glycaemic control, lipids, and other intermediate end points.²
- It is likely that a high rate of metformin use indicates good practice.
- Acarbose has a very limited place in the management of type 2 diabetes as it is generally less effective than metformin or sulfonylureas.

Total prescribing of pioglitazone and rosiglitazone

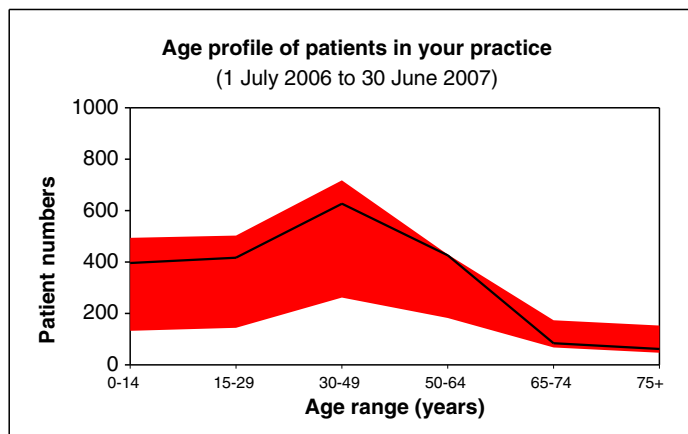
| Financial year | Number of prescriptions dispensed on the PBS | |
|----------------|--|--|
| | You | Median other GPs in your RRMA [†] |
| 2005-06 | 12 | 8 |
| 2006-07 | 7 | 14 |

Practice points

- A thiazolidinedione may be prescribed as part of dual oral therapy when the combination of metformin and a sulphonylurea is unsuitable (because of intolerance or contraindication) or as triple therapy with maximally tolerated doses of metformin and a sulphonylurea.
- The thiazolidinediones are associated with weight gain and fluid retention and should not be used in patients with moderate to severe heart failure.³
- The use of rosiglitazone is not recommended in patients with known ischaemic heart disease, particularly in those taking nitrates. Rosiglitazone has been shown to be associated with an increased risk of myocardial ischaemia.⁴

Practice profile

Some data shown earlier are presented as prescribing rates (per 1000 Medicare consultations) to adjust for volume of service. Age profile and concession card holding status of patients in your practice are provided to assist you in interpreting your prescribing data. The number of concession card holders provides an indication of the limitations of the data capture for items under the general patient co-payment.



The black line represents the age profile of patients in your practice. 25% to 75% of other GPs in your RRMA[#] fall within the shaded area.

Medicare patients and concession card holders in your practice

(1 April 2007 to 30 June 2007)

| Patients | You | Median other GPs in your RRMA [#] |
|---|-----|--|
| Total Medicare | 699 | 653 |
| Concession card holders^{##} | 144 | 174 |

(^{##}includes those reaching Safety Net)

Concession card holders include patients who have reached the Safety Net. Data from a three month period (1 April 2007 to 30 June 2007) that best represent your patient mix have been provided.

Notes

[®]Data shown are an aggregate for all your provider locations.

[#] The comparator group "other GPs in your RRMA" includes all prescribers currently located in a similar geographical region i.e. 1. capital cities, 2. other metropolitan centres, 3. large rural centres, 4. small rural centres, 5. other rural centres, 6. remote centres and 7. other remote centres.

Your RRMA peer group is 1.

[▲] 25% to 75% of all doctors fall in the range shown by the triangular symbols.

Brand names

Acarbose: *Glucobay*. Metformin: *Diabex, Diaformin, Formet, Glucohexal, Glucomet, Glucophage, Metforbell*. Metformin combinations: *Avandamet, Glucovance*. Glibenclamide: *Daonil, Glimel*. Gliclazide: *Diamicron, Glyade, Mellihexal, Nidem*. Glimepiride: *Amaryl, Aylide, Diapiride, Dimire*. Glipizide: *Melizide, Minidiab*. Pioglitazone: *Actos*. Rosiglitazone: *Avandia*.

Confidentiality

NPS has a contract with Medicare Australia to provide your prescribing feedback data directly to you. NPS does not have access to these data. The data contained in this feedback are not used for any regulatory purposes.

Discrepancies may occur between the data provided and your own prescribing practice. This may be due to either inaccurate recording of your prescriber number in the pharmacy or your prescription pad having been used by another doctor.

