Metformin: historical overview

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Abstract

Metformin (dimethyl biguanide) has become the preferred first-line oral blood glucose-lowering agent to manage type 2 diabetes. Its history is linked to *Galega officinalis* (goat's rue), a traditional herbal medicine in Europe found to be rich in guanidine which, in 1918 was shown to lower blood glucose. Guanidine derivatives, including metformin, were synthesised and some (not metformin) were used to treat diabetes in the 1920s and 1930s but were discontinued due to toxicity and the increased availability of insulin. Metformin was rediscovered in the search for antimalarial agents in the 1940s and during clinical tests proved useful to treat influenza when it sometimes lowered blood glucose. This property was pursued by the French physician Jean Sterne who first reported the use of metformin to treat diabetes in 1957. But metformin received limited attention as it was less potent than other glucose-lowering biguanides (phenformin and buformin), which were generally discontinued in the late 1970s due to high risk of lactic acidosis. Metformin's future was precarious - its reputation tarnished by association with other biguanides despite evident differences. The ability of metformin to counter insulin resistance and address adult-onset hyperglycaemia without weight gain or increased risk of hypoglycaemia gradually gathered credence in Europe, and after intensive scrutiny metformin was introduced into the USA in 1995. Long-term cardiovascular benefits of metformin were identified by the United Kingdom Prospective Diabetes Study in 1998, providing a new rationale to adopt metformin as initial therapy. Sixty years after its introduction to treat diabetes metformin has become the most prescribed glucose-lowering medicine worldwide with the potential for further therapeutic applications. [263 words]

Introduction

This short biography of metformin (dimethyl biguanide) plots a chequered history from herbal ancestry in Europe to synthesis and discovery of glucose-lowering activity in the 1920s - information that was disregarded and forgotten. In the 1940s metformin was rediscovered in the search for antimalarial agents and repurposed to treat influenza before its introduction in 1957 to treat adult-onset diabetes (Table 1). But metformin was considered weaker than other glucose-lowering biguanides and received limited use. When the other biguanides (phenformin and buformin) were withdrawn in the late 1970s due to lactic acidosis, metformin was spared but mostly rejected. However, ongoing research and minimal clinical use in the 1980s and early 1990s demonstrated a uniqueness and utility of metformin that fostered its rescue. Introduction of metformin into the USA in 1995 boosted research and clinical use, and long-term evidence from the United Kingdom Prospective Diabetes Study (UKPDS) in 1998 set metformin on course for its current position as preferred initial agent to manage hyperglycaemia in type 2 diabetes. Now exonerated, metformin is being assessed for further clinical indications. How could such a medicinal servant have received such a tempestuous journey?

Herbal history

The herbal lineage of metformin can be traced from the use of *Galega officinalis* (goat's rue, French lilac, Italian fitch, Spanish sainfoin, professor weed) as a traditional medicine in medieval Europe (Figure 1) [1]. Also known as *Herba rutae caprariae* in some herbals, *G. officinalis* was ascribed benefits against worms, epilepsy (falling-sickness), fever and pestilence in Culpeper's *Complete Herbal* of 1653, but in Hill's *The Vegetable System* of 1772 *Galega* was recommended to treat conditions of thirst and frequent urination [2-4]. Wild *G. officinalis* was widely recognised in Europe as an animal galactagogue from which it gained its name (from the Greek for milk stimulant). The plant was introduced into North America in 1891 and is classed as a noxious weed in many states of the USA [5]. Chemical analyses of *G. officinalis* dating from the mid-1800s found the plant to be rich in guanidine and related compounds, especially the immature seed pods (Figure 2) [6]. In 1918 guanidine was reported to reduce blood glucose in animals, and during the 1920s several mono-guanidine derivatives, notably galegine (isoamylene guanidine) and diguanidines such as synthalin (two guanidines separated by a methylene chain) were also shown to lower blood glucose in animals [6- 10]. This led to the introduction of galegine and the more potent synthalin as treatments for diabetes, but initial optimism was tempered with disappointment as toxicity was observed, curtailing their use during the 1930s as insulin became more widely available [6, 11-15].

