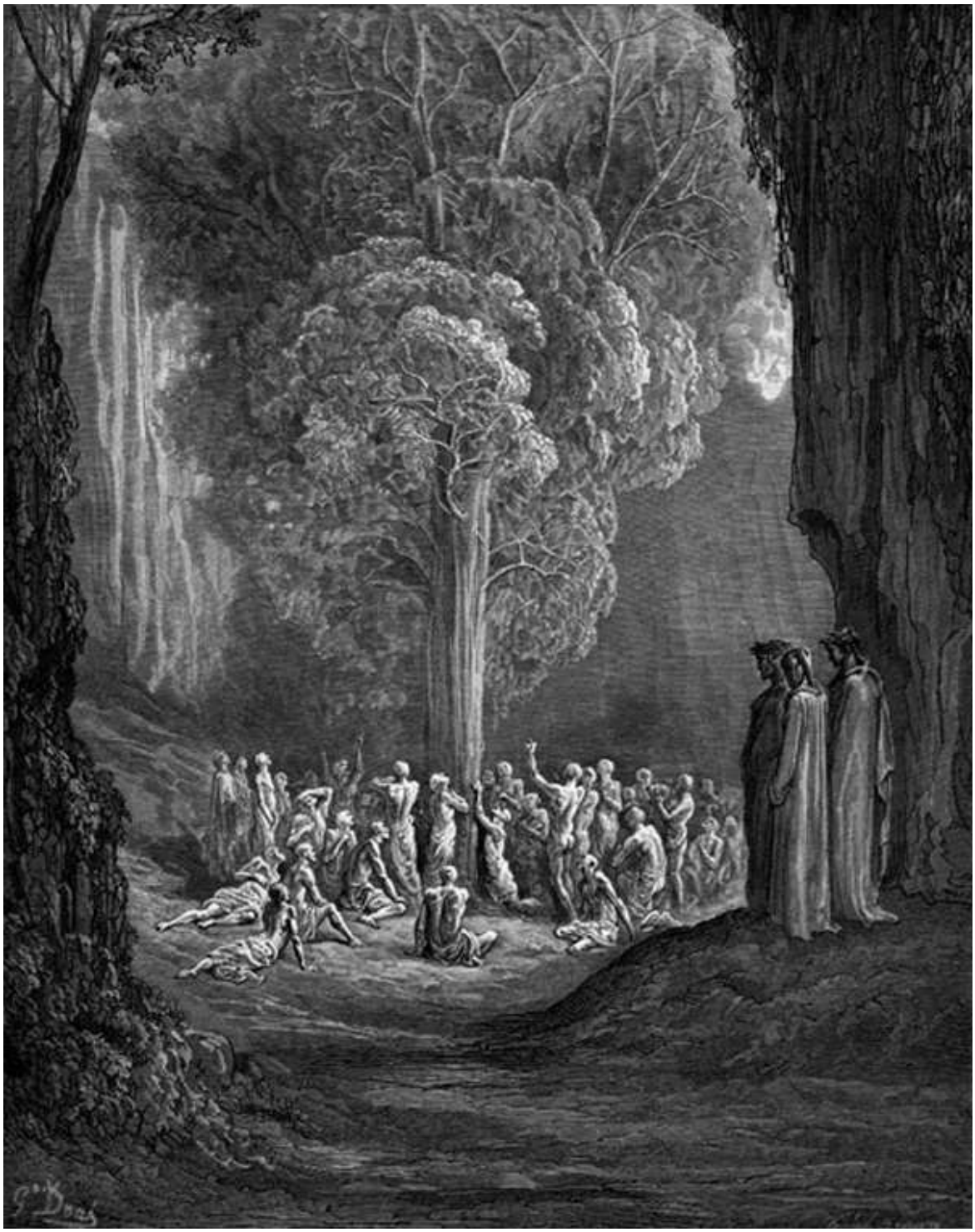
THE NORTHERN HOSPITAL

METFORMIN



Dante, Virgil and the shade Statius encounter the shades of the gluttons on the Sixth Terrace of Purgatory. Woodcut print, 1867, Gustave Dore.

…But soon their pleasant walk was interrupted
by a tree found in the middle of the path,
with fruits that smelled both savory and good,

and as a fir tree narrows as it branches upward,
this one tapered down from branch to branch,
perhaps so that no one can climb it.

On that side, where our way was blocked,
from the high rock fell pellucid water,
which was dispersed amoung the upper leaves.

As the two poets neared the tree
a voice from amoung the boughs called out:
"This is food that you shall lack"….

