Initiating oral glucose-lowering therapy with metformin in type 2 diabetic patients: an evidence-based strategy to reduce the burden of late-developing diabetes complications

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SUMMARY

A major aim of glucose-lowering therapy in people with diabetes is to delay or prevent the late-developing complications of diabetes that threaten the quality and duration of life. While intensive interventions to control hyperglycaemia may impair well-being to some extent, the balance of quality of life is usually highly positive. Diet and exercise therapy remains the cornerstone of management, and should usually be given a trial alone first. However, the magnitude and duration of benefit from this intervention is insufficient for most people. More frequent, early, use of metformin is an evidence-based strategy for reducing the risk of adverse outcomes of diabetes in people with type 2 diabetes with sub-optimal glucose control on lifestyle measures alone. This has been recognised in recent evidenced-based guidelines from the UK National Institute for Clinical Excellence and from Diabetes UK, which now support the use of metformin as initial pharmacological therapy for all people without contraindications to the drug. Other national and local guideline committees should consider updating their recommendations on diabetes management in line with these findings.

Key-words: Metformin · Oral glucose-lowering therapy · Type 2 diabetes · Diabetic complications.

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RÉSUMÉ

Initiation du traitement de l’hyperglycémie du diabétique de type 2 : une stratégie basée sur les preuves pour réduire le risque des complications dégénératives

L’objectif majeur dans le traitement des patients diabétiques est de retarder ou de prévenir leur risque de complications tardives qui menacent la qualité et l’espérance de vie de ces sujets. Quoique les traitements très rigoureux de l’hyperglycémie puissent altérer la qualité de vie des patients, la balance reste globalement très positive. Diététique et exercice physique demeurent la pierre angulaire du traitement et peuvent parfois être la seule approche thérapeutique. Toutefois le bénéfice de cette seule approche est dans la majorité des cas rapidement insuffisant. Dans ces cas la première ligne de traitement est logiquement la metformine sur la base d’étude de haut niveau de preuve quant à la réduction du risque d’événements ultérieurs. Ce haut niveau de preuves a conduit en Grande-Bretagne à des recommandations « UK National Institute for Clinical Excellence » et de « Diabetes UK » qui sont aussi celles vers lesquelles s’orientent d’autres pays aujourd’hui c’est à dire l’utilisation en première intention de la metformine, en l’absence de contre-indications. Ces « guidelines » pourraient être prises en compte par les pays ou régions pour l’actualisation future de leurs recommandations.

Mots-clés : Metformine · Antidiabétiques oraux · Diabète type 2 · Complications diabétiques.

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The need for optimised anti-diabetic therapy

Europe will not be spared by the pandemic of obesity and type 2 diabetes, currently underway worldwide. Projections of the prevalence of type 2 diabetes in European countries reveal that the number of individuals with this condition in the UK, Denmark, Germany, Italy, Spain, France, Finland and Denmark will have increased by almost 6 million between 1995 and 2010 [1]. The cost of managing diabetes already accounts for between 2% and 7% of total healthcare expenditure in European countries, most of which is required for the in-hospital management of late-developing diabetes complications [2]. The net annual excess healthcare costs due to type 2 diabetes in the UK alone will peak at more than €1.4 billion between 2040 and 2050 [2].

These trends will have major implications for the management of type 2 diabetes. For example, there is a substantial population of individuals with as yet undiagnosed type 2 diabetes, including a particularly high incidence in subpopulations at elevated risk of poor cardiovascular outcomes because of ethnic background [3], low socioeconomic status [4], or the presence of pre-existing cardiovascular disease [5, 6]. In addition, a large pool of individuals with the pre-diabetic conditions of impaired glucose tolerance or impaired fasting glucose will go on to develop type 2 diabetes in future, and are already at risk of developing cardiovascular disease [7].

Earlier diagnosis of type 2 diabetes, and more aggressive management of cardiovascular risk factors associated with the dysmetabolic syndrome, will be crucially important in blunting the expected rise in diabetes-related cardiovascular complications. Indeed, initiatives to screen individuals for diabetes or pre-diabetes, either opportunistically in defined high-risk groups or in more general populations, are already underway in a number of countries [8-12]. While intensive lifestyle interventions have the potential to reduce insulin insensitivity [13] and prevent or delay the onset of type 2 diabetes [14-16], many people find these interventions difficult to sustain over the long term [17]. Screening initiatives are supported to some extent by US guidelines for the management of type 2 diabetes [18], but screening has yet to appear in guidelines currently in force in Europe [19].