From *Galega* to biguanides

The chemical origins of metformin run in parallel with the herbal origins and date from the preparation of guanidine by Strecker (1840s -1860s) and the fusion of two guanidines into biguanide by Rathke in 1879 (Figure 2) [6, 16]. These provide the background to the synthesis of dimethyl biguanide by Werner and Bell in 1922 [17]. Despite structural proximity to the hypoglycaemic mono- and diguanidines, it was not until 1929 that metformin and other biguanides were reported to lower blood glucose in animals (rabbits and dogs) by Hesse and Taubmann and also by Slotta and Tschesche [18, 19]. Metformin exerted least toxicity of the various methyl biguanides tested, and

biguanides were deemed to be less toxic than mono- and diguanidines [19]. But the real potential of these agents was underappreciated at the time due to the high doses required to achieve modest glucose lowering in non-diabetic animals (compared with subsequent evidence in diabetic models). So the biguanides were not developed as therapies for diabetes and became forgotten during the next decade along with the other guanidine-based agents.

Rediscovery via malaria and influenza

A third strand in the history of metformin is the independent development of a guanidine-based antimalarial agent proguanil (paludrine) in the mid 1940s, which was reported to cause a lowering of blood glucose in animal studies [20, 21]. Searching for other guanidine-based antimalarials, proguanil was modified to metformin, and during tests for antimalarial activity by Garcia in the Philippines in 1949 metformin was found to be helpful in treating a local influenza outbreak [22]. This gave rise to metformin hydrochloride as an anti-influenza agent called flumamine, and a tendency for metformin to lower blood glucose in some of the influenza patients was duly noted [6, 22].

Step forward Jean Sterne

The visionary who translated the antihyperglycaemic potential of metformin into a therapeutic reality was Jean Sterne, a physician at the Aron Laboratories in Suresnes in the west of Paris (Figure 3). In 1956, encouraged by laboratory owner Jan Aron, Sterne critically assessed the evidence around flumamine and recalled his involvement with a disappointing study of galegine as an intern with Professor Francis Rathery at l'Hopital de le Pitie in Paris many years earlier [23]. Maybe metformin would be better, and working at Aron Laboratories with pharmacist colleague Denise Duval the duo embarked on an ambitious programme of research into the pharmacodynamics of several guanidine-based compounds including metformin and phenformin in normal and diabetic animals. Unknowingly they duplicated and extended studies with guanidine-based compounds from the 1920s, and noted afresh the issues of high dose, limited glucose-lowering and high toxicity. They singled out metformin for study in the diabetes clinic based on its glucose-lowering efficacy and minimal adverse effects in normal and diabetic animals, coupled with the flumamine experience in humans [6].

Sterne had a position at l'Hopital Laennec in Paris where he started metformin studies with his patients, and he persuaded Dr Elie Azerad at Hopital Beaujon in Clichy to collaborate. Their initial studies, mostly with insulin-treated patients, included a mix of juvenile-onset and maturity-onset presentations of diabetes. The studies indicated that metformin could replace the need for insulin in some maturity–onset patients and reduce the insulin dose required by others, but did not eliminate the need for insulin in juvenile-onset patients [6]. They also noted no occurrence of frank hypoglycaemia (as had recently been reported with sulphonylureas) and little or no effect in non-diabetic subjects. This was enough for Sterne to publish a brief account of his findings in a Moroccan medical journal in 1957 [24]. This is now recognised as a landmark paper for the emergence of metformin as a diabetes therapy. In this paper Sterne made the following prophetic remarks: "LA6023 [metformin] is ……. well tolerated, which, even after very prolonged administration, does not damage the organism. At low doses it is hypoglycaemic by mouth in the rabbit, chicken, rat,

guinea-pig, dog, alloxan-diabetic rabbit, and the diabetic human……..and its ultimate place in the management of diabetes requires further study."