Just as pilgrims absorbed in thought,
overtaking strangers on the road,
turn toward them without coming to a halt,

so, coming up behind us at a quicker pace than
ours and passing on, a group of souls,
silent and devout, gazed at us with wonder…

..And the shades, that seemed things dead twice
over, stared at me, amazed, from the sockets of
their eyes, once they saw I was alive…

Their eyes were dark and sunken,
Their faces pale, their flesh so wasted
that the skin took all its shape from bones...

The sockets of their eyes resembled rings
Without their gems…

Who if he did not know the reason, would
believe the scent of fruit and smell of water
could cause such craving, reducing shades to
this?

I was wondering what makes them so famished,
since what had made them gaunt, with wretched
scaling skin, was still unknown to me,

when out of the deep set sockets in his head
a shade fixed me with his eyes and cried aloud"
"What grace is granted to me now!"

I never would have known him by his features,
but the sound of his voice made plain to me
from what his looks had been erased.

That spark relit the memory
of his changed features
and I knew Forese's face…

"In God's name, tell me what withers you
away"…

And he to me: "From the eternal counsel,
a power falls onto the tree and on the water
there behind us. By it I am made so thin.

"All these people who weep while they are
singing
followed their appetites beyond all measure,
and here regain, in thirst and hunger, holiness.

"The fragrance coming from the fruit
and from the water sprinkled on green boughs
kindles our craving to eat and drink,

"and not only once, circling in this space,
is our pain renewed,
I speak of pain, but should say solace…

"He there" - and he pointed with his finger - "is
Bonagiunta, Bonagiunta of Luca, and that one
Just beyond him, the face more cracked and
scaly

"than the rest, held Holy Church within his
arms.
He was from Tours and now by fasting purges
eels from the Bolesna served alla vernaccia"…

"Pass on, do not come any closer
This is the offshoot of that tree above
from which Eve plucked and ate the fruit"

Dante Alighieri,
Purgatorio, Canto XXII - XXIII
(1306-1317)

Dante and Virgil have just climbed to the penultimate Terrace of Purgatory, the Terrace of the Gluttons, wherein walk the shades of those who in life could not control their base appetites for food and wine. Suddenly they come upon an immense and ancient tree of most unusual morphology. It seems almost inverted with the narrow branches at the base and the broader branches at its peak, as if deliberately designed to stop anyone trying to climb it. It is watered by pure cascading waters from the rocks high above. The tree suddenly talks to them, "This is food you shall lack!"

Just then a group of shades silently overtake them on the road. All are singularly focused on the tree ahead, but some catch sight of Dante, and turn their gaze back over their shoulders in amazement. He is not a shade, but still alive! Dante is horrified to see their faces, they appear as "dead twice over". Their bodies are so wasted that their skulls can be seen through their very skin. Their eyes are great empty sockets, that resemble rings without their gems. Suddenly one of the ghastly apparitions, recognizes Dante. It calls out to him "What grace is granted to me now!" Though Dante does not recognize him, he is shocked to recognized the voice of his friend Forese Donati, who had died some years ago. "In God's name, tell me what withers you away", Dante exclaims.

Forese explains that as they circle the Terrace, each time they encounter the tree its fragrances induce an irresistible desire in them to eat its fruit. As in life they are unable to resist the gratification of their stomachs, however when they eat of this tree's fruit disaster follows, rather than gratification. They become tormented by an even greater hunger, and instead of gaining weight, they lose it, yet they cannot help themselves. They have become walking skeletons. Each time they circle the Terrace, their hunger agonies are renewed. However, unlike the Shades of the Gluttons in Hell who are condemned to eternal punishment, on the Terrace of the Gluttons, an end, though far off, is in sight. Once they have completely wasted away to nothing, they are then considered finally purged of their earthly gluttony, and will be free to progress to the next Terrance above. Forese, though he suffers terribly, does find solace that it will not be forever, "I speak of pain, but should say solace…" He demonstrates to Dante, that many rich people and powerful people, have ended up doing time on the Terrace of the Gluttons. Dante cannot recognize them and so he points them out. To Dante's horror one of the shades was a Pope, "…and that one, just beyond him, the face more cracked and scaly, than the rest, held Holy Church within his arms". Scholars have determined this Pope to be Martin IV, by the statement, "He was from Tours and now by fasting purges eels from the Bolesna served alla vernaccia". Legend has it that Pope Martin, was a terrible glutton, and that he died from an excessive overindulgence of eels cooked in white wine.

Type II diabetes is one of the great health scourges of the modern Western World. Affluence in general today is enjoyed on a scale unimaginable in Dante's day. Consequently of course there are great many more souls destined for the sixth Terrace of the Gluttons when they die. Obesity remains a great risk factor for type II diabetes. Like the tormenting tree on the sixth Terrace, many people cannot help themselves when it comes to consumption of gluttonous amounts of sugar! And like the shades on the Sixth Terrace, the more they crave and consume, they sicker they will become! Happily earthly salvation is attainable however, with a little restraint, exercise and a magical potion, by the name of metformin!