If you consider your individual data to be incorrect, have other data queries or general feedback please contact NPS on 02 8217 8700 or by email at info@nps.org.au

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1. American Diabetes Association. Standards of medical care in diabetes. *Diabetes Care* 2007; 30:S1-41.
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3. GlaxoSmithKline Australia Pty Ltd. Avandia product information. 8 November 2007.
4. ADRAC. Emerging cardiovascular concerns with rosiglitazone. *Australian Adverse Drug Reactions Bulletin* 2007; 26: 17th December 2007.

Early use of insulin and oral antidiabetic drugs

Key Messages

- Early and continuing lifestyle interventions decrease disease progression
- Initiate insulin early by adding night-time basal insulin to oral antidiabetic agents
- Ensure metformin is part of ongoing therapy and use of thiazolidinediones does not delay progression to insulin
- Review use of thiazolidinediones in heart failure and ischaemic heart disease

Early and continuing lifestyle interventions decrease disease progression

Reinforce the importance of lifestyle change at every opportunity

Encourage people to eat healthily, quit smoking and be more active whenever an opportunity arises. Lifestyle changes improve outcomes among people with type 2 diabetes¹ but can be difficult to make and sustain. The SNAP (www.racgp.org.au/guidelines/snap) or Lifescripts (www.health.gov.au/lifescrpts) programs can be used to help people achieve and sustain lifestyle changes.

Prescribe 30 minutes of moderate intensity exercise at least 5 times a week

Encourage moderate intensity exercise (e.g. brisk walking) for at least 30 minutes* ≥ 5 times a week.^{2,3} This should cause a slight, but noticeable, increase in breathing and heart rate and can be accumulated in bouts of 10–15 minutes.² Unless contraindicated, encourage 3 or more 30 minute sessions of vigorous exercise (causing 'huffing and puffing') a week as well as the minimum amount to provide further health benefits.²

Assess before prescribing a more vigorous exercise program

Assess people with type 2 diabetes before prescribing exercise more strenuous than brisk walking.^{4,5} Check for symptoms and risk factors of cardiovascular disease or conditions that might rule out more strenuous exercise or increase the risk of injury (e.g. severe neuropathy, retinopathy, nephropathy, microalbuminuria, osteoporosis or arthritis).^{4,5} Vigorous exercise is contraindicated in people with proliferative and pre-proliferative retinopathy. Prescribe non-weight bearing exercise (e.g. stationary cycling or swimming) for those at greater risk of falls, injuries or foot damage.^{4,5}

Encourage resistance training in addition to aerobic exercise

Encourage people to undertake resistance or strength training (e.g. resistance bands, weights) on 2–3 non-consecutive days per week, in conjunction with aerobic exercise.^{6,7} This should include 3 sets of 8–10 repetitions, targeting all major muscle groups using weights that cannot be lifted more than 8–10 times each set.^{5,6}

Improvements in HbA_{1c} subside a few days after exercise

The beneficial effects of regular exercise on blood glucose control subside within a few days. Inform people that they should not allow more than 2 days to pass without undertaking some form of exercise.^{4,6}

*At least 60 minutes per day may be required for people who sit for ≥ 4 –5 hours a day, or who wish to lose weight.³

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Initiate insulin early by adding night-time basal insulin to oral antidiabetic agents

Aim for a target HbA_{1c} ≤ 7% in most patients

The recommended target for glycaemic control is HbA_{1c} ≤ 7%.⁸ This is suitable for most people but higher targets may be more appropriate for the elderly and those with a history of severe hypoglycaemia or comorbidities.

Consider insulin if HbA_{1c} > 7% after 3 months

Despite intensive therapy, blood glucose control will progressively deteriorate due to the destruction of beta cells.⁹ Initiation of insulin early in the disease process can reduce hyperglycaemia, reduce microvascular and macrovascular risk, and potentially improve or preserve beta-cell function.¹⁰

Consider insulin for people with inadequate glycaemic control (HbA_{1c} > 7%) for a period of 3 months — despite making lifestyle changes and taking maximally tolerated doses of metformin and a sulfonylurea — even if they do not have any symptoms.¹¹

Initiating insulin safely and simply – add bed-time isophane insulin to oral antidiabetic agents

A simple and safe way to initiate insulin is to add bed-time basal isophane insulin to oral antidiabetic agents (Table 1).¹²