Later publications would elaborate details of the studies, which revealed Sterne's insight, skill and persistence [25-31]. Sterne suggested the name 'glucophage' (glucose eater) which was adopted by Aron to market metformin, and Sterne played a prominent role in ongoing research and physician education to assist the introduction of metformin into clinical practice in Europe [6]. History might be tempted to consider the diabetes indication of metformin as serendipitous, but we must gratefully acknowledge Sterne's sharp enquiring mind, his prodigious experimentation and his perceptive clinical sixth sense.

The biguanide opportunity

During the 1950s other groups investigated guanidine derivatives and the glucose-lowering properties of phenformin were rediscovered and published in 1957 by Ungar and colleagues in the USA, followed by buformin in 1958 by Beringer and colleagues in Germany [32, 33]. A vast selection of guanidine derivatives was then synthesised and evaluated, but enthusiasm was dampened by lesser glucose-lowering efficacy in non-diabetic animals compared with agents that stimulate insulin secretion [34, 35]. However, studies in human maturity-onset diabetes indicated greater glucose-lowering efficacy with phenformin than other biguanides and this agent gained global popularity as an alternative to sulphonylureas, especially in the USA [36-38]. Metformin and buformin were not introduced into the USA and received relatively minor use in Europe, although metformin became available in the UK in 1958 and Canada in 1972, and was championed in several respected diabetes clinics. Buformin became available across Europe (but not UK) in the early 1960s, particularly in Germany, but remained in the shadow of phenformin [39, 40].

Clinical experience with metformin in small studies and anecdotal accounts with maturity-onset patients typically portrayed modest efficacy but generally good tolerability, accepting the gastro-intestinal incommode experienced by some patients [6, 41]. Large comparative trials, notably in Edinburgh, showed that metformin could achieve similar long-term glycaemic control to sulphonylureas, and without significant hypoglycaemia or weight gain [42-44]. Later studies noted that basal insulin concentrations were often lowered, consistent with the amelioration of insulin resistance, while lipid lowering and improved haemodynamics were evident in some patients [41, 45]. The requirement for renal monitoring was consolidated, contraindications were appreciated and a possible decrease of vitamin B12 absorption was recognised [41, 45].

Lactic acidosis

The risk of lactic acidosis, especially with phenformin and buformin was evident from the outset, and the controversy was fuelled when phenformin was withdrawn from the University Group Diabetes Program (UGDP) trial in the USA in 1971 [46-48]. Phenformin was removed from the market in the USA in 1978, and phenformin and buformin were discontinued in much of Europe around this time, although both agents can still be obtained in some countries [49]. The incidence of lactic acidosis amongst users of metformin was much lower and most cases could be attributed to inappropriate use in contraindicated patients with chronically impaired renal function or cases of acute kidney

disease [47, 50, 51]. Moreover, in some studies it was debatable whether incidence rates of lactic acidosis with metformin were higher than background rates amongst maturity-onset patients. Nevertheless the reputation of metformin was tarnished by association with the other biguanides, and metformin teetered on the very brink of discontinuation [49].

Ironically soon after withdrawal of phenformin it was noted that about 9% of Europids have a mutation of the CYP2D6 hydroxylation enzyme, causing build-up of unmetabolized phenformin to precipitate lactic acidosis [52, 53] - a problem that modern pharmacogenomics could deal with.

How did metformin survive the biguanide cull?

Clinical experience with metformin, albeit limited compared with phenformin, generally suggested a more favourable safety profile, and there were pharmacokinetic data to indicate distinct differences between metformin and the other biguanides (Figure 4; Table 2) [40, 41]. During the 1980s non-insulin dependent diabetes (replacing the term maturity-onset) became viewed as much from the perspective of insulin resistance as beta-cell failure, and the ability of metformin to counter insulin resistance generated interest [54, 55]. New information in the 1980s and early 1990s indicated that the ability of metformin to reduce hepatic gluconeogenesis and increase peripheral glucose utilisation was not merely an anaerobic consequence of respiratory chain disruption [45]. Rather, metformin affected a raft of insulin-dependent and insulin-independent effects that vary in different tissues due to the amount of drug exposure to these tissues and the activity of insulin, glucagon and pathways of nutrient metabolism within these tissues. In particular it became evident that high levels of metformin in the intestinal wall exert insulin-independent effects that account for most of the extra lactate production, whereas liver and muscle are exposed to lower concentrations of metformin that alter post-receptor insulin signalling pathways and redirect energy-generating and storage pathways [56-62].