METFORMIN

Galega officinalis (or French Lilac)

Introduction

Metformin is a **biguanide** oral antihyperglycaemic drug used in **type II diabetes.**

It is the first line agent used to treat type II diabetes mellitus worldwide.

It is the only oral glucose lowering drug that has been shown to reduce mortality in patients with diabetes. [5]

Its most serious adverse effect is lactic acidosis, which is uncommon, but more likely to develop in patients with significant renal impairment.

Metformin is on the World Health Organization's List of Essential Medicines, the most important medications needed in a basic healthcare system.

See also separate document:

- **Metformin Toxicity (in Toxicology folder).**

History

Galega officinalis (or French Lilac) has been used in folk herbal medicine for centuries. In medieval times, it was recognized that **French Lilac** could relieve the intense diuresis that was associated with a disease that would come to be known as diabetes mellitus.

The plant's long recognized hypoglycemic properties eventually led to the synthesis of the **biguanide** compound **metformin.**

In the 1920s, French Lilac was found to be a natural source of **guanidine alkaloids,** including **galegine (or isoamylene guanidine).** Later animal studies showed that these compounds could lower blood glucose levels.

Guanidine itself proved too toxic for the treatment of diabetes mellitus, however certain biguanide derivatives (compounds with two linked guanidine rings) were developed that were not as toxic as guanidine. Metformin was first described in the scientific literature in 1922, by **Emil Werner** and **James Bell,** as a product in the synthesis of N,N-dimethyl-guanidine. Three agents were developed by the 1950s, phenformin, buformin and metformin and they began to be used for the treatment of diabetes in conjunction with insulin.

The French physician, **Jean Sterne**, was the first to use metformin on humans for the treatment of diabetes. He coined the name "Glucophage" (or glucose eater) for his drug and published his promising results in 1957. Metformin became available in the British National Formulary in 1958, and was approved for use in Canada in 1972, but it would not be introduced in the USA until 1995.

Phenformin and buformin, were withdrawn from the market in the early 1970s when their propensity to induce serious lactic acidosis became apparent. Metformin, a less lipophilic biguanide, proved much safer in this regard. Today metformin is the first line agent used to treat type II diabetes mellitus worldwide.

Chemistry

The biguanides are compounds that contain two linked guanidine rings, (**see Appendix 2 below**).

Metformin is **dimethyl-biguanide hydrochloride.**

Classification

There are currently 6 classes of oral hypoglycemic agents available in Australia:

The two principle classes are:

1. **The Biguanides**:

These agents act by reducing hepatic glucose production (i.e. gluconeogenesis) and increasing the peripheral utilization of glucose.

Examples include:

- Metformin

2. **The Sulphonylureas**:

These agents act by increasing pancreatic insulin secretion and also possibly by enhancing peripheral sensitivity to insulin:

Examples include:

First generation:

- Tolbutamide (no longer used)

Second generation, (more potent, lower doses):

- Glibenclamide
- Gliclazide
- Glipizide

Third generation:

- Glimepiride

Other newer agents with less clinical experience include:

3. **Incretin-based therapies**:

Dipeptidyl peptidase - 4 inhibitors (i.e. **DPP - 4 inhibitors** or "**gliptins**"):

These agents increase the concentrations of incretin hormones (GLP-1 and GIP) that are produced in the gut following ingestion of food; GLP-1 stimulates insulin release, and reduces glucagon secretion.

Examples include:

- Alogliptin
- Linagliptin

- Saxagliptin
- **Sitagliptin**
- Vildagliptin

Glucagon-like peptide-1 (GLP-1) receptor agonists:

These agents are synthetic analogues of GLP-1; they increase insulin secretion and reduce glucagon secretion and also cause a small reduction in appetite.

Examples include:

- Exenatide
- Liraglutide

4. **Glucosidase inhibitors**:

These agents reduce the breakdown of complex carbohydrate in the gut, thereby reducing absorption of carbohydrate and hence insulin requirements

Examples include:

- Acarbose.

5. **Thiazolidinediones:**

These agents reduce peripheral insulin resistance and hence insulin requirements

Examples include:

- Pioglitazone
- Rosiglitazone

6. **Sodium-glucose co-transporter 2 (or SGLT2) inhibitors (or "Gliflozins")**:

These agents reduce glucose reabsorption in the kidneys.