Table 1: Stepwise guide for initiating and adjusting insulin^{8,9,12,13}

| Step 1: | <p>ADD 10 units isophane insulin at bedtime.</p> <p>CONTINUE metformin, a sulfonylurea or both (at the same dosage, but no greater than the maximum recommended dose)</p> <ul style="list-style-type: none"> • If evening blood glucose level is high then use 10 units morning isophane insulin. • If both morning and pre-evening meal blood glucose levels are high then consider using twice daily isophane. | | | | | | | | | | | | |
|-------------------|---|-------------------|-----------------------------|------|---------------------|------|---------------------|-----|---------------------|-----|-----------|-----|-----------------------|
| Step 2: | <p>ADJUST insulin therapy gradually every 3–4 days according to fasting blood glucose (FBG) level until target FBG is reached (usually 4.0–6.0 mmol/L)*</p> <table border="1"> <thead> <tr> <th>Mean FBG (mmol/L)</th> <th>Adjustment to insulin dose*</th> </tr> </thead> <tbody> <tr> <td>> 10</td> <td>Increase by 8 units</td> </tr> <tr> <td>8–10</td> <td>Increase by 6 units</td> </tr> <tr> <td>6–8</td> <td>Increase by 2 units</td> </tr> <tr> <td>4–6</td> <td>No change</td> </tr> <tr> <td>< 4</td> <td>Decrease by 2–4 units</td> </tr> </tbody> </table> | Mean FBG (mmol/L) | Adjustment to insulin dose* | > 10 | Increase by 8 units | 8–10 | Increase by 6 units | 6–8 | Increase by 2 units | 4–6 | No change | < 4 | Decrease by 2–4 units |
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| 4–6 | No change | | | | | | | | | | | | |
| < 4 | Decrease by 2–4 units | | | | | | | | | | | | |
| Step 3: | CHECK overall blood glucose control by measuring HbA _{1c} 3–6 monthly. | | | | | | | | | | | | |
| Step 4: | <p>If FBG and evening blood glucose are on target but HbA_{1c} is not, look for hidden 'hypers' – blood glucose peaks that occur during the day, often before lunch or after dinner.</p> <p>Options to correct hidden 'hypers' include:</p> <ul style="list-style-type: none"> • changing preceding meal size or composition • increasing activity after meals • adding acarbose • adding a meal-time rapid acting insulin.[†] | | | | | | | | | | | | |

* A GP, trained practice nurse, credentialled diabetes educator or the educated patient can adjust insulin dose according to this titration schedule. Adjusting the insulin dose gradually can gain patient confidence and reduce the risk of hypoglycaemia.^{9,14}

† Biphasic or pre-mixed insulin are convenient but require a more strict adherence to the size and timing of meals and dosing can be inflexible leading to blood glucose fluctuation.¹²

These are general guidelines for initiating insulin; targets and treatment regimens may differ for some people. Long-acting insulin analogues (insulin glargine or insulin detemir) may be an alternative to isophane insulin for some people.

Continuing oral antidiabetic agents minimises the risk of weight gain and hypoglycaemia

Add a single, daily injection of basal insulin to metformin and a sulfonylurea. This leads to less weight gain than using insulin alone.¹⁵ It also allows insulin to be used at a smaller dose that can be titrated gradually, minimising the risk of hypoglycaemia.^{13,16} Continue using metformin with insulin. Sulfonylureas should be discontinued if hypoglycaemia develops or once a rapid-acting insulin is added.¹⁶ If a thiazolidinedione (or 'glitazone') is being used, consider stopping it once insulin is begun (see final page).

Long-acting insulin analogues are an alternative

All three basal insulins (isophane, glargine and detemir) improve HbA_{1c} levels to a similar extent in people with type 2 diabetes.^{17,18} The risk of severe hypoglycaemia is similar with insulin glargine and insulin detemir compared with isophane insulin, while the risk of nocturnal hypoglycaemia is lower.^{17,18} However, data on the long-term safety of insulin glargine and insulin detemir is limited, and their use should be approached cautiously.^{18,19}

Both long-acting insulin analogues reduce, but do not eliminate, the risk of hypoglycaemia. Severe hypoglycaemia has been reported in 0.4% to 2.6%, and nocturnal hypoglycaemia in 17% to 31%, of participants enrolled in trials of insulin detemir or insulin glargine.¹⁸

Insulin glargine and insulin detemir are more expensive than isophane insulin.²⁰ Insulin detemir is not currently PBS-listed for use in type 2 diabetes.⁵ Insulin glargine was PBS-listed despite its higher cost as the PBAC accepted that the reduced rate of hypoglycaemic events was cost effective at the price proposed.^{21,22} Refer to the December 2006 edition of *NPS RADAR* (www.npsradar.org.au) for more information about insulin glargine.