Metformin enters the USA

With reverberations from phenformin, the US Food and Drug Administration (FDA) was hesitant about metformin, but in 1986 an approach by Lipha Pharmaceuticals (having acquired Aron Laboratories) sparked an inordinately thorough reassessment of metformin by the FDA and the sponsor. The Lipha team was headed by Dr Gerard Daniel, an inspired, meticulous and pragmatic physician reminiscent of Jean Sterne. Daniel worked tirelessly alongside another very accomplished physician, Dr Anita Goodman, to deliver answers to an avalanche of questions from the FDA [6]. This involved a proliferation of studies from Lipha Europe plus input from a group of independent clinical scientists (initially Reaven, DeFronzo and Bailey, later joined by Turner and Garber) who engaged with the FDA to design the clinical trials, discuss the data and consider the implications for routine clinical use in the USA [6, 56]. FDA approved metformin on 29 Dec 1994 and soon after its launch in the USA in 1995 new key trial data were published in the New England Journal of Medicine [63]. These and subsequent clinical studies confirmed and extended the Edinburgh findings of two decades earlier, and the design of the metformin trials has provided a template for phase 3 evaluation of subsequent glucose-lowering agents [63, 64]. Bristol Myers Squibb acquired US marketing rights to metformin and instigated an education programme of unprecedented proportion to facilitate safe introduction of the drug, emphasising its different mode of action to

sulphonylureas and the necessary cautions associated with renal impairment and hypoxaemic conditions. The value of this safety-first approach accorded with the FDA's black box reminder in the product label, and played an important role to maintain the acknowledged safety profile of the drug [64]. As prescriber confidence grew, an extended release formulation of metformin was approved in 2000 with reduced gastro-intestinal side effects [65, 66]. Also, new fixed-dose combinations of metformin with sulphonylureas and later with other classes of oral glucose-lowering agents became available, taking advantage of additive efficacy when combining agents with different modes of action [67]. The key difference from earlier European fixed-dose combinations was that the dosages were based around metformin as the primary component, with doses of the second agent tailored to complement the administration schedule for metformin and to minimise risk of hypoglycaemia [68].

The UKPDS and long-term retrospective studies

In 1998 the UKPDS revealed data from newly diagnosed type 2 diabetes patients receiving glucose-lowering treatment for more than a decade. This epic study which redefined the therapeutic strategy for management of type 2 diabetes noted that in addition to glucose-lowering, weight neutrality and low hypoglycaemia risk, long-term metformin therapy might reduce cardiovascular (CV) events and improve survival [69]. Reduced CV risk appeared to be largely independent of glucose-lowering efficacy, and attention is drawn to a substantial literature noting potentially advantageous effects of the drug on the macro- and micro-vasculature (Table 3) [70, 71]. Interrogation of large databases that captured long-term treatment of type 2 diabetes consistently confirmed the reduced CV risk with metformin, and the 10-year follow-up of the UKPDS in 2008 showed a continued CV benefit of early use of the drug [72-74].

First-line pharmacological choice

Many studies on the pharmacokinetics, pharmacodynamics, clinical efficacy and cellular mechanisms of metformin have informed a favourable benefit-risk and, alongside cost-effectiveness, have elevated this agent to preferred first-line glucose-lowering pharmacological therapy for type 2 diabetes in major national and international treatment guidelines and algorithms [eg. 75-78]. Metformin has become the most prescribed glucose-lowering therapy worldwide and it is now included in the WHO Essential Medicines List [79]. A citizens' petition in the USA prompted an update to the product label in 2016 to extend prescribing for patients with mild renal impairment. Overall, the prominent position of metformin reflects judicious prescribing, emphasising that contraindications should not be over-relaxed if the safety profile is to be retained (Table 4).