Examples include:

- Dapagliflozin
- Empagliflozin

Preparations

Metformin hydrochloride as:

Tablets (regular release):

- 500 mg, 850 mg, 1 gram

Tablets (XR or extended release):

- 500 mg, 1 gram

Fixed combination preparations:

There are many fixed dose combination preparations including:

- Metformin with the sulfonylurea, **glibenclamide.**
- Metformin with the **dipeptidyl peptidase-4 inhibitors**, (such as alogliptin, dapagliflozin, empagliflozin, linagliptin, rosiglitazone, saxagliptin, sitagliptin and vildagliptin).

Mechanism of Action

Metformin acts by two principal mechanisms:

1. Reduces hepatic glucose production (i.e gluconeogenesis)

2 Increases the peripheral utilization of glucose.

It may also delay intestinal glucose absorption.

Metformin does not stimulate insulin release but it does require the presence of insulin to exert its antihyperglycaemic effect.

Pharmacodynamics

Metformin is the only oral glucose-lowering drug that has been shown to reduce mortality in patients with diabetes

It lowers both basal and post-prandial blood glucose in diabetic patients to low normal physiological levels.

Metformin hydrochloride alone does **not** tend to cause hypoglycaemia, unless it is used *in combination* with other antidiabetic agents such as sulphonylureas, glinides or insulin.

Glycaemic control may be attained within a **few days** but will occasionally require up to **two to three weeks** of treatment. The action of metformin is progressive and no final

assessment of the patient's real response should be made before the 3 weeks of treatment; blood sugar estimations are recommended during the initial weeks of stabilization.

Metformin does not cause weight gain.

Pharmacokinetics

Absorption:

- Metformin is administered orally.

  It is absorbed along the entire gastrointestinal mucosa.

  After oral administration, metformin absorption is saturable and incomplete. Bioavailability is around 50 - 60 %.

- At usual clinical doses and dosing schedules of metformin tablets, steady-state plasma concentrations are reached in 24 to 48 hours and are generally less than 1 microgram/mL.

Distribution

- Protein binding is negligible.
- Metformin is excreted into breast milk.
- Metformin can cross the placenta.

Metabolism and excretion:

- Metformin is excreted unchanged in the urine. It does not undergo hepatic any metabolism.
  - ♥ In patients with significantly decreased renal function (based on measured creatinine clearance), the plasma half-life of metformin is prolonged and renal clearance is decreased in proportion to the decrease in creatinine clearance.
- Half-life is around 1.5 - 6.2 hours.

Indications

These include:

1. **Type 2 diabetes mellitus**:
   - Type 2 diabetes in adults, including in fixed-dose combinations with DDP-4 inhibitors

It is particularly useful in overweight patients, when dietary management and exercise alone does not result in adequate glycaemic control.

For adult patients, metformin may be used as initial treatment or in sulfonylurea failures either alone or in combination with a sulfonylurea and other oral agents or as adjuvant therapy in insulin requiring type 2 diabetes.

- Type 2 diabetes in children >10 years

2. Anovulatory infertility due to polycystic ovary syndrome (under specialist supervision):

   - With clomiphene (if unresponsive to clomiphene alone) and BMI >30

   - As monotherapy, when clomiphene unsuitable (e.g. not tolerated or lack of access to appropriate monitoring) and BMI < 30

Contra-indications/precautions

These include:

1. Stop metformin if the patient becomes acutely unwell and is **at risk of further deterioration of renal function**.

   - Conditions that may alter renal function such as dehydration, shock or sepsis, or that increase risk of tissue hypoxia and acidosis such as MI, severe heart failure, liver failure, pulmonary embolism, or ketoacidosis, may increase risk of lactic acidosis.

2. Renal impairment:

   - **Metformin should not be used in people with a calculated CrCl < 30 mL/minute.**

3. Elderly:

   - Use cautiously; check renal function and for adverse effects; reduce dose (or stop treatment) if necessary.

     Avoid combination with glibenclamide (the fixed-dose combination is particularly unsuitable as dose titration is difficult).

3. Hepatic failure:

   - Avoid use in severe hepatic impairment.

4. Known hypersensitivity to metformin (or to biguanides in general).

5. Radiological contrast studies:

- Radiological studies involving the use of intravascular iodinated contrast materials may lead to acute deterioration of renal function and have been associated with **lactic acidosis** in patients receiving **metformin**.

  Royal Australian and New Zealand College of Radiologists (RANZCR) Guidelines for Iodinated Contrast Media, April 2016

  IV Contrast:

  Patients receiving intravenous iodinated contrast media with an eGFR above **30 ml/min/1.73 m^2** should **continue taking metformin.**

  Patients with an **unknown recent eGFR** or an **eGFR less than 30 ml/ min/1.73 m^2**, or who are **unwell** or have **deteriorating renal function** should **cease metformin** for **at least 48 hours** from the time of the examination and an eGFR performed prior to restarting metformin.