It is likely, given these trends, that pharmacological therapy will be given earlier in future than at present, and to a broader range of patients. Indeed, the intervention levels and targets for blood glucose control set by current guidelines are as yet rarely achieved in practice. The manner in which glucose-lowering pharmacotherapy is initiated is of crucial importance, and will strongly influence the management of the patient throughout the further course of the disease. The current evidence base for oral glucose-lowering therapy favours the use of metformin for all patients without specific contraindications or insurmountable intolerance to this drug. The present article summarises the evidence base for early intervention with metformin in the management of type 2 diabetes.

Evidence base for metformin and other pharmacological interventions

Importance of addressing insulin insensitivity

Insulin insensitivity is an important pathophysiological feature throughout the continuum of "dysglycaemia", from impaired glucose tolerance to established type 2 diabetes [20, 21]. The presence of insulin insensitivity is associated with an elevated risk of cardiovascular disease [22]. Insulin insensitivity is thus a central target for therapeutic interventions, both for diabetes prevention and for the continuing management of type 2 diabetes. Two classes of drugs that affect insulin insensitivity are currently available: metformin (which also has other glucose-lowering effects) and the thiazolidinediones, pioglitazone and rosiglitazone.

First-line use of metformin

The evidence base currently available for metformin is strong across the full range of dysglycaemia. Metformin significantly reduced the conversion of impaired glucose tolerance to type 2 diabetes, by 31% relative to placebo, in the double-blind component of the Diabetes Prevention Program (DPP), with the largest effects apparent in younger and more obese subjects [14]. Forced withdrawal of metformin for periods up to 2 weeks at the end of the DPP in line with the protocol confirmed a sustained protective effect of metformin with the reduced risk of conversion to type 2 diabetes relative to placebo maintained at 25% [23].

The UKPDS evaluated glycaemic management with metformin (median daily dosage 2550 mg/day) in a population of overweight people with recently diagnosed type 2 diabetes [24]. Metformin was more effective in controlling blood glucose, compared with lifestyle only diet-based policy, with blood glucose-lowering efficacy comparable with that of glycaemic management with a sulphonylurea or insulin. The observed improvement of blood glucose control with metformin was not accompanied by an increase in plasma insulin, consistent with an improvement in insulin sensitivity. In addition, metformin was not associated with weight gain or clinically significant hypoglycaemia, in contrast to treatment with either a sulphonylurea or insulin.

Patients randomised to glycaemic management with metformin in the UKPDS benefited from statistically and clinically very significant reductions in the risk of all-cause death (risk reduction es lifestyle treatment -36%, p = 0.011), diabetes-related death (-42%, p = 0.017), any diabetes-related endpoint (-32%, p = 0.0023), and myocardial infarc-
Use of metformin with progression of islet B-cell failure

Preliminary data from the UKPDS group, presented at the 2003 congress of the International Diabetes Federation, suggest that the benefits experienced by participants in the metformin group of the UKPDS persisted over the 5 years of post-study monitoring [28]. In the confines of general practice, as opposed to a clinical trial setting, average HbA1c levels in people previously receiving metformin or lifestyle management converged after the close of the UKPDS, and became indistinguishable after 3 years. The magnitudes of the cardiovascular risk reductions in patients previously randomised to metformin were smaller 5 years after the study closed than at the endpoint, but remained statistically significant for indices of all-cause mortality (-16%, p = 0.0072) and myocardial infarction (-18%, p = 0.015). Moreover, the apparent excess mortality among participants in the UKPDS sub-study evaluating sulphonylurea-metformin combination therapy had decreased substantially by 5 years post-study, with the difference between groups no longer statistically significant.

While peer-reviewed full publication of the post-study monitoring results is awaited, the preliminary conclusions of the UKPDS group suggest that initiation of therapy with metformin confers long-term cardiovascular benefits above and beyond those expected from tight blood glucose control alone, for as much as 25 years after the initiation of metformin therapy in the newly diagnosed UKPDS population.

Metformin has also been evaluated in several large, retrospective, observational analyses. Interpretation of these analyses is complicated by the observation that the treatment received by people with diabetes tends to parallel the degree of progression of the underlying pathophysiology, with diet and exercise followed by oral monotherapy and then combination therapy in most cases. Duration of diabetes is a significant predictor of diabetes-related mortality [29, 30], so the observation in such an analysis of better prognosis in a diet-treated cohort compared with a metformin-treated cohort, or in a metformin-treated cohort compared with patients receiving combination therapy, is not surprising [31]. A further analysis avoided this problem by considering only the first oral glucose-lowering drug therapy, with sulphonylurea monotherapy used as the reference treatment (odds ratio for mortality defined as 1.00) [32]. Treatment with metformin was associated with reduced all-cause and cardiovascular mortality, whether used as monotherapy (odds ratios [95% CI] vs sulphonylurea alone 0.60 [0.49-0.74] and 0.64 [0.49-0.84], respectively) or in combination with a sulphonylurea (0.66 [0.58-0.75] and 0.64 [0.54-0.77], respectively).