Other indications

Possible additional indications for metformin are under investigation. Opportunities for use in type 1 diabetes to improve glycaemic control and reduce insulin dose have been appreciated since the very first clinical studies [6, 80]. Several studies have affirmed the value of metformin to slow or prevent progression of IGT/IFG 'prediabetes' to type 2 diabetes, and several studies have suggested a place for metformin in gestational diabetes [81-83]. Various insulin resistant states where metformin has improved prognosis include polycystic ovary syndrome (PCOS), human

immunodeficiency virus (HIV)-associated lipodystrophy, acanthosis nigricans and possibly dementia-type neurodegenerative disorders [84-87]. Reduced cancer risk was tentatively indicated in the UKPDS and has subsequently been identified in large database analyses, suggesting that metformin might protect against certain cancers in type 2 diabetes patients, notably in the bowel where drug exposure is high, and this has opened a whole new research arena [69, 88, 89]. Advances in pharmacogenomics may better inform responsiveness to metformin and effects on the gut microbiome, and animal studies have intriguingly noted anti-ageing effects of metformin [90, 91].

Some lessons

There are endless generic lessons for medical research thinly disguised within the history of metformin. With hindsight we are reminded that time spent searching early original literature can save valuable laboratory time, effort and money: vital clues can be concealed amidst throw-away observations in other areas of research, selecting and interpreting experimental models is fundamental, scrutiny within a drug class can reveal important differences, and we don't have to know exactly how a drug works to reap benefit, but we do need to appreciate how to use it safely.

Conclusion

The awesome voyage of metformin from herbal beginnings to respected therapeutic agent has been turbulent. It was discovered, forgotten, rediscovered, re-purposed, rejected, rescued, exonerated and may have further secrets to reveal. Each chapter has a cast of champions who helped it on its way, but the pivotal work of Jean Sterne stands aloft (Figure 5) [6, 56]. Metformin is unusual amongst pharmacotherapies as it does not appear to have a single mechanistic target: rather it counters insulin resistance and impacts metabolic, vascular and other physiological functions through multiple effects that are individually modest but collectively substantial. The value of such a favourably versatile medication requires that the contraindications (especially renal and hypoxaemic restrictions) are respected and that further potential therapeutic opportunities are explored.

Duality of interest.

The author declares that there is no duality of interest associated with this manuscript.

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LEGENDS TO FIGURES

Figure 1. *Galega officinalis* (goat's rue, French Lilac).

Figure 2. Structure of guanidine and related compounds.

Figure 3. Jean Sterne 1909-1997 (photograph courtesy of Christophe Pasik, Merck-Lipha Pharmaceuticals). Jean Sterne trained in medicine in Paris and gained experience in diabetology with Francis Rathery at Hopital de la Pitie as well as taking specialisms in infectious diseases, cardiology, psychiatry and neurology. During the 2nd world war he was a battalion medic, taken prisoner, escaped to Morocco where he worked as a musician, and return to France to assist in the liberation of Toulouse. After several years back in Morocco directing the medicines unit at a hospital in Casablanca he took a position with Aron Laboratories in Suresnes in Paris in 1956 where he investigated guanidine derivatives with Denise Duval. The rest, as they say, is history. At the end of an interview in 1996 Sterne commented "When I look back on my life, I definitely can say that I've served a purpose on earth." Metformin is his testament [23].