  Intra-arterial Contrast:

  Patients undergoing an intra-arterial procedure requiring iodinated contrast media with an eGFR above **45 ml/min/1.73 m^2** should **continue taking metformin.**

  Patients undergoing an intra-arterial procedure involving larger volumes of contrast media and/or a procedure involving a risk of renal embolization with an unknown recent eGFR or an eGFR less than 45 ml/ min/1.73 m^2, or who are unwell or have deteriorating renal function should cease metformin for at least 48 hours following intra-arterial administration of contrast media and have an eGFR estimated prior to restarting metformin.

6. Alcohol:

- The risk of lactic acidosis increases with acute intoxication, particularly in cases of fasting or malnutrition and hepatic insufficiency.

Pregnancy:

Metformin is a class C drug with respect to pregnancy

Category C drugs are those drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Specialised texts should be consulted for further details.

Maternal use of metformin has not been associated with an increased risk of congenital malformations or adverse pregnancy outcomes

Dietary modification, exercise and insulin have been considered the standard for the management of diabetes mellitus during pregnancy.

However, the use of metformin during pregnancy may provide benefits such as less weight gain and lower incidence of other complications (e.g. pregnancy induced hypertension) when compared with insulin. Further studies are required to provide robust evidence to recommend the continuous use of metformin during pregnancy.

Breast feeding:

Small amounts of metformin are excreted into breast milk, but adverse effects have not been observed in breastfed infants.

Therefore, metformin is considered safe to use during breastfeeding.

Adverse Effects

These include:

1. GIT upset:

    - Nausea, vomiting, diarrhea

      The most common adverse effect of metformin is gastrointestinal intolerance that may be dose it limiting.

      Commencing therapy at a low dose, titrating gradually, and taking with food can minimize gastrointestinal effects. Some patients however are unable to tolerate metformin even at low doses.

2. Hypoglycaemia:

    - The risk of this is very low.

      Metformin hydrochloride alone does not tend to cause hypoglycaemia, unless it is used in combination with other antidiabetic agents such as sulphonylureas, glinides or insulin.

3. **Lactic acidosis:**

    This is the most serious adverse effect of metformin but is fortunately uncommon.

    Life threatening lactic acidosis can occur due to **accumulation** of metformin.

Risk factors for lactic acidosis include:

- Renal impairment
- The elderly, (associated with reduced renal function)
- High doses of metformin, (above 2 grams per day).

When metformin is implicated as the cause of lactic acidosis, metformin plasma levels greater than 5 microgram/mL are generally found, (therapeutic levels are around 1 microgram/mL).

4. Vitamin B12 deficiency:

Metformin may cause **vitamin B12** malabsorption in some patients.

- It is prudent to measure vitamin B12 yearly in patients taking metformin, and prescribe vitamin B12 if concentrations are below the reference range.

Dosing [2]

For type 2 diabetes:

Take metformin with or after food to reduce stomach upset.

Controlled release tablets should be Swallowed whole; (i.e. they should not be chewed or crushed).

Check renal function before starting treatment and every 4 - 6 months.

The minimum effective dose should be used.

Adult:

Conventional tablet:

- Initially 500 mg 1 - 3 times daily
- May be increased up to 850 mg 2 or 3 times daily according to response.
- Maximum daily dose 3 grams.
  - ♥ Note that while the maximum daily dose of metformin immediate release is 3 grams, there is in fact limited clinical benefit in increasing the daily dose above 2 grams. [1]

Controlled release tablet:

- Initially 500 mg **once** daily:
- May be increased up to 2 grams **once** daily.
- When changing from conventional tablets, start with the patient's usual daily dose. (If > 2 grams daily is required, use conventional tablets.)

Child >10 years:

Conventional tablet, initially 500 - 850 mg once daily; maximum daily dose 2 grams in 2 or 3 doses.

Fixed-dose combinations with glibenclamide:

Adult, initially 1 tablet of 500 mg metformin with 2.5 mg glibenclamide daily with breakfast. Increase by 1 tablet (of this strength) every 2 weeks or longer according to response.

Maximum dose, 1 tablet of 500 mg metformin with 5 mg glibenclamide 3 times a day.

Elderly, the manufacturer suggests an initial dose of 250 mg metformin with 1.25 mg glibenclamide daily. Give with breakfast and increase dose according to response as above.