Other pharmacological interventions

The UKPDS also evaluated the effects of intensive glycaemic management with a sulphonylurea or insulin on clinical outcomes in people with newly diagnosed type 2 diabetes [23]. Both insulin and glibenclamide significantly reduced the incidence of any microvascular event (by 34% [p = 0.017] and 30% [p = 0.015], respectively), and of retinopathy requiring retinal photocoagulation (by 37% [p = 0.008] and 33% [p = 0.008], respectively). In addition, glibenclamide also significantly reduced the incidence of any diabetes-related complication (by 18%, p = 0.018), and reduced the incidence of myocardial infarction to a level that almost achieved statistical significance (by 22%, p = 0.056). Whether the benefits associated with glibenclamide extend to other insulin secretagogues is currently unclear, as no significant improvement in clinical outcomes was observed with intensive glycaemic management with chlorpropamide in the UKPDS. Outcome studies are currently evaluating the combined effects of a sulphonylurea [33] or a meglitinide [34] and an antihypertensive agent, in people with type 2 diabetes or impaired glucose tolerance, respectively.

The evidence base supporting other classes of pharmacological agents is less strong. Clinical outcome studies with the thiazolidinediones are currently in progress...
[34, 35], and will not report for at least 3 years. The α-glucosidase inhibitor, acarbose, significantly prevented or delayed the onset of type 2 diabetes in people with impaired glucose tolerance in the STOP-NIDDM study, though approximately one-third of people in this trial withdrew prematurely due to gastrointestinal side-effects [36]. The incidence of a combined cardiovascular endpoint was significantly reduced in the acarbose group in this trial, relative to placebo [37], although the number of events was small. The anti-obesity agent, orlistat, also reduced the rate of conversion of impaired glucose tolerance to type 2 diabetes in people also receiving intensive lifestyle intervention in the XENDOS trial [38]. The results of the DPP, STOP-NIDDM and XENDOS trials underline the potential of pharmacological interventions for diabetes prevention.

The only other cardiovascular outcome data available for an oral glucose-lowering drug arises from a meta-analysis of seven double-blind studies involving a total of 2180 people randomised to receive acarbose or placebo [39]. This analysis demonstrated a reduction with acarbose relative to placebo in the risk of myocardial infarction (hazard ratio 0.36 [95% CI 0.16-0.80], p = 0.012) and of any cardiovascular event (hazard ratio 0.65 [95% CI 0.48-0.88], p = 0.006). While these data are interesting, confirmation of the cardioprotective actions of acarbose from a prospective study of people with type 2 diabetes is awaited.

### Metformin and current guidelines

#### Current status of guidelines

International guidelines from the International Diabetes Federation relevant to Europe [19] and most national guidelines for type 2 diabetes outside the USA essentially are in agreement that metformin should be the agent of choice for initiation of pharmacological glucose-lowering therapy in overweight people with type 2 diabetes, after diet and exercise have failed to achieve glucose control targets, and where contraindications and tolerability allow (Tab I) [40]. As most people with type 2 diabetes are overweight, this advice would seem to apply to most of that population (Tab II).

Until recently, most guidelines recommended the use of other classes of oral glucose-lowering drugs as options for initiating therapy for non-overweight patients, despite the lack of clinical outcome data (see above). However, some guidelines did not provide a specific recommendation (Tab I). Furthermore, the definition of “overweight” used in the various guidelines varies from 25.0 kg/m² to 28.0 kg/m². Recent guidelines for the management of type 2 diabetes from the UK National Institute for Clinical Excellence, produced after formal systemic review of the clinical evidence, offer broader support for the use of metformin first line [48]. The authors noted the evidence of cardioprotec-