Figure 4. Metformin (1,1-dimethylbiguanide hydrochloride) is a relatively planar hydrophilic molecule, monoprotonated at neutral pH with several tautomeric configurations. Oral doses of 500-1000 mg of the standard immediate release tablet formulation are rapidly absorbed (Tmax ~2.5hr) in the small intestine (about 50% bioavailability), typically giving a Cmax ~2ug/mL and rarely >4ug/mL, with a steady state concentration range of 0.3-1.5 ug/mL. Plasma protein binding is negligible and distribution is extensive (volume of distribution Vd usually 100-300L). Metformin has an elimination $t_{1/2}$ of ~6-7 hours, longer if renal function is impaired: it is not metabolised and is excreted in the urine unchanged, about 20% is filtered and about 80% is secreted by the kidney [92].

Figure 5. Gallery of people who made metformin happen. Upper row: Jean Sterne, Denise Duval, Jan Aron, Elie Azerad, Leslie Duncan, Basil Clarke, Ian Campbell, Leif Sparre Hermann, Harry Howlett, Michel Noel. Lower row: Andre Meynaud, Nicolas Wiernsperger, Gerard Daniel, Anita Goodman, Gerald Reaven, Ralph DeFronzo, Clifford Bailey, Robert Turner, Alan Garber, Dennis Cryer, Rury Holman. Missing: Watanabe, Werner & Bell, Hesse & Taubmann, Slotta & Tschesche, Eusebio Garcia. Apologies to the thousands of scientists, healthcare professionals and pharmaceutical personnel listed in reference 56 who have made important contributions to the journey of metformin.

Table 1. Landmark events in the history of metformin for the management of type 2 diabetes.

Year	Landmark	Reference
1772	*Galega officinalis* used to treat symptoms of diabetes (Hill)	3
1844-61	Identification and synthesis of guanidine (Strecker)	6
1878-9	Synthesis of biguanide (Rathke)	6
1918	Guanidine lowers blood glucose in animals (Watanabe)	7
1922	Synthesis of dimethyl biguanide (Werner and Bell)	17
1926-8	Galegine and synthalin lower blood glucose in animals and humans	8-13
1929	Metformin and other biguanides lower blood glucose in animals (Hesse and Taubmann; Slotta and Tschesche)	18,19
1930s	Use of guanidine derivatives to treat diabetes initially grows then declines due to toxicity and availability of insulin	6
1944-7	Guanidine-based antimalarial agent - proguanil (paludrine) lowers blood glucose in animals	20, 21
1949-50	Dimethyl biguanide (Flumamine) tested as potential anti-malarial agent and used to treat influenza in Philippines: may lower blood glucose (Garcia)	22
1956	Jan Aron encourages Jean Sterne and Denise Duval to study guanidine-based glucose-lowering agents	6
1957	Jean Sterne publishes use of metformin to treat diabetes	24
1957-9	Phenformin and buformin reported as treatments for diabetes	32, 33, 37, 38
1958	Metformin introduced to treat diabetes in UK and other European countries	6
1958-64	Sterne and colleagues further evaluate metformin in diabetic patients	25-28,36
1968	First large prospective comparator trial of metformin (Edinburgh group)	42
1977-80	Phenformin and buformin withdrawn in most countries due to risk of lactic acidosis	49
1994	Metformin approved in USA and introduced in USA in 1995	6
1995-6	Key publications confirm favourable benefit-risk of metformin in management of type 2 diabetes	63, 64
1998	United Kingdom Prospective Diabetes Study (UKPDS) reports long-term metabolic effects of metformin and reduced cardiovascular risk	69
2000-2	Extended release formulation and fixed-dose combination based on metformin as primary active ingredient approved in USA	65,67
2002	Metformin reduced progression of 'prediabetes' to type 2 diabetes in Diabetes Prevention Program (DPP)	79
2005	International Diabetes Federation recommends metformin as initial glucose-lowering pharmacotherapy for type 2 diabetes. Other guidelines adopt metformin as initial glucose-lowering agent.	75
2008	UKPDS follow-up: continued reduction of cardiovascular risk with metformin	74
2011	Metformin included in WHO Essential Medicines List	79

Table 2. Some differences between metformin, phenformin and buformin.