Renal Impairment:

A reduced maximum adult dose is suggested for patients with stable renal function:

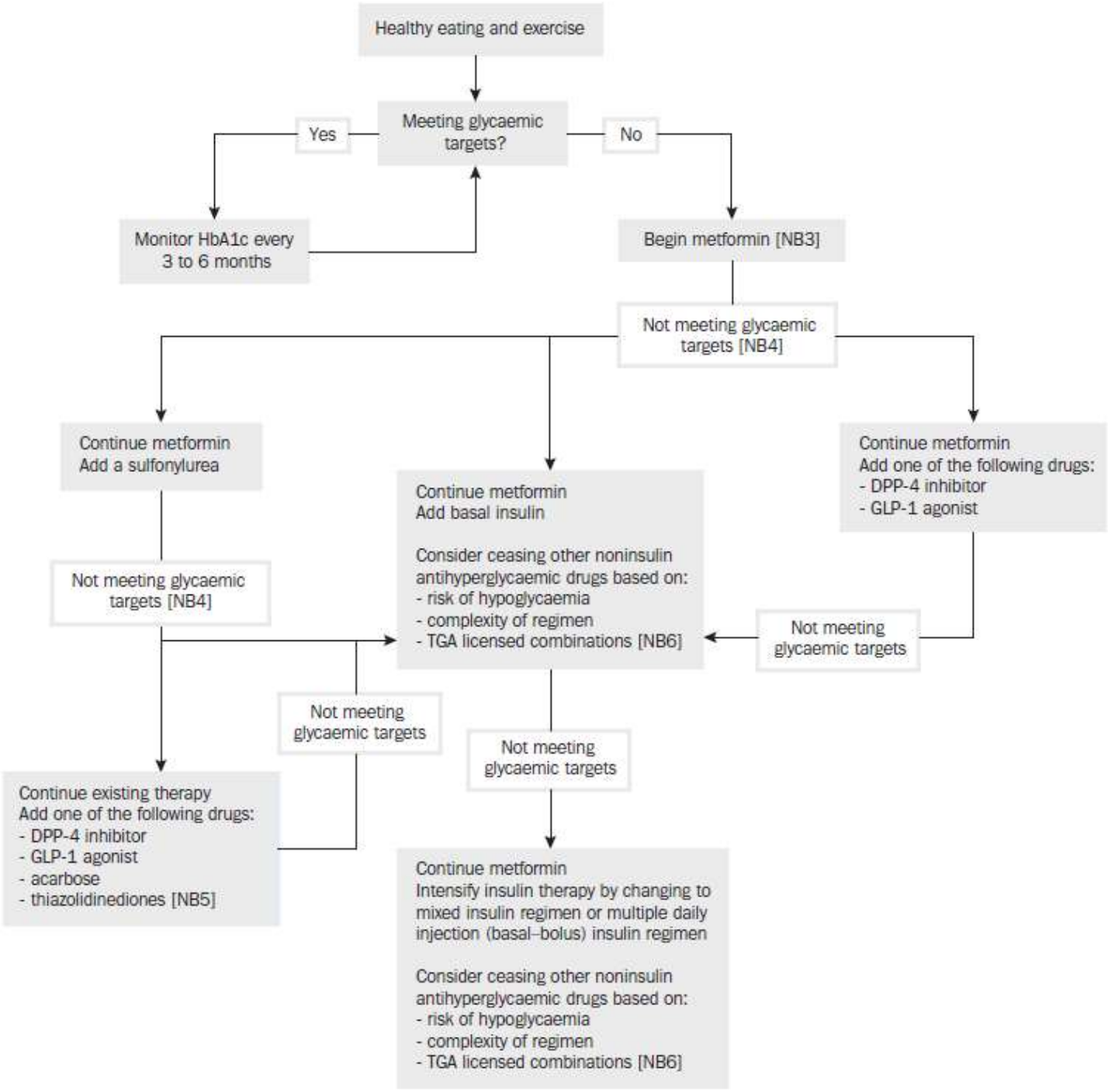
CrCl 60 - 90 mL/minute: 2 gram daily.

CrCl 30 - 60 mL/minute: 1 gram daily.

CrCl 15 - 30 mL/minute: 500 mg daily.

Appendix 1

Algorithm for the treatment of type II diabetes: [1]



HbA1c = glycated haemoglobin; TGA = Therapeutic Goods Administration; DPP-4 = dipeptidyl peptidase 4; GLP-1 = glucagon-like peptide 1 receptor

NB 1:

- Monitoring response to therapy by measuring HbA1c every 3 to 6 months is essential to allow timely escalation of treatment. See advice on monitoring type 2 diabetes in eTG complete for further information.

NB 2:

- See www.pbs.gov.au for current information on subsidised drug combinations.

NB 3:

- Gastrointestinal adverse effects from metformin can generally be overcome with dose reduction and slow up titration. See advice on metformin in eTG complete for further information.