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>BMI definition of overweight</th>
<th>Overweight patients</th>
<th>Non-overweight patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>International (IDF Europe)</td>
<td>1999</td>
<td>None given</td>
<td>Guidelines highlight strong evidence base in overweight</td>
<td>No specific recommendation</td>
</tr>
<tr>
<td>USA (ADA)</td>
<td>2004</td>
<td>≥ 25 kg/m²</td>
<td>No specific recommendations on individual treatments</td>
<td>Consider metformin</td>
</tr>
<tr>
<td>USA (AACE)</td>
<td>2002</td>
<td>None given</td>
<td>No specific recommendations on individual treatments</td>
<td>Initiate with metformin</td>
</tr>
<tr>
<td>UK (NICE)</td>
<td>2002</td>
<td>&gt; 25 kg/m²</td>
<td>Initiate with metformin</td>
<td>Initiate with metformin</td>
</tr>
<tr>
<td>Australian Guidelines</td>
<td>2004</td>
<td>None given</td>
<td>Initiate with metformin</td>
<td>Initiate with metformin, a sulphonylurea or an α-glucosidase inhibitor</td>
</tr>
<tr>
<td>France (AFSSAPS)</td>
<td>1999</td>
<td>≥ 28 kg/m²</td>
<td>Initiate with metformin</td>
<td>Initiate with a sulphonylurea</td>
</tr>
<tr>
<td>Germany (DDG)</td>
<td>2003</td>
<td>&gt; 25-27 kg/m²</td>
<td>Initiate with metformin</td>
<td>Initiate with an insulin secretagogue</td>
</tr>
<tr>
<td>Malaysia</td>
<td>1996</td>
<td>None given</td>
<td>Initiate with metformin or acarbose</td>
<td>Initiate with a sulphonylurea</td>
</tr>
<tr>
<td>South Africa (SEMDSA)</td>
<td>2002</td>
<td>&gt; 25 kg/m²</td>
<td>Consider metformin</td>
<td>No specific recommendation</td>
</tr>
<tr>
<td>Latin America (ALAD)</td>
<td>2000</td>
<td>&gt; 27 kg/m²</td>
<td>Initiate with metformin</td>
<td>Initiate with a sulphonylurea</td>
</tr>
</tbody>
</table>

Diabetes Association recommends intervention with diet
Europe [57-59]. A consensus statement from the American
and a number of cases and case series have been reported in
diabetes is increasing rapidly in the USA [53] and in Asia [54-56],
10–16 years [52]. The prevalence of paediatric type 2 diabetes.
2 randomised trial in 82 type 2 diabetic patients aged
ration used within the guidelines.

<table>
<thead>
<tr>
<th>Population</th>
<th>Clinical status</th>
<th>n</th>
<th>Mean BMI (kg/m²)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS main analysis (UK)</td>
<td>T2DMa</td>
<td>3867</td>
<td>28</td>
<td>25</td>
</tr>
<tr>
<td>T2DM: DiabHycar study (France)</td>
<td>T2DM + MA</td>
<td>4912</td>
<td>29</td>
<td>42</td>
</tr>
<tr>
<td>Observational study (Finland)</td>
<td>T2DM</td>
<td>1059</td>
<td>29</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>± T2DM</td>
<td>2342</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Framingham cohort (USA)</td>
<td>IGT</td>
<td>3234</td>
<td>34</td>
<td>44</td>
</tr>
<tr>
<td>Diabetes Prevention Program (USA)</td>
<td>T2DMb</td>
<td>588</td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td>STOP-NIDDM study (International)</td>
<td>IGT</td>
<td>1368</td>
<td>31</td>
<td>36</td>
</tr>
<tr>
<td>Framingham Offspring Cohort (USA)</td>
<td>IRc</td>
<td>1700</td>
<td>29</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>No IRd</td>
<td>1133</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td></td>
<td>± T2DM</td>
<td>2378</td>
<td>26</td>
<td>46</td>
</tr>
<tr>
<td>San Antonio Heart Study (USA)</td>
<td>No diabetes</td>
<td>1734</td>
<td>28</td>
<td>47</td>
</tr>
</tbody>
</table>

T2DM: Type 2 diabetes mellitus; IGT: impaired glucose toler-
ance; MA: microalbuminuria; IR: insulin insensitive; *Newly-
diagnosed; #free of cardiovascular disease at baseline; 3 quartiles
3–5 or 4 quartiles 1–2 for HOMA-IR insulin insensitivity.

A further recent change to the regulatory status of met-
formin from the UKPDS [24], the similar blood glucose-lowering efficacy of metformin and other
agents in meta-analyses [49-51] and the neutral or positive
effect of metformin on body weight and lipid profiles. The
resulting recommendation concerning the use of met-
formin in overweight patients is similar to that found in
previous guidelines, together with a further recommenda-
tion that consideration should be given to the use of met-
formin as first-line pharmacological therapy in non-
overweight patients (Box 1). The recommendation is
considered to be based on “category I evidence”, the highest
rating used within the guidelines.