§ Insulin detemir is PBS-listed for use in type 1 diabetes.

Ensure metformin is part of ongoing therapy and use of thiazolidinediones does not delay progression to insulin

Use metformin as a monotherapy and combine with a sulfonylurea if glycaemic control is inadequate

If lifestyle interventions do not adequately control blood glucose (HbA_{1c} > 7%), start metformin. If metformin is contraindicated[‡] use a sulfonylurea. If metformin alone (≤ 3 g/day) does not adequately control blood glucose add a sulfonylurea (glibenclamide ≤ 20 mg/day; glicazide ≤ 320 mg/day; glimepiride ≤ 4 mg/day; or glipizide ≤ 40 mg/day).²³

A thiazolidinedione may be combined with either metformin or a sulfonylurea if one of these drugs is contraindicated or not tolerated. Be aware that thiazolidinediones increase the risk of oedema and heart failure.

Triple oral therapy using a thiazolidinedione should only be prescribed in limited circumstances

Initiating insulin when metformin and a sulfonylurea no longer provide adequate glycaemic control is preferred to adding a glitazone as a third oral agent (i.e. triple oral therapy).⁴ Insulin has a better defined long-term safety profile than the thiazolidinediones and is known to reduce microvascular complications.⁹

While initiating insulin is preferred, triple oral therapy using a thiazolidinedione has a place among people with a severe needle phobia, who are very reluctant to use insulin, who require assistance to administer insulin, or whose job security may be threatened if they use insulin. Be aware that thiazolidinediones increase the risk of oedema and heart failure.

Do not delay initiating insulin if HbA_{1c} > 7% after 3 months despite triple oral therapy

Triple oral therapy (including a thiazolidinedione) should not delay the initiation of insulin if it is required. Around 25% to 30% of people in clinical trials did not respond to thiazolidinediones with an adequate reduction in HbA_{1c} or fasting plasma glucose concentration.²⁴ Consider insulin if triple oral therapy does not adequately control blood glucose (HbA_{1c} > 7%) after 3 months.¹¹

‡ Impaired renal function (creatinine clearance < 30 mL/min) or history of lactic acidosis. Use with caution in those with heart failure or ischaemic heart disease; the elderly; heavy drinkers and people with impaired liver function.

Review use of thiazolidinediones in heart failure and ischaemic heart disease

Avoid thiazolidinediones in people with heart failure

Thiazolidinediones double the risk of heart failure.^{25,26} Do not prescribe them for someone with moderate or severe heart failure (New York Heart Association Class III or IV).

Prescribe a thiazolidinedione with caution in people who are asymptomatic or have only mild cardiac insufficiency. Start at the lowest dose and monitor closely for signs of oedema or rapid weight gain.²⁷

Do not prescribe rosiglitazone to those with ischaemic heart disease

Rosiglitazone may increase the risk of myocardial infarction.²⁸ Do not prescribe rosiglitazone for people with known ischaemic heart disease.²⁸ Use with caution in people at high risk of cardiovascular events.²⁸ Pioglitazone does not appear to carry the same risk of myocardial infarction as rosiglitazone.²⁹

Be particularly cautious if adding insulin to a regimen that includes a thiazolidinedione

Rosiglitazone should not be prescribed to people already using insulin as this increases the risk of heart failure and ischaemia.³⁰ It should only be combined with insulin in exceptional circumstances under close supervision due to an increased risk of fluid retention and ischaemia.^{31,32} Monitor closely for signs of oedema, rapid weight gain or other indicators of potential cardiovascular risk.

Pioglitazone in combination with insulin is also associated with increased fluid retention.³³ If combining pioglitazone and insulin, start on a low dose and monitor closely for signs of oedema, rapid weight gain or other indicators of potential cardiovascular risk.

More information on the thiazolidinediones is available in *NPS RADAR* (www.npsradar.org.au) or in *NPS News 56: Managing hyperglycaemia in type 2 diabetes*.

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Citations available online at www.nps.org.au/healthpro

The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence. Any treatment decisions based on this information should be made in the context of the clinical circumstances of each patient.



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