NB 4:

- Choice of treatment will depend on patient-centred factors; for further information, see "Choice of antihyperglycaemic drug and combination therapies" in eTG complete. See advice in eTG complete about individual drugs for specific advice regarding benefits and risks of treatment options.

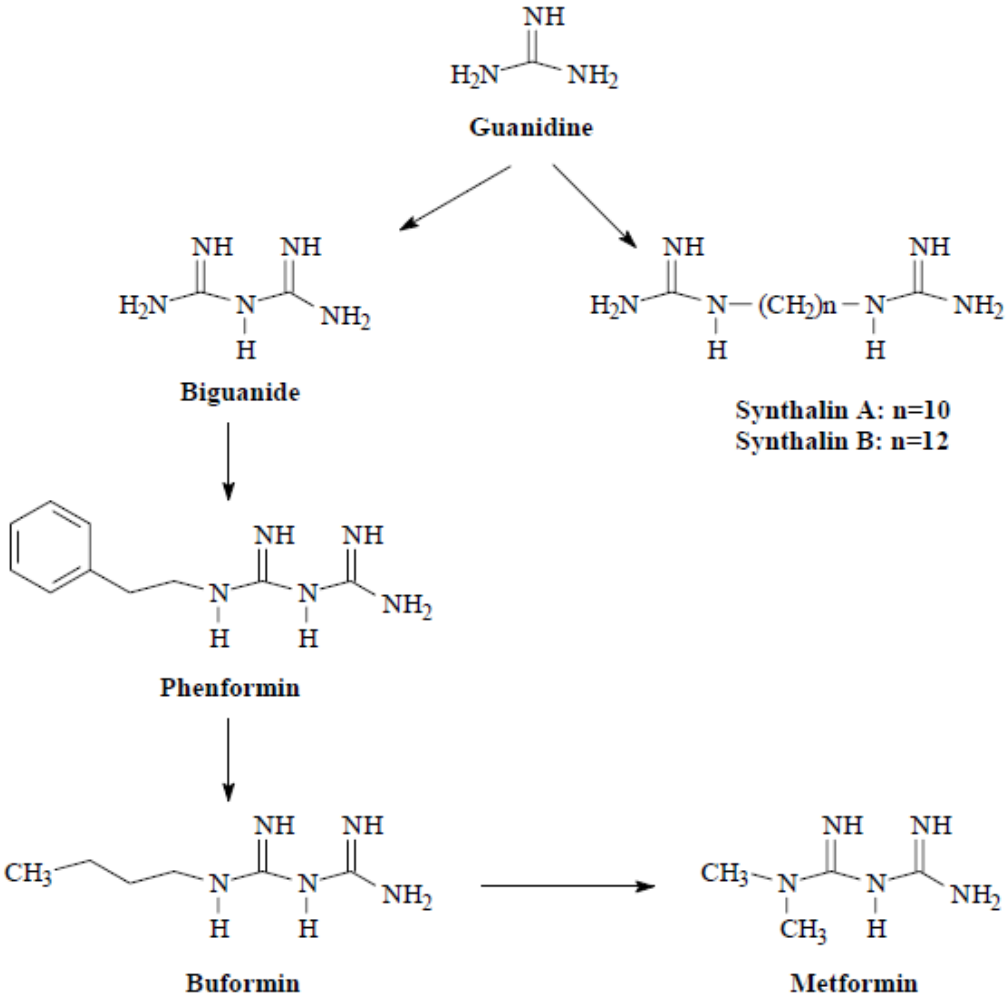
NB 5:

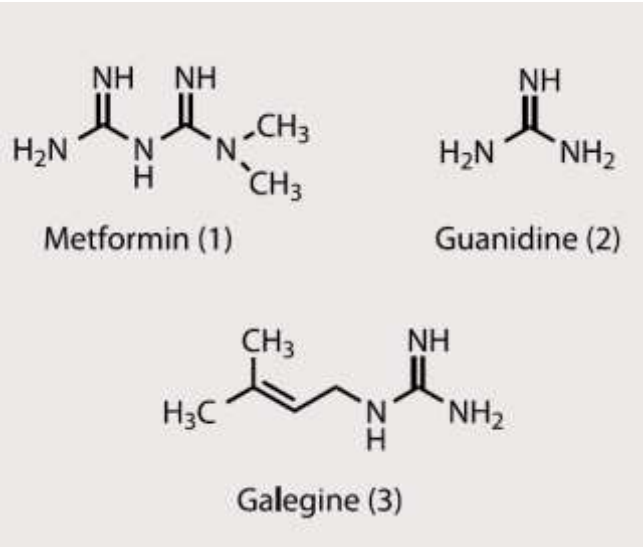
- At the time of writing, pioglitazone is the only thiazolidinedione licensed for triple therapy with metformin and a sulfonylurea; see <www.tga.gov.au> for current information.