Feature	Metformin	Phenformin	Buformin
Solubility Log P (octanol/water)	More hydrophilic -1.43	More lipophilic -0.83	More lipophilic -1.2
Binding to mitochondrial membranes and inhibition of respiratory chain	Weaker	Stronger	Stronger
Anaerobic glycolysis	Intestinal tissue exposed to high drug concentration	More generalised, including muscle	More generalised, including muscle
Metabolism	Not metabolised, eliminated unchanged	About 1/3rd hydroxylated by CYP2D6 (~9% Europids have 2D6 polymorphisms)	Almost all unchanged
Risk of lactic acidosis per 1,000 patient years	0.03-0.09	0.4-0.9	>0.1

Based on references 40, 45, 92.

Table 3. Pharmacodynamic effects of metformin in the treatment of type 2 diabetes

Clinical feature	Effect of metformin
Hyperglycaemia	Improves glycaemic control in type 2 diabetes; reduces progression of impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) to type 2 diabetes.
Insulin resistance	Counters insulin resistance by several insulin-dependent and independent actions that reduce hepatic glucose output, improve peripheral glucose disposal, increase intestinal anaerobic glucose metabolism and assist endothelial function
Hyperinsulinaemia	Reduces fasting hyperinsulinaemia
Abdominal obesity	Usually stabilizes body weight; can facilitate reduction of excess adiposity
Dyslipidaemia	May modestly improve blood lipid profile in some hypertriglyceridaemic and hypercholesterolaemic individuals
Blood pressure	No significant effect on blood pressure in most studies but blood pressure control may be improved in overweight individuals achieving weight loss
Pro-inflammatory state	May reduce C-reactive protein and some adipo-cytokines
Pro-coagulant state	Some anti-thrombotic activity eg. decreases in PAI-1, fibrinogen and platelet aggregation; improved capillary perfusion
Atherosclerosis	Reduced myocardial infarction and increased survival in type 2 diabetes: reduced carotid intima-media thickness and reduced adhesion molecules; other evidence for anti-atherogenic activity, mostly from animal studies

PAI, plasminogen activator inhibitor

Table 4. Clinical use of metformin in the treatment of type 2 diabetes.

Feature	Comment
Indications[a]	Monotherapy or in combination with other glucose-lowering agents including insulin in type 2 diabetes patients inadequately controlled by diet, exercise, and health education
Dosage forms[b]	500-, 850-, and 1,000-mg standard (IR) tablets: taken with meals 500-, 750-, and 1,000-mg XR tablets: mostly taken with evening meal 500mg/5mL liquid formulation and 500mg sachets of powder
Titration	Increase dose slowly; monitor glycaemic control; maximal dose 2,550 or 3,000 mg/day depending on country (2,000 mg/day in children)
Contraindications[a]	Renal and hepatic disease; cardiac or respiratory insufficiency; any hypoxic condition; severe infection; alcohol abuse; history of lactic acidosis; temporarily discontinue during use of intravenous radiographic contrast agents; pregnancy (although safe use demonstrated in several studies) Some guidelines have relaxed the renal contraindication and suggest metformin dose reduction in renal impairment if eGFR <60 ml/min/1.73m^2 (MDRD), avoid initiating metformin if eGFR <45 ml/min/1.73m^2 and stop metformin if eGFR <30 ml/min/1.73m^2
Side effects	Gastrointestinal symptoms (may include diarrhoea) and metallic taste, likely to improve with dose reduction and re-titration; may impair absorption of vitamin B12 and folic acid
Adverse reactions	Risk of lactic acidosis in patients with a contraindication; hypoglycaemia can occur when taken in combination with another glucose-lowering drug or during alcohol abuse
Monitoring	Check for contraindications; check plasma creatinine or eGFR and haemoglobin periodically; possible interaction with cimetidine therapy

IR, immediate release; XR, extended release (called SR – slow release in some countries); eGFR estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease

[a] exact wording of indications and contraindications varies according to labelling approved in different countries and regional and national guidelines

[b] availability of dose and formulation varies with country