A further recent change to the regulatory status of met-
formin concerns its approval in Europe for the manage-
ment of paediatric type 2 diabetes. This follows a double-
blind, randomised trial in 82 type 2 diabetic patients aged
10–16 years [52]. The prevalence of paediatric type 2 dia-
betes is increasing rapidly in the USA [53] and in Asia [54-56],
and a number of cases and case series have been reported in
Europe [57-59]. A consensus statement from the American
Diabetes Association recommends intervention with diet
and exercise in children with type 2 diabetes, followed by
addition of metformin therapy if this is insufficiently effec-
tive [53]. European guidelines now need to address the
emerging clinical problem of type 2 diabetes in children
and adolescents.

Clinical implications

The use of metformin as first-line pharmacological
therapy in type 2 diabetes should be the recommended
course of action once lifestyle interventions have been
found to fail to control blood glucose levels to target
(HbA1C of < 6.5%). The efficacy of diet and exercise ther-
apy is high, but as blood glucose levels are usually very
elevated by the time of diagnosis, they are nevertheless
unlikely to achieve adequate blood glucose control for
most people with diabetes even in the short term [60].
Treatment with metformin therapy should therefore be
started as soon as people are found not to have adequately
responded to diet and exercise, as the risk of late-develop-
ing diabetes complications increases in proportion to the
degree and duration of hyperglycaemia [61]. The efficacy
of metformin is clearly dose-related [62], so that the dose of
metformin should be optimised for each person to achieve
blood glucose control targets and thus cardiovascular pro-
tection, before consideration is given to addition of second
glucose-lowering drug. Metformin can be combined with
all other classes of oral glucose-lowering agents, including
insulin secretagogues, α-glucosidase inhibitors, PPAR-γ
agonists and insulin [63-69].

Gastrointestinal side-effects may represent the main
barrier to successful treatment with metformin, where it
is not contraindicated. These are common, around 95%
of people taking metformin can find some dose level that
balances side-effects with the benefits of its effects on pre-
vention of late-developing diabetes complications. If gas-
trointestinal side-effects threaten to cause discontinuation
of metformin, a switch to the prolonged-release formulation,
where available, may improve tolerability [70]. Ear-
lier concerns over an increased risk of lactic acidosis with
metformin have largely been resolved with continual
monitoring of renal function and immediate discontinua-
tion of the drug in high-risk acute medical situations. A
systematic Cochrane review has recently shown that, if
the contraindications and warnings related to its use are
followed adequately, metformin is not associated with
an increased risk of this rare but life-threatening event
[71, 72].

Conclusions

Metformin remains the only oral glucose-lowering
drug to reduce the risk of macrovascular complications,
and to prolong life, in patients with type 2 diabetes. The
degree of clinical benefit is large when started (where
indicated) soon after diagnosis. Similar clinical outcomes data for other drugs are unlikely to be available for some years. All people without contraindications to metformin, and without insurmountable tolerability issues, should therefore receive metformin as first-line therapy. Other oral glucose-lowering drugs should be added as required as islet-B cell function declines in order to keep glycaemia below performance targets, within the context of an aggressive multiple risk-factor intervention programme.

As such use of metformin is consistent with an evidence-based strategy for reducing the risk of the late-developing complications of diabetes, national and local guideline committees should consider updating their guidelines accordingly.

**Box 1.**

Recommendations regarding the use of metformin in guidelines issued by the UK National Institute of Clinical Excellence in the UK (September 2002) [48].

- In people who are overweight (body mass index over 25.0 kg/m²) and whose blood glucose in inadequately controlled using lifestyle interventions alone, metformin should normally be used as the first-line glucose-lowering therapy. (A)
- Metformin should be considered as an option for first line or combination therapy for people who are not overweight. (A)
- Metformin is contraindicated in those with renal impairment (serum creatinine > 130 µmol/L [1.5 mg/dL]) and those at risk of sudden deterioration of renal function. (C)

Grading of evidence base for recommendations:
- (A): Recommendation based on evidence from meta-analysis of randomised controlled trials, or from at least one randomised controlled trial
- (C): Evidence from one or more of the following: meta-analysis of randomised controlled trials, at least one randomised controlled trial, at least one controlled study without randomisation, least one other type of quasi-experimental study, or from non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies.

**Key points**

- Optimising glucose-lowering therapies is essential in the face of the coming diabetes epidemic.
- The purpose of glucose-lowering therapy is largely to prevent morbidity and mortality from the late-developing complications of diabetes.
- Only metformin is proven to reduce the risk of development of macrovascular complications in people with type 2 diabetes.
- Early use of metformin is an evidence-based strategy to improve the prognosis of people with type 2 diabetes.

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