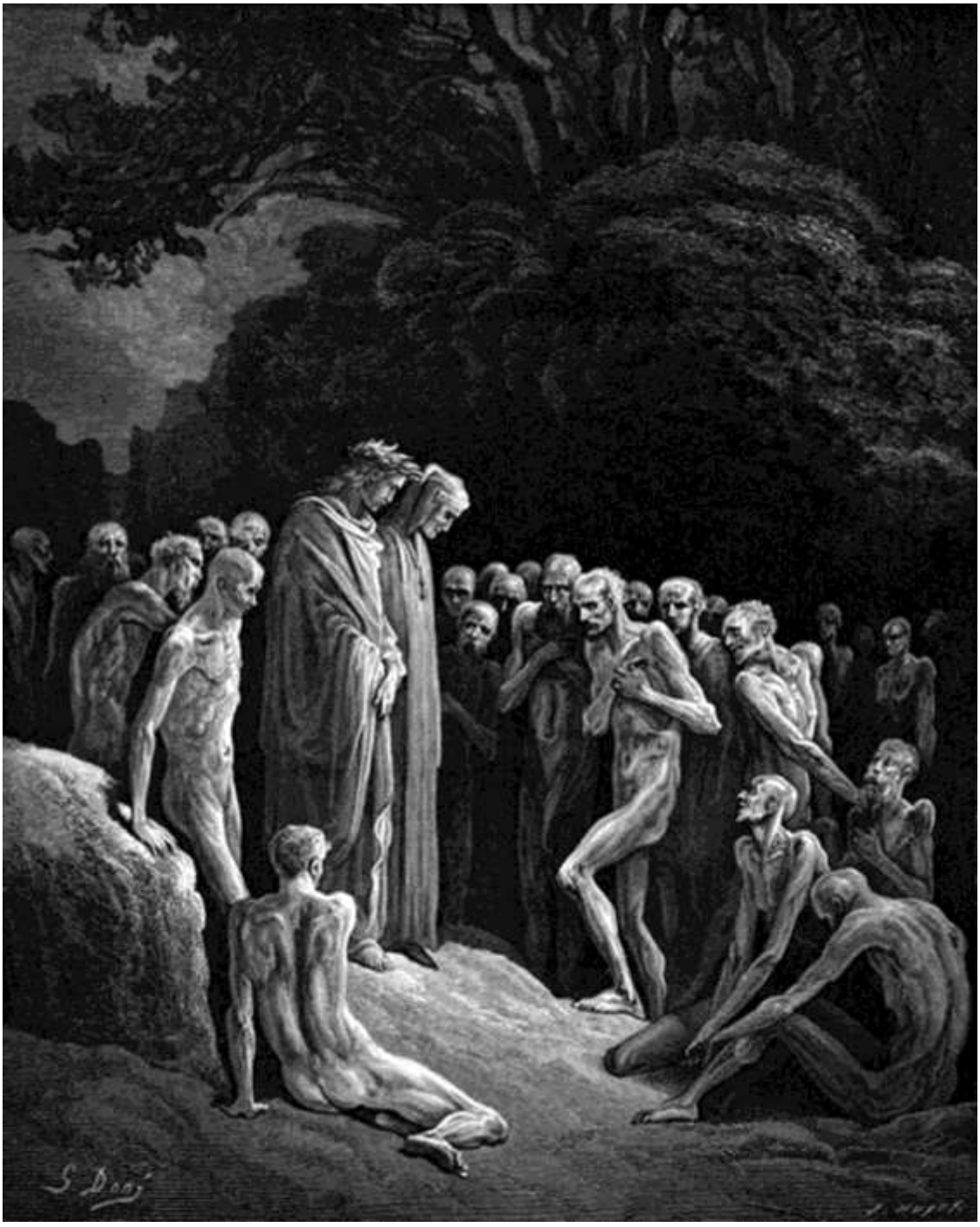
NB 6:

- See **www.tga.gov.au** for current licensed indications and combination of antihyperglycaemic drugs.

Appendix 2: *The Chemical Derivation of the Biguanides:*







Dante, recognizes his friend, Forese Donati, amoung the shades of the Gluttons, on the Sixth Terrace of Purgatory. Woodcut print, 1867, Gustave Dore.

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4. RWH Pregnancy & Breastfeeding Guidelines, 14 April 2016.

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    - http://www.ranzcr.edu.au/

Dr J. Hayes
Reviewed December 2017.